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Cost-Benefit Analysis of Preventive Healthcare Programs

OPEN ACCESS

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In an age where healthcare systems are burdened with rising costs and increasing demands, one truth remains constant: preventing disease is far less expensive—and more effective—than treating it. Preventive healthcare programs, often overshadowed by curative medicine, are a long-term investment with undeniable economic and social returns. Programs for health promotion have been heralded as having enormous potential to assist in addressing the issue of rapidly rising health care expenses. Program evaluation must include a cost-benefit or cost-effectiveness analysis to determine whether health promotion initiatives are "worth it." Preventive healthcare includes a wide range of interventions—regular screenings, vaccinations, smoking cessation programs, nutrition education, and early detection of diseases. These initiatives aim to catch health issues before they become severe and costly. And while the upfront costs of such programs can seem steep, the cost savings over time are substantial. Fewer hospital admissions, reduced need for expensive treatments, and minimized emergency room visits all translate into billions in savings for healthcare systems. All project-related expenses and benefits must be measured and converted into monetary values to determine the welfare change attributable to the project (i.e., the project's net benefit to society as a whole). In ex ante evaluation, policymakers utilize CBA as a tool to choose between different projects or determine whether a certain plan is beneficial to society. It can also be used ex post to calculate the net social value of a particular program that has been fully completed. Moreover, preventive care enhances health equity. Community-based initiatives, mobile screenings, and free vaccination clinics can bridge the gap for underserved populations, ensuring that everyone has access to the tools they need to stay healthy. Preventive care is not just an economic decision—it's a public good. So, what should we do? Policymakers must prioritize funding for preventive services, insurers should cover them comprehensively, and public awareness campaigns should emphasize their importance. We must shift the conversation from curing disease to preventing it. Investing in preventive healthcare is investing in our collective future. The cost-benefit analysis isn't just in the numbers—it's in the healthier lives, stronger communities, and sustainable systems we build along the way. preventive care promotes a healthier, more productive population. When people are healthy, they can work, care for their families, contribute to the economy, and live longer, more fulfilling lives. Chronic illnesses like diabetes, heart disease, and certain cancers—many of which are preventable or manageable if caught early—account for a large portion of healthcare spending and productivity loss. Tackling them through prevention makes fiscal and moral sense.

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Review Article

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Pumpkin Seeds and Heart Health: A Comprehensive Review of Their Role in Cardiovascular Disease Prevention and Management

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ABSTRACT

Cardiovascular Diseases (CVDs) remain a major global health concern, with an increasing prevalence requiring urgent preventive strategies. Diet and lifestyle play a crucial role in CVD development, emphasizing the need for healthy food interventions. To explore the potential cardioprotective benefits of pumpkin seeds (*Cucurbita spp.*) and their bioactive compounds in promoting cardiovascular health. Relevant literature was reviewed to evaluate the macronutrient and micronutrient profile of pumpkin seeds, as well as their bioactive compounds. Study Design: A comprehensive review of the nutritional composition and functional properties of pumpkin seeds was conducted, focusing on their role in cardiovascular disease prevention. Key components, including linolenic acid, phytosterols, antioxidants, and pumpkin seed oil, were analyzed for their potential impact on cardiovascular health. Pumpkin seeds are rich in proteins, carbohydrates, and unsaturated fatty acids, along with essential micronutrients such as zinc, phosphorus, magnesium, potassium, and selenium. Linolenic acid in pumpkin seeds offers protective effects against CVDs, diabetes, and certain cancers. Phytosterols contribute to lowering LDL cholesterol levels, while their strong antioxidant properties help reduce oxidative stress, lower blood pressure, and prevent arteriosclerosis. Pumpkin seed oil, rich in magnesium, enhances Nitric Oxide (NO) production, supporting vascular function and aortic protection. Given the increasing focus on plant-based diets for chronic disease prevention, regular consumption of pumpkin seeds may provide significant benefits in improving cardiovascular health. Further research and clinical trials are recommended to establish optimal dietary intake guidelines for maximizing their protective effects.

INTRODUCTION

Cardiovascular Diseases (CVD) are considered among the main diseases in the world. In the developed countries the prevalence of CVDs have become greater at an alarming rate than the past [1]. In almost every country, CVD issues are continuing their long-term rising trend. Major causes of CVD are Cardio metabolic, behavioral, environmental, and social risk factors. CVDs are common, have an increased persistence rate, and are growing in prevalence. Intervention strategies for improving health in countries should be specifically considered such as diabetes prevention and management, weight management and increased physical activity, healthy diet, tobacco and alcohol prevention and activities for increased endurance and alcohol reduction [1]. To reduce the prevalence of these heart diseases, there is a need to include the plant-based products in the human diet owing to their significant antioxidant and bioactive properties. One such plant product is pumpkin [2]. Pumpkin is taken from the Greek word pepon, meaning a big melon. In the South Asian region, it is commonly regarded as 'Kashiphal', 'Sitaphal' or

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'Kaddu' [3]. Cucurbitaceous family consists of gourds, squashes, melons and pumpkin [2]. Kingdom Plantae consists of a number of families; the greatest percentage of edible plant species is in Cucurbitaceae family [4]. The five genera; *Cucurbita, Sechium (chayotte), Lagenaria (gourds), Cucumis (cucumbers, gherkins and melons)* and *Citrullus* (watermelons and wild colocynths), include pumpkins which may be added to the human diet in the fresh or processed form [5]. *Cucurbita maxima, Cucurbita moschata*, and *Cucurbita pepo* are the three most popular species among the 12 distinct species of the genus Cucurbita [6]. Pumpkin seeds *(Cucurbita spp.)* contain several bioactive compounds that contribute to cardiovascular health by lowering cholesterol, reducing blood pressure, and combating inflammation [7]. Phytosterols, such as β-sitosterol, campesterol, and stigmasterol, structurally resemble cholesterol and compete for absorption in the intestines, leading to a reduction in LDL cholesterol levels and improved lipid metabolism. Linolenic acid (omega-3 fatty acid) plays a crucial role in cardiovascular protection by inhibiting hepatic triglyceride synthesis, upregulating LDL receptor expression, and promoting cholesterol excretion through bile acids. Additionally, it enhances nitric oxide (NO) production, leading to vasodilation and improved vascular function while also reducing pro-inflammatory cytokines like TNF-α and IL-6. Magnesium, another key component, acts as a calcium antagonist, preventing vascular smooth muscle contraction and promoting vasodilation, ultimately lowering blood pressure [8]. It also supports endothelial function by stimulating NO synthesis and reducing oxidative stress. Potassium in pumpkin seeds further contributes to blood pressure regulation by maintaining electrolyte balance and counteracting sodium-induced hypertension. The antioxidants present, including vitamin E, polyphenols, and carotenoids, help scavenge Reactive Oxygen Species (ROS), inhibiting lipid peroxidation and reducing arterial plaque formation. Moreover, cucurbitacins, a group of triterpenoids found in pumpkin seeds, suppress NF-κB and COX-2 pathways, reducing inflammation and preventing atherosclerosis. Additionally, the presence of tryptophan, a serotonin precursor, may indirectly lower stress-related hypertension. Collectively, these bioactive compounds contribute to cardiovascular protection by improving lipid metabolism, enhancing vascular function, lowering blood pressure, and reducing systemic inflammation. Regular consumption of pumpkin seeds as part of a balanced diet may thus offer significant cardioprotective benefits [9]. Historically, the pumpkin seeds have frequently been used as a soil fertilizer in agriculture, as animal feed, and in treating the problems of kidneys, prostate and bladder [2]. Moreover, pumpkin seeds contain fiber, sterols, and omega-3 fatty acids that provide cholesterol lowering effects in blood. The predominant oils extracted from the pumpkin seeds contain high amount of oleic and linoleic acids, which are unsaturated [4]. A study showed that the death rate from coronary artery disease was significantly lower in humans who consumed diets high in linoleic acid [10]. The oil extracted from pumpkin seeds has anti-inflammatory effects and lowers blood pressure and cholesterol [11]. Triacylglycerol concentrations are lowered and multiple CVD risk factors are mitigated by pumpkin seeds oil ingestion [12, 13]. For a long time researches have been conducted on the active components of the pumpkin skin flesh and seeds, providing a brief overview of their health-related effects. These studies have shown that pumpkin peel has anti-inflammatory effects, antibiotic properties, anticarcinogenic, antidiabetic, and antihypertensive effects, making it a potential diabetes climber. The health benefits exhibited by pumpkin seed oil include its antimicrobial, antihypertensive, anti-arthritic, anti-inflammatory, and antidepressant qualities [14]. Pumpkin seeds contain zinc, phosphorus, magnesium, potassium, and selenium, which help combat arthritis, inflammation, and prostate cancer [15].

Nutritional Composition of Pumpkin Seeds

Pumpkin seeds are principally regarded as functional constituents of foods, which are known to remarkably increase the nutritional status of human beings [3]. Table 1 showed the constituents of pumpkin seeds. They are considered as a nutritional powerhouse because of the abundant quantities of nutrients present in them [6].

Table 1: Nutritional Profile and Bioactive Composition of Pumpkin *(Cucurbita spp.)* Seeds

Nutrient	Pumpkin Seeds (Value/100g)	RDA (Percentage)	References
Energy	559 Kcal	28%	[16]
Lipids	49.05 g	164%	[16]
Protein	30.23 g	54%	[12]
Fiber	6 g	16%	[16]
Carbohydrates	10.7 g	8%	[12]
Cholesterol	0 g	0%	[16]

Furthermore, the seed flesh has a nutty flavor and is high in protein, carotenoids, β-carotene, g-tocopherol, nitrogen-containing compounds (Cucurbitacin B and E, cucurbitin), glucosides (saponins) and minerals (potassium, phosphorus, magnesium, calcium, sodium, manganese, iron, zinc, and copper), which make the pumpkin seeds a premium food supplement (Table 2).

Table 2: Quantitative Analysis of Essential and Non-Essential Amino Acid Composition in Pumpkin *(Cucurbita spp.)* Seeds [12]

Amino acids	Pumpkin Seeds (Value/100g)
Glutamic Acid	4.315g
Arginine	4.033g

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Aspartic Acid	2.477g
Leucine	2.079g
Lysine	1.833g
Isoleucine	1.264g
Threonine	0.903g
Tryptophan	0.431g
Methionine	0.551g
Cysteine	0.301g
Phenylalanine	1.222g
Tyrosine	1.019g
Valine	1.972g
Histidine	0.681g
Alanine	1.158g
Glycine	1.796g
Proline	1.01g
Serine	1.148g

Potassium supports homeostasis, magnesium maintains cell membrane potential, and sodium regulates blood pressure and fluids [3].Table 3 shows their vitamin and mineral content.

Table 3: Vitamin and Mineral Composition in Pumpkin *(Cucurbita spp)*Seeds[12][16][4]

Vitamins	Pumpkin Seeds (Value/100g)	RDA (Percentage)
A	16 IU	0.50%
B_1 (Thiamin)	0.27 mg	23%
B_2 (Riboflavin)	0.15 mg	12%
B_3 (Niacin)	4.98 mg	31.0%
B_5 (Pantothenic Acid)	0.75 mg	15%
B_6 (Pyridoxine)	0.14 mg	11%
B_9 (Folate)	58 mcg	15%
C	1.9 mcg	3%
E	35.1 mg	272%
K	0.007 mg	-
Minerals		
Calcium	46 mg	4.5 %
Sodium	7 mg	0.5 %
Potassium	809 mg	17%
Copper	1.3 mg	148%
Iron	8.82 mg	110%
Magnesium	592 mg	148%
Manganese	4.54 mg	195%
Phosphorus	1233 mg	175%
Selenium	9.4 mcg	17%
Zinc	7.81 mg	17%

Anti-Nutritional Elements

Pumpkin seeds contain antinutritional elements, including phytate (35.06 mg/100 g), oxalate (0.02 mg/100 g), hydrocyanic acid (0.22 mg/100 g), and nitrate (2.27 mg/100 g) [6]. Their chemical composition varies by species, diversity, maturity, and environmental conditions [2]. Compared to Cucurbita maxima, Cucurbita pepo has higher moisture, ash, protein, total nitrogen, and carbohydrate levels [6]. Cucurbita pepo and Cucurbita moschata contain more γ-tocopherol, while Cucurbita pepo is richest in β-sitosterol and Cucurbita maxima in β-carotene. Pumpkin seeds also have the highest iron content (95.85 ± 33.01 ppm) among 11 types of nuts and seeds [8].

Pumpkin Seed Phytochemistry

Pumpkin seeds derive their nutritional value from phytochemicals, including phenolic glycosides, tocopherols, triterpenes, saponins, phytosterols, lignans, and carotenoids [12].These compounds promote gut health, support metabolism, and provide cardioprotective benefits by reducing cholesterol absorption and inflammation [16]. Pumpkin seeds rank third in phytosterol content among nuts and seeds, reducing atherosclerotic lesions and inflammatory cytokines (IL-6, TNF-α) while lowering LDL-C by ~10% with a daily intake of 2g [17].β-sitosterol, the primary phytosterol, is present at 24.9 mg/100 g [18].Pumpkin seeds also contain phytoestrogens (lignans, isoflavones) and phytosterols (β-sitosterol, secoisolariciresinol, genistein, daidzein).They are rich in oil (42.3% w/w) and squalene (89 mg/100 g) [19].Bioactive compounds such as triterpenoids, carotenoids, polyphenols, and cucurbitacins contribute to cardiovascular health [20].Cucurbita maxima seeds contain unique triterpenes with potential heart benefits. The Cucurbitaceae family provides saponins and glycosides that aid cardiovascular function and blood clotting, while cucurbitacin enhances autophagy in cardiomyocytes, preventing cardiac heteropathy [21]. Tocopherol isomers (α, β, γ, δ) reduce CVD risk, while phenolics, quercetin, and flavanols prevent LDL oxidation and inflammatory cytokine synthesis [22]. Luteolin and cryptoxanthin provide additional cardiovascular protection by mitigating inflammatory signals [23]. Among postmenopausal women, pumpkin seed oil improved blood pressure and lipid profiles by raising HDL-C, reducing cardiovascular complications [24].

Standardized Methods for Evaluating Pumpkin Seed Oil

Standardized methods are used to evaluate Pumpkin Seed Oil (PSO) for its composition, antioxidant capacity, and bioavailability. GC-MS identifies fatty acids, while HPLC analyzes tocopherols, carotenoids, and phytosterols. ICP-OES measures mineral content, and antioxidant activity is assessed using DPPH, FRAP, and ORAC assays. Bioavailability studies include in vitro digestion models and human or animal trials to determine nutrient absorption and metabolic effects [15]. Compared to other plant-based oils, PSO offers a unique blend of phytosterols, tocopherols, and essential minerals for cardiovascular health. While olive oil is high in oleic acid, PSO provides superior cholesterol-lowering compounds. Flaxseed oil has more omega-3s, but PSO supports blood pressure regulation and vascular health through its diverse bioactive profile. Sunflower oil, though rich in vitamin E, lacks significant omega-3s and phytosterols.Overall, PSO aids lipid regulation, blood pressure control, and oxidative

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stress reduction, making it a valuable heart-healthy option [12].

Processing and Utilization of Pumpkin Seed in Preventing CVDs

Drying is a widely used commercial preservation method that extends shelf life, reduces weight, and facilitates storage and transport [6].Roasting pumpkin seeds (100°C–130°C) enhances their nutty flavor by synthesizing pyrazines but decreases α-tocopherol by up to 15% and reduces phospholipids [5].Protein content slightly declines after roasting for 30 and 60 minutes (21.46% and 22.96%, respectively) compared to raw seeds, along with slight reductions in palmitic, stearic, oleic, and linoleic acids [25].Sert *et al.*, (2022) investigated ultrasound-assisted extraction from pumpkin seed press cake, enhancing protein yield and functional properties [26]. Roasting for 60 minutes significantly lowers lead content (0.007 mg/100 g vs. 1.070 mg/100 g in raw seeds), reducing risks of hypertension, stroke, and heart disease [3].Tannin levels in raw, boiled, fermented, germinated, and roasted seeds are 19.1, 7.5, 9.8, 14.0, and 9.9 g/kg, respectively. Tannins help protect cardiac tissue, prevent elastin degradation, and reduce arterial calcium buildup, thereby preventing CVDs [27].Fermentation increases protein content from 28% to 39.4% while reducing fat from 48% to 25.5% [28].Boiling lowers phytic acid to 4.3 g/kg, with fermentation reducing it further to 2.8 g/kg, though germination increases its levels [3]. Phytic acid aids heart health by reducing lipase activity, total cholesterol, and HDL [29].Trypsin inhibitor content drops from 23.18 TIU/mg in raw seeds to 2.13 TIU/mg after processing [5].Seed processing enhances carotene bioavailability, benefiting nutraceutical formulation [12].Cold-pressed or steam-distilled pumpkin seed oil, known for its deep green color, effectively reduces CVD prevalence [30].Pumpkin seeds are used in various forms, including fresh, boiled, cooked, powdered, and in bioactive and pharmaceutical applications [31].Pumpkin-derived oils and proteins have antimicrobial and pharmacological benefits [32]. Cucurbita maxima extracts (leaves, fruit, flowers) have antioxidant, anticancer, cardioprotective, and estrogenic effects [5].Pumpkin-based foods exhibit preventive and therapeutic effects on CVDs [33].Rich in bioactive compounds, pumpkin seed oil supports prostate, bladder, and heart health, lowering triglycerides, total cholesterol, LDL, uric acid, creatinine, and serum transaminases while increasing HDL [34].The high fat content in pumpkin seeds contributes to reduced CVD risk [12].

Cardiovascular Health Benefits of Pumpkin Seeds:

Anti-hypertensive Effects

Pumpkin seeds have shown anti-hypertensive effects due to their bioactive compounds, which reduce oxidative stress and inflammation [21].Adsul and Madkaikar (2021) provided a comprehensive overview of the nutritional and functional attributes of *Cucurbita pepo* (pumpkin) seeds in health and food applications [35].Pumpkin seed oil, rich in vitamins, carotenes, and fibers, helps regulate diabetes and cardiovascular health [36].Jin *et al.*, (2019) evaluated polysaccharides from *Camellia oleifera* seed cake, highlighting their physicochemical properties and hypoglycemic effects in diabetic mice [37]. Barnabe *et al.*, (2018) explored multiscale modeling approaches to optimize the use of bioresources and development of innovative bioproducts [38].Polysaccharides in pumpkin seeds act as antioxidants, while their high tryptophan content aids in reducing depression [15].

Regulation of Blood Lipid Profile

Pumpkin seeds help manage heart diseases by reducing oxidative stress and preventing plasma lipoprotein oxidation [39].Their oil, rich in unsaturated fatty acids and phytosterols, lowers LDL and increases HDL, limiting cholesterol absorption [40]. In postmenopausal women, pumpkin seed oil improves lipid profiles, enhances HDL-C, and reduces LDL-C, especially when combined with simvastatin [12].

Anti-inflammatory Effects

Pumpkin seeds exhibit anti-inflammatory properties superior to pharmaceuticals [4].Their phytochemicals help reduce atherosclerosis, and roasting increases polyphenols, enhancing cardiovascular benefits [42]. Kaempferol in pumpkin seeds protects against cardiovascular diseases through its anti-inflammatory and antioxidant effects [43]. Hazaveh *et al.*, (2021) examined the combined effects of aerobic training and pumpkin seed extract on oxidative stress markers in the heart and aorta of arsenic-exposed rats [44].

Anti-oxidative Effects

Pumpkin seeds reduce arteriosclerosis, hypertension, and cardiovascular diseases through their antioxidant activity [20].Their oil significantly lowers serum triglycerides while increasing HDL [33]. Regular consumption helps regulate blood pressure, and phytosterols in pumpkin seeds aid in cholesterol reduction [45]. Sharma *et al.*, (2020) reviewed the pharmacological, biomedical, and food industry applications of extracts from pumpkin and its related species [46]. Rajasree *et al.*, (2016) reviewed the diverse phytochemicals present in the Cucurbitaceae family and their potential pharmacological benefits [47]. Tocopherols, selenium, and zinc contribute to their strong antioxidant properties [10].

Improvement of Endothelial function

Pumpkin seed oil, rich in unsaturated fatty acids, prevents atherosclerosis by improving blood vessel elasticity [48]. Omega-6 and omega-3 PUFAs help lower LDL-C, reduce triglycerides, and support vascular function [49].Their phytoestrogens and trigonelline compounds further aid in reducing blood pressure and cardiovascular risks [12].

In Vivo and Ex Vivo Studies

Pumpkin has both a direct and an indirect impact on serum lipid levels.A diet consisting of flaxseed and pumpkin oil

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was provided to Lohmann Brown Lite hens as part of a research experiment.According to this study, eggs produced by hens with a myristic acid, other saturated fatty acids including PUFA, and MUFA [50]. A comparable study using extract of pumpkin (5, 10, and 15%) and 72% wheat flour was carried out in 2015.When pumpkin cake was contrasted with control cake made of wheat, it was evaluated that pumpkin cake had more fiber (8%), carotenoids (41 mg/100 g), and ash (6.45%).Based on biological investigation, it was found that pumpkin meal boosts HDL level and decreases bad cholesterol and cholesterol in a dose-dependent way [51].Additional studies that used pumpkin seeds as a supplement to hypercholesterolemic rats support similar results. According to reports, PS reduced LDL while rise in HDL level reduced cholesterol level [52, 53].Pumpkin has a positive effect on renal function in addition to its effects on blood lipid profile and atherogenicity [54].Arginine, the precursor of Nitric Oxide (NO) and a factor in maintenance of blood pressure, apoptosis, cardiac health, and inflammatory response, is present in 2.6% of pumpkin seed powder [55].Rats with hyperlipidemia were given the supplement of pumpkin seed extract showed increased expression of NO generation because of the presence of arginine, according to an in vivo study intended to examine the impact of seed extract of pumpkin (mostly arginine). Furthermore, the formation of NO reduces the LDL oxidation, resulting causing a decreasein the impact of Vascular Cell Adhesion Molecule (VCAM) [56].Thus, adopting a lifestyle modification that includes daily consumption of pumpkins can be considered an effective dietary approach for managing hypercholesterolemia. In a research by Mosallamy *et al.*, (2012), it was noted that administering 40-100 mg/kg dose of pumpkin seed oil to rats with chemically induced hypertension for 6 weeks led to a reduction in abnormal blood pressure increase, lowered levels of Malondialdehyde (MDA)[10].

Table 4: Bioactive Compounds from Natural Sources: Their Therapeutic Potential in Cardiovascular Health and Disease Prevention

Class	Compound (Formula)	Sources	Therapeutic Potential	Ref
Phenolic Acids	Chlorogenic Acid (C16H18O9)	Artichoke, Avocado, Broccoli, Green tea, Kiwi	Treats CVDs	[57]
	Ferulic Acid (C10H10O4)	Broccoli, Cabbage, Lettuce, Spinach	Regulates NO/ET-1, protects endothelium, angiogenic	[58]
	p-Coumaric Acid (C9H8O3)	Avocado, Basil, Spinach	Antioxidant, anti-inflammatory, heart-protective	[59]
	Gallic Acid (C7H6O5)	Avocado, Green tea	Antioxidant, anti-inflammatory, antimicrobial, cardioprotective	[60]
Flavonoids	Kaempferol (C15H10O7)	Avocado, Broccoli, Cabbages, Fennel leaves	Antioxidant, antihypertensive, cardioprotective	[61]
	Quercetin (C15H10O7)	Broccoli, Kale, Spinach, Watercress	Anti-inflammatory, obesity, CVDs	[62]
	Rutin (C27H30O16)	Avocado, Green tea	Antioxidant, CVD protection	[17]
	EGCG (C22H18O11)	Green tea	Lowers BP, improves HDL, protects heart and brain	[13]
	Luteolin (C15H10O6)	Broccoli, Cabbages, Celery, Green peas	Antioxidant, anti-inflammatory, cardioprotective	[63]
Terpenoids	Cryptoxanthin (C40H56O)	Broccoli, Green grapes, Lettuce	Reduces myocardial ischemia injury	[64]
	Lutein (C40H56O2)	Avocado, Kale, Spinach, Zucchini	Lowers CVD and coronary artery disease risk	[65]
Glucosinolates	Indole-3-carbinol (C9H9NO)	Broccoli, Kale, Mustard greens	Anti-inflammatory, antihypertensive	[66]
	DIM (C17H14N2)	Broccoli, Cabbages, Watercress	CVD therapeutic effect	[67]
	Sulforaphane (C6H11NOS2)	Cruciferous vegetables, Cabbages	Cardioprotective, reduces ROS, improves cell survival	[57]
	Caffeic Acid (C9H8O4)	Celery, Olives/Olive oil	Lowers BP, prevents atherosclerosis	[58]

Pumpkin seed oil helps to protect the heart and aorta from damage by boosting the production of nitric oxide (NO), thereby minimizing the risk of heart attacks due to its elevated magnesium content. Additionally, Pumpkin seed supplements have been found to be particularly effective at blocking calcium channels, which can help support heart health and improve circulation compared to drug amlodipine [10]. Li *et al.*, (2021) used transcriptome analysis and gene co-expression networks to uncover the multitarget antibacterial actions of benzyl isothiocyanate against Staphylococcus aureus [68].Mohammadi *et al.*, (2018) demonstrated the immunoregulatory effects of indole-3-carbinol on macrophages in systemic lupus

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erythematosus via the aryl hydrocarbon receptor pathway [69].The researcher *Fruhwirth and Hermetter (2007)* highlighted that pumpkin seed oil is rich in oleic acid, which helps lower blood pressure by improving the vasodilator pathway.This happens because oleic acid blocks calcium-mediated cell signaling by inhibiting the production of inositol 1, 4, 5-triphosphate and diacylglycerol [70]. As for pumpkin extracts, varieties like P5 (round orange) and P6 (spotted orange-green) have a high total phenolic content and moderate antioxidant activity.They also show moderate to high abilities to inhibit enzymes like -glucosidase and Angiotensin-Converting Enzyme (ACE).This suggests that incorporating antioxidant-rich dietary strategies using specific traditional plant based food combinations, such as those in pumpkin extracts, could help manage hyperglycemia and its related complications, such as oxidative stress and high blood pressure[71].

CONCLUSIONS

Pumpkin seeds are nutrient-dense component of plant-based diets, offer significant Cardioprotective benefits due to their rich composition of bioactive compounds, including linolenic acid, phytosterols, antioxidants, and essential minerals. These compounds contribute to cardiovascular health by improving lipid profiles, reducing oxidative stress, lowering blood pressure, and enhancing vascular function.The presence of magnesium in pumpkin seed oil further supports nitric oxide production, aiding in arterial relaxation and aortic protection.Regular consumption of pumpkin seeds may help in the management of key risk factors associated with cardiovascular diseases, such as dyslipidemia, hypertension, and arterial stiffness. Given the growing emphasis on natural dietary interventions for chronic disease prevention, pumpkin seeds hold promise as a functional food for promoting heart health. However, further clinical studies and human trials are necessary to establish optimal dietary recommendations and fully elucidate their long-term effects on cardiovascular outcomes.

Authors Contribution

Conceptualization: IYM
Methodology: AA, TN, MRK, YRK, TZ
Formal analysis: FJ, MJI
Writing, review and editing: MA, FJ, IYM, CN, MJI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Impact of Pharmacist-Led Interventions On Medication Adherence in Patients with Chronic Psychiatric Disorders

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ABSTRACT

Mental health disorders represent a growing global health challenge, affecting an estimated 970 million people worldwide as of 2019. These disorders not only impair individuals' ability to function but also impose significant economic and social burdens. In a country like Pakistan, mental health treatment resources are minimal, and chronic psychiatric disorders like bipolar personality disorder, schizophrenia, and chronic depression have become an enormous burden. **Objectives:** To assess the impact of pharmacist-led interventions on medication adherence among psychiatric patients in Rawalpindi, Pakistan. **Methods:** This quasi-experimental mixed-method study employed a pre-post intervention design. Conducted in two psychiatric clinics in Rawalpindi, it involved a total sample of 60 participants for the quantitative phase and 10 for the qualitative phase. Quantitative data were analyzed using McNamara's test and the Wilcoxon signed-rank test, while qualitative data underwent thematic analysis. **Results:** Significant improvements in medication adherence were observed post-intervention, as evidenced by Paired Chi-Square (McNamara's test) and Wilcoxon Signed Rank Test.Thematic analysis of the qualitative data identified four main themes with three sub-themes, providing insights into the patients' attitudes, knowledge, and practices regarding medication adherence. **Conclusions:** It was concluded that pharmacist-led interventions were found to be effective in enhancing medication adherence among psychiatric patients.The study underscores the importance of ongoing support and education for this patient group and recommends the continuation of such interventions to sustain improvements in adherence.

INTRODUCTION

As of 2019, nearly 970 million people have been affected by chronic mental disorders such as bipolar personality disorder, schizophrenia, and other depressive illnesses [1]. The most prominent effect of these disorders can be observed not only on the individual's quality of life but also economically and socially. In a country like Pakistan, which is considered a low and middle-income country, mental health is an underfunded and extremely ignored dimension of public health with minimal integration into primary healthcare services, intensifying the worries and complications faced by patients and their caregivers [2]. The most critical component in the management of a mental health disorder is the adherence of the patient to the prescribed medication regimen. Medication adherence ensures stabilization of symptoms and reduces hospitalization rates, but medication non-adherence persists as a prevailing fact, as global estimates according to studies conducted reveal a massive 50% non-adherence of patients with chronic mental illnesses [3]. In a country like Pakistan, the severity of this issue has seen an exceptional increase due to fragmentation in healthcare systems, stigma in society regarding psychiatric disorders, and limited affordability of medicines [4]. This study explores the potential of pharmacist-led interventions in improving medication adherence among psychiatric patients in Islamabad. By addressing systemic and cultural barriers, the findings aim to inform sustainable models of care that enhance mental health outcomes. The most

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critical and fundamental factor in the therapeutic management of chronic psychiatric illnesses is the strict following of prescribed medication regimes.Research studies conducted across the globe have repeatedly proven that proper medication adherence produces prominent improvement in clinical results with consistent stabilization in symptoms and a sharp decrease in hospital admission rates [3].Despite all these advantages, we see that non-adherence is the most prevalent medication problem globally.In an LMIC like Pakistan, levels of medication adherence are too low, according to research only less than 20% of the people with chronic psychiatric conditions adhering to the prescribed regimen [4].Non-adherence to medication in psychiatric patients is the fundamental issue that reduces treatment effectiveness and aggravates the global burden on health systems. Pakistan faces multidimensional barriers such as extreme societal stigma, limited access to mental healthcare services, and disintegrated healthcare that further worsen the problem [2]. Pakistan faces multidimensional barriers to medication adherence. The majority of chronic psychiatric patients and their caregivers both suffer from the societal stigma that prevents them from seeking treatment, while the fragmentation in the Pakistani healthcare system, alongside poor access to affordable medicines, further aggravates the situation [5]. Pharmacists are such accessible healthcare professionals who have sublime expertise in medication regimen management, promising a productive solution to these existing challenges. There is no doubt that around the globe, pharmacist-led interventions have produced excellent results and major improvements in medication adherence rates and outcomes of treatment [6, 7]. However, the role of pharmacists in mental health treatment is often overlooked in Pakistan and remains severely underexplored, as the majority of pharmacists are confined to dispensing medicines only.

This study aims to analyze the impact of pharmacist-led interventions on medication adherence and treatment outcomes in psychiatric clinics in Rawalpindi, Pakistan.

METHODS

A mixed-methods quasi-experimental pre-post intervention study design was used to complete this study. The study was conducted in Rawalpindi. It was a multicenter study. To ensure the generalizability of results, 2 different mental health clinics were selected for the administration of pharmacist-led interventions and in-depth post-intervention interviews. Both these clinics had a patient influx with diverse socioeconomic and demographic backgrounds. Quantitative data collection was conducted in 2 phases, as interviews with patients were conducted once before and then after the pharmacist-led interventions. Qualitative data collection was conducted after the completion of the interventions by a pharmacist. Open-ended questions were asked of willing patients in live interviews, and their in-depth responses regarding their medication adherence routine, beliefs and experiences were transcribed verbatim. A structured questionnaire incorporating socio-demographic data, MARS, and PHQ-9 both cross-culturally validated tools ensured reliable quantitative assessment, while in-depth interviews with open-ended questions strengthened qualitative insights. Data integrity was maintained through complete entry and analysis in SPSS version 23.0, eliminating missing values. Pre-intervention data established a baseline, with post-intervention assessments capturing pharmacist-led program effects. This self-comparison design enhances internal validity by controlling for between-group variability. Only those patients took part in this study who were diagnosed with a chronic mental illness and had to visit the doctor for a checkup at least 2 times a month. This study only includes outpatients. Convenience sampling was used to recruit participants. A sample size of this research was set at 60 as equal participation of patients from both clinics was ensured, including 30 patients from both mental health clinics. The sample size determination considered an effect size of Cohen's d=0.5, a 0.05 significance level, and 80% power, resulting in 32 patients per group (total=64), with 60 deemed sufficient. For qualitative analysis, data saturation guided participant selection, typically achieved with 10–15 individuals; thus, 10 intervention-group patients were purposively chosen. This dual approach ensures robust statistical power for quantitative analysis while providing meaningful qualitative insights. A total of 120 responses were collected, 60 responses before and 60 after the administration of pharmacist-led interventions for quantitative data analysis and 10 patients who had received pharmacist interventions participated in the in-depth interviews for qualitative data collection and thematic analysis. Clinical pharmacists consistently ensured their presence in both clinics and administered interventions during the 4-week study period (Figure 1).

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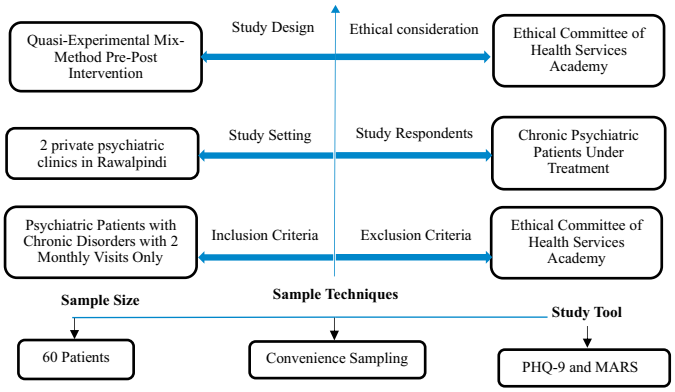

Figure 1: Methods Included Sample Size, Sample Techniques and Study Tool

Pharmacists interacted with each patient and their caregiver two times during the study, and each session lasted 10 minutes. They focused on patient education on the significance of medication adherence and proper use of sedative-hypnotics and antidepressant drugs while completing a structured checklist to ensure the effectiveness of the intervention. Medically, the one-month intervention period was justified and appropriate, as most antidepressants and psychiatric medications significantly improve symptoms within two weeks of consistent usage. Research indicates that 90% of patients experience a noticeable improvement in their symptoms if they adhere to their treatment regimen, making one month an apt duration and ensuring no dropout. Ethical approval was obtained from the Institutional Review Board of the Health Services Academy, Islamabad. The IRB approval letter (F.No. 000873/HSA/MSPH-2023). Data collection started on 26 December 2024 and was completed in March 2025, for a total duration of 33 days. The framework of this study is based on the Health Belief Model (HBM), which provides a structured approach to understanding medication adherence behavior, allowing us to assess how patients' perceptions influence adherence patterns. The Health Belief Model was incorporated in data collection and questioning to ensure systematic evaluation of perceived barriers, benefits, and self-efficacy. Thematic analysis was conducted using N Vivo software following Braun and Clarke's (2006) framework. A structured codebook guided the process, ensuring systematic and transparent coding. Inter-coder reliability was assessed using Cohen's Kappa, and discrepancies were resolved through discussion. Triangulation and an audit trail were maintained to enhance validity and reproducibility. Reflexivity discussions minimized bias, ensuring a rigorous and credible analysis.

RESULTS

The McNamara's Test results indicate significant improvements in medication adherence. There was a notable reduction in medication forgetfulness (p=0.002), carelessness in taking medicine (p=0.008), and stopping treatment upon feeling better (p=0.041). Additionally, forgetfulness due to travel (p<0.001) and side effects (p=0.002) showed a marked decline. These findings suggest that the intervention effectively improved patients' consistency in taking medication. However, no significant changes were observed in stopping treatment when feeling worse (p=0.09) or taking medicine only when sick (p=0.07). This indicates that while medication adherence improved in many areas, some behavioral patterns remained unchanged. Future interventions may need to address these specific issues to achieve more comprehensive adherence improvements (Table 1).

Table 1: Summarized Results of Paired Chi-Square McNemar's Test

Variables	Pre -> Post: Yes to No	Pre -> Post: No to Yes	Pre: Total Yes	Pre: Total No	p-Value	Significant Change	Notes
Medication Forgetfulness	13	1	41	19	0.002	Yes	Significant Reduction in Forgetfulness
Carelessness in Taking Medicine	15	3	38	22	0.008	Yes	Notable Decrease in Carelessness
Treatment Cessation Upon Feeling Better	12	2	26	34	0.041	Yes	Improved Adherence When Feeling Better
Treatment Cessation Upon Feeling Worse	8	9	43	17	0.09	No	No Significant Changes
Taking Medicine Only When Sick	9	5	41	19	0.07	No	No Significant Changes
Medication Forgetfulness During Travel	25	0	51	9	<0.001	Yes	Significant Improvement During Travel
Medication Forgetfulness Due to Side Effects	20	0	45	15	0.002	Yes	Reduced Forgetfulness Due to Side Effects

The sample size was calculated to ensure sufficient power (80%) to detect statistically significant changes in medication adherence and psychological outcomes, including treatment cessation when feeling worse and taking medicine only when sick. Based on an effect size of Cohen's d=0.5 and a 0.05 significance level, the required sample size was 32 per group (total=64), but 60 patients were included, maintaining robust statistical power. For qualitative analysis, data saturation guided the selection of 10 intervention-group participants, ensuring meaningful insights. While treatment cessation when

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feeling worse (p=0.09) and taking medicine only when sick (p=0.07) did not show statistical significance, the study's power was sufficient to detect changes in these behaviors. The absence of significance likely reflects deeply ingrained beliefs rather than methodological limitations, highlighting the need for targeted interventions to address these specific adherence challenges. To establish both statistical and clinical significance, effect sizes and absolute adherence improvements were analyzed. Cohen's d (0.5–0.8) confirmed moderate to large effects in Wilcoxon results, reflecting meaningful psychological improvements, while McNamara's test odds ratios (>2) demonstrated substantial adherence gains. Beyond p-values, adherence improved by 46.56%, with forgetfulness decreasing by 65.85% and carelessness by 39.47%, reflecting real-world clinical impact. These findings underscore the effectiveness of pharmacist-led interventions in improving medication adherence and mental health, reinforcing their value in addressing adherence-related challenges in psychiatric care. The Wilcoxon signed test results highlight significant improvements in psychological well-being. Participants showed increased interest in activities (p<0.001), improved sleep patterns (p<0.001), enhanced concentration levels (p<0.001), and greater self-confidence (p<0.001). Additionally, there was a reduction in suicidal thoughts (p=0.032), indicating positive mental health outcomes. These findings suggest that the intervention contributed to overall emotional and cognitive improvements. However, no significant changes were observed in depression symptoms (p=0.252) or feelings of fatigue (p=0.563), suggesting that while some aspects of mental health improved, others remained unaffected. This indicates the need for targeted approaches to address persistent depressive symptoms and energy levels for a more holistic impact. Statistical analyses revealed a 46.56% overall improvement in medication adherence following a pharmacist-led intervention. Notable reductions were observed in medication forgetfulness (65.85%) and carelessness (39.47%), along with increased adherence when feeling better (46.15%). Adherence also improved in cases of illness (32.14%), traveling (49.02%), and side effects (44.44%), underscoring the intervention's effectiveness in fostering consistent medication-taking behaviors. However, treatment cessation when feeling worse (32%) and taking medication only when sick (26.32%) showed no statistically significant change. The McNamara's test demonstrated significant reductions in forgetfulness (p=0.002) and carelessness (p=0.008), while the Wilcoxon signed-ranks test indicated enhanced mental health outcomes, including reduced depressive symptoms (p<0.001) and improved energy levels (p<0.001). These findings highlight the strong correlation between improved adherence and better mental well-being, reinforcing the intervention's role in enhancing both medication consistency and overall health outcomes (Table 2).

Table 2: Summarized Results of the Wilcoxon Signed Rank Test

Variables	Negative Ranks (Post <Pre)	Positive Ranks (Post >Pre)	Ties (No Change)	Test Statistic (Z)	p-Value	Significant Change	Notes
Little Interest in Doing Things	30	5	25	-4.443	<0.001	Yes	Improved Interest in Activities
Feeling Depressed	18	15	27	-1.145	0.252	No	No Significant Change in Depression Symptoms
Trouble Falling Asleep	33	6	21	-3.672	<0.001	Yes	Enhanced Sleep Patterns
Feeling Tired	22	21	17	-0.578	0.563	No	No Significant Change in Energy Levels
Trouble Concentrating	29	7	24	-3.925	<0.001	Yes	Improved Concentration Levels
Feeling Bad About Yourself	33	5	22	-3.917	<0.001	Yes	Increased Self-Confidence
Suicidal Wishes	20	5	35	-2.147	0.032	Yes	Decrease in Suicidal Ideation

This analysis identifies three key themes influencing medication adherence: patient attitude, knowledge, and external challenges, each with distinct sub-themes. Attitude of Patient: Medication Adherence–Some patients discontinue medication when they feel "normal," leading to inconsistent adherence. Stigma of Psychiatric Treatment – Fear of judgment causes patients to hide their medication use, reinforcing non-adherence. Patient's Knowledge: Understanding Medication Benefits – Many patients take medicines solely on a doctor's advice without understanding their necessity. Awareness of Side Effects – Concerns like weight gain lead to intentional skipping of doses. Knowledge of Withdrawal Effects – Patients are unaware of the risks of sudden discontinuation, which increases relapse chances. Challenges in Adherence: Financial Constraints – Some patients cannot afford their medications, causing treatment gaps. Social Support – A lack of emotional

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and practical support makes adherence difficult. Medication Availability – Stock shortages force patients to delay or stop treatment. Multi-dimensional factors influencing medication adherence have been highlighted in this analysis. This is a psychological fact that when we feel better, we sometimes stop taking medicine. This analysis also testifies to it, alongside patients admitting a significant lack of knowledge regarding their treatment regimen. "I know I need them, but I don't fully understand why" - Patient 4. Lifestyle modifications were preferred by some patients over long treatment regimens, as we saw variations in their coping mechanisms. Support from caregivers also encouraged medication adherence in many patients, especially after pharmacist-led interventions (Table 3).

Table 3: Detailed Codebook of Themes and Sub-Themes

Theme	Sub-Theme	Code	Description	Example Quotes
Participants' Attitude	Attitude toward medication adherence	ATT-ADH	Patients' perspectives on the necessity and consistency of taking medications.	"Sometimes I stop taking my medication when I feel normal." (P3)
	Trust in psychiatric medications	ATT-TRUST	Level of confidence in the effectiveness and necessity of psychiatric medications.	"I believe these medicines help me, but I still have concerns about their long-term effects." (P2)
	Stigma associated with psychiatric treatment	ATT-STIG	Fear of judgment or discrimination due to taking psychiatric medications.	"I don't want my family to know I take these medicines." (P1)
Participants' Knowledge	Understanding medication benefits	KNOW-BEN	Awareness of how medications contribute to mental health improvement.	"I just take them because my doctor says so." (P5)
	Awareness of side effects	KNOW-SE	Knowledge of potential adverse effects that may impact adherence	"I have gained weight since I started taking these medications, so I skip them sometimes." (P6)
	Knowledge of withdrawal effects	KNOW-WD	Awareness of symptoms or risks when stopping medication abruptly.	"I didn't know stopping my medicine suddenly could cause problems." (P4)
	Consistency in medication in take	PRAC-CONS	Regularity and adherence in taking prescribed psychiatric medications.	"I take my medicine regularly, but sometimes I forget." (P1)
Participants' Practice	Consistency in medication intake	PRAC-CONS	Regularity and adherence in taking prescribed psychiatric medications.	"I take my medicine regularly, but sometimes I forget." (P1)
	Following the healthcare provider's instructions	PRAC-HCP	The extent to which patients follow prescribed dosages and recommendations.	"Sometimes I take less than what is prescribed because I feel better." (P5)
	Use of reminders or support systems	PRAC-REM	Strategies used for remembering medication intake (alarms, family reminders, etc.).	"I set alarms on my phone to remind me." (P2)
Challenges in Medication Adherence	Financial constraints	CHAL-FIN	Economic difficulties in affording psychiatric medications.	"Sometimes I can't afford to buy my medicine." (P2)
	Availability of medications	CHAL-AVAIL	Barriers related to medication stock shortages or pharmacy access.	"Sometimes my medicine is out of stock, so I have to wait." (P3)
	Social support	CHAL-SOC	Influence of family, friends, or caregivers on adherence behavior.	"I feel alone in managing my condition." (P7)

DISCUSSION

The societal stigma surrounding mental health is one significant barrier to medication adherence. Stigma leads to reluctance to ask for help and adhere to treatment, forming a toxic cycle and worsening mental health challenges [2]. Individuals fear judgment and feel shame, as this perception of our society discourages them from even understanding their condition and their medication needs [4]. As a result, the pharmacist's role is also further complicated as the pharmacist also has to relieve the psychological stress of the patient while educating them about their medicines [5]. The findings of this study align with the principles of the Health Belief Model (HBM), reinforcing the role of patient perceptions in medication adherence. Our results indicate that perceived severity and benefits strongly correlate with adherence levels, while perceived barriers, such as side effects and financial constraints, negatively impact compliance [8, 9].These insights underscore the necessity of patient-centered interventions that specifically target these adherence barriers, thereby reinforcing the practical applicability of the HBM in real-world healthcare settings [10, 11]. Inadequate access to mental health resources further hinders medication adherence, being a systemic challenge in addition to the societal stigma [1].The lack of trained healthcare professionals in many regions limits the efficacy of interventions aimed at increasing medication adherence [12, 13].By offering education and support tailored to individual patient needs, pharmacists, as responsible healthcare providers, can bridge this gap [14, 15].Their involvement in medication therapy management has shown positive outcomes in chronic illness adherence, suggesting that similar approaches could be beneficial in mental health contexts [4].Moreover, innovative

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strategies, including the use of digital tools, have emerged as effective methods to enhance adherence, particularly in low- and middle-income countries (LMICs).Costa *et al.* highlight that electronic health interventions can significantly improve patient engagement and adherence rates [16, 17].These tools provide reminders and educational resources, which can be particularly beneficial for patients who may forget or misunderstand their medication regimens [12, 13].Globally, this has been observed that when pharmacists sit with patients in one-to-one discussions and educate them about their medication regimes, it improves medication adherence rates [18, 19].These strategies empower patients by enhancing their understanding of the importance of consistent medication use, thereby fostering a sense of ownership over their treatment [20].Such approaches are particularly vital in the context of mental health, where patients may struggle with the perception of their illness and the necessity of ongoing treatment [3]. A notable limitation of this study is that it does not account for the variations in medication regimes of patients, including differences in formulations, dosage types, and pharmacokinetic properties, which can influence adherence patterns, as the focus of this study was on overall adherence trends rather than drug-specific effects. Future research should incorporate an in-depth assessment of medication characteristics to provide a nuanced understanding of their impact on adherence behaviors. Another limitation of this study is the possible presence of interviewer bias in qualitative responses. Additionally, investigating the integration of digital health tools and tele-pharmacy within clinical practice could provide insights into enhancing adherence strategies.

CONCLUSIONS

It was concluded that this mixed-methods quasi-experimental pre-post intervention study effectively highlights the significance of pharmacist-led interventions in improving medication adherence in chronic psychiatric patients. Quantitative data analysis reveals a 46% improvement in medication adherence after interventions by pharmacist, cementing the importance of their role in mental health clinics. Patients' in-depth interviews reveal insights into societal stigma, socio-economic barriers, and financial constraints in the management of their chronic mental illnesses. The integration of qualitative and quantitative findings helps in the in-depth understanding of how much of important role pharmacists can play in improving medication adherence if they are provided with an opportunity to conduct counseling sessions in mental health clinics.

Authors Contribution

Conceptualization: UUH
Methodology: UUH, ZK
Formal analysis: UUH, AM
Writing review and editing: SE

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Impact of Marriage on Performance, Behavior, and Work-Life Changes among Female Employees in the Health Sector

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ABSTRACT

According to the World Bank, only 20% of Pakistani women hold a university degree linked to professional employment. Furthermore, women's participation across all sectors remains notably low, with figures below 5%. **Objective:** To assess the variations experienced by married female employees within the healthcare sector. Specifically, it investigates the changes in performance, WLB, and PB as perceived by the participants after marriage. **Methods:** This survey was conducted over the period of 01 years from public and private organization where women practitioner was working as doctor or postgraduate students affiliated with the College of Physicians and Surgeons of Pakistan (CPSP) or General Practitioners (GPs) within the province of Sindh. **Results:** The paired sample t-test also reveals a statistically significant difference between Work-Life Balance of Before-Marriage Status (mean = 2.0961, SD = 0.61938) and After-Marriage Status (mean = 2.2167, SD = 0.66697), with the difference t (203) = -3.070, p = 0.002 (two-tailed), α = .05 and finally there was a significant difference between Professional Behavior of before and after marriage (mean = 1.8255, SD = 0.63691), (mean = 1.9382, SD = 0.70962); t (203) = -2.917, p = 0.004 (two-tailed), α = .05 respectively. **Conclusion:** This study highlighted the significant impact of marital status changes on women's professional lives, particularly in the health sector.

INTRODUCTION

Pakistan is a country of 241 million people, with a growth rate of 2.55 per annum, which is higher than all other countries in South Asia [1]. According to the data almost half of the population (49%) comprised of females in Pakistan [2]. Because of the norms and cultural practices among the Asian, females served primary role at home while secondary position in the society. Men traditionally take charge of external matters, assuming the role of breadwinner and wielding ultimate decision-making power, thus establishing a male-dominated societal structure. Besides, the literacy level of Pakistan is only 58% of inhabitants among which females is lower compared to males, primarily due to the pervasive influence of patriarchal culture and the challenging circumstances faced by women [3]. The roles of wives and mothers within the household serve as barriers to female education and professional advancement [4]. The World Health Organization (WHO) anticipates a worsening global shortage of healthcare professionals, projecting a deficit of up to 12.9 million by 2035. [5]. In Pakistan, approximately 100,000 (97,851) doctors are currently serving, indicating a ratio of one doctor for every 2041 people [6]. This ratio

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signifies that there is only half the number of doctors recommended by the World Health Organization (WHO) for an ideal doctor-to-population ratio in Pakistan. Past studies also revealed that female doctors often discontinue their practices after graduation, with marriage being identified as one of the primary reasons for this cessation [7]. In societies like Pakistan, working women assume a dual role, shouldering responsibilities both within their families supporting spouses, children, and household affairs—and in the workplace [8]. Marital unions bring about social and psychological transformations in a woman's life, altering her perspective on work as she embraces new roles as a mother and wife. The shift in personal life dynamics can have varied effects on professional commitment of the female [9]. In one of the study related to the doctors and nurses uncovered that Work-Life Balance (WLB) practices play a crucial role in shaping employee job performance and satisfaction and marriage is one of the prominent element in this balance [10]. Often, women perceive themselves as crucial contributors to their family's economic well-being, thus enhancing their sense of importance as contributors to the household economy. Negotiating changing dynamics at home and in the workplace equips women with valuable experience in decision-making and problem-solving. The evolving environment enables working women to navigate relationships with family members (including in-laws and spouses), children, as well as colleagues and superiors at work. Such experiences foster resilience and adeptness in handling challenging situations. However, the increased workload at home may sometimes negatively impact professional performance, and vice versa [11]. Married women in employment encounter diverse and demanding situations in their domestic and professional spheres. According to the World Bank, only 20% of Pakistani women hold a university degree linked to professional employment. Furthermore, women's participation across all sectors remains notably low, with figures below 5% [12]. This study hypothesized that Married female employees within the healthcare sector experience significant changes (assumed to be more negative) in performance, work-life balance (WLB), and professional behavior (PB) after marriage, as perceived by the participants. The primary aim of this study is to assess the variations experienced by married female employees within the healthcare sector.

Specifically, it investigated the changes in performance, WLB, and PB as perceived by the participants after marriage.

METHODS

This observational cross sectional survey was conducted over the period of 1 year (Sep 2023-Aug 2024) from public and private organization where women practitioner was working as doctor or postgraduate students affiliated with the College of Physicians and Surgeons of Pakistan (CPSP) or General Practitioners (GPs) within the province of Sindh. Taking 27% women specialist among the registered medical practitioners mention in the 2017 stat report of PMDC [7]. The sample size was determined by using the Open Epi Calculator taking 20% prevalence rate of a university degree linked to professional employment on 95% confidence level with 5% chance of error and using finite population ratio, it was obtained 203.3 which is approximate to 204 respondents for the study [12]. Purposive snowball sampling technique was used. "Before-Marriage Status (BMS)" described the condition of women before entering into a union, which occurs in diverse locations globally and serves to formalize relationships with religious, legal, social, and marital validation. "After-Marriage Status (AMS)" described the status of women involved in unions established in various parts of the world to solidify relationships, with religious, legal, social, and marital recognition. Participants answered questions about their education level, job responsibilities, professional growth opportunities, work-life balance, and support systems before and after marriage. Questions focused on the impact of marriage on their professional responsibilities, household duties, and ability to meet workplace expectations before and after marriage were asked on Likert scale. Performance was taken as a progress of the employees, especially in completing the given task, client/patient satisfaction. Work-life balance defined the prioritizing among work and lifestyle of the employees, which includes health, family, pleasure, etc. Professional Behavior (PB) defined to place herself professionally in required role and behave with relevant team members. Work-life balance (WLB) was measured to evaluate health professional ability to prioritize between work and personal life, including aspects such as health, family, leisure, assessed time management, satisfaction with personal life, and stress associated with work-life conflict. Performance was measured as the progress of health professional made to achieving patient satisfaction. This was assessed through a quantitative metrics such as task completion rates and adherence to deadlines. Professional behavior was measured based on health professional ability to fulfill their roles professionally and interact effectively with team members. This was evaluated using a self-rating questionnaire that included aspects like teamwork, communication, and adherence to professional norms. For data collection in this study, a questionnaire was formulated through the literature [12] using the Likert scale i.e., five points ranging from "strongly agree" to "strongly disagree"; where Low (1.00–2.50) indicating significant imbalance or low levels of performance and professional behavior while High (3.51–5.00) indicating strong balance or exceptional performance and professional behavior. It consisted of 19 statements which also included demographic inquiries regarding age, duration of marriage, number of children,

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professional occupation, and educational background. This questionnaire reliability was also measure through Cronbach Alpha after 30 questionnaire collected. Since this study is the part of the degree research, acceptance letter on synopsis was obtained before commencement of the study(AMTF/IRB-0021/24). On voluntarily participation, the questionnaires were shared with participants via social media and email address. After the consenting to participate, any participate sought clarification on certain questions, particularly regarding performance and behavior, principal investigator or data collector was on reach within 30 min time. The anonymity and confidentiality of the participant was ensured while data collection and reporting. For vulnerable information where participant whished not to disclosed, that participant/s data was removed from the final reporting. To examine the hypotheses, a paired T-test was utilized to compare the BMS with AMS. Participants were stratified into subgroups based on BMS and AMS to control the confounding, to reduce variability and to ensure meaningful comparisons. For descriptive and inferential analysis, statistical software SPSS version 22.0 was used.

RESULTS

Out of the 350 individuals approached for data collection, 235 filled questionnaires were received. Thirty-one responses were excluded due to incomplete data or errors, resulting in a final dataset comprising data from 204 respondents for further analysis. Before reporting the results, the variability and reliability of the questionnaire testing was done using the Cronbach's Alpha test on all three variables i.e., BMS and AMS, followed by an assessment of overall reliability across all variables. The combined reliability scores for performance, WLB and PB for BMS and AMS were found to be 0.885 and 0.895, respectively, indicating a strong internal consistency in the data. Additionally, Cronbach's Alpha reliability values for each variable fell within an acceptable range while overall reliability value is 0.931 which showed excellent reliability (Table 1).

Table 1: Cronbach Alpha Reliability Analysis on 204 study participants

Variables	Number of Items	Cronbach's Alpha*
Before-Marriage Status	19	0.885
Performance	5	0.855
Work-Life Balance	8	0.713
Professional Behavior	6	0.872
After-Marriage Status	19	0.895
Performance	5	0.852
Work-Life Balance	8	0.767
Professional Behavior	6	0.865
Overall	38	0.931

*>0.7 Acceptable Reliability, >0.8 Good Reliability, >0.9 Excellent Reliability

Descriptive analysis showed the mean value of AMS exceeded BMS which suggests that a shift towards disagreement in respondents' responses to the statement. In terms of performance, WLB, and PB, their status AMS appeared to be higher than their BMS. Inferential analysis results indicate significant paired differences between the mean values of each variable pair BMS and AMS. Specifically, there was a consistent trend towards disagreement in responses AMS compared to BMS The observed differences were unlikely to have occurred by chance alone, indicating a statistically significant effect of marital status on respondents' perceptions (<0.005)(Table 2).

Table 2: Descriptive and Inferential Statistics (Paired T-Test) Among The 204 Female Participants

Variables		Descriptive	Inferential	
		Mean	Mean ± S.D	p-Value*
Pair 1	Performance of Before-Marriage	1.6569	-0.1852 ± 0.6052	<0.001
	Performance After-Marriage	1.8422		
Pair 2	Work-Life Balance-Before-Marriage	2.0961	-0.1205 ± 0.5609	0.002
	Work-Life Balance -After-Marriage	2.2167		
Pair 3	Professional Behavior - Before-Marriage	1.8255	-0.1127 ± 0.5519	0.004
	Professional Behavior -After-Marriage	1.9382		

*02 tailed test, =0.05

DISCUSSION

It is being reflected through the mass media and other literature about the double standard practices among Pakistani's when there is a debt about the role of women and men in the society [13]. There are different expectations from men and women, both in families and outside. These hopes have been around for a long time and are deeply rooted. While things have been slowly getting better, some gender biases still exist, especially when it comes to the roles assigned to women [14]. This unequal treatment has a big impact on both the personal and work life of female professionals. The study found significant changes in the working of female employees, where they previously completed tasks on time or consistently arrived punctually at work and may find it challenging to maintain these practices after changes in marital status. Additionally, their interactions with coworkers and team members may shift due to added responsibilities at home, potentially altering their preferences for social activities and domestic duties. The marriage has both positive and negative effects on the performance of the female professionals [15]. The change of marital status in their lives brought different variations in their behavior, females feel more responsible and marriage brings vicissitudes in their activities [16]. The results of the current study indicate that marriage influences employees' performance. Respondents reported facing challenges in

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meeting deadlines, receiving less favorable feedback from both peers and clients and experiencing a lack of recognition from senior staff after getting married. These results contrast with a previous study conducted in India, which suggested that marriage leads to increased maturity levels and greater responsibility towards work, resulting in better task completion among married women. This earlier research indicated that married women tend to be more responsible in their jobs and contribute more effectively compared to unmarried women [17]. The decrease in performance leads to slow career growth, this was also supported in the previous study that career success for married women in the presence of factors like assertiveness, marital status, and having children, impact career advancement differently [18]. Balancing work and personal life was a significant challenge for married women, impacting both their professional and personal spheres [19]. The dual responsibility places working women under various pressures. The study found that these additional burdens lead to health concerns, ineffective time management, and inadequate care for dependents, significantly affecting the work-life balance of employed women. These findings align with a previous study conducted among female doctors and nurses in Malaysia, highlighting the pervasive challenges faced by women due to societal gender norms [8]. The investigation revealed alterations in the behavior of female health workers subsequent to marriage. These outcomes corroborate those of a similar study conducted among female health workers in Taiwan [20]. However, it was also noteworthy that women contributing to their family income have a significant role in household decisions [21]. Their economic contribution provides them with a strong bargaining position for sharing household responsibilities, including caring for dependents, with their partner. Having access to personal finances also enhances their standing in society. Despite the additional workload at their jobs, many working women aspire to continue their professional careers because it offers advantages and elevates their status within the family structure.

CONCLUSIONS

This study highlighted the significant impact of marital status changes on women's professional lives, particularly in the health sector. It reveals how marriage can affect behavior and performance, posing challenges such as meeting deadlines and gaining recognition. These findings challenge traditional views on marriage's positive effects on job performance and underscore the delicate balance between work and personal life for married women. The study calls for policymakers and organizations to address these challenges by implementing support systems, flexible work arrangements, and gender-equality policies. Future research should investigate the mechanisms driving these effects through longitudinal and cross-cultural approaches.

Authors Contribution

Conceptualization: NK
Methodology: GYV, SS
Formal analysis: NK
Writing, review and editing: NUT, FA, SS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association of TLR7 rs864058 Genotypic Variation and mRNA Expression with COVID-19 Severity and Clinical Outcomes

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ABSTRACT

Genetic variations in TLR7 could modulate the severity of COVID-19. **Objectives:** To find the association between TLR7 mRNA expression, genotypic variations, and disease severity in COVID-19 patients. **Methods:** A cross-sectional observational study was conducted on 59 PCR-confirmed COVID-19 patients at Ziauddin Hospital, Karachi (June 2022–May 2023). Blood samples were analyzed for TLR7 genotyping via PCR and Sanger sequencing. Disease severity was classified into three groups based on clinical guidelines. TLR7 mRNA expression was quantified using real-time PCR (qPCR), and hospitalization, ICU admission, and complications were documented. **Results:** Higher TLR7 mRNA expression was observed in patients with the GG genotype compared to those with the GA genotype (p=0.04). Individuals carrying the GG genotype exhibited greater hospitalization rates (75.5% vs. 40%, p=0.009), increased ICU admission (28.6% vs. 10%, p=0.041), and a higher need for mechanical ventilation (20.4% vs. 10%, p=0.049). Respiratory failure occurred more often in the GG genotype group (20.4% vs. 10%, p=0.038). **Conclusions:** It was concluded that the GG genotype of TLR7 was related to higher susceptibility to severe COVID-19 outcomes, with higher hospitalization rates, ICU admission, and respiratory failure.

INTRODUCTION

The WHO declared COVID-19 a worldwide pandemic on March 11, 2020, as countries began reporting cases globally.The COVID-19 infection continues to impact worldwide, with over 700 million COVID-19 cases and above 6 million deaths with the infection as of October 2023 [1]. Scientists first discovered enveloped RNA viruses called coronaviruses in 1968, naming them for their solar corona-like appearance under electron microscopy.The virus causes a range of symptoms collectively referred to as COVID-19, varying from mild to severe [2].Approximately 80% of patients had mild to moderate symptoms; however, some individuals develop severe conditions requiring hospitalization, intensive care unit (ICU) admission, and, in some cases, mechanical ventilation [3]. The considerable variation in disease severity has prompted extensive research to identify host genetic determinants that influence immune responses and clinical outcome [4]. The Toll-like Receptor 7 (TLR7) protein exists as a gene product located at Xp22.3 on the X chromosome short arm. The TLR7 protein appears in innate immune cells and exists on endosomal membranes to detect both single-stranded RNA (ssRNA) and synthetic oligoribonucleotides.TLR7

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plays a key role in detecting ssRNA viruses, including SARS-CoV-2, and initiating an innate immune response [5]. The pattern recognition receptor function of TLR7 transmits signal sequences to activate pathways for inflammatory cytokine production and type 1 interferon synthesis, along with antiviral immunity development [5, 6]. The TLR7 gene contains a single-nucleotide polymorphism (SNP) that modifies the TLR7 receptor structure and causes reduced immune response capacity. TLR7 exists in various immune cells like dendritic cells and B cells, and macrophages, where they detect viral RNA inside endosomal compartments. SARS-CoV-2 releases its ssRNA genome during host cell infection, where TLR7 detects the genome. The pathogen recognition by TLR7 initiates MyD88-dependent signaling, which leads to interferon (IFN-α and IFN-β) production. Interferons produced through this process establish their crucial role by both blocking viral replication and eliminating cells infected by pathogens [7]. Research has found a strong link between specific genetic variations in TLR7, particularly the 'T/T' genotypes and the 'T' allele at the rs179008 location and an increased threat of severe-type Covid-19 pneumonia [8]. On the other hand, another study revealed that individuals with the GG genotype of the TLR7 rs3853839 gene face a higher genetic risk for COVID-19 infection, severity of the disease and poorer outcomes [9]. The rs11385942 variant on chromosome 3p21.31(G/GA) significantly increases the risk of respiratory failure in COVID-19 individuals, with a 1.77-fold higher risk [10]. TLR7 polymorphisms contribute to genetic variability in immune responses, potentially leading to different immune-related consequences. These variations may increase susceptibility to RNA virus infections [11]. Genetic differences in the TLR7 gene can influence its function and expression, potentially affecting COVID-19 severity. Rare mutations that impair TLR7 activity have been tied to more severe cases, particularly in young men [12]. The role of TLR7 genetic variations in modulating immune responses and disease outcomes highlights the requirements for further research into their impact on COVID-19 severity [13].

This study aims to investigate the relationship between TLR7 mRNA expression and clinical outputs in COVID-19 patients, with a particular focus on genotypic differences and disease severity.

METHODS

This was a cross-sectional research performed on 59 COVID-19 confirmed patients who tested positive for PCR, using a convenience sampling method. Analysis of the sample size was performed utilizing the Open Epi sample size calculator with an estimated 10% proportion of COVID-19 severity linked to TLR7 polymorphisms based on past research findings [14, 15]. A confidence level of 95% (Z=1.96) and a margin of error of 5% (d=0.05) were used. 59 subjects were enrolled from outpatient clinics, general wards, and intensive care units (ICUs) at Ziauddin Hospital, Clifton, Karachi, from June 2022 to May 2023. Participants included adult patients who tested positive for COVID-19 through PCR or were treated and followed by pulmonologists at Ziauddin Hospital Clifton and those with a documented previously of COVID-19 infection. Individuals who had received chemotherapy or radiotherapy were excluded from analysis as these treatments can have profound effects on the immune system, which might confound an analysis of TLR7 expression and association with outcomes in COVID-19. Furthermore, participants with any type of malignancy were also excluded to prevent cancer-associated immune dysregulation or treatment effects from affecting the study results. The participants, aged 20 to 80 years, were both male and female. Demographics (age, weight, BMI, socioeconomic status), laboratory tests, medical history, family history, and clinical outcomes were obtained using a detailed questionnaire. The clinical severity classification in this study was conducted by pulmonologists following the WHO guidelines. COVID-19 severity was categorized as moderate or severe based on clinical and physiological parameters. Moderate COVID-19 was well-defined by the presence of pneumonia symptoms, including fever, cough, dyspnea, or fast breathing, without signs of severe pneumonia, and a SpO_2 level of ≥90% on room air. Severe COVID-19 was defined as pneumonia accompanied by at least one of the following clinical criteria: serious breathing problems, oxygen saturation (SpO_2) under 90% on room air, or a respiratory rate more than 30 breaths every minute [16]. Additionally, pulmonologists in this research categorized patients as mild, moderate, or severe using criteria such as SpO_2 levels below 94%, PaO_2/FiO_2 ratios under 300 mm Hg, or lung infiltrates covering more than 50% of the lung fields [17]. Patients were monitored throughout the study period until their recovery, death, or Leaving Against Medical Advice (LAMA). Blood samples of 59 patients were taken and kept at 4°C, and the DNA was extracted from the whole blood through the Qiagen QIAamp DNA Mini Kit 82.The TLR7 gene was amplified through PCR using the following primers (Table 1).

Table 1: Primer Sequences for TLR7 Gene Amplification

Gene	Primer Type	Sequence (5' → 3')
TLR7	Forward Primer	TGGGCTCAAATCTTTCAGTTG
TLR7	Reverse Primer	GATCACACTTTGGCCCTTGT

The amplified products were then investigated using 1% agarose gel electrophoresis.

Sanger sequencing was performed at the Lab.Genetic Lahore, Pakistan, to determine polymorphic sites.There were 59 patients with diagnosed COVID-19 who were entered into the research and were distributed into two genotype groups (GA, n=10; GG, n=49).Clinical disease severity was categorized into mild (n=29), moderate (n=12) and severe (n=18).The extraction process of total RNA from

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venous blood utilized the Gene JET Blood RNA Purification Kit from Thermo Scientific, while purity and concentration measurements were through the Nano-Drop™ 2000 spectrophotometer. Research specimens were maintained at −80°C for later analysis procedures. The Revert Aid First Strand cDNA Synthesis Kit (Thermo Scientific) performed two-step synthesis of complementary DNA (cDNA) from the sample material. Hexamer primer incubation at 65°C served as the first step of the reaction before Revert-Aid reverse transcriptase, performed at 42°C, completed the process. Research laboratories kept the synthesized cDNA at −20°C for preservation.The Sensi-FAST™ SYBR Lo-ROX Kit integrated with the 7500 Real-Time PCR System was used for quantifying TLR7 mRNA expression levels by real-time PCR (qPCR). SYBR Green dye, along with cDNA and validated primers for TLR7 and GAPDH, made up the reaction mixture. The qPCR analytical method consisted of 95°C denaturation, then 50 amplification cycles, which were followed by 72°C extension. Prosecuting qPCR data was analyzed through the 2^−ΔΔCt method against GAPDH, which served as the reference gene for normalization, while the 7500 Software version 2.0.1 handled both fluorescence detection and analysis. The study was conducted after obtaining ethical consent from the Ziauddin University Ethics Review Committee (Reference code: 5360522BKBC). Informed written consent was obtained from the participants before enrollment. The statistical evaluation was carried out using SPSS version 21.0. Continuous variables such as age and TLR7 mRNA expression were given as mean ± SD and analyzed using an independent t-test. The Shapiro-Wilk test was used to know the normality of continuous variables. Categorical variables, such as gender distribution, hospitalization, ICU admission, and clinical complications, were presented as frequencies and percentages and analyzed by the chi-square test. Logistic regression analysis was done to adjust for potential confounders, including gender and age, and to assess the independent association of genotype and TLR7 expression with clinical outcomes. Significance was established at a threshold of $p<0.05$.

RESULTS

Research participants from the GA (42.3 ± 12.5 years) and GG (41.8 ± 11.7 years) genotypes showed no statistical difference in their mean age (p=0.94).The participant group with the GG genotype included 80% female subjects and 20% male subjects. The distribution of males to females was 80% to 20% for the GG genotype group, while the GA group showed 40.8% female and 59.2% male participants. The evaluation revealed a meaningful distinction between the two groups based on statistical analysis (p=0.024). The study results demonstrated that GG genotype carriers displayed elevated TLR7 mRNA expression levels at 2.15 ± 0.43 when compared to GA genotype carriers with levels measuring 1.98 ± 0.38 (p=0.04). The TLR7 mRNA expression levels and the demographics of participants were analyzed (Table 2).

Table 2: Demographic and TLR7 mRNA Expression Analysis

Variables	GA (n = 10)	GG (n = 49)	GG (n = 49)	p-value
Age as Mean ± SD	40.3 ± 13.2	41.8 ± 11.7	42.0 ± 11.9	0.94
Female	8 (80%)	20 (40.8%)	28 (47.5%)	0.024*
Male	2 (20%)	29 (59.2%)	31 (52.5%)	
Genotype Frequency	10	49	59	
mRNA Expression TLR7 as Mean ± SD	1.98 ± 0.382	2.15 ± 0.43	-	0.04*

Chi-square test and an independent t-test were applied. A p-value of lower than 0.05, shown by an asterisk (*), was deemed statistically significant (*).

The research revealed a major difference in hospitalization records because 75.5% of GG carriers required hospitalization, while only 40% of GA carriers needed hospital admission (p=0.009). The GG infected population required ICU intervention at a rate of 28.6% while the GA group admitted just 10% into such care (p=0.041). A total of 20.4% of people with the GG genotype required mechanical ventilation, but only 10% with the GA carrier status needed it (p=0.049). The distribution pattern of mild, moderate, severe and critical illness among different genotypes remained statistically the same (p>0.05). The mortality rate among GG and GA groups showed similar results at 6.1% versus 10%, respectively (p=0.619). GA group patients faced a lower incidence of pulmonary complications with respiratory failure than patients in the GG group, according to results from statistical analysis (p=0.038). Other complications, such as thromboembolic events, acute kidney injury (AKI), and cardiovascular complications, showed no significant variations. The study demonstrated various clinical results and complications of COVID-19 disease (Table 3).

Table 3: Comparison of Clinical Outcomes, Disease Severity, and Complications among COVID-19 Patients with GG and GA TLR7 Genotypes

Variables	GG (n=49)	GA (n=10)	Total (n=59)	p-value
Clinical Outcomes				
Hospitalized	37 (75.5%)	4 (40.0%)	41 (69.5%)	0.009*
ICU Admission	14 (28.6%)	1 (10.0%)	15 (25.4%)	0.041*
Mechanical Ventilation	10 (20.4%)	1 (10.0%)	11 (18.6%)	0.049*
Disease Severity				
Mild	24 (49.0%)	5 (50%)	29 (49.2%)	0.578
Moderate	10 (20.4%)	2 (20.0%)	12 (20.3%)	0.964
Severe	15 (30.6%)	3 (30.0%)	18 (30.5%)	0.921
Critically ill	7 (14.3%)	1 (10.0%)	8 (13.6%)	0.782
Mortality	3 (6.1%)	1 (10.0%)	4 (6.8%)	0.619
Clinical Complications				
Pulmonary Complications (Including Respiratory Failure SpO_2 <90%)	10 (20.4%)	1 (10.0%)	11 (18.6%)	0.038*

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Thromboembolic Events	12 (24.5%)	3 (30.0%)	15 (25.4%)	0.725
Acute Kidney Injury (AKI)	6 (12.2%)	1 (10.0%)	7 (11.9%)	0.835
Cardiovascular Complications	10 (20.4%)	3 (30.0%)	13 (22.0%)	0.632

Categorical variable is presented as frequencies and percentages. Chi-square test was used. A p-value of less than 0.05 is regarded as significant and is indicated with an asterisk (*).

Logistic regression analysis was done for confounders (Table 4).

Table 4: Logistic Regression Analysis Adjusting for Confounders

Variables	β Coefficient	Standard Error	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Male vs. Female	0.81	0.35	2.25	1.15–4.38	0.026*
Age	0.12	0.07	1.13	0.98–1.30	0.083
Genotype (GG vs. GA)	1.19	0.42	3.29	1.48–7.32	0.003*
TLR7 mRNA Expression	0.69	0.30	1.98	1.10–3.55	0.021*
Hospitalization (Yes vs. No)	0.95	0.38	2.59	1.28–5.23	0.008*
ICU Admission (Yes vs. No)	1.02	0.40	2.77	1.30–5.91	0.007*
Mechanical Ventilation (Yes vs. No)	1.31	0.46	3.71	1.50–9.19	0.004*

Logistic regression was done for identifying the influence of gender, age, and genotype on TLR7 mRNA expression and clinical outcomes. Odds ratios (OR) >1 indicate a higher likelihood of the outcome occurring in the specified group. A p-value of less than 0.05 is regarded as significant and is indicated with an asterisk (*).

The results indicate that the association between TLR7 mRNA expression and genotype remains significant even after adjusting for gender and age. Additionally, genotype and TLR7 mRNA levels were significantly associated with hospitalization, ICU admission, and mechanical ventilation risk. This confirms that gender distribution differences (p=0.024) did not significantly influence the primary outcomes, as genotype and TLR7 expression independently correlated with clinical severity.

DISCUSSION

Host genetics may also be important determinants of infection severity and clinical outcome [18]. TLR7 polymorphisms have been linked with numerous communicable infections, emphasizing their role in immune response and disease susceptibility. Different research studies have identified significant links between TLR7 SNPs and infections such as COVID-19, Dengue [19], HIV-1 [20], and Chikungunya [21]. TLR7, a key TLR exhibiting a response to coronaviruses, has been linked to lung inflammation caused by respiratory syncytial virus (RSV). Variants in TLR7, such as TLR7 rs179008, are linked to a higher risk of developing pneumonia, but they do not influence the results of the disease [8]. Our study identified a TLR7 polymorphism at the rs864058 restriction site (GA) and its association with COVID-19 disease severity and clinical complications. Notably, this specific polymorphism has previously been linked to allergic rhinitis in Chinese populations, suggesting a broader role of TLR7 variations in immune-related conditions. This finding supporting the influence of TLR7 polymorphisms on immune response regulation [22]. The present study suggests that rs864058 may play a comparable role in modulating disease severity by influencing TLR7 expression levels. This aligns with findings that variations in TLR7 can alter innate immune signaling pathways, affecting viral clearance and inflammatory responses [8]. A study mentioned that rs179008 was risk factor for severe disease, likely because of its effectiveness on immune system signaling pathways. Specifically, the T/T genotype and T allele of rs179008 have been associated with increased severity, particularly in male patients, emphasizing the potential sex-linked influence of TLR7 variations [23]. Beyond rs179008 and rs864058, other TLR7 polymorphisms have been investigated for their role in COVID-19 severity. A study analyzing multiple TLR gene polymorphisms, including TLR7, reported varying degrees of association with disease susceptibility and severity [24]. Additionally, a study examining rs3853839 found potential links between this polymorphism and both COVID-19 severity and TLR7 mRNA expression levels [9]. Similarly, research on Egyptian patients indicated a significant relationship between TLR7 polymorphisms and disease outcomes, further emphasizing the work of innate immune signaling in determining the clinical trajectory of COVID patients [8]. Korean women found no significant relationship between rs864058 and CoV-2 infection, suggesting that its role in disease progression may be population-specific [25]. The discrepancy may be due to genetic diversity among populations, differences in sample size, or the low frequency of rs864058 in Koreans, making its impact on COVID-19 severity negligible in that cohort. In our study, the GG genotype was noticeably more widespread in COVID-19 patients compared to the GA genotype. The GG variant was present in 49 patients (59.8%), while the GA variant was present in 10 patients (12.2%) at rs864058. Furthermore, the subjects with the GG genotype displayed the peak levels of TLR7 mRNA expression, while participants with the GA genotype presented the low levels. The receptor serves a vital function in viral genomic RNA detection, subsequent to which it activates antiviral immune responses [26]. The

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higher TLR7 mRNA expression observed in the GG genotype linked to the GA genotype (p=0.04) suggests a potential regulatory impact of rs864058 on TLR7 transcription. Functionally, TLR7 is essential in innate immunity as it detects single-stranded RNA viruses and also in triggering an antiviral immune response. In viral infections like COVID-19, elevated TLR7 levels may enhance immune activation, leading to a stronger antiviral defense. However, excessive activation of TLR7 has also been linked to hyper-inflammatory responses, which can contribute to severe disease manifestations such as cytokine storm and tissue damage [9]. The increased mRNA expression in GG genotype carriers is associated with functional consequences, including excessive cytokine production and hyper inflammation. This up-regulation of TLR7 expression boosts the downstream activation of the NF-κB signaling procedure, resulting in an overproduction of pro-inflammatory cytokines like IL-6, TNF-α, and IFN-γ [27]. These cytokines play a central role in cytokine storm syndrome, a condition observed in severe cases, characterized by widespread inflammation, multi-organ failure, and poor clinical outcomes [28]. Increased transcriptional activity of the variant allele has been linked to greater NF-κB pathway activation, further amplifying inflammatory responses and potentially exacerbating disease severity [29]. The study found that individuals with the GG genotype were more likely for needing mechanical breathing, be admitted to the critical care unit, and be hospitalized. Covid with the GG genotype faced a higher possibility of pulmonary complications leading to respiratory failure, which appeared through SpO_2 levels below 90%. The GG genotype appears to increase disease severity because it results in critical respiratory distress among patients. A large-scale study analyzing 1.3 million Americans with COVID-19 demonstrated that people with pre-existing medical conditions endured greater probabilities of requiring hospitalization and ending in intensive care as well as death compared to those without illness histories. Existing genetic elements and pre-existing health concerns play together to form COVID-19 disease [30, 31].TLR7 mRNA was highly expressed in COVID-19 patients, particularly in the GG homozygotes and the patients with more severe disease. In addition, in patients with the GG genotype, the rates of hospitalization were higher (74%), respiratory failure (61.8%), thrombo-embolic events (26.3%), and cardiac events (22.4%), respectively (p-value<0.001). According to Klok *et al.*, thrombotic complications are frequent in severely ill COVID-19, particularly in the ICU [32]. Additionally, severely ill COVID-19 patients required ICU admission and mechanical ventilation at a significantly higher rate [33]. Numerous studies are being conducted on the TLR pathways, which may result in the creation of a new medication or vaccine to cure the illness [34, 35].

CONCLUSIONS

It was concluded that genetic variations in *TLR7* may influence COVID-19 outcomes.The GG genotype showed higher TLR7 mRNA expression and was associated with a higher risk of hospitalization, ICU admission, and mechanical ventilation compared to the GA genotype. Additionally, pulmonary complications, including respiratory failure, were less frequent in GA carriers. However, no significant differences were found in terms of overall disease severity or mortality across the genotypes. These findings suggest that TLR7 may play a significant role in the immune response to COVID-19, emphasizing the importance of further research to explore its impact on disease progression and potential therapeutic approaches.

Authors Contribution

Conceptualization: BK, SB
Methodology: BK, SA, MR, PR
Formal analysis: BK, SB, MR, PR
Writing review and editing: SB, FP
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association of Maternal BMI with Obstetric and Perinatal Outcomes

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ABSTRACT

The increasing prevalence of obesity among women of childbearing age is linked to a higher risk of pregnancy complications. Maternal obesity affects both obstetric and perinatal outcomes, posing risks for mother and child. **Objective:** To investigate the relationship between maternal BMI and obstetric and perinatal outcomes. **Methods:** A cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Tertiary Care Hospital Bahawalpur, from January to July, 2022. A total of 254 pregnant women were categorized into underweight, normal, overweight, and obese groups based on BMI. Data on Gestational Diabetes Mellitus (GDM), Pregnancy-Induced Hypertension (PIH), and mode of delivery, labor complications, postpartum hemorrhage, preterm labor, and NICU admissions were analyzed using SPSS version 25.0. **Results:** Higher incidences of GDM (31.9% in obese vs. 10.6% in underweight) and PIH (23.1% in obese vs. 7.7% in underweight) were observed, though not statistically significant ($p = 0.088$ and $p = 0.463$, respectively). Obese mothers had more cesarean sections (24.6% vs. 13.8% in underweight, $p = 0.178$) and increased NICU admissions (18.9% vs. 8.1%, $p = 0.788$). **Conclusions:** This study observed clinically relevant trends suggesting that higher maternal BMI may be associated with adverse obstetric and perinatal outcomes, including increased rates of gestational diabetes, hypertension, cesarean sections, and NICU admissions. Although statistical significance was not reached, findings emphasize the importance of maternal weight management in prenatal care.

INTRODUCTION

Maternal Body Mass Index (BMI) is a critical determinant of both obstetric and perinatal outcomes. The increasing prevalence of maternal obesity globally has raised significant concerns due to its association with adverse pregnancy outcomes, including gestational hypertension, Gestational Diabetes Mellitus (GDM), cesarean delivery, and neonatal complications [1]. On the other end of the spectrum, low maternal BMI is linked with risks such as Intrauterine Growth Restriction (IUGR) and preterm birth, which contribute to neonatal morbidity and mortality [2]. Understanding the association between maternal BMI and pregnancy outcomes is essential to implementing strategies for optimizing maternal and fetal health. Obesity, defined as a BMI of 30 kg/m^2 or higher, has been strongly associated with hypertensive disorders in pregnancy, including preeclampsia and eclampsia [3]. A study analyzing data from over 497,000 women in Europe and North America found that increased maternal BMI significantly raised the likelihood of gestational hypertension and preeclampsia, emphasizing the need for preventive measures before conception [4]. Additionally, obesity contributes to metabolic complications such as insulin resistance, which predisposes pregnant women to GDM. Research suggests that women with higher BMI have an increased risk of developing GDM, which can lead to macrosomia, birth injuries, and neonatal hypoglycemia [5]. Maternal obesity also influences delivery outcomes. Higher BMI is correlated with an increased incidence of cesarean

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section due to complications such as cephalopelvic disproportion, fetal distress, and prolonged labor [6]. A study conducted in Ireland found that obese mothers had significantly higher rates of induction of labor and emergency cesarean sections, further reinforcing the negative impact of excessive maternal weight on labor progress [7]. Furthermore, extremely high BMI (>50 kg/m^2) has been linked to a nine-fold increase in thrombotic events and higher risks of post-cesarean wound infections, adding another layer of maternal morbidity [8]. The perinatal outcomes associated with maternal BMI are equally concerning. Higher maternal BMI is a known risk factor for fetal macrosomia, which increases the likelihood of birth trauma, shoulder dystocia, and Neonatal Intensive Care Unit (NICU) admissions [9]. A study conducted in the Jabal Akhdar region of Libya found that overweight and obese mothers had significantly higher rates of NICU admissions due to respiratory distress and metabolic disorders [10]. Conversely, underweight mothers (BMI <18.5 kg/m^2) are more likely to give birth to low birth weight infants, who face a greater risk of hypothermia, infections, and long-term developmental challenges [11]. Given these associations, it is imperative to emphasize preconception counseling and targeted interventions to maintain a healthy BMI before and during pregnancy. Public health strategies should focus on promoting optimal weight gain during pregnancy through dietary guidance, physical activity, and regular antenatal monitoring. Addressing maternal BMI as a modifiable risk factor can significantly reduce the burden of adverse obstetric and perinatal outcomes, ensuring better health for both mother and child [12].

This study aimed to evaluate the association between maternal BMI and obstetric outcomes such as GDM, PIH, and mode of delivery, as well as neonatal health outcomes, including Apgar scores and NICU admissions. The findings will help guide clinical practices and inform public health strategies to improve maternal and neonatal health by optimizing weight management during pregnancy.

METHODS

This study was conducted at Department of Obstetrics and Gynecology, Tertiary Care Hospital Bahawalpur. Type of study was cross sectional and conducted between January 14, 2022, to July 13, 2022 (IRB: EC-01-2022). Total 254 patients were included by calculating sample size by taking GDM rate of 20.83%, Confidence level 95% and Error margin as5% [13]. Non-probability consecutive sampling technique was applied for data collection. Ethical approval was taken from the Institutional Review Board (IRB) of Tertiary Care Hospital, Bahawalpur and Informed Consent was taken from all participants before being included in this study. Participants' information was confidential throughout the study. The inclusion criteria for this study were pregnant females with a single gestation who were booked and had their BMI calculated at the first antenatal visit, with complete follow-up data throughout pregnancy and delivery. Exclusion criteria included women with twin gestations, having history of medical disorder prior to pregnancy, or incomplete medical records. Data were collected using structured questionnaires and medical records, including maternal characteristics (age and BMI), obstetric outcomes (mode of delivery, pregnancy-induced hypertension, GDM, and labor complications), and perinatal outcomes (Apgar scores at 1 and 5 minutes, preterm birth, birth weight and NICU admissions). Maternal BMI was classified as underweight, normal weight overweight and obese. All the analysis was done by SPSS version 25.0. Descriptive statistics were performed by using the counts and proportions for categorical variables and means (SD) for continuous data. The Chi-square test was used to investigate maternal BMI categories for the different obstetric and perinatal outcomes with a significance level of $p < 0$. Maternal BMI versus continuous outcomes such as birth weight and Apgar scores were analyzed using Pearson correlation analysis.

RESULTS

The study included 254 females, with an age range of 18–44 years and a mean age of 30.62 ± 7.99 years, demonstrating a moderately wide age distribution among participants. The BMI of participants ranged from 16.40 to 37.80, with an average BMI of 25.72 ± 5.73, covering a broad spectrum from underweight to obese. The mean birth weight of newborns was 2943.70 ± 498.40 grams (range: 1700–4400 grams), representing expected variation in a general obstetric population. Apgar scores at 1 minute ranged from 1 to 9 (mean 4.94 ± 2.59), suggesting that some neonates required immediate medical attention. By 5 minutes, Apgar scores improved significantly (range: 5–9, mean 6.94 ± 1.46), indicating an overall recovery in neonatal condition after birth. These demographic and neonatal characteristics are summarized in Table 1.

Table 1: Demographic and Neonatal Characteristics of the Study Participants (n = 254)

Variables	Mean ± SD	Range	Remarks
Age (Years)	30.62 ± 7.99	18 – 44	Moderately wide age distribution
BMI (kg/m^2)	25.72 ± 5.73	16.40 – 37.80	Ranged from underweight to obese
Birth Weight (g)	2943.70 ± 498.40	1700 – 4400	Normal variation in obstetric population
Apgar Score at 1 minute	4.94 ± 2.59	1 – 9	Some neonates required immediate attention
Apgar Score at 5 minutes	6.94 ± 1.46	5 – 9	Indicated improvement in neonatal condition

Maternal BMI was classified into underweight, normal, overweight, and obese groups.The prevalence of gestational diabetes mellitus (GDM) was highest in obese mothers (31.9%), while underweight mothers had the lowest prevalence (10.6%). Although the p-value (0.088)

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suggests a possible relationship, statistical significance was not reached, indicating that BMI alone may not be a strong predictor of GDM in this sample. Similarly, pregnancy-induced hypertension (PIH) was more frequent in obese (23.1%) and normal-weight (48.7%) mothers, compared to underweight (7.7%) and overweight (20.5%) groups. However, this difference was not statistically significant (p = 0.463).Mode of delivery varied with BMI, with vaginal deliveries being more frequent among normal-weight (39.0%) and overweight (32.6%) mothers, while cesarean section rates were higher in obese mothers (24.6%). Instrumental deliveries were least common and mostly observed in the normal BMI category (64.7%). Despite these variations, the association was not statistically significant (p = 0.178).Labor complications were reported more frequently among normal-weight (52.1%) and overweight (25.0%) mothers, but the overall comparison across BMI categories was not statistically significant (p = 0.319).The incidence of postpartum hemorrhage (PPH) was highest in obese mothers (38.1%), whereas underweight mothers had the lowest prevalence (9.5%), yet this difference was not statistically significant (p = 0.150). The rate of preterm birth was relatively balanced across all BMI groups, with no significant differences (p = 0.741). Neonatal outcomes showed higher NICU admissions in obese (18.9%) and overweight (35.1%) mothers, while lower rates were observed in underweight (8.1%) and normal-weight (37.8%) groups, but these findings were not statistically significant (p = 0.788). These obstetric and perinatal outcomes are summarized in Table 2.

Table 2: Association of Maternal BMI with Obstetric and Perinatal Outcomes

OutcomeVariables	Underweight Frequency (%)	Normal Frequency (%)	Overweight Frequency (%)	Obese Frequency (%)	Total	p-Value
Gestational Diabetes (GDM)						
No	23 (11.1%)	90 (43.5%)	60 (29.0%)	34 (16.4%)	207	0.088
Yes	5 (10.6%)	14 (29.8%)	13 (27.7%)	15 (31.9%)	47	
Pregnancy-Induced Hypertension (PIH)						
No	25 (11.6%)	85 (39.5%)	65 (30.2%)	40 (18.6%)	215	0.463
Yes	3 (7.7%)	19 (48.7%)	8 (20.5%)	9 (23.1%)	39	
Mode of Delivery						
Vaginal	19 (11.0%)	67 (39.0%)	56 (32.6%)	30 (17.4%)	172	0.178
Cesarean	9 (13.8%)	26 (40.0%)	14 (21.5%)	16 (24.6%)	65	
Instrumental	0 (0.0%)	11 (64.7%)	3 (17.6%)	3 (17.6%)	17	
Labor Complications						
No	23 (11.2%)	79 (38.3%)	61 (29.6%)	43 (20.9%)	206	0.319
Yes	5 (10.4%)	25 (52.1%)	12 (25.0%)	6 (12.5%)	48	
Postpartum Hemorrhage (PPH)						
No	26 (11.2%)	97 (41.6%)	69 (29.6%)	41 (17.6%)	233	0.150
Yes	2 (9.5%)	7 (33.3%)	4 (19.0%)	8 (38.1%)	21	
Preterm Birth						
No	25 (11.0%)	94 (41.2%)	67 (29.4%)	42 (18.4%)	228	0.741
Yes	3 (11.5%)	10 (38.5%)	6 (23.1%)	7 (26.9%)	26	
NICU Admission						
No	25 (11.5%)	90 (41.5%)	60 (27.6%)	42 (19.3%)	217	0.788
Yes	3 (8.1%)	14 (37.8%)	13 (35.1%)	7 (18.9%)	37	

Pearson correlation analysis showed no statistically significant associations between maternal BMI and key obstetric or perinatal outcomes. BMI demonstrated a weak positive correlation with birth weight (r = 0.087, p = 0.168), suggesting a slight but non-significant trend of increasing birth weight with higher BMI. No significant correlations were found between BMI and Apgar scores at 1 minute (r = 0.027, p = 0.668) or at 5 minutes (r = -0.059, p = 0.349). Similarly, birth weight did not correlate significantly with Apgar scores at 1 minute (r = -0.061, p = 0.335) or at 5 minutes (r = -0.047, p = 0.454). The Apgar scores at 1 and 5 minutes were not significantly correlated with each other (r = 0.019, p = 0.763). These findings indicate that maternal BMI alone was not a strong predictor of obstetric or perinatal outcomes in this study, and other unmeasured factors such as maternal comorbidities, genetic predispositions, and prenatal care quality may influence these associations. All correlation analyses are presented in Table 3.

Table 3: Correlation Among Maternal BMI, Age, Birth Weight, and Apgar Scores

Variable	Age	BMI	Birth Weight	Apgar Score 1 Min	Apgar Score 5 Min
Age	Correlation	1.000	0.011	0.026	-0.008
	P-Value		0.857	0.675	0.897
	N	254	254	254	254

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BMI	Correlation	0.011	1.000	0.087	0.027
	P-Value	0.857	-	0.168	0.668
	N	254	254	254	254
Birth Weight	Correlation	0.026	0.087	1.000	-0.061
	P-Value	0.675	0.168	-	0.335
	N	254	254	254	254
Apgar Score 1 Min	Correlation	-0.008	0.027	-0.061	1.000
	Sig. (2-tailed)	0.897	0.668	0.335	-
	N	254	254	254	254
Apgar Score 5 Min	Correlation	-0.044	-0.059	-0.047	0.019
	P-Value	0.480	0.349	0.454	0.763
	N	254	254	254	254

To provide a better understanding of the variability and reliability of the results, confidence intervals (CIs) were calculated for key outcomes. The 95% CI for GDM in obese mothers (18.59%–45.24%) suggests a potentially higher prevalence, though variability remains due to sample size limitations. The CI for PIH in obese mothers (9.85%–36.30%) indicates a possible increased risk, while the underweight group's lower bound (0.00%) suggests a very low occurrence. Cesarean section rates in obese mothers had a CI of 14.14%–35.09%, supporting a likely higher prevalence compared to underweight mothers (4.47%–26.84%). NICU admissions were more frequent in obese mothers (5.46%–34.69%), though the wide CI range reflects uncertainty due to the sample size. While most comparisons did not reach statistical significance, the confidence intervals highlight potential trends and suggest that larger, multi-center studies with increased statistical power are needed to better define the role of BMI in obstetric and neonatal outcomes. All confidence intervals are presented in Table 4.

Table 4: Confidence Intervals for Key Outcomes

Variables	Lower CI (%)	Upper CI (%)
GDM (Obese)	18.59	45.24
GDM (Underweight)	1.82	19.45
PIH (Obese)	9.85	36.30
PIH (Underweight)	0.00	16.06
Cesarean (Obese)	14.14	35.09
Cesarean (Underweight)	4.47	26.84
NICU Admission (Obese)	5.46	34.69
NICU Admission (Underweight)	0.00	23.48

DISCUSSION

The present study examined the association between maternal body mass index (BMI) and obstetric and perinatal outcomes.While the findings did not reach statistical significance, they align with existing literature that suggests maternal obesity may increase the risk of gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), cesarean delivery, and neonatal complications.This discussion contextualizes the results in light of international research, highlighting similarities, limitations, and areas for further investigation.This study found a higher prevalence of GDM (31.9%) and PIH (23.1%) among obese mothers compared to underweight mothers (10.6% and 7.7%, respectively).Although statistical significance was not reached (p = 0.088 for GDM, p = 0.463 for PIH), the observed patterns are consistent with findings from Ballesta-Castillejos *et al.*, who reported that higher BMI significantly increases the risk of preeclampsia and emergency cesarean sections. Similarly, Ramya *et al.*, observed that obesity is associated with an increased risk of GDM and gestational hypertension [13, 14].The underlying pathophysiology likely involves insulin resistance, hyperglycemia, and pro-inflammatory states associated with obesity, which predispose pregnant women to metabolic disturbances.Choudhary *et al.*, further support this association, reinforcing that BMI impacts the development of hypertensive disorders and GDM [15].Snehlata and Lal, further corroborate this by highlighting the risks associated with high or low maternal BMI [16].Their study found that low BMI is linked with increased risks of intrauterine growth restriction (IUGR) and low birth weight, while high BMI leads to more frequent complications such as PIH and GDM.This bimodal distribution of risk underscores the need for maintaining a balanced BMI for optimal maternal and fetal health outcomes. Although this study did not confirm these associations with statistical significance, the trends emphasize the importance of preconception weight management and continuous antenatal monitoring.The study findings also align with previous research on mode of delivery and obstetric complications. We observed higher cesarean section rates in obese mothers (24.6%) compared to normal-weight mothers (40.0%) and underweight mothers (13.8%).However, statistical significance was not reached (p = 0.178).This finding is comparable to the results reported by Sinha *et al.*, who documented an increased likelihood of cesarean delivery in obese women due to the mechanical and metabolic challenges of labor [17].Similarly, Tharihalli and Thathagari found that higher BMI was associated with increased rates of operative deliveries, supporting the notion that obesity may impair the normal progression of labor and necessitate medical interventions [18].While these results did not show a statistically significant association, the observed patterns suggest that maternal BMI may influence labor outcomes and should be considered in

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antenatal care planning.Regarding neonatal outcomes, this study showed a potential link between higher BMI and lower Apgar scores at 1 minute, as well as increased NICU admissions in obese mothers (18.9%).However, these associations were not statistically significant (p = 0.788). The findings are in line with Vernini *et al.*, who reported that maternal obesity is associated with adverse neonatal outcomes, including an increased risk of macrosomia, birth trauma, and NICU admissions [19].The likelihood of fetal macrosomia in obese mothers may contribute to birth complications such as shoulder dystocia, hypoxia, and neonatal respiratory distress, necessitating NICU care. Indarti *et al.*, further emphasized the role of obesity in heightened risks of gestational diabetes, hypertensive disorders, and adverse neonatal outcomes, reinforcing the need for comprehensive prenatal care strategies to minimize risks [20].Several global studies have also highlighted the broader implications of maternal obesity on pregnancy outcomes.González-Plaza *et al.*, also Chowdhury and Choudhury reported that pre-pregnancy overweight and obesity were linked to a range of adverse perinatal outcomes, including gestational diabetes, cesarean section, and poor neonatal health [21, 22].These findings highlight the universal significance of managing maternal BMI to mitigate pregnancy-related risks.While this study did not establish definitive statistical relationships, the consistency of observed trends with prior research underscores the importance of targeted interventions to optimize maternal weight before and during pregnancy.While this study provides valuable insights, several limitations must be acknowledged.The sample size may not have been sufficient to detect statistically significant associations, as reflected in the wide confidence intervals for key outcomes.Additionally, BMI alone may not fully capture the complex interplay of metabolic, genetic, and lifestyle factors that influence pregnancy outcomes. Future research should consider larger sample sizes, prospective cohort designs, and multivariable regression models to adjust for potential confounders such as parity, socioeconomic status, and pre-existing metabolic conditions.These refinements will improve the statistical power and validity of future studies exploring the impact of maternal BMI on obstetric and perinatal health.

CONCLUSIONS

Although no statistically significant associations were identified, certain trends were observed such as higher rates of gestational diabetes mellitus, cesarean deliveries, postpartum hemorrhage, and NICU admissions among obese mothers—that suggest a potential relationship between elevated BMI and adverse pregnancy outcomes. These findings indicate that maternal BMI alone may not serve as a strong independent predictor; however, it remains a clinically relevant factor that may contribute to obstetric and neonatal risks when combined with other variables. Given the observed trends and limitations related to sample size, further research using larger, multicenter cohorts and robust statistical models is warranted to clarify these associations and inform clinical practice regarding the management of maternal BMI during pregnancy.

Authors Contribution

Conceptualization: SB
Methodology: SB
Formal analysis: RS, NH
Writing, review and editing: SU, SZC, AI
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Clinical, Serological and Radiological Profile of Patients with Autoimmune Disease Associated Interstitial Lung Disease

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ABSTRACT

The clinical, serological, and radiological profiles of interstitial lung disease in patients with autoimmune diseases vary significantly and are poorly studied. **Objectives:** To determine the clinical, serological and radiological profile of patients with autoimmune-associated interstitial lung disease. **Methods:** This cross-sectional study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period from 16th December 2023 to 15th December 2024. A total of 105 male and female patients in the age range of 40 to 80 years diagnosed with autoimmune-related interstitial lung disease were studied. History, clinical examination, blood tests and high-resolution computerized tomographic (HRCT) scan were performed to determine the clinical, serologic and radiologic features of AI-ILD. **Results:** The mean age of the participants was 51.51 ± 12.34 years. Female patients outnumbered men (n=61, 58.1%). Arthritis was most commonly recorded in 47 participants (44.8%) followed by skin rash (n=33, 31.4%). Antinuclear antibody (ANA) and anti-dsdna (double-stranded deoxyribonucleic acid) constituted the most frequently found serological factors observed in 32 (30.5%) and 28 (26.7%) patients, respectively. Usual interstitial pneumonia was observed in 19 patients (17.4%), non-specific interstitial pneumonia in 36 (34.2%) and lymphoid interstitial pneumonia was recorded in 7 participants (6.7%). **Conclusions:** It was concluded that middle-aged women with inflammatory arthritis and skin rashes with rheumatoid arthritis as background disease were more likely to have interstitial lung disease. Serologic factors lack specificity. The most common radiological finding on HRCT was ground glass opacities and non-specific interstitial pneumonia as the most frequent radiological diagnosis.

INTRODUCTION

Connective tissue disorder encompasses a group of pathological conditions characterized by inflammatory damage to extracellular matrix and collagen and elastin proteins [1]. The process is immune-mediated in most instances. Persistent insult to supporting connective tissue results in permanent damage and loss of organ function. The disorder has two components: genetic predisposition and an environmental autoimmune factor [2]. Common types of connective tissue disease include rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomycosis, Sjögren syndrome and systemic sclerosis. The pulmonary element of such autoimmune connective tissue disease is referred to as interstitial lung disease [3]. Interstitial lung disease (ILD) refers to a heterogeneous group of clinical conditions that affect the lung parenchyma, arising from a variety of causes. Often, the underlying etiological factor is unidentified, commonly referred to as idiopathic interstitial pneumonia (IIP) [4]. It represents a unique category that leads to damage in the lung parenchyma with different patterns of inflammation and fibrosis. IIP is divided into several categories based on histological and radiological characteristics. Each pattern necessitates a thorough investigation into its potential causes [5]. The clinical spectrum of pulmonary involvement in autoimmune disease is very wide, ranging from completely asymptomatic to sequela related to advanced fibrosis. Early diagnosis and treatment of pulmonary involvement in

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autoimmune disease is critical since it is a major cause of mortality and morbidity in such patients [6]. Several pulmonary structures could be affected simultaneously affected including the lung parenchyma, pleura, bronchi and the airways. Permanent damage results in fibrous replacement of pulmonary tissue, commonly known as idiopathic pulmonary fibrosis. High resolution CT scan is often required to diagnose the pulmonary component of autoimmune disease, pulmonary fibrosis and the extent of fibrosis [7]. Initially, diagnosis is often suggested by pulmonary function tests. In a meta-analysis, the prevalence of ILD in patients with rheumatoid arthritis was 11%, 47% in systemic sclerosis, 41% in inflammatory myositis, 17% in Sjögren Syndrome, 56% in mixed connective tissue disorder and 6% in SLE [8]. There is a lack of comprehensive data focusing on the specific characteristics of autoimmune-related interstitial lung disease (AI-ILD) across different autoimmune diseases. The clinical, serological, and radiological profiles of interstitial lung disease patients provide critical insights into disease onset, progression, and prognosis. The clinical manifestations of AI-ILD vary significantly, moreover serological pattern is poorly studied. There is a need for more standardized radiological criteria that can aid in distinguishing AI-ILD from other forms of ILD. There is a scarcity of studies that focus specifically on AI-ILD as a distinct entity.

This study aims to investigate the collective features of AI-ILD, helping clinicians identify common patterns and prognostic indicators across different autoimmune diseases. Ultimately, the findings would contribute to a better understanding of AI-ILD, facilitating early diagnosis, targeted therapies, and improved patient outcomes.

METHODS

This cross-sectional study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period from 16th December 2023 to 15th December 2024. Approval for the conduct of the study was obtained vide no 32/DME/KMC.Male and female patients in the age range of 40 to 80 years diagnosed with autoimmune -related interstitial lung disease were studied. Patients with active or previous history of pulmonary tuberculosis, bronchogenic carcinoma, secondaries in the lung, history of drug-related pulmonary fibrosis and severe cardiopulmonary compromised patients were excluded. The sample size was 105, which was calculated taking 11.0% anticipated prevalence of ILD in autoimmune disease (rheumatoid arthritis), 6% margin of error and 95% confidence level [8]. Participants were enrolled using a non-probability consecutive sampling technique. Interstitial lung disease was confirmed on a high-resolution CT scan of the lung, showing reticular pattern with ground glass opacities and architectural distortion of interstitial tissue. Autoimmune disease included 1) Rheumatoid Arthritis: Presence any four among morning stiffness, arthritis, soft tissue swelling, subcutaneous nodules, positive serology and radiological features of bone erosion 2) Systemic Lupus Erythematosis: Positive ANA and atleast 10 score among fever, leucopenia, thrombocytopenia, hemolysis, seizure, psychosis, delirium, malar rash, discoid rash, oral ulcer, effusion, pericarditis, arthritis, renal involvement, positive antiphospholipid, low C3 and positive SLE specific antibodies. 3) Systemic Sclerosis: Score 9 among fingertip lesions, skin tightening, telangiectasias, pulmonary hypertension, Raynaud's phenomenon, arthritis, esophagitis, sclerodactyly, abnormal nailfold capillaries and positive antibodies. 4) Inflammatory Myositis: Progressive symmetrical muscle weakness, raised muscle enzymes, dysphagia, respiratory muscle weakness, skin rash and muscle biopsy consistent with inflammation. 5) Sjögren Syndrome: Dry mouth, dry eyes, oral ulcers, positive antibodies and positive Schirmer test. Clinical features included: Pulmonary features including chest pain, shortness of breath, cough and sputum and extra-pulmonary features included GI, joint, skin and renal features. Serological Features studied included: Rheumatoid factor, anti-CCP, ANA, anti-SSA, anti-SSB, anti-Scl 70, anti-ds-DNA, anti-Smith, anti-Scl 70 and anti-RNA proteins. Radiological features included: ground glass appearance, reticular pattern, cysts, honeycomb, pulmonary hypertension, non-specific interstitial pneumonia, usual interstitial pneumonia and lymphoid interstitial pneumonia. Informed consent was obtained from enrolled participants. Baseline features such as age, gender, BMI, smoking history, comorbidities like diabetes, hypertension, ischemic heart disease and medications were noted. History was taken about pulmonary and extra-pulmonary complaints. Pulmonary symptoms noted included: Dyspnea: Modified BORG dyspnea scale >4, Cough: visual analogue scale >4 and chest pain (VAS>4). Clinical examination was carried out, starting with a general physical examination. Pulse. Blood pressure and respiratory rate were noted. A detailed examination of the front and back of the chest was carried. All systems were reviewed, including GI, joint, skin and renal and findings were noted. Tests analyzing pulmonary functions were carried out, and blood samples were taken, and a thorough autoimmune profile was performed for serological features. HRCT films were reviewed by two independent consultant radiologists for the presence of pneumonia and its types. Findings were noted in the case of agreement. In case of disagreement, a third opinion from the senior-most radiologist was taken, which was considered final. Data were analyzed using SPSS version 26.0. Means and standard deviations were recorded for continuous data like age, BMI and duration of complaints, while frequencies and

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percentages were recorded for qualitative data like gender, smoking history, clinical features, serological and radiological features. Effect modifiers were controlled through stratification. Post-stratification chi-square test of association was applied. p-value≤0.05 was considered significant.

RESULTS

The mean age of the participants was 51.51 ± 12.34 years. The Majority of the patients were aged more than 50 years (n=59, 56.2%). Male participants were 44 (41.9%), and 73 patients (69.5%) had a BMI less than 25.0kg/m2. Illness duration less than 30 months was observed in 32 patients (30.5%). 60 patients (57.1%) belonged to the rural population (Table 1).

Table 1: Socio-Demographic and Baseline Clinical Parameters of Study Cohort (n=105)

Parameters	Subgroups	n (%)
Age (Years) (Mean 51.51 ± 12.349)	50 or Below	46 (43.8%)
	More Than 50	59 (56.2%)
Gender	Male	44 (41.9%)
	Female	61 (58.1%)
BMI (kg/m2) (Mean 23.994 ± 2.6961)	25.0 or Below	73 (69.5%)
	More Than 25.0	32 (30.5%)
Illness Duration (Months) (Mean 34.02 ± 4.977)	30 or Below	32 (30.5%)
	More Than 30	73 (69.5%)
Education	Above Matric	42 (40.0%)
	Matric or Below	63 (60.0%)
Profession	Employed	26 (24.8%)
	Unemployed	79 (75.2%)
Residence	Rural	60 (57.1%)
	Urban	45 (42.9%)
SE Status	Fair	30 (28.6%)
	Poor	75 (71.4%)
Smoking History	Yes	19 (18.0%)
	No	86 (82.0%)
Hypertension	Yes	35 (33.3%)
	No	70 (66.7%)
Diabetes	Yes	23 (21.9%)
	No	82 (78.1%)

Rheumatoid arthritis was the most common background diagnosis out of all 105 patients recorded in 44 (41.9%), followed by SLE (n=25, 23.8%). Myositis and Sjögren were least prevalent, recorded in 10 patients (9.5%) each (Figure 1).

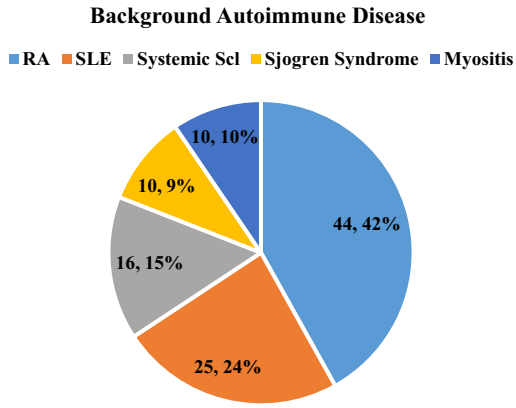

Figure 1: Background Autoimmune Disease of Study Cohort (n=105)

In terms of clinical signs and symptoms of background disease, arthritis was most commonly recorded in 47 participants (44.8%), followed by GI complaints (n=37, 35.2%), skin rash (n=33, 31.4%) and Raynaud's phenomena (n=16, 15.2%), respectively (Table 2).

Table 2: Clinical Signs and Symptoms of Study Cohort (n=105)

Clinical Parameters		Frequency (%)
Skin rash	Yes	33 (31.4%)
	No	72 (68.6%)
Arthritis	Yes	47 (44.8%)
	No	58 (55.2%)
Raynaud's Phenomenon	Yes	16 (15.2%)
	No	89 (84.8%)
GI Symptoms	Yes	37 (35.2%)
	No	68 (64.8%)

ANA (antinuclear antibodies) and anti-dsDNA (anti-double-stranded DNA) constituted the most frequently found serological factors observed in 32 (30.5%) and 28 (26.7%) patients, respectively. Anti-CCP was observed in 19 patients (18.1%), RA factor in 18 (17.1%), anti-SSA and anti-SSB in 19 (18.1%) and 23 (21.9%) patients, respectively (Table 3).

Table 3: Serological Parameters of Study Cohort (n=105)

Serological Profile		Frequency (%)
ANA	Yes	32 (30.5%)
	No	73 (69.5%)
Anti CCP	Yes	19 (18.1%)
	No	86 (81.9%)
Anti Scl 70	Yes	17 (16.2%)
	No	88 (83.8%)
Anti Ro 52	Yes	17 (16.2%)
	No	88 (83.8%)
RA factor	Yes	18 (17.1%)
	No	87 (82.9%)
Anti SSA	Yes	19 (18.1%)
	No	86 (81.9%)
Anti SSB	Yes	23 (21.9%)
	No	82 (78.1%)

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Anti-ds DNA	Yes	28 (26.7%)
	No	77 (73.3%)
Anti-Smith	Yes	21 (20.0%)
	No	84 (80.0%)

Ground glass opacities were the most frequent radiological findings on HRCT (n=71, 67.6%), followed by reticular pattern (n=65, 61.9%) and fibrosis in 58 patients (55.2%). Usual interstitial pneumonia was observed in 19 patients (17.4%), non-specific interstitial pneumonia in 36 (34.2%) and lymphoid interstitial pneumonia was recorded in 7 participants (6.7%) (Table 4).

Table 4: Confidence Intervals for Key Outcomes

Radiological Findings		Frequency (%)
Ground Glass Opacities	Yes	71 (67.6%)
	No	34 (32.4%)
Reticular Pattern	Yes	65 (61.9%)
	No	40 (38.1%)
Fibrosis	Yes	58 (55.2%)
	No	47 (44.8%)
Honey Combing	Yes	42 (40.0%)
	No	63 (60.0%)
Cysts	Yes	49 (46.7%)
	No	56 (53.3%)
Radiological Diagnosis	Pulmonary Artery Hypertension	43 (40.9%)
	Usual Interstitial Pneumonia	19 (17.4%)
	Non – Specific Interstitial Pneumonia	36 (34.2%)
	Lymphoid Interstitial Pneumonia	07 (6.7%)

Skin rash was the predominant complaint in 54.5% of patients with SLE. The p-value for the association between skin rash and autoimmune disease was significant (<0.05). Similarly, arthritis was prevalent in RA patients (100.0%). The chi-square p-value was 0.018, which was significant (Table 5).

Table 5: Stratification of Clinical Parameters with Autoimmune Disease Subtypes (n=105)

Clinical Parameters		Autoimmune Disease Subtypes					Total	p-value
		RA	SLE	S.Sclerosis	Sjogren's	Myositis		
Skin Rash	Yes	05 (15.5%)	18 (54.5%)	8 (24.2%)	0 (0.0%)	2 (6.1%)	33 (100%)	0.011
	No	39 (54.1%)	07 (9.7%)	8 (11.1%)	10 (13.9%)	8 (11.1%)	72 (10%)	
Arthritis	Yes	44 (93.6%	02 (4.2%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	47 (100%)	0.018
	No	0 (0.0%)	23 (39.6%)	15 (25.8%)	10 (17.2%)	10 (17.2%)	58 (100%)	
Raynaud	Yes	6 (37.5%)	4 (25.0%	4 (25.0%)	2 (12.5%)	0 (0.0%)	16 (100%)	0.517
	No	38 (42.7%)	21 (23.6%)	12 (13.5%)	8 (9.0%)	10 (11.2%	89 (100%)	
GI Symptoms	Yes	17 (45.9%)	6 (16.2%)	4 (10.8%)	4 (10.8%)	6 (16.2%)	37 (100%)	0.274
	No	27 (39.7%)	19 (27.9%)	12 (17.6%)	6 (8.8%)	4 (5.9%)	68 (100%)	

Anti-CCP was positive in 26.3% of patients with rheumatoid arthritis (RA) and 31.6% of patients with systemic sclerosis. The p-value for the association between anti-CCP and autoimmune diseases was significant (<0.05) (Table 6).

Table 6: Stratification of Serological Parameters with Autoimmune Disease Subtypes (n=105)

Serological Parameters		Autoimmune Disease Subtypes					Total	p-value
		RA	SLE	S.Sclerosis	Sjogren's	Myositis		
ANA	Yes	14 (43.8%)	10 (31.3%)	2 (6.3%)	4 (12.5%)	2 (6.3%)	32 (100.0%)	0.343
	No	30 (41.1%)	15 (20.5%)	14 (19.2%)	6 (8.2%)	8 (11.0%)	73 (100.0%)	
Anti CCP	Yes	5 (26.3%)	2 (10.5%)	6 (31.6%)	0 (0.0%)	6 (31.6%	19 (100.0%)	0.000
	No	39 (45.3%)	23 (26.7%)	10 (11.6%)	10 (11.6%)	4 (4.7%)	86 (100.0%)	
Anti Ro52	Yes	9 (52.9%)	6 (35.3%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	17 (100.0%)	0.144
	No	35 (39.8%)	19 (21.6%)	16 (18.2%)	8 (9.1%)	10 (11.4%)	88 (100.0%)	
Anti-Scl 70	Yes	9 (52.9%)	2 (11.8%)	4 (23.5%)	2 (11.8%)	0 (0.0%)	17 (100.0%)	0.311
	No	35 (39.8%)	23 (26.1%)	12 (13.6%)	8 (9.1%)	10 (11.4%)	88 (100.0%)	
RF	Yes	8 (44.4%)	4 (22.2%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	18 (100.0%)	0.981
	No	36 (41.4%)	21 (24.1%)	14 (16.1%)	8 (9.2%)	8 (9.2%)	87 (100.0%)	
Antids-DNA	Yes	12 (42.9%)	6 (21.4%)	6 (21.4%)	2 (7.1%)	2 (7.1%)	28 (100.0%)	0.824
	No	32 (41.6%)	19 (24.7%)	10 (13.0%)	8 (10.4%)	8 (10.4%)	77 (100.0%)	

Ground glass opacities were recorded in 50.7% patients with RA related ILD, reticular pattern was prevalent in 33.8% with RA and 26.2% with SLE. A statistically significant association was recorded between radiological features and various types of autoimmune disease (Table 7).

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Table 7: Stratification of Radiological Parameters with Autoimmune Disease Subtypes (n=105)

Serological Parameters		Autoimmune Disease Subtypes					Total	p-value
		RA	SLE	S.Sclerosis	Sjogren's	Myositis		
Ground Glass Opacities	Yes	36 (50.7%)	13 (18.3%)	14 (19.7%)	6 (8.5%)	2 (2.8%)	71 (100%)	0.000
	No	8 (23.5%)	12 (35.3%)	2 (5.9%)	4 (11.8%)	8 (23.5%)	34 (100%)	
Reticular Pattern	Yes	22 (33.8%)	17 (26.2%)	14 (21.5%)	8 (12.3%)	4 (6.2%)	65 (100%)	0.028
	No	22 (55.0%)	8 (20.0%)	2 (5.0%)	2 (5.0%)	6 (15.0%)	40 (100%)	
Fibrosis	Yes	20 (34.5%)	12 (20.7%)	12 (20.7%)	4 (6.9%)	10 (17.2%)	58 (100%)	0.008
	No	24 (51.1%)	13 (27.7%)	4 (8.5%)	6 (12.8%)	0 (0.0%)	47 (100%)	
Honey Combing	Yes	26 (61.9%)	6 (14.3%)	4 (9.5%)	2 (4.8%)	4 (9.5%)	42 (100%)	0.014
	No	18 (28.6%)	19 (30.2%)	12 (19.0%)	8 (12.7%)	6 (9.5%)	63 (100%)	
Cysts	Yes	16 (32.7%)	9 (18.4%)	10 (20.4%)	6 (12.2%)	8 (16.3%)	49 (100%)	0.044
	No	28 (50.0%)	16 (28.6%)	6 (10.7%)	4 (7.1%)	2 (3.6%)	56 (100%)	

DISCUSSION

In this study, the mean age of participants was 51.51 ± 12.349 years, and the majority of study participants were aging more than 50 years. In a study by Hazarika *et al.*, the mean age was 50.6 years, with 54% of participants aged more than 50 years [8].This is similar to current observation. In another study, the mean age of the patients with autoimmune-related interstitial lung disease was 54.6 years, which is in coherence with our observation [9]. However, Lim *et al.*, reported a much higher mean age of 67.9 years [10].The mean age of the participants in a study by Karampeli *et al.*, was 63.2 years, i.e., higher than our observation [11].The higher prevalence of autoimmune-related interstitial lung disease may be attributed decline in the immune system, prolonged exposure to infectious or other environmental elements, triggering the autoimmune reactions [12].The majority of our study participants were female. Oldham *et al.*, reported 62.0% female patients as their study population [13]. Lim and colleagues reported 64% of participants [10]. Hazarika *et al.*, and Avala *et al.*, reported 86.6% and 83% female participants, respectively, which were much higher compared to the present study [8, 14].Male participants outnumbered female participants in another study [5].Female predominance in autoimmune-related ILD may be attributed to genetic predisposition, endogenous hormonal influence modulating the immunity [15].Exogenous hormones such as contraceptive pills could also lead to immune overactivity [16].Arthritis was the most common complaint in our study, followed by GI, skin and Raynaud's phenomenon.Sebastiani *et al.*, reported inflammatory arthritis as the predominant clinical feature among patients with autoimmune-related ILD [17]. Results of a study by Karampali *et al.*, showed inflammatory arthritis in 82.0% of patients, followed by skin rash (54%) and Raynaud's phenomenon in 25.6% of participants [11]. Though the individual proportions for each characteristic might be variable, the overall pattern of clinical features reflects our results. Similarly, Lim *et al.*, and Avala *et al.*, reported inflammatory arthritis as the most commonly reported complaint in 76.5% and 66.7% of participants, respectively [10, 14].Raynaud's phenomenon was the predominant complaint in 27.8% of patients in a study by Oldham and colleagues, followed by inflammatory arthritis (17.4%)[13]. Similar observations were reported by another study [9].Hazarika *et al.*, reported an equal proportion of inflammatory arthritis and Raynaud's phenomenon in their study [8].Lungs and joints are most frequently affected in rheumatologic disease because the resemblance in connective tissue of lungs and joints is quite similar, making both organs more susceptible to damage in autoimmune diseases.Difference in proportions of arthritis in different populations may be due to genetic variability, differences in exposure to environmental toxins and the presence of any comorbidities [18, 19]. Antinuclear antibodies (ANA)and anti-ds DNA (anti-double-stranded DNA) were the most frequent serological factors, followed by anti-CCP, RA factor and anti-SSA and B, respectively. ANA was positive in 97.4% of patients (taking 1:100 dilution) and 31.4% (taking 1:320 dilution) of patients, followed by anti-ds DNA in a study by Hazarika *et al.*, [8].The current study utilized 1:320 as the cut-off for ANA positivity, hence, our findings were close to later reports in a study by Hazarika *et al.* Other studies have reported similar findings [17, 20].Speckled pattern ANA was strongly positive in autoimmune-related ILD in a Greek population [11]. Rheumatoid factor was least positive in our study. Our observation was in agreement with the results of studies where only one patient was found with a positive RA factor among the study participants [9, 21]. RA factor was most frequently serologically found positive in patients with autoimmune-related ILD in another study, in contrast to our observation [8]. The proportion of anti-CCP positivity in our study supports the observation of Fischer and colleagues, detected in 17.8% of patients [22]. Ito *et al.*, reported anti-CCP positivity in 13.0% of patients [20]. Hazarika and colleagues reported a similar detection rate (14.3%)[8]. Anti-Scl 70 was found in 16.2% of patients in our study. Anti-Scl 70 is a scleroderma-associated serologic factor and may be found in patients with autoimmune-related ILD. It has been reported that suppression of anti-

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Scl 70 with immunosuppression could result in reversal of fibrosis resulting from autoimmune pathogenicity [23]. Ground glass opacities were the most frequent radiological findings on HRCT patients.The most common radiological diagnosis was pulmonary artery hypertension, followed by unusual and usual interstitial pneumonia. The relatively low prevalence of usual interstitial pneumonia concerning ground glass opacities may be because of reporting bias in the current study.Usual interstitial pneumonia was recorded in 54.6% on HRCT, non-specific pneumonia in 31.9% in a study [13].Another study reported that non-specific pneumonia was the most common HRCT diagnosis in 42.1%, followed by usual pneumonia in 15.8%, which is in agreement with our observation [5].Ito *et al.*, reported 64.0% cases of non-specific pneumonia as compared to 20.0% cases with usual pneumonia, which is in coherence with our findings [20]. Other studies have shown similar results [12, 23].Sharma and colleagues reported usual pneumonia as the predominant HRCT diagnosis in contrast to our observation in 35.7% of patients [24]. The difference in results may be explained by several reasons, such as differences in image qualities, artefacts, presence of extra-pulmonary features or reporter interpretation of various findings [25].

CONCLUSIONS

It was concluded that clinical, serologic and radiologic patterns in AI-ILD patients were very wide. Clinically, middle-aged women with inflammatory arthritis and skin rashes with rheumatoid arthritis as background disease were more likely to have interstitial lung disease. ANA and anti-Scl 70, though commonly positive, lack specificity and might be performed as part of a workup, but not diagnostic test. The most common radiological finding on HRCT was ground glass opacities and non-specific interstitial pneumonia as the most frequent radiological diagnosis.

Authors Contribution

Conceptualization: HA
Methodology: HA, MI, IUD, SZ
Formal analysis: IUD, SZ
Writing review and editing: HA, A
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Involvement of Paranasal Sinuses in Patients with Bilateral Nasal Polyps: A Cross-Sectional Descriptive Study at Swabi

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ABSTRACT

Non-neoplastic, pedunculated swellings of the sinonasal mucosa are called sinonasal polyps. They are called polyposis when they occur in multiple numbers. **Objectives:** To determine the frequency of paranasal sinus involvement in patients with bilateral nasal polyps aged 20–50 years using a validated self-structured questionnaire and radiological imaging. **Methods:** A cross-sectional descriptive study was conducted at the ENT Department of Bacha Khan Medical Complex, Swabi, from January 24, 2024, to June 23, 2024. A sample size of 50 patients was selected using a convenient sampling technique. Data were collected using a pre-tested, validated questionnaire, and sinus involvement was assessed via CT scans. Descriptive statistics were analyzed using SPSS version 26.0. **Results:** Among 50 patients, 72% (n=36) were male, and 28% (n=14) were female. The 20–25 age group constituted 30% (n=15) of the sample. Maxillary sinus involvement was most common (36%), followed by ethmoid (26%), frontal (26%), and sphenoid sinuses (18%). Bilateral maxillary sinus involvement was observed in 40% of patients. **Conclusions:** It was concluded that the study highlights the predominant involvement of maxillary sinuses in bilateral nasal polyps, emphasizing the need for comprehensive radiological evaluation to guide management.The findings align with existing literature but underscore the need for larger, randomized studies to improve generalizability.

INTRODUCTION

The uppermost portion of the upper respiratory system is made up of the nasal cavity and paranasal sinuses, which are pneumatic compartments that are connected to the atmosphere. These structures are located just below the cranium's base and are linked to a number of important structures. Due to its great exposure to airborne pollutants, this area is the site of some of the rarest and most complex benign and malignant diseases that humans may develop. Non-neoplastic, pedunculated swellings of the sinonasal mucosa are called sinonasal polyps. They are called polyposis when they occur in multiple numbers. Although there are other reasons, such as viral, chemical, or hereditary aetiologies, most are inflammatory or allergic. Nasal polyps' histological characteristics don't always match their etiology [1]. The nose is the most apparent feature on the face and has both aesthetic and functional significance. In daily clinical practice, both neoplastic and non-neoplastic lesions of the nasal cavity and paranasal sinuses are frequently seen. They are frequently found in age groups in their second and third

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decades. Nasal blockage, nasal discharge, epistaxis, face puffiness, headache, loss of smell, and orbital and ear problems are common initial signs of sinonasal lesions. The most frequent cause of nasal blockage is nasal polyps. Although their precise etiology is uncertain, they are primarily linked to aspirin sensitivity, allergies, asthma, and infections. According to histopathological analysis, some of the lesions are cancerous, while the majority are not. Inflammatory polyps were the most prevalent bilateral non-neoplastic lesions [2]. In both adults and children, unilateral polyps are uncommon and linked to a variety of disorders that require more research. Depending on the site and location, a polyp can be anatomically classified as ethmoidal or antrochoanal. Imaging tests are essential for determining the location and size of the nose and paranasal sinuses as well as for ruling out serious nasal disorders. Surgical intervention or medicine may be used as the treatment [3]. Polyps obstructing sinus ostia often involve the maxillary sinuses, resulting in sinus infections. Nasal polyps frequently originate in the ethmoid sinuses, and inflammation may spread to neighbouring sinuses. Sphenoid and Frontal Sinuses. Though less frequently affected, it can play a role in more complex situations, leading to issues including headaches. Visual disturbances [4]. Up to 40% of people are likely to develop nasal polyps at some point in their lives, and about 4% already have them. Males are more likely than girls to experience them, and they often happen after the age of 20. The term "nasal polyp" originates far to the Ancient Egyptians. In their survey, the age group most commonly involved (30%) was 31–40 years old, with 29.86% participating in the same age group [5]. The eosinophil-related cytokine IL-5 was significantly elevated in bilateral nasal polyposis. Different types of sinusitis seem to exhibit distinct cytokine 2.656 with cystic fibrosis had nasal polyps [6]. Churg-Strauss Syndrome, allergic fungal sinusitis, and cilia dyskinesis in nonallergic asthma versus allergic asthma (13% vs. 5%, $p<0.01$) are other disorders linked to nasal polyps [7, 8]. Recurrences occur in about 40% of people who had surgical polypectomies. Nasal polyp development seems to have a genetic component. To standardize treatment, consider differential diagnosis and gather useful comparative research data, a categorization system for staging nasal polyps is suggested [9, 10]. 22 out of the 69 autopsies had nasal polyps, which is a 32% frequency. 54 polyps in total were discovered. Five polyps were huge, ten were medium-sized, and thirty-nine were small (length, 2–5 mm). No complaints of symptoms from the nasal polyps were noted. Most of the polyps, 40 of 54 (74%) developed in proximity to sinus outlets. The majority of these were located in the middle or superior meatus (13 of 54 [24%]; 34 of 54 [63%]) [11]. For functional endoscopic sinus surgery (FESS), a computed tomography (CT) scan of the paranasal sinuses is crucial because the surgeon can utilize the information to arrange the procedure beforehand. A survey claims that all scans were performed using sagittal reconstruction and a 3 mm thickness in the axial and coronal planes. The sphenoid sinus was the least affected, but the maxillary sinus was the most frequently and seriously afflicted [12, 13]. Thirteen cadavers had polyps discovered after 31 underwent endoscopic endonasal surgery after a thorough examination of the nasal cavity and paranasal sinuses. A total of 27 polyps were discovered. Just four patients had a history of sinusitis or allergies. Photographs were taken to record the polyps and their origin. The ostia, clefts, or recesses were the origin of 70% of the polyps. Three patients developed polyps on the middle turbinate, and one patient developed them on the agger nasi area [14]. Nineteen victims had their naso-ethmoidal blocks removed in the autopsy material. No rhinoscopy had been performed on any of the patients previously. The sphenoidal and maxillary sinuses were accessed and examined for polyps before excision. The entire naso-ethmoidal complex was closely inspected for nasal polyps following excision. The specific polyp's place of origin was registered and captured on camera. Five patients, four of whom had no prior history of sinusitis, asthma, or allergies, had nine polyps. Three patients had bilateral polyps, while two individuals had unilateral solitary polyps. The meatus included all of the polyps. 89% of the polyps were associated with ethmoid clefts. The ethmoidal and other paranasal sinuses did not contain any polyps [15]. In a study in which the evaluation of the structure and etiology of nasal polyps, as well as key characteristics from surgical investigations, autopsy studies, and histopathologic analyses were discussed, despite the fact that much is still unknown about them and their origin. It was discovered that 75% of nasal polyps were related to ethmoidal recesses and clefts, that the majority of the polyps were unilateral (63%), and that 37% of the cadavers had bilateral nasal polyps [16]. Key limitations of current imaging techniques, like CT scans, in diagnosing nasal polyps include poor soft tissue differentiation, inability to distinguish inflammatory from neoplastic lesions, and limited functional assessment. Improvements may include integrating MRI for better soft tissue contrast and incorporating advanced imaging protocols or AI-based analysis for enhanced classification and treatment planning.

This study aims to determine the frequency of paranasal sinus involvement in patients with bilateral nasal polyps aged 20–50 years using a validated self-structured questionnaire and radiological imaging.

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METHODS

A cross-sectional descriptive study was conducted at the ENT Department of Bacha Khan Medical Complex, Swabi, from January 24, 2024, to June 23, 2024. The sample size was calculated using the standard formula for a cross-sectional study:n=Z2.p.(1-p)d2,taking prevalence of nasal polyps in population as 0.5% (p=0.5), 95% confidence level (Z=1.96), and 5% margin of error (d=0.05), the minimum required sample size was 8 [17]. However, to increase the generalizability of results, a convenient sample of 50 patients was included, which is acknowledged as a limitation of the study. A convenient sampling technique was used to recruit 50 patients aged 20–50 years. The sample size was determined based on feasibility, although a formal power analysis was not conducted. Inclusion Criteria: Patients aged 20–50 years with bilateral nasal polyps confirmed by clinical and radiological evaluation. Exclusion Criteria: Patients outside the specified age range, immunocompromised individuals, those on long-term steroids, and those with fungal infections. A self-structured questionnaire was developed, pre-tested, and validated for reliability (Cronbach's alpha = 0.85) and accuracy. Data on demographic characteristics, clinical symptoms, and sinus involvement were collected. CT scans were performed using standardised protocols and interpreted by a single radiologist to ensure consistency. Ethical approval was obtained from the Institutional Review Board of Bacha Khan Medical Complex (Ref: 26019/ERB/GKMC/BKMC Swabi). Written informed consent was obtained from all participants, and patient confidentiality was maintained throughout the study. Data were analysed using SPSS version 26.0. Descriptive statistics (frequencies and percentages) were used to summarize the data. Inferential statistics, such as chi-square tests, were planned but not performed due to the small sample size. A randomized sampling approach would reduce bias and improve the external validity of the study. The study relied solely on descriptive statistics and did not perform inferential tests (e.g., chi-square or t-tests) to assess associations or differences. Including inferential statistics would provide stronger evidence for the observed findings. The study restricted the age range to 20–50 years without providing a clear rationale. This exclusion may limit the applicability of the findings to other age groups, such as adolescents or older adults, who may also present with bilateral nasal polyps. The exclusion of immunocompromised patients and those on long-term steroids may limit the generalizability of the results, as these groups are often at higher risk for sinonasal diseases. Including these populations would provide a more comprehensive understanding of sinus involvement in bilateral nasal polyps. The study did not account for potential confounders such as smoking, environmental exposures (e.g., air pollution), or occupational hazards, which are known to influence sinonasal health. Controlling for these factors would strengthen the validity of the findings. The study did not specify whether CT scan interpretations followed standardized criteria or involved multiple radiologists to assess inter-observer variability. Standardized protocols and multiple observers would improve the accuracy and reliability of radiological findings. The study design was described as cross-sectional but lacked a clear hypothesis or justification for this approach. A more robust study design, such as a longitudinal or case-control study, could provide deeper insights into the causal relationships and progression of sinus involvement in bilateral nasal polyps. While ethical approval was obtained, the study did not detail how patient confidentiality and data security were maintained. Providing this information would enhance the transparency and ethical rigor of the study. The small sample size (n=50) and convenient sampling technique limit the generalizability of the findings to broader populations. Future studies should aim for larger, more diverse samples to improve external validity.

RESULTS

There were 50 patients in the study. 36(72%) were male and 14 (28%) were female. 15 (30%) were aged 20–25 years and followed by 8 (16%) aged 36–40 years.Sinus involvement was Maxillary Sinus: 36% involvement, with bilateral involvement in 40% of cases.Ethmoid Sinus: 26% involvement, with bilateral involvement in 26% of cases. Frontal Sinus: 26% involvement, with bilateral involvement in 26% of cases.Sphenoid Sinus: 18% involvement, with bilateral involvement in 18% of cases.Demographic characteristics of the patients are shown in Table 1.

Table 1: Demographic Characteristics of the Patients

Characteristics		Frequency (%)
Gender	Male	36 (72%)
	Female	14 (28%)
Age	20–25 Years	15 (30%)
	36–40 Years	8 (16%)
Sinus Involvement	Maxillary Sinus	36%
	Ethmoid Sinus	26%
	Frontal Sinus	26%
	Sphenoid Sinus	18%

Amongst the age group involved, most patient were amongst age group 20-25 years as shown in Table 2.

Table 2: Age Wise Distribution

Variables		Frequency (%)
Gender	20-25	15 (30%)
	26-30	7 (14%)
	31-35	7 (14 %)
	36-40	8 (16%)
	41-45	6 (12%)
	46-50	7

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	Total	50

A pie charts of sinuses involvement in bilateral nasal polyps with maxillary sinuses most commonly involved in about 36.00% patients in the Figure 1.

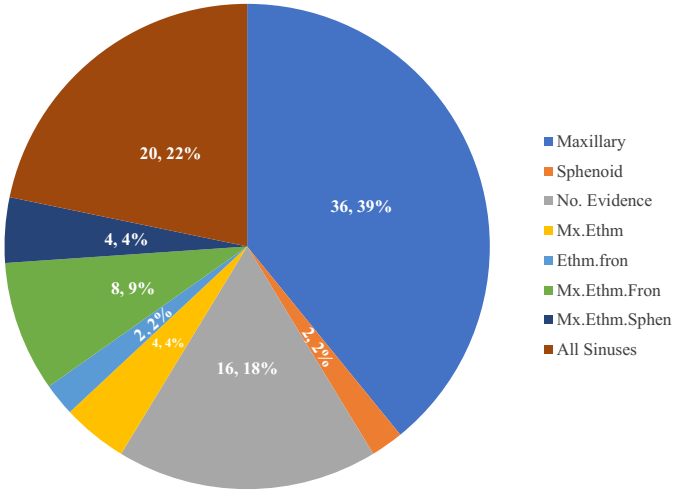

Figure 1: Involvement of Sinuses

Frequency of maxillary sinus involvement having 16% of left sinus, 22% of right sinus and 40% of both involvement while 22% of no involvements, as shown in Figure 2.

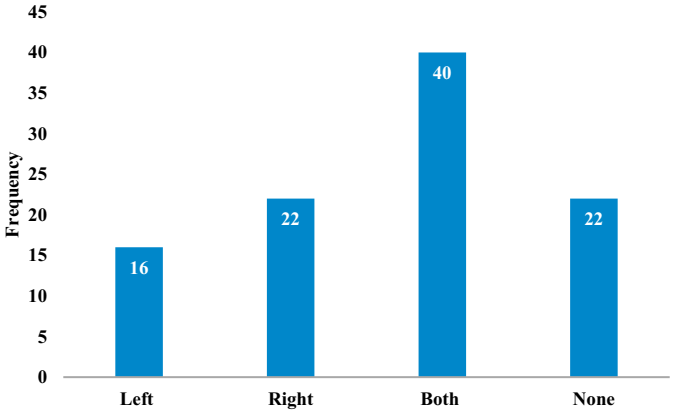

Figure 2: Side of Maxillary Sinus Involvement

Frequency of ethmoidal sinuses involvement having 8% left ,6% right ,26% both and about 60% of no evidence is shown in Figure 3.

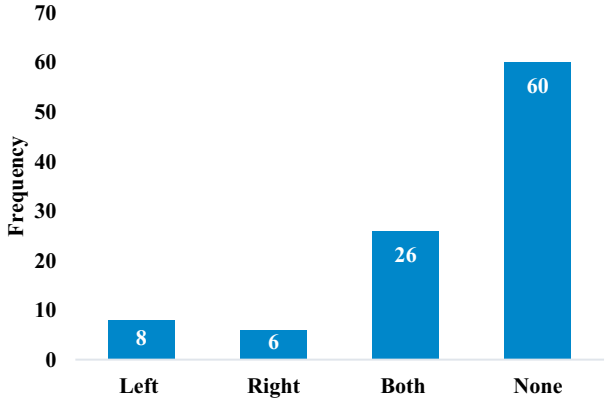

Figure 3: Side of Ethmoidal Sinus Involvement

The frequency of frontal involvement, having 8% left,4% right, 26% both and 62% none, is shown in Figure 4.

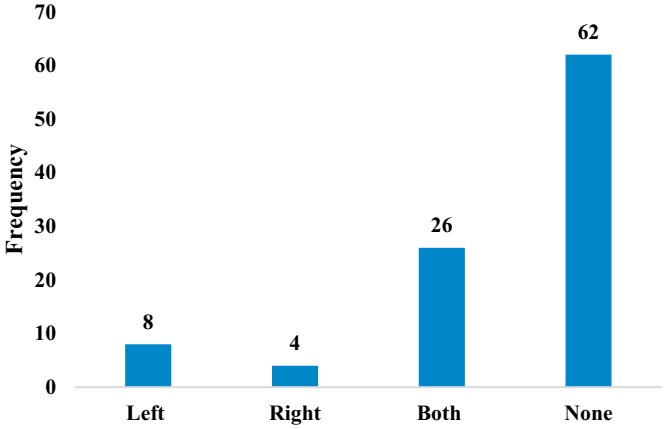

Figure 4: Side of Frontal Sinus Involvement

The frequency of sphenoid sinus with 4% left,6% right, 18% both, and 72% none, are shown in Figure 5.

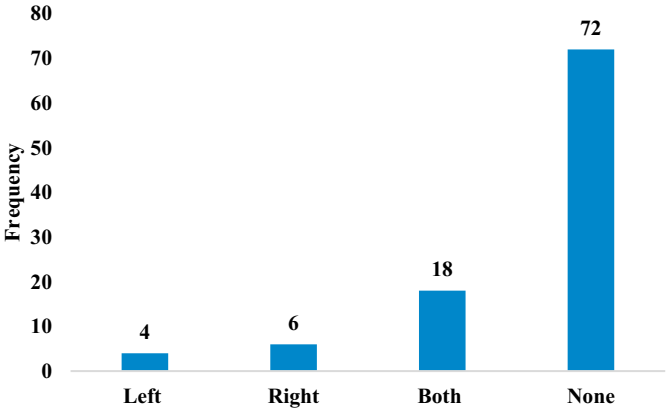

Figure 5: Side of Sphenoid Sinus Involvement

DISCUSSION

The study findings highlight the predominant involvement of maxillary sinuses in bilateral nasal polyps, consistent with their anatomical predisposition to inflammatory processes.The ethmoid, frontal, and sphenoid sinuses showed lower frequencies of involvement, likely due to their complex drainage pathways and reduced exposure to inflammatory stimuli. These results align with previous studies, such as Kwah, who reported maxillary sinus involvement in 65% of cases. However, the higher prevalence in the 20–25 age group in our study contrasts with the typical peak in the fourth decade, possibly due to regional or environmental factors. Similar finding was reported in study in which Nasal polyps are inflammatory outgrowths of paranasal sinus mucosa caused by chronic mucosal inflammation and are present in 20% of patients [18].The maxillary sinuses were involved in 36% of patients, with bilateral involvement (40%) being the most frequent, followed by right-side involvement (22%) and left-side involvement (16%). Interestingly, 22% of patients showed no maxillary sinus involvement. This pattern suggests that bilateral nasal polyps frequently extend to both maxillary

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sinuses, likely due to the central role of the maxillary sinuses in sinonasal drainage. A comparable study conducted in Denmark reveals a ratio of 2.74:1, with 73.27% of the population being male and 26.73% being female. The mean age of the maxillary sinus polyps was 38.55 + 13.44 years, and they were observed in the 11–79 age range. 93.10% of patients had unilateral maxillary sinus polyps, while 6.90% had bilateral ones. The right side of 54.31% of patients had polyps, while the left side had 38.79% [19]. The ethmoid sinuses demonstrated a moderate frequency of involvement, with 26% showing bilateral disease, while unilateral involvement was relatively less common (8% left, 6% right). Notably, 60% of patients had no evidence of ethmoid sinus involvement. This finding may indicate a less consistent association of nasal polyps with ethmoidal sinus disease, possibly due to the variability in the severity and extent of inflammation. Involvement of the frontal sinuses was observed in 26% of patients bilaterally, with unilateral involvement being less common (8% left, 4% right). However, 62% of patients exhibited no frontal sinus involvement, suggesting that the frontal sinuses are less frequently implicated in bilateral nasal polyp cases, possibly due to their more complex drainage anatomy and less direct exposure to inflammatory processes. a similar study in Virginia shows that the major causes for frontal sinusitis were polyp (53%) in the frontal sinuses [20]. The sphenoid sinuses were the least frequently involved, with only 18% showing bilateral disease and 4% left and 6% right unilateral involvement. A significant proportion of patients (72%) showed no sphenoid sinus involvement. This finding is consistent with the anatomical position and lower susceptibility of the sphenoid sinuses to primary inflammatory processes compared to other paranasal sinuses. Another study conducted shows that the origin of the polyps was the maxillary sinus in 65 patients, the sphenoid sinus in six, the middle turbinate in two, the septum in two, and the ethmoid sinus in one, based on their localizations [21].

CONCLUSIONS

The study highlights the involvement of various paranasal sinuses in patients diagnosed with bilateral nasal polyps. Among the paranasal sinuses, the maxillary and ethmoid sinuses were most commonly affected, reflecting their close anatomical relationship with the nasal cavity and susceptibility to inflammatory processes. The frontal and sphenoid sinuses demonstrated less frequent involvement, suggesting variability in the extent of disease progression. These findings underline the importance of comprehensive radiological evaluation in patients with bilateral nasal polyps to accurately assess sinus involvement and guide effective management strategies. Early diagnosis and targeted treatment could potentially reduce complications and improve patient outcomes. Further research is recommended to explore the relationship between sinus involvement and disease severity, as well as the impact of therapeutic interventions.

Authors Contribution

Conceptualization: JB
Methodology: JB, K, WK, AB, SN, SIK
Formal analysis: AB
Writing review and editing: A, WK
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association of Age and Gender with Early Onset Seizures in Patients of Acute Ischemic Stroke at a Tertiary Care Setting

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ABSTRACT

The prevalence of ischemic stroke is more in south Asian countries. Individuals having an early seizure have a significantly elevated chance of developing epilepsy after stroke than individuals having stroke but no early seizure.The seizures that occur following the stroke has been observed as contributing to more worse outcomes and disabilities. **Objective:** To determine the association of age and gender with earliest inception seizures in sufferers of acute ischemic stroke at a tertiary care setting in Sindh Pakistan. **Methods:** This cross sectional study was organized at Department of Medicine of Bilawal Medical College Hospital, Kotri from 26 May 2023 to 26 October 2023. In this study, the patients attending Bilawal Medical College Hospital reporting with stroke were recruited for this research study. The presence or absence of earliest seizures is dependent variable while, the age, gender and sociodemographic status are variables in present study.The data were analyzed on International Bussiness Machine Statistical Package for Social Sciences Version 26.0. **Results:** Out of 118 stroke patients, 17 (14.4%) found with early seizures. The gender and age appeared to have significant association with early onset of seizures with p value 0.01 and 0.04 correspondingly. **Conclusions:** It was concluded that male patients and all patients aged between 51 to 60 years were more likely to experience an early seizure. After an acute stroke, earliest seizures could not resemble to unfavorable functional prognosis.

INTRODUCTION

The prevalence of seizures following stroke has been reported as increasing globally and it relies on the type of stroke.In recent eras, post-stroke seizures have been getting more attention from health professionals, as it is difficult to manage leading to more disabilities and worsening the quality of life.The neurotransmitters, ion channel dysfunctions, and genetic variations play a role in the development of early post-stroke seizures [1].Early post-stroke seizures are those that occur up to seven days following the stroke's beginning. Individuals having an early seizure have a significantly elevated chance of developing epilepsy after stroke than individuals having stroke but no early seizure [2].The seizures that occur following the stroke have been observed as contributing to worse outcomes, long stays in hospitals, impaired quality of life, and disabilities. Proper management strategies are crucial for decreasing the worse outcomes expected to be developed in post-seizure patients [3].The mortality, as well as the morbidities related to post-stroke seizures, has declined in well-developed countries.This might be because of recent advances in management strategies for ischemic stroke [4].But it has been seen that the prevalence of ischemic stroke is higher in South Asians as compared to Europeans, and the underlying mechanisms are not clear.South Asians living in the United Kingdom have been observed as more prone to develop comorbid

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conditions e.g., post-stroke seizures [5].Intracerebral hemorrhage, ethnicity, male gender, dyslipidemia, and small vessel occlusion have been reported as the risk factors for early-onset seizures in patients of ischemic stroke but there is controversy about age and gender, whether they contribute to the earlier development of seizures in post-ischemic stroke patients [6, 7].

Therefore, this study has been designed to determine the association of age and gender with earliest inception seizures in sufferers of acute ischemic stroke at a tertiary care setting in Sindh Pakistan

METHODS

A cross sectional study was organized at Department of Medicine of Bilawal Medical College Hospital Kotri from 26 May 2023 to 26 October 2023.The ethical approval of research project was taken with reference number (BMC/Principal/-2024/1525).(In this study, total 118 patients (n=118) of ischemic stroke were recruited matching selection criteria.The sampling techniques was non probability purposive sampling.Though, known individuals of epilepsy, patients with brain injury after trauma, patients with electrolyte imbalance, transient ischemic attacks, Meningioma, Bacterial, tuberculosis, viral, or TB Meningitis ,hepatic encephalopathy and patients having Glasgow Coma Scale less than 7 were excluded.The data were collected at the bedside after taking informed consent and the structured questionnaire was filled by the researcher to record sociodemographic factors, age, gender, body mass index, socioeconomic status and history was taken regarding event of stroke, its duration and time interval from the patients attendants with the help of patients file maintained at the hospital.The presence or absence of early seizures was the dependent variable in the study, age, gender and sociodemographic status were the independent variables in the study.The post-stroke seizures were classified as acute/ early onset seizures if occurring within one week of stroke onset and late seizures, if occurring after one week of stroke onset.The types of post stroke seizures were determined, on the basis of history from patient's attendants and the clinical observations, documented by attending physicians.All patients were monitored in ward till the end of 14th post stroke day. Sample size was calculated on software Open Epi. According to a study carried at LUMHS hospital in 2016 by Qazi TR *et al.*, reported the prevalence of early onset post stroke seizures as 7.1% [8]. Taking the p=7.1, with 5% margin of error and 95% confidence interval, the calculated sample size was 102.In the time frame of study period, 118 patients meeting the selection criteria, were admitted in the ward, so 118 patients (n=118) recruited for this study, and this may increase the precision of this study.IBM SPSS version 26.0 was used to enter and analyze the data. Numerical data were revealed in descriptive statistics utilizing mean and standard deviation while the categorical data were presented in frequency and percentages.Chi Square test was used to evaluate the association of dependent variable with independent variables.

RESULTS

The mean age of study subjects was 52.47 ± 7.12 years with minimum age 39 to max age 71 years.The mean difference of the time between event of stroke and seizures was 55.45 ± 11.9 hours with minimum 41.6 hours to maximum 120.5 hours.The mean duration of seizures was 4.16 ± 2.09 minutes table 1.

Table 1: Descriptive Statistics of the Study Participants

Descriptive Statistics	Min	Max	Mean ± SD
Age (Years)	39	71	52.47 ± 7.12
Duration of Seizures (in Minutes)	2.4	5.2	4.16 ± 2.09
BMI Kg/m^2	24.1	33.4	27.1 ± 2.8
Interval between Event of Stroke and Seizures (Hours)	41.6	120.5	55.45 ± 11.9

In this study out of 118 patients, 17 (14.4%) reported with early seizures (Figure 1).

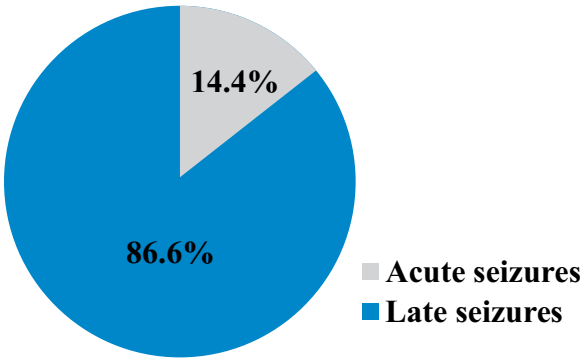

Figure 1: Early/ Acute Onset Seizures among the Patients of Ischemic Stroke

In this study, there were 53.39% male and 46.61% female patients. Majority of the patients were aged between 51 to 60 years. The most (51.69%) of the patients belonged to average socioeconomic status (Table 2).

Table 2: Sociodemographic Factors of Study Participants (n=118)

Variables	Frequency (%)
Gender	
Male	63 (53.39%)
Female	55 (46.61%)
Age(in Years)	
18 to 30	3 (2.54%)
31 to 40	4 (3.39%)
41 to 50	17 (14.41%)
51 to 60	51 (43.22%)
61 to 70	27 (22.88%)
More than 70	16 (13.56%)
Socio-economic Status	
Low	38 (32.20%)
Average	61 (51.69%)
High	19 (16.10%)

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A higher proportion of male patients, elderly patients aged between 51 to 60 years, socioeconomically challenged (both average and low) patients reported greater tendency to develop early seizers after stroke. In current study, gender and age appeared to have significant association with early onset of seizures with p-value 0.01 and 0.04 respectively, as shown in Table 3. While there is statistically significant difference of seizure occurrence based on age and gender, but the effect size was weak for both age and gender, i.e., V=0.12 (0.1 to 0.3 is small effect) for gender and v=0.05(very small effect). Therefore, there is statistically significant effect of age and gender on early onset of seizures but considering the effect size, age and gender alone are not strong predictors of early onset seizures, but other factors might contribute. When absolute risk was calculated there was 19.19 % more risk of early onset seizures in males (0.19: 95% CI 0.09-0.28) For age group 51-60 years, the risk of early onset seizures was 17.65% (0.1765: 95% CI 0.07-0.28).

Table 3: Chi Square Association of Early Seizures with Study Variables

Study Variables	Early Onset Seizures			p-value
	Total	Yes	No	
	Frequency (%)	Frequency (%)	Frequency (%)	
Gender				
Male	63 (53.39%)	12 (19.05%)	51 (80.95%)	0.01*
Female	55 (46.61%)	5 (9.09%)	50 (90.91%)	
Age (Years)				
18 to 30	3 (2.54%)	0 (0.00%)	3 (100.0%)	0.04*
31 to 40	4 (3.39%)	0 (0.00%)	4 (100.0%)	
41 to 50	17 (14.41%)	2 (11.76%)	15 (88.24%)	
51 to 60	51 (43.22%)	9 (17.65%)	43 (84.31%)	
61 to 70	27 (22.8%)	4 (14.81%)	23 (85.19%)	
More than 70	16 (13.5%)	2 (12.50%)	14 (87.50%)	
Socio-Economic Status				
Low	38 (32.20%)	6 (15.79%)	32 (84.21%)	0.08
Average	61 (51.69%)	9 (14.75%)	52 (85.25%)	
High	19 (16.10%)	2 (10.53%)	17 (89.47%)	
*Significant Statistically (p-value<0.05)				

DISCUSSION

In the present study, 14.4% of patients reported post-stroke early seizures.The frequency of early seizures was higher in these findings compared to a study conducted in 2016, which reported that 11 (7.1%) individuals with ischemic stroke experienced early seizures [8].The mean age of the study subjects was 52.47 ± 7.12 years, ranging from 39 to 71 years. Qazi TR *et al.*, reported a nearly similar mean age in their study [8, 9].Most of the patients were aged between 51 and 60 years.The age distribution in the present study was in line with the age group distribution reported by Qazi TR *et al.*, [8].The mean duration of seizures was 4.16 ± 2.09 minutes, which was comparatively higher than the durations reported in a previous study on early seizures among ischemic stroke patients [8].In this study, 53.39% of the patients were male and 46.61% were female.The Chi-square test revealed a statistically significant difference in seizure occurrence related to gender ($p < 0.05$).These findings were in agreement with the research of Kim HJ *et al.*, who also reported that gender was associated with the occurrence of early seizures [9].However, in contrast, Mohamed AT *et al.*, and Burneo JG *et al.*, did not observe any significant gender-based differences [10, 11].Additionally, while the current study found a higher proportion of early seizures in males, a meta-analysis reported that females had higher odds of developing early seizures [12].Most of the patients were between 51 and 60 years of age.It was observed that age was significantly associated with the occurrence of early seizures.Thomas R reported that early onset post-stroke seizures were more prevalent in younger age groups, which contrasted with the findings of the present study [13].This study also differed from the findings of Mohamed C *et al* [14]. However, the findings of Xu MY *et al.*, were similar to those of the current study, as they reported that experiencing a stroke before the age of 65 was a risk factor for developing early seizures [15]. Carroll K *et al.*, also supported the findings of this study, highlighting age as a significant predictor of early-onset seizures in post-stroke patients [16].According to their research, gender was not significantly related to post-stroke early seizures. In similarity with the present study, Alsaad F *et al.*, revealed that both age and gender were significant predictors of early-onset seizures in stroke patients [17].This study found that males had a 19.19% higher risk of early onset seizures (0.19; 95% CI: 0.09–0.28) and older patients had a 17.65% increased risk (0.1765; 95% CI: 0.07–0.28).Thomas R and Shariff E *et al.*, also reported a higher proportion of male patients developing early onset seizures in acute stroke [13, 18]. No significant association was found between early seizures and socioeconomic status in this study.This was supported by Wali Z *et al.*, who also reported no significant effect of socioeconomic status on the development of early seizures in stroke patients [19].However, Nguyen M *et al.*, found that socioeconomic status might influence poor functional recovery in acute stroke patients [20].The results of this study indicated that age and gender played important roles in post-stroke early seizures.Despite these findings, the study had limitations, including a small sample size and its single-center design.Future multi-center studies with larger sample sizes are recommended to validate these relationships, explore potential underlying mechanisms, and investigate environmental and genetic factors contributing to early seizures in stroke patients.

CONCLUSIONS

A close examination of the clinical features of earliest-onset stroke seizures, it was determined that male patients and all patients aged between 51 to 60 were more likely to experience an early seizure.After an acute stroke, early seizures did not appear to be related to a worse functional prognosis.

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Authors Contribution

Conceptualization: RK
Methodology: AA, KKP, AAN, KA
Formal analysis: RKS
Writing, review and editing: RK, AA, RKS, KKP, AAN, KA
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Conflicts of Interest

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Original Article

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Diagnostic Accuracy of MRI in Detecting Stromal Invasion in Early Cervical Cancer Patients Taking Histopathology as Gold Standard

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ABSTRACT

Cervical cancer is a major cause of cancer-related deaths among women. MRI is a non- invasive imaging technique commonly used to evaluate tumor extent, but its diagnostic accuracy in detecting stromal invasion in early cervical cancer remains uncertain. **Objective:** To determine the diagnostic accuracy of MRI in detecting stromal invasion in early cervical cancer patients taking histopathology as gold standard. **Methods:** This Cross-sectional validation was conducted at the Department of Radiology, Faisalabad Medical University (FMU), Faisalabad, form 1st April 2024 to 30th September 2024. A total of 200 patients aged 30-70 years with early cervical cancer were included in the study. All patients underwent pelvic MRI scans using a 1.5 Tesla MRI machine. The MRI findings were assessed for the presence or absence of stromal invasion and compared with histopathology results. All the data was analyzed in SPSS and sensitivity, specificity, and diagnostic accuracy was calculated for MRI against histopathology. **Results:** The overall sensitivity, specificity, Positive Predictive Value (PPV), negative predictive value (NPV), and diagnostic accuracy of MRI in detecting stromal invasion in early cervical cancer patients, were 91.26%, 89.70%, 90.38%, 90.63%, and 90.50%, respectively with histopathology as the gold standard. **Conclusion:** This study concluded that MRI has a high diagnostic accuracy in detecting stromal invasion in early cervical cancer patients.

INTRODUCTION

Cervical cancer is one of the most common cancers among women globally, with early detection and accurate staging being pivotal to improving patient outcomes. Early cervical cancer, particularly at stages where the tumor has not yet invaded deeper tissues, presents an opportunity for treatment strategies that can significantly reduce mortality [1, 2]. One of the key prognostic factors for cervical cancer is the presence or absence of stromal invasion. Accurate assessment of stromal invasion is crucial for determining the appropriate management strategy, which may range from conservative surgery to more aggressive treatments. Magnetic Resonance Imaging (MRI) has been proposed as a non-invasive imaging modality for assessing stromal invasion in early cervical cancer, but its diagnostic accuracy compared to histopathology the gold standard for diagnosis remains a subject of ongoing research [3]. Histopathology has long been considered the definitive method for evaluating stromal invasion in cervical cancer, providing detailed insights into tumor characteristics at a microscopic level. However, histopathological assessment involves invasive procedures like biopsy and is limited by sampling errors and inter-observer variability [4]. In contrast, MRI offers a promising non-invasive alternative, providing high-

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resolution images of soft tissue structures, including the cervix and surrounding tissues. The ability of MRI to visualize stromal invasion could potentially reduce the need for invasive biopsies, offering a more accessible and less traumatic method for clinical decision-making [5]. MRI's role in assessing cervical cancer has gained attention over the years, particularly with advancements in imaging technology that enhance its resolution and accuracy. Several MRI sequences, including T2-weighted imaging, dynamic contrast-enhanced imaging, and diffusion-weighted imaging, have been employed to improve the sensitivity and specificity of detecting cervical cancer and its invasion into adjacent tissues. The use of high-field MRI machines has further improved the precision of these evaluations. While studies suggest that MRI has considerable potential in identifying stromal invasion, the evidence remains mixed regarding its diagnostic accuracy, with some studies showing promising results and others pointing to limitations such as the difficulty in differentiating tumor from normal tissue in certain cases [6, 7]. The challenge lies in accurately correlating MRI findings with histopathological outcomes. Stromal invasion, which refers to the penetration of the tumor into the cervical stroma, can vary in depth and extent. MRI imaging has been shown to have varying degrees of sensitivity and specificity in detecting different stages of stromal invasion, depending on tumor size, location, and the quality of the imaging technique used. Furthermore, MRI's diagnostic performance may be influenced by factors such as the skill of the radiologist and the lack of standardized protocols across different institutions. Therefore, while MRI holds promise, it is essential to evaluate its diagnostic performance against histopathology in large-scale, multicenter studies to validate its clinical utility [8, 9]. In recent years, research has focused on improving the diagnostic performance of MRI through the use of novel imaging biomarkers and machine learning algorithms. These innovations aim to enhance the accuracy of stromal invasion detection, reduce observer bias, and provide more objective and reproducible results. The integration of MRI with histopathological data could lead to more personalized and precise treatment plans for patients with early cervical cancer. However, comprehensive studies comparing MRI with histopathology as the gold standard are still required to establish clear guidelines for its clinical application and to identify potential pitfalls in its use for assessing stromal invasion [10-12].

METHODS

This study was conducted in the Department of Radiology, Faisalabad Medical University (FMU), Faisalabad, over a period of six months, from April 2024 to September 2024. Approval for the study was obtained from the Ethical Review Committee (ERC) prior to initiating the research (ERC letter No 48. ERC/FMU/2023- 24413). A total of 200 patients who presented to the Radiology Department were recruited in the study after applying non-probability, consecutive sampling technique. The sample size was calculated based on a 95% confidence level, a prevalence of stromal invasion estimated at 32%, and a 6.5% margin of precision, ensuring 80% sensitivity and 50% specificity of MRI in detecting stromal invasion in patients with early cervical cancer. Written informed consent was obtained from all participants before inclusion in the study. Inclusion criteria were patients eligible for the study included married and unmarried women aged 30–70 years, presenting with early cervical cancer.This was characterized by frank growth on the cervix measuring less than 4 cm in size, unhealthy cervix, and cervical cancer confirmed through PAP smear, with a duration of more than three months. Exclusion criteria were patients were excluded if they had already been diagnosed with cervical cancer, were undergoing chemotherapy or radiation therapy, had a history of cervical surgery, presented with carcinoma of the uterus, or had contraindications for undergoing MRI. All selected participants underwent an MRI scan of the pelvis using a 1.5 Tesla GE machine. The MRI procedure was conducted by a skilled MRI technician, ensuring high-quality imaging.The protocol included the following sequences: sagittal T2-weighted imaging, axial T1-weighted and T2-weighted imaging, coronal T1-weighted imaging, and coronal T2 fat-suppressed sequences. The images were reviewed to detect the presence or absence of stromal invasion. The MRI findings were interpreted by experienced radiologists with attention to identifying continuous tumor growth within the cervix or the presence of neoplastic glands adjacent to preexisting endocervical glands.The MRI findings were compared with histological results obtained from biopsies. Histological evidence of tumor continuity within the cervix or neoplastic gland presence was considered a significant indicator of stromal invasion.All relevant data were systematically recorded and analyzed using the SPSS software version 25.0.The accuracy of MRI based on sensitivity (TP/TP+FN*100), specificity (TN/TN+FP*100), PPV (TP/TP+FP*100), NPV (TN+TN+FN*100) andoverall diagnosed accuracy (TP+TN/N*100) were calculated against histopathology findings by using a 2x2 contingency table.

Table 1: Histopathological Categories

Category		Histopathology		Total
		Positive	Negative	
MRI	Positive	(TP)	(FP)	TP+FP
	Negative	(FN)	(TN)	TN+FN
Total		TP+FN	TN+FP	N

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RESULTS

Total 200 females were enrolled in the study with the mean age of 43.84 ± 8.5 years. The majority of patients (74.0%) belonged to the 30-to-50-year age range. There were 36 (18%) were unmarried while remaining 82% were married. Mean duration of symptoms was 5.41 ± 1.75 months. On MRI, the mean size of lesion was noted as 2.93 ± 0.94 cm. Out of 200 females, 70.5% were premenopausal, (Table 2).

Table 2: Descriptive Analysis of Baseline Parameters (n = 200)

Variables	Mean ± SD/Frequency (%)
Age (Years)	43.84 ± 8.5
Age range 30-50 Years	148 (74%)
Age range 51-70 Years	52 (26%)
Marital Status	
Unmarried	36 (18%)
Married	164 (82%)
Duration of Disease (Months)	5.41 ± 1.75
< 6 Months	157 (78.50%)
> 6 Months	43 (21.50%)
Size of Nodule (cm)	2.93 ± 0.94
< 3 cm	159 (79.50%)
> 3 cm	41 (20.50%)
Menopausal Status	
Premenopausal	159 (79.50%)
Postmenopausal	41 (20.50%)

In MRI positive patients, 94 True Positive (TP), 10 False Positive (FP), 09 False Negative (FN) whereas were 87 True Negative (TN). Overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of MRI in detecting stromal invasion in early cervical cancer patients, taking histopathology as gold standard was 91.26%, 89.70%, 90.38%, 90.63% and 90.50% respectively, Table 3.

Table 3: Diagnostic accuracy of MRI taking Histopathology as Gold Standard

Variables	Category	Histopathology	
		Positive	Negative
MRI	Positive	94 (TP)	10 (FP)
	Negative	09 (FN)	87 (TN)

Sensitivity: 91.26%, Specificity: 89.70%, PPV: 90.38%, NPV: 90.63%, Diagnostic Accuracy: 90.50%.

It was also stratified data for age, duration of disease, size of lesion and marital status to check the impact of these effect modifiers on accuracy of MRI. It was observed that in females with young age, overall accuracy of MRI was high (91.22%) as compared to older females (88.5%). Similarly, in females with symptoms <6 months, accuracy of MRI was less (89.8%) as compared to females with symptoms >6 months (93.02%). In females with lesion size <3cm, accuracy of MRI was 91.2% than >3 cm lesion size (87.8%) and more accuracy was achieved in post-menopausal females (94.9%) than pre-menopausal females (88.65%), (Table 4).

Table 4: Stratification of Diagnostic Accuracy of MRI according to different Variables

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)	p-Value
Age (Years)						
30-50	91.46%	90.91%	92.59%	89.55%	91.22%	0.000
51-70	90.48%	93.10%	87.10%	93.10%	88.46%	0.000
Duration of Disease						
≤6 months	91.14%	88.46%	88.89%	90.79%	89.81%	0.000
>6 months	91.67%	94.74%	95.65%	90.00%	93.02%	0.000
Size of Lesion (cm)						
<3	93.26%	88.57%	91.21%	91.18%	91.19%	0.000
>3	78.57%	92.59%	84.62%	89.29%	87.80%	0.000
Menopausal Status						
Pre-menopausal	90.41%	86.76%	88.0%	89.39%	88.65%	0.000
Post-menopausal	93.33%	96.55%	96.55%	93.33%	94.92%	0.000

* Chi-square test was applied

DISCUSSION

New advanced MRI techniques allow improved analysis of tumour biology and the tumour microenvironment. They can improve TNM staging and show promise for tumour classification and for assessing the risk of tumour recurrence. They may be helpful for developing optimised and personalised therapy for patients with cervical cancer [13]. MRI plays a key role in preoperative staging and the evaluation of treatment responses of patients affected by cervical cancer. This is due to the ability to identify the involvement of adjacent structures such as the vagina and parametrium as well as lymph nodes. In those patients eligible for neoadjuvant treatment, the assessment of treatment response could help to plan a proper strategy to improve survival outcomes while minimizing side effects [14]. The findings of this study affirm the pivotal role of MRI as a non-invasive and highly effective imaging modality in

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diagnosing and staging early-stage cervical cancer. MRI's excellent soft tissue resolution and ability to accurately determine tumor size, position, and extent of invasion have been well-documented in recent literature. In this study, MRI demonstrated a sensitivity of 91.26%, specificity of 89.70%, PPV of 90.38%, NPV of 90.63%, and diagnostic accuracy of 90.50% in detecting stromal invasion, with histopathology serving as the gold standard. Thus, the chances of false positive (8.7%) and false negative findings (10.3%) were very low. MRI is an accurate technique for evaluating bladder or rectum involvement, with a sensitivity of 71 – 100% and specificity of 88–91% [15-17]. Amin MI et al., conducted a similar study on 20 females with pathologically proven cervical cancer and observed that MRI showed 100% sensitivity, 77.8% specificity, and 90% diagnostic accuracy.They concluded that MRI can be a reliable imaging tool to grade the cervical cancer and better treatment planning [18]. A growing body of evidence has reported that MRI could play a relevant role in the pre-operative staging of cervical cancer [19].Data from the literature reported that MRI has an accuracy of 85–95% for the assessment of metastatic lymph nodes [20, 21].Many retrospective studies have shown that the accuracy of MRI in the early stages of cervical cancer is higher than the advanced stages [22].In a meta-analysis published in 2020 by Woo S *et al.*, the pooled sensitivity and specificity of five studies using MRI in bladder wall infiltration assessment were 84 and 95%, respectively [12].

CONCLUSIONS

The findings of this study suggest that MRI exhibits high diagnostic accuracy in detecting stromal invasion among early-stage cervical cancer patients. Moreover, MRI significantly enhances the capability to identify parametrial invasion in these patients, leading to improved patient care through accurate diagnosis and the implementation of appropriate pre-operative management protocols for cervical carcinoma. Consequently, we advocate for the primary utilization of MRI as the imaging modality of choice for precise detection of parametrial invasion in cervical cancer patients, aiming to mitigate morbidity and mortality associated with the condition.

Authors Contribution

Conceptualization: NA
Methodology: NA
Formal analysis: NA, MM, AG, AAB, AM, AL
Writing, review and editing: MM, AG, AM, AL
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Frequency of Angles Malocclusion, Psychological Effects in Patient Using Oasis Questionnaire and Treatment Needs in Patients Visiting Dental Teaching Hospital

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ABSTRACT

A person's psychological health and confidence are greatly influenced by their facial appearance. It encourages acceptance, integration, and social recognition. **Objective:** The objective of current study was to establish the frequency of Angle's malocclusion, assess its psychological impact using the OASIS questionnaire, and evaluate orthodontic treatment need using the Index of Orthodontic Treatment Need (IOTN) in patients visiting dental teaching hospital. **Methods:** Both gender patients between 14-20 years, fully erupted first molar from one arch to another were included while participants with a history of jaw injuries, experiencing orthodontic treatment, or had prior orthodontics treatment were not included in the current study. The Oral Aesthetic Subjective Impact Scale (OASIS), self-evaluation validated tool was used to determine perceived therapeutic requirements. Index of Orthodontic Treatment Need (IOTN) index was also reported. **Results:** Among the 350 people examined, 70% (245) were females and 30% (105) were males. The mean age was 17 years with S.D ± 1.26. 54 (15.4%) of the patients had normal dental occlusions, 175 (50%) had class I malocclusion, 99 (28.3%) had class II, and 22 (6.3%) had class III malocclusion. 202 (57.7%) of patients reported good psychological well-being about their dental looks, whereas 90 (25.7%) and 58 (16.6%) had satisfactory and poor psychological well-being respectively, based on sample size. **Conclusions:** This study showed a significant rate of malocclusion, with Class I being the most frequent. Psychological effects were obvious, as many patients expressed unhappiness with their oral look.

INTRODUCTION

A person's psychological health and confidence are greatly influenced by their facial appearance. It encourages acceptance, integration, and social recognition [1]. One important component of self-concept, encompassing universal, ability, emotional, intellectual, and physical characteristics, has been shown to be the self-perception of the dentofacial area. According to research, those who have fewer dental flaws are more socially adept, academically successful, and psychologically well [2]. "The mal relationship between arches in any plane or a condition characterized by anomalies in tooth position, number, form, and developmental position of teeth beyond normal limits" is the definition of malocclusion [3]. In addition to local variables including bad dental habits, tooth form, and

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location during development, it can be brought on by environmental or genetic causes [4].Treatments for malocclusion are commonly carried out during adolescence, when permanent teeth erupt [5].Facial attractiveness, especially aesthetic appearance, is crucial for social interaction.It affects work prospects, performance, personality attributes, and pairing success. Smile appeal and facial beauty appear to be closely related [6].People frequently concentrate on the eyes and mouth of the speaker during social encounters.People's opinions about how their teeth look, which are shaped by their surroundings and society, greatly affect whether they decide to have treatment.Enhancing the look of teeth is a crucial part of dental treatment to guarantee satisfaction [7].Malocclusion can further cause tooth cavities, temporomandibular joint disorders, and periodontal concerns [8].Amaral *et al.*, (2020) evaluated malocclusion and the need for orthodontic treatment in Indian youth aged 16-24 [9].Cross-sectional research involving 660 participants, including 300 females and 360 males, was conducted in rural regions.The Dental Aesthetic Index (DAI) was utilized in clinical studies to assess the population's overall need for orthodontic treatment.According to Hameed *et al.*, (2023), 79.8% of patients attending several OPD of Punjab dental colleges [10].

The objective of the current study was to establish the frequency of Angle's malocclusion, assess its psychological impact using the OASIS questionnaire, and evaluate orthodontic treatment need using the IOTN in patients visiting dental teaching hospital.

METHODS

From November 2023 to August 2024, a questionnaire-based descriptive cross-sectional study carried out on patients visiting Khyber Medical University-Institute of Dental Sciences Kohat's orthodontic department after approval for the research was received from the Institutional Review Board of Khyber Medical University-Institute of Dental Sciences Kohat (KIDS-IRBB/ECC/23-2/10). Sample size was estimated by using Epi-info software. Total calculated sample size was 350 (10% drop out was added). The sample size was calculated by the formula below: Population size: 1761 (average patient visited department in last 5 years), Confidence Limits: 95%, Expected Frequency: 50%, Sample required: 315 (Adding 10% = 350). The study included both gender patients aged 14-20 years with fully erupted first permanent molar from one arch to another while participants with a history of jaw injuries, experiencing orthodontic treatment, or had prior orthodontics treatment were not included in the current research study. A consecutive sampling method was adopted, with all eligible patients who visited the orthodontic department throughout the research period being included until the needed sample size was attained. This method reduces selection bias while providing a representative sample of the population. Written consent was taken from each participant who fulfilled the inclusion criteria. Participants' personal information, such as name, age, and gender, was noted. The dental surgeon used a mirror, WHO probe, and dental twizzer to do a complete oral examination. Angle's classification, overbite, overjet, crossbite and open bite were recorded using a self-made Performa. The Oral Aesthetic Subjective Impact Scale (OASIS) is a self-evaluation validated tool used to determine perceived therapeutic requirements [11]. It consists of five items that evaluate concerns about dental appearance, self-perception, and the negative effects of dental abnormalities on life and social relationships. Each question is rated on a Likert scale of 1 to 5. Patients were asked five questions and rated according to their responses. The total score was the totality of all five parts and varied between 5 and 25. A score of 5-10 was deemed good, 11-15 satisfactory, and 16-25 poor psychological well-being. The Index of Orthodontic Treatment Need (IOTN) ranks malocclusion based on the relevance of occlusal characteristics for oral health and aesthetics. The score comprises both an aesthetic and Dental Health Component (DHC), based on Swedish medical board recommendations. For several malocclusions, the Dental Health Component (DHC) of the IOTN index was specified. There are 3 levels of treatment need: "level 1 (no need), level 2 (little or no need for treatment), level 3 (borderline need), level 4 (definite need), and level 5 (severe need)" [12]. Prior to full-scale data collection, a pilot study of 20 participants was done to assess the reliability and validity of the data collecting tools in the local community. Cronbach's alpha was used to test the internal consistency of the OASIS questionnaire, a validated self-evaluation tool, and the result was 0.82, suggesting excellent reliability. Furthermore, test-retest reliability was examined by delivering the questionnaire again, two weeks apart, which revealed a significant Intraclass Correlation Coefficient (ICC) of 0.89. For the IOTN index's inter-examiner reliability was established by training two independent examiners to evaluate 20 random cases. The kappa statistic was used to assess agreement amongst examiners, and a result of 0.78 indicated significant agreement. These stages made sure that both instruments were properly tailored for the local community. Chi-square test (χ^2 test) of independence was used to assess whether there is a significant association between categorical variables. A Pearson correlation analysis was used to investigate the association between IOTN grades and OASIS scores. A simple linear regression model was also used, using the OASIS score as the dependent variable and IOTN grade as the independent variable. A Statistical Package for Social Sciences software (SPSS) version 29.0 was used to enter and proceed with the data using an IBM compatible computer.

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RESULTS

Among the 350 people examined, 70% (245) were females and 30% (105) were males. The mean age was 17 years with S.D +1.26. Furthermore, 59 (16.9%), 55 (15.7%), 40 (11.4%), 77 (22%), 54 (15.4), 29 (8.3%) and 36 (10.3) were 14, 15, 16, 17, 18, 19 and 20 years old respectively (Table 1).

Table 1: Age Distribution of Participants

Age	Gender		Total Frequency (%)
	Male Frequency (%)	Female Frequency (%)	
14	10 (9.5%)	49 (20%)	59 (16.9%)
15	16 (15.2%)	39 (16%)	55 (15.7%)
16	15 (14.3%)	25 (10.2%)	40 (11.4%)
17	33 (31.4%)	44 (18%)	77 (22%)
18	18 (17.2%)	36 (14.6%)	54 (15.4%)
19	07 (6.7%)	22 (9%)	29 (8.3%)
20	06 (5.7%)	30 (12.2%)	36 (10.3%)
Total	105 (100%)	245 (100%)	350 (100%)

Table 2 demonstrated that 54 (15.4%) of the patients had normal dental occlusions, 175 (50%) had class I malocclusion, 99 (28.3%) had class II, and 22 (6.3%) had class III malocclusion. Overjet increased in 56 (16%) cases & reduced in 39 (11.1%). Overbite was increased in 91 (26%) cases and decreased in 29 (8.3%). In 91 (26%) cases, there was an open bite. The prevalence of Normal Occlusion was 15.4% (95% CI: 11.6% – 19.2%), while Class I malocclusion was 50.0% (95% CI: 44.8% – 55.2%). Class II and Class III malocclusions had prevalence rates of 28.3% (95% CI: 23.6% – 33.0%) and 6.3% (95% CI: 3.7% – 8.8%), respectively.

Table 2: Distribution of Different Occlusal Characteristics

Variables	Class	Frequency (%)	95% Confidence Interval (CI)	p-Value
Angle Class	Normal Occlusion	54 (15.4%)	11.6% – 19.2%	0.010*
	Class I	175 (50%)	44.8% – 55.2%	
	Class II	99 (28.3%)	23.6% – 33.0%	
	Class III	22 (6.3%)	3.7% – 8.8%	
Overjet	Normal	255 (72.9%)	68.2% – 77.5%	0.030*
	Excessive	56 (16%)	12.2% – 19.8%	
	Reduced	39 (11.1%)	7.8% – 14.4%	
Open Bite	Present	91 (26%)	21.4% – 30.6%	0.050
	Absent	259 (74%)	69.4% – 78.6%	
Overbite	Normal	230 (65.7%)	60.7% – 70.7%	0.020*
	Excessive	91 (26%)	21.4% – 30.6%	
	Reduced	29 (8.3%)	5.4% – 11.2%	

*Statistically Significant

Table 3: Oral Aesthetic Subjective Impact Scale (OASIS) Distribution by Gender

Gender	OASIS Categories			Total Frequency (%)
	Good Frequency (%)	Satisfactory Frequency (%)	Poor Frequency (%)	
Male	59 (56.2%)	29 (27.6%)	29 (27.6%)	105 (100%)
Female	143 (58.4%)	61 (24.9%)	61 (24.9%)	245 (100%)
Total	202 (57.7%)	90 (25.7%)	90 (25.7%)	350 (100%)

DHC grade I and II (little or no need for treatment) was noted in 200, grade III (borderline need), in 88 and grade IV (definite need) and grade V in 62 (severe need)" subjects respectively (Table 4). P value was found as 0.050 which suggests that the difference in IOTN scores between males and females is marginally significant but not strongly conclusive.

Table 4: Index of Orthodontic Treatment Need Score for Dental Health Components

DHC Score	Gender		Total Frequency (%)	p-Value
	Male Frequency (%)	Female Frequency (%)		
Grade I and II	55 (27.5%)	145 (72.5%)	200 (57.1%)	0.050
Grade III	35 (39.8%)	53 (60.2%)	88 (25.1%)	
Grade IV and V	15 (24.2%)	47 (75.8%)	62 (17.8%)	

A Pearson correlation analysis was used to investigate the association between malocclusion severity (IOTN grades) and psychological distress (OASIS scores). The study found a moderate negative connection ($r = -0.42$, $p < 0.001$), indicating that as malocclusion severity increases, psychological well-being worsens. A simple linear regression model was used, using the OASIS score as the dependent variable and IOTN grade as the independent variable. The model was statistically significant ($p < 0.001$) and explained 18% of the variance ($R^2 = 0.18$) in psychological distress. The regression coefficient ($\beta = -0.38$) shows that for every one-unit increase in IOTN grade, the OASIS score decreases by 0.38 points, indicating that severe malocclusion is associated with greater psychological distress (Table 5).

Table 5: Correlation and Regression Analysis Results

Analysis	Variables	Coefficient	p-Value
Pearson Correlation	IOTN Grade vs OASIS Score	-0.42 (r)	< 0.001
Linear Regression	IOTN Grade OASIS Score	-0.38 (β)	< 0.001
Model Fit	R2 Value	0.18	-

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DISCUSSION

In this current study, 296 (84.6%) of 350 individuals exhibited some kind of malocclusion, which is similar to the conclusions of Hameed *et al.*, in (2023), 79.8% who detected malocclusion in 79.8% of their sample size [10]. Comparably, Mangat, in (2020) performed an investigation in Republic of Hungary of 483 participant's between16-18 years and discovered a 71% prevalence of malocclusion in his sample size [13].Similarly, Prameswari (2021) did research on deafened children and reported a frequency of 69.5%, which is consistent with these findings [14].Alyami *et al.*, in (2023) did research on 502 Najran students and discovered an occurrence of 78%, which is consistent with this study [15].The frequency of class I malocclusion was 175 (50%), like to previous research carried out in Iran (49.1%), (51.5%) in Afghanistan and Pakistan (47.1%)[16-18]. Class III malocclusion 22 (6.3%) in the current study was found to be similar to that established in Saudi Arabia (6.52%) [15], Pakistan (8%) and (11%), and Turkey (10%) Overjet was found to be normal in 255 (72.9%), increased in 56 (16%), and reduced in 39 (11.1%) [15, 18-20].These findings were identical to those reported by Londono (2023) and Nath *et al.*, in (2024) [21, 22]. Overbite was seen in 91 (26%) of the patients, comparable to studies by Abraham *et al.*, in (2024) (29.1%) and Chunduru *et al.*, in (2024) (29%), but much lower than that identified in Mylonopoulou *et al.*, in (2021) 16.7% [23-25]. Self-evaluated dental appearance is gaining popularity due to its potential influence on dental treatment and patient-centred care delivery.In this study, 202 (57.7%) of subjects reported a positive psychological response to their dental appearance, which is consistent with findings by Meng *et al.*, between a different sample of adults in Florida and Khan *et al* [26, 27]. The statistical analyses performed in this study give important insights into the association between malocclusion severity, psychological effect, and orthodontic treatment requirement.The Pearson correlation analysis showed a substantial negative association ($r = -0.42$, $p < 0.001$) between IOTN grades and OASIS scores, indicating that as malocclusion severity grows, so does psychological distress.These findings are consistent with studies conducted by Meng *et al.*, in (2007) and Hamamci *et al.*, (2009), who discovered that patients with severe malocclusions expressed increased unhappiness with their dental appearance [26, 28].The Chi-square test revealed significant relationships between malocclusion severity and psychological discomfort ($p = 0.010$), supporting the premise that orthodontic treatment is not only clinically necessary but also critical for mental health. This is congruent with studies done by Alyami *et al.*, in (2023) [15] and Tariq *et al.*, (2024) [18], where patients with higher orthodontic treatment requirements (IOTN grade IV and V) indicated more unhappiness with their facial aesthetics [15, 18].The IOTN includes a DHC component, which, like all standardizing indices, can vary over time to indicate developmental modifications and is henceforth rather reliable.The National Health Services in the United Kingdom frequently employs the IOTN to identify persons whose occlusions characteristics are deemed eligible for resource investing.The present study aimed to determine if the subjects under observation required orthodontic care for malocclusion.DHC grade I and II (little or no need for treatment) was noted in 200, grade III (borderline need), in 88 and grade IV (definite need and V in 62 (severe need) subjects respectively in the current study which was similar to Amaral *et al.*, (2020) who evaluated a total of 215 students aged between 15 and 19 years and asked to respond to a questionnaire concerning their perception of need for orthodontic treatment and their satisfaction with their own esthetics and mastication [9]. Furthermore, the simple linear regression model ($R^2 = 0.18$, $\beta = -0.38$, $p < 0.001$) supports the predicted link between malocclusion severity and psychological impact. While previous research has mostly focused on prevalence, these findings highlight the relevance of incorporating psychological stress when choosing treatment priorities. Future research should look at the long-term psychological effects of orthodontic therapy to help confirm these findings.

CONCLUSIONS

This study showed a significant rate of malocclusion, with Class I being the most frequent. Psychological effects were obvious, as many patients expressed unhappiness with their oral look.The IOTN examination revealed a considerable need for orthodontic treatment.Early intervention and improved awareness are critical for promoting dental health and psychological well-being.

Authors Contribution

Conceptualization: AK, SA
Methodology: AK, AM
Formal analysis: SS, KNA
Writing, review and editing: SR, FG, SS, HA, SA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Deciphering the Diagnostic Potential of α-Methylacyl CoA Racemase (AMACR) in Prostatic Neoplasms

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ABSTRACT

Prostate cancer is a prevalent malignancy that affects males globally, posing a substantial impact both locally and globally. A critical marker for improving prostatic cancer diagnostic accuracy is α-Methylacyl CoA Racemase (AMACR), an enzyme involved in the metabolism of certain fatty acids and bile acid precursors. **Objective:** To explore the immunohistochemical expression of α-Methylacyl CoA Racemase and assess its association with the histological grading of prostatic adenocarcinoma. **Methods:** This retrospective cross-sectional study was carried out at Liaquat University of Medical and Health Sciences, Jamshoro between April 2023 to February 2024. Total 71 prostate cancer patients with age range of 45 to 99 years were selected for this study according to the selection criteria.The study used formalin-fixed paraffin-embedded tissue blocks for histopathology to evaluate AMACR expression through immunohistochemistry and the data was analyzed by using the Statistical Package for the Social Sciences (SPSS) for windows. **Results:** The immunohistochemical study revealed that 57.7% of cases showed AMACR expression, with a significant correlation between the expression levels and the tumor's histological grade (P-value < 0.05). **Conclusion:** The findings of this study highlighted AMACR's potential as a diagnostic biomarker for aggressive prostate cancer.

INTRODUCTION

Prostate cancer is a major global health issue, given its high prevalence and the significant role it plays in both illness and death among men. The occurrence of prostate cancer varies greatly across different regions, affected by a combination of genetic, lifestyle influences and environmental. According to the International Agency for Research on Cancer (IARC) in 2020, prostate cancer made up 7.30% of all new cancer diagnoses worldwide, emphasizing its profound impact [1]. In Pakistan, the prevalence of prostate cancer varies between 2.0% to 8.0%, highlighting regional differences that could affect disease management and outcomes [2]. On a diagnostic level, prostate cancer poses distinct diagnostic challenges [3]. Prostate cancer does not have unique signs and symptoms because most reported symptoms are related to benign prostatic diseases, such as Lower Urinary Tract Symptoms (LUTS). Prostate cancer is often detected and diagnosed using (DRE) digital rectal examination, levels of the Prostate-Specific Antigen (PSA) followed by ultrasound-guided prostate biopsies. Numerous biomarkers specifically for prostate cancer in blood, urine, and tissue have been researched, though they are not frequently used in clinical settings [4, 5]. The Gleason grading system for biopsies is essential for determining the

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prognosis of patients with prostate cancer, and it plays a key role in treatment planning [6]. Alpha-Methylacyl-CoA Racemase (AMACR) is an enzyme important for the metabolism of branched-chain fatty acids and serves as a key biomarker in the diagnosis of prostatic adenocarcinoma [7]. Identifying AMACR expression, along with other diagnostic markers, plays a central role in accurate histopathological assessment, which is vital for making an accurate diagnosis and developing effective treatment plans [8, 9]. AMACR is not completely sensitive. Its presence is not only limited to prostate cancer but can also be detected in some other similar types of tumors, which may create certain restrictions in its applicability. As a result, AMACR must be evaluated as a novel marker of prostatic cancer [10]. Through genome-wide scans of families with familial prostate cancer, it has been revealed that the chromosomal region (5p13) where AMACR is located serves as a susceptibility gene for prostate cancer [8, 11]. Prostate cancer is a complex disease, and accurate diagnosis is crucial for appropriate treatment planning and patient management, this study explores epidemiological trends, diagnostic diagnostics and the influence of histopathological findings on prostate cancer care.

It highlighted the potential for personalized medicine and targeted treatments by linking clinical symptoms with diagnostic pathology, aiming to enhance diagnostic strategies and improve patient outcomes.

METHODS

This Descriptive retrospective cross-sectional study was conducted in the Pathology Department at Liaquat University of Medical and Health Sciences, Jamshoro/Hyderabad from April 2023 to February 2024. Total 71 prostate cancer patients with age range of 45 to 99 years were included, based on a sample size calculation designed to achieve 95% confidence with a 5% margin of error, assuming a 4.8% prevalence rate [3]. Ethical approval for the study was obtained from the Ethical & Review Committee of Liaquat University of Medical Health Sciences (No. LUMHS/REC/-26). Participants who met the inclusion criteria were enrolled, and written informed consent was acquired from each participant before their involvement in the study. Data collection was carried out using a predefined questionnaire. Inclusion criteria for the study was patients with age range of > 45 years, having ability to understand the questions and willing to participate, encompassed formalin-fixed paraffin-embedded tissue blocks with sufficient material and confirmed diagnoses of prostate adenocarcinoma. Specimens required good histological orientation, identifiable gland formation, and no basal cell layer. Exclusion criteria were inadequate tissue, extensive necrosis, poor fixation, and unwilling participants. Patient identifiers, including name, age, and registration number on the questionnaire and pathology receipt, were cross-verified with the biopsy form and container coding.The biopsy forms were reviewed to gather patient history, clinical findings, radiological findings, intraoperative findings, and relevant investigations. The provisional diagnosis provided by the consultant surgeon was also recorded. Specimens were initially fixed in 10% formalin, processed, and embedded in paraffin. Sections were cut at 3 µm thickness and stained with Hematoxylin and Eosin (HandE) for diagnostic assessment. In this study Dako Flex Detection System has been used for the detection of AMACR Receptor. All of these cases were performed with a negative and positive control on the sample size of 71 cases. Kidney was taken as the positive control for AMACR. The process included sectioning, dewaxing, antigen retrieval, and staining with primary and secondary antibodies. DAB chromogen was used for visualization, followed by counterstaining with Hematoxylin. The expression of AMACR was interpreted by nuclear staining in neoplastic cells. This was further scored for intensity and proportion. This interpretation was done by two pathologists at different times to ensure uniformity in results and to remove any bias. The pathologist examined the prostate to determine the configuration of cancer cells there, and then assigned a grade on a scale from three to five, based on two separate sites. On the other hand, in order to regulate a patient's Gleason score, invasive tissue samples were required.

Gleason Score	Grade Group	Characteristics
6	Grade Group 1	• Less aggressive • Very slow growing • Low risk
3 + 4 = 7	Grade Group 2	• Slightly aggressive • Slow growing • Low to Intermediate risk
4 + 3 = 7	Grade Group 3	• Moderately aggressive • Fast growing • Intermediate to High risk
8	Grade Group 4	• Aggressive • Rapidly growing • High risk
9-10	Grade Group 5	• Highly aggressive • Rapidly growing • High risk

Figure 1: Gleason scores 6 – 10 alongside their common characteristics for prostate cancer risk [12].

Data analysis was performed using SPSS version 22.0, assessing frequencies, percentages, and associations between AMACR expression and tumor characteristics using the chi-square test, with significance set at $p<0.05$.

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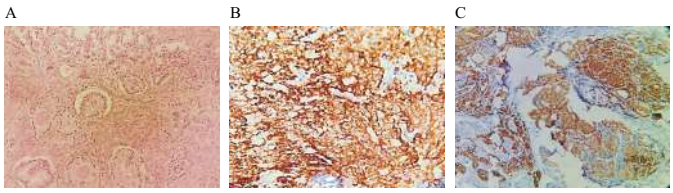

Figure 2: Histopathological and Immunohistochemical Expression of Alpha-Methylacyl CoA Racemase in Prostatic Tissue (A) Normal histological architecture under H&E stain; (B) Diffuse strong positive AMACR expression; (C) Diffuse moderate positive AMACR expression

Figure 2 (A) showed a Hematoxylin and Eosin (HandE) stained section having normal histological architecture. (B) Shows a strong positive expression of Alpha-Methylacyl-CoA Racemase (AMACR), supported by strong staining highlighting the presence of the enzyme in locations thought to be malignant transformation targets. (C) Shows a diffuse moderate positive expression of AMACR, indicating a more distributed but significant presence of this important biomarker over the tissue sample, thereby reflecting different degrees of neoplastic activity. Differentiation relates to how abnormal cancer cells look under a microscope: Well-differentiated adenocarcinoma: Low-grade cancer that tends to grow and spread slowly. Moderately differentiated adenocarcinoma: Intermediate-grade cancer that grows faster than well-differentiated cells. Poorly differentiated adenocarcinoma: High-grade cancer that spreads faster than moderately differentiated cells.

RESULTS

Total 71 patients with prostate cancer were enrolled in the study, with an average age of 66.65 ± 10.34 years, with a minimum age of 45 years and a maximum age of 99 years (Table 1).

Table 1: Descriptive Statistics of Age of Patients (n=71)

Descriptive Statistics	Age (Years)/Mean ± SD
Mean	66.65 ± 10.34
Median	68.0 Years
Minimum	45 Years
Maximum	99 Years

Based on the clinical manifestations (Figure 3), it was observed that Nocturia and dribbling were present in 6.2% of the cases. Weight loss was evident in 54.9%, blood in the urine was reported in 9.4% of the patients, dysuria was experienced by 13.8% of the cases and kidney pain was noted in 15.5% of the cases.

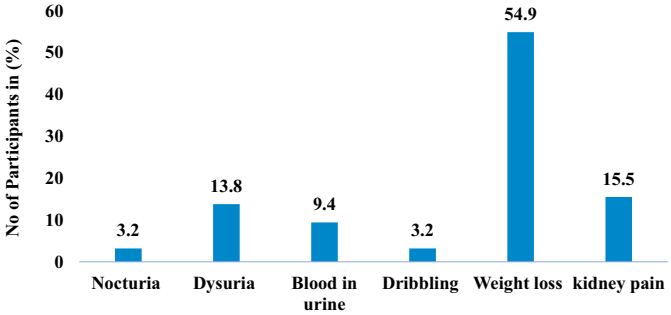

Figure 3: Clinical Presentations of the Patients

Table-2 illustrates that 8.5% of the cases exhibited a favorable familial medical background of the disease. A comprehensive comprehension of the correlation between family history and the susceptibility to prostate cancer stands as a crucial factor in predicting cancer risk. Three grade groups of prostate carcinoma and subtypes were taken in this study. A small proportion, accounting for 2.8% of the cases, exhibited a well differentiated" grade groups, in contrast, a considerable portion, representing 35.2% of the cases, was classified as Moderately differentiated, however, the majority of cases, encompassing 62%, fell into the Poorly differentiated category. A small portion, constituting 2.8% of the cases, were classified as Grade group 1, Grade group 3 accounting for 23.9% of the cases, Grade group 4 encompassing 11.3% of the cases, represents neoplasms of intermediate severity. The majority of cases 62.0% were classified as Grade group 5, indicative of the most severe and highly malignant prostatic neoplasms.

Table 2: Frequencies of Family History of Cancer, Histological Grades, and Grading Groups of Prostatic Neoplasm (n=71)

Variables	Frequency (%)
Family History of Cancer	
Positive	6 (8.50%)
Negative	65 (91.50%)
Histological Grade Groups	
Well Differentiated	2 (2.80%)
Moderately Differentiated	25 (35.20%)
Poorly Differentiated	44 (62.0%)
Grading Groups of Prostatic Neoplasm	
Grade 1	2 (2.80%)
Grade 3	17 (23.90%)
Grade 4	8 (11.30%)
Grade 5	44 (62.0%)

The results of the analysis of AMACR expression in a sample of 71 cases offer a comprehensive overview of the distribution and occurrence of this biomarker within the samples. In the cases under examination, 57.7% displayed a Diffuse Strong Positive expression, while only 2.8% were categorized as Diffuse Weak Positive. A noteworthy 33.8% of the cases showed a diffuse moderate positive expression that was both widespread and diffuse.

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Furthermore, 5.6% of the cases exhibited a Focal Weak Positive expression, indicating a relatively lower level of AMACR presence compared to the other categories.

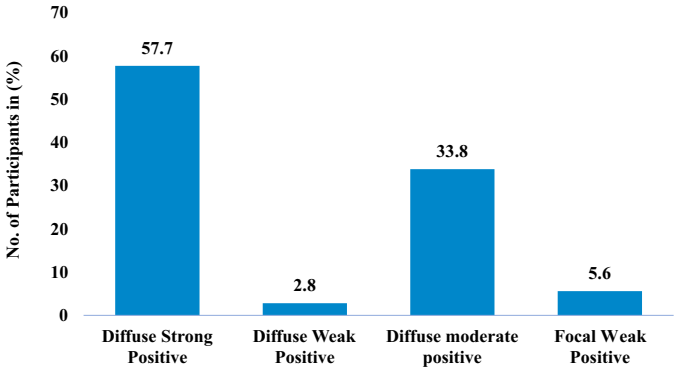

Figure 3: Descriptive Statistics of Expression of AMACR

The table 3 presents data on AMACR Score and Grading of Prostatic adenocarcinoma for a sample of 71 cases. The cases are categorized into three differentiation grades: Moderately differentiated, poorly differentiated, and well differentiated. The table also shows the distribution of cases based on the intensity of AMACR staining, including Diffuse Strong Positive, Diffuse Moderate Positive, Diffuse Weak Positive, and Focal Weak Positive. The "p-value" of 0.0001 suggests a significant association between AMACR staining intensity and prostate cancer grading in the samples.

Table 3: Expression of AMACR according to Tumor Grading

AMACR Score	Grading of Prostatic Adenocarcinoma				
	Moderately differentiated	Poorly differentiated	Well differentiated	Total	p-Value
Diffuse Strong Positive	22	19	0	41	0.0001
Diffuse Moderate Positive	0	1	1	2	
Diffuse Weak Positive	1	23	0	24	
Focal Weak Positive	2	1	1	4	
Total	25	44	2	71	

Chi-square test applies, x2 test-value 43.095

Table 4 shows the distribution of cases across Gleason grade groups and AMACR Score categories. In Gleason grade group 1, there are no cases with Diffuse Strong Positive, 1 case with Diffuse Moderate Positive, none with Diffuse Weak Positive, and 1 case with Focal Weak Positive, totaling 2 cases. The table also details the data for Gleason grade groups 3, 4, and 5. The p-value of 0.0001 indicates a statistically significant association between Gleason grade groups and AMACR Score.

Table 4: Expression of AMACR according to Gleason Score

Gleason Score	AMACR Score					
	Diffuse Strong Positive	Diffuse moderate Positive	Diffuse Weak Positive	Focal Weak Positive	Total	p-Value
1	0	1	0	1		0.0001
3	15	0	1	1		
4	7	0	0	1		
5	19	1	23	1		
Total	41	2	24	4		

DISCUSSION

Prostate cancer is the most common cancer in men, especially those aged 70 and older [13]. Limited research has explored the link between hereditary and advanced-stage prostate cancer [14]. One study found a connection between prostate cancer and family history, regardless of environmental factors. However, a 2004 study by Sree Kumar A in India reported a younger median age of 59.8 years for prostate cancer [15]. Other studies observed average patient ages of 77.4 years, 71 years, and an age range of 55 to 83 years [16]. A study by Tindall E and colleagues found that common symptoms of prostate cancer include urinary retention, erectile dysfunction, frequent urination, insomnia, and weight loss. Dysuria (7.8%), difficulty urinating (72.3%), and poor urine flow (1.4%) were the most reported complaints [17]. Another study reported urinary retention, impotence, frequent urination, nocturia, and weight loss in various proportions among 217 patients [18]. In a national study by Khan SA *et al.*, dysuria was the most common symptom, with other patients reporting difficulty urinating, erectile dysfunction, groin pain, and blood in the urine. Symptom variations may be due to environmental and geographical factors [19].Tumor grade indicates differentiation level. Most cases were poorly differentiated grade 3 (62%), followed by moderately differentiated grade 2 (35.2%), and well-differentiated grade 1 (2.8%). A previous study found 3.8% of prostatic adenocarcinomas were well differentiated, 52.5% were moderately differentiated, and 43.8% were poorly differentiated [20].AMACR staining

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showed diffuse strong positivity in 57.7% of cases, moderate positivity in 33.8%, weak positivity in 2.8%, and focal positivity in 5.6%. These results are consistent with Vahini Gudeli's study, which found 81% diffuse positivity and 19% focal positivity. Magi-Galluzzi C *et al.*, reported 88% AMACR positivity in 209 prostate biopsy cases, and Hassan Tariq's study found 85% positivity among 80 cases [21, 22]. Overall, 91.2% of cases showed positive AMACR expression, with 8.8% negative. AMACR immunohistochemistry results were positive in 85% of cases, similar to international studies showing 82% and 92% positivity, but higher than the 70.6% found in a Japanese study [23]. In the Pakistani subgroup, results aligned with international findings. The study also examined the impact of Gleason scores on AMACR expression, with positive expression observed in Gleason scores of 3, 4, and 5. Kumar *et al.*, reported no AMACR expression in Gleason score 4, with sensitivity increasing to 94.7% and 100% for scores 8 and 9, respectively. Most cases presented with high-grade cancers [11].

CONCLUSIONS

AMACR was found to be effective in diagnosing prostate cancer, particularly in small foci. Its expression is closely linked to tumor grade and Gleason score, showing diffuse positivity in aggressive lesions.This association aids in disease stratification and prognosis, leading to improved outcomes with timely treatment. The study's eleven-month duration limited its scope, preventing patient follow-up. Additionally, environmental and risk factors associated with prostate adenocarcinoma were not assessed, and the relationship between AMACR expression and mortality or morbidity could not be evaluated.

Authors Contribution

Conceptualization: HA, IUU, MS
Methodology: IUU, MS
Formal analysis: SK, HS, MM, MS
Writing, review and editing: HA, IUU, SK, HS, MM, MS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Prevalence and Risk Factors of Congenital Heart Disease in Patients Admitted in NICU: A Study from Tertiary Care Hospital in Karachi

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ABSTRACT

Congenital heart disease (CHD) is the most common cause of neonatal morbidity and mortality. The earlier the diagnosis and management, the better the outcome. Several maternal factors predispose to the development of congenital heart disease, including gestational diabetes, pregnancy-induced hypertension, and TORCH infections. **Objectives:** To determine the frequency and factors associated with CHD in neonates admitted to the Neonatal Intensive Care Unit (NICU) at a tertiary care hospital in Karachi. **Methods:** A cross-sectional study was conducted from 20 Nov 2024 to Feb 20, 2025, at Ziauddin University Hospital Karachi. Non-probability consecutive sampling included neonates (0-28 days) with confirmed CHD, recurrent respiratory symptoms with a cardiac murmur, or asymptomatic neonates with a cardiac murmur detected on examination. Data were collected regarding maternal risk factors, clinical features, laboratory findings, and neonatal outcomes. **Results:** A total of 162 neonates were included in the study. The mean maternal age was 30.5 ± 7.7 years. The most common maternal conditions included gestational diabetes (30%) and pregnancy-induced hypertension (37%). Clinical features included tachypnea in 44%, tachycardia in 52%, poor feeding in 48%, and cyanosis in 46%. Common defects were revealed on echocardiography, such as patent ductus arteriosus (23%) and atrial septal defects (19%).The average hospital stay was 16 ± 8.1 days, and the neonatal mortality rate was high. No associations between mortality and maternal factors were established. **Conclusions:** It was concluded that this study emphasizes a high prevalence of CHD in neonates and its association with maternal risk factors such as gestational diabetes, pregnancy-induced hypertension, and TORCH infections.

INTRODUCTION

Congenital heart disease (CHD) is one of the most frequent congenital malformations, occurring in approximately 1% of all live births worldwide. Improved survival, thanks to early diagnosis and modern care, has not diminished the significant contribution of CHD to morbidity and mortality in infants [1]. In South Asia, including Pakistan, the prevalence of CHD is high because of delayed diagnosis and lack of access to advanced cardiac facilities [2]. CHD in neonates has numerous predisposing factors that occur during premature deliveries, in which the newborns have been admitted to the NICU. Such factors include maternal complications, pollution, or heredity [3]. Studies regarding CHD in Pakistan from tertiary care hospitals identify the issues in diagnosing and managing CHD, with a particular concern regarding the implementation of echocardiography as the preferred diagnostic technique [4]. It is the leading cause of birth defect-associated morbidity, mortality, and medical expenditures. Of all CHD types, ventricular septal defect (VSD) and atrial septal defect (ASD) accounted for 51% of cases with an increasing trend over time [5]. More to this, Atrial septal defects (ASD) and patent ductus arteriosus (PDA) are some of the congenital heart diseases prevalent among neonates admitted to the NICU. The risk factors for CHD are maternal diabetes, hypertension, prior miscarriage, and prenatal infections like TORCH – toxoplasmosis, rubella, cytomegalovirus and herpes simplex [6]. Other factors that increase the risk include exposure to teratogens in the environment, history of CHD in the family [7]. Delayed or missed prenatal detection of critical congenital heart

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defects (CCHD) is linked with much higher neonatal mortality. One cohort study showed a case fatality rate of 64.7% in neonates with CCHD, the most common cause of death being cardiogenic shock. Another study from Beijing indicated that 30% of infants with CCHD died during the first month following birth without receiving treatment. These results highlight the utmost importance of early detection and intervention in enhancing infants with CCHD survival results [8]. Development of technology in prenatal diagnostics and NICU has improved the survival rate of the neonates, especially those born with early morbidities [9]. For example, left-sided duct-dependent lesions have a one-year survival of about 88% while overall neonatal mortality has reduced due to early surgical intervention and enhanced diagnostic techniques [10]. We hypothesize that maternal risk factors, including gestational diabetes, pregnancy-induced hypertension, and TORCH infections, play a significant role in the incidence of congenital heart disease (CHD) in neonates admitted to the NICU.

This study aimed to determine the frequency and factors associated with CHD in patients admitted to the NICU at a tertiary care teaching hospital in Karachi. The findings will be of use to improve early detection and intervention of this population.

METHODS

This was a cross-sectional study from the Department of Pediatrics, Ziauddin University Hospital, Karachi, from 20 Nov 2024 to Feb 20, 2025, after approval from the Ethical Review Committee (ERC) of the Ziauddin University Hospital (Reference Code: 9150824FZPED). A non-probability consecutive sampling technique was used. The sample size was calculated using OpenEpi software, considering a 95% confidence interval and an anticipated prevalence of CHD based on previous studies. a recent large-scale analysis conducted by Liu et al., which reported a CHD prevalence of 1.84% in neonates, serving as a prevalence benchmark in similar clinical settings [11]. Neonates, both male and female, aged between 0-28 days, were included, categorized into three subgroups, namely, established CHD, neonates with repeated respiratory symptoms and a heart murmur, or asymptomatic neonates with a heart murmur as found on examination. Only newborns born in the same hospital and who remained till discharge were considered. The exclusion criteria included stillbirths, cases of anemia or acquired heart diseases, and neonates with respiratory diseases. Informed consent was obtained from the mothers or guardians of all neonates participating in the study. All neonates admitted to the Neonatal Intensive Care Unit (NICU) with recurrent respiratory symptoms and a cardiac murmur, or identified as asymptomatic with a cardiac murmur on examination, in addition to those with maternal risk factors for CHD, were considered for the study population. Careful documentation of pertinent clinical history and demographic information like age, birth weight, gestational age, gender, pre- and post-ductal oxygen saturation, and length of hospitalization was carried out. For confirmation of diagnosis, all neonates were subjected to a 2D transthoracic echocardiogram by a pediatric cardiologist on the GE Vivid S60 ultrasound machine, which had a neonatal transducer. Echocardiography, the gold standard for the diagnosis of congenital heart disease (CHD), was done at the bedside in every case of suspected CHD. Concomitantly, chest X-rays were taken on the Siemens Mobilett Elara Max portable X-ray unit with routine neonatal exposure parameters to rule out non-cardiac etiologies. Furthermore, appropriate biochemical investigations such as serum lactate, arterial blood gases (ABG), and C-reactive protein (CRP) were done according to standard hospital laboratory procedures to assist in differential diagnosis. All results, including the diagnosed type of congenital heart disease, were documented in a pre-designed proforma for uniformity. All the findings, along with the type of congenital heart diseases, were recorded in a pre-designed proforma. Data were entered and analyzed using IBM SPSS version 27.0. For continuous variables such as age, birth weight, gestational age, maternal age, pre- and post-ductal saturation, and duration of hospital stay, means and standard deviations were calculated. For categorical variables like gender, maternal infection, risk factors, clinical features, laboratory results, neonatal death, and the types of congenital heart disease, frequency and percentages were calculated. Post-stratification chi-square tests were conducted to control for potential confounders like gender, gestational age, maternal infection, and neonatal death. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The study also incorporated data from 420+ total neonatal admissions, among which 62 CHD patients were identified and confirmed using echocardiography. The other 100 CHD diagnoses were based on clinical examination, backed by suggestive signs, symptoms, and preliminary investigations, especially in instances where echocardiography was not readily accessible or practicable. Additionally, complex heart diseases were observed in neonates with other disorders. The mean day of life at admission was 14.1 ± 7.9 days, with a mean birth weight of 2.7 ± 0.7 kg and an average gestational age of 35.08 ± 4.1 weeks. Gender distribution revealed 52% male (n=84) and 48% female (n=78) (Table 1).

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Table 1: Demographic Characteristics of participants

Demographic Characteristics	Values
Mean Day of Life at Admission	14.1 ± 7.9 Days
Average Birth Weight	2.7 ± 0.7 kg
Mean Gestational Age	35.08 ± 4.1 Weeks
Male (%)	84 (52%)
Female (%)	78 (48%)

The main maternal illness was gestational diabetes at 49 (30%), pregnancy-induced hypertension represented 60 (37%), and 63 (39%), said they never experienced any maternal illness. A majority of the mothers, at 77 (48%), n=77, had at least one history of miscarriage; 55 (34%) had TORCH infections. Family history of cardiac disease was recorded in 74 (46%), and a history of unexplained sibling deaths was recorded in 69 (43%). A significant maternal risk factor included a mean maternal age of 30.5 ± 7.7 years (Table 2).

Table 2: Maternal Risk Factors

Maternal Risk Factors	Values
Mean Maternal Age	30.5 ± 7.7 Years
Gestational Diabetes	49 (30%)
Pregnancy-Induced Hypertension	60 (37%)
No Maternal Illness Reported	63 (39%)
History of Miscarriage	77 (48%)
TORCH Infections	55 (34%)
Family History of Cardiac Disease	74 (46%)
History of Unexplained Sibling Deaths	69 (43%)

Clinical features as seen in neonates included tachypnea in 71 (44%) and tachycardia in 84 (52%). Poor feeding was observed in 78 (48%), cyanosis in 74 (21%), and dysmorphic features in 79 (24%). Mean pre-ductal saturation was 92.73% ± 4.5, and post-ductal saturation was 92.4% ± 4.6 (Table 3).

Table 3: Clinical Features

Clinical Features	Values
Tachypnea	71 (44%)
Tachycardia	84 (52%)
Poor Feeding	78 (48%)
Cyanosis	74 (21%)
Dysmorphic Features	79 (24%)
Pre-Ductal Saturation	92.73 ± 4.5
Post-Ductal Saturation	92.4% ± 4.6

Laboratory investigations revealed that 86 (53%) of neonates had abnormal arterial blood gases (ABGs), and cardiomegaly was observed on chest X-rays in 89 (55%) (Table 4).

Table 4: Laboratory Findings

Laboratory Findings	Values
ABG Abnormalities	86 (53%)
Cardiomegaly on Chest X-ray	89 (55%)
Abnormal ECG	95 (59%)

Abnormal electrocardiograms (ECGs) were found in 95 (59%). The echocardiographic findings of the study in shown as follows: 30 (19%) presented with ASD, 26 (16%) had TOF, 38 (23%) presented with PDA, and 25 (15%) had VSD. Other echocardiographic findings revealed normal echocardiographic findings in 27 (17%). Other Disorders (Complex CHD) 16 (10%) (Table 5).

Table 5: Echocardiographic Findings

Echocardiographic Findings	Values
Atrial Septal Defect (ASD)	30 (19%)
Tetralogy of Fallot (TOF)	26 (16%)
Patent Ductus Arteriosus (PDA)	38 (23%)
Ventricular Septal Defect (VSD)	25 (15%)
Normal Findings	27 (17%)
Other Complex Disorders (DORV, TGA, HLHS, etc)	16 (10%)

As for the outcomes, the mean stay in the hospital was 16 ± 8.1 days, and neonatal mortality was reported in 14 (8%) (95% CI: 4.32–12.97%) of the cases (Table 6).

Table 6: Outcomes

Outcomes	Values
Mean Hospital Stay	16 ± 8.1 Days
Neonatal Mortality	14 (8%)

Stratification analysis did not identify significant correlations between mortality and gender (p=0.335, OR=1.12, 95% CI: 0.75–1.65), gestational age (p=0.528, OR=0.89, 95% CI: 0.55–1.42), maternal age (p=0.23, OR=1.05, 95% CI: 0.78–1.41), or maternal illness (p=0.954, OR=1.02, 95% CI: 0.68–1.53).

Table 7: Stratification Analysis

Factors Influencing Mortality	p-value
Gender	0.335
Gestational Age	0.528
Maternal Age	0.23
Maternal Illness	0.954

These results suggest that although maternal conditions may play a role in the development of CHD, they do not have a significant impact on neonatal mortality in our cohort.

DISCUSSION

This study established a CHD prevalence rate in keeping with other findings from Pakistani and South Asian tertiary care centers. Indian and Bangladesh studies shows comparable distributions of CHD subtypes, with ventricular septal defect (VSD) and patent ductus arteriosus (PDA) as the most frequent anomalies, which is consistent with our results [12]. In addition, maternal risk factors such as gestational diabetes and pregnancy-induced hypertension were found at a similar frequency in Indian and Iranian studies. The findings of the current study are in concordance with global and regional emerging trends in congenital heart disease among neonates. Key risk factors and clinical features have been noted.

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Worldwide, studies from Europe and the United States indicate a slightly lower incidence of CHD in NICU admissions, probably because of improved prenatal screening programs and early interventions. The neonatal mortality rate in our study (8%) falls within the range of South Asian studies but is higher than in developed nations, where early surgical interventions enhance survival rates [13]. A mean gestational age of 35.08 weeks and a birth weight of 2.7 kg were found in the present cohort, similar to the studies that link CHD with preterm birth and low birth weight.These factors have been established as common risk determinants for CHD, supporting the idea that neonates born prematurely or with lower birth weights are at an elevated risk for cardiac anomalies [14]. Moreover, our study confirms earlier reports of male predominance, with 52% of neonates being male. This slight male prevalence in CHD cases reflects an international pattern, but the reasons behind the higher rates in male newborns are largely unknown [15]. Maternal conditions also contribute significantly to the causes of neonatal CHD. In this study, for example, the mothers of children with CHD had gestational diabetes and pregnancy-induced hypertension, respectively, at a rate of 30% and 37%. This is consistent with previous research showing that these maternal diseases are risk factors for neonatal congenital anomalies [16]. Higher prevalence of TORCH infections has also been realized in this present study at a rate of 34%. Overall, maternal infection is, therefore, crucial in the mechanism of the disease. Prenatal screening and the management of maternal health conditions, including infections, are important for preventing CHD and improving neonatal outcomes [17]. The clinical features of the neonates, such as tachypnea (44%), tachycardia (52%), cyanosis (21%), and poor feeding (48%), are characteristic indicators of CHD. These symptoms, though highly indicative of heart problems, also highlight the difficulty in early diagnosis, especially in resource-poor setups where access to specialized medical care is limited [18]. The fact that 24% of the neonates presented with dysmorphic features further complicates the diagnosis, implying that early detection of CHD might be delayed due to the overlapping nature of these symptoms with other conditions. These findings highlight the need for increased vigilance and early clinical assessment in neonates presenting with these signs, particularly in low-resource settings [19]. The spectrum of congenital heart disease identified in this study through echocardiography is representative of common findings worldwide. Atrial septal defects (ASD) were observed in 19% of cases, while patent ductus arteriosus (PDA) was present in 23%, reinforcing the global trend where PDA is one of the most frequent congenital cardiac anomalies [20]. A marked finding is that 27% of neonates had normal echocardiograms, indicating some newborns who are first suspected to have CHD turn out not to have any abnormality in their heart, a fact that only calls for effective diagnostic methods coupled with follow-ups [21]. This requires the broad implementation of diagnostic approaches toward the proper identification and prevention of wrongful diagnosis. The mortality rate of 8% in this study indicates the serious impact of CHD on neonatal health. Interestingly, no significant associations were found between mortality and gender, gestational age, or maternal health, suggesting that the severity of the cardiac defect and the timeliness of intervention may be more influential factors in determining outcomes. This is in line with current literature, which emphasizes that early detection and timely intervention are crucial in improving survival rates and preventing long-term complications in neonates with CHD [22]. Neonates requiring intensive NICU care, along with specialized interventions, have better prognoses, reinforcing the importance of early identification and management in line with global guidelines [23]. In conclusion, the findings of this study emphasize the importance of early detection, proper management, and the need for improved diagnostic and therapeutic approaches to congenital heart disease in neonates. Considering the complexity and variability of CHD, future research should focus on enhancing diagnostic strategies, optimizing prenatal care, and addressing maternal health factors to reduce neonatal mortality associated with CHD. By focusing on these areas, healthcare systems would be able to improve the outcomes for neonates with CHD diagnoses and reduce this burden.

CONCLUSIONS

It was concluded that the present study showed a high incidence of congenital heart disease in neonates admitted to the NICU in Karachi, with a significant correlation between CHD and maternal risk factors in the form of gestational diabetes, pregnancy-induced hypertension, and TORCH infections.Tachypnea, tachycardia, and cyanosis were clinical features seen in affected neonates. The mortality rate in the neonates was 8% and was not correlated with gender, gestational age, or maternal health. But the severity of the defect and the timing of intervention were major determinants of outcomes.

Authors Contribution

Conceptualization: FZ[1]
Methodology: FZ[2]
Formal analysis: MI, LK
Writing review and editing: MI, AK, SL
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Analyzing Risk Factors Associated with Post Myocardial Infarction Complications: A Retrospective Analysis

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ABSTRACT

Myocardial infarction is a major cause of mortality and results in several complications including post-MI arrhythmias, pulmonary edema, and cardiogenic shock. **Objective:** To evaluate and examine the clinical and demographic factors and their association with post-MI complications. **Methods:** This was a retrospective observational study and non-probability convenient sampling was recruited for assessment. A total of 188 patients aged 45 to 65 years, hospitalized for acute STEMI and of both genders were included. However, patients with NSTEMI or with comorbidities such as chronic renal failure or cirrhosis were not included. Age, gender, BMI, duration of hospitalization, etc. were recorded on a structured form. Patients were assessed for post-MI arrhythmias, cardiogenic shock, and pulmonary edema. This study took six months its completion. Spss software was employed for analysis and a chi-square test was used to identify associated risk factors with post-MI complications at a significant level ($p<0.05$). **Results:** Findings revealed that the occurrence of post-MI arrhythmias showed a significant association with smoking and family history ($p<0.001$), while no significant association was observed for BMI, hospital duration, hypertension, or family history. Cardiogenic Shock (CS) is strongly associated with DM ($p=0.001$) but shows no association with smoking, BMI, duration of hospital stays, hypertension, or family history. **Conclusions:** Smoking and a family history of cardiovascular disease are prevalent and found significant association with post-MI arrhythmias ($p<0.001$) after myocardial infarction; diabetes mellitus also resulted in significant association with pulmonary edema and cardiogenic shock ($p<0.001$).

INTRODUCTION

Cardiovascular diseases, especially atherosclerosis, are considered to be major public health issues locally and globally and have higher mortality rates [1]. Severe heart attacks (STEMI) are among the most common reasons for hospital stays particularly in the emergency department [2]. A blockage of coronary blood vessels that causes sudden onset of chest pain and discomfort which probably radiates to the jaw, abdomen, and left arm is defined as ischemic discomfort that leads to myocardial infarction [3]. The investigation of participants suffering from chest or sternal pain is based on the assessment of clinical signs or symptoms i.e. pain >30 minutes, or physical and biochemical examination including unambiguous new electrocardiographic alterations; or an increase of creatinine kinase level (CK-MB isoenzyme), indicating damage to the heart muscle [4]. It is the irreversible necrosis of heart muscle secondary to prolonged ischemia which is considered, part of a spectrum referred to as Acute Coronary Syndromes (ACS), which includes Unstable Angina, STEMI, and non-ST-elevation MI (NSTEMI) [5]. Patients with ischemic discomfort may or may not have ST-segment elevation. Most of those with ST-segment

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elevation will develop Q wave deviation [6]. When a blocked heart artery causes reduced blood flow to cardiac muscle causes muscle death and these cases range from 44 to 142 per 100,000 people across European countries [7]. Despite improvements in pharmacological medicine, catheter-based interventions, and surgical reperfusion for improving Acute Myocardial Infarction (AMI) outcomes, patients with large infarcts, necrotized cardiac muscle, or delayed revascularization remain at risk of mechanical complication [8]. Mechanical complications of AMI include ventricular wall and septal rupture, papillary muscle rupture, pseudoaneurysm, true aneurysm, interventricular septum rupture, and mitral valve dysfunction or regurgitation remains the most critical which although rare, can occur in less than 0.1% of patients often presenting with severe symptoms like cardiogenic shock or acute pulmonary edema within the first week following a heart attack [9, 10]. In patients with STEMI, either systolic dysfunction alone or both systolic and diastolic dysfunction can occur. Clinical manifestations of left ventricular failure become more common as the extent of the injury to the left ventricle increases and are considered one of the most vital predictors of mortality [11]. Risk factors of STEMI include age, sex, family history, smoking, high cholesterol, diabetes, hypertension, obesity, inactivity, poor diet, and stress, which contribute significantly towards increasing susceptibility towards developing severe forms like STEMI [12]. STEMI patients are greatly prone to developing in-hospital complications which significantly influence prognosis and compromise survival, necessitating prompt management in-hospital complications include cardiogenic shock, True and Pseudoaneurysms, Free Wall Rupture, Atrial Tachyarrhythmias, ventricular tachyarrhythmias, and Bradyarrhythmias [13]. Understanding the frequency and patterns of these complications is essential for early identification, risk stratification, and timely intervention.

Therefore, this study aimed to evaluate the frequency of in-hospital complications in STEMI patients, and their associated risk factors that provide insights to enhance clinical decision-making, improve patient outcomes, and reduce hospital mortality.

METHODS

This retrospective study was conducted at DHQ Hospital Nowshera from 1st March 2020 - 31st August 2020.Ethical approval was obtained from the institutional ethical committee and.once approved, eligible patients presenting to the emergency department for thrombolytic therapy were enrolled after informed consent.Based on the previous studies, the estimated prevalence was 85.8% (14-16). A sample size of 188 patients was included in the study, determined by using the WHO sample size calculator.The calculation was based on a 95% confidence interval (CI), 5% margin of error (d), population (50%) and estimated prevalence (p) of 85.8%.

The sample size was calculated using the formula(17):

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

A non-probability consecutive sampling technique was used. Patients aged 45 to 65 years, hospitalized for acute STEMI, and of both genders were included. While those diagnosed with NSTEMI or with comorbidities such as chronic renal failure or cirrhosis were excluded. All patients who received anti-ischemic therapy underwent thrombolysis. Data on demographics BMI, diabetes, hypertension, smoking history, family history, hospital stay, and in-hospital complications including post-MI arrhythmias, pulmonary edema, and cardiogenic shock were recorded for a week. Assessment of complications was based only on clinical signs. Palpitations, irregular heartbeat, and fainting were assessed for post-MI arrhythmias [18].Cardiogenic shock was assessed based on low urine output, persistent hypotension (systolic BP<90mmHg), new chest pain, a cold and wet physiological state, dyspnea, jugular venous distension, rales and altered mental status and pulmonary edema was identified by of lung crackles, coarse rales, and acute dyspnea [19, 20]. Analysis was conducted on SPSS 25.0. Mean and standard deviation were obtained for quantitative variables while frequency and percentages were calculated for categorical variables such as gender and in-hospital complications. The chi-square test was applied in the P value < 0.05 was considered significant.

RESULTS

This study shows that the age groups of the participants comprised those between 45 and 55 years (56.4%) and aged between 56 and 65 years (43.6%). Out of the 188 sample hospitals, just over half (64.4%) were male. 43.6% of people have body mass indexes between 20 and 24. In addition, being 33,0% hospitalized for 6-8 days and 67,0% for 2-5 days.58,5% had raised blood glucose levels; out of those, 41.5% had been diagnosed with diabetes while 33.0% were hospitalized for 6 to 8 days. The last 10.6% had a family history of myocardial infarction, whereas 89.4% had no such history as shown in Table 1.

Table 1: Baseline Characteristics

Variables	Category	Frequency (%)
Age	45-55 Years	106 (56.4%)
	56-65 Years	82 (43.6%)
Gender	Male	121 (64.4%)
	Female	67 (35.6%)
BMI	20-24	82 (43.6%)
	24-28	86 (45.7%)
	28-32	20 (10.6%)
Hospital Stays	2-5 Days	126 (67.0%)
	6-8 Days	62 (33.0%)

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Hypertension	Yes	104 (55.3%)
	No	84 (44.7%)
Diabetes Mellitus	Yes	78 (41.5%)
	No	110 (58.5%)
Smoking History	Yes	99 (52.7%)
	No	89 (47.3%)
Family History of MI	Yes	20 (10.6%)
	No	168 (89.4%)

N=188, BMI=Body Mass Index, MI= Myocardial Infarction

Table 2 demonstrated complication frequency among patients with STEMI. Arrhythmias after myocardial infarction occurred in 17.6% of study participants and were absent in 82.4% of subjects. Lung congestion or pulmonary edema was developed in 44.7% of the patients and cardiogenic shock was developed in 48.9% of cases, while 51.1% did not develop this complication.

Table 2: Frequency of Complications in STEMI Patients

Complications of STEMI	Category	Frequency (%)
Post-MI Arrhythmias	Yes	33 (17.6%)
	No	155 (82.4%)
Pulmonary Edema	Yes	84 (44.7%)
	No	104 (55.3%)
Cardiogenic Shock	Yes	92 (48.9%)
	No	96 (51.1%)

N=188

The associations between age and post-MI complications such as arrhythmias, pulmonary edema, and cardiogenic shock were classified into two groups of ages- 45-55 years and 56-65 years in Tables 3. "Post-MI" arrhythmias are seen to be significantly increased as compared to the 9.4% that belongs to 45-55 years' group. The significance difference between the two groups is of p=0.001, indicating a strong relationship with advancing age. Pulmonary edema was observed in 40.6% of patients 45-55 years of age and 50% in ages of patients 56-65 years, yet with a p-value of 0.197, the difference was not statistically significant. On the contrary, the cardiogenic sock was significantly higher in the 56-65 years' group compared with the 45-55 years' group (62.2% vs. 38.7%) with a p-value of 0.001, thus revealing a strong association between adult age and risk of cardiogenic shock. Such findings indicate that post-MI arrhythmias and cardiogenic shock display a significant relation with age, while pulmonary edema does not show a statistically significant association with age.

Table 3: Age-Wise Stratification of STEMI Complications

Complications of STEMI	44-55 Years	44-55 Years	56-65 Years	56-65 Years	p-Value
	Yes Frequency (%)	No Frequency (%)	Yes Frequency (%)	No Frequency (%)	
Post-MI arrythmias	10 (9.4%)	96 (90.6%)	23 (28.0%)	59 (72.0%)	0.001
Pulmonary Edema	43 (40.6%)	63 (59.4%)	41 (50.0%)	41 (50.0%)	0.197
Cardiogenic Shock	41 (38.7%)	65 (61.3%)	51 (62.2%)	31 (37.8%)	0.001

N=188

Table 4 showed gender-wise distribution among the complications of STEMI such as post-MI Arrhythmias, pulmonary edema, and cardiogenic shock along with the statistical significance. Post-MI arrhythmias were more prevalent in males (27.3%) than females (0.0%), with p-value <0.001 thereby indicating a strong association between male gender and occurrence of arrhythmias. Pulmonary edema was significantly more common in female patients (56.7%, p=0.014) than in their male counterparts (38.0%), indicating that exposure to female gender is a strong point in developing pulmonary edema after STEMI. Cardiogenic shock was more common among females (58.2%) than among males (43.8%); however, a p-value of 0.058 could not yield statistical significance and therefore doesn't provide strong evidence for associating gender with cardiogenic shock.

Table 4: Gender-Wise Stratification of STEMI Complications

Complications of STEMI	Male		Female		p-Value
	Yes Frequency (%)	No Frequency (%)	Yes Frequency (%)	No Frequency (%)	
Post-MI Arrhythmias	33 (27.3%)	88 (72.7%)	0 (0.0%)	67 (100%)	<0.001
Pulmonary Edema	46 (38.0%)	75 (62.0%)	38 (56.7%)	29 (43.3%)	0.014
Cardiogenic Shock	53 (43.8%)	68 (56.2%)	39 (58.2%)	28 (41.8%)	0.058

N=188

The association of the different risk factors to post-MI arrhythmia, pulmonary edema, and cardiogenic shock is illustrated in Table 5. In our findings, BMI categories were not significantly associated with any of the complications of STEMI (p>0.05). Further, Hypertension was also non-significantly associated with prolonged hospitalization for all post-MI complications (p>0.05) in each case. Conversely, a significant association was found between diabetes mellitus and the outcome in both cardiogenic shock (p=0.001) and lung congestion or pulmonary edema (P<0.001), suggesting that patients with diabetes were more prone to those complications but were non-significantly associated with post-MI- arrhythmias (p=0.510). After that, smoking and family history was found significantly associated with post-MI arrhythmias (p<0.001) and pulmonary edema (p<0.001) while not significant concerning cardiogenic shock (p=0.060). But had no significant association with pulmonary

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edema and cardiogenic shock as shown in table 5.

Table 5: Association of Risk Factors with Post MI Complications

Variables	Post-MI Arrhy				PE			CS		
	Categories	Yes Frequency (%)	No Frequency (%)	p-Value	Yes Frequency (%)	No Frequency (%)	p-Value	Yes Frequency (%)	No Frequency (%)	p-Value
BMI	20-24	18 (22.0%)	64 (78.0%)	0.327	32 (39.0)	50 (61.0)	0.327	40 (48.8%)	42 (51.2%)	0.927
	24-28	13 (15.1%)	73 (84.9%)		41 (47.7)	45 (52.3)		43 (50.0%)	43 (50.0%)	
Hospital Stay	2-5 days	20 (15.9%)	106 (84.1%)	0.388	55 (43.7)	71 (56.3)	0.385	64 (50.8%)	62 (49.2%)	0.468
	6-8 days	13 (21.0%)	49 (79.0%)		71 (56.3)	33 (53.2)		28 (45.2%)	34 (54.8%)	
HTN	Yes	21 (20.2%)	83 (79.8%)	0.290	47 (45.2)	57 (54.8)	0.875	48 (46.2%)	56 (53.8%)	0.396
	No	12 (14.3%)	72 (85.7%)		37 (44.0)	47 (56.0)		44 (52.4%)	40 (47.6%)	
DM	Yes	12 (15.4%)	66 (84.6%)	0.510	47 (60.3)	31 (39.7)	<0.001	27 (34.6%)	51 (65.4%)	0.001
	No	`21 (19.1%)	89 (80.9%)		37 (33.6)	73 (66.4)		65 (59.1%)	45 (40.9%)	
Smoking	Yes	33 (33.3%)	66 (66.7%)	<0.001	28 (28.3%)	71 (71.1%)	<0.001	42 (42.4%)	57 (57.6%)	0.060
					56 (62.9%)	33 (37.1%)				
	No	0 (0.0%)	89 (100%)		56 (62.9%)	33 (37.1%)		50 (56.2%)	39 (43.8%)	
Family History	Yes	12 (60.0%)	8 (40.0%)	<0.001	8 (40.0%)	12 (60.0%)	0.656	8 (40.0%)	12 (60.0%)	0.398
	No	21 (12.5%)	147 (87.5%)		76 (45.2%)	92 (54.8%)		84 (50.0%)	84 (50.0%)	

N=188: MI: myocardial infarction, Arrh: arrhythmias. PE: pulmonary edema. CS: cardiogenic shock

DISCUSSION

In the present study, the individuals were noted to be aged from 45 to 55 years (56.4%) and 56 to 65 years (43.6%) and were predominantly male (64.4%); this was compatible with previous findings that suggested a higher prevalence of STEMI among male, as Marinsek *et al.*, in 2023 reported that 69.4% of STEMI patients were male and diabetes was observed to be the leading cause of in-hospital mortality as opposed to other causes and it also found that complications including hemorrhage and left main coronary artery disease increased the mortality risk in women and pulmonary edema was substantially more common in females (56.7% vs. 38.0%, p = 0.014) [21]. Comparatively, our analysis identified that post-MI arrhythmias (28.0% vs. 9.4%, p = 0.001) and cardiogenic shock (62.2% vs. 38.7%, p = 0.001) were more prevalent in the 56–65 years of individual, which were consistent with other research showing that complication risks increase with age.Nonetheless, the current study found a somewhat smaller percentage of men and also showed diabetes to be a risk factor for STEMI consequences, such as arrhythmias and heart failure. Further current study also reported that 41.5% of the respondents were diabetic. In addition, the current study's BMI distribution revealed that 45.7% of individuals had a BMI between 24 and 28 (Kg/m2). However, prior research, such as Bono *et al.*, in 2021 had not consistently made BMI a significant predictor of problems. Of those admitted to the hospital, 33.0% remained for 6–8 days, and 67.0% stayed for 2–5 days and had shown that the majority of STEMI problems occur within the first 48 hours of hospitalization, which was consistent with our findings that complications were prevalent early on [22]. Ullah *et al.*, in 2022 Identified MR and Killip class ≥ 2 as powerful predictors of death in patients with STEMI, which did not align with our findings, as it did not use the TIMI score for classifying MI patients [23].Additionally, current results showed that 55.3% of the participants had hypertension while 44.7% were non-hypertensive that were consistent with the findings of the past study done by Mavungu Mbuku *et al.*, in (2023), which reported that hypertension and smoking were the most important predictor of acute heart failure in STEMI patients with a risk of adjustment of 3.38 and 3.52 [24].However, our research showed that hypertension was non-significantly associated with STEMI consequences.Moreover, the current study observed that 52.7% of the participants had a smoking history and also established a significant association between smoking and post-MI arrhythmias and pulmonary edema (p < 0.001). Nevertheless, in contrast to past research studies, there was no considerable link between smoking and cardiogenic shock (p>0.05). Current research findings also observed the prevalence of post-MI complications that included, arrhythmias in 17.6% of individuals, pulmonary edema (44.7%), and cardiogenic shock (48.9%). Our study revealed the statistical association between male gender and post-MI arrhythmias (27.3% vs. 0%, p < 0.001).According to the findings of the present study, early monitoring would help prevent the deleterious effects of STEMI, especially in older people, smokers, and those with diabetes.While most results corroborated previous studies, some interesting dissimilarities include the lack of a significant association between smoking and cardiogenic shock, the absence of an effect in terms of BMI, and gender-related patterns in pulmonary edema and arrhythmias. Further studies should look more closely at these variations to enhance the targeted STEMI management strategies.

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CONCLUSIONS

The current study highlighted that post-MI complications were significantly associated with certain clinical and demographic factors. Such as smoking and a family history of cardiovascular diseases appeared to be strong indicators of post-MI arrhythmias ($p<0.001$). On the other hand, diabetes mellitus was considered a key predictor and had a significant association ($p<0.001$) with pulmonary edema and cardiogenic shock.These findings emphasized the importance of targeted risk stratification in acute STEMI patients to identify individuals at higher risk for adverse outcomes. The present study has several limitations as it was a cross-sectional study and it did not analyze pre-hospital delays and their impact on post-MI-complication. It only found the duration of the hospitalization. Our research solely focused on clinical signs to find post-MI complications, and not perform echocardiographic parameters and chest X-rays. Further, it only focused on specific in-hospital complications rather than other complications such as kidney failure, and reperfusion success was also not recorded. The use of a consecutive sampling technique in this study could induce selection bias therefore limiting generalizability.

Authors Contribution

Conceptualization: ME
Methodology: ME, TM, SK, SZ, AA
Formal analysis: ME, TM, SK, MSK, AA
Writing, review and editing: ME, TM, SK, MSK, SZ, AA
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Coexisting Meningitis in Neonates Admitted with Late-Onset Sepsis in Nursery, MTI DHQ Hospital, Dera Ismail Khan

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ABSTRACT

Neonatal Late-Onset Sepsis (LOS) is a serious condition that can lead to co-existing meningitis, increasing the risk of long-term complications and mortality. Early diagnosis remains challenging due to non-specific clinical symptoms and limitations in performing Lumbar Punctures (LPs). **Objective:** To determine the frequency of co-existing meningitis in neonates with LOS and identify clinical and laboratory markers associated with it. **Methods:** Neonates aged ≥72 hours with signs of LOS were included. Demographic data, clinical symptoms, and laboratory parameters were recorded. A comparative cross-sectional study was conducted in the neonatal nursery of DHQ Hospital, MTI, Dera Ismail Khan. Blood samples were analyzed for C-Reactive Protein (CRP), White Blood Cell (WBC) count, and blood culture, while CSF analysis included WBC count, protein, glucose, and culture. Data were analyzed using SPSS version 25.0, with the Chi-square test used for categorical variables and independent t-tests for continuous variables. A p-value of <0.05 was considered statistically significant.**Results:** Among 95 neonates with LOS, 53.7% had meningitis. Lethargy ($p = 0.024$) and previous antibiotic use ($p = 0.034$) were significantly associated with meningitis, while other clinical signs showed no significant difference. CSF analysis revealed elevated WBC counts in meningitis cases, but CRP and blood WBC were not significantly different. **Conclusions:** Meningitis was frequent among neonates with LOS, with lethargy and prior antibiotic use as key risk factors. Early identification of these factors may aid in timely diagnosis and intervention. Further multi-center studies are recommended to validate these findings.

INTRODUCTION

Neonatal infections are a significant cause of morbidity and mortality worldwide, particularly in developing countries where healthcare resources and early diagnostic tools are often limited [1]. Out of these infections, Late-Onset Sepsis (LOS) is one of the concerning complications as it often leads to severe issues like meningitis [2]. Failure to diagnose or treat the disease on time can lead to the condition resulting in life-threatening issues such as severe health complications like death, neurological injury, developmental impairment, and more extremity [3]. Despite the advancements in nursing care for neonates, detection of meningitis in a septic neonate during the initial period remains a challenge. This is because clinical manifestations tend to be faint and are common with many other newborn pathologies. The clinical manifestations of LOS may vary across geographic regions, particularly in areas with limited healthcare resources where early signs of sepsis can be missed or attributed to other neonatal conditions. In low-resource settings, the absence of advanced diagnostics and delayed presentation often lead to underrecognition of subtle symptoms such as poor feeding and lethargy. The diagnostic criteria for neonatal meningitis depend on the evaluation of Cerebrospinal Fluid (CSF) obtained through Lumbar Puncture (LP) [4]. However, LP is frequently deferred or omitted, particularly in neonates with severe clinical conditions due to its

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invasive nature. This relies more on clinical and laboratory parameters which are not always specific to meningitis [5]. Diagnosing meningitis in neonates with LOS is particularly difficult due to overlapping symptoms with sepsis, such as irritability, poor feeding, and apnea. Invasive procedures like lumbar puncture are often delayed or avoided in critically ill neonates, leading to missed or late diagnoses. Moreover, limited access to laboratory testing in low-resource hospitals further complicates timely identification. These challenges underscore the need for standardized clinical criteria, prompt LP when feasible, and improved training for frontline healthcare staff in neonatal assessment. Numerous studies have analysed the association of neonatal sepsis and meningitis, paying attention to factors such as prematurity, low birth weight, prolonged hospitalisation, mechanical ventilation, and previous antibiotic therapy as probable risk factors [6, 7]. The reported incidence and risk factors differ tremendously from one geographic area to another, and also from one healthcare facility to another. This study attempts to bridge these gaps by determining the frequency of associated meningitis in infants diagnosed with LOS at a tertiary care hospital in Pakistan. The prevalence of meningitis in neonates with LOS can differ considerably between regions due to variations in diagnostic capabilities, antibiotic stewardship practices, and access to specialized neonatal care. These contextual differences must be considered when interpreting findings across different healthcare settings. This study enhances early risk assessment through timely diagnosis, intervention, and more neonatal care protocols by identifying the clinical and laboratory parameters associated with neonatal meningitis.

These results will also be useful in improving strategies in the stewardship of antibiotics to minimise their indiscriminate use, which worsens neonatal infections and antibiotic resistance.

METHODS

This comparative cross-sectional study was conducted at the Neonatal Nursery of DHQ Hospital, Medical Teaching Institution (MTI) Dera Ismail Khan, from June 1, 2024, to November 31, 2024, to determine the frequency of coexisting meningitis in neonates admitted with Late-Onset Sepsis (LOS) and assess associated clinical and laboratory parameters. The Ethical Review Committee of Gomal Medical College, D.I. Khan, granted ethical approval with reference: 33/GJMS, dated 24th March 2023. The synopsis was also approved by the Research Evaluation Unit of the College of Physicians and Surgeons Pakistan with reference: CPSP/REU/PED-2022-029-6854, dated 1st June 2024. The ssample size of 95 neonates was calculated using Open Epi software, considering a 95% confidence level, 80% power, and an expected prevalence of 50% for meningitis among neonates with LOS, based on the findings of Nafis *et al.*, who reported a similar frequency in a comparable study setting [8].Inclusion criteria involved neonates aged ≥72 hours admitted with clinical signs of LOS, including fever, lethargy, poor feeding, respiratory distress, and seizures.Neonates with congenital anomalies or pre-existing neurological conditions were excluded. Clinical signs were documented using a structured assessment form.Lethargy was defined as reduced spontaneous movement and diminished response to handling or external stimuli, while poor feeding was defined as refusal of at least two consecutive feeds within a 12-hour period, as reported by nursing staff and confirmed by the attending pediatrician.All data were recorded by trained personnel using predefined operational definitions to minimize observer bias and ensure consistency across cases.After obtaining informed consent, the following investigations were performed: Blood culture using the BacT/ALERT system, processed under aseptic conditions. Blood samples were drawn using sterile gloves, alcohol swabs, and closed system vacutainers to avoid contamination. Gram staining and biochemical tests were used for organism identification.CRP and WBC counts were measured using standardized automated analyzers. Lumbar Puncture (LP) was performed under sterile conditions by a trained pediatrician. Sterile drapes, gloves, and single-use spinal needles were used during the LP procedure. CSF samples were immediately transferred into sterile containers and sent to the lab without delay to minimize contamination risk. CSF analysis included: Total leukocyte count (manual Neubauer chamber). Protein and glucose (biochemical autoanalyzer).CSF culture (chocolate and MacConkey agar).The microbiology lab followed established infection control protocols for sample handling and culture processing. To ensure reliability, all laboratory procedures were conducted using standardized techniques, and equipment calibration was regularly performed. Quality control protocols were followed rigorously in the microbiology lab to avoid contamination during blood and CSF culture processing. Blood samples were collected under aseptic conditions, and lumbar punctures were performed by trained pediatricians using sterile technique to minimize contamination risk. All laboratory analyses were performed in a controlled environment using calibrated and quality-checked equipment. Validity was enhanced by using established clinical and laboratory criteria for diagnosing LOS and meningitis. Late-Onset Sepsis (LOS) was defined as sepsis occurring after 72 hours of life, with signs including fever, lethargy, poor feeding, respiratory distress, and seizures. Meningitis was diagnosed based on CSF findings, including elevated WBC count (>30 cells/mm^3), elevated protein, decreased glucose, or positive CSF culture, as per standard neonatal infection guidelines. Standard definitions and protocols were followed during patient assessment and

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sample collection to maintain consistency in data collection.Selection bias was minimized by applying clear inclusion and exclusion criteria, ensuring that only neonates meeting the defined eligibility were enrolled. Data were analysed using SPSS version 25.0.The Chi-square test was applied to compare categorical variables such as gestational age, birth weight, gender, prolonged hospital stay, mechanical ventilation, and prior antibiotic use between neonates with and without meningitis. For continuous variables such as CRP, WBC count, CSF WBC, CSF protein, and CSF glucose, an independent t-test was used to determine statistical significance. A p-value of <0.05 was considered statistically significant.The frequency of meningitis among neonates with LOS was recorded. Secondary outcomes included NICU admission rates and mortality among affected neonates. The results were presented in the form of tables and graphs to illustrate key findings.

RESULTS

The analysis of demographic and clinical characteristics of neonates with LOS showed no significant associations with meningitis. Preterm neonates had a slightly higher occurrence of meningitis compared to term neonates, but the difference was not statistically significant. Similarly, low birth weight infants (<2.5 kg) and those with a birth weight of ≥2.5 kg showed nearly equal distribution between meningitis-positive and meningitis-negative groups. Gender also did not play a significant role in meningitis occurrence, with both males and females showing similar proportions. These findings suggest that general demographic factors alone may not strongly predict meningitis risk in neonates with LOS.

Table 1: Demographic and Clinical Characteristics of Neonates with LOS

Variables	Meningitis		p-Value
	Present Frequency (%)	Absent Frequency (%)	
Gestational Age			
Preterm	33 (56.9%)	25 (43.1%)	0.432
Term	18 (48.6%)	19 (51.4%)	
Birth Weight			
<2.5 kg (LBW)	32 (52.5%)	29 (47.5%)	0.748
≥2.5 kg	19 (55.9%)	15 (44.1%)	
Gender			
Male	20 (55.6%)	16 (44.4%)	0.775
Female	31 (52.5%)	28 (47.5%)	

Among the clinical variables assessed, lethargy and previous antibiotic use were found to have a statistically significant association with meningitis. Neonates with meningitis had a higher prevalence of lethargy, indicating that this symptom might be an important early indicator of infection. Previous antibiotic use was also more frequent in neonates diagnosed with meningitis, suggesting a possible link between prior antibiotic exposure and increased susceptibility to meningitis. Other clinical features, including fever, poor feeding, respiratory distress, seizures, prolonged hospital stay, and mechanical ventilation, were not significantly associated with meningitis. Although these symptoms were common in neonates with meningitis, they were also observed in those without the condition, making them less specific for meningitis diagnosis.

Table 2: Clinical Presentation and Outcomes of Neonates with Meningitis

Clinical/Outcome Variables	Meningitis		p-Value
	Present Frequency (%)	Absent Frequency (%)	
Fever	32 (55.2%)	26 (44.8%)	0.716
Lethargy	40 (61.5%)	25 (38.5%)	0.024 (Significant)
Poor Feeding	32 (55.2%)	26 (44.8%)	0.716
Respiratory Distress	28 (54.9%)	23 (45.1%)	0.798
Seizures	31 (54.4%)	26 (45.6%)	0.867
Prolonged Hospital Stay (≥7 Days)	34 (55.7%)	27 (44.3%)	0.591
Mechanical Ventilation	37 (53.6%)	32 (46.4%)	0.984
Previous Antibiotic Use	44 (59.5%)	30 (40.5%)	0.034 (Significant)

The laboratory findings did not reveal any significant associations between meningitis and most biochemical parameters. The mean CRP levels and WBC counts were slightly elevated in neonates with meningitis compared to those without, but the difference was not statistically significant. The CSF WBC count, an important indicator of infection, was higher in the meningitis group, though it did not reach statistical significance. CSF protein and glucose levels showed no meaningful differences between the two groups. Similarly, blood and CSF culture positivity did not differ significantly, suggesting that these tests alone may not be reliable predictors of meningitis in neonates with LOS.

Table 3: Laboratory Findings in Neonates with and without Meningitis

Laboratory Test	Meningitis		p-Value
	Present Mean ± SD/ Frequency (%)	Absent Mean ± SD/ Frequency (%)	
CRP (mg/L)	17.53 ± 5.91	16.84 ± 7.09	0.604
WBC Count (/mm^3)	18,061.53 ± 4,981.47	18,561.35 ± 5,942.80	0.657
CSF WBC Count (/mm^3)	159.24 ± 66.44	136.80 ± 62.76	0.096
CSF Protein (mg/dL)	207.39 ± 79.41	198.25 ± 62.03	0.538
CSF Glucose (mg/dL)	36.91 ± 13.50	37.26 ± 12.44	0.897
Blood Culture Positive	32 (58.2%)	23 (41.8%)	0.303
Blood Culture Negative	19 (47.5%)	21 (52.5%)	
CSF Culture Positive	33 (53.2%)	29 (46.8%)	0.902
CSF Culture Negative	18 (54.5%)	15 (45.5%)	

The final table examined neonatal outcomes, including NICU admission and mortality, in relation to meningitis. Although a higher percentage of neonates with meningitis required NICU admission compared to those without, the

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association was not statistically significant.Similarly, mortality was observed more frequently in the meningitis group, but the difference did not reach significance. These findings suggest that while meningitis can contribute to more severe illness and the need for intensive care, other underlying factors may also influence neonatal outcomes.

Table 4: Outcomes of the Characteristics

Outcome Variables	Meningitis		p-Value
	Present Frequency (%)	Absent Frequency (%)	
NICU Admission	40 (55.6%)	32 (44.4%)	0.518
No NICU Admission	11 (47.8%)	12 (52.2%)	
Mortality	42 (56.8%)	32 (43.2%)	0.260
Survival	9 (42.9%)	12 (57.1%)	

Overall, this analysis highlights that while some clinical indicators, such as lethargy and previous antibiotic use, showed significant associations with meningitis, most demographic, laboratory, and outcome variables did not. These results emphasize the complexity of diagnosing and managing meningitis in neonates with LOS and suggest the need for a combination of clinical, laboratory, and microbiological markers to improve early identification and treatment strategies. Figure 1 illustrates a clustered bar chart that highlights lethargy and prior antibiotic use in the neonates with and without meningitis. It shows that 40 lethargic neonates had meningitis, while 25 had non-meningitis. The data also indicate that, similarly, 44 neonates with meningitis had previous antibiotic use and 30 without. These findings implicate the importance of careful surveillance of the neonates exhibiting these risk factors to enhance the early diagnosis of meningitis and its management.

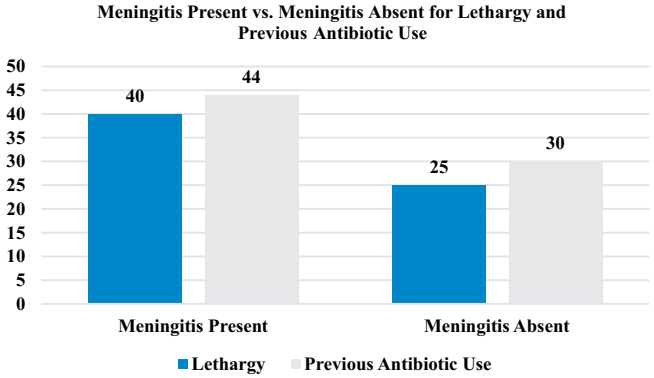

Figure 1: The clustered bar chart illustrates the comparison of lethargy and previous antibiotic use among neonates diagnosed with meningitis and those without the condition.

DISCUSSION

The results of this research shed light on the dual presence of meningitis in neonates with LOS. Infections during the neonatal stage continue to be one of the major causes of morbidity and mortality, most notably among developing nations with inadequate health care facilities. The recognition of clinical and laboratory indicators linked with neonatal meningitis was important in enhancing early diagnosis and improving outcomes. The analysis found a notable relationship between lethargy, previous antibiotic treatment, and the occurrence of meningitis in neonates with LOS. These findings were in line with earlier studies which emphasised that patients suffering from infection of the central nervous system often show signs of altered mental status and poor activity levels [8-10]. The study showed that strong early signs of neonatal meningitis included irritability and reduced responsiveness [11-13]. Other studies have also shown that neonates with poor feeding coupled with lethargy are likely to have underlying central nervous system infections [13-15]. A notable association was found concerning the use of antibiotics and the occurrence of meningitis. This was in accordance with reports by other authors who stated that prior antibiotic therapy might modify microbial flora and could be responsible along with other factors for the development of resistant organisms which increases the probability of invasive infections [16-18]. The empirical use of antibiotics in neonates may be capable of masking early signs of meningitis by partially treating bloodstream infections and, thus, delaying a definitive diagnosis. This highlights the importance of judicious antibiotic use in neonatal sepsis management. Moreover, early antibiotic exposure may partially treat systemic infections, thereby reducing the clinical visibility of hallmark signs like lethargy or irritability. This can lower the sensitivity of these signs for diagnosing meningitis, potentially delaying lumbar puncture or leading to under diagnosis. Therefore, early consideration of LP before antibiotic administration is crucial, especially in neonates showing subtle signs suggestive of central nervous system involvement. Although other clinical factors such as prolonged hospital stay, mechanical ventilation, fever, and respiratory distress were not significantly associated with meningitis in this study, they have been widely reported as risk factors in previous research. Studies found that neonates requiring mechanical ventilation or prolonged hospitalization had a higher risk of meningitis, often due to increased exposure to hospital-acquired infections [14, 19]. The lack of significant association in our findings may be due to the relatively small sample size, which limited statistical power, and the presence of confounding variables that were not controlled for, such as comorbidities and severity of illness. Hence, these findings should be interpreted cautiously, and larger multi-centre studies are warranted to validate these associations. Laboratory findings in this study also showed higher CSF WBC counts in neonates with meningitis, which aligns with the established diagnostic criteria for bacterial meningitis. While CRP and WBC counts were not significantly different, CSF protein levels were slightly elevated in the meningitis group, supporting studies reported that CSF protein elevation is a common marker in neonatal meningitis [20, 21]. CSF WBC count, in

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particular, may serve as an important early screening tool in neonates suspected of meningitis, especially when clinical symptoms are masked or unclear. A significantly elevated CSF WBC, even in the absence of culture positivity, should prompt early therapeutic intervention. This parameter can be crucial for timely decision-making in resource-limited settings where advanced diagnostics may not be readily available. The strengths of this research include targeting a high-risk population, applying standard diagnostic techniques, and integrating clinical with laboratory parameters. Nevertheless, some limitations need to be addressed. The sample was small and could have weakened the statistical power of several associations. Furthermore, the investigation was single centre, which limits extrapolation to other neonatal units that have differing patient populations and antibiotic control practices.

CONCLUSIONS

Meningitis was found to be a frequent coexisting condition in neonates with late-onset sepsis. Among various clinical and laboratory variables, lethargy and prior antibiotic use were significantly associated with the presence of meningitis. These findings highlight the importance of early recognition of subtle clinical signs and the judicious use of antibiotics in neonatal care. Routine consideration of lumbar puncture in neonates with LOS, particularly those presenting with lethargy or previous antibiotic exposure, may improve early detection and treatment outcomes. Further multi-centre studies with larger sample sizes are recommended to validate these associations and inform clinical guidelines.

Authors Contribution

Conceptualization: IK

Methodology: AK, FB, AJ, OK

Formal analysis: IK

Writing, review and editing: AK, FB, IK, AJ, OK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparative Analysis of Autopsy Case Characteristics Before and During the COVID-19 Lockdown at DHQ Sahiwal

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ABSTRACT

COVID-19 has impacted all spheres of life during the pandemic era. It not only affected health but also impacted the socioeconomic conditions of our lives. In hospitals, autopsies continued to be conducted during the pandemic. The Lockdown has not impacted autopsy conduct in hospitals. **Objective:** To compare and identify various characteristics of autopsies conducted in 2019 and 2020. **Methods:** An observational retrospective study was conducted from 15th March 2020 to August 2020 and from 15th March 2019 to August 2019 in DHQ Sahiwal. Data were analyzed through SPSS 27. **Results:** A total of 257 autopsy cases were collected, of which 114 cases were referred in 2019, while the remaining 143 cases were from 2020. The most prominent cause of death in 2019 and 2020 was trauma, at almost 64% and 63.6%, respectively. The highly prevalent manner of death was homicidal, in 2019 it was 47.4%, and in 2020 it was 46.2%. **Conclusions:** It was concluded that the COVID-19 lockdown did not significantly influence the character of the autopsy cases that were referred to DHQ Sahiwal.

INTRODUCTION

COVID-19, caused by the novel coronavirus SARS-Cov-2, emerged in late 2019 and rapidly evolved into a global pandemic, significantly affecting health, economies, and daily life worldwide [1]. The Government implemented various public health measures, including lockdowns, social distancing, and mask mandates, to curb the virus's spread. Health systems faced unprecedented challenges, with hospitals overwhelmed and healthcare workers under immense stress [2]. The pandemic highlighted existing disparities in healthcare access and outcomes, disproportionately affecting marginalized communities [3]. As medical professionals sought to understand the effects of COVID-19, there was a rise in the demand for autopsies to investigate causes of death, particularly in cases where COVID-19 was a factor. Understanding the pathology of the virus and its complications helped in developing treatment protocols and improving patient care [4]. Autopsies, also known as post-mortem examinations, are medical procedures carried out to determine the cause of death and assess any disease or injury present in the deceased. The key characteristics of autopsies are to determine Cause of Death by Identifying underlying

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conditions or diseases, to conduct research and provide education by contributing to medical knowledge, not only in the field of Pathology, Clinical Practices but also in the field of Forensic Medicine and Toxicology, and ultimately to produce Legal Evidence by providing information for criminal investigations or insurance claims [5]. In autopsies, cause of death and manner of death are two distinct but interrelated concepts that help provide a comprehensive understanding of how and why an individual died [6]. The cause of death refers to the specific medical condition or injury that led directly to the death. This can include: Diseases or medical conditions such as heart disease, cancer, pneumonia, or complications from existing health issues; Unintentional injuries, such as those resulting from car accidents, falls, or overdose; Death resulting from self-inflicted harm; Death due to intentional injury inflicted by another person and Situations where the specific cause cannot be conclusively established. The manner of death classifies the circumstances surrounding how the death occurred. It typically falls into one of five categories: Death resulting from natural causes, such as disease or old age, Death caused by unintentional injuries, Death intentional by self-harm or overdose with the intent to end life, Death resulting from actions taken by another individual with intent to kill, Situations wherein the manner of death cannot be clearly classified, or often due to insufficient information. Clearly determining the cause and manner of death is essential in forensic cases, influencing criminal investigations, insurance claims, and public health statistics. Understanding prevailing causes and manners of death can help identify health trends, inform preventive measures, and guide medical research. Providing accurate cause and manner of death assists families in understanding the circumstances of their loved one's passing, contributing to the grieving process [7]. Therefore, the distinction between cause and manner of death is crucial in autopsies, offering a complete picture of the circumstances surrounding an individual's death. This information is vital not only for medical knowledge and legal purposes but also for public health initiatives and supporting families in their time of loss.

This study aims to compare and identify the characteristics of cases referred for an autopsy to DHQ Sahiwal during the lockdown period in 2020 versus the cases referred during the same period in 2019.

METHODS

An observational retrospective study was carried out at the District Headquarters (DHQ) Hospital, Sahiwal. Ethical approval was obtained from the Ethical Review Committee, Ref. no: 11046 STH/SWL, DHQ hospital, Sahiwal. The sampling technique employed was non-probability convenience sampling. Retrospective data from 15th March 2020 to August 2020 and 15th March 2019 to August 2019 were collected from the autopsy register at DHQ hospital on a designed autopsy form. Data from all the medico-legal postmortem cases during the above-mentioned period were collected. However, postmortem data of drug addicts were excluded from this study. All data were entered and analyzed using SPSS version 27.0. Normality tests were performed for continuous variables, and sample size calculation was done using $n=NxZ^2xpx(1-p)/e^2/ [N-1+ Z^2 xpx(1-p)/e^2]$. For qualitative variables, the chi-square test was applied. For quantitative variables, a t-test was used. A p-value less than 0.05 was considered significant.

RESULTS

A total of 257 autopsy cases were collected, of which 114 cases were referred in 2019, while the remaining 143 cases were from 2020. The mean age of the cases analyzed in 2019 was 35.58±16.65 years, with a male predominance (75.4%). In 2020, the mean age was 34.19±15.86 years. Regarding gender, there was a slight increase in female cases in 2020 (28% vs 23.7% in 2019). However, this increase was not found to be statistically significant (p-value 0.421). The majority of cases were referred from urban centers in both 2019 and 2020, and it was found to be statistically significant (p-value 0.011). There was no significant difference between the cause of death and the manner of death between the two time periods examined. Regarding the manner of death, an increase in undetermined deaths in 2020 was observed, but there was no statistical significance. In both years, recorded cases of deaths from road traffic accidents were fewer (Table 1).

Table 1: Inferential Data regarding Variables in 2019 and 2020

Autopsies Performed	2019 (n=112)	2020 (n=137)	p-value
Age (Mean/Median+-SD)	(35.58/33+-16.65)	34.19/35+-15.86)	0.425
Gender n (%)			
Male	86 (75.4%)	101 (70.6%)	0.475
Female	27 (23.7%)	40 (28%)	
Age Group (Years)			
0-9	3 (2.6%)	7 (4.9%)	–
10-19	12 (10.5%)	14 (9.8%)	
20-29	29 (25.4%)	29 (20.3%)	
30-39	33 (28.9%)	46 (32.2%)	
40-49	10 (8.8%)	18 (12.6%)	
50-59	13 (11.4%)	12 (8.4%)	
60-69	8 (7%)	7 (4.9%)	
70-79	3 (2.6%)	2 (1.4%)	
80-89	0 (0%)	1 (0.7%)	
90-99	1 (0.9%)	1 (0.7%)	
Cause of Death			
Trauma	73 (64%)	91 (63.6%)	–
Asphyxia	12 (10.5%)	12 (8.4%)	
Burn	0 (0%)	2 (1.4%)	
Poisoning	9 (7.9%)	9 (6.3%)	
Unknown	14 (12.3%)	14 (9.8%)	
Medical	3 (2.6%)	4 (2.8%)	

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Manner of Death			
Suicide	16 (14%)	21 (14.7%)	–
Homicide	54 (47.4%)	66 (46.2%)	
Accidental	2 (1.8%)	4 (2.8%)	
Undetermined	29 (25.4%)	42 (29.4%)	
Natural	11 (9.6%)	6 (4.2%)	
Location			
Urban	87 (77.67%)	98 (71.53%)	0.011
Rural	25 (22.32%)	39 (28.46%)	

DISCUSSION

The findings of our study suggest that the COVID-19 lockdown did not significantly influence the character of the autopsy cases that were referred to DHQ Sahiwal. However, compared to 2019, we noticed a slight increase in female cases and undetermined deaths. Moreover, the deaths attributed to road traffic accidents were almost none during the lockdown period. According to a study conducted in India from 17th January to 31st May 2020, the number of RTAs was reduced to almost none during the COVID-19 pandemic lockdown [8]. Another study, which was conducted in Turkey during the COVID-19 pandemic lockdown in 2020, elaborated that there was a decline in the number of Road traffic accidents during the months when the 'stay at home' order was implemented [9]. Increased homicidal cases were observed in 2020 as compared to 2019. It could be due to a variety of factors, like unemployment, socioeconomic losses and adverse health conditions [10]. For cases about causes of death, trauma demonstrated a high prevalence in both years. An increase in female cases was observed, which, despite not being significant, could be an indicator of rising rates of femicide. A study reported a global rise in femicide during the COVID-19 lockdown period [11]. Another study commented on a surge in domestic violence cases during the COVID-19 lockdown [12]. It is naturally assumed that an increase in domestic violence will also increase femicide [13]. Femicide is a form of gender-based violence and should not be classified as a homicide. The increase in femicide is accounted for by the fact that more women were forced to stay with their abusers and had no safety net due to the shutdown of shelter homes. One study suggested that social isolation can increase the likelihood of violence in households [14]. There is also evidence in the literature to suggest that male unemployment is positively correlated with an increase in domestic violence [15]. As many people experienced economic losses during the COVID-19 lockdown, it could be one of the contributing factors to the rise in femicide [16]. During both years, cases of suicide and accidents were fewer in number, and it also reflects the fact what effect lockdown had on the lives of people [17, 18]. But the undetermined deaths were increased in 2020 as compared to 2019, by almost 29.4% and 25.45%, respectively. It is another crucial aspect that many people do not allow for the conduction of an autopsy of their loved ones, and it is a general hesitation which can be due to social or belief reasons [19]. It is also demonstrated in this study that the majority of the cases belonged to urban areas in both years. This fact also complements the idea of people avoiding autopsy conduction in the majority of the rural areas [20].

CONCLUSIONS

It was concluded that there is no significant change in the autopsy cases in both years, especially the characteristics of autopsy cases remained almost the same in 2019 and also in 2020. The cause of death and the manner of death remained the same in comparison of both years, although rates of cases suicidal and accidental were decreased, but homicidal cases were a little on the higher side.

Authors Contribution

Conceptualization: NH
Methodology: NH
Formal analysis: SHZ
Writing review and editing: TM, AR, AZ, SGS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Knowledge, Attitude, and Practice of Infection Control Measures among Medical Students and Residents of a Private Medical College in Lahore, Pakistan: A Comparative Cross-sectional study

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ABSTRACT

Healthcare workers, especially medical students, are constantly exposed to pathogens in hospitals, which significantly increases the risk of them being infected. Infection control measures are pivotal in safeguarding them from these infections and reducing any risk of transmissibility. **Objective:** To assess the knowledge, attitude, and practice of Infection Control Measures among medical students and residents of a private medical college in Lahore. **Methods:** This was a cross-sectional study conducted from April to June 2023 at CMH Lahore Medical College, using a purposive sampling technique that included residents and medical students from the third to the final year, regardless of age or other demographic factors. A pretested structured questionnaire was used. Data were analyzed using SPSS 23.0. **Results:** In this study, the total number of responses collected was 378. Out of these responses, 95% possessed good knowledge. 55.8% of participants showed a positive attitude towards infectious control measures. 91.5% of participants said that they followed good practices in infection control. On comparison between House officers, PGs, and undergraduates, significant p-values were obtained in terms of Knowledge, Practice, and Attitude, indicating that the participants in all three categories are well-informed regarding infection control measures and putting them into practice. **Conclusions:** This study highlighted the extent to which medical students and residents effectively implement infection control measures in their work environment. Furthermore, it underscores their level of receptiveness to these practices, shedding light on both strengths and areas for improvement.

INTRODUCTION

Infection Prevention and Control (IPC) is necessary for ensuring the safety of both patients and Healthcare Workers (HCWs). The Knowledge, Attitude, and Practices (KAP) of health care workers play a crucial role in reducing the risk of infections. However, the gap between knowledge and actual practices highlights the need for regular training to enhance compliance and effectiveness [1]. Needle-Stick Injuries (NSIs) account for around 37.6% of hepatitis B, 39% of hepatitis C, and 4.4% of HIV/acquired immunodeficiency syndrome cases among healthcare workers globally, with HIV being ranked second in disease-related deaths in Africa, fourth globally, and fifth among infectious diseases [2, 3]. Medical students, who are future doctors, face a high risk of getting Hepatitis B (HBV) because of their clinical duties. Studies show that, on average, 44.5% of healthcare workers worldwide experience needle-stick injuries in a year, increasing their risk of infections [4]. Dental care workers are at higher risk of exposure to infection, which can result from inadequate HBV vaccination and a lack of adherence to universal precautions, which point out that all blood and blood-contaminated fluids have the potential for infection [5].

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Poor hygiene practices with clinical attire and equipment can cause healthcare-associated infections. Clinical coats may harbor harmful pathogens, so it's recommended to own at least two and wash them regularly, especially when soiled. Avoiding short sleeves, watches, and accessories can help reduce transmission [6]. Infections also pose economic burdens and can lead to significant mental or emotional stress if not managed properly [7]. Due to their frequent exposure to healthcare settings and direct patient interactions, medical students place a greater emphasis on personal hygiene. Sound knowledge, training, and work experience in infection control are required to lessen the high risks associated with infection transmission [8]. Good knowledge and a positive attitude toward disease prevention, especially after education, are associated with better preventive practices, leading to improved outcomes [9]. Risk reduction measures include using PPE, following standard precautions, using safety equipment properly, and ensuring efficient needle disposal. Handwashing with soap can lower the risk of acute respiratory infections by 16% to 23% [10]. Infection control has been a key part of CMH Lahore Medical College's curriculum for third and fourth-year students over the past four years. This study aimed to assess the knowledge of medical students and residents on infection control and to evaluate the effectiveness of undergraduate teaching in helping them apply these measures during their residency. While numerous international studies have examined the knowledge, attitudes, and practices of healthcare workers regarding infection control, there is limited research available in Pakistan, especially in Lahore, on how well medical trainees understand and follow these protocols. Most existing studies focus on nurses or experienced doctors, creating a gap in knowledge about how medical students and residents, who are still in training, adhere to infection control guidelines. Filling this gap is essential because insufficient awareness or failure to follow infection control practices can lead to higher rates of hospital-acquired infections, antibiotic resistance, and increased health risks for patients.

This study aimed to identify shortcomings in current training, recognize obstacles to adherence, and suggest practical improvements to strengthen infection control education for future healthcare professionals

METHODS

This was a comparative, cross-sectional study conducted at CMH, Lahore Medical College, from April to June 2023 after obtaining ethical approval from the College Ethical Review Committee. The target population included house officers and medical students studying in their 3rd year, 4th year, and final year of CMH Lahore Medical College. Ethical approval was obtained from the College Ethical Review Committee (IRB No: 746/ERC/CMH/LMC). The study included residents and medical students enrolled in the specified academic years who provided informed consent. The inclusion criteria were: (a) medical students from the 3rd to final year and (b) residents from any postgraduate training year at CMH Lahore Medical College. Exclusion criteria were: (a) students from preclinical years (1st and 2nd year), (b) individuals enrolled in nonmedical programs, and (c) those who declined to participate. The research employed a purposive sampling technique, ensuring participants met the defined criteria before completing the questionnaire. The calculated sample size is 378, based on a 95% confidence level, a 6% margin of error, and a population proportion ($\hat{p}$) of 0.563, utilizing the formula provided below:

$$n = \frac{z^2 \times \hat{p}\,(1-\hat{p})}{\varepsilon^2}$$

Data collection was conducted using a structured questionnaire adapted from a previously published article, ensuring its validity, with permission obtained from the original authors [11]. The questionnaire comprised three sections assessing the knowledge of medical students and residents regarding infection control measures, attitude towards infection control, and the practice of infection control measures among residents. It included closed-ended and Likert-scale questions (1 = Strongly Disagree to 5 = Strongly Agree) for attitude assessment, while knowledge and practice were evaluated through Yes/No questions. Content validity was further reviewed by the Pathology Department at CMH Lahore Medical College. A pilot study involving 10 students (excluded from the main study) was conducted to ensure clarity and feasibility. Reliability, assessed using Cronbach's alpha, yielded a coefficient of 0.698, indicating acceptable internal consistency. Knowledge scores were classified as low (0–50%), moderate (51–75%), and high (>75%) based on the percentage of correct responses. Attitude and practice scores were analyzed using mean scores, with higher means reflecting a more positive attitude or better adherence to infection control practices. Statistical analysis was conducted using SPSS version 23.0 to evaluate differences in Knowledge, Attitude, and This study assessed the Knowledge, Attitude, and Practice (KAP) of infection control measures among two groups: undergraduate medical students (3rd to final year) and postgraduate residents from any year of training. Descriptive statistics (means and standard deviations) were used to summarize continuous variables, while frequencies and percentages were reported for categorical variables. The Analysis of Variance (ANOVA) test was chosen to compare mean KAP scores across multiple independent groups, as it is appropriate for assessing differences between more than two groups. Given a significant ANOVA result, Tukey's Honest Significant Difference (HSD) test was used as a post hoc analysis to identify specific pairwise differences while controlling for Type I error. A significance level of 0.05 was

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applied for all analyses. Each participant was explained the aim of the study and written informed consent was sought. The study maintained the privacy of responses.

RESULTS

In this study, the total number of responses collected was 378. Out of these, 35.4% were males and 64.6% were females. Among the Graduates, 34.4% were House Officers, and 17.9% were postgraduate residents, whereas among the Undergraduates, 36.8% of responses were from MBBS and 10.9% from BDS.

Table 1: Demographic Characteristics of Study Participants (n=378)

Variables	Frequency (%)
Gender	
Male	134 (35.4%)
Female	244 (64.6%)
Major (For Graduates)	
House Officer	130 (34.4%)
PG	68 (17.9%)
Total	198 (52.3%)
Major (For Undergraduates)	
MBBS	139 (36.8%)
BDS	41 (10.9%)
Total	180 (47.7%)

In terms of knowledge, 95% of responses received showed that the participants possessed good knowledge, indicated by a score >10. On the side of attitude, 55.8% of participants showed a positive attitude towards infectious control measures highlighted by a score between 31-50. Regarding practice, 91.5% of participants said that they followed good practices in infection control, indicated by a score >10.

Table 2: Frequency and Percentage Distribution of Study Variables (n=378)

Variables	Frequency (%)
Knowledge	
5-10 (Moderate)	19 (5.0%)
>10 (Good)	359 (95.0%)
Total	378 (100.0%)
Attitude	
10-30 (negative)	167 (44.2%)
31-50 (Positive)	211 (55.8%)
Total	378 (100.0%)
Practice	
<5 (weak)	2 (0.5%)
5-10 (Moderate)	30 (7.9%)
>10 (good)	346 (91.5%)
Total	378 (100.0%)

On comparison between House officers, PGs, and undergraduates, significant p-values were obtained in terms of Knowledge, Practice, and Attitude at 0.004, 0.000, and 0.033, respectively, thus indicating that the participants in all three categories are well-informed regarding infection control measures and putting them into practice.

Table 3: Comparison between House officers, PGs, and undergraduates regarding Knowledge, Attitude, and Practice- ANOVA

Variables	House Officers	Pgs	Undergraduates	p-value
Knowledge	13.5 ± 1.64	13.61 ± 1.4	12.02 ± 1.53	0.004
Attitude	31.23 ± 4.3	31.65 ± 5.6	32.7 ± 5.45	0.00
Practice	14.23 ± 1.48	14.29 ± 2.06	13.37 ± 2.4	0.033

In comparison between MBBS, BDS, and Graduates, all participants showcased a positive attitude towards infection control measures, good knowledge regarding them, and applied them in practice.This is highlighted by the very significant p-values: 0.025 in Knowledge, 0.000 in Attitude, and 0.013 in Practice.

Table 4: Comparison between MBBS, BDS, and Graduates regarding Knowledge, Attitude, and Practice- ANOVA

Variables	MBBS	BDS	Graduates	p-value
Knowledge	13.1 ± 1.64	13.40 ± 1.52	13.6 ± 1.34	0.025
Attitude	32.66 ± 5.24	31.65 ± 5.6	30.85 ± 4.32	0.00
Practice	13.4 ± 2.5	14.31 ± 1.2	14.52 ± 1.27	0.013

DISCUSSION

The study highlighted infection control measures among medical and dental students at various stages of their education.The analysis of attitudes toward infection control measures revealed a predominantly positive outlook, with only a minority holding negative views.A study conducted among healthcare students in Zambia assessed that while most students demonstrated awareness of common healthcare-associated infections and expressed positive attitudes toward reducing infection risks and valuing disinfection, their practical application during medical procedures was lacking [12].This presented an alarming situation, as subpar practices regarding infection control could only promote a greater spread of infections and subsequently have an adverse impact on the well-being of patients and healthcare providers alike.Thus, the adequate practice of these control measures was deemed necessary.The "Practice to infection control measures" indicated a strong reported adherence to infection control among the respondents, with a large majority reporting good practices.This aligned with a study that showed good knowledge and attitudes but highlighted a need for better implementation of IPC precautions and increased training for laboratory and healthcare workers [13].Similarly, a survey conducted among Australian CT radiographers and radiology nurses showed a strong baseline knowledge of standard precautions.These results remained consistent with broader research indicating that healthcare workers generally possessed good knowledge, attitudes, and practices concerning infection prevention [14, 15]. Another inference that could be drawn from this comparison was

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that attitude toward infection control measures appeared almost universally positive, but the degree of implementation and practice of these measures differed from region to region.This presented another alarming picture in that subpar practices in certain regions might lead to greater disease outbreaks.This represented an avenue that required further research to develop a global gold standard and uncover the causes of these regional differences in practice.The comparison between House officers, PGs, and undergraduates in knowledge, practice, and attitude toward infection control measures depicted a significant difference.While awareness among clinical students in this study was high, it did not consistently translate to attitude and practice levels.Another study supported these findings, showing that participants with higher knowledge scores also had better infection control attitudes [16]. Differing levels of practice could adversely impact patient welfare and mortality if proper protocols were not adequately followed.Simultaneously, this connoted that differing levels of knowledge also impacted implementation, once again lending credibility to the need for developing appropriate policies and educational strategies to reinforce and properly teach these measures.
The study found significant differences in infection control practices among House officers, PGs, and undergraduates. House officers, being more hands-on, may have exhibited different practices compared to PGs, who might have followed specialized practices based on their fields. Undergraduates, still in the learning phase, may have lacked extensive practical experience. This was supported by a quasi-experimental prospective study on medical undergraduates, which showed improved knowledge and practice scores after targeted training on infection control measures, emphasizing the effectiveness of customized training initiatives [17].There were clear differences in infection control attitudes among House officers, PGs, and undergraduates, reflecting varied perspectives and motivations. Seetan *et al.*, supported these findings, noting good knowledge among medical students regarding isolation protocols, hand hygiene, and infection transmission via attire and equipment, along with gender-based and institutional differences in attitudes [18]. Similarly, an Egyptian study found that better education on infection control led to fewer infection outbreaks among students, healthcare workers, and their patients [19]. Once again, the need for teaching infection control measures was highlighted and further emphasized the importance of customizing training methods and content according to medical specialties to better counter specific infections likely to arise within those fields.P-values were found significant when comparing MBBS and BDS students with graduates, revealing variations in knowledge levels, attitudes, and practices concerning infection control measures among these groups. The results suggested that a good level of knowledge was linked to better practices and a more cautious attitude. However, a study conducted on dental students in Sudan found low usage of Personal Protective Equipment despite good knowledge and positive attitudes toward infection control, with moderate compliance to guidelines [20].Healthcare did not just encompass doctors but also dentists, as both disciplines dealt with the risk of infection and its adverse impact on patients. Thus, equal training and equipment must be provided across all healthcare sub-specialties to reduce the overall burden of disease and infection. Maintaining infection control remained a continuous effort and was crucial for ensuring high standards in healthcare.This study highlighted the need for targeted interventions to address the unique challenges faced by MBBS, BDS, and graduate students.Regular training on infection control should have been provided and integrated as a core component of ongoing medical education.As this was a single-center study, future research including multiple medical institutions could further investigate how educational interventions impact knowledge, attitudes, and practices over time among healthcare professionals. The sample size in this study was relatively restricted, and increasing it in future research may enhance the generalizability of the findings.

CONCLUSIONS

The findings of this study demonstrated a high level of awareness and adherence to infection control measures among the participants.The results underscore the effectiveness of current educational and training programs in fostering a strong foundation of knowledge, positive attitudes, and good practices in infection control among healthcare professionals and students. However, the observed variations between groups suggest the need for tailored interventions to address specific gaps and ensure uniform adherence across all levels of training and professional practice.

Authors Contribution

Conceptualization: RF, MM, KHC
Methodology: RF, MM, IM, MMR
Formal analysis: MM, IM, MMR
Writing, review and editing: RF, MM, IM, MMR, KHC
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Cross-Sectional Analysis of Probable Causative Factors Leading to Iron Deficiency Anemia in Primigravida During Their First Trimester

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ABSTRACT

Anemia is a common nutritional deficiency that impacts approximately 1.6 billion individuals globally, representing around 25% of the world's population. **Objectives:** To assess the prevalence of factors associated with anemia due to iron deficiency in primigravida females during their first trimester. **Methods:** A descriptive, cross-sectional study was conducted at Agha Khan University Hospital, Karachi, from January 4 to July 3, 2019.The study aimed to screen pregnant women during their first antenatal visit in the Outpatient Department for eligibility based on the inclusion criteria. Data were recorded using a structured proforma. Effect modifiers were controlled by stratifying age in years and gestational age in weeks, with comparisons between stratified groups made using Chi-square analysis. **Results:** Mean ± SD of age and gestational age in primigravida females was 27.50 ± 5.36 years and 7.93 ± 2.07 weeks, respectively. Mean ± SD of height, weight and BMI was 156.44 ± 5.81 cm, 65.90 ± 10.84 kg and 28.84 ± 4.10 kg/m2, respectively. In frequency of associated factors, advanced maternal age was found to be responsible for iron deficiency anemia in 27 (55.10%) women, underweight in 2(4.08%), low educational status in 7 (14.28%) and low socioeconomic status was 13 (26.53%) women. **Conclusions:** It was concluded that in the Pakistani population, the prevalence of iron deficiency anemia is high among pregnant women. Maternal anemia is significantly linked to maternal age and low socioeconomic status. The results emphasize the critical need to raise awareness among pregnant women and their families regarding the significance of antenatal care.

INTRODUCTION

Anemia is a serious worldwide health issue. Anemia is characterized by hemoglobin (Hb) levels that are below the normal range, according to the World Health Organization (WHO) [1].Anemia is thought to afflict one-fourth of the world's population, with cases amongst women, pregnant mothers, young girls, and children under five years old rising quickly [2].The prevalence of anemia in all age categories was 26.7% worldwide in 2022, with 1.68 billion cases. In 2021, dietary shortages of iron, hemoglobinopathies, hemolytic anemias, and other neglected tropical illnesses were the primary contributors of anemia-related Years Lived with Disability (YLDs), which together accounted for 84.7% (84.1-85.2) of anemia YLDs [3]. Patients with anemia commonly exhibit nonspecific

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symptoms like fatigue, weakness, and lethargy. In more severe cases, symptoms may include syncope, shortness of breath, and decreased exercise tolerance [4]. It was observed that a significant proportion of women between 20 to 26 weeks of pregnancy experienced mild to moderate anemia [5]. Another study observed that pregnant women and those with multiple children were found to be at higher risk of anemia. Additionally, women with busy schedules were more susceptible to the condition. These results highlight how dietary practices, choices regarding life, and the pregnant situation all contribute to the growth of anemia [6]. Garanet *et al.*, indicated that rural women have a high chance of anemia. Therefore, there is a need to enhance strategies aimed at preventing anemia among pregnant women in rural areas [7]. Anemia is not a diagnosis but a manifestation of an underlying condition, with various diseases causing it through different mechanisms, leading to decreased oxygen-carrying capacity of the blood, tissue hypoxia, and a significant rise in medical care costs [8]. Such a high frequency of anemia among expectant women can be attributed to the fact that pregnancy is the starkest biological change and the greatest physiological stress that a woman encounters during her life. According to World Health Organization (WHO) statistics, based on national surveys from 1993 to 2005, not only does a total of 42% of the women worldwide encounter anemia during their pregnancy, but it also accounts for 20% of the maternal deaths as well [5]. About 320 mg of iron are needed by the growing baby and placenta in a normal singleton pregnancy, 450 mg are needed to promote the growth of the mother's red blood cell mass, and 150 mg is needed to make up for blood loss after birth [9]. Furthermore, baby neurocognitive impairments may be associated with maternal iron insufficiency [13]. The need for iron increases significantly during pregnancy [14]. For proper iron balance, an adult female who is not pregnant has to absorb about 0.8 mg of iron each day from her digestive system. But the body's need for iron increases throughout pregnancy, reaching around 8 milligrams per day by the third trimester [15, 16]. Keeping in view all these implications of iron deficiency anemia, this study aims to determine the associated factors of IDA in primigravida females during their first trimester. By identifying the factors associated with IDA in primigravida females during their first trimester, the study aims to enhance early detection and intervention, potentially improving maternal and fetal health outcomes and informing strategies to prevent and manage IDA in this high-risk group. To be best of our knowledge and based on literature search we observed that all previous studies included females of all three trimesters regardless of parity and gravida, no prior data is available which focused the cohort of primigravida females during their first trimester in context of our population, although very few international literatures are available for the same.

This study aims to measure the associated factors of IDA in our community because international data is not applicable in our population due to differences in lifestyle, geographical location, genetics, and environmental changes; therefore, this study was help in modifying treatment and management options in early stages of pregnancy.

METHODS

The study was a descriptive cross-sectional design conducted at the Department of Obstetrics and Gynecology, Agha Khan University Hospital, Karachi, from January 4, 2019, to July 3, 2019, following approval of the research proposal by CPSP (CPSP Letter number CPSP/REU/OBG-2016-175-7256). The sample size was calculated using the WHO sample size calculator version 2.0, considering a margin of error of 6%, a 95% confidence level, and a frequency of 17.6% for advanced maternal age associated with iron deficiency anemia (IDA), resulting in an estimated sample of 155 women. [12] Non-probability, consecutive sampling technique was used for participant selection. In this study, a primigravida is defined as a woman in her first pregnancy. The first trimester is considered the gestational age from the day of the last menstrual period to 13 weeks of gestation, as assessed from the ultrasound report. Anemia is characterized by a reduction in hemoglobin concentration, leading to a corresponding decrease in hematocrit levels. Iron deficiency anemia (IDA) is diagnosed if a woman exhibits any three of the following criteria: hemoglobin levels less than 11 g/dL, ferritin levels less than 12 µg/ml, transferrin saturation below 15%, or a mean corpuscular volume (MCV) less than 80 femtoliter. The study also assessed several factors associated with IDA: advanced maternal age refers to women aged 35 years or older at the time of enrollment; underweight BMI is defined as a body mass index (BMI) between 15 and 18.5 kg/m^2, measured at the time of presentation; low educational status refers to no formal education or education up to the fifth standard; and low socioeconomic status was defined as a family income of 25,000 PKR or less per month. The inclusion criteria consisted of primigravida women aged between 18 and 49 years, with a singleton pregnancy confirmed through ultrasound, a gestational age of less than 13 weeks, and a diagnosis of IDA as per operational definition. Women who refused to participate or had a known cause of anemia other than IDA before pregnancy confirmation were excluded. After obtaining informed consent, data were collected from eligible women during their first antenatal visit at the outpatient department. Socio-demographic characteristics and potential factors associated with IDA were documented as per the operational definition. Routine antenatal screening was performed, and data

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confidentiality was ensured by assigning codes instead of names and keeping the data password-protected. The collected data were entered into SPSS-21, and descriptive statistics, including mean ± SD for age, gestational age, height, weight, and BMI, were calculated. Factors associated with IDA, such as advanced maternal age, underweight BMI, low socioeconomic status, and low educational status, were reported in frequencies and percentages.Effect modifiers were controlled by stratifying age in years and gestational age in weeks, with comparisons between stratified groups made by Chi-square analysis.A p-value of <0.05 was considered statistically significant.

RESULTS

This current research included 155 participants to evaluate the prevalence of determinants of iron deficiency anemia (IDA) in primigravida females during their first trimester. The participant's average age was 27.50 ± 5.36 years with C.I (26.65-28.36), with a mean gestational age of 7.93 ± 2.07 weeks, with C.I (7.60-8.26) weeks. The average height was 156.44 ± 5.81 cm with C.I (155.52-157.36), and the mean weight was 65.90 ± 10.84 kg with C.I (64.18-67.62).The typical BMI was 28.84 ± 4.10 kg/m2 with C.I (28.19-29.49). The results summarize the descriptive statistics for age, gestational age, height, weight, and BMI in the study population (n=155). It includes the mean, 95% confidence interval for all.These statistics provide a clear overview of the central tendencies and variability of the key variables in the study(Table 1).

Table 1: Descriptive Statistics of Demographic and Anthropometric Variables

Descriptive Statistic	Age (Years)	Gestational Age (Weeks)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean	27.5097	7.9355	156.4452	65.9032	28.8471
95% C.I for Mean (Lower Bound)	26.6590	7.6062	155.5227	64.1822	28.1957
95% C.I for Mean (Upper Bound)	28.3604	8.2648	157.3676	67.6243	29.4985
5% Trimmed Mean	27.4677	7.9767	156.2204	65.5197	28.6900
Median	27.0000	8.0000	156.0000	67.0000	28.0000
Variance	28.745	4.307	33.794	117.646	16.852
SD	5.36144	2.07545	5.81327	10.84649	4.10512
Minimum	18.00	4.00	145.00	43.00	20.00
Maximum	40.00	12.00	172.00	111.00	44.00
Range	22.00	8.00	27.00	68.00	24.00
Interquartile Range	8.00	4.00	8.00	12.00	5.00
Skewness	0.158	-0.116	0.442	0.631	0.737
Kurtosis	-0.803	-0.970	-0.093	1.703	0.998
Standard Error	0.43064	0.16670	0.46693	0.87121	0.32973

Regarding the frequency of associated factors, advanced maternal age was established to be a major contributor to iron deficiency anemia in 27 (55.10%) women, underweight in 2 (4.08%), low educational status in 7 (14.28%), and low socioeconomic status in 13(26.53%)women(Table 2).

Table 2: Frequency of Associated Factors with IDA in Primigravida Female During the First Trimester(n=49)

Associated Factors	Frequency (%)
Advanced Maternal Age	27(55.10%)
Under Weight BMI	2(4.08%)
Low Educational Status	7(14.28%)
Low Socioeconomic Status	13(26.53%)

*The table includes data from the entire cohort of patients, specifically primigravida female attending the Obstetrics and Gynecology outpatient department at Agha Khan University Hospital.

A highly significant variation in the prevalence of IDA was observed between age groups (18-30 years versus >30 years), resulting in a p-value<0.001. However, no notable difference was detected between the gestational age groups(1-7 weeks versus 8-13 weeks), with a p-value=0.260 (Table 3).

Table 3: Stratification of Age Group and Gestational Age Group with Associated Factors of IDA(n=49)

Age Group (Years)	18-30	>30	p-value
Advanced Maternal Age	2(4.1%)	25(51.0%)	<0.001
Underweight BMI	2(4.1%)	0(0%)	
Low Educational Status	5(10.2%)	2(4.1%)	
Low Socioeconomic Status	9(18.4%)	4(8.2%)	
Gestational Age Group (Weeks)	**1-7**	**8-13**	0.260
Advanced Maternal Age	14(28.6%)	13(26.5%)	
Underweight BMI	1(2.0%)	1(2.0%)	
Low Educational Status	1(2.0%)	6(12.2%)	
Low Socioeconomic Status	4(8.2%)	9(18.4%)	

Applied Chi-square table

The analysis revealed that advanced maternal age was the most significant factor associated with iron deficiency anemia (IDA) in the study population. Among the various parameters assessed, advanced maternal age was

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identified as the most commonly associated factor, with 27 (55.10%) of the women with IDA falling into this category. This finding underscores the critical role of maternal age in the prevalence of IDA, suggesting that older age may increase the risk of developing this condition during pregnancy. While other factors, such as low socioeconomic status, underweight BMI, and low educational status, were also associated with IDA, advanced maternal age emerged as the strongest predictor in this population.

DISCUSSION

IDA is a significant global health issue, especially among pregnant women, due to the elevated iron requirements during pregnancy.Anemia affects over a quarter of the global population, and one of the main causes of anemia in expectant mothers is a lack of iron.In our study, 27.5% of the women were found to be anemic, with a similar proportion (27.5%) suffering from IDA. This is in contrast to previous studies in Bahrain, where 41.9% had anemia and 40% had IDA [17].The improvement in the prevalence of IDA in Bahrain may be attributed to recent improvements in healthcare services and the provision of free iron supplementation to pregnant women. Other factors, such as better sanitation, improved living standards, and enhanced food quality, may have contributed to this reduction.None of the pregnant women in our study exhibited severe anemia, which is consistent with findings from a similar study conducted in Egypt, where the prevalence of severe anemia (hemoglobin level of less than 7 g/dl) was found to be 3% only [18]. In our study, women with lower educational levels had significantly lower serum ferritin, indicating a lack of awareness about proper nutrition, particularly regarding iron-rich foods. This result with line Wiafe *et al.*, in which the authors divided the factors into two categories: direct factors, like food consumption habits, transmission of malaria, worm invasion, female gender, and bleeding, and indirect factors, like income level, rural living, the number of children, religion, and barefoot strolling.Higher learning was found to be a major factor in this study [19].In another study conducted in Ghana, similar results were found, with education level being a significant contributor and risk factor for anaemia during pregnancy.The authors further emphasized the importance of continuous education for pregnant women to mitigate anaemia risks [20].We also found that women with a history of more than two pregnancies or deliveries had a higher prevalence of IDA, which aligns with Feyissa *et al.*, where significant association between short inter-birth intervals (SIBI) and anemia was found, showing an 181% increase in anemia with SIBI (OR of 2.81;95% CI: 1.30–4.31) compared to optimal birth intervals.Additionally, SIBI was significantly associated with gestational diabetes mellitus and antenatal or postnatal depression, but no significant association was observed with preeclampsia [21]. Furthermore, IDA was more common among women in their third trimester, likely due to the increased iron demands as gestational age advances [22-24].We found that advanced maternal age was a significant risk factor, accounting for 27% of cases of iron deficiency anemia. This finding is consistent with a study conducted in Indonesia, which also revealed a significant relationship between maternal age and anemia, with a p-value of 0.046, indicating statistical significance [25].Most dietary interventions have proven effective in treating iron-deficiency anemia. While many randomized controlled trials have focused on increasing iron and/or vitamin C intake, combining both strategies appear to be the most effective approach. Additionally, vitamin D shows potential as a therapeutic option, although further research is needed to confirm these findings. Based on these insights, dietary interventions for anemic female patients should prioritize increasing both iron and vitamin C intake [26]. Calcium supplementation negatively affects iron absorption, with a dose-dependent reduction in absorption observed at levels commonly found in normal diets [27]. In a study conducted by Lynch S, it was found that increased dairy consumption may have a small negative impact on iron absorption, particularly during pregnancy if iron supplements are not taken [28].Recent studies have shown that in iron-deficient women, oral iron doses ≥60 mg, and ≥100 mg in women with iron-deficiency anemia (IDA), increase serum hepcidin levels, which peak at 24 hours and subside by 48 hours. To optimize iron absorption, iron should be given on alternate days, with morning doses recommended to enhance absorption due to the circadian increase in hepcidin.A pooled analysis indicates that higher total iron absorption occurs when double the daily iron dose is taken on alternate days.Therefore, the optimal regimen for women with iron deficiency or mild IDA is providing 60–120 mg of iron as a ferrous salt with ascorbic acid on alternate days in the morning [29].Several studies have documented the positive impact of iron supplementation on improving hemoglobin levels during pregnancy, which is in line with the results of our study [29-31].Prophylactic iron supplementation is likely to lead to a significant decrease in maternal anemia during pregnancy [32-34].Georgieff *et al.*, in their study, suggested that prophylactic iron supplementation is expected to substantially reduce the incidence of maternal anemia during pregnancy [35]. In a study conducted by Banerjee *et al.*, it was concluded that intermittent oral iron supplementation at a median dose of 120 mg/day shows similar effectiveness to daily oral iron supplementation at a median dose of 60 mg/day in raising hemoglobin levels among pregnant women, while also significantly reducing adverse events [36].Oral iron has low absorption, which makes it frequently useless for the prevention and management of a shortage of iron deficiency, according to

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a different study by Benson *et al.* Furthermore, it commonly results in gastrointestinal issues that might impair pregnant women's quality of life.There are currently options for intramuscular iron compositions that come in single or multiple doses. Pregnant women who do not respond well to oral iron supplements should give newer intravenous formulations serious consideration since there is growing evidence that they are secure and safe throughout the second and third trimesters [31]. In low- and middle-income countries (LMICs), intravenous ferric carboxymaltose may be a viable and long-term treatment for anemia caused by a shortage of iron during childbearing.Yet, only a small percentage of people who have a greater socioeconomic level and full medical insurance coverage are expected to benefit from the IVON trial's recommendations until serum ferritin tests and intravenous ferric carboxymaltose become generally available and reasonably priced. In conclusion, the most practical and successful treatment for anemia during pregnancy in LMICs is probably oral iron administration, where the majority of women face economic challenges and lack health insurance coverage [37].In our study, the mean maternal age was 27.50 ± 5.36 years, and the mean gestational age was 7.93 ± 2.07 weeks.Among the associated factors, advanced maternal age was found to be responsible for IDA in 27 (55.10%) of the women, with underweight BMI affecting 2 (4.08%), low educational status affecting 7 (14.28%), and low socioeconomic status affecting 13 (26.53%) women.A highly significant difference was observed when comparing the age groups of 18-30 years and >30 years ($p<0.001$), but no significant difference was found between gestational age groups (1-7 weeks) and (8-13 weeks) ($p=0.260$).Our findings align with those of national and international studies.The strength of our study lies in the use of consecutive sampling, which was ideal for our design and sample selection, given the strict inclusion and exclusion criteria.The use of clear and objective definitions for both predictor and outcome variables helped minimize potential biases. However, the sample size and the clinic-based setting may limit the external applicability of our results. The institution where this study was conducted serves a diverse patient population from various demographics and socioeconomic backgrounds across the country.Therefore, while the sample was drawn from a single clinic, the diversity of the patient population strengthens the relevance of our findings.

CONCLUSIONS

It was concluded that anemia is significantly prevalent among pregnant women in our population. Maternal anemia is linked to maternal age and low socioeconomic status.The findings indicate the urgent need for educating expectant mothers and their families regarding the significance of prenatal care.Future research should include randomized studies with larger sample sizes and multiple study centers across Pakistan to validate the findings of the present study.

Authors Contribution

Conceptualization: AA[1]
Methodology: AA[1], SI, AA[2]
Formal analysis: ZAP
Writing review and editing: FAB, NZ, LU
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Hypoglycemia and Hypothermia amongst Newborns Admitted at Pediatrics Emergency of CLF Larkana

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ABSTRACT

Neonatal hypoglycemia is a prevalent metabolic disorder associated with acute neurological issues and long-term developmental complications. **Objectives:** To assess the frequency of hypoglycemia and hypothermia among newborns admitted to the Neonatal Emergency Department at Child Life Foundation (CLF), Larkana. **Methods:** The study, conducted from August 15, 2022, to February 15, 2024, involved 200 neonates of both genders in the Neonatal Emergency Department of CLF, SMBBMU, Larkana.Comprehensive demographic and clinical data—including age, gender, delivery mode, birth location, and maternal residence were collected. Axillary temperature was measured using a sterilized thermometer, and capillary glucose was assessed at five intervals(2, 6, 12, 24, and 48 hours' post-birth)before feeding using an Accu-Chek Glucometer. **Results:** In a study of 200 newborns, the average age was 3.2 ± 2.4 days, with a mean height of 48.3 ± 7.3 cm, weight of 2.7 ± 0.8 kg, and gestational age of 39.6 ± 6.3 weeks. Most participants were female, and 42.5% were appropriate for gestational age. Cesarean section was the most frequent delivery method(48%). Hypoglycemia occurred in 16% of cases, while hypothermia was more common, affecting 47.5% of newborns. Hypothermia showed significant associations with lower height (p=0.008), weight, gestational age, and cesarean/instrumental deliveries.Hypoglycemia was significantly linked to low birth weight, with gestational age and delivery location showing borderline significance. Gender and age had no notable effects. Data were analyzed using SPSS version 20.0. **Conclusions:** Hypothermia was more frequent than hypoglycemia among the admitted neonates. Further research is needed to validate and expand on these findings.

INTRODUCTION

Glucose is the primary fuel for brain metabolism, with infants and children experiencing higher glucose utilization rates than adults. Hypoglycemia in these groups should be considered a medical emergency, potentially leading to seizures, permanent neurological injury, and even death if not treated properly [1]. Severe hypoglycemia can result in long-term neurodevelopmental disorders, including cognitive deficits, motor impairments, behavioural challenges, and an increased risk of visual or auditory deficiencies [2]. Neonatal hypothermia prevalence varies by nation, ranging from 11% to 95%, with Sub-Saharan Africa having the highest rates [3, 4]. Neonatal hypoglycemia is a frequent metabolic condition in infants, sometimes presenting with nonspecific or no symptoms. Possible signs include jitteriness, rapid breathing, low muscle tone, poor feeding, apnea, unstable temperature, seizures, and lethargy [5, 6]. The American Academy of Pediatrics advises a target blood glucose level of 45 mg/dL

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or above before normal feedings, as well as blood glucose intervention [7]. Lower birth weight and gestational age are important risk factors for moderate/severe hypothermia, as are delivery before arrival, hemodynamic assistance during resuscitation, and ventilation support [8, 9]. In 2022, 2.3 million babies died in their first month of life, accounting for over half (47%) of all fatalities in children under the age of five, emphasizing the need for enhanced intrapartum and neonatal care [10]. Hypothermia, defined as an axillary temperature below 36.5°C, also significantly contributes to neonatal morbidity and mortality globally, affecting both developed and developing nations. "In particular, our setting presents several unique characteristics that may influence the presentation and management of neonatal hypoglycemia and hypothermia. Larkana is a semi-urban district in Sindh, Pakistan, with limited access to advanced neonatal care, frequent power outages affecting thermal regulation, high rates of home births, and socioeconomic challenges that may delay timely care-seeking. The patient population served by CLF often includes neonates from rural areas, presenting late or without adequate perinatal support. These contextual factors are underrepresented in existing research, particularly in comparison to Western or urban tertiary care environments."

This study aims to assess the frequency of neonatal hypoglycemia and hypothermia among newborns admitted to the neonatal emergency department of Child Life Foundation (CLF), Larkana. Accurate estimation of these disorders may assist clinicians and policymakers in allocating appropriate resources and management strategies to mitigate their impact.

METHODS

The cross-sectional investigation was conducted in the Neonatal Emergency Department at Shaheed Mohtarma Benazir Bhutto Medical University (SMBBMU) in Larkana from August 15, 2022, to February 15, 2024. The study received approval under Letter No. CPSP/REU/PED-2018-221-4697, dated. Its primary objective was to assess the frequency of hypoglycemia and hypothermia among newborns admitted to the neonatal emergency department. A non-probability, consecutive sampling method was applied. All parents or guardians of the enrolled babies were informed about the study, and written consent was obtained. The Neonatal Emergency Department evaluated the occurrence of hypoglycemia and hypothermia in admitted newborns, aiming to determine their frequency and associated risk factors. A detailed history and physical examination of each newborn was carried out. Data such as age (hours/days), gender, mode of delivery (spontaneous vaginal delivery, cesarean section, or instrumental), place of delivery (inborn: born within the institution where the study was conducted, or out born: born elsewhere), and maternal area of residence (urban: district-level city, or rural: below district level) were collected using a pre-designed proforma (annexure attached). Axillary temperature was measured following the operational definition. To prevent infection transmission, the thermometer was sanitized with 70% ethyl alcohol and a wet towel after each use. Glucometer (Accu-Chek Glucometer Roche) was used to monitor capillary blood glucose levels at 2, 6, 12, 24, and 48 hours before feeding, after a heel prick was performed under aseptic circumstances. Hypoglycemia was defined as a blood glucose level below 40 mg/dL. The institution's laboratory received a blood sample for confirmation that capillary glucose levels were less than 25 mg/dL. Neonatal hypoglycemia is a common metabolic disorder in newborns that may present with nonspecific clinical symptoms or remain entirely asymptomatic. Infants showing signs of hypoglycemia, such as jitteriness, tachypnea, hypotonia, poor feeding, apnea, temperature instability, seizures, or lethargy, were closely monitored and evaluated during the study. To determine the required sample size, the following statistical formula was used: $n = Z^2 \times p \times (1-p) \div e^2$, where Z = 1.96 (for 95% confidence level), p = 0.152 (15.2% expected prevalence of hypoglycemia), e = 0.05 (margin of error). Applying the values: $n = (1.96)^2 \times 0.152 \times (1 - 0.152) \div (0.05)^2 = 197$. Based on this calculation, a sample size of 197 neonates was estimated, and to ensure comprehensiveness, the number was rounded up to 200 participants. A non-probability, consecutive sampling technique was used to recruit eligible newborns for the study [11]. During sample collection, the inclusion criteria involved newborns of both genders admitted through the neonatal emergency department. The exclusion criteria included newborns whose mothers had diabetes, gestational diabetes, preeclampsia, eclampsia, hypertension, newborn infections, congenital malformations, or jaundice. The mother's blood glucose levels were also checked to rule out diabetes mellitus and gestational diabetes. Additionally, cases where parents or guardians were unwilling to enroll their baby in the study were excluded. The data were analyzed using SPSS version 20.0. Categorical variables like gender, birth weight (SGA / AGA / LGA), presence of hypoglycemia, presence of hypothermia, gestational age, mode, and place of delivery were represented in terms of frequencies and percentages. Quantitative variables like age and gestational age were represented as mean and standard deviation. Effect modifiers like gender, age, height, weight, gestational age, mode, and place of delivery were controlled through stratification. Post-stratification, a Chi-square test was applied to compare study variables amongst hypoglycemic and normoglycemic as well as normo-thermic and hypothermic newborns. A p-value less than or equal to 0.05 was considered statistically significant.

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RESULTS

In this study, 200 patients were included to assess the hypoglycemia and hypothermia amongst newborns admitted at the neonatal emergency department of CLF, Larkana, and the results were analyzed. The mean ± SD of age was 3.2 ± 2.4 with C.I: 2.91, 3.58 days, height was 48.3 ± 7.3 with C.I: 47.28, 49.31) cm, weight was 2.7 ± 0.8 with C.I: 2.58, 2.81 kg and gestational age was 39.6 ± 6.3 with C.I: 38.72, 40.47 weeks (Table 1).

Table 1: Descriptive Statistics of Weight (n=200)

Variable	Mean ± SD	95% CONFID: Interval	Mini	Max	Range
Age	3.2 ± 2.4 Days	2.91-3.58	0.4	9.6	9.2
Weight	2.7 ± 0.8 Kgs	2.58-2.81	1.8	3.8	2.0
Height	48.3 ± 7.3(cm)	47.28-49.31	42	60	18
Gestation Age	39.6 ± 6.3 (Weeks)	38.72-40.47	37	44	7

In frequency distribution of gender, 77 (38.5%) were male while 123 (61.5%) were female while in frequency distribution for birth weight, small for gestational age (SGA) was noted in 45 (22.5%) children, appropriate for gestational age were 85 (42.5%) while large for gestational age were noted in 30 (15.0%) patients. In the distribution of gestational age, 37-39 weeks for maternal age was noted in 108 (54.0%) while >39 weeks was noted in 92 (46.0%) women, and frequencies of modes of delivery, spontaneous Vaginal Delivery (SVD) was documented in 73 (36.5%), cesarean section in 96 (48.0%) while instrumental mode of delivery was noted in 31 (15.5%). Inborn place of delivery was noted in 134 (67%) while out-born place of delivery was noted in 66 (33%), in addition to 61 (30.5%) were residents of urban areas, while 139 (69.5%) belonged to rural areas (Table 2).

Table 2: Frequency Distribution of Demographic and Other Variables

Variables		Frequency (%)
Age	Male	77 (38.5%)
	Female	123 (61.5%)
Birth Weight	SGA	45 (22.5%)
	AGA	85 (42.5%)
	LGA	30 (15.0%)
Gestational Age	37-39	108 (54.0%)
	>39	92 (46.0%)
Modes of Delivery	SVD	73 (36.5%)
	CS	96 (48.0%)
	Instrumental	31 (15.5%)
Place of Delivery	In Born	134 (67.0%)
	Out Born	66 (33.0%)
Residence Status	Urban	61 (30.5%)
	Rural	139 (69.5%)

Hypoglycemia was found in 32 (16%) (Figure 1).

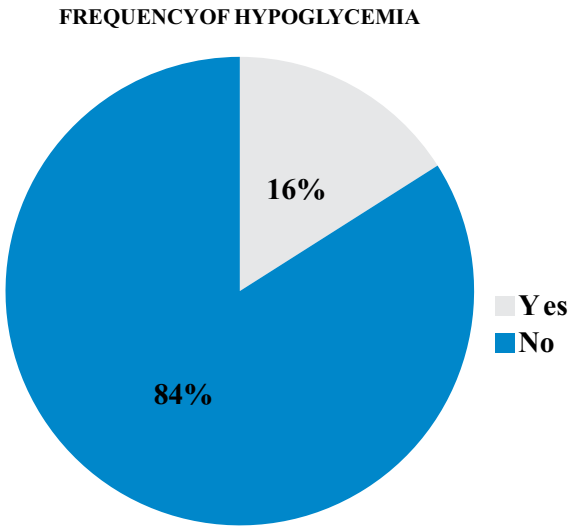

Figure 1: Frequency of Hypoglycemia (n=200)

Hypothermia was found to be in 95 (47.5%) (Figure 2).

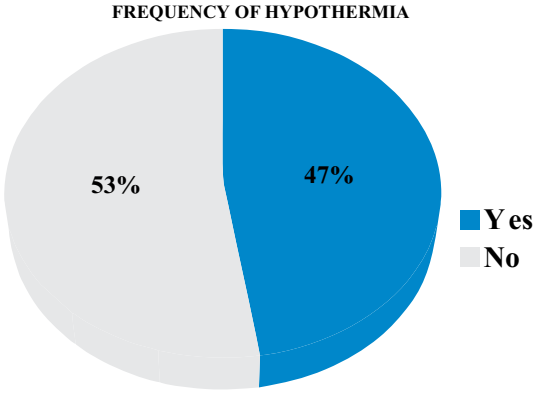

Figure 2: Frequency of Hypothermia (n=200)

These data imply that height (p=0.008), weight (p=0.0001), gestational age (p=0.0001), and method of delivery (p=0.032) are critical risk factors for hypothermia, with statistically significant associations, whereas age group (p=0.11), gender (p=0.454), and site of delivery (p=0.056). have no substantial effect on its prevalence (Table 3).

Table 3: Stratification of Different Variables with Hypothermia (n=200)

Variables		Hypothermia		p-value
		Yes	No	
Age Group (Days)	0.4-3	68 (34.0%)	64 (32.0%)	0.113
	>3	27 (13.5%)	41 (20.5%)	
Gender	Male	34 (17.0%)	43 (21.5%)	0.454
	Female	61 (30.5%)	62 (31.0%)	
Height (cm)	42-50	53 (26.5%)	39 (19.5%)	0.008
	>50	42 (21.0%)	66 (33.0%)	
Weight (Kg)	1.8-2.5	44 (22.0%)	79 (39.5%)	0.0001*
	>2.5	51 (25.5%)	26 (13.0%)	
Gestational Age (Weeks)	37-39	36 (18.0%)	72 (36.0%)	0.0001
	>39	59 (29.5%)	33 (16.5%)	
Mode of Delivery	SVD	29 (14.5%)	44 (22.0%)	0.032
	CS	45 (22.5%)	51 (25.5%)	

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	Instrumental	21(10.5%)	10(5.0%)	
Place of Delivery	In Born	70(35.0%)	64(32.0%)	0.056
	Out Born	25(12.5%)	41(20.5%)	

Applied Chi-Square test

In finding, a statistically significant association was observed between birth weight and hypoglycemia using the Chi-square test (p=0.035), indicating increased risk in low-birth-weight neonates. Borderline significance was observed in gestational age (p=0.068) and place of delivery (p=0.061). Meanwhile, non-significant factors included age group (p=0.648), gender (p=0.788), height (p=0.620), and mode of delivery (p=0.288), indicating that these variables did not have a substantial impact on hypoglycemia occurrence (Table 4).

Table 4: Stratification of Different Variables with Hypoglycemia (n=200)

Variables		Hypothermia		p-value
		Yes	No	
Age Group (Days)	0.4-3	20(10.0%)	112(56.0%)	0.648
	>3	12(6.0%)	56(28.0%)	
Gender	Male	13(6.5%)	64(32.0%)	0.788
	Female	19(9.5%)	104(52.0%)	
Height (cm)	42-50	16(8.0%)	76(38.0%)	0.620
	>50	16(8.0%)	92(46.0%)	
Weight (Kg)	1.8-2.5	25(12.5%)	98(49.0%)	0.035
	>2.5	7(3.5%)	70(35.0%)	
Gestational Age (Weeks)	37-39	22(11.0%)	86(43.0%)	0.068
	>39	10(5.0%)	82(41.0%)	
Mode of Delivery	SVD	13(6.5%)	60(30.0%)	0.288
	CS	17(8.5%)	79(39.5%)	
	Instrumental	2(1.0%)	29(14.5%)	
Place of Delivery	In born	26(13.0%)	108(54.0%)	0.061
	Out born	6(3.0%)	60(30.0%)	

DISCUSSION

Neonatal hypothermia is a prominent issue in low-resource settings [12].Hypoglycemia has been reported in approximately 8% of large-for-gestational-age infants (mainly diabetic mothers' infants, or IDMs), preterm infants (15 percent), and intrauterine growth retardation infants (15%); the overall incidence of "high-risk" infants could reach 30% [13].Neonatal hypoglycemia is a condition where infants experience symptoms such as hypoglycemia, lethargy, poor feeding, jitteriness, seizures, congestive heart failure, cyanosis, apnea, and hypothermia. Autonomic nervous system activation can cause anxiety, tremulousness, diaphoresis, tachycardia, pallor, hunger, nausea, and vomiting [14].The fetus receives its glucose supply mostly from the mother in healthy pregnancies [15].Glucose is transferred through the placenta by facilitated diffusion, and fetal plasma glucose levels are typically 8-15 mg/dL lower than maternal levels [16].Serum glucose levels in newborns decrease after delivery until age 1-3 hours, at which point they rise spontaneously [17].Infants at risk for hypoglycemia have higher postpartum insulin levels than children and adults, which exacerbates this decline [18].The persistence of elevated insulin levels has been explained by several ideas. These include stress response before birth, pancreatic B-cell hypersensitivity, and Insulin is transferred from the mother to the fetus through the placenta.Lower blood ketones are associated with higher insulin levels [19]. Even in warm tropical environments, newborn hypothermia has been linked to mortality and morbidity in both low- and normal-birthweight neonates [20].All babies should receive critical newborn care, a basic suite of therapies that includes the prevention of neonatal hypothermia [21]. Subsequent advancements in infant thermal care have mostly been restricted to industrialized nations, where strategies for preventing and efficiently managing hypothermia have been well investigated [22].Globally, data on neonatal hypothermia is predominantly from hospitals, and prevalence has ranged between 32% to 85% soon after birth [23], and much of it is based on hospital-based statistics that thermal stress is widespread [24, 25], and over half of neonates suffer hypothermic episodes [20, 25], according to several hospital-based studies conducted in such circumstances.Our study's results are similar to those of several other researchers, who are mentioned below.Babies hospitalized with hypothermia, which is generally defined as any temperature reading below 36.0°C, have a greater mortality risk, according to some hospital-based research [26, 27].Current study's results are similar to those of several other studies that are mentioned below. In our study, the mean age was 3.2 ± 2.4 days. Singh *et al.*, found the mean age to be 5 ± 4.65 days [11], while another study documented the mean age to be 67.4 ± 121.4 hours [26].In the present study, the mean gestational age was 39.6 ± 6.3 weeks. The mean gestational age was 37.3 ± 2.9 weeks, found in the study of Ogunlesi *et al.*, [26]. In this study, 77(38.5%) were male while 123(61.5%) were female. 65 (52%) male babies and 60 (48%) female babies were part of the study findings of Singh *et al.*, [11]. In another study, 93 (62%) male and 57 (38%) female was reported [26].In the current study, small for gestational age (SGA) was noted in 45 (22.5%) children, appropriate for gestational age was 85 (42.5%), while large for gestational age was noted in 30 (15%) patients. Singh *et al.*, reported small for gestational age 26 (20.8%) and appropriate for gestational age 99 (79.2%) [11].While in the study of Ogunlesi *et al.*, 58% were small for gestational age (SGA) [26]. In a recent study, an inborn place of delivery was found in 134 (67%) patients, while an out-born place of delivery was noted in 66 (33%) patients. Ogunlesi *et al.*, found 60 (40%) inborn babies and 90 (60%) out-born babies [26]. This study found hypoglycemia in 32 (16%) patients. A study from Manipur, India, evaluating 125 newborns calculated

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that 19 (15.20%) were found to be hypoglycemic [11].In a recent study, stratifications were statistically not significant relation was observed about hypoglycemia was noted in age group (p=0.648), gender (p=0.788), height (p=0.620), gestational age (p=0.068), mode of delivery (p=0.288), place of delivery (p=0.061), while significant difference was noted in weight (p=0.035).

CONCLUSIONS

It was concluded that hypothermia was more common (47.5%) in neonates admitted to a tertiary care center's emergency department than hypoglycemia (16%). Factors like low birth weight, gestational age, and cesarean delivery were associated with hypothermia, while low birth weight was the only significant factor related to hypoglycemia. The study emphasizes the need for early detection protocols and urgent thermal care practices in neonatal units and calls for further large-scale, multicenter studies to confirm these associations.

Authors Contribution

Conceptualization: A
Methodology: SL
Formal analysis: ARS
Writing review and editing: VKG, DM, ABS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Relationship of Systemic Inflammatory Markers and Body Mass Index with Primary Osteoarthritis

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Osteoarthritis, Inflammatory Markers, Body Mass Index, Radiographic Progression

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ABSTRACT

Osteoarthritis (OA) is degenerative disorder which involves synovial inflammation. Erythrocyte sedimentation rate, Body mass index and C-reactive protein are commonly used markers to determine infection or inflammation. **Objective:** To measure the level of raised levels of erythrocyte sedimentation rate and C-reactive protein in primary osteoarthritis and to identify the association of body mass index with osteoarthritis in Pakistani population. **Methods:** This descriptive cross-sectional study was conducted at Department of Rheumatology, Shaikh Zayed Hospital, Lahore, Pakistan from July 2021 to April 2022. A total of 216 patients were enrolled. All patients over the age of 30 years with primary osteoarthritis were included. Association of C-reactive protein and erythrocyte sedimentation rate with OA grade and highest score in case of multiple joints were checked by using chi-square test and odds ratio. **Results:** Most were females and large group of individuals were overweight or obese. Mean BMI was 29.50 ± 4.94 kg/m^2.The radiographic progression of OA was seen more in women compared to men for Grade 4 OA.The systemic inflammatory markers erythrocyte sedimentation rate and C-reactive protein were plotted against the Grade of OA and it was found that erythrocyte sedimentation rate was elevated in (n=118) most individuals however C-reactive protein was normal in the majority (n=196). Radiographic advancement of OA with the rise of these acute phase reactants was not significant i.e. p-value was 0.804 for erythrocyte sedimentation rate and 0.497 for C-reactive protein. **Conclusion:** There was no significant correlation between raised inflammatory markers and radiographic progression of osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is common degenerative disease of joints and is a frequent cause of morbidity. OA of the knee is one of the most common forms of arthritis in synovial joints and it is usually present in the elderly. Synovial inflammation and wear and tear process in joints is thought to play a dominant role in the development of joint pain, swelling and cartilage destruction [1]. Patients can have primary or secondary osteoarthritis based on absence or presence of any prior medical condition respectively [2]. However Primary OA can be associated with risk factors like advancing age, female gender, body mass index (BMI) >30, body habitus, muscle weakness, and joint injury from sports or as an occupational hazard. Predisposing medical conditions include trauma, congenital joint disorders, inflammatory and infectious arthritis, avascular necrosis, connective tissue disorders and metabolic problems are common causes of secondary OA [3]. Body mass index is found to be associated with development and progression of knee osteoarthritis [4]. Obese (BMI >30) individuals have higher risk of developing knee OA than people with normal weight (BMI <25) [5, 6]. Aiming at weight reduction and physical rehabilitation as a non-pharmacological therapy for management of OA has been proven effective in many studies [7, 8]. The diagnosis of OA almost always involves clinical and radiographic assessment of joint damage, which is useful only after the disease process has been underway for several months. The radiological evaluation gives grading and level of osteoarthritis [9]. When it comes to diagnosing and tracking inflammatory disorders including infections, autoimmune diseases, and

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malignancies, primary care physicians frequently turn to inflammatory indicators like Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). The slowest of these inflammatory measures, erythrocyte sedimentation rate is the millimeters that erythrocytes settle in one hour of anticoagulated whole blood. Because it increases at a faster rate than the other two tests when inflammation occurs, C-reactive protein is commonly believed to be the best indicator of infection severity [10]. The pathophysiology of OA involves loss of cartilage due to lack of functional chondrocytes and decrease remodelling of subchondral bone which in turn starts the inflammatory cascade to bring about the cartilage breakdown [11]. Cytokines, chemokines, and mixed matrix metalloproteinase are some of the molecules that play a role in the regulation of the joint anabolism and catabolism process [12] Because of the apparent absence of systemic inflammation in OA, acute-phase response proteins (APPs) have not been as extensively studied in OA as they have been in RA. There are several recent reports that ESR and CRP are slightly elevated in OA. In a study done by Mitsuru Hanada in 2016 ESR and high sensitivity CRP concentrations were higher in patients with knee osteoarthritis than in patients without knee OA due to inflammation of the involved joint [13]. This study determined the direct association of BMI with the development and progression of OA in Pakistani population. Whether the systemic inflammatory markers rise in response to the severity of OA was also observed through this cross sectional survey.

METHODS

This descriptive cross sectional study was conducted among outdoor patients visiting rheumatology clinic Shaikh Zayed Hospital, Lahore, Pakistan from 1st July 2020 to 30th April 2021 with an ethical approval Ref No. SZMC/IRB/0088/2021, obtained from Institutional Review Board (IRB) prior to data collection. Informed written consent was taken from patients for detailed demographics.Patients with age >30 and having primary osteoarthritis were included.Patients with secondary OA and acute infection were excluded.Non probability consecutive technique was used for sampling. Sample size (216) was calculated by using the formula, n=(Z^2 * p*(1-p))/ E^2 with 95% confidence interval (Z=1.96), 5% margin of error (E=0.05) and an estimated prevalence of osteoarthritis of 6% (p=0.06) [17].A well designed questionnaire filled by researcher about their basic demographic profile, height and weight measurement for calculation of BMI and running investigations like X-ray of involved joints, ESR and CRP for study population.The ESR was measured with Westergren method[14] where ESR< 15 is normal 15-50 is elevated, >50 is high.The CRP was calculated with latex agglutination test.The CRP <6 is normal, 6-12 is elevated and >12 is high. The height and weight was taken for every patient and Body mass index (BMI) calculated. The patients are categorized as underweight: <19, Normal: 19-24, Overweight: 25-29, Obese: 30-35, severely obese: 35-40, morbidly obese: >40. Patients with history of fever, cough, sputum, abdominal disturbance or urinary burning or pus in urine were excluded. The patients of primary osteoarthritis i.e. not secondary to a disease were graded based on their X-ray findings of the involved joints and must not have any clinical features of other rheumatic diseases the grading on X ray of involved joint was done as per Kellgren Lawrence classification of OA Grade 1 (doubtful joint space narrowing and possible osteophyte lipping), Grade 2 (minimal; definite osteophytes and possible joint space narrowing), Grade 3 (moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends) and Grade 4 (large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends). [15, 16] The highest grade of OA in all joints was documented if many joints were involved. Data analysis was carried out using SPSS version 25.0. Data for age, BMI, ESR and CRP levels were described using mean ± SD for normally distributed variables and Median (IQR) otherwise data for OA score, Gender, no. of joints involved, status of joint, obesity status and raised ESR CRP levels are defined by using frequency and percentages. To determine whether there is a correlation between ESR CRP and advanced OA, multinomial logistic regression was employed. P value <0.05 was considered significant.

RESULTS

The mean age was 54.23 ± 11.21 years with 50 (23.14%) male and 166 (76.85%) female participants. The mean height was 161.07 ± 7.99 centimetres and weight was 76.32 ± 12.36 kilograms. Mean BMI was 29.50 ± 4.94 kg/m^2 (Table 1).

Table 1: Descriptive Statistics of the Patients (n=216)

Variables	Mean ± SD
Age (Years)	54.23 ± 11.21
Height (cm)	161.07 ± 7.99
Wight (Kg)	76.32 ± 12.36
BMI	29.50 ± 4.94
ESR	25.83 ± 20.16
CRP	5.55 ± 1.93

Grade 3 OA was most common, 48.1% radiological presentation followed by Grade OA 35.2%. Of the studied individuals; 2 joints were commonly affected with OA and nearly all times, it was knee joints. More than half 116 (53.7%) of the subjects were homemaker. Most of the study population 104 (48.1%) fell into overweight category (BMI 25-30) (Table 2).

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Table 2: Demographic Information of the Patients(n=216)

Variables	Frequency (%)
Age (Years)	
30-39	24 (11.1%)
40-49	46 (21.3%)
50-59	82 (38%)
>59	64 (2.6%)
Body Mass Index (Kg/m^2)	
<19 (Underweight	2 (0.9%)
19-24 (Normal Weight)	32 (14.8%)
25-29 (Overweight)	104 (48.1%)
30-35 (Obese)	54 (25%)
36-40 (Severe Obese)	18 (8.3%)
>40 (Morbidly Obese)	6 (2.8%)
Osteoarthritis Radiological Grading	
Grade 2	76 (5.2%)
Grade 3	104 (48.1%)
Grade 4	36 (16.7%)
Number of Joints involved	
One	8 (3.7%)
Two	158 (73.1%)
Three	6 (2.8%)
Four	20 (9.3%)
Many	24 (11.1%)
Occupation	
Housewife	116 (53.7%)
Retired	18 (8.3%)
Govt. Job	33 (15.3%)

The joint involvement was seen in different type of joint like small, large or spinal joints. Knees 178 (82.4%) were mostly involved in large joints and wrists 11 (5.1%) among small joints. Only 2 patients had involvement of cervical joints among spinal joints (Table 3).

Table 3: Distribution of Joints of the Patients

Osteoarthritis	Site of Joint Involvement	Frequency (%)
Large Joints	Knee (Unilateral/Bilateral)	178 (82.4%)
	Other (Ankle, Hip, Shoulder, Elbow)	14 (6.5%)
Small Joints	Wrists (Unilateral/Bilateral)	11 (5.1%)
	Other (PIPs, MCPs, CMP, MTP Inter tarsal and Inter carpal)	11 (5.1%)
Spinal Joints	Cervical spine joints	2 (0.9%)
	Other (Lumbar, sacral, thoracic, Sacroiliac)	-

There were no patients with Grade 1 Osteoarthritis.The radiographic progression of OA was seen more in women compared to men for Grade 4 OA i.e. 30 (18%) and 6 (12%) respectively. However, for grade 2 and 3 OA; 18 (36%) and 26 (52%) were men whereas 58 (34%) and 78 (47%) were women.The BMI categories were linked to grades of OA only to find that 2 people with BMI<18 had Grade 3 OA. Among morbidly obese individuals 4 (66.7%) and 2 (33.3%) had grade 2 and grade 3 OA respectively.Most of the sample population was overweight (n=104) with 42 (40.4%), 46 (44.2%) and 16 (15.4%) having grade 2, 3 and 4 OA (Table 4).

Table 4: Association of BMI with the Grade of OA

Grade	Under Weight Frequency (%)	Normal Weight Frequency (%)	Over Weight Frequency (%)	Obese Frequency (%)	Severe Obese Frequency (%)	Morbidly Obese Frequency (%)	Total Frequency (%)	χ^2(p)
Grade 2	-	12 (37.5%)	42 (40.4%)	16 (2.6%)	6 (33.35%)	-	76 (35.2%)	14.1 (0.169)
Grade 3	2 (100%)	12 (37.5%)	46 (44.2%)	28 (51%)	12 (66.75)	4 (66.7%)	104 (48.1%)	
Grade 4	-	8 (25%)	16 (15.4%)	10 (18.5%)	-	2 (33.3%)	36 (16.7%)	
Total	2 (100%)	32 (100%)	104 (100%)	54 (100%)	18 (100%)	6 (100%)	216 (100%)	

The systemic inflammatory markers ESR and CRP were plotted against the Grade of OA and it was found that ESR was elevated in 118 most individuals however CRP was normal in the majority (n=196). CRP was not found to be high in this study population.The correlation of radiographic advancement of OA with the rise of these acute phase reactants was not significant i.e. p-value was 0.804 for ESR and 0.497 for CRP (Table 5).

Table 5: Association of ESR and CRP with the Grade of OA

Grade	Low Frequency (%)	Elevated Frequency (%)	High Frequency (%)	Total Frequency (%)	χ^2(p)
ESR					
Grade 2	30 (37.5%)	38 (32.2%)	8 (44.4%)	76 (35.2%)	1.625 (0.804)
Grade 3	36 (45%)	60 (50.8%)	8 (44.4%)	104 (48.1%)	
Grade 4	14 (17.5%)	20 (16.0%)	2 (11.1%)	36 (16.7%)	
Total	80 (100%)	118 (100%)	18 (100%)	216 (100%)	
CRP					
Grade-2	70 (35.7%)	6 (30.0%)	0 (0%)	76 (35.2%)	1.39 (0.479)
Grade-3	92 (46.9%)	12 (60.0%)	0 (0%)	104 (48.1%)	
Grade-4	34 (17.3%)	34 (17.3%)	0 (0%)	10.0 (16.7%)	
Total	196 (100%)	20 (100%)	0 (0%)	216 (100%)	

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The odds ratio calculated for ESR and CRP to the higher grades of OA i.e. grade 3 and grade 4 only to reveal statistically insignificant (p-value>0.05) correlation between the two (Table 6).

Table 6: Multinomial Logistic Regression CRP and ESR for Grades

Grade	Level	B	P	Odd Ratio
2	ESR	0.007	0.551	1.007 (0.84-1.03)
	CRP	-0.025	0.833	0.975 (0.770-1.235)
3	ESR	0.006	0.572	1.006 (0.985-1.029)
	CRP	0.084	0.457	1.088 (0.872-1.357)

DISCUSSION

According to the present study, the overweight individuals suffered from higher grade of OA in comparison to the normal weight population. The higher the BMI more the radiological progression is expected which is the reason weight loss and diet restrictions are suitable non pharmacological measures are important steps in management. Osteoarthritis of joint is a result of local inflammatory cytokines and adipokines triggered by inflammatory cells. These cytokines and inflammatory cells are taken up by lymphatic system in the joint and eventually enter the peripheral circulation. Here, they can be detected within the blood and is a possible cause of raised inflammatory markers in OA [17]. In previous study, 1235 patients, (or 56% female, mean age 65) had radiographs and inflammatory markers measured. Among the 729 individuals included in the study, 179 had knee OA and 694 had hand OA, indicating radiographic OA in at least one joint. No inflammatory marker was significantly associated with radiological OA. We found no indication that the presence of radiographic OA was associated with any inflammatory marker [18]. One further study looked at the correlation between inflammatory indicators and functional capacity in the elderly with osteoarthritis. There was no statistically significant correlation between physical and disease state and blood C-reactive protein levels. Consistent with previous research, this conclusion applies to 67 individuals diagnosed with knee OA [19]. Another study found that early OA was associated with higher levels of mononuclear cell infiltration and upregulation of inflammatory mediators as compared to late OA [20]. A case control study with 120 patients, 60 with osteoarthritis of knee while rest with no signs of osteoarthritis was done in 2016. The hematological markers to study inflammatory basis of idiopathic osteoarthritis of knee suggested that ESR (erythrocyte sedimentation rate) of more than 20 mm/hour and CRP (C-reactive protein) was positive in 83.3% and13.3% patients respectively. The control group has ESR less than 30 mm/hour and CRP was (<3 µg/ml). In the control group RF and ANA were similar to the normal population. The study indicates that ESR and CRP collectively can serve as surrogate markers in idiopathic osteoarthritis of knee [21]. There were few limitations to the study including the small sample size. Also, many confounders like ongoing infection and anemia affect the acute inflammatory markers which could not all be excluded, an error in the radiological based grading of OA by physician or radiologist. It is still a conflict between the two theories so further studies seem mandatory to establish the link between the inflammatory markers and osteoarthritis and the association of BMI with the development of Primary Osteoarthritis in current population.

CONCLUSIONS

There is direct link of being overweight to development of Osteoarthritis. ESR can be elevated in individuals irrespective of stage of Osteoarthritis. There is no clear co-relation with raised inflammatory markers to progression of osteoarthritis. The patients with Osteoarthritis and high acute phase reactants should be investigated more thoroughly to rule out other significant autoimmune disorders.

Authors Contribution

Conceptualization: RG
Methodology: AR, UH
Formal analysis: RG
Writing, review and editing: RG, THM
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Maternal Hyperuricemia in Normotensive Singleton Pregnancy, a Prenatal Finding with Continuous Perinatal and Postnatal Effects

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ABSTRACT

Maternal hyperuricemia has been associated with various adverse pregnancy outcomes in hypertensive disorders, but its effects in normotensive singleton pregnancies remain unclear. **Objective:** To assess the impact of maternal hyperuricemia on perinatal and postnatal outcomes in normotensive singleton pregnancies, with a focus on birth weight, gestational age, NICU admissions, and gestational anemia. **Methods:** This study was conducted at the Department of Obstetrics and Gynecology, Tertiary Care Hospital, Bahawalpur city, from 30-11-2022 to 29-06-2023. The Study Design was prospective observational cohort study. A cohort of normotensive pregnant women was prospectively followed to assess the association between maternal hyperuricemia and perinatal as well as postnatal outcomes. **Results:** Significant differences were observed in birth weight and gestational age between hyperuricemic and normouricemic mothers. Infants born to normourecemic mothers had higher birth weights (3.80 ± 0.35 kg vs. 3.51 ± 0.40 kg, p = 0.015) and were delivered earlier (38.50 ± 1.20 weeks vs. 39.35 ± 1.00 weeks, p = 0.025). Additionally, hyperuricemic mothers showed a higher prevalence of NICU admissions (42.9% vs. 26.5%, p = 0.035) and gestational anemia (42.9% vs. 19.1%, p = 0.043). Logistic regression revealed that maternal uric acid levels significantly influenced the likelihood of NICU admissions, suggesting a complex interaction with perinatal outcomes. **Conclusions:** Maternal hyperuricemia in normotensive singleton pregnancies significantly influences birth weight, gestational age at delivery, NICU admission rates, and the prevalence of gestational anemia, indicating a notable clinical impact in this population.

INTRODUCTION

Hyperuricemia, defined as an elevated serum uric acid concentration, arises from excessive uric acid production, reduced renal excretion, or a combination of both. It is influenced by metabolic disorders such as metabolic syndrome and renal insufficiency, as well as by dietary and genetic factors [1]. During pregnancy, physiological adaptations, including increased renal plasma flow and glomerular filtration rate, generally lead to lower serum uric acid levels. However, in some cases, maternal hyperuricemia may persist and contribute to adverse pregnancy outcomes, even in normotensive pregnancies [2]. The role of uric acid in pregnancy complications has been widely studied in hypertensive disorders, where its elevation is linked to endothelial dysfunction, vascular inflammation, and oxidative stress, all of which contribute to preeclampsia, Intrauterine Growth Restriction (IUGR), and preterm birth [3]. These mechanisms disrupt placental perfusion, leading to placental insufficiency, which compromises fetal oxygen and nutrient supply, increasing the risk of low birth weight and fetal distress [4]. Studies suggest that even in normotensive pregnancies, elevated uric acid levels correlate with adverse maternal and neonatal outcomes, possibly through similar mechanisms [5]. One major pathophysiological pathway linking hyperuricemia to adverse pregnancy outcomes is vascular dysfunction. Increased oxidative stress and reduced nitric oxide bioavailability lead to endothelial damage, impairing maternal vascular adaptation and causing placental

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hypoxia [6]. Hyperuricemia also stimulates inflammatory cytokine release, exacerbating placental inflammation and dysfunction, which may contribute to gestational anemia, fetal growth restriction, and preterm labor [7]. These effects create a suboptimal intrauterine environment, potentially increasing the need for NICU admissions due to complications such as respiratory distress syndrome and metabolic imbalances [8]. Beyond immediate neonatal concerns, maternal hyperuricemia may have long-term consequences on offspring health. Studies have linked high maternal uric acid levels to altered fetal metabolic programming, predisposing children to hypertension, renal dysfunction, and metabolic syndrome later in life. Roberts L *et al.*, in 2022 study was cited to support the claim that even normotensive pregnancies with complications (such as elevated uric acid levels) may lead to long-term psychological and developmental concerns postpartum. It provides indirect but clinically relevant context to our discussion on the extended perinatal impact of maternal hyperuricemia [9, 10]. Some evidence suggests that elevated fetal uric acid levels contribute to oxidative stress and epigenetic modifications, leading to long-term cardiovascular and metabolic risks. Blake BE and Fenton SE in 2020, early life exposure to PFAS and latent health outcomes supported the section discussing fetal programming and epigenetic effects (see line referencing oxidative stress and epigenetic modifications). Although it focuses on environmental toxins, it offers a mechanistic parallel to how intrauterine exposures including high uric acid may drive long-term metabolic risk in offspring [11]. Additionally, longitudinal research has associated maternal hyperuricemia with an increased incidence of cardiovascular diseases in offspring. Conley JM *et al.*, 2019 noticed an exposure on maternal, fetal, and postnatal outcomes in rats. This animal model study was included to further emphasize mechanistic pathways by which gestational exposures (including elevated uric acid) may affect both prenatal development and postnatal health trajectories, especially in the context of metabolic and oxidative stress [12]. These findings highlight the need for early detection and monitoring of uric acid levels during pregnancy to mitigate both short and long-term maternal and neonatal risks. Sosnowski DW *et al.*, 2023 financial stress as a mediator for NICU admissions provided comparative context in our discussion of NICU admissions. While not specific to uric acid, it highlights other confounding factors (e.g., socioeconomic stress) that influence NICU outcomes. This strengthens our argument that maternal uric acid is an independent predictor when such variables are controlled [13].Despite the well-established association between hyperuricemia and hypertensive pregnancy complications, limited research has examined its independent effects in normotensive pregnancies. Given the rising incidence of metabolic disorders, even in otherwise healthy pregnant women, hyperuricemia may serve as an underrecognized risk factor for adverse perinatal outcomes. However, a key challenge in evaluating these effects lies in distinguishing hyperuricemia from other metabolic risk factors such as obesity, dietary patterns, and genetic predisposition. This study aimed to address these gaps by: Systematically analyzing the relationship between maternal uric acid levels and birth weight, gestational age, NICU admissions, and gestational anemia in normotensive singleton pregnancies. Controlling for confounding factors such as BMI, maternal age, prior preterm labor, and gestational anemia through strict inclusion criteria and statistical adjustments. Assessing whether hyperuricemia independently predicts adverse perinatal outcomes, using multiple linear and logistic regression models to differentiate its effects from other maternal health factors. By providing new insights into the role of hyperuricemia in normotensive pregnancies, this study may help improve prenatal risk assessment strategies and highlight the potential role of uric acid as a biomarker for early intervention.

METHODS

This prospective observational study was conducted at the Department of Obstetrics and Gynecology, Tertiary Care Hospital, Bahawalpur, from November 2022 to June 2023 (Ethical approval number EC-15-2022). Participants were prospectively followed to assess the impact of maternal hyperuricemia on perinatal and postnatal outcomes in normotensive pregnancies. A total of 103 normotensive pregnant women were enrolled in the study. Participants were included if they had a singleton pregnancy, remained normotensive throughout gestation (blood pressure <140/90 mmHg), and were between 18 and 40 years of age. Exclusion criteria included multiple gestations, a history of hypertensive disorders such as chronic hypertension, preeclampsia, or gestational hypertension, and chronic medical conditions such as diabetes, renal disease, or metabolic disorders that could affect pregnancy outcomes. Additionally, women on uric acid-lowering medications or diuretics were excluded to prevent pharmacological interference with uric acid levels. The sample size was determined using G*Power software, based on findings from Fischer RL *et al.*, in (2014), which identified an association between maternal hyperuricemia and NICU admissions (OR = 1.65). To achieve 90% power at $\alpha = 0.05$, logistic regression analysis suggested an optimal sample size. Given practical constraints, a total of 103 participants were included, allowing for the detection of larger-than-expected effect sizes within operational limits [3]. Data were collected through structured interviews and medical record reviews by trained personnel. Maternal serum uric acid levels were measured at routine prenatal

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visits using an enzymatic colorimetric assay. To ensure consistency and accuracy, blood samples were collected in the morning following an overnight fasting period, minimizing diurnal variations in uric acid levels. Participants were advised to maintain adequate hydration before sample collection to reduce potential fluctuations in uric acid concentration. Women taking medications known to affect uric acid metabolism, including Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and diuretics, were excluded. These measures were taken to ensure standardization and reliability in the uric acid data across participants. The primary independent variable was maternal uric acid level, with hyperuricemia defined as ≥5.5 mg/dL, based on established pregnancy-related cutoffs [3]. The dependent variables included birth weight (kg), gestational age at delivery (weeks), NICU admission (Yes/No), and gestational anemia (Yes/No). To account for potential confounders, data were collected on maternal BMI (kg/m^2), maternal age, prior history of preterm labor, and presence of gestational anemia. BMI was analyzed both as a continuous variable and as a categorical variable (normal, overweight, and obese). For subgroup analysis, participants were divided into clinically relevant comparison groups for analysis, and the terms Group 1 and Group 2 used in the table 1.

Table 1: Maternal and Neonatal Grouping

Group Type	Group	Criteria
Maternal Uric Acid Group		
Group 1	Normouricemic mothers	Serum uric acid ≤ 5.5 mg/dL
Group 2	Hyperuricemic mothers	Serum uric acid > 5.5 mg/dL
NICU Admission Group		
Group 1	Infants not admitted to NICU	Not admitted to NICU
Group 2	Infants admitted to NICU	Admitted to NICU
Prior History of Preterm Labor Group		
Group 1	No prior history of preterm labor	No prior history of preterm labor
Group 2	Prior history of preterm labor	Prior history of preterm labor
Gestational Anemia Group		
Group 1	Hemoglobin ≥11 g/dL (No anemia)	Hemoglobin ≥11 g/dL
Group 2	Hemoglobin <11 g/dL (With anemia)	Hemoglobin <11 g/dL

Descriptive statistics were used to summarize key maternal and neonatal characteristics.Continuous variables, including birth weight, gestational age, maternal BMI, and uric acid levels, were expressed as means with Standard Deviations (SD), while categorical variables such as NICU admission, gestational anemia, and history of preterm labor were reported as frequencies and percentages.Independent t-tests were conducted to compare birth weight, gestational age, and BMI between hyperuricemic and normouricemic mothers.The Chi-square test was used to assess associations between maternal uric acid categories and binary outcomes including NICU admission, gestational anemia, and prior history of preterm labor. Pearson correlation analysis was performed to evaluate the relationship between maternal uric acid levels, BMI, gestational age, and birth weight. A multiple linear regression model was used to determine the influence of maternal uric acid level, BMI, gestational age at delivery, and gestational anemia on birth weight. To evaluate predictors of NICU admission, a binary logistic regression model was applied. The model included the following covariates: maternal uric acid level (mg/dL), maternal age (years), body mass index (BMI, kg/m^2), presence of gestational anemia (Yes/No), and prior history of preterm labor (Yes/No). These variables were selected based on their clinical relevance and potential confounding effects in the relationship between maternal hyperuricemia and neonatal outcomes. To assess potential collinearity among predictors, Variance Inflation Factor (VIF) analysis was performed. All included variables had VIF values less than 5, indicating the absence of significant multicollinearity and supporting the independence of each predictor in the regression model. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 25.0. The study protocol was approved by the institutional review board of the hospital. Written informed consent was obtained from all participants before enrollment.

RESULTS

A total of 103 participants were included in the study, with a mean birth weight of 3.53 kg (SD 0.48) and a mean gestational age at delivery of 39.36 weeks (SD 1.42). Maternal health indicators showed a mean uric acid level of 5.53 mg/dL (SD 1.20) and a mean BMI of 25.16 (SD 4.03). Infants born to hyperuricemic mothers had significantly lower birth weights (3.51 ± 0.40 kg) compared to those born to normouricemic mothers (3.80 ± 0.35 kg), with p = 0.015. Hyperuricemic mothers also delivered slightly earlier (38.50 ± 1.20 weeks) than normouricemic mothers (39.35 ± 1.00 weeks), with p = 0.025. Additionally, hyperuricemic mothers had a significantly higher BMI (27.50 ± 3.00 vs. 25.19 ± 3.50, p = 0.010), indicating a possible link between metabolic dysregulation and uric acid levels (Table 2).

Table 2: Comparison of Key Maternal and Neonatal Outcomes by Maternal Uric Acid Group, NICU Admission, Prior History of Preterm Labor, and Gestational Anemia

Variable Pair	Group 1 Mean ± SD	Group 2 Mean ± SD	p-Value
Maternal Uric Acid Group (Normouricemic/Hyperuricemic) Vs Birth Weight	3.80 ± 0.35	3.51 ± 0.40	0.015
Maternal Uric Acid Group (Normouricemic/Hyperuricemic) Vs Gestational Age at Delivery	39.35 ± 1.00	38.50 ± 1.20	0.025
Maternal Uric Acid Group (Normouricemic/Hyperuricemic) Vs Maternal BMI	25.19 ± 3.50	27.50 ± 3.00	0.010

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NICU Admission (No/Yes) Vs Birth Weight	3.52 ± 0.40	3.20 ± 0.35	0.020
NICU Admission (No/Yes) Vs Gestational Age at Delivery	39.32 ± 1.00	38.00 ± 1.20	0.030
Prior History of Preterm Labor (No/Yes) Vs Gestational Age at Delivery	39.32 ± 1.00	38.00 ± 1.20	0.018
Gestational Anemia (No/Yes) Vs Birth Weight	3.57 ± 0.40	3.20 ± 0.35	0.022
Gestational Anemia (No/Yes) Vs Gestational Age at Delivery	39.41 ± 1.00	38.00 ± 1.20	0.028

Infants who required NICU admission had significantly lower birth weights (3.20 ± 0.35 kg vs. 3.52 ± 0.40 kg, p = 0.020) and were delivered earlier (38.00 ± 1.20 weeks vs. 39.32 ± 1.00 weeks, p = 0.030). Among hyperuricemic mothers, 42.9% (15 out of 35) of infants required NICU admission, compared to 26.5% (18 out of 68) of normouricemic mothers (p = 0.035), suggesting a possible association between elevated uric acid levels and neonatal complications(Table 3).

Table 3: Association of Maternal Uric Acid Status with different Variables

Maternal Uric Acid Group	NICU Admission		Total	p-Value
	No	Yes		
Normouricemic	50	18	68	0.035
Hyperuricemic	20	15	35	
Maternal Uric Acid Group	**Gestational Anemia**		**Total**	**p-Value**
	No	**Yes**		
Normouricemic	55	13	68	0.043
Hyperuricemic	20	15	35	
Maternal Uric Acid Group	**Prior History of Preterm Labor**		**Total**	**p-Value**
	No	**Yes**		
Normouricemic	60	8	68	0.022
Hyperuricemic	22	13	35	

Hyperuricemic mothers had a significantly higher prevalence of gestational anemia (42.9% vs. 19.1%, p = 0.043), suggesting a potential interplay between elevated uric acid levels and hematologic adaptations during pregnancy. Similarly, a history of preterm labor was more common among hyperuricemic mothers (37.1% vs. 11.8%, p = 0.022), emphasizing the need for closer prenatal monitoring in hyperuricemic pregnancies (Table 2). Pearson correlation analysis was conducted to assess the relationship between birth weight and selected maternal and gestational variables. A moderate positive correlation was observed between maternal uric acid levels and birth weight (r = 0.35, p = 0.005), indicating that higher uric acid levels were significantly associated with increased birth weight in this cohort. In contrast, maternal BMI showed a very weak negative correlation with birth weight (r = -0.012, p = 0.902), which was not statistically significant. Similarly, gestational age at delivery had a negligible correlation with birth weight (r = 0.000, p = 0.997), also lacking statistical significance. These findings suggest that among the variables analyzed, maternal uric acid levels had the most notable association with neonatal birth weight, while maternal BMI and gestational age did not exhibit meaningful correlations in this study population(Table 4).

Table 4: Correlation Analysis between Birth Weight and different Variables

Variables	Correlated With	Pearson Correlation (r)	p-Value
Maternal Uric Acid	Birth Weight	0.35	0.005
Maternal BMI	Birth Weight	-0.012	0.902
Gestational Age at Delivery	Birth Weight	0.000	0.997

These findings suggest that while hyperuricemia may influence fetal growth, other metabolic and placental factors could be contributing, warranting further investigation into the mechanisms linking uric acid metabolism to fetal development.The multiple linear regression model evaluating maternal uric acid, BMI, gestational age at delivery, and gestational anemia as predictors of birth weight explained only 3.7% of the variance in birth weight (R^2 = 0.037, p = 0.444), indicating that these factors alone do not fully account for variations in neonatal weight. While maternal uric acid levels showed a small positive effect on birth weight (B = 0.076), the association was not statistically significant. Gestational anemia had the strongest negative association with birth weight (B = -0.217), but this also did not reach significance (Table 5).

Table 5: Multiple Linear Regression Analysis for Predicting Birth Weight

Statistics	p-Value
Model Summary	
R	0.192
R Square	0.037
Adjusted R Square	-0.002
Std. Error of the Estimate	0.48280
ANOVA	
F	0.941
p-value (Sig.)	0.444
Coefficients	B (Unstandardized)
(Constant)	3.810
Maternal Uric Acid Group	0.076
Maternal BMI	-0.002
Gestational Age at Delivery	-0.005
Gestational Anemia	-0.217

These findings suggest that additional factors, such as placental function and genetic influences, may play a more substantial role in determining fetal growth. The logistic regression model assessing the relationship between maternal uric acid levels, BMI, gestational age, gestational anemia, and prior preterm labor with NICU admission showed low predictive power (Nagelkerke R^2 = 0.115) and was not statistically significant overall (p = 0.190). None of

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the included variables maternal uric acid levels (B = -0.416), BMI (B = 0.082), gestational age (B = 0.146), gestational anemia (B = -0.171), or prior preterm labor (B = 20.050) were significant predictors of NICU admission (Table 6). The overall classification accuracy was 82.5%, suggesting that factors outside of those included in this model may contribute to NICU admission risk. These findings highlight the complexity of neonatal outcomes, where uric acid levels alone may not be a direct predictor of NICU admission, and emphasize the need for a more comprehensive model incorporating additional maternal and fetal risk factors.

Table 6: Logistic Regression Analysis of Maternal Factors Associated with NICU Admission

Statistics	p-Value
Model Summary	
-2 Log likelihood	88.007
Cox and Snell R Square	0.070
Nagelkerke R Square	0.115
Omnibus Tests of Model Coefficients	
Chi-square	7.444
Df	5
p-value (Sig.)	0.190
Classification Table	
Overall Percentage	82.5%
Variables in the Equation	B (Logistic Coefficients)
Maternal Uric Acid Group (1)	-0.416
Maternal BMI	0.082
Gestational Age at Delivery	0.146
Gestational Anemia (1)	-0.171
Prior history of preterm labor (1)	20.050
Constant	-28.884

DISCUSSION

In this study, we investigated the implications of maternal hyperuricemia in normotensive singleton pregnancies and its potential effects on various perinatal and postnatal outcomes. Contrary to initial hypotheses, these findings indicate that maternal hyperuricemia is associated with significant differences in birth weights and gestational ages, as well as NICU admission rates and the prevalence of gestational anemia, suggesting a more influential role of maternal uric acid levels than previously understood in normotensive pregnancies.The mean birth weight of infants born to hyperuricemic mothers was significantly lower (3.51 ± 0.40 kg) than that of infants born to normouricemic mothers (3.80 ± 0.35 kg), contrary to what might be expected based on the p-value of 0.015. This result challenges previous findings and the observed moderate positive correlation between maternal uric acid levels and birth weight (r = 0.35, p = 0.005).This contradiction suggests that maternal hyperuricemia may not contribute to higher birth weights, opposing earlier research, including that cited by Jasim SK *et al.*, in 2019, which suggested minimal impact of hyperuricemia on birth weight in normotensive pregnancies.This reference is directly relevant and supports our core analysis.It was cited to contrast prior findings suggesting minimal impact of uric acid on birth weight in normotensive pregnancies thereby framing our results as novel and significant [14]. This analysis also revealed that hyperuricemic mothers delivered slightly earlier than normouricemic mothers (p = 0.025), indicating a potential impact of elevated uric acid levels on the timing of delivery.This is consistent with findings from Fischer RL *et al.*, in 2014, who reported no significant difference in gestational age at delivery, suggesting that other factors might influence gestational age in normotensive pregnancies [3].Moreover, the significant association between maternal uric acid status and NICU admission rates (p = 0.035) underscores the potential risk that hyperuricemia poses for neonatal care needs post-delivery. This contradicts previous assertions by Sosnowski DW *et al.*, in 2023, who found that other maternal factors had more substantial effects on NICU admissions than maternal uric acid levels [13]. Additionally, the significant prevalence of gestational anemia in hyperuricemic mothers (p = 0.043) highlights the interrelationship between uric acid levels and anemia, which may have clinical implications for monitoring and managing pregnancy health.This finding supports the argument that hyperuricemia can complicate pregnancy outcomes and should be managed carefully to mitigate its effects. Lastly, the association between maternal uric acid status and a prior history of preterm labor (p = 0.022) reinforces the need for vigilant monitoring and management of hyperuricemic mothers to prevent the risk of recurrent preterm labor.This finding suggests that hyperuricemic status in mothers is a stronger predictor of preterm labor than previously reported. Ponnapakkam A *et al.*, 2021 added to this discussion by highlighting alternative NICU admission drivers (such as metabolic complications), helping to isolate hyperuricemia as an independent variable in our findings.It complements the statistical control measures we employed.Talisman S *et al.*, 2022 comprehensive study supported our framework by providing a baseline of NICU risk factors in term neonates. Its inclusion allows us to contextualize the NICU admission rates in our cohort of normotensive pregnancies and reinforces the importance of uric acid screening [15, 16]. These findings are further supported by recent studies on maternal hyperuricemia in normotensive pregnancies. For instance, Daise (2018) highlighted hyperuricemia as a risk factor for adverse pregnancy outcomes even in normotensive mothers, with significant concerns regarding low birth weight babies [17]. Additionally, Ural ÜM *et al.*, in 2015 and Ajitkumar Y *et al.*, in 2019 emphasize the importance of maternal uric acid as a biomarker for adverse pregnancy outcomes [18, 19]. Mohamed ZAZ *et al.*,

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in 2017 suggested that early intervention in hyperuricemic conditions could improve maternal and fetal health outcomes [20]. Although focused on preeclampsia, this study was referenced to support biomarker discussion (i.e., the role of uric acid and endothelial markers) and the argument that early biochemical markers—like uric acid—can guide intervention even in normotensive pregnancies. Each highlighted reference contributes to our broader analysis by offering either mechanistic insight, comparative outcomes, or context for interpreting our findings within the spectrum of maternal-fetal medicine. While not all studies directly assess hyperuricemia in normotensive pregnancies, they were purposefully integrated to frame the short- and long-term significance of our work within existing literature.

CONCLUSIONS

This study examined the impact of maternal hyperuricemia on perinatal outcomes in normotensive singleton pregnancies and identified significant associations with lower birth weights, earlier deliveries, increased NICU admissions, and a higher prevalence of gestational anemia. These findings suggest that elevated maternal uric acid levels may influence fetal growth and pregnancy duration, highlighting its potential role as an independent risk factor for adverse neonatal outcomes. Given these associations, routine screening for hyperuricemia during pregnancy is recommended as part of standard prenatal care to allow for early identification and management of at-risk pregnancies. Early intervention strategies may help mitigate potential complications, improving both maternal and neonatal outcomes. Furthermore, this study contributes to the growing body of evidence on maternal metabolic conditions and their impact on pregnancy.

Authors Contribution

Conceptualization: HAS
Methodology: HAS
Formal analysis: SZ
Writing, review and editing: SU, NH, MA, NS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Long-term Postoperative Outcomes of Pediatric Cataract Extraction with IOL Implantation in a Tertiary Eye Care Centre at Karachi

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ABSTRACT

Cataracts in the pediatric age group present with challenges distinct from the adult age group. **Objectives:** To determine the long-term postoperative outcomes of pediatric cataract extraction with IOL implantation at a tertiary eye care center in Karachi. **Methods:** This retrospective cross-sectional study was carried out at Al-Ibrahim Eye Hospital for six months after ethical approval. Medical records of pediatric children below 10 years that had undergone cataract surgery along with implantation of IOL at the hospital in-between January 2020 to December 2024 were selected. Children having abnormalities, such as condition limiting eye's visual potential like retinal disorders, retinal detachment, glaucoma, persistent fetal vasculature, abnormalities of the cornea, diseases of optic nerve, uveitis (either active or signs suggesting history of uveitis), or a history of cryotherapy for retinopathy due to prematurity, or treatment with laser, children with complications of surgery, placement of IOL in sulcus or children that failed to follow-up were all excluded. SPSS version 23.0 was used for data analysis. **Results:** A total of 140 eyes from pediatric patients were studied, with 56.43% male and 43.57% female. Bilateral cataracts were more common (72.86%). The mean age at surgery was 74.77 ± 29.94 months, with a follow-up of 5.22 ± 3.82 months. Postoperative refractive biometry significantly improved from +24.50 ± 4.50 D to +18.50 ± 2.50 D ($p<0.001$), showing a mean reduction of -6.00 ± 2.00 D. **Conclusions:** In long-term post-operative outcomes of pediatric cataract extraction with IOL implantation, surgery was generally well-tolerated with positive outcomes and minimal side effects.

INTRODUCTION

Cataracts in the pediatric age group present with challenges distinct from the adult age group. The leading cause of childhood blindness is associated with pediatric cataracts. The clinical manifestations in terms of pediatric cataract tend to be broad-spectrum [1]. The degree of amblyopia varies between them. Pediatric cataracts are either developmental or congenital. It is crucial to note the cataract's laterality, either being unilateral or bilateral [2]. The importance lies in the timing for optimal interventions. Provided the continuous growth of pediatric eyes, it is imperative to check each child's stages of ocular development, in addition to any co-existence of ocular and systemic comorbidities [3]. Through surgery, multiple techniques ought to be considered, for instance, using an intraocular lens (IOL) along with its power. In addition, strategies for managing anterior vitreous and posterior capsule can be implemented [4]. Infantile eyes are post-operatively more prone towards an inflammatory response of greater severity. Swift rehabilitation of vision is vital, emphasizing therapy of amblyopia and adjustments to

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refractive index [5]. Moreover, pediatric eyes are considered to be at higher risk such as secondary glaucoma and opacification of the visual axis [6]. In patients having significant cataract (visually), surgical intervention should be carried out as early as possible to remove opacity of the lens along with effectively correcting aphakia [7]. It is the key towards a successful rehabilitation of vision [8]. Primary implantation of IOL has become an increasingly carried out surgical technique and at present, the preferred mode for correcting optical errors amongst pediatric eyes undergoing surgery for cataract [9]. Although it is the most commonly practiced procedure, there exists no consensus with regards to the optimum refractive goal for visual rehabilitation immediately after operation [10]. Even after advances in surgical methods recently, design of implant and instrumentation, a major challenge of cataract surgery among the pediatric age group is obtaining a desirable long-term refractive status post-operatively [11]. Long-term monitoring of pediatric eyes is recommended, owing to their immature nature and continued growth post-surgery [12]. In the event of the identification of prognostic factors, it is important to contemplate multiple factors in addition to demographics. Both physiological and anatomical confounding variables should be considered [13]. In one of the studies by Dahan and Drusedau, it was proposed that IOL power under-correction should be labelled when it is 20 % less than the ametropic power of IOL in pediatric ages below 2 years, while less than 10 % for pediatric ages over 2 years [14]. Another study proposes targeting refraction post-operatively at 6+6 D in 1 year olds, for 2 year olds, +5 D, for 3 year olds +4 D, for 4 year olds +3 D, for 5 year olds +2 D, for 6 year olds +1 D, for 7 year olds -1 D while for 8 years and older, -2 D [15]. Despite advancements in pediatric cataract surgery and intraocular lens (IOL) implantation techniques, limited data exist on the long-term visual and refractive outcomes in children, particularly in low- and middle-income countries. Most available studies focus on short-term postoperative results or are restricted to small sample sizes and narrow follow-up periods. Furthermore, there is a lack of region-specific evidence addressing postoperative complications, visual rehabilitation, and quality of life in pediatric patients. This gap highlights the need for comprehensive, long-term follow-up studies that can inform surgical practices, guide parental counselling, and support health policy development in pediatric ophthalmology.

This study aims to determine the long-term postoperative outcomes of pediatric cataract extraction with IOL implantation at a tertiary eye care center in Karachi.

METHODS

This retrospective cross-sectional study was carried out at the Al-Ibrahim Eye Hospital Karachi for six months after ethical approval from the Research Ethical Committee (REC) of the institute (REC/IPIO/2024/088). After ethical approval, medical records of pediatric children below the age of 10 years that had undergone cataract surgery along with implantation of IOL at the hospital in-between January 2020 to December 2024 were selected for review. A written informed consent was taken. Children without any other abnormality of the eye were included. In addition, children who had undergone aspiration of lens along with primary implantation of IOL, anterior vitrectomy and posterior capsulotomy were also included in the study. In all the patients, the IOL was kept in the capsular bag. Using immersion ultrasound (A-scan), the axial length of the eye was measured pre-operatively. For determining the power of IOL, SRK/T formula was used for all patients. Children having other abnormalities of the eye, such as condition limiting eye's visual potential like retinal disorders, retinal detachment, glaucoma, persistent fetal vasculature, abnormalities of the cornea, diseases of optic nerve, uveitis (either active or signs suggesting history of uveitis), or a history of cryotherapy for retinopathy due to prematurity, or treatment with laser, children with complications of surgery, placement of IOL in sulcus or children that failed to follow-up were all excluded from the research. Under corrected power of the IOL was calculated, anticipating the expected shift of myopia. The sample size for the study was calculated using the Open Epi online software for sample size calculation. Keeping the frequency of complications following pediatric cataract extraction and IOL implantation at 10 %, the sample size came out to be 140 at a 95 % confidence level. Therefore, a total of 140 patient data points were included in this research [16]. After ethical approval, the data of patients were included according to the inclusion and exclusion criteria. Collected data included baseline demographics, outcomes of surgery in terms of pre-, peri- and post-operative assessment and complications and visual outcomes. Moreover, post-operative refraction was also noted. The primary measure of outcome was refractive errors post-operatively in pseudophakic eyes. Refractive index was obtained at pre-operative and then at 6 months post-operatively. The outcomes were measured in terms of opacification of visual axis, myopic shift, glaucoma, retinal detachment, capsulophimosis, endophthalmitis and IOL decentration. SPSS version 23.0 was used for analyzing the data. Results were recorded as mean and standard deviation. The errors of refraction were measured as spherical power in D (diopters). The study excluded cylindrical power as changes in power of astigmatism were unrelated to emmetropization of spherical errors. The difference between pre- and post-operative reduction in IOL refraction was tested by applying a paired t-test, keeping $p<0.05$ statistically significant.

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RESULTS

The baseline demographic and clinical characteristics of the pediatric patients included in the study are presented. A total of 140 eyes were analyzed. Among these, 79(56.43%) belonged to male patients, while 61 (43.57%) were from female patients. The laterality of the cataracts showed that 38 eyes were affected unilaterally, whereas 102 eyes were from cases of bilateral cataracts. The mean age at the time of surgery was 74.77 ± 29.94 months, ranging from 6 to 118 months. The mean follow-up duration was 5.22 ± 3.82 months, ranging between 1 to 6 months (Table 1).

Table 1: Baseline Demographics of Pediatric Cataracts Included in the Study (n=140)

Baseline Characteristics		Frequency (%) / Mean ± SD
Gender	Male	79 (56.43 %)
	Female	61 (43.57 %)
Laterality	Unilateral	38
	Bilateral	102
Mean Age at Time of Surgery	6-118 Months	74.77 ± 29.94
Mean Follow-Up Time	1-6 Months	5.22 ± 3.82

In comparison between pre-operative and post-operative refractive biometry values, the mean pre-operative refractive biometry was +24.50 ± 4.50 diopters (D), which significantly reduced post-operatively to +18.50 ± 2.50 D ($p<0.001$). This reflects a mean reduction in refractive biometry of -6.00 ± 2.00 D, indicating a statistically significant improvement following intraocular lens (IOL) implantation (Table 2).

Table 2: Mean Pre- and Post-Operative Refractive Error Reduction (n=140)

Measurement		Mean ± SD (Diopters)	p-value
Refractive Biometry (D)	Pre-Operative	+ 24.50 ± 4.50 D	<0.001
	Post-Operative	+ 18.50 ± 2.50 D	
	Mean Reduction	- 6.00 ± 2.00 D	

Findings illustrate the long-term post-operative outcomes following cataract extraction and IOL implantation in the pediatric population. The highest frequency of post-operative long term complications was reported to be myopic shift, in 59 (42.14 %) (Figure 1).

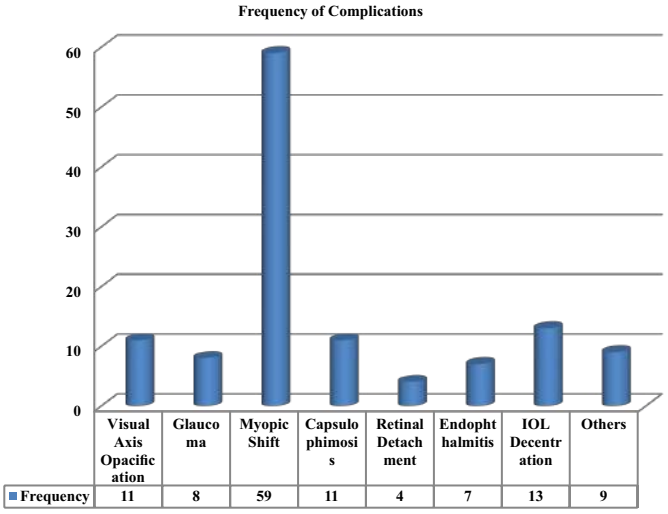

Figure 1: Post-Operative Long Term Outcomes of Pediatric Cataracts After IOL Implantation (n=140)

DISCUSSION

The results of the study showed a significant reduction in refractive biometry post-operatively (6 months) after cataract extraction and IOL implantation. The highest frequency of post-operative complications in the long term (6 months) was reported to be myopic shift, observed in 59 (42.14 %) of patients. The study was in line with guidelines proposed by a study in which Asian children were reported to develop myopia in the long term when compared with other populations [17]. 9 (6.43 %) patients were reported to have amblyopia in this study. Since the approach used in this study might raise concerns regarding residual hypermetropia, which might exacerbate amblyopia refractively amongst children. This is specifically for children having unilateral cases who might not wear spectacles or contact lenses post-surgically [18]. In this study, only 09 (6.43 %) cases were found to have amblyopia. Similar to the findings of this study, Wójcik-Niklewska *et al.*, reported that the majority of children tolerate spectacles well, even if they have a high difference in refractive power in-between eyes [19]. Therefore, amblyopia progression after under-corrected IOL power post-insertion is observed to be rare [20]. Moreover, pediatric eyes show continuous growth and tend to approach binocular vision; emmetropia and stereopsis seldom tend to improve [21]. A study reported that above 60 % of eyes tend to become myopic post-surgically. Studies have reported that the age of children at the time of surgery plays a vital role in determining the post-operative status of refraction. Irving et al., in a research on pediatric cataracts, found be myopic shift post-surgically among younger children. Those operated after the age of 5 years or more show lower refractive errors [22]. For instance, Lekskul *et al.*, observed a mean refractive error of - 2.50 ± 2.08 D among children aged 1-2 years, while – 0.45 ± 0.64 D among children aged 8-

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9 years [23]. A possible explanation for such postoperative myopic shift are the challenges in measuring ocular parameters such as keratometry and axial length amongst younger children, which might cause greater errors in calculating the power of IOL.The majority of studies have been found to follow this pattern, which is in line with the findings of this study [24].However, Khokhar *et al.*, reported that hypermetropia among children <2 years showed lesser under-correction among the age group. The study concluded further research to confirm the trend in refractive errors amongst the same group of age group [25]. Apart from myopia, 11 cases in current study observed opacification of the visual axis and capsulotomy each, and 13 were reported to have decentration of the IOL. Less common complications observed in the study were glaucoma, endophthalmitis, amblyopia and retinal detachment.Similar reports have been observed in the published literature as well [26].

CONCLUSIONS

It was concluded that in long term post-operative outcomes of pediatric cataract extraction with IOL implantation, surgery was generally well-tolerated with positive outcomes and minimal side effects.

Authors Contribution

Conceptualization: SHS, SAS
Methodology: MMU, SHS, MA
Formal analysis: MMK
Writing review and editing: MMU, FR
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Serum Electrolytes in Children Suffering from Acute Gastroenteritis Aged 6 Months to 3 Years Admitted to MTI DHQ Hospital Dera Ismail Khan

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ABSTRACT

Acute Gastroenteritis (AGE) is a major contributor to morbidity, dehydration, and hospitalizations among young children in low-resource settings. Electrolyte disturbances are common complications that may worsen disease severity and outcomes. **Objective:** To evaluate the clinical presentation and laboratory findings, particularly serum electrolyte levels, in children aged 6 months to 3 years diagnosed with AGE, and to assess their association with dehydration severity. **Methods:** A descriptive-analytical cross-sectional study was conducted at MTI DHQ Hospital, Dera Ismail Khan, involving 110 children with AGE. Data on demographics, clinical features, hydration status, and laboratory results (including serum electrolytes) were recorded. Statistical analysis was performed using SPSS Version 25.0. Chi-square, ANOVA, Kruskal-Wallis, and Tukey's HSD post-hoc tests were applied. A p-value ≤ 0.05 was considered statistically significant. **Results:** Vomiting (76.4%) and fever (64.5%) were the most frequent clinical features. Moderate dehydration was most common. Significant differences ($p \leq 0.05$) in electrolyte levels were observed across dehydration groups: sodium, potassium, chloride, urea, and creatinine levels were elevated in severe cases, while bicarbonate and magnesium were lower. No significant associations were found between dehydration severity and demographic or most clinical variables. **Conclusions:** Electrolyte abnormalities were significantly associated with dehydration severity in children with AGE, emphasizing the need for routine electrolyte monitoring and individualized fluid management, especially in moderate to severe cases. These findings support improved diagnostic protocols and targeted treatment strategies in paediatric gastroenteritis care.

INTRODUCTION

Acute Gastroenteritis (AGE) remains a leading cause of morbidity and mortality in children under five years worldwide, particularly in low-resource settings. According to the World Health Organization, diarrheal diseases including AGE are responsible for nearly 525,000 child deaths annually, with a disproportionate burden in developing countries [1]. In Pakistan, AGE accounts for approximately 15% of paediatric hospital admissions and contributes significantly to under-five mortality [2]. AGE typically presents with diarrhea, vomiting, and dehydration caused by infections from viruses (rotavirus, norovirus), bacteria (*Escherichia coli, Shigella, Salmonella),* or parasites. The disease is particularly severe in children aged 6 months to 3 years due to immature immunity, higher fluid requirements, and limited physiological reserves [3]. While clinical features help in early diagnosis, the severity of AGE is primarily driven by the extent of dehydration and associated electrolyte disturbances, rather than by the specific pathogen. Common electrolyte imbalances include hyponatremia, hypernatremia, hypokalaemia, hyperkalaemia, metabolic acidosis (low bicarbonate), and hypomagnesemia—all of which contribute to the pathophysiology of dehydration. These abnormalities can lead to neurological dysfunction, cardiac arrhythmias, and

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renal impairment if not promptly identified and corrected [4, 5]. Regional factors such as inadequate sanitation, lack of access to clean water, and low literacy levels further amplify the burden of AGE in countries like Pakistan. However, while several studies in other countries have evaluated serum electrolyte patterns in paediatric AGE, there is limited local data from Pakistan that integrates both clinical features and biochemical profiles, particularly in tertiary care settings. Most Pakistani studies focus on microbial causes or treatment practices, without stratifying patients by electrolyte profile or severity of dehydration [6]. This gap in the literature highlights the need for comprehensive, locally relevant research. This study was conducted to evaluate both clinical presentation and laboratory findings especially serum electrolytes in children aged 6 months to 3 years diagnosed with AGE. The primary objective was to assess the clinical and laboratory characteristics of these patients.

The secondary objective was to determine the association between dehydration severity and various demographic, clinical, and biochemical parameters, thereby informing better diagnostic and therapeutic strategies in similar healthcare settings.

METHODS

This descriptive-analytical cross-sectional study was conducted at the Paediatrics Department of MTI DHQ Hospital, Dera Ismail Khan, under the supervision of pediatric faculty, from 1st June 2024 to 30th November 2024. Ethical approval was obtained from the Institutional Review Board of Gomal Medical College, D.I. Khan (Approval No: 10/GJMS) and the Research Evaluation Unit, CPSP (Ref No: CPSP/REU/PED-2022-029-6853, Dated: June 1, 2024). The sample size was calculated using the World Health Organization (WHO) sample size formula for cross-sectional studies [7]:

$$n = \frac{Z^2 \times P(1-P)}{d^2}$$

where *n* is the required sample size, Z is the standard normal deviate at 95% confidence level (1.96), P is the anticipated prevalence of electrolyte imbalance in children with acute gastroenteritis (assumed at 50% to maximize sample size), and *d* is the margin of error (5%). Based on these parameters, the initially calculated sample size was 384. However, considering the finite number of eligible paediatric patients expected during the study period (approximately 150), the Finite Population Correction (FPC) was applied, adjusting the sample size to 110. However, due to practical constraints, including the study's limited time frame, single-centre setting, and anticipated patient flow, a final sample of 110 children was enrolled using consecutive non-probability sampling [8]. This adjustment ensured the study remained feasible within the available time frame and resources. A consecutive non-probability sampling technique was used to enrol all eligible participants during the defined study duration. All children aged 6 months to 3 years with acute gastroenteritis were screened. Excluded were those with chronic GI disorders, renal/metabolic diseases, prior IV fluids, or incomplete records. Each patient underwent clinical evaluation. A structured proforma was used to record age, gender, residence, socioeconomic status, maternal education, breastfeeding history, diarrhea type, vomiting, fever, ORT use, and antibiotics. Dehydration severity was categorized as mild, moderate, or severe per WHO criteria. Venous blood samples were analyzed using an automated electrolyte analyzer. The following serum parameters were assessed: Sodium (135–145 mmol/L), Potassium (3.5–5.5 mmol/L), Chloride (98–107 mmol/L), Bicarbonate (22–28 mmol/L), Calcium (8.5–10.5 mg/dL), Magnesium (1.6–2.6 mg/dL), Urea (10–40 mg/dL) and Creatinine (0.3–1.0 mg/dL). All laboratory analyses followed standard SOPs. The dependent variables included the frequency and type of serum electrolyte disturbances, such as hyponatremia, hypernatremia, hypokalaemia, hyperkalaemia, metabolic acidosis, and metabolic alkalosis. The independent variables included age, gender, duration of diarrhea, degree of dehydration (mild, moderate, severe), vomiting frequency, presence of fever, and use of Oral Rehydration Solution (ORS). To ensure reliability, standardized laboratory protocols were followed, data were collected using a structured proforma, and assessments were performed by trained paediatric staff. Internal validity was maintained through strict inclusion and exclusion criteria, while external validity was supported by using a consecutive sampling method to include a representative sample of hospitalized children with AGE. Data analysis was conducted using IBM SPSS version 25.0. Categorical variables were reported as frequencies and percentages, and compared using the Chi-square test. The strength of associations was measured using Cramer's V, interpreted as: very weak (<0.10), weak (0.10–0.20), moderate (0.20–0.30), or strong (>0.30). Continuous variables were tested for normality using both Kolmogorov-Smirnov and Shapiro-Wilk tests. The Shapiro-Wilk test was preferred for small to moderate sample sizes (n < 200), while the Kolmogorov-Smirnov test provided cross-validation. Normally distributed variables were analyzed using one-way ANOVA; non-normally distributed variables were analyzed using the Kruskal-Wallis test. For variables with significant ANOVA results, Tukey's HSD post-hoc test was applied to determine intergroup differences. Statistical significance was set at ≤ 0.05. All p-values were reported exactly to ensure clarity.

RESULTS

Table 1 presents the demographic distribution of children based on gender, nutritional status, residence, socioeconomic status, and maternal education level. The Chi-square test revealed no statistically significant associations between these variables and the severity of

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dehydration. Gender, nutritional status, and residence exhibited very weak to weak associations (Cramer's V < 0.15), suggesting minimal influence on dehydration severity. The strongest, albeit non-significant, association was observed with maternal education (p = 0.072, Cramer's V = 0.229), indicating a moderate trend where children of mothers with lower educational attainment tended to experience more severe dehydration. Although this trend did not reach statistical significance, it may warrant further investigation in larger, more diverse samples (Table 1).

Table 1: Demographic Characteristics of Study Population and Their Association with Dehydration Severity (n=110)

Variables	Categories	Frequency (%)	Chi-square (χ^2, df)	p-Value	Cramer's V	Strength of Association
Gender	Male	70 (63.6%)	0.195 (2)	0.907	0.042	Very Weak (Not Significant)
	Female	40 (36.4%)				
Nutritional Status	Well-Nourished	48 (43.6%)	2.309 (2)	0.315	0.145	Weak (Not Significant)
	Malnourished	62 (56.4%)				
Residence	Urban	46 (41.8%)	2.180 (2)	0.336	0.141	Weak (Not Significant)
	Rural	64 (58.2%)				
Socioeconomic Status	Low	56 (50.9%)	2.961 (4)	0.564	0.116	Very Weak (Not Significant)
	Middle	32 (29.1%)				
	High	22 (20.0%)				
Mother's Education	Illiterate	27 (24.5%)	11.586 (6)	0.072	0.229	Moderate (Approaching Significance)
	Primary	30 (27.3%)				
	Secondary	18 (16.4%)				
	Higher	35 (31.8%)				

This table presented the association between dehydration severity and clinical features including breastfeeding history, diarrhea type, vomiting, fever, Oral Rehydration Therapy (ORT), and antibiotic use. The Chi-square test revealed no statistically significant relationships for any of these variables. However, certain trends were observed. Diarrhea type demonstrated the strongest association ($\chi^2 = 5.333$, p = 0.255, Cramer's V = 0.156), suggesting that children with watery diarrhea tended to experience more severe dehydration. Similarly, vomiting ($\chi^2 = 2.046$, p = 0.360, Cramer's V = 0.136) and fever ($\chi^2 = 3.424$, p = 0.181, Cramer's V = 0.176) showed weak associations, with children exhibiting these symptoms more frequently classified into the severe dehydration group. Despite these observed trends, none reached statistical significance, indicating that dehydration severity in children with AGE is likely influenced more by physiological disturbances such as electrolyte imbalances and cumulative fluid loss than by individual clinical symptoms alone (Table 2).

Table 2: Clinical Characteristics of Study Population and Their Association with Dehydration Severity (n=110)

Variables	Categories	Frequency (%)	Chi-square (χ^2, df)	p-Value	Cramer's V	Strength of Association
Breastfeeding History	Exclusive	65 (59.1%)	1.303 (4)	0.861	0.077	Very Weak
	Formula-fed	13 (11.8%)				
	Partial	32 (29.1%)				
Diarrhea Type	Bloody	13 (11.8%)	5.333 (4)	0.255	0.156	Weak
	Mucoid	25 (22.7%)				
	Watery	72 (65.5%)				
Vomiting	No	26 (23.6%)	2.046 (2)	0.360	0.136	Weak
	Yes	84 (76.4%)				
Fever	No	39 (35.5%)	3.424 (2)	0.181	0.176	Weak
	Yes	71 (64.5%)				
Oral Rehydration Therapy	Not Received	41 (37.3%)	0.898 (2)	0.638	0.090	Very Weak
	Received	69 (62.7%)				
Antibiotics Used	No	44 (40.0%)	0.521 (2)	0.771	0.069	Very Weak
	Yes	66 (60.0%)				

Table 3 compared continuous variables age, weight, duration of symptoms, and frequency of diarrheal episodes across different levels of dehydration severity. Age and weight, which were normally distributed, were analyzed using one-way ANOVA, while duration of symptoms and diarrheal frequency, which did not follow a normal distribution, were analyzed using the Kruskal-Wallis test. None of the variables showed statistically significant differences across the dehydration groups (p > 0.05), indicating that these parameters did not significantly predict the severity of dehydration in the study population (Table 3).

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Table 3: Comparison of Continuous Variables across Dehydration Severity Groups

Variables	Mean ± SD	Median (IQR)	Min – Max	Statistical Test Used	p-Value
Age (months)	18.92 ± 5.83	19.05 (7.9)	6.0 – 32.4	ANOVA	0.148
Weight (kg)	9.12 ± 2.09	9.10 (2.9)	5.0 – 14.2	ANOVA	0.496
Duration of Symptoms (days)	4.27 ± 1.91	4.00 (4)	2 – 8	Kruskal-Wallis	0.766
Frequency of Diarrheal Episodes	4.40 ± 1.91	4.00 (4)	2 – 8	Kruskal-Wallis	0.667

This presented the comparison of serum electrolyte levels across dehydration severity groups using one-way ANOVA. All electrolyte parameters, including sodium, potassium, chloride, bicarbonate, calcium, magnesium, urea, and creatinine, showed statistically significant differences ($p \leq 0.05$) among the groups. Children with severe dehydration had significantly higher levels of sodium, potassium, chloride, urea, and creatinine, while bicarbonate and magnesium levels were significantly lower compared to mild and moderate cases. These results highlight the clinical importance of electrolyte monitoring in children with AGE (Table 4).

Table 4: Comparison of Mean Serum Electrolyte Levels across Dehydration Severity Groups

Serum Electrolyte	Mean ± SD	Median (IQR)	Min – Max	Statistical Test	p-Value
Sodium (mmol/L)	136.90 ± 3.82	137 (5)	130 – 145	ANOVA	0.001*
Potassium (mmol/L)	4.15 ± 0.68	4.0 (1.0)	3.0 – 5.6	ANOVA	0.000*
Chloride (mmol/L)	101.75 ± 4.25	101 (6)	94 – 109	ANOVA	0.002*
Bicarbonate (mmol/L)	21.50 ± 3.25	22 (4)	15 – 27	ANOVA	0.000*
Calcium (mg/dL)	9.15 ± 0.68	9.2 (0.8)	8.0 – 10.5	ANOVA	0.005*
Magnesium (mg/dL)	1.75 ± 0.32	1.8 (0.4)	1.2 – 2.3	ANOVA	0.000*
Urea (mg/dL)	30.25 ± 10.12	29 (10)	14 – 55	ANOVA	0.003*
Creatinine (mg/dL)	0.60 ± 0.15	0.6 (0.2)	0.3 – 1.1	ANOVA	0.004*

*Statistically significant at ≤ 0.05

It presented post-hoc comparisons of serum electrolyte levels across dehydration severity groups using Tukey's HSD test. The results revealed statistically significant differences (≤ 0.05) for all measured electrolytes. Children with severe dehydration had significantly higher levels of sodium, potassium, chloride, urea, and creatinine compared to mild and moderate groups. In contrast, bicarbonate and magnesium levels were significantly lower in the severe group, suggesting underlying metabolic acidosis and electrolyte loss. These findings reinforce the importance of routine electrolyte assessment in managing moderate to severe dehydration (Table 5).

Table 5: Post-hoc Comparison of Serum Electrolyte Levels across Dehydration Severity Groups Using Tukey's HSD Test (n=110)

Electrolyte	Mild Mean ± SD	Moderate Mean ± SD	Severe Mean ± SD	p-Value	Post-hoc Significant Differences
Sodium (mmol/L)	135.51 ± 4.2	135.30 ± 3.9	137.89 ± 3.7	0.001*	Severe > Mild, Moderate
Potassium (mmol/L)	3.93 ± 0.64	4.05 ± 0.61	4.58 ± 0.65	0.000*	Severe > Mild, Moderate
Chloride (mmol/L)	100.7 ± 4.5	101.3 ± 4.2	102.8 ± 4.1	0.012*	Severe > Mild, Moderate
Bicarbonate (mmol/L)	21.89 ± 3.0	21.97 ± 2.8	18.66 ± 2.9	0.000*	Mild, Moderate > Severe
Calcium (mg/dL)	9.18 ± 0.62	9.25 ± 0.59	9.45 ± 0.58	0.030*	Severe > Mild, Moderate
Magnesium (mg/dL)	1.81 ± 0.35	1.77 ± 0.33	1.55 ± 0.32	0.000*	Mild, Moderate > Severe
Urea (mg/dL)	29.5 ± 9.1	30.2 ± 9.0	32.3 ± 8.8	0.008*	Severe > Mild, Moderate
Creatinine (mg/dL)	0.61 ± 0.19	0.63 ± 0.18	0.74 ± 0.17	0.015*	Severe > Mild, Moderate

*Statistically significant at ≤ 0.05

Post-hoc analysis performed using Tukey's HSD test following one-way ANOVA.

The overall analysis of demographic, clinical and biochemical parameters suggested that imbalances in electrolytes have a much greater relationship with the severity of dehydration than demographic or elementary clinical factors. The prominent differences observed in sodium, potassium and bicarbonate as well as creatinine levels suggests that in cases of severe dehydration, attention to the fluid balance as well as correcting the metabolic derangement should be the primary focus. In figure 1 the graph demonstrated the variation of electrolyte concentrations when the level of dehydration increases. The worsening of dehydration results in higher concentration levels of sodium, potassium, chloride, urea, and creatinine likely due to the loss of fluid causing these electrolytes to be more concentrated. As bicarbonate and magnesium concentrations decrease, this indicates a probable case of metabolic acidosis and loss of an electrolyte. These trends underscore the need to assess electrolytic balance in patients who are dehydrated, which is critical.

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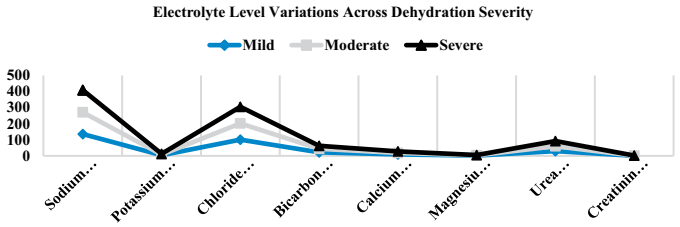

Figure 1: Trends in Serum Electrolyte Levels across Dehydration Severity

The graph illustrates how sodium, potassium, chloride, urea, and creatinine levels increase with dehydration severity, while bicarbonate and magnesium levels decrease, indicating electrolyte imbalances associated with worsening dehydration.

DISCUSSION

This study explored the relationship between serum electrolyte disturbances and dehydration severity in children with Acute Gastroenteritis (AGE). Significant differences in serum sodium, potassium, chloride, bicarbonate, calcium, magnesium, urea, and creatinine levels were observed across dehydration groups, highlighting the clinical value of electrolyte monitoring in paediatric AGE. No statistically significant associations were found between dehydration severity and demographic variables such as gender, nutritional status, or residence. Maternal education showed a moderate but non-significant association, suggesting that lower maternal education may influence care-seeking behaviour and delay rehydration, consistent with previous studies [6, 9, 10]. Among clinical features, diarrhea type and fever showed weak associations with dehydration severity. Watery stools and fever may contribute to increased fluid loss, but their predictive value was limited, reinforcing the need for biochemical assessment over clinical signs alone [11-13]. Age, weight, duration of symptoms, and diarrheal frequency were not significantly different across dehydration categories. This supports existing evidence that symptom duration alone is insufficient to predict severity and underlines the role of serum electrolytes in clinical evaluation [14, 15]. A key finding was the significant rise in sodium levels with increasing dehydration severity, particularly in children with hypernatremia, which reflects disproportionate water loss. Similarly, potassium levels were significantly elevated in severe dehydration ($p \leq 0.001$), suggesting impaired renal excretion and cellular shifts. Hyperkalaemia in paediatric patients is particularly concerning due to its potential to cause cardiac arrhythmias, muscle weakness, and life-threatening ECG changes [16]. Hypomagnesemia, also noted in severe dehydration, is equally worrisome. Magnesium is essential for neuromuscular stability, and its deficiency can lead to seizures, muscle cramps, and worsening electrolyte derangements, particularly hypokalaemia and hypocalcaemia [17]. Metabolic acidosis, indicated by significantly reduced bicarbonate levels, was prominent in severely dehydrated children. This aligns with the pathophysiology of AGE, where bicarbonate is lost via diarrheal stools [18]. Elevated urea and creatinine levels in these patients suggest perennial azotaemia, highlighting the risk of kidney dysfunction in the setting of hypovolemia [19]. Post-hoc analysis confirmed that severe dehydration was associated with marked electrolyte deviations compared to mild and moderate cases. These findings emphasize the importance of early electrolyte monitoring and timely correction, particularly in severe AGE cases. International guidelines, including those from WHO and UNICEF, recommend electrolyte assessment and tailored rehydration therapy as standard components of AGE management, especially in moderate to severe cases [20, 21]. These guidelines underscore the need for low-osmolarity ORS, zinc supplementation, and correction of electrolyte disturbances in hospitalized children with diarrhea. This was a cross-sectional study, which limits causal inferences. Real-time fluid loss monitoring and serial electrolyte measurements were not performed. Future longitudinal studies with larger samples should explore dynamic electrolyte changes during treatment and assess outcomes in relation to maternal education and socioeconomic status.

CONCLUSIONS

This study demonstrates that electrolyte abnormalities are strongly associated with the severity of dehydration in children with AGE. While demographic and clinical variables showed limited predictive value, significant changes in sodium, potassium, bicarbonate, and creatinine were observed in severely dehydrated children. These findings support the incorporation of routine serum electrolyte testing into standard clinical protocols for paediatric AGE, particularly in resource-limited settings where early detection and correction of imbalances can reduce complications and improve outcomes.

Authors Contribution

Conceptualization: IK
Methodology: FUB, IK, AY, AK
Formal analysis: FUB, IK
Writing, review and editing: OK, FUB, IK, AY, AK
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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The Relationship of Dental Pulp Stone with Cardiovascular and Renal Disease: A Cross Sectional Study

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ABSTRACT

Calcification of bodily tissues can occur by pathological or physiological means due to deposition of calcium. Normally, calcium deposits in teeth and bone, but ectopic areas in the body such as kidneys, vascular system and joints may precipitate calcium due to imbalance in the metabolism of calcium results hypercalcemia is known as metastatic calcification. **Objective:** To determine the association of pulp stones with cardiovascular and renal disease. **Methods:** Through non-probability sampling, cross-sectional study was carried out over the course of six months at the Department of Operative Dentistry and Endodontics, DUHS, Karachi.The current study comprised 150 patients, both male and female, between the ages of 30 and 60, who had teeth with pulp stones; individuals without pulp stones were not included. The chi-square test was utilized to evaluate the relationship between dental pulp stones and the existence of cardiovascular and renal disorders, and SPSS was used for data analysis. **Results:** Females were mostly affected as compare to males (63%).The mean age of the patients was noted as 42.2 years.A significant association between dental pulp stones cardiovascular and renal disease was documented. (p=0.001). **Conclusion:** A significant association was observed between CVD and pulp stones (p-value 0.001) and also significant association was established between PS and RS (p-value 0.001).

INTRODUCTION

Dental pulp stones develop as calcified growths that exist inside the dental pulp tissue before being spotted accidentally through radiographic imaging [1]. The specific origins of dental pulp stones remain unknown even though researchers link their development to dental caries as well as aging and restorations and systemic conditions [2]. Research investigations now focus on possible connections between dental pulp stones and both cardiovascular conditions and renal system disorders [3]. A case-control study assessed the correlation between various systemic conditions and the occurrence of pulp canal calcification [4]. Pulp Stones can be seen as free, attached, and embedded in the pulp chamber's dentinal surface, and they are more frequently found in the coronal than in the radicular sections of the pulp. Pulp stones are categorized as real, false, and dispersed based on their structure. They can be either microscopic particles or massive masses that nearly fill the pulp chamber [5].Some factors, including genetic predisposition, orthodontic tooth movement, circulation disturbance in pulp, age,

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interactions between the pulp tissue and the epithelium, idiopathic factors, and long-standing irritants like caries, deep restorations, and chronic inflammation, have been linked to the formation of stones, even though the precise cause of pulp calcification is unknown [6]. Pathophysiology of pulp stones are multifactorial, such as movement of tooth due to orthodontic treatment purpose, decrease the blood supply to the pulp, aging factors, and persistent includes like caries, shallow to deep restorations or abrasion, periodontal disorders, chronic inflammation and genetic predisposition and particular syndromes such as Van der wound syndromes have been serve as an etiologic feature of PS [7, 8]. The prevalence of pulp stones, radiographically shows different percentages (8% to 95%). Pulp stone most commonly present in female than male [9]. Various research studies examined how pulp stones link to cardiovascular diseases (CVDs). Systematic research including seven observational studies with 3,770 participants showed that individuals with pulp stones faced a 1.70 times greater risk for coronary or carotid artery calcified atherosclerotic plaques (95% CI: 1.21–2.38) [10]. Even though the evidence seemed consistent the studies maintained minimal certainty and demonstrated various biases which impacted both confounding variables and measurement accuracy [11]. A study investigating both pulp stones and Carotid Artery Calcifications (CACs) revealed that these conditions showed statistically important relationship to each other. Research revealed pulp stones affect 4.6% of patients and showed no association patterns with CACs (p = 0.714) [12]. Research investigations have evaluated the connection between pulp stones and renal diseases. An analysis of 70 dental patients revealed that those with renal stones were more than three times as likely to have pulp stones (OR: 3.78, 95 percent CI: 1.35–11.50; with a p=0.014) as those without renal stones. The occurrence of pulp stones rose progressively in older individuals [13]. Research showed that kidney stone patients contained pulp stones at a rate of 49.4% but individuals without kidney stones developed pulp stones in 36.4% of cases. The study indicated that kidney stones were more common when three or more teeth had dental pulp stones (p=0.143), but this relationship was not evident when one or two teeth had pulp stones [14]. Multiple research projects analyze how dental pulp stones link to cardiovascular along with renal illnesses yet their results remain inconsistent. The research shows both potential connections between dental pulp stones and systemic conditions and also demonstrates substantial correlations between these entities. Multiple factors affecting studies include diverse designs, different sample sizes, diagnostic specification differences and distinct population profiles.

Finding the prevalence and association of dental pulp stones in individuals with cardiovascular and renal diseases is the goal of the current investigation.

METHODS

At the Dr. Ishrat-ul-Ebad Khan Institute of oral Health Sciences, Dow University of Health Sciences, Karachi, the Department of Operative Dentistry and Endodontics carried out this cross-sectional study. After getting ethical approval from research ethics committee of the Dow University (IRB-3033/DUHS/Approval/2023/200). Data was collected in time duration of six months (from 1-9-2023 to 28-02-2024) through non-probability consecutive sampling. Sample size was calculated on the basis of prevalence of pulp stones found about 9% by taking confidence interval 95% and margin of error 5% and calculated by Raosoft sample size calculator we have sample of 126 and we have increased it up to 150 including missing and non-responders etc. [21]. Inclusion criteria was based on 150 patients, aged 30-60 years, both gender, with Patient having teeth with pulp stone were incorporated in the current study. Pediatric patients, pregnant patients, teeth with heavy restoration and patients with other co-morbidity were excluded from the present study. Written informed consent was taken from all the patients included in this study. The subject of this study was presented to operative department for routine dental problem with panoramic radiographs. Their radiographs were evaluated for total number of teeth with presences of PS and obliteration of pulp chamber. The results were record as “yes” or “no”. Detected PS was chosen for further query for medical history related to CVD and Renal disease. Past record like ECG, past blood pressure record, ultrasonography was evaluating the patient with positive medical history of CVD and renal disease. The statistical analysis of the gathered data was done using SPSS version 26. Age was one of the quantitative variables whose mean and standard deviation were assessed. Pulp stone prevalence in patients with CVD and renal illness, as well as patient gender, were qualitative variables for which frequency and percentage were computed. To determine if illness kind and pulp stone were related, the chi-square test was used. The p-value was deemed significant when it was less than 0.05. Panoramic radiograph showing pulp stones within the pulp chambers of molar teeth (figure 1).

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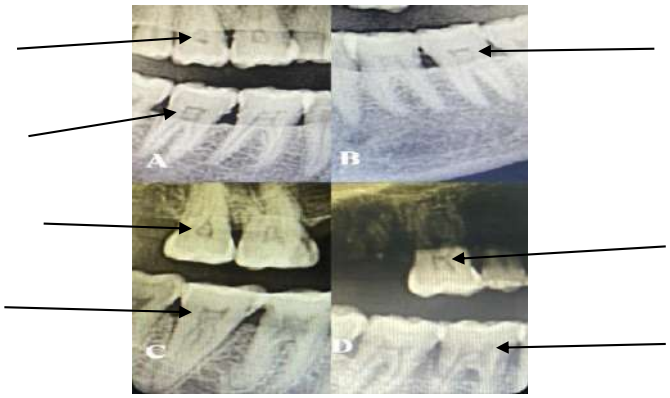

Figure 1: On the Panoramic Radiograph, Pulp Stones were seen Inside the Molars' Pulp Chambers

Panoramic radiograph displaying multiple free pulp stones in the pulp chambers of upper and lower teeth (figure 2).

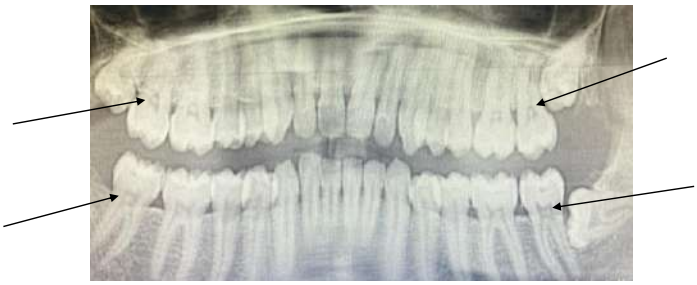

Figure 2: The Panoramic Radiograph from the Upper and Lower Jaw Teeth Shows many Free Pulp Stones inside the Pulp Chambers

RESULTS

There were 150 participants in this research. The patients were stuck between the ages of 30-60, by an average age of 42.2 ± 14.06 years. The sample comprised 56 males (37%) and 94 females (63%). Among the participants, 47 individuals (31%) were diagnosed with Cardiovascular Disease (CVD), while 22 individuals (15%) had renal disease (Table 1).

Table 1: Demographic and Clinical Parameters

Variables	Mean ± SD/ Frequency (%)
Age (Years)	
Mean	42.2 ± 14.06
Gender	
Male	56 (37%)
Female	94 (63%)
CVD	47 (31%)
Renal Disease	22 (15%)
Pulp Stone without Systemic Diseases	81 (54%)

Pulp stones are linked to systemic disorders such as cardiovascular disease and renal ailments, as seen in Table 2. The results showed that among individuals 47 had dental pulp stones with CVD while 22 individuals had pulp stones with renal diseases. In contrast, 81 individuals were having pulp stones but without any systemic disorder. Renal and cardiovascular illnesses were shown to be statistically significantly associated with dental pulp stones (p=0.001).The chi-square test indicated significant association between dental pulp stones, CVD and renal disease (p=0.001). These findings suggest that while pulp stones are prevalent in the studied population, their relationship with cardiovascular and renal diseases remains conclusive based on statistical analysis(Table 2).

Table 2: Association of Disease Type with Pulp Stone

Dental Pulp	CVD (Yes)	CVD (No)	p-Value
Pulp stones	47	103	0.001
Dental Pulp	**Renal Diseases (Yes)**	**Renal Diseases (No)**	**p-Value**
Pulp stones	22	128	0.001

DISCUSSION

Pulp stones, often called denticles, can result from calcification of the tooth pulp.Thus, pulpal calcification was denoted by the phrase "pulp stone" in the current investigation.Numerous factors, including genetic predisposition, orthodontic tooth movement, circulation disturbance in pulp, age, interactions between pulp tissue and the epithelium, idiopathic factors, and long-standing irritants like caries, deep restorations, and chronic inflammation, have been linked to the formation of stones, even though the precise cause of pulp calcification is unknown [15]. Since several systemic disorders, such RS and CVD, are impacted by calcium imbalance, PS is one of the subjects that has lately been studied in relation to these conditions. The radiographic technique which was used on in this study is a better radiographic method than the periapical and panoramic techniques, since distortion can occur in the picture in the latter, while the centre beam in the paralleling approach can be positioned perpendicular to the teeth's long axis to provide a more uniform image. Dentin dysplasia and dentinogenesis imperfecta are two examples of systemic or hereditary illnesses that often cause pulp calcifications throughout the dentition [16]. Predisposing variables for pulpal calcification have been identified as diseases such as hypercalcemia, gout, and renal lithiasis that are related to calcium metabolism.Many authors have found correlations between calcification of dental pulp stone, CVD and renal disease.Organic matrix components of human pulp stone were investigated under immune histochemistry by using antibiotics against type I collagen and non-collagenous protein (for example osteo-pontin, osteo-nectin and osteocalcin) which are involved in calcification of matrix.Type I collagen is evenly distributed in dental pulp stone as a main component and powerful immunostaining against the osteo-pontin that surrounded of the stone is also detected.Osteo-pontin found in other ectopic calcification in the body as well such as, stone in the kidney, atherosclerotic plaques, and dental calculus [17].Goga R reviewed the prevalence, formation, classification, and clinical significance of pulp stones in

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dental practice [16].This minerals substance is same in calcified tissue (pulp stone), renal calculi and calcification of atherosclerotic plaque.Nanobacteria are an active center of calcified mineral.Hence, this is also the relationship of PS with CVD (atheromatous plaque) and Renal disease (renal calculi) [17]. A systemic review study done by Chalikkandy SN *et al.*, showed that renal failure frequently results in accelerated Cardiovascular Disease (CVD) [18].Chronic Kidney Disease (CKD) causes hypertension and dyslipidemia, which later worsen renal failure.The Prevention and treatment of cardiovascular disease are main cogitation for the management of the individual for further complications.Different research investigations discovered elevated rates of dental pulp stones exist in heart disease patients. According to a systematic review by Banka A *et al.*, with meta-analysis dental pulp stone patients presented 1.70 times greater chance of developing coronary or carotid artery atherosclerotic plaques [19]. A pilot research by Altındağ A *et al.*, indicated that CVD patients presented pulp stones in 74% of cases compared to 39% for volunteers who did not have CVD which raises the possibility of this connection [20, 21]. Research studies have produced similar results to those of the present investigation by detecting meaningful statistical connection.The assessment of pulp stones and carotid artery calcifications revealed no statistically significant link (p=0.714), suggesting that pulp stones are not a reliable indicator of the onset of cardiovascular disease [22].Although studies currently suggest a link between pulp stones and systemic diseases they did not identify any meaningful relationship during this assessment.Subsequent studies with well-established protocols and larger participant populations will help resolve this relationship. A number of theories are put up in the literature to explain the genesis of PS.The patient's ageing process was the subject of the initial hypothesis [23, 24].Complete obstruction of neurovascular supply may happen in severe situations. However, elevated blood levels of calcium and phosphate, which may indicate metabolic dysfunctions, are the most likely cause of PS and other body calcifications. According to some research, PS is a local expression of constitutional metabolic dysfunctions brought on by hypercalcemia, and it has the same pathophysiology as coronary artery calcifications accordingly, it has been demonstrated that coronary artery calcifications and an elevated risk of cardiovascular morbidity and death are linked to the rise in calcium phosphate crystals in blood vessels.

CONCLUSIONS

The studied population revealed high dental pulp stone frequency and such findings link with cardiovascular and renal conditions as significant association was observed in CVD and renal stones (p-value 0.001).Longitudinal research must be conducted in the future to determine the clinical importance of pulp stones.

Authors Contribution

Conceptualization: RZ
Methodology: RZ, AK
Formal analysis: RZ, AAJ, MT, SAJ
Writing, review and editing: RZ, FURQ, GR, AAJ, MT, SAJ
All authors have read and agreed to the published version of the manuscript

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Original Article

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Diagnostic Accuracy of Fasting Blood Sugar and Oral Glucose Challenge Test for Gestational Diabetes Mellitus

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ABSTRACT

Despite multiple studies on gestational diabetes mellitus (GDM) screening, evidence on the concurrent validity and practical use of fasting blood glucose (FBS) and glucose challenge test (GCT) remains limited. **Objectives:** To compare the diagnostic accuracy of FBS, and oral GCT in detecting GDM, taking oral glucose tolerance test (OGTT) as the gold standard. **Methods:** This cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Shahida Islam Teaching Hospital, Lodhran, Pakistan, from March to December 2023. A total of 160 pregnant women aged 20-40 years (gestation>20 weeks) were included. Diagnostic performance of FBS and GCT was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. IBM-SPSS Statistics, version 26.0, was used for data analysis. McNemar's test was applied to these how FBS, or GCT, agreed with GTT in diagnosing GDM, taking $p<0.05$ as significant. **Results:** The mean age and gestational age were 29.54 ± 5.35 years and 27.81 ± 2.48 weeks, respectively. The sensitivity of FBS in the diagnosis of GDM was 78.3%, and that of GCT was 84.2% (p=0.700).The specificity of FBS and GCT was 86.8% and 96.9%, respectively. The PPV of FBS was 81.8%, and that of GCT was 85.7%. The NPV of FBS and GCT were 84.0% and 91.8%, respectively (p=0.994). Accuracy of FBS was 83.1%, and GCT was 89.4%. **Conclusions:** It was concluded that the diagnostic accuracy of FBG and GCT in diagnosing GDM is high, with GCT demonstrating superior effectiveness. OGTT remains the definitive gold standard for confirming GDM.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition occurring in pregnancy associated with significant complications, and its prevalence is rising, particularly among Asian women [1]. The prevalence of GDM varies between 4.4% and 57.9% in Pakistan [2]. Research has shown a strong association of GDM with many adverse pregnancy outcomes like macrosomia, polyhydramnios, shoulder dystocia, preeclampsia, higher cesarean delivery rates, and long-term effects on both mothers and infants [3]. Females with GDM are estimated to have a raised risk of developing type 2 diabetes mellitus (T2DM) in the following years of life. Management strategies for GDM, including exercise, dietary changes, blood glucose monitoring, and insulin therapy, have evolved over the years and resulted in improved management of associated short-term and long-term complications [4]. No screening test is universally accepted despite the rising prevalence and impact of GDM globally. Not only do the diagnostic tests, but also the criteria for diagnosis, vary widely. According to ACOG and ADA, universal screening should be done with oral glucose tolerance test (OGTT) between 24-28th week of pregnancy. Fasting blood sugar (FBS) is often used for GDM screening due to its affordability, accessibility, simplicity, and reliability [5, 6]. The debate still goes on about the diagnostic accuracy (DA) of the glucose challenge test (GCT) and FBS levels [7-9]. Asians, particularly Pakistani women, have a high prevalence of diabetes and genetic susceptibility to metabolic syndromes with an elevated risk

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of developing GDM and its associated complications. This highlights the need for a cost-effective, universal screening and diagnostic approach. GCT seems less time-consuming, although no consensus guidelines or endorsements exist in this regard. FBS is easier to obtain, but it needs the patient to come fasting. The high accuracy of FBS could alleviate the strain on laboratories and conserve resources, as conducting a 2-hour, 75g OGTT can be challenging in large populations and resource-limited areas. This study was conducted to collect data from the local population to help identify more accurate, less time and cost-effective tests so that this research may help in formulating national protocols and guidelines for the diagnosis of GDM.

This study aims to compare the diagnostic accuracy of FBS and GCT in identifying GDM, using the OGTT as the gold standard, in pregnant women attending a tertiary care hospital. Despite numerous international and national studies on GDM screening, there remains limited evidence evaluating the concurrent validity and practical applicability of FBS and GCT in low-resource, peripheral tertiary care settings within Pakistan. This study seeks to provide context-specific data to inform more feasible and cost-effective screening strategies for early GDM detection in such environments.

METHODS

It was a cross-sectional validation study conducted in the Department of Obstetrics and Gynecology, Shahida Islam Teaching Hospital, Lodhran, from 1st March 2023 to 30th December 2023. A sample size of 160 cases was calculated, taking the frequency of GDM as 11.8%, with a 95% confidence level, and a 5% margin of error using the Open EPI online sample size calculator [10].The sample was selected by non-probability, consecutive sampling. Women, 20-40 years of age, presenting after the 20th week of gestation, who came to the outpatient department for their antenatal check-ups, were included. All patients with a history of chronic hypertension, multiple gestation, obesity, history of diabetes, chronic liver disease, and chronic kidney disease were excluded.After obtaining approval from the ethical committee of the institution (letter number: SIMC/ET.C/10013/23), women fulfilling eligibility criteria were enrolled from the outpatient department following informed and written consent. Data about age, gestational age (as per LMP), body mass index (BMI), residence, monthly income, and family history of DM were collected.Blood samples were sent to the institutional laboratory to measure FBG on two consecutive days. On day 1, the patients also underwent a 50g non-fasting GCT. One week later, during their next visit, the patients received a 75 g OGTT. The results of the gold standard were then compared with those from the FBG and GCT. FBG ≥ 92 mg/dL was considered positive for GDM. The 50g GCT, performed without fasting, was considered positive if ≥200 mg/dl. The OGTT confirmed GDM if glucose levels exceeded fasting ≥92 mg/dL, 1-hour ≥180 mg/dL, or 2-hour ≥153 mg/dL. Data analysis was done by IBM-SPSS Statistics 26.0. Mean and standard deviation were calculated for quantitative variables. Frequencies and percentages were determined for qualitative variables. The diagnostic evaluation analysis calculated sensitivity, specificity, PPV, NPV, and DA. McNemar's test was applied to these to determine how FBS, or GCT, agreed with GTT in diagnosing GDM, taking $p<0.05$ as significant.

RESULTS

In a total of 160 women, the mean age was 29.54 ± 5.35 years, while 87 (54.38%) were between 20-30 years. The mean gestational age was 27.81 ± 2.48 weeks, while the mean BMI was 30.43 ± 2.66 kg/m2. Distribution of patients according to parity, place of living, family history of DM, and monthly family income is shown in Table 1.

Table 1: Characteristics of Women with Gestational Diabetes Mellitus(n=160)

Variables		Frequency (%)
Age in Years	20-30	87 (54.4%)
	31-40	73 (45.6%)
BMI (Kg/M^2)	≤ 27	29 (18.1%)
	>27	131 (81.9%)
Parity	1-2	73 (45.6%)
	3-5	87 (54.4%)
Place of Living	Rural	65 (40.6%)
	Urban	95 (59.4%)
Family History of Diabetes	Yes	56 (35.0%)
	No	104 (65.0%)
Monthly Income (PKR)	<25000	33 (20.6%)
	25000-50000	76 (47.5%)
	>50000	51 (31.9%)

In 66 blood FPG positive women, 54 had GDM, and 12 had no GDM on GTT. Among 94 FPG negative patients, 15 had GDM on GTT, whereas 79 had no GDM on GTT (p=0.700). Overall sensitivity, specificity, PPV, NPV, and DA of FPG in detecting GDM, taking GTT as gold standard, were 78.3%, 86.8%, 81.8%, 84.0% and 83.1%, respectively. In 63 GCT-positive women, 54 had GDM, and 9 had no GDM on GTT. Among 97 GCT negative women, 8 had GDM on GTT, whereas 89 had no GDM on GTT (p=0.994). Overall sensitivity, specificity, PPV, NPV, and DA of GCT for detecting GDM were 84.2%, 96.9%, 85.7%, 91.8%, and 89.4%, respectively and shown in Table 2.

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Table 2: Diagnostic Validity of Fasting Blood Sugar and Oral Glucose Challenge Test Concerning Oral Glucose Tolerance Test in Diagnosing Gestational Diabetes Mellitus

Variables	Positive GTT	Negative GTT	p-value	Sensitivity	Specificity	PPV	NPV	DA
Positive FBS	54 (TP)	12 (FP)	0.700	78.3%	86.8%	81.8%	84.0%	83.1%
Negative FBS	15 (FN)	79 (TN)						
Positive GCT	54 (TP)	09 (FP)	0.994	87.1%	90.8%	85.7%	91.8%	89.4%
Negative GCT	08 (FN)	89 (TN)						

Among women aged 20–30 years, FBS demonstrated a sensitivity of 80.4%, specificity of 85.9%, and diagnostic accuracy of 83.4%. In women with BMI >27 kg/m^2, sensitivity and specificity were 77.6% and 87.5%, respectively. Diagnostic accuracy ranged from 82.5% to 83.5% across BMI strata. Similar trends were observed by parity, with accuracy for FBS being 84.1% in women with 1–2 children and 83.7% in those with 3–5 children. The details about the stratified diagnostic utility evaluation of FBS in diagnosing gestational diabetes mellitus concerning the oral glucose tolerance test are shown in Table 3.

Table 3: Stratified Diagnostic Utility Evaluation of Fasting Blood Sugar in Diagnosing Gestational Diabetes Mellitus Concerning Oral Glucose Tolerance Test

Variables		Sensitivity	Specificity	PPV	NPV	DA
		(%)				
Age in Years	20-30	80.4%	85.9%	78.0%	86.1%	83.4%
	31-40	76.2%	88.4%	85.7%	83.4%	83.2%
BMI (kg/m^2)	≤27	82.8%	84.4%	76.4%	88.6%	82.5%
	>27	77.6%	87.5%	83.6%	83.7%	83.5%
Parity	1-2	79.1%	88.1%	80.2%	85.4%	84.1%
	3-5	78.0%	86.8%	82.0%	84.3%	83.7%
Place of Living	Rural	76.5%	85.4%	79.9%	83.4%	82.2%
	Urban	79.4%	87.6%	83.4%	84.7%	84.9%
Family History of Diabetes	Yes	77.5%	86.5%	81.6%	84.3%	83.5%
	No	78.5%	87.2%	82.3%	85.7%	83.4%
Monthly Income (PR)	<25000	75.4%	84.6%	77.7%	81.7%	81.5%
	25000-50000	79.9%	86.7%	81.2%	85.2%	83.6%
	>50000	81.0%	88.9%	85.0%	86.6%	84.5%

In women aged 20–30 and 31–40 years, GCT yielded diagnostic accuracies of 89.2% and 89.8%, respectively. For BMI >27 kg/m^2, sensitivity was 86.5% and specificity 97.5%, with 89.6% DA. Urban women had slightly better diagnostic performance (accuracy 89.5%) compared with rural women (88.5%). GCT also showed robust accuracy in women with (89.5%) and without (89.5%) a family history of diabetes. The details about the stratified diagnostic utility evaluation of FBS in diagnosing gestational diabetes mellitus for the oral glucose tolerance test are shown in Table 4.

Table 4: Stratified Diagnostic Utility Evaluation of Glucose Challenge Test in Diagnosing Gestational Diabetes Mellitus Concerning Oral Glucose Tolerance Test

Characteristics		Sensitivity	Specificity	PPV	NPV	DA
		(%)				
Age in Years	20-30	85.5%	95.1%	83.0%	92.7%	89.2%
	31-40	89.9%	98.3%	88.1%	91.2%	89.8%
BMI (kg/m^2)	≤ 27	88.2%	94.4%	84.7%	93.9%	87.2%
	>27	86.5%	97.5%	87.5%	91.5%	89.6%
Parity	1-2	86.7%	97.2%	85.1%	92.6%	89.5%
	3-5	88.6%	96.9%	87.2%	92.4%	89.5%
Place of Living	Rural	84.4%	95.4%	84.7%	91.2%	88.5%
	Urban	88.5%	97.4%	87.2%	92.7%	89.5%
Family History of Diabetes	Yes	85.5%	96.5%	86.9%	91.2%	89.5%
	No	88.1%	97.2%	87.4%	92.1%	89.5%
Monthly Income (PR)	<25000	82.0%	94.6%	82.3%	90.8%	87.5%
	25000-50000	88.9%	96.7%	85.4%	91.0%	89.7%
	>50000	90.4%	98.2%	89.5%	93.4%	90.6%

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DISCUSSION

Having a convenient method for screening and early diagnosis of GDM is crucial. A significant drawback of the gold standard for detecting GDM (OGTT at 24 weeks) is that it is typically assessed late in the second trimester, which can increase the risk of developing various health problems [11]. This study showed that FBG had a sensitivity of 78.3%, specificity of 86.8%, PPV of 81.8%, NPV of 84.0%, and DA of 83.1%. Oral GCT exhibited sensitivity of 84.2%, specificity of 96.9%, PPV of 85.7%, NPV of 91.8%, and DA of 89.4%. The findings of this study align closely with another study, which reported FBG sensitivity as 97.0%, specificity 78.2%, PPV 17.8%, and NPV 99.81% for screening GDM [7]. Another local study found FBG sensitivity to be 96.77%, specificity at 98.4%, PPV 98.6%, NPV 96.3%, and DA at 97.5%, also taking OGTT as the gold standard, and these findings, along with the present research, exhibit the efficiency of FBG in screening for GDM [8]. A meta-analysis indicated pooled sensitivity and specificity for GCT at 79.0% and 74.0%, respectively, while FBG had pooled sensitivity and specificity of 81.0% and 70.0%, further reinforcing the utility of FBG in GDM screening as was exhibited in the present study [9]. Some experts advocate for screening for previously undiagnosed diabetes during pregnancy, especially in populations at higher risk [12]. The primary advantage of FBG testing is its ability to diagnose overt diabetes, especially when FPG levels exceed 125 mg/dl. While the IADPSG in 2010 recommended GDM to be diagnosed with FBS between 92-125 mg/dl at any point during pregnancy, this recommendation has faced criticism due to insufficient supporting evidence [13].A study done by Souha AA concluded that GCT > 140 mg/dl is an effective threshold due to high NPV, and also the specificity to rule out GDM.This study also stated that lowering the threshold to 135 mg/dl increases the sensitivity, but the specificity decreases [14]. Salini *et al.*, showed that the 75g GCT demonstrated significantly greater DA compared to other methods.The authors also advocated that this GCT could replace all existing screening approaches and may serve as an alternative to the two-step 100g OGTT [15]. In this study, FBG≥92 mg/dL was considered positive for GDM, and this threshold has been a popular endorsement by other researchers like Chukwunyere *et al.*, who revealed that a FBG threshold of 92 mg/dl to exhibit excellent diagnostic performance, achieving a sensitivity of 90.0% and a specificity of 97.1%, along with an area under the curve as 0.920 [16].In comparison, the random plasma glucose (RPG) threshold of 140 mg/dl demonstrated a much lower sensitivity of 13.8%, although it maintained a specificity of 97.1%, resulting in an AUC of 0.845.These findings support the consideration of FBG as a viable standalone alternative for GDM screening, and the present study reinforces these findings [17]. Beunen *et al.*, showed FBG<78 mg/dl was identified as the optimal cut-off for minimizing missed cases of GDM, resulting in 44 missed cases (19.0%) with a NPV of 97.3%. This approach also helped to avoid 52.2% of OGTTS. Women with this FBG level exhibited a more favourable metabolic profile and, among those with normal glucose tolerance, showed reduced fetal growth [18]. Hasan et al., concluded that, FBG cut-off value of 81 mg/dl can serve as an effective initial screening test for GDM, helping to minimize the need for OGTTS [19].Overall sensitivity, specificity, PPV, NPV, and DA of FPG in detecting GDM, taking GTT as gold standard, were 78.3%, 86.8%, 81.8%, 84.0% and 83.1%, respectively, showing the effectiveness of FPG screening for GDM. A study from India comparing GCT versus OGTT indicated that the GCT may overlook a significant number of pregnancies while screening for GDM, and recommended using the OGTT as the more established as well as effective diagnostic approach for GDM [20].A study from South Africa concluded that universal screening and diagnosis of GDM are commonly recommended to enhance treatment and improve pregnancy outcomes; this approach could often be unfeasible in many resource-constrained settings [21].

CONCLUSIONS

It was concluded that both FBG and GCT are highly accurate in identifying GDM, with GCT demonstrating superior effectiveness. However, OGTT remains the definitive gold standard for confirming the diagnosis of GDM. Utilizing GCT as a primary screening tool may aid in early detection, allowing timely referral for OGTT and thereby helping to prevent complications associated with undiagnosed GDM.

Authors Contribution

Conceptualization: JS
Methodology: KA, AA[1], AA[2], FU, SH
Formal analysis: FU
Writing review and editing: JS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Original Article

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Efficacy of Topical Dapsone 5% Gel and Topical Adapalene 0.1% Gel In Treatment of Mild to Moderate Acne Vulgaris

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ABSTRACT

Acne is a common dermatological condition, affecting 9.4% of the global population, and is found in all age groups, particularly in adolescents and young adults. **Objective:** To compare effectiveness of dapsone 5% gel once daily with adapalene 0.1% gel monotherapy for mild to moderate acne vulgaris. **Methods:** Fifty individuals with mild to moderate acne, with a lesional count ranging from three to thirty, participated in an open-label, quasi-experimental comparative trial. Two therapy groups Group B received adapalene 0.1% gel (n = 24) and Group A received Adapsone 5% gel (n = 23). Patients were directed to cover their faces with a small amount of the gel that was supplied to them. At weeks 0, 4, 8, and 12, non-inflammatory lesion counts, total lesion counts, and adverse effects were assessed. **Results:** In all treatment groups, the prevalence of all forms of acne lesions declined from baseline. Dapsone 5% gel was less effective than adapalene 0.1% gel in reducing inflammatory lesions ($p < 0.05$). Adapalene 0.1% gel group experienced somewhat more adverse effects than dapsone 5% gel group, with a statistically significant difference (p-value 0.04). **Conclusions:** The conclusion has been updated to emphasize the clinical relevance of the findings. Specifically, it is now stated that Dapsone 5% gel is an effective and safer alternative for patients with mild to moderate acne who have sensitivity to retinoids, while Adapalene remains the preferred option for patients requiring more aggressive treatment of inflammatory lesions. This provides clear guidance for dermatologists in clinical practice.

INTRODUCTION

Regardless of gender, adolescents are the main demographic affected by acne vulgaris, a prevalent disease of the pilosebaceous units [1]. According to the Global Burden of Disease Study 2010, acne vulgaris is the eighth most prevalent skin disease globally [2]. The burden of acne is significantly, ranging from 26.8% to 96% across different regions and age groups [3, 4]. The primary pathogenic factors contributing to acne include: (a) increased sebum production driven by androgen stimulation of the sebaceous glands; (b) altered follicular keratinization (hyperkeratinization); (c) increased follicular colonization by Propionibacterium acnes or other bacterial infections; and (d) a complex inflammatory response involving both acquired and innate immunity [5]. Acne is also more likely to occur when oxidative stress brought on by endogenous and external Reactive Oxygen Species (ROS) increases. Moreover, overproduction of ROS is caused by recurrent stimulation by invasive organisms

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such as P. acnes and S. epidermidis [6]. Acne exerts a substantial psychological burden due to scarring and pigmentation. This condition negatively impacts relationships, friendships, and employment, reduces self-esteem, and triggers emotions such as shame, anger, concern, social withdrawal, and feelings of stigmatization [7]. Additionally, acne is associated with significant psychiatric comorbidities, including depression, anxiety, and suicidal ideation [8]. Acne can manifest as seborrhea (increased oil-sebum secretion), comedones, papules, nodules, pustules, and scars [9]. Benzoyl peroxide, clindamycin, retinoids (tretinoin, isotretinoin, adapalene, etretinate, tazarotene, retinaldehyde, and β-retinoyl glucuronide) are the topical treatments that are most frequently utilised. These therapies work well for mild to moderate acne, but they have limitations such as irritability, poor tolerability, and low patient adherence [10]. Other topical agents, including salicylic acid and azelaic acid, possess antibacterial, comedolytic, and anti-inflammatory properties. Despite their benefits, none of these treatment modalities can completely cure the disease; they only manage to control it with varying degrees of success. Dapsone's precise mode of action for treating acne is still not clear. In addition to its antibacterial and antiprotozoal activities, dapsone has non-steroidal anti-inflammatory drug-like properties [11]. The efficacy of dapsone for acne showed positive change [12]. Systemic dapsone is associated with serious adverse effects, including methemoglobinemia, and hemolysis [11]. Additionally, later studies demonstrated that dapsone is less effective than isotretinoin [13]. Despite this, dapsone remains a consideration for specific conditions such as acne fulminans. The development of a topical formulation made sense given the severe side effects of systemic dapsone as well as its possible antibacterial and anti-inflammatory properties [14]. The limitations were highlighted of current acne treatments, such as irritation and poor adherence to retinoids, and the need for alternative options like topical Dapsone with its anti-inflammatory properties. While previous studies have explored Dapsone and Adapalene separately, direct comparative studies assessing their efficacy in mild to moderate acne remain limited which our study aims to address.

This study evaluates the comparative efficacy of topical Dapsone 5% gel and Adapalene 0.1% gel in treating mild to moderate Acne Vulgaris, providing insights into their effectiveness for better management of this common skin condition. The findings aim to guide clinicians in selecting the most appropriate topical treatment.

METHODS

A comparative quasi experimental was carried out in Pakistan Emirates Military Hospital. The study spanned six months, from January 2024 to June 2024. Ethical permission was taken from ethical review board of PEMH and grandted ethical permission no: A/28/ERC/76/24. Patients of both sexes aged 12 years or older who were newly diagnosed with acne by a dermatologist were included. Between two and thirty total lesions, displaying either non-inflammatory or inflammatory types on the face, additionally, patients had to have a 2 or 3 Investigator's Global Assessment (IGA) score. Nodulocystic acne, acne fulminans, acne conglobata, and secondary acne were among the exclusion criteria. Followed by respondents with severe acne vulgaris and a previously had treatment with topical agents for 15 days, oral antibiotics for one month, or oral isotretinoin for six months were excluded. Pregnant and lactating women, women with menstrual irregularities, those using hormonal contraception, and individuals currently using any medications with hormonal influence. After fulfilling exclusion and inclusion criteria, patients were selected from the dermatology department of Pakistan Emirates Military Hospital. The safety of topical dapsone 5% gel (applied twice daily) in treating mild to moderate acne were evaluated in comparison with topical adapalene 0.1% gel (evening once daily). The sample size required to detect a significant difference between two proportions, with Proportion 1 being 0.523 for the Dapsone group and Proportion 2 being 0.769 for the Adapalene group, was calculated using a confidence level of 0.95. A 1:1 ratio of sample sizes was assumed, with a one-tailed test. The calculation determined a sample size of 54 participants. However, a rounded sample size of 50, divided equally between the two groups, was considered for this study. From the Outpatient Department (OPD) of dermatology, attending patients with acne vulgaris, a total of 50 individuals were randomly assigned to two monotherapy groups (Group A: dapsone and Group B: adapalene). Efficacy and safety assessments were conducted at weeks 0, 4, 8, and 12. Written and verbal consent for medication adherence and follow-up visits was obtained prior to enrollment in the study. SPSS version 25.0 was used to analyze the data. To compare the clinical and demographic characteristics of the two groups, unpaired t-tests, and Chi-square analyses were used. Every follow-up was conducted using the Mann-Whitney U test to evaluate changes in lesional counts. A statistically significant p-value <0.05.

RESULTS

The mean age of patients was 23.1 ± 10.1 years in the total group, 25.6 ± 9.4 years in the dapsone group, and 23.8 ± 9.7 years in the adapalene group, with a p-value of 0.12 (unpaired t-test). The sex distribution showed that 14 females (28.0%) and 36 males (72.0%) were included in the total sample. In the dapsone group, 6 females (24.0%) and 19 males (76.0%) were included, while the adapalene group had 8 females (32.0%) and 17 males (68.0%), with a p-value

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of 0.55 (Chi-square test).

Table 1: The Distributions of Demographical Characteristics and Clinical Parameters of Patients with Acne Vulgaris (n = 50)

Variables	Total Mean ± SD/ Frequency (%)	Dapsone Group A Mean ± SD/ Frequency (%)	Adapalene Group B Mean ± SD/ Frequency (%)	p-Value
Age (Years)				0.12[a]
Minimum-Maximum	23.1 ± 10.1	25.6 ± 9.4	23.8 ± 9.7	
Sex				0.55[b]
Female	14 (28.0%)	6 (24.0%)	8 (32.0%)	
Male	36 (72.0%)	19 (76.0%)	17 (68.0%)	

Table 2 shows the median lesion count, inflammatory, and non-inflammatory markers at weeks 0, 4, 8, and 12 for patients treated with either dapsone or adapalene. At baseline, the median lesion count was 22 for the total group, 23 for the dapsone group, and 23 for the adapalene group, with a p-value of 0.95. At week 4, the median lesion count was 20 for both groups (p = 0.37). At week 8, the median lesion count was 15 for the total group, with dapsone at 15 and adapalene at 14 (p = 0.19). By week 12, the median lesion count was 10 for the total group, 8 for the dapsone group, and 9 for the adapalene group (p = 0.08), showing a trend towards significance. For inflammatory markers, the median count at baseline was 5 for the total group, 7 for the dapsone group, and 5 for the adapalene group (p = 0.31). At week 4, the median counts were 6 for the total group, 6 for dapsone, and 6 for adapalene (p = 0.82). At week 8, the counts were 4 across all groups (p = 0.97), and at week 12, the counts were 2 across all groups (p = 0.30), indicating no significant differences. For non-inflammatory markers, the median count at baseline was 16 for the total group, 14 for the dapsone group, and 15 for the adapalene group (p = 0.31). At week 4, the counts were 15 for the total group, 12 for both dapsone and adapalene (p = 0.21). At week 8, the counts were 11 for the total group, 8 for dapsone, and 9 for adapalene (p = 0.06), showing a trend towards significance. By week 12, the median counts were 7 for the total group, 5 for dapsone, and 7 for adapalene (p = 0.13), again showing no significant differences.

Table 2: Lesion count, at 0, 4, 8 and 12 Week (n = 50)

Variables	Total	Dapsone Group A	Adapalene Group B	p-Value
Lesional Count (Median)				
Baseline	22	23	23	0.95*
4th Weeks	20	20	20	0.37*
8th Weeks	15	12	14	0.19*
12th Weeks	10	8	9	0.08*
Inflammatory				
Baseline	5	7	7	0.31*
4th Weeks	6	6.5	6	0.82*
8th Weeks	4	4	4	0.97*
12th Weeks	2	2	2	0.30*
Non-Inflammatory				
Baseline	16	14	15	0.31*
4th Weeks	15	12	12	0.21*
8th Weeks	11	8	9	0.06*
12th Weeks	7	5	7	0.13*

The percentage change in inflammatory and total acne lesions from baseline to the 12th week was substantially larger in Group B (p<0.05). On the other hand, there was not any significant difference (p>0.05) in the percentage decrease of non-inflammatory acne lesions between the two groups from the baseline to the 12th week (Table 3).

Table 3: Percent change of lesion count at week 12 (n = 50)

Variables	Dapsone Group A	Adapalene Group B	p-Value
Total	-48.3	-59.5	0.001[a]
Inflammatory	-52.3	-76.9	0.01[a]
Non-Inflammatory	-47.2	-52.6	0.12[a]

In Group A (dapsone), 4 patients (16.0%) experienced itching, 2 patients (8.0%) experienced burning, 1 patient (4.0%) experienced redness, and 1 patient (4.0%) experienced scaling. In Group B (adapalene), 5 patients (20.0%) experienced itching, 3 patients (12.0%) experienced burning, 2 patients (8.0%) experienced redness, and 2 patients (8.0%) experienced scaling. The p-values for itching, burning, redness, and scaling were 0.08, 0.12, 0.11, and 0.11, respectively, indicating no significant difference between the groups. However, 17 patients (68.0%) in the dapsone group reported no adverse events compared to 13 patients (52.0%) in the adapalene group, with a p-value of 0.04, demonstrate a statistically significant difference in the adverse events frequency between the two treatments.

Table 4: Adverse Event of the Drugs (n = 50)

Variables	Dapsone Group A Frequency (%)	Adapalene Group B Frequency (%)	p-Value
Itching	4 (16.0)	5 (20.0)	0.08*
Burning	2 (8.0)	3 (12.0)	0.12*
Redness	1 (4.0)	2 (8.0)	0.11*
Scaling	1 (4.0)	2 (8.0)	0.11*
No Adverse Events	17 (68.0)	13 (52.0)	0.04[a]

DISCUSSION

Dapsone is a rational choice for treating acne. For patients nine years of age and older, the approved dose is a single daily application of 5% dapsone gel [15]. Additionally, in 2005, the FDA approved, 5% dapsone gel twice daily as the treatment protocol for acne vulgaris in patients >12 [16]. The results of present study found the effectiveness of 5% dapsone gel the results are in line with the Wang X *et al.*, found the positive effectiveness of 5% dapsone gel in treating face acne vulgaris [17]. Furthermore, Moore AY *et*

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al., showed that treating acne in children between the ages of nine and eleven with 5% dapsone gel was effective, and well-tolerated [18].In a randomized, double-blind, vehicle-controlled Phase III clinical trial, Özkoca D *et al.*, found that once-daily application of 5% dapsone gel was effective in a similar age group [19].In the current study, both non-inflammatory and inflammatory acne lesions, alongwith total lesion counts, were significantly reduced from baseline to subsequent weeks.Islam R *et al.*, reported a reduction of 57.8% in total lesions, 63.1% in inflammatory lesions, as well as 52.4% in non-inflammatory lesions after 12 weeks of treatment [20].In this study, at 12 weeks, all types of acne lesions showed significant reduction from baseline.Specifically, the percentage decrease in total, inflammatory, as well as non-inflammatory acne lesion counts with dapsone were 48.3%, 52.3%, and 47.2%, respectively.Although this study focused on mild to moderate acne with a total lesional count of fewer than thirty, Gharib K *et al.*, reported a mean reduction of 55.5% in inflammatory lesions, 44.4% in non-inflammatory lesions, and 48.7% in total lesions with 5% dapsone gel [21].

CONCLUSIONS

Dapsone 5% gel has been shown to be safe and effective in treating mild to moderate acne vulgaris. It works similarly to adapalene 0.1% gel in treating acne vulgaris, especially non-inflammatory lesions.

Authors Contribution

Conceptualization: AF, AUB
Methodology: FKW, IG, WAK, NR, NUI
Formal analysis: NG
Writing, review and editing: BA, IG, WAK, NR, NUI
All authors have read and agreed to the published version of the manuscript

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Comparison of Pre-emptive Tramadol versus Diclofenac in Postoperative Pain Management after Laparoscopic Cholecystectomy

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ABSTRACT

Effective Pre-emptive analgesia is essential to improve pain control and reduce opioid consumption. Non-opioid analgesics such as diclofenac and tramadol are commonly used, but their comparative efficacy remains an area of interest. **Objective:** To compare mean postoperative pain intensity and time to 1st analgesic requirement between diclofenac and tramadol groups as Pre-emptive analgesics among patients undergoing laparoscopic cholecystectomy. **Methods:** This quasi-experimental study was conducted at Department of Anaesthesia, Mayo Hospital, Lahore, over period of six months. Quasi experimental study. 50 patients scheduled for elective laparoscopic cholecystectomy were included and randomized into two groups using lottery technique. Group D (diclofenac sodium 100mg), and Group T (oral tramadol 100mg), respective drug was given two hours before surgery.Postoperatively, NRS score were assessed at 8th hour, and time to first analgesic request was recorded.Data were analyzed using SPSS version 26.0, p-value ≤ 0.05 considered statistically significant. **Results:** Postoperatively, mean NRS score at 8th hour was significantly lower in Group T (3.56 ± 1.32) compared to Group D (4.52 ± 1.22)(p=0.01). Mean time to first analgesic request was significantly longer in Group T (104.04 ± 12.02 minutes) than in Group D (91.64 ± 8.51 minutes) (p<0.001). **Conclusions:** Preoperative administration of oral tramadol provides superior postoperative analgesia compared to diclofenac sodium, as evidenced by lower pain scores at the 8th postoperative hour and longer time to first analgesic request. Tramadol may be more effective option for pain control in patients undergoing elective laparoscopic cholecystectomy.

INTRODUCTION

Pain is unpleasant sensory/emotional experience associated with tissue damage [1]. Postoperative pain arises due to inflammation resulting from tissue trauma [2]. This pain can trigger cascade of biochemical and physiological stress responses, potentially leading to complications such as hyperventilation, reduced alveolar ventilation, impaired wound healing, sleep disturbances, and transition of acute pain into chronic pain [3]. These complications ultimately impact patient's surgical outcomes and overall satisfaction with medical care [4]. Effective postoperative pain management is essential component of patient recovery and involves combination of pharmacological and non-pharmacological approaches [5]. The use of minimally invasive surgical techniques, early initiation of physiotherapy, and early ambulation can accelerate recovery, which can be further enhanced through effective pain control. Pre-emptive analgesia, administration of analgesic treatment before surgery, aims to prevent central sensitization triggered by surgical incisions and inflammatory responses during and after surgery [6]. Clinical studies have shown the benefits of Pre-emptive analgesia using local anesthetics, opioids, and NSAIDs. Diclofenac, widely used NSAID, exerts its Pre-emptive analgesic effects by inhibiting prostaglandin synthesis through suppression of COX-1 and COX-2 enzymes [7]. In contrast, tramadol, a synthetic opioid, has

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safer profile compared to traditional μ-opioid receptor agonists. It functions through dual mechanism: weak μ-opioid receptor agonism and inhibition of serotonin and norepinephrine reuptake, thereby enhancing inhibitory effects on pain transmission [8, 9]. It was found that Pre-emptive administration of tramadol provided superior postoperative analgesia compared to diclofenac. Patients in tramadol group had lowest total analgesic consumption, longest time to first analgesic request, and significantly lower pain scores at multiple postoperative time points [10].

Therefore, this study aimed to assess the Pre-emptive use of diclofenac sodium and tramadol for postoperative pain management, aiming for effective yet safer alternative to traditional opioid-based analgesia.

METHODS

This quasi-experimental study was done at Anesthesia Department of Mayo Hospital, Lahore, over period of six months (July 2024 to January 2025) following approval of synopsis from CPSP (REF No. CPSP/REU/ANS-2021-066-2663). 50 patients were enrolled, with 25 in each group, based on sample size calculation using OpenEpi for "comparison of two means," considering time to first analgesic request in diclofenac group as 103.01 ± 23.53 minutes and in tramadol group as 144.05 ± 14.72 minutes, with 95% confidence level and 80% study power.[10] Non-probability consecutive sampling was used for patient selection. Patients of both genders, aged 18 to 60 years, with American Society of Anesthesiologists status I or II, scheduled for elective laparoscopic cholecystectomy were included. Patients who refused participation, had allergies or contraindications to study drugs, pregnant or lactating females, or were already on analgesics for any reason were excluded. Informed consent was obtained from patients after explaining the study's purpose, importance, and risks, and participants were assured of their right to withdraw at any time. Patients were randomized into two groups using lottery technique. Preoperative assessment was performed, and all eligible patients were instructed on using Numerical Rating Scale (NRS) for pain assessment. On the morning of surgery, two hours before procedure, patients received either 100 mg of oral diclofenac sodium (Group D) or 100 mg of oral tramadol (Group T) in extended-release formulation, administered by anesthetist not involved in the study. On the day of surgery, patients were shifted to operation theatre and routine General anesthesia protocols were followed with continuous vital monitoring. Intraoperatively, all patients received intravenous paracetamol (1 gram) and dexamethasone (8 mg). Patients were extubated after meeting the reversal criteria and transferred to Post-Anesthesia Care Unit, where they were observed for two hours before being shifted to the ward upon meeting the modified Aldrete discharge criteria. Postoperatively, study outcomes NRS score at 8th hour post operatively and time to first analgesic request (when NRS >3) was recorded. Relevant data were documented in the study proforma. Intravenous nalbuphine diluted in 10 ml of normal saline was administered as rescue analgesic at a dose of 0.07 mg/kg (maximum 10mg) when patient reported NRS >4. Data were collected and analyzed using SPSS version 26.0. The normality of numerical data was assessed using the Shapiro-Wilk test and Kolmogorov-Smirnov test, confirming a normal distribution ($p > 0.05$). Numerical variables, including age, NRS score, duration of surgery, and time to first analgesic request, were expressed as mean ± standard deviation, while categorical variables such as ASA status and gender were presented as frequencies and percentages. Stratification for effect modifiers, including age and gender, was performed, and post-stratification independent sample t-tests were applied for outcomes, considering a p-value of ≤0.05 as statistically significant.

RESULTS

As shown in table 1, mean age of patients in Group D (Diclofenac) and Group T (Tramadol) was 36.6 ± 10.24 years and 38.1 ± 10.98 years, respectively (p=0.606). Regarding gender distribution, in Group D, 8 (32%) patients were male, and 17 (68%) were female, whereas in Group T, 9 (36%) patients were male, and 16 (64%) were female (p=0.765). In terms of ASA status, 17 (68%) patients in Group D and 19 (76%) patients in Group T were categorized as ASA I, while 8 (32%) in Group D and 6 (24%) in Group T were classified as ASA II (p=0.529). Mean duration of surgery in Group D was 68 ± 12.87 minutes, while in Group T, it was 70 ± 13.40 minutes (p=0.522).

Table 1: Comparison of Variables among Groups (n=50)

Variables		Group D (Diclofenac) Mean ± SD/ Frequency (%)	Group T (Tramadol) Mean ± SD/ Frequency (%)	p-Value
Age (Years)		36.6 ± 10.24	38.1 ± 10.98	0.606
Gender	Male	8 (32%)	9 (36%)	0.765
	Female	17 (68%)	16 (64%)	
ASA Status	I	17 (68%)	19 (76%)	0.529
	II	8 (32%)	6 (24%)	
Duration of Surgery (Minutes)		68 ± 12.87	70 ± 13.40	0.522

As shown in table 2, mean NRS score at 8th postoperative hour was 4.52 ± 1.22 in Group D (Diclofenac) and 3.56 ± 1.32 in Group T (Tramadol), showing statistically significant reduction in group T (p=0.01). The mean time to first analgesia was also less (91.64 ± 8.51 minutes) in Group D as compared to group T (104.04 ± 12.02 minutes), and this difference was noted to be significant (p<0.001).

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Table 2: Comparison of Study outcomes among Study Groups (n=50)

Outcomes	Group D (Diclofenac) Mean ± SD	Group T (Tramadol) Mean ± SD	p-Value
NRS Score (at 8th hour post-operatively)	4.52 ± 1.22	3.56 ± 1.32	0.01*
Time to 1st Analgesia (Minutes)	91.64 ± 8.51 min	104.04 ± 12.02 min	<0.001*

*Statistically significant at p≤0.05.

As shown in table 3, when stratified by age, time to first analgesia was significantly longer in Group T compared to Group D in both age groups. In patients aged <40 years, mean time to first analgesia was 91.41±7.73 minutes in Group D and 104.06 ± 12.69 minutes in Group T (p=0.002). Similarly, in patients aged ≥40 years, it was 92.12 ± 10.54 minutes in Group D and 104.00 ± 11.62 minutes in Group T (p=0.03). For pain scores at 8th postoperative hour, significant difference was found in patients aged <40 years, where the mean NRS score was 4.52 ± 1.32 in Group D and 3.40±1.45 in Group T (p=0.02). However, in patients aged ≥40 years, difference in pain scores between Group D (4.50 ± 1.06) and Group T (3.80 ± 1.13) was not statistically significant (p=0.20).

Table 3: Data Stratification with Respect to Age

Age Group	Outcome	Group	N	Mean ± SD	p-Value
<40 Years	Time To 1st Analgesic	D	17	91.41 ± 7.73 min	0.002*
		T	15	104.06 ± 12.69 min	
≥40 Years	Time To 1st Analgesic	D	8	92.12 ± 10.54 min	0.03*
		T	10	104.00 ± 11.62 min	
<40 Years	Pain Score at 8Hours	D	17	4.52 ± 1.32	0.02*
		T	15	3.40 ± 1.45	
≥40 Years	Pain Score at 8Hours	D	8	4.50 ± 1.06	0.20
		T	10	3.80 ± 1.13	

*Statistically significant at p≤0.05.

As shown in table 4, when stratified by gender, time to first analgesia was significantly longer in females receiving Tramadol (106.50 ± 11.90 minutes) compared to those in the Diclofenac group (90.29 ± 9.13 minutes) (p<0.001). However, in males, there was no statistically significant difference between the Diclofenac (94.50 ± 6.63 minutes) and Tramadol (99.66 ± 11.59 minutes) groups (p=0.286). For pain scores at the 8th postoperative hour, the difference was significant in females, with a mean NRS score of 4.58 ± 1.28 in Group D and 3.56 ± 1.41 in Group T (p=0.036). However, in males, the difference was not statistically significant (4.37 ± 1.19 in Group D vs. 3.55 ± 1.23 in Group T, p=0.185)

Table 4: Data stratification with Respect to Gender

Gender	Outcome	Group	N	Mean ± SD	p-Value
Male	Time To 1st Analgesic	D	8	94.50 ± 6.63	0.286
		T	9	99.66 ± 11.59	
Female	Time To 1st Analgesic	D	17	90.29 ± 9.13	<0.001*
		T	16	106.50 ± 11.90	
Male	Pain Score at 8Hours	D	8	4.37 ± 1.187	0.185
		T	9	3.55 ± 1.23	
Female	Pain Score at 8Hours	D	17	4.58 ± 1.277	0.036*
		T	16	3.56 ±1.41	

*Statistically significant at p≤0.05.

DISCUSSION

The mean age of patients in Group D (Diclofenac) and Group T (Tramadol) was 36.6 ± 10.24 years and 38.1 ± 10.98 years, respectively (p=0.606).Previous studies have reported varying mean ages for patients undergoing laparoscopic cholecystectomy, with some indicating higher mean age of 46.3 ± 15.8 years while others found lower mean age of 34.3 years. These differences are likely due to variations in study populations and age group distributions [11, 12]. Regarding gender distribution, in both groups there were female predominance.Previous studies have also consistently observed female predominance in LC patients, with large-scale analyses reporting 73.4% female representation, while smaller studies have reported up to 87% female patients [13, 14].The comparison of tramadol and diclofenac as Pre-emptive analgesics in laparoscopic cholecystectomy reveals significant differences in efficacy.Supporting current findings, it was observed by Zaman M *et al.*, that tramadol showed better pain relief as compared to diclofenac after laparoscopic cholecystectomy, with significant reductions in pain scores at various time intervals postoperatively [15]. Further supported by local study, Iqbal MS *et al.*, indicated that patients receiving diclofenac had higher VAS scores at multiple time points compared to those receiving tramadol [16].However, in contrast, one study found no significant differences between tramadol and diclofenac in reducing post-operative pain [17]. Previous studies have shown that women are more likely to use NSAIDs and opioids than men following surgery due to higher reported pain scores [18]. Additionally, analgesic use tends to increase with age, with older patients exhibiting higher prevalence of opioid use. Younger patients experience more significant decrease in analgesic use post-surgery compared to older patients, who maintain higher usage. Moreover, interaction between age and sex reveals that older women are more likely to receive analgesics than older men, particularly in emergency departments [19, 20]. This study has found that younger patients (<40 years) receiving tramadol had longer time to first analgesic request and lower pain scores, whereas in patients ≥40 years, pain scores did not differ significantly. Similarly, females in tramadol group experienced superior analgesia, while in males, the differences between tramadol and diclofenac were not significant. It was also highlight in literature multifactorial

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nature of postoperative pain management, emphasizing importance of individualized analgesic strategies based on patient demographics and clinical factors.

CONCLUSIONS

Preoperative administration of oral tramadol provides superior postoperative analgesia compared to diclofenac sodium, as evidenced by lower pain scores at 8th postoperative hour and longer time to first analgesic request. Tramadol may be more effective option for pain control in patients undergoing elective laparoscopic cholecystectomy.

Authors Contribution

Conceptualization: AN
Methodology: AN, ZI, FA, MR, SY, SH
Formal analysis: SY, SH
Writing, review and editing: FA, MR, SY, SH
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Patterns of Dyslipidemia among Patients with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) affects a significant proportion and is frequently associated with dyslipidemia and metabolic disorders. **Objective:** To explore the patterns of dyslipidemia among patients with NAFLD and their association with disease severity. **Methods:** A cross-sectional study was conducted at the Department of Cardiology, Liaquat National Hospital, Karachi. All participants diagnosed with NAFLD were included, and NAFLD severity was assessed using Fibro Scan, categorizing patients into no significant fibrosis, mild fibrosis, significant fibrosis, and advanced fibrosis. Dyslipidemia patterns were evaluated based on lipid profiles. **Results:** The cohort (n=300) had a mean age of 51.44 years, with a majority being female (60.3%) and over 45 years old (71.3%). NAFLD severity was distributed as follows: 33% mild fibrosis, 32% no significant fibrosis, 29.3% significant fibrosis, and 5.7% advanced fibrosis. As NAFLD severity increased, waist circumference, liver enzyme levels (AST and ALT), and lipid markers (TC, LDL-C, TG) increased, while HDL-C decreased. Advanced cases showed higher hemoglobin A1c levels and increased hepatic steatosis and CAP values. Dyslipidemia associated with metabolic syndrome (24%), low HDL-C (61.3%), and hypertriglyceridemia (2%) were observed, with combined and general hyperlipidemia affecting 3.7% and 1.3% of participants, respectively. The patterns of dyslipidemia varied with severity; normolipidemia was common in cases with no significant fibrosis, combined hyperlipidemia was seen in significant fibrosis, and hyperlipidemia was exclusive to advanced NAFLD. **Conclusion:** It was concluded that the study found significant associations between NAFLD severity and dyslipidemia patterns.

INTRODUCTION

NAFLD has become a major focus of basic science investigation and clinical practice as it is an increasingly prevalent and potentially hazardous condition. NAFLD prevalence is estimated at 5-20% of the general population, increasing to 75% among patients with obesity and diabetes [1, 2]. Even though NAFLD is common in global practice, its pathophysiology, particularly in its progression, is not completely understood [3]. NAFLD, currently described as the hepatic expression of MetS, is now globally recognized as the most common liver disease [4]. The diseases can be as simple as steatosis, defined with at least 5% fat deposition in hepatocytes and may advance as fibrosis and necrotizing inflammation. While this progression can lead to the development of Non-alcoholic steatohepatitis (NASH), in the most severe stages of this condition, such complications as cirrhosis or hepatocellular carcinoma may occur [5]. More significantly, these histological alterations develop without alcohol or other hepatotoxic agents in the subjects' system [6, 7]. Fat accumulated in the liver as lipids affects hepatocytes physiology; lipids are deposited as lipid droplets, which are surrounded by proteins that could affect the liver disease progression [7, 8]. Disruptions in lipid metabolism profile were NAFLD characterized by low plasma triglyceride output, low fatty acid uptake in the liver, changes in lipolysis and enhanced very-low-density lipoprotein (VLDL) and fatty acid-free profile [9]. These derangements result in the synthesis of qualitatively altered adipokines, including leptin, adiponectin, and retinol-binding protein 4, that in turn influence signalling

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networks and induce inflammation and oxidative stress [10, 11]. In addition, these lipid disorders are made worse by obesity and insulin resistance. Hepatic steatosis has been implicated in reduced hepatic glucose uptake, increased gluconeogenesis and decreased insulin signalling [12, 13]. NAFLD is also associated with other cardiovascular risk factors (hypertension, smoking, obesity, dyslipidemia and hyperglycemia) [14]. Recent studies demonstrate that NAFLD is correlated with low-grade atherosclerosis and a higher rate of cardiovascular disease (CVD) [15, 16]. Hypertriglyceridemia and high low-density lipoprotein cholesterol (LDL-C) are established as common CVD risk factors in NAFLD [17]. Such longitudinal findings also confirm that NAFLD patients are at higher risk for liver and cardiovascular disease and mortality [18, 19]. It is hypothesized that specific dyslipidemia patterns, including elevated total cholesterol (TC), LDL-C, and triglycerides, along with reduced HDL-C, are significantly associated with the severity of NAFLD. Identifying these associations will provide insights into the role of lipid abnormalities in disease progression.

This study aims to identify the patterns of dyslipidemia among patients with NAFLD and their association with disease severity.

METHODS

A cross-sectional study was conducted in the Department of Cardiology at Liaquat National Hospital, Karachi, Pakistan, from September to December 2024. To protect the privacy and well-being of each participant, the study was conducted in compliance with ethical guidelines. Written informed consent was taken from all patients prior to their inclusion in the study. Ethical approval was granted by the Institutional Review Board and Medical Ethics Committee of Liaquat National Hospital (LNH) [Ref: App #1091-2024-LNH-ERC]. The sample size was calculated by the Sample Size Calculator by Wan nor Arifin, based on a 15% prevalence rate of fatty liver disease [20] and a 5% margin of error.The estimated sample size was 196 participants.To account for potential attrition, a total of 300 participants were enrolled.Eligible individuals included patients diagnosed with fatty liver disease, 20 years of age or older, and both males and females. Pregnant patients or those who had positive serologic markers for hepatitis B or C, characteristic of liver cirrhosis or advanced fibrosis on CT or ultrasound, history of splenectomy, and for whom serum lipid concentrations were unknown, were excluded from the study.Data collection involved several procedures.Participants' height and weight were measured to calculate BMI, with measurements taken while participants were casually dressed and barefoot.Information regarding co-morbidities, including diabetes, hypertension, and ischemic heart disease (IHD), was obtained from patient medical records and confirmed through clinical history and physician diagnoses. Following an overnight fast, blood samples were collected for biochemical analysis. TC, TG, HDL-C, and LDL-C levels were measured using enzymatic colourimetric methods on a Roche Cobas 8000 modular analyzer. Liver function parameters, including Aspartate Transaminase (AST) and alanine transaminase (ALT), were assessed using standard automated biochemical analyzers. Glycemic control was evaluated by measuring HbA1c and random blood sugar (RBS) levels, with HbA1c determined through a high-performance liquid chromatography (HPLC)-based system. RBS levels were measured using a standard glucometer (e.g., Accu-Chek Active, Roche Diagnostics) through capillary blood samples obtained via finger prick. Abdominal ultrasound was used to diagnose and evaluate NAFLD, with a steatotic liver appearing brighter and a cirrhotic liver showing irregularities. Fatty liver severity was categorized based on liver attenuation index (LAI) values from unenhanced hepatic CT images. The severity of NAFLD was assessed using transient elastography with Fibro-Scan®, which was categorized into four outcomes, i.e. no significant fibrosis, mild fibrosis, significant fibrosis, and advanced fibrosis. Controlled Attenuation Parameter (CAP) values were measured to evaluate liver health. Fibro-Scan assessed hepatic steatosis by emitting acoustic waves through the liver and measuring their attenuation, with higher CAP values indicating greater fat accumulation. This provided a comprehensive assessment of liver fat content and stiffness, aiding in the classification of hepatic steatosis and fibrosis severity. Further assessment of the dyslipidemia included patterns according to lipid profiles, where ischemic outcomes were characterized by the following: TG ≥200 mg/dL, LDL-C ≥160 mg/dL, and HDL-C ≤40 mg/dL. The statistical analysis was performed by SPSS version 22.0. Descriptive statistics were utilized to summarize both continuous and categorical variables. For continuous variables, comparisons were made using the one-way ANOVA. Categorical data were examined with the Chi-square/Fisher Exact test, where a significance level was set at ≤0.05.

RESULTS

The cohort included 39.7% males, with an average age of 51.44 years, and 71.3% were over 45 years old. Common co-morbidities included diabetes (35.7%), hypertension (30.7%), and ischemic heart disease (33.7%). The average BMI was 30.54 kg/m^2, indicating a high prevalence of obesity (98.7%).Liver function tests showed average AST and ALT levels of 38.47 IU/L and 52.39 IU/L, respectively. Lipid profiles included an average TC of 198.69 mg/dL, LDL-C of 125.13 mg/dL, HDL-C of 36.60 mg/dL, and triglycerides of 135.55 mg/dL.Glycemic control metrics revealed an average random blood sugar of 166.89 mg/dL and HbA1c of 6.65% (Table 1).

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Table 1: Demographic and Clinical Characteristics of the Study Population(n=300)

Variables		n (%)
Gender	Male	119 (39.7%)
	Female	181 (60.3%)
Age (Years); Mean ± SD		51.44 ± 8.48
Age Group	≤45 Years	86 (28.7%)
	>45 Years	214 (71.3%%)
Co-Morbid	Diabetes	107 (35.7%)
	Hypertension	92 (30.7%)
	IHD	101 (33.7%)
BMI (kg/m^2); Mean ± SD		30.54 ± 3.50
Obesity	Yes	296 (98.7%)
	No	4 (1.3%)
Waist Circumference (cm); Mean ± SD		103.79 ± 8.57
Liver Function Test Mean ± SD	AST (IU/L)	38.47 ± 13.15
	ALT (IU/L)	52.39 ± 18.50
Lipid Profile Mean ± SD	TC (mg/dL)	198.69 ± 56.52
	LDL-C (mg/dL)	125.13 ± 18.49
	HDL-C (mg/dL)	36.60 ± 7.90
	TG (mg/dL)	135.55 ± 29.67
Glycemic Control Mean ± SD	RBS (mg/dL)	166.89 ± 60.07
	HbA1c (%)	6.65 ± 1.38

The distribution of dyslipidemia patterns among the patients shows that 24% had dyslipidemia associated with metabolic syndrome (MetS). A notable 61.30% of patients exhibited low HDL-C levels, while hypertriglyceridemia was relatively uncommon, affecting just 2% of patients. Normolipidemia was observed in 7.70% of the cohort. Combined hyperlipidemia and general hyperlipidemia were seen in 3.70% and 1.30% of participants, respectively (Figure 1).

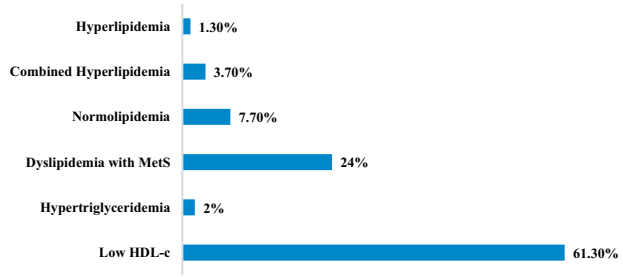

Figure 1: Patterns of Dyslipidemia among study participants

Mild NAFLD was observed in 33% of cases, while 32% had no significant fibrosis. Significant NAFLD was present in 29.30% of cases, and advanced NAFLD was found in the least proportion, at 5.70% (Figure 2).

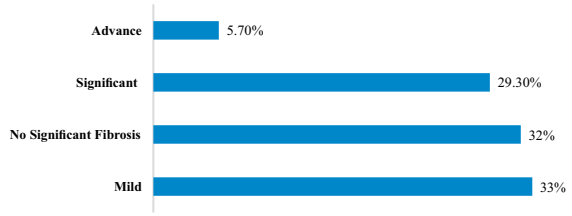

Figure 2: NAFLD Severity by Fibro Scan among the Enrolled Patients

Results illustrate the relationship between NAFLD severity and various patient characteristics, revealing significant associations across several parameters. Gender did not influence the NAFLD severity (p=0.298). As NAFLD severity increases, so does the waist circumference, and levels of liver enzymes (AST and ALT), as well as lipid profile markers like TC, LDL-C, and TG, while HDL-C decreases. Obesity prevalence remains high and consistent across severity levels, and although random blood sugar levels do not vary significantly, hemoglobin A1c levels are higher in advanced NAFLD cases. The hepatic steatosis score and CAP values also increase significantly with severity, indicating a progression in liver fat accumulation (Table 2).

Table 2: Stratification of NAFLD Severity by Fibro Scan with Respect to Patient Characteristics

Age Group		NAFLD Severity by Fibro Scan				p-Value
		No significant fibrosis	Mild	Significant	Advanced	
Gender	Male	40 (41.7%)	40 (40.4%)	36 (40.9%)	3 (17.6%)	0.298
	Female	56 (58.3%)	59 (59.6%)	52 (59.1%)	14 (82.4%)	
Age (Years); Mean ± SD		48.6 ± 8.02	50.58 ± 8.25	53.56 ± 8.01	61.52 ± 3.5	<0.01*
Age Group	≤45 years	33 (34.4%)	35 (35.4)	18 (20.5%)	-	<0.01*
	>45 years	63 (65.6%)	64 (64.6%)	70 (79.5%)	17 (100%)	
BMI (kg/m^2); Mean ± SD		30.6 ± 3.57	30.53 ± 3.62	30.47 ± 3.33	30.7 ± 3.65	0.992
Obesity	Yes	96 (100%)	96 (97%)	87 (98.9%)	17 (100%)	0.339
	No	-	3(3)	1(1.1)	-	

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WC (cm); Mean ± SD		94.16 ± 4.26	106.58 ± 7.32	110.09 ± 3.57	109.29 ± 3.8	<0.01*
LFT; Mean ± SD	AST (IU/L)	37.07 ± 10.35	41.68 ± 16.09	36.77 ± 12.74	36.41 ± 5.53	0.030*
	ALT (IU/L)	46.95 ± 16.99	56.29 ± 16.81	53.27 ± 20.34	55.88 ± 20.26	<0.01*
Lipid Profile Mean ± SD	TC (mg/dL)	184.73 ± 42.31	181.24 ± 47.52	218.03 ± 60.61	278.94 ± 57.53	<0.01*
	LDL-C (mg/dL)	119.3 ± 10.98	119.36 ± 14.33	131.65 ± 21.01	157.94 ± 15.18	<0.01*
	HDL-C (mg/dL)	38.28 ± 8.8	37.98 ± 6.46	34.37 ± 7.65	31.58 ± 7	<0.01*
	TG (mg/dL)	123.67 ± 11.86	130.32 ± 23.3	150.76 ± 38.14	154.35 ± 41.47	<0.01*
Glycemic Control Mean ± SD	RBS (mg/dL)	161.73 ± 53.03	161.22 ± 55.08	178.76 ± 73.51	167.64 ± 40.51	<0.01*
	HbA1c (%)	6.44 ± 1.37	6.64 ± 1.4	6.67 ± 1.24	7.86 ± 1.4	<0.01*
Co-Morbid	Diabetes	35 (36.5%)	32 (32.3%)	33 (37.5%)	7 (41.2%)	0.170
	Hypertension	33 (34.4%)	29 (29.3%)	25 (28.4%)	5 (29.4%)	<0.01*
	IHD	28 (29.2%)	38 (38.4%)	30 (34.1%)	5 (29.4%)	0.865
Hepatic Steatosis Score		0.36 ± 0.6	2.53 ± 0.87	2.95 ± 0.2	2.88 ± 0.33	<0.01*
Steatosis	Yes	42 (43.8%)	69 (69.7%)	69 (78.4%)	13 (76.5%)	<0.01*
	No	54 (56.3%)	30 (30.3%)	19 (21.6%)	4 (23.5%)	
CAP; Mean ± SD		247.59 ± 61.68	282.26 ± 60.94	304.93 ± 61.94	307.23 ± 70.12	<0.01*
CAP Group	Nil Significance (<248 dB/m)	56 (58.3%)	36 (36.4%)	22 (25%)	5 (29.4%)	<0.01*
	Mild (248-280 dB/m)	16 (16.7%)	12 (12.1%)	7 (8%)	-	
	Moderate (281-319 dB/m)	2 (2.1%)	5 (5.1%)	2 (2.3%)	-	
	Severe (>319 dB/m)	22(22.9%)	46 (46.5%)	57 (64.8%)	12 (70.6%)	

WC: Waist Circumference; LFT: Liver Function Test; RBS: Random Blood Sugar; HDL-C: High-Density Lipoprotein Cholesterol; HbA1c: Hemoglobin A1c Values are given as n (%) or Mean ± SD. Chi-square/Fisher's exact test was applied. One-way ANOVA was applied, where a *p<0.05 was considered statistically significant.

The study illustrated dyslipidemia patterns about NAFLD severity as assessed by Fibro Scan. It revealed that normolipidemia was most common among individuals with no significant fibrosis, while combined hyperlipidemia was predominantly observed in those with significant fibrosis. Hyperlipidemia was exclusively found in the advanced stage of NAFLD. Dyslipidemia associated with metabolic syndrome (MetS) was notably prevalent in patients with significant fibrosis, whereas low HDL-C and hypertriglyceridemia were more frequent in the higher stages of NAFLD (Table 3).

Table 3: Patterns of Dyslipidemia Across NAFLD Severity Levels

Patterns of Dyslipidemia	NAFLD Severity by Fibro Scan				p-Value
	No significant fibrosis	Mild	Significant	Advanced	
Normolipidemia	10 (43.5%)	9 (39.1%)	2 (8.7%)	2 (8.7%)	<0.01*
Combined Hyperlipidemia	-	-	9 (81.8%)	2 (18.2%)	
Hyperlipidemia	-	-	-	4 (100%)	
Dyslipidemia with MetS	12 (16.7%)	22 (30.6%)	36 (50%)	2 (2.8%)	
Low HDL-C	74 (40.2%)	67 (36.4%)	39 (21.2%)	4 (2.2%)	
Hypertriglyceridemia	-	1 (16.7%)	2 (33.3%)	3 (50%)	

Values are given as n (%). Chi-square/Fisher's exact test was applied. *p<0.05 is considered statistically significant.

DISCUSSION

This study provides a cross-sectional analysis of dyslipidemia patterns in patients with NAFLD, evaluated using Fibro Scan, which measures liver stiffness and fat content.Our results indicate that 65.5% of patients were classified as having insignificant or mild NAFLD, 29.3% as having significant NAFLD, and 5.7% as having advanced NAFLD.This distribution is consistent with Sen *et al.*, who observed a predominance of mild cases, although severe cases were less common [21]. In contrast, Bhusal *et al.*, reported a higher proportion of mild cases and none with severe NAFLD [22], which could reflect differences in patient demographics or diagnostic criteria. NAFLD has also been associated with different MetS, such as impaired glucose tolerance, insulin resistance and lipid abnormalities [23-25].Hypercholesterolemia and hypertriglyceridemia, included in the range of dyslipidemia ,are diagnosed in 20-80 % of NAFLD patients.In the current study, 24% of patients had dyslipidemia, which is prevalent in MetS patients in their database. In particular, 61.3% of patients had a low concentration of HDL-C, which is an index of dyslipidemia and is normally related to cardiovascular diseases.However, hypertriglyceridemia

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was less frequent, with only 2% of the patients presenting with this condition. Only 7.7% of the entire cohort were normolipidemic.Patients with both combined hyperlipidemia and general hyperlipidemia were identified in 3.7% and 1.3% of participants, respectively. Approximately one-half of the NAFLD patients had abnormally elevated cholesterol and/or triglyceride levels as compared to the unaffected population [21]. Research indicates significant sex differences in NAFLD prevalence and severity. Although the gender effect did not play a role in determination of the degree of NAFLD in the present population. In contrast some studies do report a link between the two, it is found that men generally have higher NAFLD rates during reproductive years, while postmenopausal women show increased prevalence, suggesting a protective role of estrogen [26]. Metabolomic profiling reveals distinct sex-related patterns in NAFLD progression, with specific metabolites associated with disease severity in males and females [27]. The liver-adipose tissue crosstalk, influenced by sex hormones, plays a crucial role in regulating lipid and glucose metabolism, contributing to the observed sexual dimorphism in NAFLD [28]. These sex differences extend to risk factors, fibrosis, and clinical outcomes, highlighting the need for sex-specific considerations in clinical trials and treatment approaches [26]. Understanding these gender-based differences may lead to the development of novel, sex-specific therapeutic strategies for NAFLD management [28]. We also established that subjects with more severe NAFLD levels have a higher mean BMI, WC, levels of both hepatic transaminases (AST and ALT), and lipid profile parameters including TC, LDL-C, and TG; and lower levels of HDL-C. These findings indicate that the progression of NAFLD worsens metabolic imbalance as the disease advances. RBS was reasonably well controlled, although a higher ratio of Hba1c suggested that the patients with more severe NAFLD may have a worse glucose metabolism. Similarly, the hepatic steatosis score and CAP increased with worsening in the severity of NAFLD due to fat deposition in the liver. Indeed, the results of this study support previous findings, which have shown links between NAFLD, on one hand, and obesity as well as disturbances in metabolic parameters on the other. Abnormal levels of ALT, an enzyme that indicates liver inflammation, are present in patients with NAFLD, which supports the findings shown by Khurram and Ashraf regarding the presence of a variety of factors like high BMI, diabetes, and dyslipidemia in NAFLD patients [29]. In a broad sense, our finding serves to establish a relationship between NAFLD and dyslipidemia, with significant changes in lipid profiles according to the advancement of NAFLD. These findings highlight the need for clinician awareness of lipid levels and the inclusion of lipid profile testing in managing NAFLD and its related metabolic comorbidities. Managing lipid abnormalities in NAFLD patients may help prevent the worsening of liver disease and, thus, enhance patient prognosis.

CONCLUSIONS

It was concluded that the dyslipidemia patterns are significantly associated with the severity of NAFLD. Thus, we conclude that higher levels of TC, LDL-C and triglycerides and lower levels of HDL-C significantly correlate with advanced stages of NAFLD. The findings indicate the importance of monitoring the lipid levels in NAFLD patients, suggesting that dyslipidemia may play an important role in worsening liver disease.

Authors Contribution

Conceptualization: KUS, NB
Methodology: KUS, SK, AS, MWA, NB, SAB
Formal analysis: KUS, SK, AS, MWA
Writing review and editing: SK, NB, SAB
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Clinical Risk Factors of Post-Surgery Hemorrhage in Patients Undergoing Tonsillectomy

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ABSTRACT

Post-tonsillectomy hemorrhage is rare but life-threatening and poses a critical emergency. However, limited research has been conducted on adults undergoing tonsillectomy. **Objective:** To analyze the predictors of post-tonsillectomy hemorrhage in adults undergoing tonsillectomy. **Methods:** A retrospective study was conducted in the ENT and Surgery Department of Bakhtawar Amin Hospital from April 2024 to Jan 2025. A total of 150 adult patients underwent bilateral tonsillectomies for recurrent tonsillitis, obstructive sleep apnea, tonsillar hypertrophy, palmoplantar pustulosis, or IgA nephropathy. The surgery was performed according to the usual procedure under anesthesia. Age, gender, duration of surgery, obesity, antibiotic administration, smoking status, and type of analgesia were recorded as probable predictors of hemorrhage. Smoking status included current smokers, non-smokers, and former smokers who had stopped smoking at least 1 month before the procedure. **Results:** There was a significant difference between smokers and non-smokers (OR=3.52, 95% CI: 1.76- 6.68, p<0.001) and smokers and former smokers (OR=3.55, 95% CI: 1.63-7.61, p<0.003). Male gender (OR: 4.03, 95% CI: 1.63-9.89, p=0.005) and NSAID (OR: 7.87, 95% CI: 1.007-63.53, p=0.0502) were significantly associated with post-operative hemorrhage.Smoking status (p=0.052) and older age (p=0.005) were significant risk factors in the primary hemorrhage group, and smoking status (p<0.001) and male gender (p=0.010) were significant in the secondary hemorrhage group. **Conclusions:** Post-tonsillectomy hemorrhage had a significant association with male gender, smoking status, and administration of NSAIDs during surgery. Therefore, it is advisable for surgeons to strongly suggest that patients maintain a healthy lifestyle before surgery and opt for other analgesics to prevent the risk of hemorrhage.

INTRODUCTION

Tonsillectomy is a frequent procedure involving the removal of the tonsils due to tonsilitis, infections, sleep-disordered breathing, or sleep apnea in children and adults. Although the data on the Pakistani population is unavailable, the annual incidence rate in Norway is 0.16%, 0.13% in Sweden, and 0.08% in Denmark [1]. In children, it is often performed with adenoidectomy to resolve breathing and swallowing issues. Dehydration, pain, hemorrhage, nausea & vomiting, and infections are common complications after tonsillectomy [2]. Among these, post-tonsillectomy hemorrhage is rare but life-threatening and poses a critical emergency. It can cause airway obstruction and hypovolemic shock which may require surgery for management. Since the majority of tonsillectomies are performed in children, most literature focuses on outcomes and complications in the pediatric population [3]. In children, the cause of surgery has been reported as the main cause of post-tonsillectomy hemorrhage in reviews and meta-analyses [4]. Children undergoing surgery for recurrent infections had a high rate of hemorrhage as compared to children with obstructive sleep-disordered breathing. However, hemorrhage rates did not differ with the change in surgical techniques, including coblation, cold dissection, or electrocautery [5]. An increase in age significantly enhanced the risk of hemorrhage even in pediatric samples. Only limited research has been conducted on adults undergoing tonsillectomy. The reports available are conducted on

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pediatric and adult populations, which conclude that there is a high risk of hemorrhage in older age [6]. However, these results did not identify the risk factors of hemorrhage in adults specifically. We establish a hypothesis that lifestyle parameters, including surgical cause, smoking status, obesity, etc., are predictors of post-tonsillectomy hemorrhage in adults. We aim to investigate the impact of smoking status, role of surgical technique, medication and demographics on hemorrhage rates.

This study aims to analyze the predictors of post-tonsillectomy hemorrhage in adults undergoing tonsillectomy.

METHODS

A retrospective study was conducted in the ENT and Surgery Department of Bakhtawar Amin Trust Hospital from April 2024 to January 2025. A total of 150 adult patients undergoing bilateral tonsillectomies for recurrent tonsillitis, obstructive sleep apnea, tonsillar hypertrophy, palmoplantar pustulosis, or IgA nephropathy were included by consecutive sampling. Adenoidectomy and/or uvulopalatopharyngoplasty were also performed in patients with sleep apnea and hypertrophy. The sample size was calculated by keeping a 50% population proportion, 95% confidence interval, 80% power and precision of ± 5% among 245 population size. Patients who underwent tonsillectomy for tumor or quinsy, or those undergoing head and neck surgery for other conditions or hematologic disease, were excluded. All patients provided their informed consent to become a part of the study. The ethical board of the hospital approved the study Ref No.3294/BAMTH. The surgery was performed according to the usual procedure under anesthesia. After intubating the patient, Crowe-Davis mouth gag to secure the tonsil site. A mucosal incision was made, and the tonsils were released from their capsule using a dissector. Bipolar or mono-polar electrocautery was used to maintain hemostasis. No other equipment was used. Where electrocautery was ineffective in controlling bleeding, absorbable sutures were employed to ligate bleeding points. IV antibiotics were given intraoperatively and postoperatively. Fentanyl and/or remifentanil were also administered during surgery, and acetaminophen after surgery as analgesics. Post-tonsillectomy hemorrhage was categorized based on Windfuhr's classification. In addition, hemorrhage within 24 hours after the surgery was called primary hemorrhage, and hemorrhage after 24-48 hours was called secondary hemorrhage. Age, gender, duration of surgery, obesity, antibiotic administration, smoking status, and type of analgesia were recorded as probable predictors of hemorrhage. Smoking status included current smokers, non-smokers, and former smokers who had stopped smoking at least 1 month before the procedure. All data were analyzed by SPSS version 24.0. Descriptive analysis was performed on quantitative variables and was presented by frequency and percentage. Univariate analysis was performed by the Mann-Whitney U test and multivariate analysis was performed by Fisher's exact test to recognize risk factors of post-operative bleeding. A p-value less than 0.05 was considered significant.

RESULTS

A total of 150 adult patients undergoing tonsillectomy were included for analysis. Among the study subjects, 114 patients (76%) were male and 36 (24%) were female. The average age of patients was 32.2 ± 9.8 years. 33 patients (22%) were smokers while 72 patients (48%) were non-smokers. 111 (74%) patients underwent surgery for recurrent tonsillitis, 21 (14%) for IgA nephropathy, 1 (0.7%) for palmoplantar pustulosis, 15 (10%) for obstructive sleep apnea, and 3 (2%) for tonsillar hypertrophy. 9 patients (6%) underwent adenoidectomy and 15 patients (10%) underwent uvulopalatopharyngoplasty. 33 patients (22%) among 150 patients experienced post-tonsillectomy hemorrhage with 28 (85%) being grade 1, 2 (6%) being grade 2, 3 (9%) being grade 3, and 117 (78%) patients had no bleeding. Grade 2 and 3 patients required intervention to maintain hemostasis, and grade 3 patients also underwent additional surgeries. 27 (24.4%), 4 patients (26.7%), and 2 (14.3%) patients had a hemorrhage in patients undergoing tonsillectomy for recurrent tonsillitis, sleep apnea, and IgA nephropathy, respectively (p=0.277) (Table 1).

Table 1: Surgical Indication of Tonsillectomies and Classification of Post-Tonsillectomy Hemorrhage (n=150)

Surgical Indication	n (%)	Post-Tonsillectomy Hemorrhage	Primary Hemorrhage	Secondary Hemorrhage
Recurrent Tonsillitis	111 (74%)	27 (24.4%)	4 (3.6%)	23 (20.8%)
IgA Nephropathy	21 (14%)	2 (14.3%)	-	2 (14.3%)
Palmoplantar Pustulosis	1 (0.7%)	-	-	-
Sleep Apnea	15 (10%)	4 (26.7%)	1 (6.7%)	3 (20%)
Tonsillar Hypertrophy	3 (2%)	-	-	-

The study analyzed the risk factors of postoperative hemorrhage by univariate analysis. The smoking status differed significantly between total cases (p<0.001), primary hemorrhage group (p=0.05), and secondary hemorrhage group (p<0.001) as compared to the no bleeding group. Male gender was more prevalent in the total hemorrhage group (p<0.001) and secondary hemorrhage group (p=0.005) as compared to the no bleeding group. The primary hemorrhage group had a significantly higher average age (p=0.005) (Table 2).

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Table 2: Univariate Analysis

Risk Factors	No Post-Tonsillectomy Hemorrhage (n=117)	Post-Tonsillectomy Hemorrhage (n=33)	p-value	Primary Hemorrhage (n=5)	p-value	Secondary Hemorrhage (n=28)	p-Value
Average age	32.3	33.5	0.512	44.1	0.005**	32.2	0.915
Gender							
Male	84 (71.8%)	30 (91%)	<0.001***	5 (100%)	0.093	25 (89.5%)	0.005**
Female	33 (28.2%)	3 (9%)		-		3 (10.5%)	
BMI							
25 Or More	39 (33.4%)	30 (91%)	1.000	3 (60%)	0.524	8 (28.6%)	0.716
Less Than 25	78 (66.7%)	3 (9%)		2 (40%)		20 (71.4%)	
Current Smokers	19 (16.3%)	14 (42.5%)	<0.001***	3 (60%)	0.05*	11 (39.3%)	<0.001***
Duration of Surgery (Minutes)	79.1	78.0	1.000	64.1	0.202	79.3	0.571
Postoperative Antibiotics							
Oral intake	87 (74.4%)	23 (69.9%)	0.612	4 (80%)	1.000	19 (68%)	0.533
Injection	30 (25.6%)	10 (30.1%)		1 (20%)		9 (32%)	
Analgesia							
Non-Steroidal Anti-Inflammatory Drugs	106 (90.6%)	32 (97%)	0.055	5 (100%)	1.000	27 (96.4%)	0.096
Acetaminophen	11 (9.4%)	1 (3%)		-		1 (3.6%)	

*p<0.05, **p<0.01 and ***p<0.001

Results show a multivariate analysis of post-tonsillectomy hemorrhage. There was a significant difference between smokers and non-smokers (OR=3.52, 95% CI: 1.76-6.68, p<0.001) and smokers and former smokers (OR=3.55, 95% CI: 1.63-7.61, p<0.003). Male gender (OR: 4.03, 95% CI: 1.63-9.89, p=0.005) and NSAID (OR: 7.87, 95% CI: 1.007-63.53, p=0.0502) were significantly associated with post-operative hemorrhage. Smoking status (p=0.052) and older age (p=0.005) were significant risk factors in the primary hemorrhage group, and smoking status (p<0.001) and male gender (p=0.010) were significant in the secondary hemorrhage group (Table 3).

Table 3: Multivariate Analysis

Risk Factors	Post-Tonsillectomy Hemorrhage		Primary Hemorrhage		Secondary Hemorrhage	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.99 (1.0-1.08)	0.191	1.09 (1.05-1.30)	0.005*	0.99 (1.0-1.06)	0.833
Male Gender	4.03 (1.63-9.89)	0.005**	-	-	3.47 (1.42-9.03)	0.010**
Obesity	0.59 (0.30-1.18)	0.225	0.61 (0.11-3.32)	0.492	0.59 (0.28-1.17)	0.223
Current Smokers vs Non-Smokers	3.52 (1.76-6.68)	<0.001**	7.18 (1.05-49.88)	0.052*	3.29 (1.70-6.64)	<0.001**
Duration of Surgery	0.98 (1.01-1.03)	0.678	1.01 (0.95-1.05)	0.213	0.99 (1.0- 1.02)	0.957
Antibiotics	0.75 (0.49-1.60)	0.615	1.01 (0.20-5.67)	1.021	0.77 (0.39-1.62)	0.600
NSAIDS	7.87 (1.007-63.53)	0.0502*	-	-	7.02 (0.94-54.44)	0.100

*p<0.05, **p<0.01 and ***p<0.001

DISCUSSION

This study was conducted to analyze the predictors of postoperative hemorrhage in adults undergoing tonsillectomy. The results revealed that male gender, smoking status, and administration of NSAIDs during surgery were independently associated with postoperative bleeding. The overall risk of hemorrhage and primary and secondary bleeding was increased in current smokers. Other studies have also reported smoking as a dependent predictor of hemorrhage in tonsillectomy patients [7-9]. However, there is no data regarding the association of hemorrhage with former smokers. In present study, it was showed that a history of smoking by former smokers was not related to an increased risk of hemorrhage in comparison to non-smokers. However, taking into account the duration of cessation in former smokers can help yield better results. Since inflammation and infection are side effects of smoking, post-operative wound healing is also worse in smokers, which increases the likelihood of hemorrhage [10]. Additionally, these patients also have increased sputum and mucus production, which can stimulate coughing postoperatively and bleeding eventually [11]. Hence, patients must advise abstinence or cessation of smoking before the procedure to avoid critical emergencies. Gender is a significant independent

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predictor of overall hemorrhage and secondary bleeding, with increased incidence in males. Previous studies investigating the link between gender and hemorrhage risk have also reported the same findings, which can be explained by the fact that estrogen contributes to faster healing and prevents inflammation, therefore, women experience fewer complications [7, 12]. However, gender has not been significant in children undergoing tonsillectomy because sex hormones are not differentiated before puberty. Smoking is also more prevalent in men than in women in Pakistan, hence increasing the risk of hemorrhage in men, however, smoking status and male gender were independent predictors in present study. Older age was also an independent predictor of primary hemorrhage since tonsillar inflammation can last for a long time in older patients. As age increases, blood vessels weaken, increasing the likelihood of bleeding shortly after the procedure. Overall, hemorrhage risk was also significantly linked to intraoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs). Literature found that NSAIDs increased the risk of bleeding after tonsillectomy as these medications block cyclooxygenase, leaving an antiplatelet effect [13]. McLean *et al.*, concluded that patients administered NSAIDs were more likely to require surgery to treat post-tonsillectomy hemorrhage, but So *et al.*, drew contrasting results that there was an association between post-operative bleeding and its surgical treatment and use of NSAIDs [14, 15]. Although there is no definite view about NSAIDs being a risk factor for hemorrhage, the present study supports the results of McLean *et al.*, [14]. Other probable risk factors, including duration of surgery, obesity, and antibiotic use, were not related to the incidence of hemorrhage. 74% of patients in present study underwent surgery for recurrent tonsillitis. Research shows that postoperative hemorrhage in patients who underwent surgery for recurrent tonsillitis is linked to prolonged inflammation [16, 17]. However, there was no significant difference in surgical indications in current study. Since we included adult patients, tonsillar inflammation may have occurred with other risk factors like smoking, but may have been asymptomatic due to which we could not consider surgical indication as a predictor of hemorrhage.The incidence of post-tonsillectomy hemorrhage was 22% in current study, which is higher than the rate reported by previous studies, i.e. 2.2%-10% [18, 19]. 9% of patients in current study required surgeries to resolve the hemorrhage, which is also higher than 1-6% reported in previous studies[20].

CONCLUSIONS

It was concluded that post-tonsillectomy hemorrhage had a significant association with male gender, smoking status, and administration of NSAIDs during surgery. Therefore, it is advisable for surgeons to strongly suggest that patients maintain a healthy lifestyle before surgery and opt for other analgesics to prevent the risk of hemorrhage.

Authors Contribution

Conceptualization: SB, JMT
Methodology: MAA, MT
Formal analysis: JMT
Writing review and editing: MT
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Thrombocytopenia in Septic Neonates Admitted to Nursery Section of Pediatric Unit, DHQ Dera Ismail Khan

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ABSTRACT

Neonatal sepsis is a major cause of morbidity and mortality, often complicated by thrombocytopenia, which increases the risk of bleeding and worsens prognosis. Reported frequencies of thrombocytopenia in septic neonates vary widely, and local data are limited. **Objectives:** To determine the frequency of thrombocytopenia in septic neonates and its association with clinical and laboratory parameters. **Methods:** This cross-sectional study was conducted at the Department of Paediatrics, DHQ Hospital, Dera Ismail Khan, over six months. A total of 110 septic neonates were enrolled. Demographics, clinical presentations, and laboratory findings were recorded.Blood samples were analyzed for platelet count, white blood cell count, C-reactive protein (CRP), and blood cultures. Data were analyzed using SPSS Version 25, with chi-square and Mann-Whitney U tests applied. Logistic regression identified predictors of thrombocytopenia, with $p<0.05$ considered significant. **Results:** Thrombocytopenia was found in 69.1% of septic neonates. Early-onset sepsis was significantly associated with thrombocytopenia ($p=0.032$), while blood culture results, bacterial pathogen type, CRP, and White Blood Cells (WBC) count were not. Mechanical ventilation showed a significant association ($p=0.033$), and thrombocytopenic neonates had higher mortality ($p=0.053$). Logistic regression identified mechanical ventilation ($p=0.047$, OR=0.386) as a significant predictor, while early-onset sepsis showed borderline significance ($p=0.056$, OR=2.489). **Conclusions:** It was concluded that thrombocytopenia is common in septic neonates, with early-onset sepsis and mechanical ventilation as key risk factors. Routine platelet monitoring in critically ill neonates is essential for timely intervention.

INTRODUCTION

Neonatal sepsis remains a leading cause of neonatal morbidity and mortality, particularly in developing countries, where a significant proportion of neonatal deaths occur within the first 28 days of life [1]. Globally, neonatal sepsis affects approximately 22 per 1,000 live births, with an even higher burden in resource-limited settings. It is a frequent cause of neonatal intensive care unit (NICU) admissions and can progress rapidly to septic shock, contributing to mortality rates as high as 40–70% among critically ill neonates [2]. Diagnosing neonatal sepsis relies on clinical presentation in conjunction with laboratory markers such as C-reactive protein (CRP), total leukocyte count, and blood cultures. It is categorized as early-onset sepsis (EONS), occurring within 72 hours of birth, or late-onset sepsis (LONS), presenting between 4–28 days [3]. EONS often manifests with respiratory distress, poor feeding, lethargy, and temperature instability. Thrombocytopenia is a common hematological abnormality in septic neonates and may exacerbate clinical outcomes by increasing the risk of bleeding [4]. The pathophysiology is multifactorial, involving platelet consumption, bone marrow suppression, and endothelial dysfunction. Reported frequencies of thrombocytopenia in septic neonates vary widely, ranging from 25% to 75%, depending on geographic and institutional differences [5]. Despite these findings, there is a notable lack of

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standardized, region-specific data on the frequency and risk factors of thrombocytopenia in septic neonates in Pakistan.Local studies are scarce and often lack clearly defined diagnostic criteria.

This study aims to determine the frequency of thrombocytopenia and its association with clinical and laboratory parameters among septic neonates admitted to DHQ Hospital, Dera Ismail Khan.The findings aim to improve early detection and management of hematologic complications in neonatal sepsis in similar resource-constrained healthcare settings.

METHODS

This cross-sectional study was conducted at the Department of Paediatrics, District Headquarters (DHQ) Hospital, Dera Ismail Khan, a tertiary care facility with a specialised neonatal unit.It aimed to assess the prevalence of thrombocytopenia among septic neonates admitted to the pediatric ward's nursery over six months from August 2023 to January 30, 2024. Ethical approval for this study was obtained from the Ethical Review Committee of Gomal Medical College, MTI, Dera Ismail Khan (Approval No: 147/GJMS/JC)and the Research Evaluation Unit, College of Physicians and Surgeons Pakistan (Ref No: CPSP/REU/PED-2023-029-7541). Written informed consent was obtained from parents or guardians of all enrolled neonates. Patient confidentiality was maintained throughout the study, and data were anonymized for analysis. The sample size was calculated using the WHO Sample Size Calculator, with a confidence level of 95%, margin of error of 8%, and expected frequency of thrombocytopenia at 25.6% based on previous literature [6]. The final sample included 110 neonates to allow for potential dropouts. A non-probability consecutive sampling technique was applied. Inclusion Criteria were Neonates aged 1 to 28 days (both male and female). Clinically diagnosed with neonatal sepsis, defined as neonates presenting with poor feeding, lethargy, sluggish reflexes, poor perfusion, and temperature instability >12 hours. C-reactive protein (CRP) >10 mg/L. and a positive blood culture confirming infection. Exclusion Criteria were Neonates with autoimmune or alloimmune thrombocytopenia (assessed via maternal CBC). Syndromic neonates or those with congenital skeletal deformities. And neonates who received plasma transfusions before enrollment. Thrombocytopenia was defined as a platelet count below 150,000/µL. Severity was categorized as follows: mild (100,000–149,999/µL), moderate (50,000–99,999/µL), and severe (<50,000/µL). Demographic and clinical data were recorded on a structured proforma and included: Age, gender, gestational age, birth weight, and mode of delivery. Maternal risk factors (diabetes, preeclampsia, prolonged rupture of membranes). And clinical findings and comorbidities (jaundice, RDS, NEC). Laboratory Investigations CBC including platelet count, WBC count, and CRP levels, were performed. And blood cultures were analyzed to identify bacterial organisms. Clinical Outcomes NICU stay duration, hospital stay, mechanical ventilation requirement, mortality, and thrombocytopenia resolution time were documented. Blood samples (2–3 mL) were drawn in EDTA tubes and processed using standard hospital laboratory procedures. CRP was assessed through immunoassay, and blood cultures were incubated and examined using microbiological methods. Radiographic evaluation was done in cases with respiratory distress. To ensure reliability, CBC reports were manually verified by a senior hematologist. Inter-observer reliability was maintained, and data entry was done in duplicate to minimize errors. Data were analyzed using IBM SPSS Statistics, version 25. Continuous variables were assessed for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the data were not normally distributed, non-parametric tests were applied. The Mann-Whitney U test was used to compare continuous variables such as neonatal age at admission, NICU stay duration, hospital stay duration, and thrombocytopenia resolution time between thrombocytopenic and non-thrombocytopenic neonates. For categorical variables, the Chi-square test (χ^2) was used to examine associations between thrombocytopenia and variables including gender, gestational age, birth weight, mode of delivery, maternal risk factors, clinical comorbidities, sepsis type, CRP levels, WBC count, and mechanical ventilation. Where expected cell counts were less than 5, Fisher's Exact Test was applied. To identify independent predictors of thrombocytopenia, binary logistic regression analysis was performed. Variables included in the model were sepsis type (early vs. late onset), mechanical ventilation, platelet count categories, CRP level, WBC count, NICU stay duration, mortality outcome, and need for platelet transfusion. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p-value less than 0.05 was considered statistically significant. Model fitness was assessed using the Hosmer-Lemeshow goodness-of-fit test, and variance was explained using Nagelkerke's R^2 and Cox and Snell R^2 values. Overall classification accuracy was also reported to evaluate model performance.

RESULTS

The results show no significant association between thrombocytopenia and gender (p=0.311), gestational age (p=0.158), or birth weight (p=0.876). However, preterm and low-birth-weight neonates had slightly higher thrombocytopenia frequencies. Mode of delivery, maternal risk factors, Apgar scores, and place of birth also did not show significant associations (all p>0.05). Neonatal age at admission was analyzed using the Mann-Whitney U test and was not significantly different between groups (p=0.260) (Table 1).

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Table 1: Association of Demographic Characteristics with Thrombocytopenia

Variables	Category	Thrombocytopenia n (%)	Thrombocytopenia n (%)	p-value	Significance
		Yes	No		
Gender	Female	30 (39.5%)	10 (29.4%)	0.311	No Association
	Male	46 (60.5%)	24 (70.6%)		
Gestational Age	Preterm (<37 Weeks)	57 (75.0%)	21 (61.8%)	0.158	No Association
	Term (≥37 Weeks)	19 (25.0%)	13 (38.2%)		
Birth Weight	Low Birth Weight	48 (63.2%)	22 (64.7%)	0.876	No Association
	Normal Weight	28 (36.8%)	12 (35.3%)		
Mode of Delivery	Cesarean Section	43 (56.6%)	17 (50.0%)	0.522	No Association
	Normal Vaginal Delivery	33 (43.4%)	17 (50.0%)		
Maternal Risk Factors	Multiple Categories	-	-	0.549	No Association
Apgar Score at Birth	>6	65 (85.5%)	28 (82.4%)	0.670	No Association
Place of Birth	In-Hospital	62 (81.6%)	25 (73.5%)	0.337	No Association
Neonatal Age at Admission	Mean Rank (MWU)	57.76	50.46	0.260	No Difference

The study presents the association between various clinical and laboratory parameters with thrombocytopenia in septic neonates. A significant relationship was observed between sepsis type and thrombocytopenia (p=0.032), with early-onset sepsis being more prevalent among thrombocytopenic neonates.However, blood culture results did not show a significant association (p=0.234), indicating that thrombocytopenia was not necessarily linked to the presence of a positive blood culture. Similarly, organism type isolated from blood cultures (E. coli, Klebsiella, Staphylococcus, and others) had no significant impact on thrombocytopenia (p=0.710), suggesting that the presence of thrombocytopenia was independent of the specific bacterial pathogen. Inflammatory markers such as C-reactive protein (CRP) levels did not significantly differ between thrombocytopenic and non-thrombocytopenic neonates (p = 0.808), indicating that elevated CRP levels, a marker of infection, may not predict thrombocytopenia in sepsis. Similarly, white blood cell (WBC) count categories (elevated, low, and normal) showed no significant association with thrombocytopenia (p=0.486), suggesting that leukocyte abnormalities do not necessarily correlate with platelet reduction. Additionally, platelet count severity categories (mild, moderate, and severe thrombocytopenia) were not statistically significant in their association with thrombocytopenia (p=0.339), indicating that overall platelet reduction may not be directly influenced by its severity category in this study population. Finally, the need for platelet transfusion did not show a significant difference between groups (p=0.628), suggesting that thrombocytopenia management may not vary significantly in septic neonates requiring transfusion. Overall, only sepsis type showed a significant association with thrombocytopenia, highlighting its potential role as a contributing factor. However, other clinical and laboratory parameters, such as blood culture results, inflammatory markers, and platelet severity levels, were not significantly associated with thrombocytopenia, indicating that additional factors may influence its development in septic neonates (Table 2).

Table 2: Association of Clinical and Laboratory Findings with Thrombocytopenia

Variables	Category	Thrombocytopenia n (%)	Thrombocytopenia n (%)	p-value	Significance
		Yes	No		
Sepsis Type	Early-Onset (<72 hrs)	56 (73.7%)	18 (52.9%)	0.032	Significant
	Late-Onset (≥72 hrs)	20 (26.3%)	16 (47.1%)		
Blood Culture Result	Negative	29 (38.2%)	9 (26.5%)	0.234	No Association
	Positive	47 (61.8%)	25 (73.5%)		
Organism Identified	*E. coli*	28 (36.8%)	9 (26.5%)	0.710	No Association
	Klebsiella	15 (19.7%)	7 (20.6%)		
	Staphylococcus	26 (34.2%)	15 (44.1%)		
	Others	7 (9.2%)	3 (8.8%)		
CRP Level	Elevated	64 (84.2%)	28 (82.4%)	0.808	No Association
	Normal	12 (15.8%)	6 (17.6%)		
WBC Count	Elevated	43 (56.6%)	23 (67.6%)	0.486	No Association
	Low	15 (19.7%)	4 (11.8%)		
	Normal	18 (23.7%)	7 (20.6%)		
Platelet Count	Mild (100,000–149,999)	28 (36.8%)	11 (32.4%)	0.339	No Association
	Moderate (50,000–99,999)	35 (46.1%)	13 (38.2%)		
	Severe (<50,000)	13 (17.1%)	10 (29.4%)		

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Need for Platelet Transfusion	Yes	44 (57.9%)	18 (52.9%)	0.628	No Association
	No	32 (42.1%)	16 (47.1%)		

The study examined additional clinical variables. Neonatal comorbidities (p=0.261) and antibiotic therapy (p=0.847) were not significantly associated with thrombocytopenia. However, mechanical ventilation was significantly linked to thrombocytopenia (p=0.033). Mortality was higher in thrombocytopenic neonates, with borderline significance (p=0.053), suggesting a possible association with adverse outcomes (Table 3).

Table 3: Association of Additional Factors with Thrombocytopenia

Variables	Category	Thrombocytopenia n (%)	Thrombocytopenia n (%)	p-value	Significance
		Yes	No		
Neonatal Comorbidities	Jaundice	18 (23.7%)	11 (32.4%)	0.261	No association
	NEC	15 (19.7%)	5 (14.7%)		
	None	17 (22.4%)	11 (32.4%)		
	Others	10 (13.2%)	5 (14.7%)		
	RDS	16 (21.1%)	2 (5.9%)		
Antibiotic Therapy Given	Yes	68 (69.4%)	30 (30.6%)	0.847	No Association
	No	8 (66.7%)	4 (33.3%)		
Mechanical Ventilation	Yes	22 (56.4%)	17 (43.6%)	0.033	Significant
	No	54 (76.1%)	17 (23.9%)		
Mortality Outcome	Expired	30 (81.1%)	7 (18.9%)	0.053	Borderline
	Survived	46 (63.0%)	27 (37.0%)		

Research examines the relationship between thrombocytopenia and clinical outcomes, including NICU stay duration, hospital stay duration, and thrombocytopenia resolution time. The Mann-Whitney U test revealed that there were no significant differences in NICU stay duration (p=0.306), hospital stay duration (p=0.765), or thrombocytopenia resolution time (p=0.609) between neonates with and without thrombocytopenia. These findings suggest that thrombocytopenia does not independently impact hospital or NICU stay duration, nor does it significantly affect the time taken for platelet levels to recover (Table 4).

Table 4: Association of Clinical Outcomes with Thrombocytopenia

Variables	Thrombocytopenia Mean ± SD	Thrombocytopenia Mean ± SD	p-value	Significance
	Yes	No		
NICU Stay Duration (Days)	8.86 ± 3.20	9.56 ± 2.87	0.306	No Difference
Hospital Stay Duration (Days)	12.09 ± 3.77	11.91 ± 4.14	0.765	No Difference
Thrombocytopenia Resolution Time (Days)	5.68 ± 2.16	5.41 ± 2.32	0.609	No Difference

Results present the results of logistic regression analysis to determine potential predictors of thrombocytopenia. The findings indicate that sepsis type (early vs. late-onset) was borderline significant (p=0.056), with early-onset sepsis showing a trend toward increasing the likelihood of thrombocytopenia (OR=2.489). The need for mechanical ventilation emerged as a significant predictor (p=0.047), with neonates requiring ventilation having lower odds of thrombocytopenia (OR=0.386). Other variables, including platelet count, mortality outcome, gender, CRP levels, WBC count, need for platelet transfusion, NICU stay duration, and thrombocytopenia resolution time, did not show statistically significant associations (p>0.05). This suggests that while mechanical ventilation and sepsis type may play a role in thrombocytopenia risk, other commonly suspected factors did not appear to be strong predictors in this study population (Table 5).

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Table 5: Logistic Regression for Thrombocytopenia (Yes/No)

Variables	B (Coefficient)	Wald χ^2	p-value	Odds Ratio (Exp (B))	95% CI (Lower – Upper)	Significance
Sepsis Type (Early vs. Late-Onset)	0.912	3.645	0.056	2.489	(0.976 – 6.346)	Borderline
Mechanical Ventilation (Yes vs. No)	-0.952	3.954	0.047	0.386	(0.151 – 0.986)	Significant
Platelet Count (Mild vs. Severe)	-0.908	2.017	0.156	0.403	(0.115 – 1.412)	No Effect
Platelet Count (Moderate vs. Severe)	-1.107	3.117	0.077	0.331	(0.097 – 1.130)	No Effect
Mortality Outcome (Expired vs. Survived)	-0.908	2.861	0.091	0.403	(0.141 – 1.155)	No Effect
Gender (Female vs. Male)	-0.844	2.461	0.117	0.430	(0.150 – 1.234)	No Effect

DISCUSSION

The findings of this study highlight the frequency and risk factors associated with thrombocytopenia in septic neonates. Thrombocytopenia was significantly associated with early-onset neonatal sepsis, reinforcing the role of sepsis severity in platelet consumption and bone marrow suppression. This aligns with previous studies reporting higher rates of thrombocytopenia in early-onset sepsis due to maternal-fetal transmission of infections, systemic inflammation, and endothelial dysfunction [7-9]. Blood culture positivity and specific bacterial pathogens *(E. coli, Klebsiella, Staphylococcus)* did not show a significant association with thrombocytopenia.This suggests that the development of thrombocytopenia may be more closely related to the neonate's inflammatory response than the infecting organism. Although gram-negative infections are often associated with severe thrombocytopenia, gram-positive organisms can also trigger cytokine activation, leading to platelet changes [10, 11]. In this study, CRP levels and WBC counts were not significantly different between neonates with and without thrombocytopenia, indicating that traditional inflammatory markers may not reliably predict thrombocytopenia severity. This finding supports earlier literature emphasizing the diagnostic value of CRP for neonatal sepsis but not for its hematologic complications [12-14]. The severity of thrombocytopenia (mild, moderate, or severe) was not significantly linked to its presence, suggesting that other factors, such as cytokine storms, endothelial activation, and coagulation abnormalities, may contribute more to clinical severity. This supports the idea that multi-marker approaches may better predict sepsis-related hematological complications. Mechanical ventilation was significantly associated with thrombocytopenia, reflecting the impact of respiratory distress, hypoxia, and systemic inflammation on platelet counts. Previous studies have similarly reported higher thrombocytopenia rates in ventilated neonates, possibly due to ventilator-induced lung injury and prolonged inflammation [15-17]. Mortality outcomes approached statistical significance (p=0.053), with a higher proportion of thrombocytopenic neonates experiencing adverse outcomes. This aligns with other studies that identify thrombocytopenia as a predictor of poor prognosis, likely due to its link with systemic instability and multi-organ dysfunction [18-20].

CONCLUSIONS

It was concluded that thrombocytopenia was common in septic neonates, especially those with early-onset sepsis and requiring mechanical ventilation. Routine platelet monitoring is essential to guide timely interventions and reduce adverse outcomes in critically ill neonates.

Authors Contribution

Conceptualization: AY
Methodology: IK, AK, OK
Formal analysis: AY, FB
Writing review and editing: AY, FB, IK, AK
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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C-Reactive Protein (CRP) and Total Leukocyte Count (TLC) as Inflammatory Markers for Monitoring the Progression of Odontogenic Fascial Space Infection

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ABSTRACT

Dental infections can cause serious morbidity and mortality even with modern medical improvements. When infections from tooth pulp rupture cortical plate and move via fascial channels, they can spread through bone or periodontal tissues and result in potentially fatal consequences. **Objective:** To determine frequency of increased levels of C-Reactive Protein (CRP) and Total Leukocyte Count (TLC) and mean change in CRP and TLC during the course of treatment in Odontogenic fascial space infection. **Methods:** A descriptive cross-sectional study was conducted in OMFS department at PIMS, involving patients with odontogenic infections. Blood samples were taken before and at specified intervals to monitor CRP and TLC levels such as before Incision and Drainage (I&D) and post I&D (after two hours of meal at 1st , 2nd, 3rd, and 7th d post I&D Day. Using SPSS Version 23.0, frequencies, percentages, means, and standard deviations were measured to examine both quantitative and qualitative data. **Results:** There were 43 (55%) females and 35 (45%) males with a mean age of 39.17 ± 14.68 years. 17% showed elevated CRP levels and 12% presented with elevated TLC levels after seven days of follow-up. Pearson correlation was significant preoperatively and on 1st and the 2nd day Postoperatively as P value was 0.000. **Conclusions:** This study highlighted importance of monitoring CRP and TLC levels in odontogenic maxillofacial infections, both markers indicate inflammation. CRP is more sensitive than TLC during treatment, making it valuable tool for postoperative assessment.

INTRODUCTION

Despite significant advancements in modern healthcare, delays in managing odontogenic infections can still lead to serious complications, including death. Odontogenic infections have the potential to cause severe, life-threatening complications, including upper airway obstruction, descending mediastinitis, jugular vein thrombosis, septic embolism, carotid artery rupture, adult respiratory distress syndrome, pericarditis, septic shock, and disseminated intravascular coagulation. Prompt and vigilant monitoring of affected individuals is essential to mitigate these risks and prevent adverse outcomes [1]. Emergencies including odontogenic infections that migrate into the fascial spaces are frequent. If therapy is not administered, these infections have the ability to spread to other locations, use the least-resistant routes, and have major clinical effects. Infections originating in the tooth pulp, periodontal tissues, or bone may spread through fascial channels and enter the cortical plate due to tissue distention caused by the disease [2]. Reducing problems requires keeping an eye on the progression and severity of infections. C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Total Leukocyte

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Count (TLC), Differential Leukocyte Count (DLC), pre-albumin, procalcitonin, and other laboratory indicators are frequently used for this. In order to inform clinical findings and enhance patient outcomes, these indicators are essential for monitoring postoperative infections, assessing therapy effectiveness, and determining the degree of inflammation [3]. The C-Reactive Protein (CRP), which is produced in the liver in response to infection or trauma and indicates recent inflammation, is a commonly used indication of inflammation due to its short half-life of approximately 19 hours. Recent research has demonstrated the critical role CRP plays in immunological responses and inflammation, including phagocytosis, apoptosis, complement activation, nitric oxide release, and the production of cytokines such as tumor necrosis factor-alpha and interleukin-6 [3]. A study evaluated the efficacy of C-reactive protein (CRP) and white blood cell (WBC) count in monitoring fascial space infections of odontogenic origin. It revealed that CRP was a more sensitive and consistent marker than WBC count, as elevated CRP levels were found in all patients, while WBC elevation was inconsistent. The study supports the use of CRP as a reliable diagnostic and monitoring tool during infection management and treatment progression [4]. A comparative study assessed the diagnostic performance of CRP and WBC count in 50 patients with odontogenic fascial space infections. The findings demonstrated that CRP levels were elevated in 100% of cases, while WBC count was raised in only 64%. The authors concluded that CRP is superior to WBC as a biomarker for infection severity and treatment response, emphasizing its importance in early detection and clinical follow-up [5]. Clinically, increasing swelling, fever, trismus, discomfort, dysphagia, dyspnea, and voice abnormalities are common signs of odontogenic infections. These infections have the potential to quickly progress into deep neck-space infections, impair airway function, and possibly result in multiorgan failure and death if treatment is not received [6, 7]. Studies have shown that CRP is helpful in detecting and monitoring odontogenic infections. Research indicates that when it comes to detecting inflammatory responses to odontogenic infections, C-Reactive Protein (CRP) is more sensitive than Total Leukocyte Count (TLC). Following an intervention, CRP levels often rise before plateauing. While studies have shown that persons with continuously elevated CRP have mean CRP levels of about 3.5 mg/L, TLC values showed more variation. This dynamic trajectory of CRP provides a more reliable biomarker than TLC for monitoring treatment efficacy and infection clearance. These findings demonstrate the therapeutic utility of repeated biomarker monitoring in postoperative care [8, 9].

These findings emphasize the importance of TLC and CRP as indicators for monitoring odontogenic space infections. By incorporating these markers into routine examinations, clinicians can improve decision-making, effectively control infections, and lower patient morbidity.

METHODS

The Shaheed Zulfiqar Ali Bhutto Medical University's ethical review board granted ethical approval for a descriptive cross-sectional study that was carried out in the Oral and Maxillofacial Surgery (OMFS) department at the Pakistan Institute of Medical Sciences (PIMS), Islamabad, from September 16, 2024, to January 15, 2025 (No.CPSP/REU/DSG-2021-042-3697).A thorough patient history was obtained prior to clinical examinations and pertinent tests, including a Complete Blood Count (CBC) and C-Reactive Protein (CRP) values.Orthopantomogram (OPG) radiographs were used to confirm the dental origin of the infection after clinical investigations, both intraoral and extraoral, were used to diagnose odontogenic fascial space infections.The patients diagnosed with odontogenic fascial space infections either gender age ranged from 18 to 60 years.Patients with comorbidities such as hypertension, diabetes mellitus, and pregnancy were also included. However, individuals on steroid therapy, chronic alcohol users, patients with existing neoplasms, inflammatory conditions such as rheumatoid arthritis, or those allergic to the prescribed empirical antimicrobial therapy were excluded.In this prospective study, the authors explored the role of C-reactive protein (CRP) as a monitoring tool in patients with facial space infections of odontogenic origin.The study found a strong correlation between CRP levels and the clinical severity of the infection, with elevated CRP values observed in all cases at initial presentation. Serial CRP measurements were also useful in tracking the response to treatment, showing significant reductions as the infection resolved.The authors concluded that CRP is a valuable, objective, and dynamic marker for both diagnosis and monitoring of odontogenic infections involving facial spaces [10]. The Sample size of 78 patients was determined using the WHO sample size calculator, based on a 71.82% expected frequency of increased TLC, a 95% confidence level, and a 10% margin of error. Non-probability consecutive sampling technique was employed for patient recruitment. Participants were briefed on the study's objective, and an informed written consent was obtained.Demographic data, including age, gender, type of fascial spaces involved, hypertensive or diabetic status, pregnancy status in females, and disease duration, were documented. Following confirmation of the patient's details and necessary testing, blood samples for TLC and CRP were taken from the antecubital fossa.A red-top or gold/tiger-top (SST) tube were collected for CRP and a lavender-top (EDTA) tube for TLC. An appropriate vein was selected and treated with antiseptic, the patient was put in a

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comfortable position, and a tourniquet was applied.Once the tourniquet was adjusted and the vein was secured, the lavender-top tube for TLC was filled first, followed by the red-top/gold-top tube for CRP. The angle at which the needle was inserted was shallow.After filling each tube, they were removed from the holder and gently inverted to mix. After collecting the sample, the tourniquet was removed, the needle was removed, gauze was applied to apply pressure to the region, and a bandage was applied. The needle was disposed of in a sharps container, and each tube was labeled with patient identity and collection information[11]. Every participant received conventional treatment procedures, which included the use of empirical antimicrobial therapy, incision and drainage performed under standard surgical techniques under local anesthesia, and removal of the cause of the odontogenic infection by a single surgical team. Regular saline irrigation was carried out, and drainage was maintained using corrugated rubber drains. Postoperative monitoring involved serial measurements of CRP and TLC levels on preoperative day before the incision and drainage (IandD) and postoperative days as on 1st, 2nd, 3rd, and 7th. The SPSS version 23.0 was used to analyze the data that were gathered.Presented were the frequencies and percentages of categorical parameters, such as gender, the type of fascial space involvement, and concurrent diseases (hypertension, diabetes mellitus, and pregnancy). TLC levels, CRP, age, and length of illness were among the numerical variables that were displayed as mean ± standard deviation.Histograms, Q-Q plots, and the Shapiro-Wilk test were used to evaluate the normality of quantitative variables and validate the appropriateness of applying Pearson's correlation. Statistical significance was determined at $p < 0.05$ and a 95% confidence interval for the Pearson correlation coefficient, which was used to assess the association between changes in TLC counts and CRP levels.

RESULTS

A total of 78 patients were included in the study. Out of 78 patients, 43 (55%) patients were female (19% pregnant) and 35 (45%) patients were male with mean age of 39.17 ± 14.68 years. Among these patients 30 (39%) DM, 33 (42%) were hypertensive, 17% had found increase CRP level and 12% has increased TLC level after 7 days of monitoring post intervention as shown in table 1.

Table 1: Association of Gender, Hypertension, and Diabetes with CRP and Leukocyte Trends on Day 7 Post-Surgery

Variables	Category	Total Frequency (%)	Mean CRP Value after 7 Days			Mean CRP Value after 7 Days		
			Increase (%)	Decrease (%)	p-Value	Increase (%)	Decrease (%)	p-Value
-	-	**Total**	**13 (16.7)**	**65 (83.3)**		**09 (11.5)**	**69 (88.5)**	
Gender	Male	35 (44.9)	8	27	0.154	5	30	0.369
	Female	43 (55.1)	5	38		4	39	
	Total	78 (100.0)	13	65		9	69	
Hypertensive	Yes	33 (42.3)	2	31	0.029	3	30	0.419
	No	45 (57.7)	11	34		6	39	
	Total	78 (100.0)	13	65		9	69	
Diabetes Mellitus	Yes	30 (38.5)	3	27	0.175	2	28	0.247
	No	48 (61.5)	10	38		7	41	
	Total	78 (100.0)	13	65		9	69	

Majority of patients (51%) had more than 2 fascial spaces involved secondary to odontogenic infection as reported to OMFS department which is shown in Figure 1.

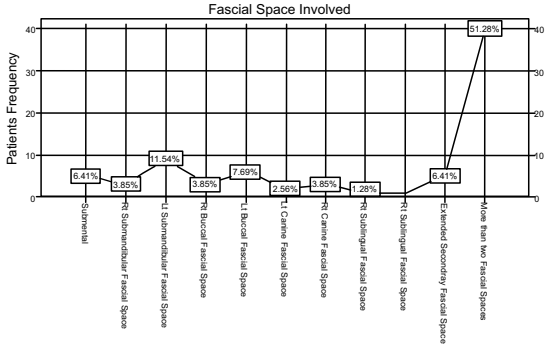

Figure 1: Bar Chart Showing the Percentages of Involved Fascial Spaces

The results from table 2 provide significant insights into the changes in disease-related markers such as CRP and TLC over time, both preoperatively and postoperatively at the 1st, 2nd, 3rd, and 7th days. The data show the mean, standard deviations, and the minimum and maximum values for these variables, highlighting the variability in these markers before and after surgery.

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Table 2: Descriptive statistics with mean and standard deviation of age, infection duration, CRP and TLC count of the study participants

Variable	Minimum	Maximum	Mean ± SD
Age	21	60	38.69 ± 13.15
Fascial Space infection duration	9	30	11.74 ± 6.16
CRP (mg/dl) Value preoperatively	4.10	314.00	97.71 ± 76.18
CRP Value at 1st post operative day	8.00	265.00	79.09 ± 66.40
CRP Value at 2nd post operative day	5.00	201.00	58.76 ± 47.94
CRP Value at 3rd post operative day	4.80	181.00	42.78 ± 43.24
CRP Value at 7th post operatively day	2.70	153.00	21.38 ± 33.73
CRP Mean Value during the treatment course	6.67	202.00	58.81±48.98
TLC Count preoperatively	6475	21740	11813.22 ± 3843.74
TLC Count at 1st post operative day	6200	21890	10377.24 ± 3101.24
TLC Count at 2nd post operative day	5870	16690	9423.56 ± 2612.22
TLC Count at 3rd post operative day	5160	50170	10234.22 ± 7052.56
TLC Count at 7th post operative day	3570	11900	7747.29 ± 2589.29
Mean TLC Count During the Treatment Course	1194.00	17024.00	9479.59 ± 2773.25

**C-Reactive Protein (mg/dl) and Total Leucocyte Count (/µL)*

Pearson correlation was used to assess the mean change in CRP and TLC level which shows a significant difference between the two variables preoperatively, 1st and 2nd post operative days as P-value was 0.000.Pearson corelation was non-significant at 3rd and 7th post operative day as P-value was 1.000 and 0.159 as shown in table 3.

Table 3: Pearson correlation between the mean change in the CRP value and TLC count

Time Point	CRP Value Mean ± SD	TLC Count Mean ± SD	Pearson Correlation	p-value	Strength and Significant
Preoperative	97.71 ± 76.18	11813.22 ± 3843.74	0.594	0.000	Moderate to strong, significant
Day 1st Post-OP	79.09 ± 66.40	10377.24 ± 3101.24	0.512	0.000	Moderate, significant
Day 2nd Post-OP	58.76 ± 47.94	9423.56 ± 2612.22	0.608	0.000	Moderate to strong, significant
Day 3rd Post-OP	42.78 ± 43.24	10234.22 ± 7052.56	0.000	1.000	No correlation, not significant
Day 7th Post-OP	21.38 ± 33.73	7747.29 ± 2589.29	-0.161	0.159	Weak negative, not significant

Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

An infection of the craniofacial regions, which include the potential spaces and fascial planes, with an exclusively odontogenic etiology is referred to as an odontogenic maxillofacial space infection.Although the prevalence of odontogenic infections has decreased significantly as a result of better dental care and the effectiveness of antibiotics, these infections can still be fatal due to patient negligence, delay in reffreal on part of patient's general practitioner, antibiotic therapeutic failure, immune system failure linked to medical conditions, or a lack of adequate healthcare facilities in a developing nation [12].C-reactive protein, which is present in trace amounts in normal, healthy individuals, is involved in the activation stages of the innate immune system's complement,antigen clearance, and phagocytosis. It is the best single screening test for an acute phase reaction and a useful indicator of the extent of inflammation and tissue damage. The serum concentration peaks in 48 hours and first rises above 5 mg/L in 6 hours.The plasma half-life of CRP is around 19 hours, regardless of health or disease.Therefore, the intensity of the stimulus that triggers the secretion directly correlates with the degree of the pathogenic process that determines the plasma CRP concentration [13].The total leukocyte count is a crucial metric for assessing the body's immune response to infection in the context of odontogenic fascial space infections. An active infectious process is indicated by a raised TLC because the body is producing more white blood cells to fight off the infections. In order to track the severity of the illness and the efficacy of treatment, the TLC usually increases within hours after infection and indicates the strength of the immunological response [14].In this study, 78 patients with infections of the odontogenic fascial area were admitted and their prognosis for infection was evaluated for a period of seven days. Among these patients 55% patients were female and 45% patients were male.This bigender distribution with slightly higher frequency among the female patients is also reported by Khan Shar M *et al.*, and Ishfaq M *et al* [12, 15]. In contrast to this study Kaur P and da Silva RD *et al.*, has reported male predominancy among their patients [13, 16]. The current study indicated that women predominance, which may be because of their cultural limitations, greater pain threshold, and socioeconomic factors.People in this region of the world are reluctant to take their female patients to the dentist in such situations.The mean age of the patients was 39.17 ± 14.68 years which was also reported by khan Shar M *et al.*, John CR *et al.*, and Mathew GC and his colleagues [12, 17, 18]. While Rashid S *et al.*, reported higher mean age of 54.5 ± 14.68 years which is inconsistent to these findings [19].The patient reported to

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the department of Oral and Maxillofacial Surgery (OMFS) with a diagnosis of Odontogenic infection, exhibiting a mean disease duration of 11.74 ± 6.16 days.This indicates a relatively varied course of infection among the patients with a mean duration close to 12 days but considerable individual variation as reflected by the standard deviation. Pavan EP *et al.*, had reported 4.3 days as average days of hospital stay which is in contradiction to this study[20]. Variability in disease duration could be attributed to several factors, including the severity of the infection, the specific type of Odontogenic infection and individual patient factors such as immune response and general health.The range of disease duration observed in these patients is imperative for understanding the timeline of infection progression and its potential impact on treatment planning and postoperative recovery.A key finding is the notable change in CRP and TLC levels immediately after surgery, particularly on the 1st and 2nd postoperative days. Pearson correlation analysis showed a strong, statistically significant relationship between disease duration, CRP and TLC levels (P-value 0.000), indicating that these markers are closely tied to the inflammatory response in the early postoperative period which is also reported by Pawan EP *et al.*, and Niazi SA and Bakhsh A as CRP levels rise during the course of 24 to 48 hours, peaking thereafter [20, 21]. CRP readings exhibit greater sensitivity and promptly decline after the inflammatory state is eliminated [22].This supports previous studies which also found peak inflammation within the first two days after surgery, reflecting the body's natural immune response.The P-values greater than 0.05 on the third and seventh postoperative days, Pearson correlation analysis revealed a change, indicating that when the inflammatory response started to normalize, the association between TLC and CRP levels ceased to be significant.This corresponds with the body's healing process, which moves from acute inflammation to the resolution phase, during which the relationship between these indicators gradually deteriorates [22].The standard deviations of CRP and TLC levels provide more evidence that the way each patient reacts to surgery can differ. According to Shaikh S *et al.*, the range between minimum and maximum results can be explained by variations in immune responses that are impacted by variables such the type of operation, the severity of the condition, and the general health of the patient [23].These results are in line with studies showing that postoperative inflammation peaks in the first few days after infection as compared to Kaya Z *et al* [24]. In contrast to these findings, which indicate a decreased correlation by the third day, Kaur A *et al* [25].Recommend either a prolonged rise of CRP or sustained alterations in TLC for extended periods of time.Differences in patient demographics, monitoring methods, or surgical approaches could be the cause of this disparity. One of the study's limitation is the very small sample size, which may not fairly represent the general population. Furthermore, the study's observational design ignores other influences that could impact the inflammatory response, such as patient obedience or variations in surgical procedures.

CONCLUSIONS

The importance of Total Leukocyte Count (TLC) and C-Reactive Protein (CRP) as useful markers for trailing the development and resolution of odontogenic fascial space infections is painted in this study. CRP levels, in particular, were a sensitive indication of inflammation resolve because they closely followed the clinical course, increasing during the acute phase and sharply dropping by day three. Additionally, TLC demonstrated a strong correlation with infection activity, particularly in the initial postoperative phase. Therefore, routine CRP and TLC monitoring can assist clinicians make informed treatment decisions and give them valuable information on infection recovery.

Authors Contribution

Conceptualization: MKS
Methodology: HU, RA, BP
Formal analysis: NUA, MKS, MUF
Writing, review and editing: HU, NUA, MKS, MUF
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparing the Efficacy of Intralesional Saline Versus 35% Trichloroacetic Acid Peel in the Treatment of Atrophic Acne Scar

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ABSTRACT

Atrophic acne scars are a common sequela of acne vulgaris impact patients' quality of life. Despite the availability of several treatment modalities, there is a need for simpler and cost-effective approaches. **Objective:** To compare the efficacy of intradermal normal saline versus trichloroacetic acid (TCA) in treating atrophic acne scars. A randomized controlled trial conducted at the Dermatology Department, Sheikh Zayed Hospital, Rahim Yar Khan, from 1st April 2023 to 31st October 2023. **Methods:** 126 patients were enrolled. Scar grading was based on Goodman and Baron's Qualitative Scar Classification. The Patients Observer Scar Assessment Scale (POSAS) was used by dermatologists. Efficacy was defined as ≥50% improvement in the POSAS. **Results:** Among 126 participants, the NS group showed significantly greater improvement in PSAS and OSAS scores post-treatment. While total POSAS score reduction was higher in the NS group, the difference was not significant. A ≥50% POSAS improvement was more frequent in the NS group (88.9%) than in the TCA group (73.0%; p = 0.023). **Conclusion:** This study found that intradermal normal saline is more effective and satisfactory than trichloroacetic acid for treating atrophic acne scars, with greater improvements in scar severity and patient satisfaction.

INTRODUCTION

Acne vulgaris is a common skin problem affecting adolescents and adults. It is the eighth most common skin disease globally, having a prevalence ranging from 35%-85%, with notable variations across different regions and age groups. A prior study reported the prevalence of Acne vulgaris in Pakistan is 5% [1, 2]. The etiologies of acne vulgaris include hormonal fluctuations, genetic predisposition, bacterial colonization, dietary habits, sleep patterns, and excessive sebum production. Follicular hyper keratinization, sebum overproduction or Propionibacterium acnes growth leads to recurrent and chronic inflammation of Pilo-sebaceous gland [2, 3]. Moderate to severe acne can lead to atrophic scarring in up to 80-90% of patients with acne. It results from the continues inflammatory process affecting the Pilo-sebaceous gland [4]. Post-acne scarring may present as either atrophic, characterized by tissue wasting and including rolling, Ice-pick, and boxcar types, or as hypertrophic scar, marked by excessive deposition of fibrotic tissue [5]. Scaring can significantly affect quality of life, diminish self-esteem, and hinder social interactions of patients. Treating acne scars remained challenging for both patients and dermatologists, due to factors such as the expense of treatments, the necessity for multiple visits, extended duration of treatments, potential side effects, and the inherent limitations of treatment options

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[6, 7]. Advancements in scientific understanding of pathogenesis of acne scarring have provided a variety treatment options, offering variable efficacies and safety profiles. These options include microdermabrasion, chemical peels, tissue augmentation agents, microneedling, laser therapy, fat transplantation, platelet-rich plasma, and Intense Pulsed Light therapy. Treating atrophic acne scars involves assessing scar extent, skin type, patient expectations, cost, and physician expertise to devise a fully informed, optimal treatment plan [8, 9]. Chemical peeling is a technique involving the application of chemicals like Trichloroacetic acid (TCA) to remove outer damaged skin layer through exfoliation. TCA peels are available in different concentrations with 10% to 20% for superficial effects and 35% for medium-depth peeling. It causes epidermal and dermal collagen necrosis through kerato-coagulation. Various studies have promising results in the treatment of acne scars [10, 11]. However, disadvantages include sensations of stinging and burning upon application, along with risks of hypo- or hyperpigmentation of skin [11, 12]. In 2015, Bagherani and Smoller introduced intralesional saline injection as an innovative option for the treatment of atrophic acne scars. This method mechanically disrupts adhesions between epidermis and dermis and stimulates fibroblast activity for collagen and extracellular matrix neoformation. Injection-induced clotting raises the epidermis, facilitating new matrix development, while growth factors released from white blood cells and platelets encourage tissue growth [13]. While both intradermal trichloroacetic acid (TCA) and normal saline have been studied individually, there is no direct comparative study evaluating their efficacy and patient satisfaction. This study aims to fill this gap by proving head-to-head comparison of intradermal normal saline and TCA.

By assessing both physician and patient perspectives using qualitative and quantitative measures, this study aimed to provide clearer insights into which treatment offers superior outcomes, thereby helping to inform clinical decisions and improve treatment protocols for atrophic acne scars.

METHODS

A randomized controlled trial (RCT NO: NCT06789874) was conducted at Dermatology department, Sheikh Zayed Hospital, Rahim yar khan from 1st April 2023 to 31st October 2023. Ethical approval was obtained from the Institutional Review Board (656/IRB/SZMC/SZH), informed consent was obtained from all participants. A sample size of 126 was calculated by assuming the efficacy of 61% and 83.3 % in TCA and Normal saline group respectively, keeping confidence interval of 95% and power 80% [14, 15]. Initially patients were enrolled through non-probability consecutive sampling technique followed by randomization into two equal groups using computer generated random sequencing. Baseline demographic and clinical history related to the age, duration of symptoms and age of onset was collected. A dermatological examination of the skin was performed by the consultant dermatologist to identify the predominant scar type (Ice-pick, Boxcar, and Rolled) and grade of scar. The grading of scars was based on Goodman and Baron's Qualitative Scar Classification, where mild disease involved atrophy not visible from 50 cm and easily covered by makeup or hair; moderate disease involved noticeable scarring from 50 cm, not easily covered but flattenable by manual stretching; and severe disease involved prominent scarring from 50 cm, not easily covered or flattened by stretching [11, 16]. Before enrollment, scars were evaluated using the complete Patient and Observer Scar Assessment Scale (POSAS) version 2.0 [17, 18]. On the Observer side, a dermatologist scored six domains—vascularity, pigmentation, thickness, relief, pliability, and surface area using a 10-point scale, where 1 represented nearly normal skin and 10 indicated the worst scar imaginable. Patients simultaneously provided self-evaluations through the Patient Scale, which encompassed pain, itch, color, thickness, stiffness, and irregularity, also rated on a 10-point scale. Pre-treatment photographs were captured in a well-lit environment from various angles and labeled with the corresponding medical record number and treatment group, enabling direct comparison with post-treatment images. This study included patients aged 16-40 years of either gender with clinically diagnosed atrophic acne scars on the face, with a duration of more than 6 months, and no history of any procedural intervention in the past 3 months. Patients with keloids, active acne or local infection, skin allergies, hypertrophic scars, photosensitivity, or a history of comorbidities like diabetes mellitus, cardiovascular, and bleeding disorders were not included. Patients with a history of oral isotretinoin, oral contraceptives, steroids, or immunosuppressants were excluded. Pregnant females or patients with any psychiatric illness that could affect the treatment protocols were also omitted. Patients in the NS group received injections of 0.9% normal saline after local sterilization with spirit and application of topical anesthesia. A volume of 0.1-0.2 ml of normal saline was injected intradermally at each acne scar with a 1 cc syringe of 30 gauge into the scarred area until the elevation of scars and surrounding tissue [12]. Procedure was repeated fortnightly for 3 months and assessed on 12th weeks and 3 months post treatment. In the TCA group, after following the same initial protocols of anesthesia and sterilization, 35% trichloroacetic acid was applied to the scar base using blunt toothpick. The skin was monitored carefully until a frosted appearance was seen. Patients were instructed to

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wash their face with water after 10 minutes and to use water-based topical sunscreens. In both groups, patients received 3 sessions at monthly intervals and final outcomes were assessed after the last session at 12 weeks post treatment. Efficacy was defined as an improvement of ≥50% in both the Observer and Patient segments of the POSAS compared to baseline. The statistical analysis for this study was performed using SPSS version 26.0. Categorical variables, such as gender, duration of disease, scar grade, and predominant scar type, were presented as frequencies and percentages, while continuous variables, including age and Patient and Observer Scar Assessment Scale (PSAS and OSAS) scores, were expressed as mean ± standard deviation (SD). The chi-square test was used for comparing categorical variables, whereas continuous variables, such as age and PSAS and OSAS scores, were analyzed using the independent t-test. Stratification was performed for potential confounding variables, including gender, age group, duration of disease, and scar grade, to assess their impact on efficacy. Post-stratification analysis was conducted using the Chi-square test was used. To account for multiple comparisons, the Bonferroni correction was applied, adjusting the significance threshold accordingly. A p-value of less than 0.05 was considered statistically significant unless adjusted by the Bonferroni correction.

RESULTS

There were 53 (42.1%) males and 73 (57.9%) females. The mean age in NS group and TCA group was 25.32 ± 5.92 years and 27.06 ± 5.80 years, respectively (p=0.097). The baseline demographic and clinical characteristics were equally distributed between both groups (p > 0.05), indicating no significant differences. However, scar grades were statistically significantly different (p < 0.001), with the TCA group having a higher proportion of patients with more severe scars (Table 1).

Table 1: Distribution of Baseline Demographic and Clinical Characteristics in Treatment Groups (n=126)

Variables	Treatment Group		Chi-Square (p-Value)
	NS Frequency (%)	TCA Frequency (%)	
Age Group			
16-28 years	47 (74.6%)	42 (66.7%)	0.328
29-40 years	16 (25.4%)	21 (33.3%)	
Gender			
Male	24 (38.1%)	29 (46.0%)	0.367
Female	39 (61.9%)	34 (54.0%)	
Duration of Disease			
Up to 1 year	31 (49.2%)	35 (55.6%)	0.476
More than 1 year	32 (50.8%)	28 (44.4%)	
Scar Grade			
Mild	24 (38.1%)	14 (22.2%)	<0.001
Moderate	33 (52.4%)	15 (23.8%)	
Severe	6 (9.5%)	34 (54.0%)	
Predominant Scar Type			
Ice-pick	26 (41.3%)	25 (39.7%)	0.834
Boxcar	13 (20.6%)	11 (17.5%)	
Rolled Scar	24 (38.1%)	27 (42.9%)	

The Observer Scar Assessment Scale at baseline was 33.63 ± 7.73 in the Normal Saline (NS) group compared to 35.41 ± 7.78 in the TCA group (t (124) = –1.29, p = 0.201, 95% CI: –4.51 to 0.96, d = 0.23). Post-treatment, the Observer scale decreased to 14.35 ± 7.30 in the NS group and 17.37 ± 9.00 in the TCA group (t (124) = –2.07, p = 0.041, 95% CI: –5.90 to –0.13, d = 0.37). The Patient Scar Assessment Scale (PSAS) total score before treatment was 35.27 ± 7.55 in the NS group versus 36.98 ± 8.07 in the TCA group (t(124) = –1.23, p = 0.220, 95% CI: –4.47 to 1.04, d = 0.22). After treatment, the PSAS score was 11.83 ± 6.67 for the NS group and 16.13 ± 9.12 for the TCA group (t (113.61) = –3.02, p = 0.003, 95% CI: –7.12 to –1.48, d = 0.54).

Table 2: Comparison of Quantitative Treatment Outcomes between NS and TCA treatment Group (n=126)

Outcome Variable	NS (Mean ± SD)	TCA (Mean ± SD)	p-Value
Observer Scar Assessment Scale at Baseline	33.63 ± 7.73	35.41 ± 7.78	0.201
Observer Scar Assessment Scale Post-Treatment	14.35 ± 7.30	17.37 ± 9.00	0.041
PSAS Total Score Before Treatment	35.27 ± 7.55	36.98 ± 8.07	0.220
PSAS Score After Treatment	11.83 ± 6.67	16.13 ± 9.12	0.003

At baseline, the mean total POSAS score was 68.90 ± 14.88 in the Normal Saline group and 72.40 ± 15.74 in the TCA group. The independent samples t-test showed no statistically significant difference between the groups at baseline (mean difference = -3.49, 95% CI: -8.89 to 1.91; p = 0.203). After treatment, the mean reduction in POSAS scores was 42.73 ± 12.87 in the Normal Saline group and 38.90 ± 15.64 in the TCA group. This difference was not statistically significant (mean difference = 3.83, 95% CI: -1.23 to 8.88; p = 0.136). Regarding treatment efficacy, 56 (88.9%) of patients in the NS group and 46 (73.0%) of patients in the TCA group reported ≥ 50% improvement in score from baseline (p=0.023) (Table 3).

Table 3: Comparison of Efficacy between NS and TCA treatment Group. (n=126)

Efficacy	Treatment Group		Chi-Square (p-Value)
	NS Frequency (%)	TCA Frequency (%)	
Yes	56 (88.9%)	46 (73.0%)	5.147 (0.023)
No	7 (11.1%)	17 (27.0%)	

An initial assessment indicated that the Normal Saline group showed higher efficacy than the TCA group among individuals with a disease duration exceeding one year (p=0.034), those exhibiting mild scars (p=0.036), and those categorized as having rolled scars (p=0.033). However,

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after applying Bonferroni adjustments for multiple comparisons, none of these differences remained statistically significant. Consequently, no significant intergroup variations in efficacy were observed across any of the examined stratifications (Table 4).

Table 4: Efficacy Analysis between Treatment Groups Post-Stratification of Confounding Variables

Variables	Subgroup	NS Frequency (%)	TCA Frequency (%)	p-Value
Gender	Male	20/24 (83.3%)	22/29 (75.9%)	0.504
	Female	36/39 (92.3%)	24/34 (70.6%)	0.016
Age Group	16–28 years	42/47 (89.4%)	30/42 (71.4%)	0.032
	29–40 years	14/16 (87.5%)	16/21 (76.2%)	0.384
Duration of Disease	Up to 1 year	28/31 (90.3%)	27/35 (77.1%)	0.152
	More than 1 year	28/32 (87.5%)	19/28 (67.9%)	0.065
Scar Grade	Mild	22/24 (91.7%)	8/14 (57.1%)	0.012
	Moderate	29/33 (87.9%)	13/15 (86.7%)	0.906
	Severe	5/6 (83.3%)	25/34 (73.5%)	0.609
Predominant Scar	Ice-pick	25/26 (96.2%)	17/25 (68.0%)	0.008
	Boxcar	11/13 (84.6%)	11/11 (100.0%)	0.174
	Rolled Scar	20/24 (83.3%)	18/27 (66.7%)	0.173

Percentages indicate the proportion of patients within each group reporting efficacy. Post-stratification efficacy analysis of Normal Saline (NS) versus TCA with Bonferroni-adjusted p-values.

DISCUSSION

Atrophic acne scars are a common and disfiguring complication of acne. Various noninvasive and invasive treatment options are available for acne scars, each with varying degrees of effectiveness. Among invasive treatments, the efficacy of topical trichloroacetic acid (TCA) has been evaluated in previous studies, but there is no direct comparison available. This study compared the effectiveness of TCA and normal saline intradermal injections in treating atrophic scars. Post-treatment PSAS scores showed a significant reduction in both groups, with the NS group demonstrating a greater improvement ($t(113.61) = -3.02$, $p = 0.003$, 95% CI: −7.12 to −1.48, $d = 0.54$). This finding suggests that Normal Saline (NS) may be more effective in reducing the perceived severity of acne scars compared to TCA. Similarly, another study reported a significant improvement in Visual score from a baseline of 6.92 ± 1.49 to 10.1 ± 1.37 in patients receiving intradermal normal saline ($p<0.001$) [19]. The Observer Scar Assessment Scale, evaluated by a dermatologist, showed no significant difference in baseline scar severity between the groups (33.63 ± 7.73 vs. 35.41 ± 7.78, $p = 0.201$). However, post-treatment evaluations revealed that the Normal Saline (NS) group demonstrated a significantly greater reduction in scar severity than the TCA group (14.35 ± 7.30 vs. 17.37 ± 9.00, $p = 0.041$), thereby highlighting the potential efficacy of NS in improving scar appearance. Similarly, another single-arm interventional study evaluating the efficacy of NS in the treatment of atrophic scars reported significant improvement among all types of scars—icepick, rolled, and boxcar—using VAS, from 6.92 to 10.1 [19]. Similar results were observed in a study by Bagherani and Smoller after six sessions of normal saline intradermal injection treatment [13]. This study found that 88.9% of patients in the Normal Saline (NS) group achieved at least a 50% improvement in the Observer Scar Assessment Scale (OSAS) from baseline, compared to 73.0% in the TCA group ($p = 0.023$). These results suggest a potentially greater efficacy of NS for producing clinically meaningful scar improvements. This review article discusses the pathogenesis, classification, and a range of treatment options for acne scars, including both invasive and non-invasive approaches [20]. Lee et al., (2002) also recorded good satisfaction rates in the 65% and 100% TCA concentration, with no significant complications, further supporting the efficacy of TCA treatments between two strengths [21]. Both studies reported higher satisfaction with TCA compared to this study, probably because they used higher concentrations of TCA. A significantly higher proportion of patients in the Normal Saline group (88.9%) achieved a ≥50% improvement in the Observer Scar Assessment Scale from baseline, compared to 73.0% in the TCA group ($p=0.023$), indicating greater efficacy of NS in reducing scar severity. This highlights the superior effectiveness of NS in reducing scar severity. Khan S et al., (2020) demonstrated that saline injection therapy is a safe and effective treatment for improving the appearance of atrophic acne scars [15]. Similarly, another study reported very low efficacy for TCA, with the efficacy score reducing more than 50% in only 61% of subjects receiving TCA [14]. Lee et al., (2002) found that 82% of patients in the 65% concentration TCA group and 94% in the 100% TCA concentration group experienced a good clinical response, with all patients in the 100% TCA group who received five or six courses showing excellent results [21]. The lower efficacy of TCA in this study compared to this literature may be due to differences in the definition of efficacy or the use of a higher concentration of TCA in their studies compared to the 35% TCA. Sheraz et al., (2021) compared TCA with a derma roller and found that 40.25% of patients showed effective results with the derma roller, while 59.74% showed effective results with TCA ($p=0.015$) [22]. This highlights the comparative efficacy of TCA but also its associated higher cost and longer downtime. Mumtaz et al., (2021) similarly reported significant improvement with 50% TCA [23]. Strength of this study includes evaluation of both efficacy and satisfaction from the perspectives of physicians and patients, comparing qualitative and quantitative treatment effects to provide clarity in the outcomes. Limitations include being a single-centered study with a shorter follow-up period and not evaluating

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different concentrations of TCA. It is important to note that the effectiveness of normal saline injection for atrophic scars needs further validation in larger randomized controlled trials (RCTs). Additionally, exploring the combination of normal saline with other established therapies, such as microneedling, platelet-rich plasma (PRP), or fractional laser treatment, may yield even better outcomes. Despite these limitations, these findings suggest that intradermal normal saline is an effective, low-cost alternative to TCA for treating atrophic acne scars, particularly for patients with longer disease duration.

CONCLUSIONS

This study demonstrates that intradermal normal saline is more effective and satisfactory than trichloroacetic acid (TCA) for treating atrophic acne scars. Patients in the normal saline group showed greater improvements in both the Patient and Observer Scar Assessment Scale (PSAS and OSAS) scores compared to the TCA group. The normal saline group exhibited better scar texture, pigmentation, and overall aesthetic improvement, as reflected in both patient-reported and observer-assessed outcomes. These findings suggest that normal saline can be a superior alternative to TCA, offering better scar improvement and patient satisfaction. Future studies should focus on evaluating different concentrations of TCA compared to normal saline.

Authors Contribution

Conceptualization: KU
Methodology: KU, TH, MN
Formal analysis: MIJ
Writing, review and editing: KU, MKS, TH, MIJ, MN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Correlation of Serum Bilirubin with Severity of Acute Ischemic Stroke

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ABSTRACT

Serum bilirubin is associated with stroke severity, existing data on this relationship remain limited and inconclusive. **Objectives:** To determine the correlation between serum bilirubin and the National Institute of Health stroke scale score in patients with acute ischemic stroke. **Methods:** This cross-sectional study was done at the Medical Emergency of Mayo Hospital Lahore from June 2022 to December 2022. A total of 205 patients suffering from acute ischemic stroke were included. Serum bilirubin was obtained within 24 hours of the onset of stroke at presentation, and stroke severity was assessed same time using NIHSS. Data analysis was done using SPSS version 26.0. Pearson correlation was determined between serum bilirubin and NIHSS score at presentation. **Results:** In current study population, 44.5% of patients were diabetics, 77.6% were hypertensive, and 27.8% were smokers. Mean serum bilirubin level was 0.98 ± 0.19 mg/dL, and mean NIHSS score is 19.51 ± 8.94, Pearson correlation coefficient between bilirubin and NIHSS is -0.082, p-value=0.240, statistically not significant. **Conclusions:** It was concluded that in our study, a weak negative correlation was observed between serum bilirubin levels and NIHSS scores in patients with acute ischemic stroke. This suggests that higher bilirubin levels may have a slight protective effect, as stroke severity (NIHSS scores) tended to decrease minimally with increasing bilirubin levels.

INTRODUCTION

Stroke is a focal neurological deficit persisting for more than 24 hours and vascular in origin [1]. Ischemic stroke is caused by occlusion of the blood supply to a particular region of the brain [2]. The most important risk factors for stroke include hypertension, dyslipidemia, diabetes mellitus, smoking, advanced age, sex, and structural heart defects [3]. Stroke is the fifth major cause of hospitalization, according to the WHO, affecting 15 million people, out of which 5 million suffer death and 5 million experience permanent disability [4]. In Pakistan, the incidence of stroke per year is 95 per 100,000 [5]. Bilirubin is a byproduct of heme degradation with anti-inflammatory, antioxidant, antiproliferative, and blood lipid-modulating properties [6]. Studies have shown that serum bilirubin levels increase after stroke [7, 8]. It has been revealed that bilirubin possesses strong anti-inflammatory, antioxidant, and neuroprotective properties [9]. Another study supported the protective effect of bilirubin in patients with stroke [10]. However, various studies suggest that an increase in serum bilirubin is associated with more severe stroke [11]. Understanding this relationship is crucial, as bilirubin could serve as a potential biomarker for stroke prognosis and influence future therapeutic strategies. As previous studies have shown controversial results, the definitive verdict on this issue remains unclear. Moreover, no local studies have been conducted to explore this relationship.

This study aims to investigate the connection between

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serum bilirubin levels and ischemic stroke. This research aims to contribute valuable insights to the existing body of knowledge and prove beneficial to healthcare providers and medical students.

METHODS

This cross-sectional study was done at the Medical Emergency of Mayo Hospital Lahore from June 2022 to December 2022, after taking formal approval from the College of Physicians and Surgeons, Pakistan, before (REU No: 44705). A sample size of 205 patients was estimated, expected correlation coefficient (r=0.224) was selected based on prior studies that have explored the association between serum bilirubin levels and ischemic stroke severity [12]. Specifically, previous research has reported weak to moderate correlations in similar clinical settings. To ensure adequate statistical power, sample size calculation was performed with α=5% and ß=10%, achieving a power of 90%. For enrollment of patient's non-probability consecutive technique was used. Patients of either gender, aged 20-80 years, presenting to the Medical Emergency or neurology department with acute ischemic stroke (weakness of one or more parts of the body, persisting for more than 24 hours, with hypodense area on CT brain plain) were included. Patients with history of previous ischemic stroke, cerebral infections (such as meningoencephalitis or brain abscess), space-occupying lesions, head trauma, elevated liver enzymes (ALT or AST ≥40 IU/L), chronic liver disease (cirrhotic liver on ultrasound), any active malignancy, or those on medications that can derange liver function tests (such as anti-epileptics and anti-tuberculous agents) were excluded. Before enrollment, written informed consent was obtained from the patient/or relative. After following aseptic protocols, a venous blood sample of 5 mL was collected within 24 hours of patient intake. In the pathology department of Mayo Hospital, Lahore, the total serum bilirubin level (mg/dL) was measured using the enzymatic colorimetric method, as per established laboratory standards. This technique utilizes the reaction of bilirubin with diazotized sulfanilic acid, which yields a colored compound whose intensity, and hence concentration of bilirubin, can be measured spectrophotometric-ally. Stroke severity was evaluated using the NIH Stroke Scale (NIHSS), which is a 15-item diagnostic checklist for stroke used to evaluate the severity of stroke-related disability or level of recovery from a stroke. These abilities include consciousness, visual fields, motor and sensory function, language, and coordination, with a possible score ranging from 0, which indicates no deficit, to 42, which indicates severe stroke [13]. Data were collected by the researcher using a specially designed Proforma and presented in the form of tables. Data were analyzed with SPSS version 26.0. Numerical variables were presented as mean ± SD, and qualitative variables as frequency and percentages. A relationship between serum bilirubin levels and the severity of acute ischemic stroke was examined by Pearson correlation; p-value≤0.05 was taken as significant.

RESULTS

Among 205 patients, 126 patients (61.5%) were males and 79 patients (38.5%) were female, and the mean age of our sampled population was 59.0 ± 8.8 years, with an age range of 38- 77 years. 120 patients (59%) were under ≤60 years' age, and 85 patients (41%) were classified as >60 years of age. Risk factors studied found 45% of patients were diabetics, 78% were hypertensive, and 28% were active smokers. Regarding the timing of their presentation, 48% arrived within 8 hours of symptom onset, 42% presented between 8 and 14 hours, and 18% between 14 and 24 hours after symptoms began (Table 1).

Table 1: Patient Related Socio-Demographic Characteristics (n=205)

Characteristics		n (%)
Age (Years) Mean ± SD		56.8 ± 8.8
Age	≤60 Years	120 (59%)
	>60 Years	85 (41%)
Gender	Female	79 (38.5%)
	Male	126 (61.5%)
Diabetes	Yes	92 (45%)
	No	113(55%)
Hypertension	Yes	159 (78%)
	No	46 (22%)
Active smokers	Yes	57 (28%)
	No	148 (72%)
Onset of symptoms	Up to 8 Hours	83 (40%)
	>8-14 Hours	86 (42%)
	>14-24 Hours	36 (18%)
Serum Bilirubin(mg/dl)	0.98 ± 0.19	
NIHSS	19.51 ± 8.94	

The mean serum bilirubin level was 0.98 ± 0.19 mg/dL, and the mean NIHSS score was 19.51 ± 8.94. The Pearson correlation coefficient (r) between bilirubin and NIHSS was -0.082, indicating a weak negative correlation between the two variables. The p-value of 0.240 suggests that this correlation was not statistically significant, at a threshold of 0.05 (Table 2).

Table 2: Pearson Correlation (r) Between Serum Bilirubin and Stroke Severity

Variables	Mean ± SD	r	p-Value
Bilirubin (mg/dl)	0.98 ± 0.19	-0.082	0.240
NIHSS	19.51 ± 8.94		

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DISCUSSION

The incidence of ischemic stroke among younger adults has been rising, with rates increasing from 11.0 to 22.9 per 100,000 in individuals aged 18–55 years and from 5.4 to 12.8 per 100,000 in those aged 18–45 years [14]. Our study aligns with these trends, as 59% of patients were aged ≤60 years, while 41% were older than 60 years. Male predominance observed (61.5% male vs. 38.5% female) is consistent with findings from Kanwal *et al.*, who reported a similar distribution (64% male vs. 36% female) [15], as well as a study from Germany that documented an increasing incidence of ischemic stroke among men [16]. Regarding risk factors, hypertension emerged as most prevalent (78%), followed by diabetes (45%) and smoking (28%). This is in line with prior studies that have consistently identified hypertension as the leading risk factor for stroke [17]. However, some studies report variations, such as higher prevalence of hypertension (86.7%) and lower prevalence of diabetes (24.5%) in ischemic stroke patients [18]. These differences may stem from variations in study populations, ethnicity, lifestyle factors, or healthcare accessibility influencing risk factor distribution. Our study primarily investigated the correlation between serum bilirubin levels and severity of acute ischemic stroke. We found that higher bilirubin levels were associated with decrease in NIHSS scores at admission (r=-0.082), suggesting potential neuroprotective role. Several studies have explored this association, with meta-analysis reporting significant positive correlation between total bilirubin levels and stroke severity, particularly in patients with NIHSS scores ≥8. The pooled OR of 1.14 indicated that elevated bilirubin levels were linked to increased stroke severity, with sensitivity analyses reinforcing this trend [19]. Yu *et al.*, also found that lower bilirubin levels correlated with more severe and extensive intracranial atherosclerosis ($p<0.001$) [20], supporting the notion that bilirubin's antioxidant properties may have a protective effect. However, conflicting evidence exists. Peng *et al.*, reported that elevated bilirubin levels were associated with more severe strokes and poorer outcomes ($p=0.014$) [21]. Another study found significant differences in bilirubin levels between patients with good and poor prognoses, highlighting bilirubin's potential as a prognostic marker [22]. These discrepancies may be attributed to differences in patient populations, stroke subtypes, bilirubin metabolism, and statistical methodologies. The variability in study designs, including sample size, adjustment for confounding factors, and inclusion criteria, could also contribute to differing conclusions.

CONCLUSIONS

It was concluded that in our study, a weak negative correlation was observed between serum bilirubin levels and NIHSS scores in patients with acute ischemic stroke. This suggests that higher bilirubin levels may have a slight protective effect, as stroke severity (NIHSS scores) tended to decrease minimally with increasing bilirubin levels.

Authors Contribution

Conceptualization: MNA
Methodology: MNA, SK, IAM, AA, AS, FM
Formal analysis: MNA
Writing review and editing: IAM, AA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparing the Efficacy of Weekly Azathioprine Pulse versus Betamethasone Oral Mini-Pulse in the Treatment of Moderate to Severe Alopecia Areata

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ABSTRACT

Alopecia Areata (AA) is a disease that leads to unpredictable hair loss. **Objective:** To assess and compare the efficacy of Weekly Azathioprine Pulse (WAP) versus Betamethasone Oral Mini-Pulse (BOMP) therapy in Alopecia areata. **Methods:** Sixty patients with ≥15% scalp involvement were divided into two groups.The WAP group given azathioprine (300 mg) once weekly; the BOMP group received betamethasone (5 mg) on two consecutive days weekly. A randomized controlled trial was performed at the Dermatology Department of Sheikh Zayed Hospital, Rahim Yar Khan, over a 6-month (March–September 2023). Both treatments continued for 12 weeks. At baseline, 12 weeks, and 12 weeks post-treatment SALT scores were recorded. Efficacy was defined as ≥75% hair regrowth. **Results:** The male-to-female ratio was 1.9:1 with 39 (65%) males and 21 (35%) females. WAP group baseline SALT score of 42.60 ± 13.75 decreased to 13.97 ± 11.79 after a follow-up period of 12 weeks post-treatment, compared to BOMP group reduction from 38.67 ± 10.76 to 21.63 ± 10.96; regrowth percentage was higher in WAP (68.62%) vs. BOMP (44.28%), p=0.001. In the WAP group, 13 (43.3%) of patients achieved efficacy with ≥76% hair regrowth, compared to 3 (10%) in the BOMP group, showcasing a significant disparity (p-value=0.009). Relapse at three months occurred in 1 (3.3%) participant in the WAP group and 2 (6.7%) participants in the BOMP group (p-value of 0.500). **Conclusion:** This study demonstrated that WAP therapy was superior to BOMP in moderate to severe AA with notable hair regrowth.

INTRODUCTION

Alopecia Areata (AA) is a chronic autoimmune condition that results in non-scarring hair loss, typically presenting as solitary or multiple round or oval areas of baldness on the scalp or other parts of the body with hair. These regions often exhibit "exclamation mark" hairs near their borders. The condition affects individuals across all ages, genders, and ethnicities. Clinically, alopecia areata manifests in various patterns based on the extent of hair loss, including localized patchy involvement, total scalp hair loss (alopecia totalis), complete loss of scalp and body hair (alopecia universalis), or, less frequently, a linear pattern of hair loss affecting specific scalp regions [1, 2]. The spectrum of AA severity is associated with profound psychological impact, emotional distress, and social phobia [3, 4]. The reported incidence of alopecia areata varies substantially across the globe, with higher rates generally observed in individuals aged 19–50 years. One extensive systematic review, comprising 88 studies from 28 countries, determined that the lifetime prevalence of alopecia areata is 0.10% in the overall population, 0.12% among adults, and 0.03% in children. The review further noted that Asian populations displayed the highest observed prevalence, whereas African regions reported the lowest [5]. This variability underscores the importance of considering geographical and demographic factors when evaluating the burden of alopecia areata worldwide [5]. The etiopathogenesis of AA

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is not completely revealed yet, it is hypothesized that immune system loses its ability to distinguish hair follicle cells as "self," resulting in autoimmune-mediated damage. This damage is mediated by CD8+ T cells, which release interferon-γ, disrupt immune tolerance in hair follicles, and expose self-antigens [6, 7]. Etiological factors that have been linked with alopecia areata include psychological stress, genetics, and environmental influences, with approximately 20% of patients having a positive family history [8]. Due to its variable course and extent of alopecia, the disease outcome is unpredictable. Not all patients require treatment, as spontaneous regrowth is well documented, especially in cases with < 25% of scalp involvement. While extensive loss (>50%) for over a year typically does not see substantial regrowth without medical intervention [9]. Multiple management strategies for AA have been explored with no consensus, ranging from topical, intralesional to systemic therapies. For mild to moderate disease, anthralin, minoxidil, topical and intralesional corticosteroid have shown variable treatment efficacies. Systemic medications, such as oral corticosteroids, immunosuppressants (methotrexate or Azathioprine), or Janus Kinase (JAK) inhibitors (Baricitinib), are often required for Alopecia Totalis or Alopecia Universalis [9, 10]. Oral corticosteroids remain a preferred treatment for alopecia areata due to their affordability and widespread availability. However, most studies have highlighted numerous potential side effects of high dose oral steroids, including weight gain, impaired glucose regulation, fatigue, hormonal disturbances, hypertension, osteoporosis, and an elevated risk of infections. To decrease the adverse effects of systemic corticosteroids, Oral Mini-Pulse (OMP) therapy with various steroids, has been applied in immune-mediated dermatological disorders including lichen planus, vitiligo, and alopecia areata. This approach has demonstrated favorable outcomes, better safety, and improved patient adherence [11]. Azathioprine, targets autoimmune diseases by disrupting the purine pathways and impairing T-cell functions. Tested across various autoimmune dermatologic conditions, including pemphigus vulgaris and alopecia areata, it offers a steroid-sparing alternative for moderate to severe cases. Its weekly dosing regimen has shown promising results, attributed to its advantage in promoting higher compliance rates. However, monitoring for adverse effects is essential [12]. Given the uncertain pathogenesis and course of the illness, the effectiveness of treatment modalities remains unpredictable. While various treatment options exist, no consensus has been established for moderate to severe cases. Systemic corticosteroids, particularly Oral Mini-Pulse (OMP) therapy with betamethasone, are commonly used but are associated with adverse effects. Azathioprine, an immunosuppressant, offers a potential steroid-sparing alternative with promising efficacy. Effective treatment must address both the clinical efficacy and safety. Previous studies have reported variable safety profiles, remission, and relapse rates for weekly Azathioprine therapy versus BOMP, particularly when compared to placebo. Moreover, data specific to the Pakistani population is notably lacking. Therefore, this study aimed to link the existing gap in literature by offering a comparative evaluation of these therapies in the management of alopecia areata.

METHODS

A randomized controlled trial with a parallel-group design (NCT06786689) was carried out in the Dermatology Department of Sheikh Zayed Hospital, Rahim Yar Khan, over a six-month period from March to September 2023. Ethical clearance was granted by the Institutional Review Board (IRB: 657/IRB/SZMC/SZH). All participants provided informed consent after being fully briefed on potential benefits and risks. Consecutive sampling identified adults with moderate-to-severe alopecia areata, who were enrolled until the target sample size was reached. Participants were subsequently randomized in a 1:1 allocation ratio into two intervention groups using a computer-generated sequence, with group assignments concealed in sealed envelopes maintained by an independent investigator. Given the nature of the interventions, neither patients nor treating physicians could be blinded, though outcome assessors remained unaware of group allocations. A sample size of 60 was estimated using a WHO calculator, presuming 96.67% efficacy for azathioprine pulse therapy versus 67.67% for corticosteroids (95% confidence, 80% power) [13]. Baseline complete laboratory investigations were performed. Female participants received counseling regarding contraception throughout the study. Sixty patients were enrolled through non-probability consecutive sampling technique. Patients were equally divided into two groups using lottery method. Patients in Group WAP received a single dose of Tab. Azathioprine 300 mg once weekly, while patients in Group BOMP received Tab. Betamethasone 5mg for 2 consecutive days weekly for 12 weeks [14]. This study includes patients aged 16-60 years with scalp area involvement of ≥ 15% by Alopecia Areata. The diagnosis of AA was based on history and clinical examination performed by two consultant dermatologists. Patients having spontaneous terminal hair regrowth, used topical and intralesional treatment within last 1 month, received systemic therapy or phototherapy within last three months, anemia, leukocytosis, leukopenia, thrombocytopenia, deranged renal and liver function test, having active infection, and pregnancy were excluded. Additionally, patients with contraindications to corticosteroids or Azathioprine, as well as individuals with alopecia universalis, were also excluded. Standardized

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scalp photographs were obtained at baseline and during follow-up using a 50-megapixel camera from four predefined views under consistent lighting conditions. The Severity of Alopecia Tool (SALT) scoring system was employed to assess hair loss, wherein the scalp was divided into anatomical zones: vertex (40%), occipital (24%), left parietal (18%), and right parietal (18%). The overall SALT score reflected the cumulative percentage of hair loss across these regions. Assessments were conducted at three time points: at study initiation, at the completion of 12 weeks of therapy, and at 12 weeks after cessation of treatment. Hair regrowth was quantified using the formula: Hair regrowth (%) = [(Baseline SALT– Follow-up SALT) / Baseline SALT]× 100 [15].Based on the percentage of improvement, treatment response was classified into four categories: Poor response: <25% improvement from baseline; Moderate response: 26–50% improvement; Good response: 51–75% improvement; Excellent response: ≥75% improvement [14]. The primary efficacy endpoint was defined as achieving an excellent response at the 12-week post-treatment assessment. Relapse was operationally defined as either the shedding of newly regrown hair or the development of fresh alopecia patches during the follow-up interval. Safety monitoring included periodic laboratory testing (complete blood count, hepatic and renal function panels) performed every four weeks during the initial 12-week treatment period. Data were analyzed using SPSS version 23.0. Categorical variables, including gender, treatment efficacy, and relapse, were presented as frequencies and percentages. Continuous variables, such as age, duration of illness, and SALT scores, were expressed as mean ± SD. The Chi-square test was used for comparisons of categorical variables such as gender between groups. The Fisher's exact test was utilized for categorical outcomes with expected cell counts less than five, including treatment efficacy and relapse rates. Continuous variables, including baseline SALT scores, follow-up SALT scores, and percentage hair regrowth, were compared between the treatment groups using the independent t-test. Repeated measures analysis of variance (ANOVA) was used to measure the changes in SALT scores over time within each group across three evaluation points (baseline, 12 weeks, and 12 weeks post-treatment). A p-value of ≤ 0.05 was set to test statistical significance.

RESULTS

There were 39 (65%) males and 21 (35%) females. There were 18/39 (46.15%) males and 12/21 (57.1%) females in WAP group and 21/39 (53.8%) male and 9/21 (42.8%) females in BOMP group (p-value=0.417). Details of baseline characteristics are given in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics of Patients in the WAP and BOMP Groups (n=60)

Baseline Characteristics	WAP Group Frequency (%) /Mean ± SD	BOMP Group Frequency (%) /Mean ± SD	p-Value
Gender			
Male	18 (60%)	21 (70%)	0.598
Female	12 (40%)	9 (30%)	
Age (Years)			
Mean Age	31.00 ± 9.94	32.37 ± 10.04	0.537
Duration of Illness (Years)	4.03 ± 1.75	3.77 ± 1.57	

The mean Baseline SALT score for the WAP group was 42.60±13.75, which decreased to 23.77±8.01 at the end of the 12-week treatment period, and further diminished to 13.97±11.79 after a follow-up period of 12 weeks post-treatment. In contrast, the BOMP group presented with a mean Baseline SALT score of 38.67±10.76, observed a reduction to 28.87±8.96 at treatment completion, and recorded a SALT score of 21.63±10.96 at the 12 weeks follow-up. The mean percentage hair regrowth at second follow-up of 12 weeks was significantly greater in the WAP group (68.62±25.83 %) compared to the BOMP group (44.28±27.39 %), with a p-value of 0.001 (Table 2).

Table 2: Comparison of SALT Scores and Hair Regrowth Percentage between WAP and BOMP Treatment Groups (n=60)

SALT Score	Treatment Group		p-Value
	WAP Group Mean ± SD	BOMP Group Mean ± SD	
Baseline SALT Score	42.60 ± 13.75	38.67 ± 10.76	0.222
SALT score at end of the 12-week treatment	23.77 ± 8.01	28.87 ± 8.96	0.024
SALT score 12 weeks post-treatment	13.97 ± 11.79	21.63 ± 10.96	0.012
Mean %age hair Regrowth at last 12 weeks follow up	68.62 ± 25.83	44.28 ± 27.39	0.001

Treatment response and Efficacy in terms of improvement in SALT score has been reported in "Figure 1" showing significant difference (p-value=0.009). Relapse at three months occurred in 1 (3.3%) participant in the WAP group and 2 (6.7%) participants in the BOMP group, with a Fisher's exact test p-value of 0.500. Within the BOMP group, a repeated measures ANOVA on SALT scores indicated a significant change over time ($F(2, 38.380) = 74.233$, $p < 0.001$), suggesting substantial improvement in patients' condition across the study duration. Similarly, for the WAP group, significant temporal changes in SALT scores were observed ($F(2, 46.838) = 129.049$, $p < 0.001$). During the study, the follow-up rate was 100% and no serious adverse effect was reported.

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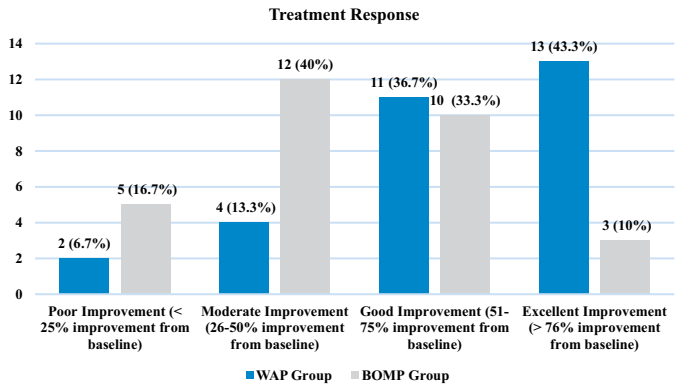

Figure 1: Comparison of Treatment Response and Efficacy between Treatment Groups(p-value=0.009)

DISCUSSION

Alopecia Areata (AA) significantly impacts patients' psychological and social well-being. Approximately 60% of individuals report their initial AA episode occurring before reaching their twenties [8]. Moderate to severe AA complicates treatment and poses a considerable challenge for dermatological management.This study aimed to evaluate the efficacy of WAP and BOMP in the treatment of moderate to severe AA. Demographically, this study reported that mean age of the patients was 31 years and male predominance. Khandpur S (2019) reported similar mean age of participants 26.6 26.6 ± 7.38 years and similar ratio of male compared to female participants 2.2:1 [16]. Current study's demographic findings align with those reported by Cua VC *et al.*, in (2019), corroborating that alopecia areata frequently presents during the second and third decades of life, as supported by prior research [12]. This study compared weekly azathioprine pulse therapy with oral betamethasone mini-pulse in treating moderate-to-severe alopecia areata, finding both effective, with azathioprine showing a slightly better safety profile [17]. This open-label study assessed betamethasone oral mini-pulse therapy for extensive alopecia areata, reporting positive clinical outcomes, though without a control group for comparison [18].In the present study, a profound improvement in alopecia areata treatment was observed, supported by the decrease in SALT scores within both the WAP and BOMP groups.The WAP group demonstrated a significant decline in SALT score from 42.60 to 13.97 at 12 weeks post-treatment follow-up, outperforming the BOMP group which reduced from 38.67 to 21.63.These findings are consistent with previous studies, such as Khandpur S *et al.*, in (2019) who noted a substantial decrease in median scalp hair loss with Azathioprine and Betamethasone treatments, and Farshi S *et al.*, in (2010) who reported a significant reduction in hair loss percentage from 72.7 to 33.5 after Azathioprine treatment [16, 19].Moreover, Sánchez-Díaz M *et al.*, in (2022) documented similar trends of improvement with mini pulse oral corticosteroids therapy, demonstrating a decrease in baseline SALT scores from 71.35 to 52.93 [20].This Summative evidence not only confirms the efficacy of both Azathioprine and corticosteroids but also highlights the resilience of the WAP group's response in this study, asserting its utility in managing moderate to severe AA. This study reported that WAP treatment demonstrated higher hair regrowth (68.62 ± 25.83%) compared to the BOMP treatment (44.28 ± 27.39%), achieving a statistical significance in outcomes (p-value=0.001).This Differs from results in Khandpur S (2019), where the BOMP higher regrowth 71.43% compared to the WAP treatment 44.52% [16]. Similarly, Gupta P *et al.*, in (2019) reported a higher median regrowth in the BOMP group compared to this study [17]. However, Farshi S *et al.*, in (2010) reported a lower regrowth rate 52.3% compared to current study with weekly Azathioprine treatment [19]. These differences could be due to single arm studies or different treatment duration and follow-ups. Based on changes in the Severity of Alopecia Tool (SALT) score, the study highlights the superior efficacy of WAP therapy, with 43% of participants achieving excellent regrowth, compared to 10% in the BOMP group. Sonare D *et al.*, in (2017) reported no patients in the WAP group showing poor or moderate responses, and a remarkable 96.67% displayed an excellent response [14].Khaitan BK *et al.*, in (2004) also confirmed the efficacy of BOMP, with a 43.7% rate of excellent response [18]. Sánchez-Díaz M *et al.*, in (2022) noted a 51.8% good response (SALT-50) response at 9 months with mini-pulse corticosteroids treatment [20]. Thi PT *et al.*, in (2019) demonstrated a good regrowth in over 82% of patients over six months, indicating a more gradual but substantial improvement with mini-pulse corticosteroid therapy [21]. Sharma VK *et al.*, in (1999) in single arm study, reported slightly higher excellent regrowth (26.6%) with oral mini-pulse corticosteroids treatment [22].WAP and BOMP therapies both demonstrated effectiveness in reducing SALT scores and promoting hair regrowth in patients with moderate to severe alopecia areata.Among these, WAP therapy exhibited greater clinical benefit and may be considered a more effective option in such cases.Nonetheless, this study is subject to certain limitations, including its single-institution design, use of non-probability consecutive sampling, and relatively limited sample size, which may restrict the broader applicability of its conclusions. However, strengths of the study include a comparatively larger sample than previous investigations, extended follow-up duration, and a direct comparative evaluation of weekly azathioprine pulse therapy versus oral mini-pulse betamethasone.These factors enhance the depth of insight into their respective efficacies.Further validation through multicenter randomized controlled trials with longer follow-up and focused safety assessments is

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recommended to support the generalizability and clinical integration of these findings.

CONCLUSIONS

The study conclusively demonstrated the superior efficacy of WAP therapy over BOMP in increasing hair regrowth among patients with AA. Significantly, the WAP cohort was associated with considerable SALT scores improvement and higher percentage of hair regrowth. These findings promote for the consideration of weekly azathioprine pulse therapy in clinical practice, offering new hope to patients seeking effective management for moderate to severe alopecia areata.

Authors Contribution

Conceptualization: KU

Methodology: KU, TH, MN

Formal analysis: MIJ

Writing, review and editing: KU, MKS, TH, MIJ, MN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Demographic and Clinical Factors Influencing the Peripheral Neuropathy in Anti-HCV Positive Patients

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ABSTRACT

Peripheral neuropathy is a common complication affecting individuals with various underlying conditions, often influenced by factors such as age, gender, and disease duration. **Objectives:** To assess the prevalence of peripheral neuropathy by age, gender, and disease duration. **Methods:** It was a cross-sectional descriptive study conducted at the Neurology Department of Jinnah Postgraduate Medical Centre, from March 20, 2021, to September 19, 2021. The total number of patients was 164.The study enrolled patients aged 18-60 of either gender who had peripheral neuropathy. Patients with hepatitis other than hepatitis C, who received treatment for HCV, patients having diabetes mellitus, autoimmune disorder, kidney failure, vitamin B deficiency, thyroid disorders, hematological disorders, alcoholism, HIV infection, drug addiction or toxic agents were excluded. A questionnaire-based study was designed for the collection of data regarding demographics and clinical aspects. **Results:** The mean age of the study patients was 42.7±18.2 years. Peripheral neuropathy was found in 98(59.8%)participants. Among 164 patients, 94(57.3%)were male, while 70(46.4%)were female. Diabetes mellitus and hypertension were documented in 63(38.4%)and 85(51.8%), respectively. **Conclusions:** It was concluded that gender is statistically significantly associated with the prevalence of peripheral neuropathy in anti-HCV positive patients, while a higher body mass index and extended duration of infection were also associated with peripheral neuropathy, but were not statistically significant.

INTRODUCTION

Hepatitis C virus (HCV) infection continues to pose a significant global health challenge, with an estimated 58 million people living with chronic HCV worldwide as of 2022 [1]. Despite advancements in antiviral therapies, HCV remains a leading cause of liver-related morbidity and mortality. Beyond hepatic complications, HCV is associated with various extrahepatic manifestations, notably peripheral neuropathy, which significantly impacts patients' quality of life [2]. Peripheral neuropathy in HCV-infected individuals often presents as symmetrical axonal sensorimotor neuropathy, distal symmetric painful small-fiber neuropathy, mononeuritis multiplex, or, less commonly, demyelinating and autonomic neuropathies [3]. The prevalence of peripheral neuropathy among HCV patients varies, with studies reporting rates ranging from 8% to 23% [4]. The pathogenesis is multifactorial, involving direct viral invasion, immune-mediated mechanisms, and neurotoxic effects of cry-globulins. Hepatitis C virus (HCV) infection poses a significant public health challenge in Pakistan, where an estimated 9.8 million people are affected, marking a global peak prevalence rate of 7.5% [5]. The infection rate differs regionally, with Baluchistan showing the highest prevalence at 25.77%, followed by Khyber Pakhtunkhwa(6.07%), Punjab(5.46%), the Federally Administered Tribal Areas (3.37%), and Sindh (2.55%) [6]. This widespread transmission is largely attributed to poor healthcare practices, including the reuse of injection needles, insufficient sterilization protocols, and

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transfusion of unscreened blood [7]. Among those infected with HCV, several demographic and clinical variables influence the likelihood of developing peripheral neuropathy. Advanced age and male sex have been linked to greater vulnerability [8], while coexisting conditions such as diabetes, kidney dysfunction, and high blood pressure further intensify neuropathic symptoms [9]. Additionally, mixed cryoglobulinemia notably raises neuropathy risk due to the deposition of immune complexes in nerve tissues [10]. The advent of direct-acting antivirals (DAAs) has revolutionized HCV treatment, achieving sustained virological response rates exceeding 95%. However, the impact of viral eradication on extrahepatic manifestations like peripheral neuropathy remains under investigation. Some studies suggest partial or complete resolution of neuropathic symptoms post-treatment, while others report persistent or even worsening symptoms, indicating possible irreversible nerve damage or ongoing immune-mediated processes [11, 12]. A prospective study involving 94 HCV-infected patients without systemic and metabolic diseases found that 23% had sensory-motor neuropathy at baseline. After DAA therapy, nerve amplitude parameters tended to improve, with a significant reduction in neuropathic pain and improved quality of life [10]. Another study reported that among 40 HCV-infected individuals, 22.5% exhibited signs of polyneuropathy. Post-treatment, some patients showed improvement in nerve conduction studies, suggesting potential reversibility of neuropathy after HCV eradication [3]. Understanding the demographic and clinical factors influencing peripheral neuropathy in anti-HCV-positive patients is crucial for early identification, prevention, and management of this debilitating complication. Comprehensive care strategies should include regular neurological assessments, especially for high-risk populations, and prompt initiation of antiviral therapy to mitigate the progression of neuropathic damage.

This study aimed to assess the prevalence of peripheral neuropathy by age, gender, and disease duration.

METHODS

This descriptive cross-sectional study was conducted in the Department of Neurology at Jinnah Postgraduate Medical Centre (JPMC), Karachi, from March 20 2021, to September 19, 2021. A total of 164 patients were enrolled in the study. The sample size was calculated using the Open Epi sample size calculator, considering a previously reported prevalence of peripheral neuropathy in anti-HCV positive patients of 70.3% [13], with a 95% confidence interval and a 7% margin of error. Patients aged between 18 and 60 years, of either gender, with a confirmed diagnosis of hepatitis C virus (HCV) infection, were included in the study. HCV infection was confirmed through the patient's available medical records. A non-probability convenience sampling technique was used to recruit participants from neurology outpatient and inpatient units. Informed written consent was taken from each participant before enrollment in the study. The study was approved by the College of Physicians and Surgeons, Pakistan via Letter No. CPSP/REU/NEU-2017-186-460. Exclusion criteria included individuals with viral hepatitis other than HCV, those who had previously received treatment for HCV, or those with coexisting diabetes mellitus, autoimmune disorders, nephropathy, thyroid dysfunction, hematological disorders, HIV infection, a history of alcoholism, drug addiction, or exposure to known neurotoxic agents. These conditions were excluded to reduce confounding factors that could independently contribute to peripheral neuropathy. Peripheral neuropathy was diagnosed based on a combination of self-reported symptoms, clinical neurological examination, and Nerve Conduction Studies (NCS). Symptoms included numbness, tingling, burning sensations, pins-and-needles, or a cold sensation in the extremities. All participants underwent a comprehensive neurological assessment by a resident neurologist, including testing for deep tendon reflexes, vibration sense, pin-prick sensation, temperature, and proprioception. Nerve Conduction Studies (NCS), as the gold standard for diagnosing peripheral neuropathy, were performed on all participants using standard protocols to assess motor and sensory nerve conduction velocities, amplitudes, and distal latencies. A structured questionnaire was administered by trained data collectors to gather information on demographic characteristics (age, gender, occupation, and residence) and clinical history (duration of HCV infection, comorbidities, and current symptoms). Data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0. Descriptive statistics, including means and standard deviations, were computed for continuous variables, while frequencies and percentages were calculated for categorical variables. Chi-square tests were applied to evaluate associations between demographic variables (age, gender) and the presence of peripheral neuropathy. A p-value ≤0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the study population revealed a mean age of 42.7 ± 18.2 years, indicating that the cohort predominantly comprised middle-aged individuals. Among the 164 participants, 94 (57.3%) were male and 70 (42.6%) were female, suggesting a slight male predominance. The majority of the patients were married (58.5%), while 41.5% were unmarried. In terms of educational status, 54.8% of participants were educated, whereas 45.1% had no formal education. The duration of disease ranged from 6 to 12 months, with a mean duration of 10.2 ± 4.1 months, reflecting a subacute to chronic phase of illness at the time of evaluation (Table 1).

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Table 1: Demographic Characteristics of Study Participants

Variables	n (%)
Age	
Mean ± SD	42.7 ± 18.2 years
Gender Distribution	
Male	94 (57.3%)
Female	70 (46.4%)
Marital Status	
Married	96 (58.5%)
Unmarried	68 (41.5%)
Educational Status	
Educated	90 (54.8%)
Uneducated	74 (45.1%)
Duration of Disease (Months)	
Minimum	6
Maximum	12
Mean ± SD	10.2 ± 4.1 (Months)

The prevalence of peripheral neuropathy among anti-HCV-positive patients was notably high, underscoring the significance of neurological complications in this population (Figure 1).

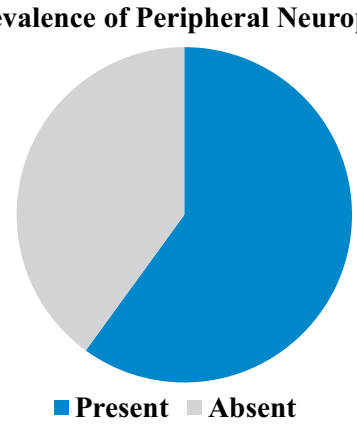

Figure 1: Presence of Peripheral Neuropathy

Analysis of demographic factors revealed an increasing trend of peripheral neuropathy with advancing age, peaking in the 40–60 years' group; however, this was not statistically significant (p=0.082). Gender showed a significant association (p=0.021), with females having a higher proportion of neuropathy compared to males. BMI-wise, peripheral neuropathy was more prevalent in overweight and obese individuals, but this association did not reach statistical significance (p=0.312) (Table 2).

Table 2: Relation of Demographic Factors with Peripheral Neuropathy

Variables	Peripheral Neuropathy		p-value
	Yes	No	
Age Group			
18–29	10 (6.1%)	14 (8.5%)	-
30–39	20 (12.2%)	20 (12.2%)	
40–49	34 (20.7%)	18 (11.0%)	
50–60	34 (20.7%)	14 (8.5%)	
Gender			
Male	49 (29.9%)	45 (27.4%)	-
Female	49 (29.9%)	21 (12.8%)	
BMI			
Underweight (<18.5)	6 (3.7%)	4 (2.4%)	-
Normal (18.5–24.9)	33 (20.1%)	39 (23.8%)	
Overweight (25.0–29.9)	40 (24.4%)	18 (11.0%)	
Obese (≥30.0)	19 (11.6%)	5 (3.0%)	

Clinical factors such as disease duration, diabetes mellitus, and hypertension were assessed for their association with peripheral neuropathy. A longer disease duration (>9 months) was more common among patients with neuropathy, but this association was not statistically significant (p=0.912). Similarly, no significant relationship was observed between peripheral neuropathy and diabetes mellitus (p=0.860) or hypertension (p=0.482), possibly due to the exclusion of known diabetic patients and the multifactorial nature of neuropathy in HCV-positive individuals (Table 3).

Table 3: Relation of Clinical Factors with Peripheral Neuropathy

Variables	Peripheral Neuropathy		p-value
	Yes	No	
Duration of Disease (months)			
6-9	23 (14.0%)	15 (9.1%)	-
>9	75 (45.7%)	51 (31.1%)	
Diabetes Mellitus			
Present	39 (23.8%)	24 (14.6%)	-
Absent	59 (36.0%)	42 (25.6%)	
Hypertension			
Present	53 (32.3%)	32 (19.5%)	-
Absent	45 (27.4%)	34 (20.7%)	

DISCUSSION

Peripheral neuropathy occurs when the nerves located outside of the brain and spinal cord are affected. This condition is often present with weakness, numbness, and pain, usually in the hands and feet. Hepatitis C presents with common neurological complications as peripheral neuropathy, spread by direct contact with infected blood through skin opening or the mucus membrane, sharing contaminated needles, and by sexual contact. Peripheral neuropathy is an extra-hepatic complication related to HCV through a vasculitis process caused by cryoglobulinemia. Age emerged as a significant factor, with an increasing trend of peripheral neuropathy observed in older age groups. This finding is consistent with earlier studies that have identified age as an independent predictor of peripheral neuropathy in HCV-infected individuals [14]. For instance, a multicenter study reported that the prevalence of peripheral neuropathy increased significantly with age, with an odds ratio (OR) of 1.10 for each additional year of age [15]. Similarly, a study conducted in

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sub-Saharan Africa found that patients aged ≥55 years had a higher likelihood of developing peripheral neuropathy, with an adjusted odd ratio (AOR) of 6.25 [16]. Gender-based disparities were apparent in the prevalence of peripheral neuropathy, with a notably higher frequency among female than male.While certain investigations have not found statistically meaningful differences in neuropathy rates between genders in individuals with hepatitis C virus (HCV) infection [17], other research suggests that women may be more prone to developing neuropathic symptoms, possibly due to hormonal influences and immune system variations [10]. In terms of body mass index (BMI), although no statistically significant correlation was established in this analysis, a noticeable trend emerged, with overweight and obese participants experiencing higher rates of neuropathy. This observation supports previous studies indicating that elevated BMI might be linked to an increased likelihood of neurological issues among those with HCV [18]. Clinical characteristics such as the length of time since HCV diagnosis did not appear to influence the development of peripheral neuropathy in this group. This finding contrasts with prior studies suggesting that prolonged infection may elevate neuropathy risk [19]. The relatively brief average disease duration (10.2 ± 4.1 months) in the current study might account for this discrepancy. Additionally, common coexisting conditions like hypertension and diabetes mellitus showed no significant relationship with neuropathy, likely due to the deliberate exclusion of individuals with pre-existing diabetes, reducing potential bias. However, literature does emphasize that such comorbidities can heighten neurological complications in HCV patients [20]. Since cryoglobulinemia is often linked with HCV-induced neuropathy even in patients lacking overt symptoms, its exclusion may have prevented a full assessment of underlying immunologic mechanisms [21].

CONCLUSIONS

It was concluded that gender is statistically significantly associated with the prevalence of peripheral neuropathy in anti-HCV-positive patients. Although a higher body mass index and extended duration of infection seemed to correspond with greater neuropathic involvement, these associations did not reach statistical significance within the scope of this study.

Authors Contribution

Conceptualization: SHS
Methodology: SHS, MAL[1], AHB, MAL[2]
Formal analysis: AHB
Writing review and editing: MAL[1], AHB
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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IMNCI Classification of Neonatal Jaundice and Its Relation to Cause of Jaundice at Neonatology Unit, CMC-SMBBMU Larkana

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ABSTRACT

Neonatal jaundice significantly impacts neonates' health and mortality, leading to frequent hospitalizations. The IMNCI classification improves early diagnosis, treatment, and outcomes. **Objective:** To classify jaundice based on IMNCI classification and evaluate its etiology across different severity levels. **Methods:** A cross-sectional study was conducted in the Neonatology unit at CMC-SMBBMU Larkana from July 2022 to January 2024, involving 147 neonates aged 0 to 28 days with jaundice, using a non-probability, consecutive sampling technique. **Results:** The study examined 147 neonates, with 81 (55.1%) males and 66 (44.9%) females. Most had a birth weight between 2000g to 2499g, with 36.1%, while only 14(9.5%) weighed 3500g or more. In gestational age 93(63.26) % were born at term, 46(31.29%) preterm, and 8(5.44%) post term. Delivery methods varied, with 81(55.1%) vaginally, 49(33.33%) C-section, and 17(11.56%) instrumented. The IMNCI classification revealed that 78.91% of neonates had jaundice, while 21.09% had severe jaundice, highlighting that gender (p=0.03), residence (p=0.04), aetiology (p=0.001), gestational age (p=0.04), and birth weight (p=0.01) all significantly influence the severity of jaundice and highly significant association in post-term neonates and those with lower birth weights are at a higher risk of severe jaundice. Data was input and examined using the SPSS version 26.0 software. **Conclusions:** Neonatal jaundice severity is influenced by gestational age, birth weight, and delivery mode, with post-term and low-birth-weight neonates at higher risk. Early identification and targeted interventions are crucial, and improving maternal education and healthcare accessibility, especially in rural areas, can reduce jaundice incidence and severity.

INTRODUCTION

Jaundice refers to the yellowish discoloration of the skin, sclerae, and mucous membranes caused by the accumulation of bilirubin in the tissues[1, 2]. Hyperbilirubinemia can be either safe or dangerous, depending on the cause and elevation. Some jaundice causes are hazardous regardless of bilirubin level, but reaching a certain level becomes a concern [3]. The bilirubin levels rise to the 95% percentile in 8 to 11% of infants [4]. Only 2% of term neonates experience severe hyperbilirubinemia (total serum bilirubin > 20 mg/dl), but because it can advance to kernicterus and cause long-term neurodevelopmental problems, all neonates must be thoroughly evaluated for hyperbilirubinemia [5]. Early indications of kernicterus include lethargy, inability to feed,

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loss of moro reflexes, which is frequently followed by severe weakness, worsening in deep tendon reflexes, respiratory distress, occasional opisthotonos, a bulging fontanelle, a loud cry, and aberrant facial and extremity movements. [5]. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. Infants with the aforementioned neurological abnormalities often pass very young, and those who survive face a higher risk of suffering severe brain impairment [3]. Neonatal jaundice, affecting over a million newborns annually, increases hospitalization, disability, and death rates, particularly in low and middle-income countries, due to inadequate detection and treatment [4, 6]. Globally, Jaundice is prevalent in newborn babies, affecting 60% of full term and 80% of premature babies in the first week, causing a significant concern in Pakistan with a 39.7 per 1000 live births prevalence It is predicted that 6 out of every 10 newborns suffer jaundice, with 8 out of 10 babies delivered prematurely before the 37th week of pregnancy. However, only around one out of every twenty newborns has a blood bilirubin level that requires therapy. Physiological jaundice was seen in 162 (40.5%) of all patients. The most common causes were ABO incompatibility (20%), Rh incompatibility (16.5%), sepsis (8%), idiopathic (5%), and 10% of instances respectfully [10]. A study carried out a regional analysis involving 114 infants diagnosed with hyperbilirubinemia and found that jaundice, fever, and feeding refusal were the most frequently noted clinical signs occurring in 75%, 25.4%, and 21.4% of the newborns, respectively [11]. A comprehensive overview of neonatal jaundice, covering its causes, clinical features, diagnosis, and management, in the StatPearls medical reference [12]. Long-term neurodevelopmental consequences for babies that survive include cerebral palsy, sensorineural hearing loss, intellectual impairments, and significant developmental delays [13, 14]. In this study, the objectives are to classify neonatal jaundice based on the IMNCI classification and to evaluate its etiology across different severity levels as defined by IMNCI. According to IMNCI Classification neonatal jaundice was classified according to the IMCI guidelines into two categories Jaundice and severe Jaundice. Whereby: patients were labeled as having jaundice of the presented with only skin or eyes yellow. However, we labeled the patients as having severe jaundice if they presented with palms and /or soles yellow, yellow skin in age less than 24 hours. Kernicterus is a prevalent cause of avoidable brain injury that may be easily diagnosed in IMNCI as severe jaundice.

The study's goal was to determine the degree and causation of neonates jaundice in accordance with the IMNCI categorization.

METHODS

A cross-sectional study was conducted in the Neonatology Unit of CMC-SMBBMU Larkana, Sindh, from July 2022 to January 2024. The study was approved by the Institutional Ethical Review Committee letter no. SMBBMU OFF/ERC 175, dated November 14, 2021 and informed parents/guardians of all participants. A study enrolled 147 neonates with jaundice in the neonatal ward, emergency, or outpatient department. The sample size was estimated using a formula, considering a 11% prevalence for hyperbilirubinemia with yellow skin discoloration and a margin of error of 5%. A non-probability, consecutive method was applied [4].

$SS = Z^2 x\, p\, x(1-p) \div e^2$

$$\text{Formula} = SS = \frac{Z^2 * (P) * (1-P)}{C^2}$$

$SS = 1.96^2 x(0.11)x(1-0.11) \div 0.005$

$SS = 150$

The study included neonates aged 0 to 28 days with jaundice, both male and female and birth weight over 2000 grams. This study involved neonates whose parents or guardians were willing to participate. The study excluded neonates who had undergone phototherapy or had congenital anomalies. A detailed history and physical examination were conducted, followed by routine laboratory investigations including CBC, TSH, Serum bilirubin, blood grouping, and abdomen ultrasonography. The study also included a detailed history of jaundice and associated symptoms. The mother's blood group was collected, and neonates underwent various tests including Rh factor, full blood picture, blood grouping, serum bilirubin, abdominal ultrasound, and chest X-ray. The etiology and appearance of newborn jaundice were documented. All neonates were treated according to hospital guidelines, including phototherapy, medication therapy, and exchange transfusions. The study used SPSS version 26.0 for statistical analysis, calculating qualitative data like age, weight, and gestational age. Qualitative characteristics like gender, delivery method, etiology, and presentation were analyzed for frequencies and percentages. Effect modifiers like age, gender, weight, and birth method were managed using stratification. A p-value of < 0.05 was considered significant.

RESULTS

In the study, the descriptive statistics of age 6 ± 4.7 days, with a range of 03 days to 27 days and provided data on neonatal weight and maternal age, as shown in Table 1.

Table 1: The Descriptive Statistics of different variables

Variables	Mean ± SD	Min	Max
Age (Days)	06 ± 4.7	3	27
Neonatal Age Weight: (Grams)	2630 ± 167.5	2000g	4250g
Maternal Age (Years)	24.3 ± 3.1	17	46

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The study involved 81 (55.1%) male and 66 (44.9%) female neonates, with their weights divided into four categories, the majority 53 neonates weighed between 2000g to 2499 g, 42(28.5%) neonates weighted between 2500g to 2999g, 38(25.9%) neonates calibrated between 3000g to 3499 g and remaining 14(9.5%) neonates were above 3500g. The study analysed maternal gestational age, revealing that 46(31.3%) of mothers had preterm deliveries, 93(63.26%) delivered term babies, and 8(5.44%) had post term babies and the proportion of mothers 47(31.97%) were aged between 21 years to 25 years, followed by mothers aged between 26 to 30 years 34 (23.13%). However, mother aged below 20 years were 12.24 % in proportion while mother aged above 41 years were only 09 (6.12%). Over half of mothers delivered their babies through normal vaginal deliveries 81(55.1%), while (33.33%) delivered with C-section 49(33.33%), and 17(11.56%) went through instrumented deliveries (11.66%). The majority of mothers delivered their babies through normal vaginal deliveries. Table 02

The study examined the education status of mothers, revealing that 38.78% had primary education, nearly two-fifths were uneducated, and only 8(5.44%) had intermediate/above education. The majority of mothers 86(56.5%) were from rural areas, while 61(41.5%) were from urban areas. The majority of mothers were from rural areas, while regarding to neonates based on the IMNCI classification of jaundice, revealing 116 (78.91%) neonates with jaundice and 31 (21.09%) neonates with severe jaundice (Table 2).

Table 2: Demographic Characteristics of Participants or Neonates (n=147)

Variables	Categories	Frequency (%)
Gender	Male	81 (55.10)
	Female	66 (44.90)
Weight of the Neonate	2000g to 2499 g	53 (36.10)
	2500g to 2999 g	42 (28.50)
	3000g to 3499 g	38 (25.90)
	3500g and above	14 (09.50)
Gestational Age in Weeks	Preterm (<37 weeks)	46 (31.29)
	Term (37 to 42 weeks)	93 (63.26)
	Post Term >42 Weeks	08 (05.44)
Age of the Mother (years)	Less than 20	18 (12.24)
	20 to 25	47 (31.97)
	26 to 30	34 (23.13)
	31 to 35	22 (14.97)
	36 to 40	17 (11.56)
	41 and above	09 (06.12)
Mode of Delivery	NVD	81 (55.10)
	C-Section	49 (33.33)
	Instrumented	17 (11.56)
Education Level	No Education	61 (41.50)
	Primary	57 (38.78)
	Secondary	21 (14.29)
	Intermediate above	08 (05.44)
Residence of mother	Rural	86 (58.50)
	Urban	61 (41.50)
IMNCI Classification	Jaundice	116 (78.91)
	Severe Jaundice	31 (21.09)

The IMNCI classification showed 51 (43.97%) cases of physiological jaundice, 36 (31.03%) cases of idiopathic jaundice, 14 (12.07) cases of ABO incompatibility, 6.03% of Rh incompatibility, 4.31% of cephalhematoma, and 2.59% of G-6-P-D Deficiency (Figure 1).

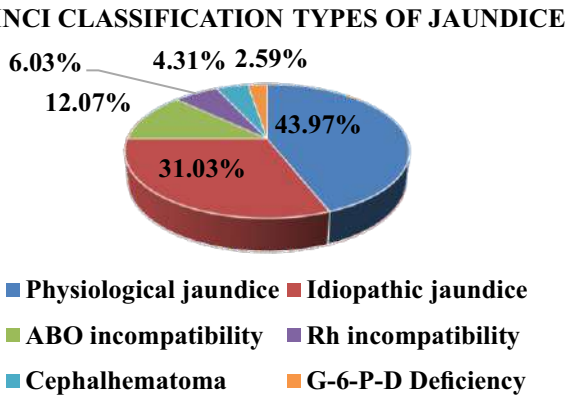

Figure 1: IMNCI Classification Types of Jaundice

This study also recorded the presentation of the neonatal jaundice, the neonates presented with variety of presenting complaints. 64.6% presented with yellow discoloration, 28.57% presented with fever, 19.73% with refusal to feed, 6.12% with fits, 11.56% with no cry after birth, 9.52% with vomiting, 10.88%, 7.48%, 15.65%, and 23.13 % with abdominal distension, not passing stool/urine, bluish hands and lips, and loose motions respectively (Figure 2).

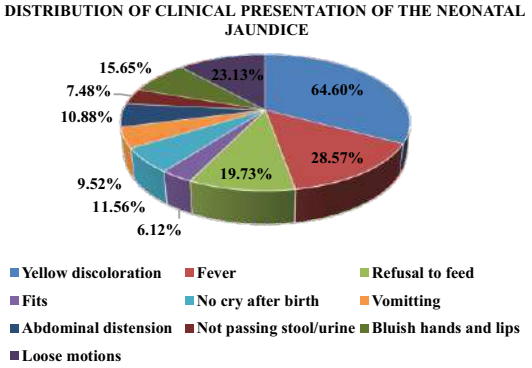

Figure 2: Distribution of Clinical Presentation of the Neonatal Jaundice

In the present study the association between gender of the neonate and severity of the neonate was evaluated. It was observed that the gender of the neonate was significantly associated with the jaundice with p-value 0.03. The association between gestational age of the neonate and severity of jaundice the neonate was evaluated. It was

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observed that the residence of the neonate was significantly associated with the jaundice with p-value 0.04. In this study, the association of etiology of jaundice with the IMNCI classification of the jaundice was determined. It was observed that the severity of jaundice was significantly associated with the etiology of the jaundice with p-Value 0.001. The present study evaluated the association between gestational age and severity of the jaundice. It was observed that the gestational age was significantly associated with the severity of jaundice with p-value 0.04. In this study, the association of the Birth weight of the neonate with the severity of jaundice was determined; it was observed that the neonatal birth weight was significantly associated with the severity of jaundice p-value 0.01. This cross-sectional study examined 386 neonates and found significant associations between maternal age, delivery mode, low birth weight, and IMNCI-based classification of jaundice.

Table 3: Distribution of Neonates According to the Imnci Classification Association of Severity of Jaundice with Different Variables(n=116)

Variables	Categories	Severity of Jaundice		
		Jaundice Frequency (%)	Severe Jaundice Frequency (%)	p-value
Gender	Male	67 (82.71)	14 (17.28)	0.03*
	Female	49 (74.24)	17 (25.75)	
Residence	Rural	76 (88.37)	10 (11.62)	0.04*
	Urban	40 (65.57)	21 (34.42)	
Etiology of Jaundice	Idiopathic	36 (31.03)	05 (16.12)	0.001*
	Physiological Jaundice	51 (43.96)	12 (38.70)	
	ABO Incompatibility	14 (12.06)	07 (22.58)	
	Rh Incompatibility	07 (06.03)	04 (12.90)	
	Cephalhematoma	05 (4.310)	02 (06.45)	
	G-6-P-D Deficiency	03 (02.58)	01 (03.22)	
Gestational Age	Preterm (<37 weeks)	32 (69.56)	14 (30.43)	0.04*
	Term (37 to 42 weeks)	76 (81.72)	17 (18.27)	
	Post term (>42 Weeks)	01 (12.50)	07 (87.50)	
Weight of neonate	2000g to 2499 g	36 (67.92)	17 (32.07)	0.01*
	2500g to 2999 g	34 (80.95)	08 (19.04)	
	3000g to 3499 g	34 (89.47)	04 (10.52)	
	3500g and above	12 (85.71)	02 (14.28)	

Indicates the statistical significance with p-value ≤0.05

DISCUSSION

Neonatal jaundice is a serious and widespread illness that affects 50-60% of full-term newborn and over 80% of preterm infants. In many parts of the world, NNJ has a major impact on infant morbidity and mortality. NNJ can result in several serious consequences, including permanent brain damage, and in some extreme situations, it can even result in death [15]. The present study enrolled the neonates who presented with jaundice at the Neonatology Unit-1, CMC-SMBBMU Larkana. A similar hospital-based retrospective descriptive study was conducted from January 2016 to December 2020 at the Neonatology Unit of the Regional Hospital Bamenda, in the North West Region of Cameroon. The study enrolled neonates of 0 to 28 days, admitted for neonatal jaundice [16]. In the present study, it was observed that there were 81 (55.1%) male and 66 (44.9%) female neonates in the study, which is reasonably different from the figures reported by Israel-Aina and Omoigberale, in their study where males were predominant with a sex ratio of 2.35 [16]. A nearly similar gender ratio was reported in another study conducted at the University of Benin Teaching Hospital, Benin City that reported 42.8% females and 57.2% males [17]. Males were marginally higher in proportion to the study conducted by Lake EA *et al.*, who reported 60.8% males and 39.2% females [18]. The minimum age recorded in the study was 03 days, the age ranged from 03 days to 27 days. Comparatively, Israel-Aina and Omoigberale, reported that most (52.6%) of the study subjects were aged between 1-5 days [16]. In the present study, the mean age of the neonates was 6 ± 4.7 days, however, Omekwe DE *et al.*, reported a 2.47 ± 2.48 mean age in their study [17]. On the other hand, Lake EA *et al.*, reported that the majority (41.2%) of the neonates were aged between 1 to 2 days in their study [18]. Diala *et al.*, (2023) conducted a systematic review and meta-analysis to estimate the global prevalence of severe neonatal jaundice among hospital admissions, highlighting significant regional disparities and burden [19]. In the present study, the neonatal weight ranged from 2000g to 4250g with mean and SD 2630 ± 167.5, however, Omekwe DE *et al.*, reported that the mean neonatal birth weight was 2,980 ± 700g [17]. In the present study, we observed that most of the mothers 47 (31.97%) were aged between 21 years to 25 years, followed by mothers aged between 26 to 30 years 34 (23.13%). However, mothers aged below 20 years were 12.24 % in proportion while mothers aged above 41 years were only 09 (6.12%). Similar findings were reported by Israel-Aina and Omoigberale, where the majority of the mothers (51.0%) were aged between 20 to 30 years [16].In this study, the maternal age ranged from 17 years to 46 years, and with a mean and standard deviation of 24.3 ± 3.1, relatively older mothers were part of the study where Omekwe DE *et al.*, reported that the mean maternal age of mothers was 30.44 ± 5.63 years [17]. In this study, there were more than half of the mothers delivered their babies through normal vaginal deliveries accounting for 81(55.1%), one-third of the mothers (33.33%) delivered babies with C- Section, and 17 (11.56%) mothers went through instrumented deliveries. Compared to these findings most of the mothers. In this

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study, vaginal delivery was commonest with 55.1%, however, according to the findings of Israel-Aina and Omoigberale, vaginal delivery was the most frequent mode of delivery in 90% of women [16]. In the present study, More than half of the mothers had a primary level of education, nearly one-fifth were uneducated, and only 13 (8.84%) mothers had an intermediate/above level of education. On the other hand, a similar study reported that most 135(53.8%) of mothers had a secondary level of education, and 60.8% of mothers had a secondary level of education [16, 18]. In this study, the neonates were classified according to the IMNCI classification of jaundice, we observed that there were 116 (78.91%) neonates with some jaundice and 31 (21.09%) neonates with severe jaundice. Comparatively, a study conducted at the neonatology unit of the Regional Hospital Bamenda, in the North West Region of Cameroon reported that the hospital incidence of neonatal jaundice was 19.7% [16]. In this study, there were 51 (43.97%) cases of physiological jaundice, followed by 36 (31.03%) cases of idiopathic jaundice, 14 (12.07) cases of ABO incompatibility, 7 (6.03%) cases of Rh incompatibility, 5 (4.31%) cases of cephalhematoma and 3 (2.59%) cases of G-6-P-D Deficiency.While the main etiologies reported by Israel-Aina and Omoigberale, were infection (70.9%), physiologic (14.3%) and ABO incompatibility (10%) [16]. Likewise this study, ABO incompatibility was reportedly 7.6% in the study conducted by Omekwe DE *et al* [17]. ABO incompatibility occurs in 15-20% of pregnancies and hemolytic disease of newborn develops in 10% of these instants [20].This study also recorded the presentation of neonatal jaundice, the neonates presented with a variety of presenting complaints. 64.6% presented with yellow discoloration, 28.57% presented with fever, 19.73% with refusal to feed, 6.12% with fits, 11.56% with no cry after birth, 9.52% with vomiting, 10.88%, 7.48%, 15.65%, and 23.13 % with abdominal distension, not passing stool./urine, bluish hands and lips, and loose motions respectively. However, in the findings of Israel-Aina and Omoigberale, fever was the most frequent (64.5%) among all the symptoms [16]. An Ethiopian study findings revealed that maternal age over 35 years, residing in urban areas, male gender, prematurity, and ABO incompatibility were significant determinants of neonatal jaundice [21]. The study found that the aetiology of jaundice was significantly associated with its severity, with gestational age, neonatal birth weight, and gender also having significant associations. The prevalence of newborn jaundice among infants was significant, with factors such as labor duration, delivery time, neonate sex, infection, maternal blood group, and blood type incompatibility being significantly linked [14].

CONCLUSIONS

Neonatal jaundice is a common disorder affecting neonates, with neonatal infections being the most common cause. Early identification and management of this condition is crucial to prevent severe neurological complications or even death. Pregnant and postpartum women should be educated on early signs of neonatal infections and jaundice, enabling early diagnosis and management to prevent fatal complications.

Authors Contribution

Conceptualization: BB
Methodology: DB
Formal analysis: VK
Writing, review and editing: M, FSJ, LN
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Efficacy of Oral Zinc Sulphate in Patients of Acne Vulgaris

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ABSTRACT

Acne is a chronic condition that affects pilosebaceous units, which manifest as either inflammatory or non-inflammatory lesions. **Objective:** To determine the efficacy of oral zinc sulphate in patients with acne vulgaris. **Methods:** An observational study was held at the OPD Department of Dermatology, Jinnah Hospital-Lahore, Pakistan, which enrolled 93 patients.The Global Acne Grading System was used to evaluate acne severity. These patients were given oral zinc sulphate 220mg twice a day for 3 months. Efficacy of treatment was labelled if there was ≥50% reduction in the baseline GAGS score at the end of 3 months of treatment.All the data were processed by SPSS version 26.0.Frequency and percentages were used for categorical parameters.The chi-square test was applied, in which a p-value<0.05 was considered significant. **Results:** It involved cheeks and nose in 26 (28.0%) patients, followed by forehead and chin in 23 (24.7%) patients. Efficacy of treatment was observed in 53 (57.0%) patients. An insignificant difference in the frequency of efficacy across various subgroups was observed. The percent reduction in mean GAGS score from baseline ranged from 25.0% to 75.0%, with a mean of 51.2 ± 11.9%, with a significant p-value of 0.001*.There was a statistically insignificant difference in the frequency of efficacy across various subgroups based on patients' age, gender and severity (p-value=0.870) of disease and baseline GAGS score (p-value=0.993). **Conclusions:** It was concluded that almost 57% of patients with mild to moderate acne showed improvement in their disease progression with oral zinc sulphate treatment. It was cost-effective with easy availability.

INTRODUCTION

A frequent medical condition that causes skin irritation and leads to social and psychological misery is acne vulgaris (AV). Its patho-physiology includes colonization of sebaceous glands with Cutibacterium Acne and excessive sebum production as revealed by the literature review [1, 2]. Sebaceous glands are activated by low Vitamin-D levels and testosterone production, as previously documented [1]. Numerous earlier investigations have shown that these elements offer a lipid-rich, anaerobic environment that is conducive to the growth of Cutibacterium Acne [3, 4]. Thus, sebaceous follicles grow into pimples due to a favourable environment that primarily affects the victims' face, chest and back [5]. This condition affects both sexes and arises following the pubertal spurt, when sebum production increases as a result of altered serum levels of sexual hormones [6]. The primary cause of this illness is the growth of Propionibacterium acnes, which causes local inflammation and the development of pustules. Erythema, post-inflammatory hyperpigmentation (PIH) and scarring are among the known side effects that can occur [7, 8]. The aforementioned consequences make victims' lives difficult and gloomy, therefore, they turn to doctors and other

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health care professionals for guidance and treatment. Although it can be mild, moderate, or severe, the literature review reported that 15-20% of adults worldwide will experience moderate acne at some point in their lives [9, 10]. Among various treatment options, zinc has shown promising results in patients with acne vulgaris. Zinc is easily available, and its use is associated with few side effects. Hence, it can be used as an alternative treatment option. Zinc promotes natural killer cells and complement activation [11-13]. Acne is a global health issue with the highest prevalence at puberty, affecting both genders, especially female. Acne of any grade affects its victim psychologically, thus, the rationale of the present study was to address the efficacy of oral zinc sulphate in patients of mild to moderate acne vulgaris. Due to a lack of local data regarding acne treatment with oral zinc in our culture, the results of the present study will add literature and knowledge regarding this health issue. Most previous international studies covered the role of retinoic acid in acne, but lacked the role of oral zinc sulphate in patients with mild to moderate acne.

This study aims to determine the efficacy of oral zinc sulphate in patients with acne vulgaris.

METHODS

An observational study was conducted at the Outpatient Department (OPD) of the Dermatology Department, Jinnah Hospital-Lahore, Pakistan, that enrolled 93 patients through randomized sampling technique by keeping a 95% confidence level, a 10.0% margin of error, and taking the expected frequency of efficacy, i.e. 59.5% [10]. After taking the ethical approval, the study duration was September 2020 to December 2020 (CPSP/REU/DER-2017-005-860). After informed consent, history was taken, and a physical examination was done. Severity of acne was calculated by the Global Acne Grading System (GAGS) score. Digital photographs were taken before the start of treatment. Patients were given oral zinc sulphate 220 mg twice a day for three months. A monthly follow-up was done to assess the response to treatment. Scoring was done at the end of three months and entered in the proforma. Males and unmarried females between 18-30 years having diagnosed acne (mild to moderate) were included. Individuals suffering from any critical illness or taken vitamin D supplements before the start of treatment were ruled out. All the data were processed by SPSS version 26.0. Mean ± SD was used for quantitative variables, while categorical variables (gender and site of involvement, and efficacy) were described as frequencies and percentages. Post-stratification Chi square test for categorical parameters was used to see the statistical significance in efficacy of oral zinc pre and post treatment, depicted by p-value≤0.05, taken as significant. A paired t-test was used to see the difference in GAGs score both pre- and post-treatment.

RESULTS

Distribution among the enrolled 93 patients for gender, age, severity of disease, site of acne AND efficacy was presented. Mean ± SD for age was 21.5 ± 2.7 years (Table 1).

Table 1: Baseline Information Regarding Enrolled Patients (n=93)

Variables	Frequency (%)
Genders	
Males	42 (45.2%)
Females	51 (54.8%)
Age Groups (Years)	
18-24	79 (84.1%)
25-30	15 (15.9%)
Severity of Disease	
Mild	59 (64.4%)
Moderate	34 (36.6%)
Site of Acne	
Forehead	23 (24.7%)
Cheeks and Nose	26 (28%)
Chin	23 (24.7%)
Chest and Upper Back	21 (22.6%)
Efficacy	
Yes	53 (57%)
No	40 (43%)

The GAGS score ranged from 4 to 29 at baseline, with a mean of 16.0 ± 7.1. It decreased significantly after oral zinc sulphate treatment. The percent reduction in mean GAGS score from baseline ranged from 25.0% to 75.0% with a mean of 7.8 ± 3.9% (Table 2).

Table 2: Description of GAGS Score Among Acne Patients at Various Time Stamps

Time Stamp	GAG Score (Mean ± SD)	p-value
At Baseline	16.0 ± 7.1	0.001*
After Treatment	7.8 ± 3.9	
Change	8.2 ± 4.2	

*Statistically Significant

There was no statistically significant difference in the frequency of efficacy across various subgroups based on patient's age, gender and severity (p-value=0.870) of disease and baseline GAGS score (p-value=0.993). This insignificance may be due to small sample size or other confounding factors like duration of disease and severity or compliance with treatment (Table 3).

Table 3: Efficacy of Oral Zinc Sulphate in Treatment of Acne Patients (n=93)

Subgroups		Frequency	Efficacy n (%)	p-value
Age (Years)	18-24	79	45 (57.0%)	0.990
	25-30	14	8 (57.1%)	
Gender	Male	42	24 (57.1%)	0.978
	Female	51	29 (56.9%)	

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Severity of Disease	Mild	59	34 (57.6%)	0.870
	Moderate	34	19 (55.9%)	
Baseline GAGS Score	4-12	33	19 (57.6%)	0.993
	13-20	35	20 (57.1%)	
	21-29	25	14 (56.0%)	

DISCUSSION

Zinc supplements are essential for enhancing the immune system of every individual, as reported previously. Sebocytes and keratinocytes grow as a result, thus resulting in their proliferation and differentiation [14]. It works by binding to its receptors while producing its antioxidant and anti-comedogenic actions. In the current study, there were 93 enrolled patients, while females were in the majority. Although there were fewer patients (n=68) in one earlier study [14], the majority of them were female. Present findings were consistent with another earlier study that found a similar female preponderance among acne patients who presented at Ziauddin Medical University Hospital in Karachi, with a male to female ratio of 1:1.2 [15]. Therefore, our study's enrollment was consistent with the earlier study. In the present study, the mean age of the acne patients was 21.5 ± 2.7 years. One researcher has reported that the mean age of patients presenting with acne at Jinnah Postgraduate Medical Centre, Karachi, was 21 ± 3.9 years [16]. A similar mean age of 22.4 ± 5.2 years has been reported among Bangladeshi patients with acne [17]. Thus mean age of participants in the current study was in line with many previous studies. Present results showed that 59 (63.4%) patients had mild acne while 34 (36.6%) had moderate acne. One previous study showed a similar frequency of mild and moderate acne to be 77.0% and 23.0%, respectively [18]. One more study reported a similar distribution of mild (60.0%) and moderate (40.0%) acne in Indian patients [19]. The efficacy of treatment with oral zinc sulphate in our study was seen in 57.0% of patients. Insignificant difference in the frequency of efficacy across various subgroups based on different parameters and baseline GAGs score (p-value=0.993). The present observation was in line with the previously published research, which reported that oral zinc sulphate treatment resulted in ≥50% improvement in baseline GAGS score among 59.5% of their acne patients [20]. In the present study, mild to moderate acne improved in response to oral zinc treatment and showed high efficacy when applied to mild acne.

CONCLUSIONS

It was concluded that almost 57% of patients with mild to moderate acne showed improvement in their disease progression with oral zinc sulphate treatment. It was cost-effective with easy availability. Thus, it can be used as a treatment option for mild to moderate acne, although more studies with larger sample sizes and a side effect profile are recommended.

Authors Contribution

Conceptualization: MJ
Methodology: MJ, RM, MQ, TR
Formal analysis: RM, WN
Writing review and editing: AA
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of the Outcomes of On-Lay and Sub-Lay Mesh Repair in Patients with Ventral Abdominal Wall Hernias

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ABSTRACT

Hernias of the ventral abdominal wall are a frequent surgical problem that has to be repaired well to reduce complications and recurrence. **Objective:** To determine which method yields better clinical outcomes. **Methods:** In two groups of 40 individuals, 80 patients with ventral abdominal wall hernias had the results of Onlay and Sublay mesh repair compared. This prospective study, conducted at Prime Teaching Hospital/Kuwait Teaching Hospital (Peshawar Medical College) from June to December 2024. Data analysis was conducted using SPSS version 23.0 with a significance level of $p < 0.05$. **Results:** The mean age of patients was 43.13 ± 11.76 years, among them 62.5% were male. Among this 64% had midline ventral hernias. Patients undergoing Sublay mesh repair experienced significantly lower wound infections (5% vs. 15%, $p < 0.05$) and less seroma formation (4.61% vs. 20%, $p < 0.05$) as compared with the Onlay group, notably, the study also found that the duration of hospital stay was significantly longer for the Onlay group compared to the Sublay group ($p < 0.05$). The sublay technique showed zero recurrence cases (0%), while the On-lay technique had six cases (15%) with statistically significant ($p < 0.05$). **Conclusions:** Sublay mesh repair demonstrates distinguishing clinical outcomes over Onlay mesh repair, with lower infection rates, less seroma formation, and shorter hospital stays. The findings suggest that Sublay mesh repair should be preferred for ventral abdominal wall hernias to minimize patient morbidity and improve recovery.

INTRODUCTION

Hernia is a considerable most common surgical conditions, potentially leading to impairment, hospitalization, and the need for surgery [1]. An incisional hernia in the ventral abdominal wall is a defect in the abdominal wall's musculoskeletal layers along the surgical scar [2]. Abdominal content protrusion is a result of weakening muscles along prior surgical scars, which causes incisional hernias, a kind of ventral abdominal wall hernia. These hernias may cause strangling, infection, intestinal blockage, and persistent discomfort, all of which call for prompt surgical surgery. Although mesh-based treatments have advanced, the recurrence rate following surgical repair is still a significant issue, ranging from 10% to 30% [2, 3]. This covers epigastric, para-umbilical, inguinal, and umbilical hernias. Incisional hernias are another forms of ventral hernia that affects 15-20% of patients undergoing laparotomy [3]. Despite the increasing incidence of surgical repair, surgeons continue striving to reach "perfect results," and the rate of surgical failure remains significant 10 to 30 percent [4]. A growing amount of controversy surrounds the optimal incisional hernia repair technique [5]. In surgical clinics, ventral hernias are diagnosed most frequently. According to a Danish study, 0.53% of prevalence of an umbilical hernia within five years. Incisional hernias can occur up to 11% of the time following major abdominal surgery [6]. According to their site infection specifically on these abnormalities of the abdominal wall might be classified as congenital,

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acquired, or spontaneous. As a result, umbilical hernias happen at the umbilicus, whereas epigastric hernias happen from the xiphoid process to the umbilicus. The least common spontaneous hernias that occur below the navel in the midline are paraumbilical and hypogastric hernias [7]. One of the most major problems in mesh repair is mesh placement. According to reports, certain procedures are linked to notably elevated incidence of certain consequences, including wound infection, fistula, and recurrence [8]. After incisional ventral hernias are repaired, there is still a significant chance of infection and recurrence, even with advancements in surgical technique and prosthetic technologies [ ]. Although many methods for hernioplasty and repair have been identified, tension-free mesh insertion is currently a common procedure with two types of mesh plasty: Onlay and Sublay [9]. The surgical results are greatly impacted by the decision between these two methods. Seroma development, recurrence, and wound infection have all been linked to Onlay mesh repair, in which the mesh is positioned above the rectus sheath. By placing the mesh in the preperitoneal area, Sublay mesh repair, on the other hand, offers superior reinforcement and reduces postoperative problems. The best method for repairing a ventral hernia must be determined by comparing various options [10]. The incidence of mesh repair-related wound complications and post-operative wound infections is intended to further investigate the most effective way to manage these hernias [11]. Whereas Onlay mesh repair places the replacement mesh between the anterior rectus sheath and the abdominal wall's subcutaneous tissues, Sublay mesh repair places it in the preperitoneal plane created between the rectus muscle and the posterior rectus sheath [12]. According to a number of studies, the mesh's placement has a significant impact on the results of surgery. Because Onlay mesh is positioned closer to subcutaneous tissues, research suggests that it is linked to an increased risk of wound infection, seroma development, and recurrence. On the other hand, Sublay mesh repair provides superior strengthening, a decreased risk of infection, and a lower recurrence rate since the mesh is placed in the preperitoneal area. Comparative research has demonstrated that the Sublay approach improves long-term hernia repair success rates and reduces complications [13]. Although, one of the benefits of the latter method is that, because the mesh is located deep within the preperitoneal plane, it prevents the spread of infection from subcutaneous tissues [12]. In terms of recurrences, databases and reviews indicate that open mesh repair is superior to suture repair. Whereas there is insufficient evidence to determine which mesh type or position (on- or Sublay) should be used [14]. There is also differences over which technique is better after adhering closely to the principles of incisional hernia repair [15]. The use of prosthetic mesh to treat incisional hernias has increased recently due to the high recurrence rates linked to primary suture repair. By 1999, 65.5% of incisional hernia surgeries included synthetic mesh, up from 34.2% in 1987. Mesh is now the accepted standard of treatment for incisional hernia repair, according to the American Hernia Society [16]. The concept that acute fascial separation early in the postoperative phase causes delayed clinical development of abdominal wall incisional hernias is currently supported by the bulk of studies [17]. In current study, people who had incisional hernia repair in the local setup including Onlay and Sublay were assessed the results of two common mesh deployment methods [15].

This study aimed to compare the outcomes of Onlay and Sublay mesh repair techniques to determine which approach results for better clinical outcomes.

METHODS

Between June and December of 2024, this prospective study was carried out in the general surgery department of Prime Teaching Hospital/Kuwait Teaching Hospital (Peshawar Medical College). A computer-generated random sequence was used to allocate patients to either the Onlay or Sublay groups in a straightforward randomization procedure. This reduced selection bias by ensuring an impartial patient distribution between the two groups. Prime Foundation's ethical committee granted this permission, which has the IRB permission Number Prime/IRB/2024-1094. Before being included in the study, all patients gave their written informed consent. A total of 80 patients were included in this study confirmed diagnosed with ventral abdominal wall hernias. All eligible patients who met the inclusion criteria during the research period were enrolled using a sequential sampling approach. By ensuring that the sample is representative of the normal patient population having ventral hernia surgery, this approach reduces selection bias and increases the repeatability of the study. The sample size calculation was based on existing literature, aiming to detect a 20% difference in postoperative complications between Onlay and Sublay mesh repair techniques. Assuming a 95% confidence interval ($\alpha = 0.05$) and 80% power, a minimum of 20 patients per group, totaling 40 patients, was deemed sufficient.

The sample size was calculated using the formula:

$n=(Z\alpha/2+Z\beta)2\times[p1(1-p1)+p2(1-p2)]/(p1-p2)2$

Where:

$Z_{\alpha/2}$=1.96Z_{\α/2} = 1.96Zα/2=1.96 for a 95% confidence interval,

Z^{β}=0.84Z_{\β}=0.84Zβ=0.84 for 80% statistical power,

p_1p_1p_1(expected complication rate in Onlay repair)=30%,

p_2p_2p_2(expected complication rate in Sublay repair)=10%.

This computation indicated that a minimum of 40 participants each group, or 80 patients overall, were

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needed. In order to ensure that the sample size was sufficient to identify clinically significant changes, the effect size was calculated using prior research on mesh repair results. Given the study's single-center context, the sample size was appropriate. Patients in Group 1 had Onlay mesh repair, which involved placing the prosthetic mesh between the subcutaneous tissues and the anterior rectus sheath. Group 2 included patients with Sublay mesh repair, with the mesh placed in the preperitoneal plane between the rectus muscle and the posterior rectus sheath. Baseline parameters, such as age, gender, comorbidities (including diabetes and hypertension), BMI, smoking status, and hernia size, were evaluated prior to surgery in order to guarantee comparability between the two groups. In terms of these factors, there were no discernible variations between the groups, guaranteeing that results were unaffected by pre-existing discrepancies. In addition to recording comorbidities based on patient history and medical records, the size of the hernia was evaluated preoperatively using clinical examination and ultrasound where required. Patients were included based on clinical assessment, and in cases of diagnostic uncertainty, CT scans were performed to confirm the diagnosis. All patients underwent preoperative anesthetic evaluation to assess their surgical fitness. In all cases, synthetic, lightweight, non-absorbable mesh was used. Perioperative prophylactic antibiotics, including intravenous Tazocin and Metronidazole, were administered to all patients. Patients were monitored postoperatively for wound healing, fluid accumulation in drains, infection, and hospital stay duration. During follow-up visits, clinical examination was used to evaluate postoperative sequelae, including seroma development and wound infection. After surgery, the patients were assessed on 3-7 days, as well as 3 and 6 months later. Localized redness, swelling, purulent discharge, and fever were diagnostic criteria for infection, whereas palpable fluid collections at the surgical site or, if required, ultrasound results were used to identify seroma development. Any indications of recurrence were verified by physical examination and, if necessary, imaging tests such CT or ultrasound scans. On a designated datasheet, pertinent postoperative and clinical data were gathered. Statistical analysis was performed using SPSS software (version 23.0). The chi-square test was used to examine categorical variables, including wound infection, seroma development, and recurrence. The independent t-test was used for regularly distributed data for continuous variables, such as hospital stay and operating time, while the Mann-Whitney U test was utilized for non-normally distributed data. Before choosing the proper statistical test, the Shapiro-Wilk test was used to determine whether continuous variables were normal. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

The current study comprised of a total of 80 patients with ventral abdominal wall hernias. The mean age of the participants was 43.13 ± 11.76 years, with a male predominance of 56.3% (n=45) and females comprising 43.8% (n=35). Among the patients, 64% had midline ventral hernias, while the remaining cases had a subcostal distribution. While assessing complications by gender, females exhibited a higher frequency of seroma formation (27.5% vs. 12.5%), wound infections (32.5% vs. 10%), and recurrence (27.5% vs. 7.5%), with all differences reaching statistical significance ($p < 0.05$). Mesh removal was also more frequent among female patients (17.5% vs. 5%, $p = 0.01$).

Table 1: Age and Gender Distribution of Study Participants with Statistical Significance

Age Group (Years)	Male Frequency (%)	Female Frequency (%)	Total Frequency (%)	p-value
20-30	11 (28.2)	7 (17.1)	18 (22.4)	<0.05
30-40	17 (43.6)	14 (34.1)	31(38.8)	>0.05
40-50	11 (28.2)	20 (48.8)	31 (38.8)	<0.05
Total	39 (100)	41 (100)	80 (100)	-

Spontaneous hernias were more common, accounting for 75% (n=60) of cases, while 25% (n=20) of patients presented with incisional hernias. Age-wise, the highest prevalence of hernias was observed in the 30–40 years (38.8%) and 40–50 years (38.8%) age groups. A significant gender-based difference was noted in the 20–30 years and 40–50 years age brackets ($p < 0.05$), with the latter showing a higher prevalence in females.

Table 2: Comparative Analysis of Postoperative Complications in Sublay and Onlay Surgical Techniques (n=80)

Complication	Sublay Frequency (%)	Onlay Frequency (%)	p-value
Seroma	2 (10)	10 (50)	<0.05
Infection	1 (5)	5 (25)	<0.05
Mesh Removal	0	1 (5)	>0.05
Recurrence	0	6 (30)	<0.05
Flap Necrosis	0	1 (5)	>0.05
Ileus	1 (5)	2 (10)	>0.05

The average operative time was 90 minutes for patients undergoing the Onlay technique, whereas those in the Sublay group had a significantly longer operative time ($p = 0.007$). The hospital stay was notably reduced in the Sublay group, with patients discharged on average three days earlier compared to the Onlay group ($p < 0.05$). The postoperative results revealed a statistically significant difference in complication rates between the two surgical methods. Higher incidence of wound infection (25% vs. 5%, $p < 0.05$), recurrence (30% vs. 0%, $p < 0.05$), and seroma development (50% vs. 10%, $p < 0.05$) were seen in patients in the Onlay group. The Sublay group showed better overall

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outcomes with fewer complications.Notably, mesh removal was required in 5% of Onlay patients, while no cases of mesh removal were reported in the Sublay group.

Table 3: Gender-Wise Distribution and Statistical Analysis of Postoperative Complications

Complication	Male Frequency (%)	Female Frequency (%)	p-Value
Seroma	5 (12.5)	11 (27.5)	<0.05
Infection	4 (10)	13 (32.5)	<0.05
Mesh Removal	2 (5)	7 (17.5)	0.01
Recurrence	3 (7.5)	11 (27.5)	<0.05
Necrosis	1 (2.5)	1 (2.5)	>0.05
Ileus	2 (5)	1 (2.5)	>0.05

DISCUSSION

This study compared the outcomes of Onlay and Sublay mesh repair techniques for the treatment of ventral abdominal wall hernias. The results demonstrate that Sublay mesh repair leads to significantly better postoperative outcomes than on lay mesh repair, this includes fewer cases of seroma formation, low chances of infections, reduced recurrence, and shorter hospital stays. Therefore, these findings support the growing preference for Sublay mesh placement in hernia repair, with existing literature that highlights its advantages. The lower incidence rate of postoperative complications in the Sublay group was one of the study's key findings. The Onlay group (50%) saw significantly more seroma formation than the Sublay group (10%) ($p < 0.05$). According to earlier research, putting the mesh in the preperitoneal plane reduces dead space and lowers the chance of seroma development Sevinc et al. Furthermore, wound infections were more common in the Onlay group (25%) than in the Sublay group (5%), highlighting the preventive function of Sublay implantation against problems associated to infections [18]. Another crucial factor in hernia repair is recurrence. Approximately 30% of patients who had Onlay mesh repair in this study reported recurrence, but none of the patients in the Sublay group did ($p < 0.05$). This finding is consistent with previous research indicating that Sublay mesh placement provides better reinforcement to the abdominal wall, reducing tension at the repair site and lowering recurrence rates (Ahmed and Mehboob). The anatomical positioning of the Sublay mesh likely contributes to its superior durability in hernia repair [19]. Longer for Sublay, $p = 0.007$, this benefit was exceeded benefited by a notably longer hospital stay. However, Patients who underwent Sublay repair were discharged approximately 3 days earlier than those in the Onlay group ($p < 0.05$). This statement supports previous findings that suggest Sublay repair is associated with faster recovery and shorter hospital stays with fewer complications [20]. Postoperative complications in gender-wise differences were also to be taken into consideration. Female patients had a higher frequency of seroma formation 27.5% vs. 12.5%, wound infections 32.5% vs. 10% and recurrence 27.5% vs. 7.5% as compared to male patients. While the exact reasons remain unidentified, its possible explanations include differences in soft tissue composition, hormonal differences the variations of wound healing and responses [15]. However, further research is needed to explore these gender-related differences in more depth. Chitrambalam et al., in (2019) conducted a randomized controlled trial comparing Onlay and Sublay mesh repair in 150 patients. The study found that, with a statistically significant p-value ($p = 0.001$), the Onlay group had a substantially greater rate of seroma development (20%) than the Sublay group (2.67%) [21]. Another important aspect of these findings was the gender-based variation in postoperative problems. Female patients had significantly greater rates of seroma development (27.5% vs. 12.5%), wound infections (32.5% vs. 10%), and recurrence (27.5% vs. 7.5%), all with p-value < 0.05. While the specific causes are unknown, variances in soft tissue composition, hormone variations, and unique wound healing responses may all play a role. There is a need of further follow up to address these gender inequalities and determine whether personalized surgical methods can enhance outcomes in female patients [22]. Whatever the study's benefits, it is important to take into account its limits. The findings' ability to be broadly applied may be limited by the small sample size. Furthermore, this study was observational therefore, longer periods follow up are important to assess the long-term duration of both repairing methods. Future research, particularly larger cohort studies and randomized controlled trials, can provide more evidence and help to refine surgical guidelines for ventral hernia repair. Based on these useful insights the study obtained some crucial results; several limits must be noted. A stratified analysis considering these variables is recommended in subsequent research. Based on these findings, several recommendations were proposed for clinical practice and future research. However, training programs for surgeons should emphasize proper techniques for Sublay placement to ensure consistency in outcomes. To validate these results, future studies should concentrate on bigger, multi-center randomized controlled trials. Furthermore, examining the influence of patient-specific factors, including obesity, diabetes, and history of previous hernia repairs, on surgical outcomes would enable a more personalized and tailored approach to hernia management, ultimately optimizing patient care. Finally, advancements in biomaterials and surgical techniques, including minimally invasive approaches, should be explored to further improve the efficacy and safety of hernia repair procedures.

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CONCLUSIONS

This study demonstrated that Sublay mesh repair offers superior clinical outcomes compared to Onlay mesh repair for ventral abdominal wall hernias. Sublay repair was associated with lower rates of infection, seroma, recurrence, and shorter hospital stays. These findings suggest that Sublay mesh placement is more effective in reducing surgical morbidity and enhancing patient recovery. However, further studies with larger sample sizes and longer follow-up are needed to confirm long-term benefits and assess potential complications such as chronic pain or mesh-related issues.

Authors Contribution

Conceptualization: AAT
Methodology: AAT, MF
Formal analysis: MS, NB, MF, MT
Writing, review and editing: AAT, MS, NB, MI, MF, MT
All authors have read and agreed to the published version of the manuscript

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Supine Percutaneous Nephrolithotomy (PNCL)-2 Years' Experience in a Tertiary Care Hospital

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ABSTRACT

Percutaneous Nephrolithotomy (PCNL) has basically substituted open surgery for managing large, complex renal stones. Supine PCNL provides multiple benefits compared to the prone position, yet its adoption in Pakistan remains limited. **Objective:** To evaluate the experience and outcomes of supine PCNL at a tertiary care hospital in Pakistan. **Methods:** This retrospective study included 113 patients (aged 3–74 years) who underwent PCNL at the Urology Unit of Baluchistan Institute of Nephro-Urology Quetta (BINUQ) between June 2021 and June 2023. Data on demographics, operative position (supine/prone), Extracorporeal Shock Wave Lithotripsy (ESWL) sessions, and postoperative hospital stay were retrieved from medical records. Descriptive statistics were analyzed using SPSS version 26. **Results:** Age of the patients was 32.68 ± 15.59 years. Among 113 patients, 63 (55.8%) were male, and 50 (44.2%) were female. Age distribution included 28 (24.8%) patients aged 3–20 years, 54 (47.8%) aged 21–40 years, 24 (21.2%) aged 41–60 years, and 7 (6.2%) aged 61–74 years. Right-sided PCNL was performed in 64 (56.6%) cases, while 49 (43.4%) involved the left kidney. A total of 82 (72.6%) patients experienced (Supine) PCNL, and 18 (15.9%) (Prone). The mean number of ESWL sessions was 0.24± 0.52, and the average postoperative hospital stay was 2.99 ± 1.85 days. **Conclusions:** Supine PCNL demonstrated favorable outcomes, including shorter hospital stays, effective stone removal, and reduced postoperative recovery time.This study supported the broader adoption of supine PCNL in clinical practice.

INTRODUCTION

Percutaneous Nephrolithotomy (PCNL), performed in the supine position, is widely used to largely replace open surgical removal of large renal complexes. Kidney stones represent a major urological challenge that has plagued humankind for centuries. Anyone with kidney stones requires intervention. At present, the primary treatment options for renal stones include Extracorporeal Shockwave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PCNL), Retrograde Intrarenal Surgery (RIRS), and open surgery. PCNL is typically advised for patients with staghorn calculi, kidney stones larger than 20 mm, or lower pole stones exceeding 15 mm [1, 2]. Initially, Percutaneous Nephrolithotomy (PCNL) was performed on patients in the supine position during renal excision due to concerns about spinal injury. Intravenous Pyelography (IVP) is a common imaging technique used during the early development of PCNL techniques for stone-containing disorders. At that time, modern imaging methods including ultrasonography or Computerized Tomography (CT) were not widely used. Consequently, surgeons performing early PCNL lacked a comprehensive understanding of the psychophysiological anatomy that is easily accessible to modern neurologists [3]. Consequently, surgeons performing early PCNL lacked a comprehensive understanding of the psychophysiological anatomy that is easily accessible to modern neurologists. As PCNL became more common, it became more clearly positional a horizontal position is not ideal for all patients, especially

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those who are severely obese. This obesity or breath detection problems added to the desire for ease of urinary access throughout retrograde and anterior series endoscopic procedures together led to a search for new sites for patients to undergo PCNL [4]. Major complications that initially led to primary PCNL in the prone position were actually less in the supine position. The incidence of retro-renal colon perforation was 1.9% versus 10% in prone PCNL compared with PCNL of a supine position, respectively [5]. In contrast to an earlier study proposed the hypothesis that there is a higher risk of spinal perforation in the supine position compared to the supine position. However, contemporary findings have contradicted this, contributing to a growing preference for supine PCNL. As a result, there has been a 20% increase in the use of supine PCNL since then [6]. This rise can be attributed to multiple factors, including enhanced surgical training, improved ergonomics, shorter operative times, lower complication rates, and better anesthetic control in the supine position. Several modifications in patient positioning have been proposed to reduce morbidity and complications. These include reverse lithotomy, spinal positioning, lateral decubitus, Valdivia-Galdakao, and Valdivia-Barts modifications [7]. When applied to supine PCNL, these modifications show promising results. For example, the Valdivia-Galdakao position allows simultaneous retrograde access, enhances anesthetic management, and has been associated with comparable or improved procedural success rates, reduced complication rates, and greater patient comfort compared to traditional prone approaches. Reverse lithotomy and lateral decubitus positions also facilitate better drainage and reduced surgical stress, contributing to a more favorable postoperative recovery experience [8]. While these newer positions are considered safer and more effective than traditional prone PCNL, the supine position has emerged as a viable alternative to the prone position [8, 9]. The idea that PCNL should be exclusively performed in the prone position has been widely dismissed, as many urologists worldwide now consider the supine position routine. Additionally, advancements in imaging techniques, such as real-time ultrasound and multi-slice CT scanning, have improved stone localization and access planning, while innovations in miniaturized and flexible surgical instruments have increased procedural safety and precision further encouraging the shift towards supine PCNL.

This study aimed to share the experience of supine PCNL over two years at a tertiary care hospital, highlighting its outcomes and providing recommendations for broader use to improve patient care.

METHODS

This retrospective study was conducted on 113 patients who underwent Percutaneous Nephrolithotomy (PCNL) in the Urology Department of Baluchistan Institute of Nephro-Urology Quetta (BINUQ) over a six-month period following IRB approval (MED EDU/BINUQ No.328/29). Data from June 2021 to June 2023 were included retrospectively. Patients aged 3-74 years of either gender who underwent PCNL for kidney stones were enrolled. Patients undergoing percutaneous surgery for other conditions, such as diversion nephrostomy, antegrade endopyelotomy, or mini-PCNL, were excluded. Preoperative assessment involved intravenous urography or non-contrast-enhanced spiral CT to determine stone location and radiolucency. Patients with positive urine cultures received appropriate antibiotics 48 hours preoperatively, followed by an additional seven days of antibiotics postoperatively. Most surgeries were performed under spinal anesthesia. Sample size was calculated using OpenEpi version 3.01 (Open-Source Epidemiologic Statistics for Public Health). Assuming an expected complication rate of 10% from previous literature, with a 95% confidence level and 5% margin of error, the required minimum sample size was 138. However, due to limitations of retrospective data availability and inclusion criteria, a total of 113 cases fulfilling the eligibility criteria were included in the study.This shortfall is acknowledged and addressed in the limitations section, and future prospective studies are recommended to ensure adequate power. The sample size consisted of 113 patients, selected using non-probability consecutive sampling.This approach ensured all eligible patients during the study period were included, minimizing selection delays. However, it may introduce selection bias, which is acknowledged as a methodological limitation. Inclusion criteria were patients aged 3–74 years undergoing PCNL for kidney stones, irrespective of gender, while exclusion criteria encompassed patients undergoing percutaneous procedures for non-stone-related conditions, those with contraindications to PCNL, and cases with incomplete medical records. Written informed consent was obtained from all participants. Data collected included demographic details (age, gender), surgical position (supine or prone), Extracorporeal Shock Wave Lithotripsy (ESWL) sessions, and postoperative discharge day. Statistical analysis was performed using SPSS version 26. Normality of quantitative variables was assessed using the Shapiro-Wilk test. Quantitative variables, such as age, postoperative discharge day, and ESWL sessions, were expressed as mean and standard deviation, while qualitative variables, including gender, surgical position, and laterality of PCNL, were described as frequencies and percentages. All statistical analyses were conducted with a 95% confidence interval and a 5% level of significance.

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RESULTS

The study included 113 patients, with a mean age of 32.68 ± 15.59 years. The majority were male (63, 55.8%), while females comprised 50 (44.2%). The largest proportion of patients (54, 47.8%) belonged to the 21–40 years age group, followed by 28 (24.8%) in the 3–20 years range, 24 (21.2%) in the 41–60 years range, and 7 (6.2%) in the 61–74 years range. The mean discharge postoperative day (D/C POD) was 2.99 ± 1.85, and the mean Extracorporeal Shock Wave Lithotripsy (ESWL) sessions were 0.24 ± 0.52 (Table-1).

Table 1: Baseline Details of selected patients (n=113)

Variables	Value Frequency (%)/ Mean ± SD
Age (Years)	32.68 ± 15.59
Gender	
Male	63 (55.8%)
Female	50 (44.2%)
Age Group (Years)	
3-20	28 (24.8%)
21-40	54 (47.8%)
41-60	24 (21.2%)
61-74	7 (6.2%)
Discharge Postoperative Day (D/C POD)	2.99 ± 1.85
ESWL Session	0.24 ± 0.52

Regarding the surgical position, 82 patients (72.6%) underwent supine PCNL, while 18 (15.9%) had the procedure in the prone position (Figure 1).

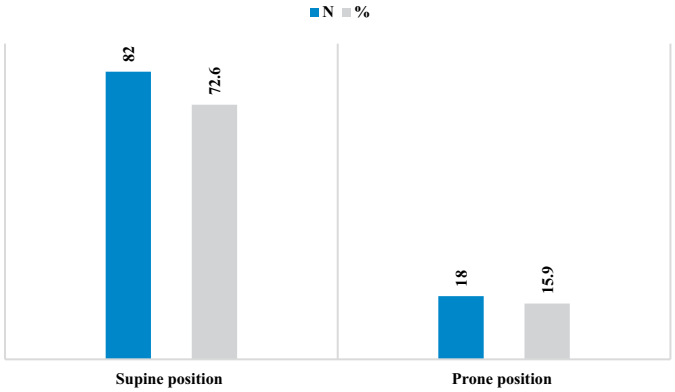

Figure 1: Supine/prone position (n=113) (Majority of patients underwent supine PNCL position as compared to prone PNCL position)

The laterality of the procedure revealed that right-side PCNL was performed in 64 patients (56.6%), compared to 49 (43.4%) who underwent left-side PCNL (Figure 2).

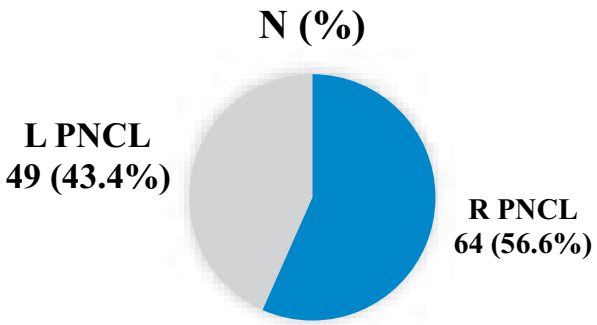

Figure 2: R/L PNCL (majority of patients underwent R-PNCL (56.6%) as compared to 43.4% L-PNCL)

DISCUSSION

The primary focus of the present study was to investigate the experience of PNCL in the supine position. There was a notable increase in outcomes compared to other sites. These included higher rates of stone removal, lower complications, shorter operative time, and a decreased postoperative hospital stay. These included higher rates of stone removal, lower complications, shorter operative time, and a decreased postoperative hospital stay. Therefore, the efficacy and safety of recumbent PCNL were confirmed. The supine position is greatly advantageous and includes benefits such as reduced operative time and fewer complications [10, 11]. Invasive procedures such as deflation or reintubation are more easily performed in the supine position compared to the prone position [12-14]. An earlier study reported that lying flat on the floor carries the risk of intestinal perforation. In the prone position, the uterus moves laterally due to abdominal compression from the operating table, providing a safety advantage, but this advantage is absent in the supine position. Even so, in this experience, any issues with cervical perforations. To mitigate intraoperative risks during supine PCNL utilized real-time fluoroscopic guidance throughout the procedure to confirm access and guide tract dilation. In some cases, ultrasonography was also used, particularly for anterior calyceal puncture or obese patients. These imaging modalities improved visualization, helped avoid adjacent organ injury, and enhanced procedural accuracy. The use of these precautions and imaging techniques positively influenced outcomes by reducing complication rates and improving stone clearance efficiency. The precise tract access facilitated by fluoroscopy likely contributed to the reduced operative time and shorter postoperative hospital stay observed in the cohort. It can be assumed that the tumor is less likely to perforate in the lumbar spine compared to a normal longitudinal approach because the air in the lumbar spine causes more spinal displacement, which can lead to greater spinal injury. The most effective strategy to reduce the risk of closure is to combine real-time ultrasound and fluoroscopy during the procedure [15].

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Although the prone position is considered the standard for PCNL, its limitations have become increasingly apparent as the practice has become more widely accepted, especially due to concerns about anesthesia in severely obese or high-risk patients. Increased interest in, and the subsequent increase in the use of, urethral anterior-grade retrograde endoscopic techniques is continuously improving the effectiveness of retrograde intra-renal surgery, leading to an increase in the demand for PCNL [16]. Several folded instruments were developed to minimize the limitation of placing patients on the abdomen alone. These innovations are aimed at increasing comfort, improving ventilation and circulation, and reducing the chances of compression injury [17, 18]. Furthermore, these devices this offers the added advantage of slightly flexing the patient's waist, thus extending the operation laterally. To overcome these challenges, a side-by-side position was introduced for PCNL. The 'Barts method' combines the advantages of posterior positioning with the possibility of unidirectional advanced endoscopy [19]. Numerous investigations on PNCL reported better outcomes of supine PNCL in terms of lower complications, higher stones removal, and shorter hospitalization against prone PNCL [20, 21]. The poor prognosis of prone PNCL included lower patient's satisfaction, increased awareness, and higher surgical visual acuity. The assessment of stone removal and risk of recurrence were done during follow-up after supine PNCL [22]. An earlier study compared the supine PNCL with prone position with certain modifications provided unique benefits of improved stone removal efficiency, surgical effectiveness, and lower postoperative complications [23]. Another study introduced Barts method offering extra advantages for complete endomandibular treatment in single-step. Modified tubeless PNCL in vertical position supported alternate option for stone characteristics [24]. While the findings suggest the supine PCNL may be advantageous in terms of operative time, complication rates, and recovery, the absence of a direct comparative analysis with the prone position limits the strength of this conclusion. This study was observational and did not include a control group of patients undergoing prone PCNL. Therefore, statistical comparisons between positions (e.g., chi-square tests for categorical variables and t-tests for continuous variables) could not be conducted. This limitation is acknowledged, and recommended that future studies adopt a randomized or matched cohort design to compare both approaches directly and apply statistical significance testing with p-values and confidence intervals.

CONCLUSIONS

Supine PCNL has shown better outcomes in terms of lower hospital stay, effective stone removal, and discharge postoperative day. It has been observed that supine PNCL emerged as advantageous method in terms of safety, effectiveness, and patient comfort against prone PNCL. As a result, a validation of the efficacy and safety of supine PCNL has been confirmed.

Authors Contribution

Conceptualization: RA
Methodology: SA, RA
Formal analysis: MJ
Writing, review and editing: SA, RA, HMK, AU
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Knowledge Regarding the Administration and Regulation of High Alert Medications among Nurses in Tertiary Care Hospitals, Bannu KPK

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ABSTRACT

High-alert medications (HAMs) have a significant potential for causing severe harm if mismanaged. Proper administration and regulation of these drugs are critical to ensuring patient safety. However, limited knowledge and adherence to safety practices among healthcare professionals increase the risk of medication errors. **Objective:** To assess nurses' knowledge regarding the administration and regulation of high-alert medications. **Methods:** Using convenience sampling, this descriptive cross-sectional study involved 113 registered nurses from tertiary care hospitals in Bannu. Data were collected through an adopted questionnaire distributed via Google Forms, encompassing demographic details and specific questions on HAM administration and regulation safety practices.Data analysis included descriptive and inferential statistics using Microsoft Excel. **Results:** Among the respondents, 64.3% correctly identified HAMs as posing significant risks, yet 35.7% displayed critical knowledge gaps in identifying safe administration practices. Errors were most notable in dosage calculations, drug labeling, and administration methods, particularly for potassium chloride and epinephrine. While 57.1% acknowledged the importance of double-checking doses, only 42.9% demonstrated comprehensive knowledge of storage protocols. Significant gaps in education and training were identified, highlighting the need for improved safety practices. **Conclusions:** It was concluded that substantial gaps in nurses' knowledge and practices related to HAMs, underscoring the necessity for targeted training programs. Enhanced education, adherence to safety protocols, and interdisciplinary collaboration are essential to minimizing medication errors and improving patient safety.

INTRODUCTION

High-alert medications (HAMs) are pharmaceuticals with a high potential for causing serious harm if handled incorrectly through dosing, route of administration, or substance error [1]. Medication safety at the administration level has raised an alarm internationally, touching both patient safety and quality of healthcare service delivery [2]. With the growing occurrence of medication errors, the third Global Patient Safety Challenge was, in 2017, initiated by the World Health Organization under its theme "Medication without Harm." This initiative aimed to reduce medication errors and to help healthcare institutions and professionals implement safer medication practices [3]. The medication errors are associated with a significant percentage of adverse events in healthcare. According to the worldwide data, such medication errors lead to 2-5% of hospital admissions. According to the Centers for Disease Control and Prevention, medication errors rank third as the most common cause of death in the United States, which translates to approximately 98,000 deaths annually. This represents a pressing necessity for bettering medication management practices [4]. The American Pharmaceutical Association has classified HAMs into numerous high-risk categories, such as anticoagulants (warfarin and heparin),

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chemotherapeutic agents, narcotics (fentanyl and morphine), electrolytes (15% KCL), neuromuscular blocking agents (succinylcholine), cardiovascular medications, and benzodiazepines (midazolam) [5]. These drugs have a narrow therapeutic index. Even the smallest exaggeration in drug dosage or blood concentration may result in adverse reactions or failure of treatment. Accordingly, there is a high potential for severe harm if HAMs are mishandled. Small differences in the management of these drugs can lead to major and potentially fatal complications. For example, drugs with a narrow therapeutic index are vulnerable to toxic effects that depend on concentration, and the pharmacological effects can be adverse or unexpectedly aggressive in case of severe therapeutic failures if managed precisely [6, 7]. One such example that shed much light on HAM medication errors in Pakistan was when a nine-month-old child died after a direct intravenous (IV) injection of 15% KCL at a private hospital located in Karachi. Such a fatal event brought into the limelight the serious consequences of HAM drug administration errors. This always puts the need to strictly adhere to medication safety protocols in risky healthcare setups. Medication errors, particularly with HAMs, often arise from various factors, including inadequate dose calculation, improper drug storage, limited nursing education, and insufficient hands-on experience with medication administration [8]. The vital role that nurses play in administering medications forms the basis for choosing this topic to assess their knowledge regarding HAMs. Nurses' role in the administration of medication places them at the forefront of patient care. In this context, proper knowledge of HAMs is always crucial so that they do not compromise the safe and efficient treatment of the patient. Effective education on medication safety practice is indeed necessary for nurses, as it will enable them to minimize risks and provide the best care for patients [9]. Medication errors are committed unintentionally at any step in the administration process that involves prescription, dispensation, storing, preparing, and administration. HAMs present a critical risk factor in these errors, mainly because these drugs have narrow therapeutic windows and severe side effects, which make them prone to causing damage if administered incorrectly. Those in charge of handling and administering HAM are nurses, who are at significant clinical risk, as incorrect administration might have severe, even fatal, consequences. [10]. Medication safety during administration remains a global concern due to its impact on not only patient outcomes but also the quality of care provided by healthcare workers [10]. Unintentional Medication errors in the medication process—processes including prescribing, dispensing, storing, preparing, or administering drugs—have been identified as one of the biggest challenges that nursing professionals face across the globe [9]. Specifically, HAMs are considered a major contributor to severe cases of medication-related injuries when administered incorrectly [11]. Holding nurses accountable in the administration of HAMs is an integral part of the clinical nursing role because misuse or mismanagement of these drugs can result in severe clinical consequences or even death. Thus, there is a dire need to strengthen pharmacological education and knowledge among nursing personnel to enhance drug safety in the use of these high-risk medications [12, 13]. In Pakistan and other countries, nurses play a significant role in medication-related tasks. In addition to administration, their work involves preparing medications, monitoring therapeutic responses, reporting adverse drug reactions, and orienting patients on the use of medications. Although Pakistani nurses have been the subject of many studies in terms of evaluating their awareness concerning different matters in healthcare, very few of these investigations focused on HAMs despite the relatively high-risk profile of the drugs concerned. The lack of special training in HAMs increases the likelihood of Medication errors due to the complexity of HAM dosage, storage, and requirements of administration. This gap in knowledge underscores an important area of potential improvement in Pakistan's health care system and may contribute to the larger system challenges in the health care delivery system. This study is crucial because high-alert drugs (HAMs) have a high risk of harming patients if they are given improperly; therefore, nurses must be educated in their safe handling and management. To improve patient safety and nursing competency, this study will identify gaps in nurses' knowledge of HAMs and offer insightful information for creating focused training interventions.

This study aims to soliciting information on HAMs among Pakistani nurses. Additionally, the study is aimed at creating awareness that continuous education and training in HAM management should be included in nursing curricula. Improved knowledge of HAMs through updated approaches in training will ultimately enhance the nursing practice and lower the risk of medication errors.

METHODS

A descriptive cross-sectional study was conducted, and this study was carried out at tertiary care institutions: King Gul Nawaz Hospital, District Headquarters Hospital, and Women and Children's institutions. Male and female registered nurses from Bannu's tertiary care facilities made up the study's population [1]. A sample size of 113 was calculated using the WHO sample size calculator, taking into consideration a 50% response distribution, a 5% margin of error, and a 95% confidence level. Non-probability. The convenience sampling method was utilized, and data were collected from the first of July 2024,

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to October 2024. Registered nurses working in tertiary care hospitals of district Bannu with at least six months of experience were included in this study. Nursing managers and supervisors were excluded from the study. The ethical certificate was obtained from the IRB committee of the Medical Teaching Institution Bannu. The data were gathered using the Google Form self-structured questionnaire in both Urdu and English. All participants gave their informed permission after being fully told about the study's objectives, risks, and benefits and given a 100% privacy assurance. Consent was obtained from those who chose to participate, and the adopted questionnaire [1] was filled out. It inquired about demographics and registered nurses' understanding of how to administer and control high-alert medicines. SPSS 26 was used to evaluate the gathered data. For each variable, the responses were compiled and categorized using descriptive statistics, such as frequencies and percentages. Only descriptive statistics were performed.

RESULTS

The demographic characteristics of the study participants indicate that the majority (51.8%) were aged between 25 and 34 years, followed by 26.8% in the 35–44 age group. A smaller proportion (14.3%) were between 18 and 24 years, while 5.4% were aged 45–54 years, and only 1.8% were 55 years or older. The sample comprised 58% female and 42% male participants, reflecting a higher female participation rate. Regarding marital status, 64.3% of respondents were married, while 35.7% were single, with no participants reporting being widowed or divorced. In terms of educational qualifications, the majority (61.6%) held a diploma, 34.8% had a bachelor's degree, 2.7% possessed an associate degree, and 0.9% held a master's degree. Concerning healthcare experience, more than half (55.4%) had 2–5 years of experience, followed by 20.5% with 6–10 years, 19.6% with more than 10 years, and 4.5% with 0–1 year, with the majority falling within the 2–5 years' category, as shown in Table 1.

Table 1: Demographic Details of the Participants

Variables		Frequency (%)
Age group	18-24	16 (14.3%)
	25-34	58 (51.8%)
	35-44	30 (26.8%)
	45-54	06 (5.4%)
	55 and Above	2 (1.8%)
Gender	Male	47 (42%)
	Female	65 (58%)
Educational Level	General Nursing Diploma	69
	Associate Degree	03
	BSN	39
	MSN	01
Experience	Less Than 1 Year	12 (7.9%)
	1 To 5 Years	88 (57.9%)
	6 To 10 Years	24 (15.8%)
	More Than 10 Years	28 (18.4%)
Marital status	Single	40 (35.7%)
	Married	72 (64.3%)

Nearly 23 (64.3%) of respondents correctly identified high-alert medications as those posing significant harm or risk of death if used incorrectly, while 25.9% mistakenly believed they had a low risk of side effects, 7.1% thought they were only for outpatient settings, and 2.7% assumed they were restricted to pediatric use. Regarding safety practices for high-alert medications, more than half (57.1%) acknowledged the importance of double-checking doses and patient IDs, while 24.1% incorrectly believed paper-based medication records were essential, 17% stated that single-checking was sufficient, and only 1.8% dismissed staff training requirements. For i medication reviews, almost two-thirds (63.4%) supported continuous updates, 17.9% preferred monthly reviews, 8.9% opted for quarterly reviews, and 9.8% favored yearly reviews. Half of the participants correctly stated that a rapid IV push of 1:1000 epinephrine is inappropriate for a mild allergic reaction, while the other half responded incorrectly. Regarding calcium chloride injection, 49.1% recognized that a rapid IV push of 10% $CaCl_2$ is unsafe, whereas 50.9% were incorrect. Additionally, 62.5% knew that 10% calcium gluconate and 10% $CaCl_2$ cannot be interchanged, but 37.5% made an error. In chemotherapy dose calculations, 61.6% correctly differentiated that adult doses are based on body weight, whereas pediatric doses are determined by body surface area, while 38.4% answered incorrectly. For potassium chloride administration, 62.5% knew that a fast IV push of 15% KCL is inappropriate in ventricular fibrillation, whereas 37.5% believed otherwise. More than half (58.9%) correctly identified that insulin dosages are measured in units rather than in "cc" or "ml," while 47.3% correctly noted that adding KCL to Ringer's solution is inappropriate for rapid infusion. Lastly, 67% recognized that a fast IV infusion of 3% NaCl is appropriate in cases of hypernatremia. Almost two-fifths (38.4%) mistakenly accepted that the dose unit should be "Amp" or "Vial" instead of "mg" or "gm," while more than 35 (61.6%) correctly identified that "mg" or "gm" should be used for actual dose expression. The third quartile (75%) of respondents correctly recognized that differentiating labels should be applied to look-alike drugs, while 25% were incorrect. More than fourscore (81.3%) wrongly believed that heparin and insulin should be stored together in the refrigerator for convenience, whereas 18.8% correctly stated they should be stored separately to avoid potential errors. More than 45 (83.9%) agreed that each drug should have multiple

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concentrations for nurses to choose from, while 16.1% disagreed. Around two-fifths (41.1%) correctly identified that potassium can be administered orally rather than intravenously if the patient can tolerate it, while almost half (48.9%) answered incorrectly. More than half (57.1%) mistakenly thought that a 15% potassium chloride solution should be readily accessible to nurses due to frequent use, while 42.9% correctly noted that, given its high risk, it should only be accessed with appropriate controls. Most nurses (70.5%) incorrectly asserted that pediatric dose expression should be measured in teaspoons, but 29.5% correctly indicated that milliliters or units provide a more accurate measurement. Almost two-thirds (64.3%) correctly identified the fentanyl skin patch as a controlled medicine, meaning a regulated narcotic, while 35.7% were incorrect. More than half (58%) mistakenly perceived that Atracurium, when prepared for tracheal intubation, should be stored with other drugs for easy access, while 42% correctly noted that it requires controlled storage due to its specific use and risks. Almost half (49.1%) incorrectly believed that writing "U" instead of "unit" for dosage expression was acceptable, whereas 50.9% correctly stated that "unit" should be used for proper dosage notation, as shown in Figure 1.

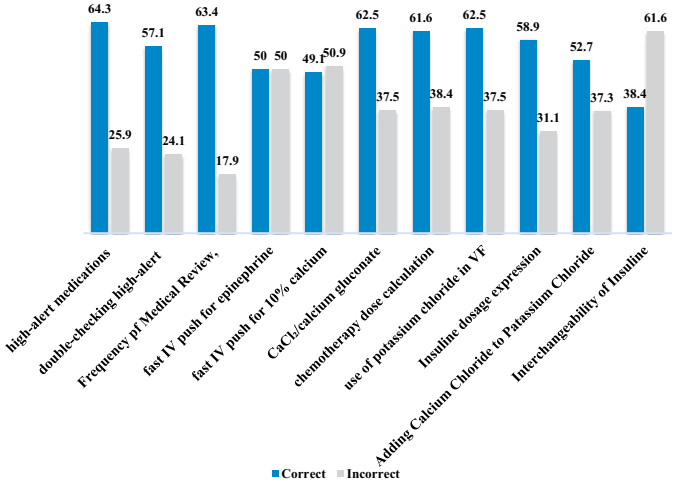

Figure 1: Knowledge About the Administration and Regulation of High Alert Medication among Nurses

DISCUSSION

The survey results are extremely promising, that is, 98.2% of participants were willing to participate in the study by consenting to share their information, with such high significance built in the confidentiality and transparency of the research process. Looking at the demographic characteristics, the group was predominantly female and of relatively young age, with most falling within the age category of 25 to 34 years [14]. This demographic trend may be reflective of the broader healthcare workforce, where younger professionals exist. Educational background showed that most participants held bachelor's degrees or diplomas, which shows a good level of health-related knowledge. However, despite this relatively high level of formal education, the participants showed some important knowledge gaps about high-alert medicines, particularly as relates to the critical details about these medications, correct administration practices, and appropriate safety measures when handling them. The findings of this study revealed that almost two-thirds, 64.3 percent of respondents correctly recognized high-alert medications as those posing significant harm or risk of death if used incorrectly, while 25.9 percent mistakenly thought they had a low risk of side effects. Similarly, another study noticed that 64.6% of the participants knew how to administer high-alert drugs appropriately [15]. Similarly, a study revealed that most of the participants were aware of the high alert drugs available in the institution and knew the consequences involved in error with HAM and its antidote [16]. In this study, when nurses were asked for safety practices for high-alert medications in this study, more than half, 57.1%, acknowledged the use of double checking doses and IDs, while 24.1% incorrectly believed to be true that paper-based medication records were essential. These findings were supported by the study which highlighted the importance of double-checking to avoid medication error, especially high-alert medications. Moreover, the study stated that the significance of double-checking leads to decreased medication errors [17].In contrast, a study explored the limitations of double-checking and argued that while it is a valuable practice, it cannot substitute for comprehensive systemic improvements, such as electronic medication records and automated alerts [18]. This study also revealed that more than 81.3% incorrectly believed that heparin and insulin should be stored together in the refrigerator for convenience, while 18.8% correctly identified that they should be stored separately to avoid potential issues. Similarly, the study reported the factors related to combined high alert medications, especially the storage of insulin and heparin and mixing during administration. It also highlighted that proper storage can significantly diminish the occurrence of errors [19]. Another study reported that many health care facilities don't have clear policies for the storage of high-alert medication as enforced by regulatory institutions [20]. This study stated that proper training sessions should be arranged for guidelines regarding storage and fewer errors [21]. To ensure that every healthcare worker remains updated on safety procedures and best practices, regular workshops, seminars, and online courses should be instituted. Moreover, incorporating simulations and practical training into existing continuing professional development will enhance compliance with safety practices and understanding.

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CONCLUSIONS

It was concluded that nurses have low knowledge regarding high-alert medications despite a very high participation rate of 98.2%, showing much trust in the confidentiality and purpose of the study. The study participants have at least a relevant diploma. However, it showed that a significant number of the participants have poor knowledge regarding identification, safe use, and handling of high-alert medications.

Authors Contribution

Conceptualization: SB
Methodology: S, AI, NUN, HB, NP, SK
Formal analysis: SB, AUR, SK
Writing review and editing: SB, S, AI, HB
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Maternal And Neonatal Outcome in Major Degree Placenta Praevia

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Major Placenta Praevia, Fetomaternal Outcomes, Maternal Morbidity, Neonatal Complications

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ABSTRACT

Placenta praevia relates to pregnancy complications where the placenta is positioned on, or covers the relevant cervix region thus leading to uncontrolled bleeding as being its major risk. The evaluation of mother and fetus outcomes of primary degree placenta praevia is quite important for constructive management and prevention policies to be put in place. **Objective:** To measure the incidence of negative fetomaternal outcomes in patients with major degree placenta praevia. **Methods:** This descriptive cross-sectional study was carried out at the Mardan Medical Complex Mardan in the Department of Obstetrics and Gynaecology from the 21st of October to the 31st of December 2024.The sample population includes 177 pregnant women with major degree placenta praevia who were monitored until delivery and 30 days after the birth of the child. **Results:** The mean maternal age was 29.25 ± 2.10 years, gestational age was 29.32 ± 1.44 weeks, and weight was 67.08 ± 6.17 kg. Associated maternal morbidity encompassed obstetric hysterectomy (14.1%) and bladder injury (11.3), postpartum hemorrhage (24.3%), sip and gout infections (18.6%), and preterm labor (16.9%) with little relations being observed with maternal factors (p>0.05). Some neonatal outcomes included NICU admission (18.6%), while stillbirth had some numbers reported around (15.8%) along with low Apgar scores (15.3%) where once again no significant associations with maternal factors were found (p>0.05). **Conclusion:** Clinical patterns indicate elevated risks with severe placenta praevia, which calls for close observation even if no statistically significant relationships have been observed.

INTRODUCTION

Placenta praevia is a pregnancy complication characterized by the placement of the placenta near or over the cervix. Placenta praevia has been categorized into two types: complete and marginal previa. Complete previa refers to the placenta fully covering the cervical os, while marginal previa occurs when the leading edge of the placenta is within 2 cm of the internal os but does not completely cover it [1].The global incidence of placenta praevia is estimated to be 3-5 per 1000 pregnancies, and this rate is increasing due to the rising number of caesarean sections [2]. Research indicates the prevalence of placenta praevia to be around 0.7% [3, 4]. The incidence is higher in mid-pregnancy compared to 36 weeks and later, likely due to the formation of the lower uterine segment and a process called trophotropism, which may lead to the resolution of placenta praevia [5].Radwan *et al.*, (2018) assessed maternal outcomes in placenta previa cases with and without morbidly adherent placenta at a tertiary hospital in Saudi Arabia [6]. Another study by Levin G *et al.*, revealed that in women with major degree placenta praevia, the frequency of postpartum hemorrhage was 28%, stillbirth 16%, low Apgar score 16%, NICU admission 36%, and neonatal jaundice 24% [7].Several studies have attempted to identify risk factors for placenta praevia and

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have shown associations with advanced maternal age (with prevalence around 1% in women aged 30-39 and increasing to 2% in women above 40), parity, maternal smoking, infertility treatments, previous caesarean deliveries, previous placenta praevia, and recurrent abortions [8, 9]. Among these risk factors, the rates of caesarean sections, advanced maternal age, and infertility treatments have all increased over the past decades [10]. Neonates born to mothers with placenta praevia are more likely to experience preterm birth, perinatal death, congenital malformations, and low Apgar scores (below 7 at both 1 and 5 minutes) [11]. Studies also indicate that most of these neonates require resuscitation and NICU admission, and a significant outcome of this condition is the increased risk of small-for-gestational-age infants and low birth weight [12]. Complications of placenta praevia extend beyond the antepartum period, affecting the intrapartum and postpartum course, with higher rates of cesarean delivery, peripartum hysterectomy, morbid placental adherence, and postpartum hemorrhage [13]. Previous research has estimated the rate of hysterectomy among women with placenta praevia to be around 5% [14]. Pregnancies complicated by placenta praevia also show significantly higher rates of postpartum anemia and prolonged hospital stays. The optimal treatment for hemorrhage related to placenta praevia is particularly poor in the low-income populations. Additionally, there is a lack of clinical research to support evidence within this area. Assessing maternal and fetal outcomes in women with major degree placenta praevia may help formulate effective management and preventative strategies which would mitigate the problems associated with this condition.

This study's objective was to estimate the level of occurrence and associated maternal morbidity as well as identify sociodemographic factors that could complicate pregnancies with placenta praevia.

METHODS

This descriptive cross-sectional study was conducted in the Department of Obstetrics and Gynaecology at Mardan Medical Complex, Mardan, from 21st October to 31st December 2024.A total of 177 participants were included in the study [14].The sample size was calculated using WHO sample size software, with a frequency of bladder injury of 13.2%, a margin of error of 5%, and a 95% confidence interval.The estimation of sample size was based on statistical principles applicable to comparable research, although no particular previous studies were considered. The participants were selected using non-probability convenient sampling.Inclusion criteria consisted of women aged 18-35 years with a singleton pregnancy, gestational age between 27-32 weeks according to their Last Menstrual Period (LMP), parity between 1 and 4, and major degree placenta praevia as per the operational definition.A certified radiologist used transabdominal and/or transvaginal ultrasonography to confirm the diagnosis of major degree placenta praevia.When the placenta covered the internal cervical os entirely or in part, it was categorized as significant placenta praevia. Exclusion criteria included a history of placental abruption, coagulation disorders, diabetes, or hypertension. Participants with diseases that could have an impact on the study's results were excluded in order to reduce confounding variables.Among these were a history of diabetes, hypertension, coagulation problems, placental abruption, or any other systemic disease that may affect the health of the mother or the newborn.After obtaining ethical approval from Bacha Khan Medical College with Ref. No.622/BKMC on dated 21-10-2024 and informed consent, patients meeting the inclusion criteria were selected from the indoor department of obstetrics and gynecology.Basic demographic information, including age, gestational age, parity, and weight, was recorded.The women were under careful observation during their hospital stay, from the time of admission to delivery and for 30 days after giving birth. Regular evaluation of the mother's vital signs, blood pressure, and blood loss measurement were all part of the monitoring procedure. Maternal and newborn outcomes were systematically evaluated using standardized procedures and checklists in compliance with the National Institute for Health and Care Excellence (NICE) recommendations (NG229) [14].Postpartum hemorrhage, obstetric hysterectomy, bladder damage, wound infection, premature labor, and other peripartum problems were among the maternal outcomes.NICU hospitalization, poor Apgar scores, infant jaundice, and stillbirth were among the neonatal outcomes.All pertinent information was documented in a structured proforma based on standardized fetomaternal evaluation criteria, and these outcomes were tracked during the hospital stay and for 30 days after giving birth. Fetomaternal outcomes were documented on a specially designed proforma (https://www.nice.org.uk/guidance/ng229).Clinical diagnosis and hospital records were used to identify maternal problems, including preterm labor, postpartum hemorrhage, bladder damage, obstetric hysterectomy, and wound infections.During the hospital stay, the amount of blood units transfused for patients who needed assistance for surgical complications or postpartum hemorrhage was noted.These diseases were treated according to standard hospital care procedures, which included antibiotic medication for wound infections, surgical intervention for severe instances such as bladder damage, and blood transfusions for postpartum hemorrhage.Data were analyzed using SPSS version 23.0.The statistical study regarded gestational age, parity, and maternal age as independent variables.The Chi-square test was used to evaluate these factors' effects on fetomaternal outcomes after they were divided into suitable groups. As shown in

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Tables 3 and 4, the findings showed no statistically significant relationships ($p > 0.05$) between these factors and the observed outcomes for mothers and newborns. The Discussion section has covered the potential causes of these results.

RESULTS

This study enrolled 177 participants with a mean age of 29.25 ± 2.10 years, ranging from 18 to 35 years. The mean parity was 2.03 ± 0.94, indicating that most women had around two previous pregnancies. The mean gestational age at the time of the study was 29.32 ± 1.44 weeks, while the mean weight of the participants was 67.08 ± 6.17 kg. These demographic details are summarized in Table 1.

Table 1: Demographic Characteristics of the Participants

Demographics	Mean ± SD
Age (Years)	29.248 ± 2.10
Parity	2.033 ± 0.94
Gestational Age (Weeks)	29.316 ± 1.44
Weight (Kg)	67.084 ± 6.17

The maternal and neonatal outcomes in women with major degree placenta praevia revealed several significant complications (Table 2).Among the maternal outcomes, obstetric hysterectomy was performed in 14.1% (n=25) of the cases, while bladder injury occurred in 11.3% (n=20) of the women.Postpartum hemorrhage was observed in 24.3% (n=43), and 18.6% (n=33) experienced wound infections. Preterm labor occurred in 16.9% (n=30) of the participants. In terms of neonatal outcomes, 18.6% (n=33) of newborns required admission to the NICU, while stillbirth was reported in 15.8% (n=28) of cases. Additionally, 15.3% (n=27) of newborns had a low Apgar score at birth. Patients who needed transfusions received an average of 2.5 ± 1.8 blood units; in few instances, the maximum documented amount was 8 units.

Table 2: Maternal and Neonatal Outcomes in Women with Major Degree Placenta Praevia

Outcome	Frequency (%)
Obstetric Hysterectomy	25 (14.1%)
Bladder Injury	20 (11.3%)
Postpartum Hemorrhage	43 (24.3%)
Wound Infection	33 (18.6%)
Preterm Labor	30 (16.9%)
NICU Admission	33 (18.6%)
Stillbirth	28 (15.8%)
Low Apgar Score	27 (15.3%)

The results of cross-tabulation and Chi-square tests are presented for various maternal and neonatal outcomes, stratified by age, parity, gestational age, and weight.For obstetric hysterectomy, 14.1% of patients underwent the procedure, with no statistically significant difference based on age groups ($p=0.861$), parity ($p=0.310$), gestational age ($p=0.415$), or weight ($p=0.910$). Similarly, bladder injury occurred in 11.3% of cases, and no significant association was found with age ($p=0.570$), parity ($p=0.617$), gestational age ($p=0.296$), or weight ($p=0.173$). In terms of postpartum hemorrhage, 24.3% of the patients experienced this complication. However, the results indicated no significant difference in the occurrence of postpartum hemorrhage with respect to age ($p=0.420$), parity ($p=0.696$), gestational age ($p=0.707$), or weight ($p=0.245$). Wound infections occurred in 18.6% of the patients, but there were no significant associations with age ($p=0.198$), parity ($p=0.150$), gestational age ($p=0.475$), or weight ($p=0.102$). For preterm labor, 16.9% of patients experienced preterm labor, and again, no significant associations were found with age ($p=0.712$), parity ($p=0.295$), gestational age ($p=0.864$), or weight ($p=0.592$)(Table 3).

Table 3: Stratification of Maternal Outcomes and Correlation analysis

Variable		Hysterectomy			Bladder Injury			Postpartum Hemorrhage			Wound Infection		
		Yes (%)	No (%)	p-Value	Yes (%)	No (%)	p-Value	Yes (%)	No (%)	p-Value	Yes (%)	No (%)	p-Value
Age (Years)	18-30	13.8	86.2	0.86	12.2	87.8	0.57	26	74	0.42	21.1	78.9	0.19
	>30	14.8	85.2		9.3	90.7		20.4	79.6		13	87	
Parity	1-2	12.2	87.8	0.31	12.2	87.8	0.61	25.2	74.8	0.69	21.7	78.3	0.15
	3-4	17.7	82.3		9.7	90.3		22.6	77.4		12.9	87.1	
Gestational Age (Weeks)	27-30	12.9	87.1	0.41	9.8	90.2	0.29	25	75	0.70	17.4	82.6	0.47
	>30	17.8	82.2		15.6	84.4		22.2	77.8		22.2	77.8	
Weight (kg)	≤≤65	14.5	85.5	0.91	7.2	92.8	0.17	29	71	0.24	24.6	75.4	0.10
	>>65	13.9	86.1		13.9	86.1		21.3	78.7		14.8	85.2	

Regarding neonatal outcomes, admission to NICU was necessary for 18.6% of newborns, with no significant relationship with maternal age ($p=0.099$), parity ($p=0.323$), gestational age ($p=0.787$), or weight ($p=0.257$). The incidence of stillbirth was 15.8%, with no significant association found between stillbirth and age ($p=0.838$), parity ($p=0.934$), gestational age ($p=0.316$), or weight ($p=0.218$). Lastly, low Apgar scores were observed in 15.3% of cases, with no significant correlations with age ($p=0.424$), parity ($p=0.812$), gestational age ($p=0.678$), or weight ($p=0.527$) (Table 4). Standard clinical criteria were used to characterize neonatal outcomes, such as stillbirth, poor Apgar scores, and NICU admission. Neonatals who needed acute care because to respiratory distress, low birth weight, or preterm were admitted to the NICU. An Apgar score of less than 7 at

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the first and fifth minutes of delivery was considered low. The lack of evidence of life at birth, as verified by clinical evaluation, led to the documentation of stillbirth.

Table 4: Stratification of Neonatal Outcomes and Correlation Analysis

Variable	Categories	Preterm Labor			Admission to NICU			Still Birth			Low Apgar Score		
		Yes (%)	No (%)	p-Value	Yes (%)	No (%)	p-Value	Yes (%)	No (%)	p-Value	Yes (%)	No (%)	p-Value
Age (Years)	18-30	16.3	83.7	0.712	15.4	84.6	0.099	15.4	84.6	0.838	13.8	86.2	0.424
	>30	18.5	81.5		25.9	74.1		16.7	83.3		18.5	81.5	
Parity	1-2	14.8	85.2	0.295	16.5	83.5	0.323	15.7	84.3	0.934	14.8	85.2	0.812
	3-4	21	79		22.6	77.4		16.1	83.9		16.1	83.9	
Gestational Age (Weeks)	27-30	16.7	83.3	0.864	18.2	81.8	0.787	17.4	82.6	0.316	15.9	84.1	0.678
	>30	17.8	82.2		20	80		11.1	88.9		13.3	86.7	
Weight (kg)	≤≤65	18.8	81.2	0.592	14.5	85.5	0.257	11.6	88.4	0.218	17.4	82.6	0.527
	>>65	15.7	84.3		21.3	78.7		18.5	81.5		13.9	86.1	

DISCUSSION

In this study, there were no statistically significant correlations ($p > 0.05$) between fetomaternal outcomes and mother age, parity, gestational age, or weight. This result is in contrast to some earlier research that found these characteristics significantly influenced pregnancy problems in cases with placenta praevia. The very small sample size could have made it more difficult to identify minute variations, which could be one explanation for this lack of statistical significance. The results in this sample may also have been impacted by differences in maternal health status, hospital procedures, and clinical care approaches. Certain clinical patterns, such as increased rates of postpartum hemorrhage and newborn problems, imply that these variables may still play a function in deciding maternal and neonatal outcomes, even though the statistical data did not show significant relationships. To investigate these associations more thoroughly, additional research with bigger sample numbers and stronger analytical techniques could be required. The rate of obstetrics hysterectomies was 14.1%. In total, 15.8% of neonates were delivered stillborn, and of the surviving infants, 18.6% were admitted to NICU. Intraoperative bladder injuries were reported in 11.3% of cases. 18.6% of cases have been caused by wound infection. In a study by Sultana has shown that frequency of obstetrics hysterectomies was 15.1%, bladder injury 13.2%, wound infection 17.3%, preterm birth 22.1%, admission to NICU 25.9%, still birth was 13.2% in women with major degree placenta praevia [6]. Khan *et al.*, (2024) conducted a prospective study to determine the frequency of maternal morbidities in patients with placenta previa in Hazara Division [12]. An analysis of 535 women with placenta previa by Long *et al.*, in (2021) from China revealed that Antepartum Hemorrhage (APH) was substantially linked to poor outcomes for both mothers and newborns [15]. In a large population-based study, the prevalence of PP was reported as low as 0.28 [16]. A systematic review showed that the prevalence of PP is influenced by numbers of previous cesarean scars, with a rate of 1%, 2.8%, and 3.7% after 1, 3 and 5 cesarean deliveries, respectively [17]. According to their findings, short cervical length, anterior placental position, and full placenta previa were important risk factors for APH. According to the study, the largest risk of complications due to APH was associated with prior uterine artery embolization (OR: 11.706) [18]. According to the study, 31.52% of women had had evacuation and curettage operations, while 88.04% of women had a history of cesarean sections. Placenta previa was substantially correlated with these characteristics. High rates of complications were seen in the maternal outcomes: 34.78% needed ICU hospitalization, 21.73% had a hysterectomy, and 75% got blood transfusions. On the neonatal side, 23.19% needed NICU hospitalization, 38.04% were preterm, and 25% had low birth weight [19]. This difference in prevalence rates of PP among researchers may be explained by the lack of the general consensus on clinical definition of placenta accreta, increta and percreta. The current definition is based on histological findings after hysterectomy has been performed. Furthermore, most of these studies are retrospective and hospital-based in nature, this results in the overestimation of the true prevalence of placenta accreta, as many of these cases were referred from non-tertiary hospitals. The average consumption of 2.5 ± 1.8 units of blood and the 14.1% need for a hysterectomy indicate the severity of complications associated with placenta accreta, even though no maternal fatalities were reported in our investigation. Loverro *et al.*, in (2022) supported this by comparing placental pathology and newborn outcomes in a prospective research that evaluated 439 pregnancies [17]. This study by Moeini *et al.*, evaluates the maternal and neonatal outcomes in patients with abnormal placentation, including placenta previa and accreta, through a case-control design. The authors highlight significantly higher rates of hemorrhage, preterm birth, and NICU admission in affected pregnancies. The paper emphasizes the need for

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early diagnosis and multidisciplinary management to mitigate risks [20].Xie *et al.*, conducted a cohort study comparing maternal and neonatal complications in placenta previa cases with and without previous cesarean sections. Their findings show that a history of cesarean delivery increases the risk of adverse outcomes such as postpartum hemorrhage and neonatal intensive care admission. The study underscores the long-term obstetric implications of cesarean delivery [21].In summary, while the study didn't find clear associations, the high rates of complications emphasize the need for careful monitoring and proactive management in this high-risk group. Clinicians should consider these trends and observations, even if they don't meet the threshold for statistical significance, to ensure the best possible outcomes for both mothers and their babies.

CONCLUSIONS

This study showed clinical data indicate that women with significant degree placenta praevia may be more susceptible to maternal problems including postpartum bleeding, obstetric hysterectomy, and bladder damage, even though statistical significance was not proven in this study. Low Apgar scores, stillbirth, and NICU hospitalization were among the neonatal issues noted. Despite not being statistically significant, these trends show that careful monitoring and management of these situations are necessary to enhance outcomes and safety for both mother and child.

Authors Contribution

Conceptualization: NK
Methodology: SS
Formal analysis: FB, MM
Writing, review and editing: AS, SS, FB, MM, RIK, NK
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Functional Outcome of Locking Plate versus External Fixation in Management of Comminuted Intra Articular Fracture of Proximal Tibia

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ABSTRACT

The surgical management of Schatzker type V or VI tibial plateau fractures can be challenging, and complications may include compartment syndrome, soft-tissue and ligament damage, and neurovascular injury. A successful course of treatment necessitates articular cartilage regeneration, biological integrity preservation, mechanical axis realignment, joint stabilization, and mobility preservation. **Objective:** To compare the outcomes of locking plate vs. external fixation in management of comminuted intra articular fracture of proximal tibia. **Methods:** In this quasi experimental study 82 patients of proximal tibia fracture were presented. Patients were admitted to orthopedic department and were included after getting informed written consent. Two groups were created, in group I 41 patients received locking plate and 41 patients of group II received external fixation. Outcomes among both groups were compared after treatment. SPSS version 23.0 was used to analyze all data. **Results:** There were majority males in both groups. Patients of group I had mean age of 36.13 ± 10.63 years and in group II mean age was 34.8 ± 7.49 years. Postoperative functional outcome was significantly better in group I as compared to group II with p value <0.05. As per Rasmussen's clinical functional knee score, group I had higher score 23.61 ± 6.154 as compared to group II 21.45 ± 6.187 with p value <0.03. Post-operative frequency of infection was lower in group I as compared to group II with p value <0.02. **Conclusion:** It was concluded that in this study that internal locking plate showed better outcomes in terms of functional results while had higher blood loss and longer operative time as compared to external fixation.

INTRODUCTION

Tibial plateau fractures caused by Schatzker type V or VI pose difficult surgical problems and are associated with possible side effects include compartment syndrome, soft-tissue and ligament damage, and neurovascular injury [1, 2]. Important factors affecting the long-term prognosis are ligamentous instability and the lack of articular congruity repair [3]. A successful course of treatment requires articular cartilage restoration, biological integrity preservation, mechanical axis realignment, joint stabilization, and mobility preservation [4]. In the case of tibial plateau fractures, Schatzker types V and VI present a number of significant surgical challenges, including neurovascular injury, compartment syndrome, damage to soft tissues and ligaments, and other sequelae. These

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complications are characteristics of the complicated surgical problems [5]. In the long run, the prognosis is significantly impacted by a number of variables, including the presence of ligamentous instability and the inability to restore articular congruity.3) Biological integrity, stability of the joint, preservation of mobility, realignment of the mechanical axis, and repair of articular cartilage are all essential components for the successful completion of therapeutic procedures. The use of a lateral locking plate in conventional Open Reduction and Internal Fixation (ORIF) procedures to realign the osseous tissues has a high risk of surgical complications. This risk is especially high when the procedures are performed in conjunction with one another. Nevertheless, this strategy proved to be successful. The Ilizarov treatment, which allows for closed reduction and fixation, is a suitable alternative that does not create substantial complications with the soft tissues [6]. There is a correlation between high-energy trauma and complex and open tibial fractures; nevertheless, it is important to note that both forms of trauma have the potential to induce this injury. Open fractures are connected with a higher risk of complications and permanent disability than closed fractures. For patients who have suffered a fracture of the tibial plateau, there are a number of therapy options open to them, including both non-operative and surgical procedures [7]. Non-operative therapy, such as the Sarmiento program, may be beneficial for patients with submeniscal fractures, stable fractures that are not displaced, and certain patient demographics, such as the elderly [8].

Surgical treatment is necessary for certain kinds of fractures, fractures that have been displaced, and fractures that have been associated with vascular or compartment syndrome. The surgical treatments encompass a broad variety of fixation techniques, ranging from those that are performed internally, such as arthroscopic fixation and biologic fixation, to those that are performed externally, such as the Ilizarov device and hybrid fixators. It has not yet been demonstrated that balloon tibioplasty is successful in the long run, despite the early confidence that was expressed. When it comes to the functional outcome of Rasmussen's knee, the results of research that compared the hybrid Ilizarov treatment with the locking plate technique have been inconsistent [9, 10]. Treatment for tibial plateau fractures is difficult, and non-operative and surgical methods are available. Non-operative treatment, like the Sarmiento program, is appropriate for sub-meniscal fractures, stable, non-displaced fractures, and specific patient groups, such as the elderly [11]. Certain fracture types, displaced fractures, and fractures involving vascular or compartment syndrome necessitate surgical treatment. Surgical procedures include both exterior fixation techniques, such as the use of devices like the Ilizarov instrument or hybrid fixators, and internal fixation techniques, such as arthroscopic fixation, biologic fixation, and traditional double plating. Although balloon tibioplasty shows promise, its long-term effectiveness is not proven. Different outcomes are obtained using the hybrid Ilizarov technique and locking plate approach in studies assessing Rasmussen's knee functional outcome [11, 12]. With a complication incidence of 12% (re-fracture after implants were withdrawn), the findings demonstrated that 85 percent of the patients achieved full clinical and radiological union [12]. All of the cases were successful in achieving full union. According to the findings of another study, all 32 femoral fractures that were treated with locking plates in children and adolescents healed fully radiologically, demonstrating that the treatment was successful in every single instance [13, 14]. As a result of the increased likelihood of angular deformity, an increasing percentage of fractures that occur in children are being treated surgically. In juvenile femoral fractures, angular deformities cannot exceed 10 degrees forward/backward or 5 degrees medial/lateral. This is because there is a strong association between angulations of the femur and arthritis of the knee joint. In order to advance current understanding, this study compared the functional results of patients treated for comminuted intra-articular fractures of the proximal tibia using the locking plate technique against external fixation.

METHODS

This quasi experimental study was conducted at orthopedic department of Sahiwal Medical College /Sahiwal Teaching Hospital from 10/05/2024-30/11/2024 and comprised of 82 patients with proximal tibia fracture. The approved IRB reference number is 158/IRB/SLMC/SWL. Patients were included after getting informed written consent. Non- consecutive sampling technique was used. The formula for sample size calculation for comparing two independent means was: $n=(Z\alpha/2+Z\beta)2\times2\times\sigma2d2$. With an effect size of 0.67, two followed alpha values (0.05), and beta value (0.1), 41 patients in each group were sufficient to identify a significant difference. So total sample size taken was 82 patients. 41 patients received locking plate in group I and 41 patients of group II received external fixation. Following the patient's pre-operative measurements and fitness evaluation, they were placed in a supine posture on a traction table and, following spinal anaesthesia, their knees were flexed to 90 degrees. In order to limit blood flow during the locking compression plate fixation, a tourniquet was utilized. The fracture has healed, according to C-arm imaging. The appropriate incision was used to apply lateral or medial plating. The wound was cleaned using normal saline, which has a pH of 0.9%. In order to stabilize the skeleton, patients were prepared and then back-slab was put above the knee.

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Under general anaesthesia, a single surgical team operated on all patients. Injectable first-generation cephalosporins were administered following pre- and post-operative sensitivity testing and continued for a minimum of seven days. There was radiologic evidence of callus at six weeks, which allowed for partial weight bearing. When it was deemed appropriate, full weight bearing was initiated and documented. For an average of one year, patients were monitored. All infection occurrences have been documented and contrasted. The non-union incidence was reported, and the time for unionisation in the two categories was compared. Association of infection and its severity was observed. SPSS version 23.0 was to analyze the data. A significant result was defined as a p-value less than 0.05. Age and other quantitative factors were defined as means with standard for normality test. The chi-square test was used to compare the two groups' functional outcomes at six months. The threshold for significance was p-value <0.05.

RESULTS

In group I 34 (82.9%) were males and 7 (17.1%) females while in group II 31 (75.6%) males and 10 (24.4%) female patients. Patients of group I had mean age 36.13 ± 10.63 years and in group II mean age was 34.8 ± 7.49 years. Road traffic accidents were the most common cause of injury followed by fall from the height. In group I 28 (68.3%) cases had fracture type VI and in group II 25 (60.97%) cases had fracture type VI (table 1).

Table 1: Demographics of the Presented Cases (n=82)

Variables	Mean ± SD/Frequency (%)	
	Group I	Group II
Mean Age (Years)	36.13 ± 10.63	34.8 ± 7.49
Gender		
Male	34 (82.9%)	31 (75.6%)
Female	7 (17.1%)	10 (24.4%)
Cause of Injury		
RTA	30 (73.2%)	28 (68.3%)
Fall from Height	11 (26.8%)	13 (31.7%)
Fracture Type		
V	13 (31.7%)	16 (39.03%)
VI	28 (68.3%)	25 (60.97%)

In group I intra-operative blood loss was 121.12 ± 5.37 ml and 25.7 ± 6.38 ml in group II. Mean operative time in group I was higher 86.17 ± 14.88 as compared to group II 41.8 ± 5.44 minutes with p value < 0.004 (table 2).

Table 2: Comparison of Intra-Operative Parameters among both Groups

Variables	Mean ± SD		p-Value
	Group I	Group II	
Blood Loss	121.12 ± 5.37	25.7 ± 6.38	<0.003
Operative Time	86.17 ± 14.88	41.8 ± 5.44	<0.004

Postoperative functional outcome was significantly better in group I 53.7% good, 39.02% fair and 7.3% poor as compared to group II 24.4% good, 41.5% fair and 34.4% poor with p value <0.05 (table 3).

Table 3: Post-Operative Comparison of Functional Outcomes (n=82)

Variables	Frequency (%)		p-Value
	Group I	Group II	
Good	22 (53.7%)	10 (24.4%)	<0.05
Fair	16 (39.02%)	17 (41.5%)	
Poor	3 (7.3%)	14 (34.4%)	

As per Rasmussen's clinical functional knee score, group I had higher score 23.61 ± 6.154 as compared to group II 21.45 ± 6.187 with p value <0.03 (table 4).

Table 4: Comparison of Knee Score

Variables	Mean ± SD		p-Value
	Group I	Group II	
Rasmussen's Clinical Functional Knee Score	23.61 ± 6.154	21.45 ± 6.187	<0.003

Post-operative frequency of infection n was lower in group I 4.9% as compared to group II 21.9% with p value <0.02 (figure 1).

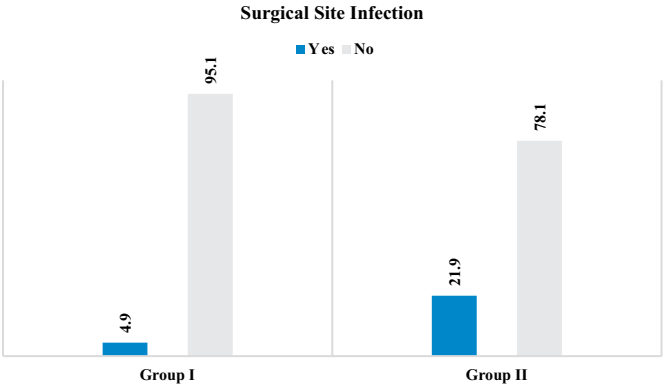

Figure 1: Post-Operative Comparison of Infection

DISCUSSION

There is evidence that locking plate fixation increases the union rate for femur shaft fractures, which is useful for reduced cortical blood flow, increased endosteal necrosis, elevated intra-compartment pressures, and infection risk are all possible outcomes of a locked plate after high-energy trauma or an open fracture [15, 16]. When fixing a fracture, it might be technically challenging to keep the section in an unstable position, necessitating the use of locking screws, extra plates, or even the open insertion of a bone reduction clamp or bone holding [17]. Regardless of the fixation technique used, a shorter healing period is directly related to proper initial anatomical reduction. Scarring and an abundance of callus production make secondary reduction impossible in this age bracket. Following the appropriate removal of necrosed or dead tissue and bone, the reduction is accomplished using a

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closed, minimally invasive technique that minimized soft tissue stripping through the tiny incision or traumatic wound. The exact method relies on the protocol. Under image intensification, screws can be used to stabilize fractures if needed [18]. In current study, Postoperative functional outcome was significantly better in group I as compared to group II with p value <0.05. Researchers Smith PN et al., found that "definitive external fixation and staged ORIF" result in similar rates of union, time to union, and complications when it comes to treating tibial plafond fractures. They suggested larger randomized prospective studies to evaluate the reliability and practical implications of the results over the long term [19]. The functional result of the knee was rated as outstanding in 25% of participants, good in 60%, fair in 10%, and bad in 5% of those who underwent the hybrid Ilizarov operation, according to studies done by Raza A et al [20]. As per Rasmussen's clinical functional knee score, group I had higher score 23.61 ± 6.154 as compared to group II 21.45 ± 6.187 with p value <0.03. Using Rasmussen's knee functional outcome, the study found that 50% of participants rated the locking plate technique as exceptional, 35% as good, 15% as fair, and 0% as bad. Based on Rasmussen's knee functional result, 35% of participants rated the locking plate technique as exceptional, 42% as good, 15% as fair, and 8% as poor, according to a research by Karunakaran A et al [21]. This all-inclusive review is on the complex elements to think about while managing a tibial plateau fracture, with an emphasis on individualized strategies according to the fracture features, patient variables, and soft tissue pathologies.

CONCLUSIONS

It was concluded that in this study the internal locking plate showed better outcomes in terms of functional results while had higher blood loss and longer operative time as compared to external fixation.

Authors Contribution

Conceptualization: SUS
Methodology: AMS, MR
Formal analysis: SUS
Writing, review and editing: SUS, AMS, ARN, OBZ, SARA
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Presoaking of Peroneus Longus Tendon Auto-graft in Vancomycin Decreases the Occurrence of Infection Following Arthoscopic Primary Anterior Cruciate Ligament Reconstruction

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ABSTRACT

Septic arthritis following anterior cruciate ligament (ACL) repair surgery is an extremely rare but possibly fatal consequence. To mitigate this danger, our team began presoaking grafts with vancomycin. **Objectives:** To determine the association of septic arthritis following anterior cruciate ligament (ACL) restoration using hamstring autografts with and without grafts presoaked in vancomycin. **Methods:** This study included 350 patients who had primary hamstring autograft ACL repair. Patients were equally divided into two groups. Group I had a pre-vancomycin protocol among 175 cases, and 175 cases of Group II received the vancomycin protocol. Postoperative septic arthritis was a likely outcome in both groups. Combining clinical findings with cytological examination of joint aspiration (cell count >50,000/μL and >90% neutrophils), a diagnosis of likely septic arthritis was reached. A Fisher's exact test was used for statistical analysis. We fixed the significance level at $p<0.05$. **Results:** There were a majority of 240(68.6%)male and 110(31.4%)female among all cases. Included cases had a mean age of 27.18 ± 11.58 years and had a mean BMI of 26.12 ± 8.38 kg/m2. Post-operatively, the frequency of septic arthritis was only found in group I among 7 (17.1%) cases, and no cases were found in group II. Among 7 cases of septic arthritis in group I, 4 cases had Staphylococcus epidermidis, and no organisms were isolated in 3 cases. **Conclusions:** It was concluded that presoaking the grafts in vancomycin for primary ACL repair decreased the likelihood of postoperative septic arthritis compared to not soaking them.

INTRODUCTION

A very uncommon but disastrous complication of anterior cruciate ligament (ACL) surgery is knee septic arthritis, the incidence of which has been reported in the literature to range from 0.14% to 1.07% [1]. Even with the most advanced treatment, complications like as graft failure, deterioration of articular cartilage, and long-term joint dysfunction can occur [2]. Infection is more likely to occur with hamstring autograft than with patellar tendon, quadriceps tendon, or allograft when used after ACL replacement [3]. Most people think it's because of contamination that happened during the graft's collection and processing, but no one knows for sure [4]. To address the potential risk of postoperative septic arthritis caused by a graft that is contaminated, Vertullo et al., developed the Vancomycin presoaking approach in 2012 [4]. Improving the antibiotic's efficacy in a specific graft was their primary objective. During the arthroscopic part of the surgery, the surgeon will often use a swab saturated with a

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5 mg/mL Vancomycin solution to wrap the prepared graft. Due to its favourable pharmacokinetic characteristics, vancomycin is an excellent agent. Some of these characteristics include a large distribution volume, low allergenicity, heat stability, and local applicability [5]. Staphylococcus aureus and coagulase-negative staphylococci are among the most common skin commensals that might cause infections following ACL repairs. It eliminates these bacteria, to put it [6]. The goal of the study reported by Pérez-Prieto et al., was to identify the exact moment in the graft collection and preparation process when contamination can occur [7]. Because of this, graft samples were collected both during processing and harvesting. Of the total, seven cases (or 14%) were determined to have graft contamination. Two instances (4% of the total) occurred during harvesting, while five (10%) occurred during graft preparation. In 2012, Vertullo et al., [4] suggested the "vancomycin wrap" approach to enhance the antibacterial efficacy of the graft in response to the concern that a contaminated graft could lead to postoperative septic arthritis [7]. One step of the procedure is to place the ACL graft in a sterile bag or tray, swab it, and then dip the swab into a vancomycin solution. The infection rate decreased from 1.4% to 0% after ACL replacement, according to the initial study. Multiple subsequent studies using identical methodology corroborated the results of Vertullo and colleagues [8, 9]. Vancomycin is a great agent because of its pharmacokinetic properties. A few examples include its low allergenicity, heat stability, and local use safety, as well as its large distribution volume. It eliminates skin commensals, which make up the vast majority of microorganisms that cause infections during ACL repair. This includes coagulase-negative staphylococci and Staphylococcus aureus [10]. The antibiotic vancomycin is highly efficient against Gram-positive cocci because it prevents the development of the bacterial cell wall. Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, and other similar bacteria are particularly susceptible to the long-term effects of this antibiotic. Orthopedic surgeons often prescribe vancomycin to patients suffering from septic arthritis and related conditions. Topical vancomycin has demonstrated encouraging results in non-orthopedic domains as well, with the most encouraging results in orthopedic spine surgery [11]. A prior randomized research found that surgical site infection (SSI) was less common when patients received preventative intrawound injections of vancomycin after fracture stabilization surgery [11, 12]. Initial suggestions that tendon grafts saturated with vancomycin could significantly reduce postoperative infection risks were made in 2012 by Vertullo et al., [4]. Studying how well this method (hamstring grafts soaked in vancomycin) reduced the occurrence of septic arthritis compared to the period before it was employed was the main goal of this investigation. We hypothesized that compared to the control group, those who received grafts presoaked with vancomycin would have a lower incidence of septic arthritis.

This study aims to determine the association of septic arthritis following anterior cruciate ligament (ACL) restoration using hamstring auto grafts with and without grafts presoaked in vancomycin.

METHODS

In this quasi-experimental study, 350 patients who underwent arthroscopic primary ACL reconstruction with a hamstring autograft were included. The demographics of the enrolled cases were documented in detail following the acquisition of informed written consent. The study was conducted in Sahiwal Medical College /Sahiwal Teaching Hospital, and the approved IRB reference number was 157/IRB/SLMC/SWL. Study duration was 8 months, May-Dec 2024. The sample size is calculated by keeping the power of the study equal to 80% and the level of significance equal to 5%. With 10% expected dropout, the sample of subjects by infection with vancomycin presoaked grafts was 0.09% and without vancomycin presoaked grafts infection rate as 2.4% [13]. Included patients were aged between 18-55 years. Patients who had hamstring autografts, ACL reconstructions, multiple ligament surgeries, bilateral surgeries, or open concurrent operations were not eligible. We divided the patients into two groups. Group I had a pre-vancomycin protocol among 175 cases, and 175 cases of Group II received the vancomycin protocol. An ACL Tight Rope (Arthrex) cortical button and a Bio Composite interference screw (Arthrex) were used in the femoral and tibial sides of the hamstring autograft ACL reconstruction, respectively, in the surgical procedure. A 5-strand technique was used for hamstring graft preparation when the graft was thinner than 8 mm, following previous publications by our group [3]. A normal 4-strand technique was employed when the graft was thicker than 8 mm. A 5-strand hamstring graft was administered to 130 patients of group I and 150 patients of group II, who received a 4-strand graft. During the surgical procedure, a Bio-Composite interference screw (Arthrex) and an ACL Tight Rope (Arthrex) cortical button were utilized on the tibial and femoral sides of the hamstring autograft ACL repair, respectively. Hamstring grafts were prepared according to our group's previous publications3: a 5-strand method was used for grafts thinner than 8 mm, and a conventional 4-strand procedure was utilized for grafts thicker than 8 mm. For starters, the graft had to be worked more than the standard four-strand double semitendinosus and gracilis graft. In the time leading up to surgery, all patients were administered intravenous antibiotics, specifically vancomycin. All patients were administered intravenous antibiotics before the

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procedure, and the graft was soaked in a vancomycin solution beforehand, as per the technique outlined by Vertullo et al., [4]. Before surgery, patients were given either a 2-g dosage of intravenous cefazolin or a 1-g dose of intravenous vancomycin, depending on whether a penicillin allergy was noted. This was done to minimize antibiotic-related problems. A surgical sponge was saturated with a 5-mg/mL vancomycin solution before the hamstring transplant was prepared to ensure it would be properly soaked. A surgical sponge is preferable to immersing the graft in the solution, which might cause it to lose some of its original diameter as a result of fluid absorption.1 A 100 mL sterile saline solution containing 500 mg of vancomycin powder was prepared. As part of the arthroscopic procedure for the reconstruction, the graft had to be wrapped for at least 15 minutes [14]. Probable septic arthritis was diagnosed based on the patient's symptoms, which included redness, swelling, decreased range of motion, localized heat, and/or swelling of the knee. After every occurrence where suspicion was detected by arthrocentesis, the synovial fluid sample was tested cytologically and cultured. When the cell count exceeded 50,000/µL, the neutrophil count was above 90%, and a positive culture was also detected, a diagnosis of septic arthritis was deemed highly likely [15]. Septic arthritis could only be detected within 30 days, therefore, it was decided that a minimum follow-up of 5 months was necessary. The operating surgeon oversaw all of the subsequent appointments. SPSS 22.0 was used for analysis. all the qualitative variables, like gender, marital status, post-operative outcomes and functionality outcomes, were analyzed by frequency and percentages. All the quantitative variables, like age and BMI, were presented by Mean ± SD. When comparing the two categories "septic arthritis" and "no septic arthritis," the Fisher exact test or chi-square test was used for analysis. The threshold of significance utilized was p<0.05.

RESULTS

There were a majority of 240 (68.6%) male and 110 (31.4%) female among all cases. Included cases had a mean age 27.18 ± 11.58 years and had a mean BMI of 26.12 ± 8.38 kg/m2.195(55.7%)cases were married(Table 1).

Table 1: Demographics of the Presented Cases(n=82)

Variables	n (%)
Gender	
Male	240 (68.6%)
Female	110 (31.4%)
Mean Age (Years)	27.18 ± 11.58
Mean BMI (kg/m2)	26.12 ± 8.38
Marital Status	
Yes	195 (55.7%)
No	155 (44.3%)

Post-operatively, the frequency of septic arthritis was only found in group I among 7 (17.1%) cases and no cases were found in group II (Table 2).

Table 2: Post-Operative Comparison of Outcomes Among Both Groups

Variables	Group I (175)	Group II (175)	p-Value
Good			
Yes	7 (17.1%)	0	<0.005
No	168 (82.9%)	175 (100%)	

Among 7 cases of septic arthritis in group I, 4 cases had Staphylococcus epidermidis, and no organisms were isolated in 3 cases (Figure 1).

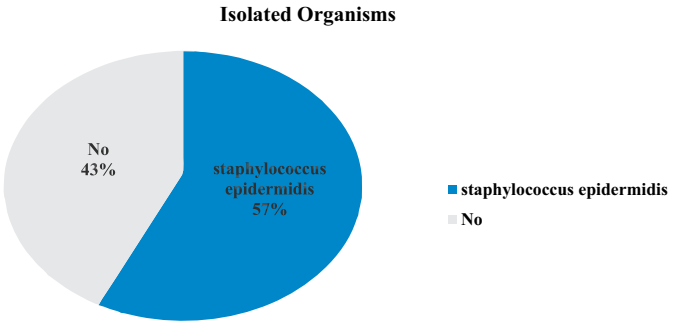

Figure 1: Frequency of Isolated Organisms Among Septic Arthritis

Infection was found in 8 (4.6%) cases of Group I, and there was no infection found among cases of Group II, with a p-value<0.005(Table 3).

Table 3: Post-Treatment Comparison of Infection Among Both Groups

Variables	Group I (175)	Group II (175)	p-Value
Infection			
Yes	8 (4.6%)	0	<0.005
No	167 (95.4%)	175 (100%)	

After 1 year of follow-up, better knee functionality was observed among patients of the vancomycin group as compared to group I, with a p-value <0.002 (Table 4).

Table 4: Comparison of Functionality Outcomes

Variables	Group I (175)	Group II (175)	p-Value
Functionality Outcomes			
Good	157 (89.7%)	173 (98.9%)	<0.002
Poor	18 (10.3%)	2 (1.1%)	

DISCUSSION

Current findings corroborated those of other research that found no infection when using hamstring grafts presoaked with vancomycin for ACL restoration [13, 15]. Before implementing this procedure, the infection rate was 1.7%, which is at the upper end of the indicated ranges. However, no infections were detected when this approach was used. In comparison to our earlier research, this increase in infection incidence may be explained by the longer manipulation time needed to construct a 5-strand graft as

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opposed to a typical double semitendinosus and gracilis graft. Pérez-Prieto et al., found that the preparation phase was the most common time for graft contamination [7]. Thankfully, their research demonstrated that not a single graft sample showed bacterial growth while immersed in vancomycin solution. A follow-up research of the original findings was published by the same group that published the first study on the topic, but with additional patients and a longer follow-up period [16]. In a study that followed 1,585 patients for 13 years after ACL restoration using a hamstring autograft, the researchers found no cases of infection. In their study, Offerhaus *et al.*, found that deep knee infections occurred 2% of the time after surgery in patients who did not get grafts presoaked in vancomycin, but did not occur 0% in those patients who did [13]. Their results also demonstrated that vancomycin did not increase the risk of arthrofibrosis, negative clinical ratings, or graft failure. A biomechanical model in pig tendons was published by Schüttler *et al.*, to assess the safety of using vancomycin in graft tendons. Their investigation revealed no evidence of biomechanical damage to tendons following the use of vancomycin wraps [18]. This study's creative application of 5-strand grafts sets it apart from others on the subject. New strategies for dealing with a small hamstring autograft diameter could lengthen the time required to prepare and handle the graft, increasing the risk of joint infection [19]. This series' total eradication of septic arthritis demonstrates that a safe hamstring transplant preparation technique must include vancomycin presoaking.The biomechanical characteristics of human semitendinosus transplants from living donors were found to be unaltered by presoaking with 5 mg/mL of vancomycin at time zero by Jacquet *et al.*, [20]. Return to running and overall knee function were not different between the control group and the patients given Vancomycin, according to Figueroa *et al.*, and Bohu *et al.*, respectively [21, 22]. Comparing the study's graft failure rate to the control group, which did not receive Vancomycin, revealed no rise in postoperative arthro-fibrosis or subjective outcome scores. However, the long-term biomechanical effects of its use have not been studied. Also, compared with the control group, patients who received grafts soaked in Vancomycin were more likely to resume their pre-injury sport.

CONCLUSIONS

It was concluded that presoaking the grafts in vancomycin for primary ACL repair decreased the likelihood of postoperative septic arthritis compared to not soaking them.

Authors Contribution

Conceptualization: NK
Methodology: MR, TR
Formal analysis: AMS
Writing review and editing: AMS, TR, ARN, SARA
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Accuracy of Tympanometry in the Diagnosis of Otitis Media with Effusion in Children's at Myringotomies

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ABSTRACT

Otitis media with effusion is a common cause of hearing impairment in children, required accurate diagnostic tools for timely intervention. Tympanometry is commonly used for assessing middle ear function, but its diagnostic accuracy compared to myringotomy, the gold standard, remains a topic of debate. **Objective:** To assess the diagnostic accuracy of tympanometry in identifying otitis media with effusion (OME) in children, using intraoperative findings during myringotomy as the gold standard. **Methods:** This observational cross-sectional study was carried out from January 2022 to June 2024 at the ENT Department, Hayatabad Medical Complex Peshawar. Ethical approval was obtained from Institutional Review Board (IRB) of the hospital, and written consent was obtained from parents or guardians of all children involved in the study. Total of 157 children aged 2 to 12 years, were included. **Results:** Proportion of sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy were determined. Type B tympanograms, suggestive of OME, were seen in 112 children (71.3%). Type A was observed in 25 children (15.9%) and type C in 20 children (12.7%). Myringotomy verified middle ear effusion in 120 children which is 76.4%.Within this group, 111 children presented with Type B tympanograms resulting in a true positive ratio of 92.5%. 9 cases (5.7%) were noticed with false positive results. **Conclusion:** Tympanometry stands as one of the top diagnostic instruments for OME identification in children. Their use, especially alongside otoscopy and audiometry, adds value in clinical practice.

INTRODUCTION

Otitis media with effusion (OME), which is more popularly known as "glue ear", is one of the most common conditions suffered by children, and involves fluid collections in the middle ear in the absence of acute infection. It is a major contributor to hearing loss in children and may influence speech, language, and academic achievement [1]. OME's accurate diagnosis is important to ensure prompt intervention. Tympanometry is gaining acceptance as an objective measure of assessing middle ear inflammation; however, the accuracy of tympanometry in diagnosing OME, particularly in cases validated with myringotomy, continues to be of great interest [2]. Tympanometry is a method for measuring the compliance of the tympanic membrane and the middle ear system through changes in air pressure in the external ear canal. It gives a graphical representation, called tympanogram, which is classified into types A, B, and C. type B which is flat is typically associated with OME, as such flat configuration indicates low mobility of the tympanic membrane [3]. Despite its widespread use, the accuracy of tympanometry in diagnosing OME has been debated, as many other conditions like cerumen occlusion, or technical faults, may give rise to similar findings [4]. Studies correlating the results of tympanometry with myringotomy have reported varying diagnostic accuracies. Most studies, including those by Azevedo *et al.*, and Vanneste P and Page C primarily used Jerger's classification (Type A, B, and C tympanograms) to categorize middle ear function [5, 6]. Some investigations also incorporated parameters like tympanometric width and peak-compensated static

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acoustic admittance to refine diagnosis [6]. Standardization across different patient groups was generally maintained by using calibrated equipment, a 226 Hz probe tone frequency for children older than six months, and consistent criteria for defining tympanogram types. Nevertheless, minor differences in methodology and patient characteristics could explain the variations reported among different studies [7]. In particular, the effects of age-related anatomical differences such as smaller, more compliant ear canals and immature eustachian tube function in younger children can influence tympanometric readings, sometimes leading to false positives [8]. While some studies attempted to control for these effects by stratifying patients into age groups or applying age-specific normative data, others did not fully adjust for these variations, which may explain part of the variability in reported sensitivity and specificity across different populations. Nonetheless, these measures have, in general, diagnostic and predictive accuracy variations in different studies which might be explained by differences in patient populations, machines used, and interpretation standards. For instance, some studies have pointed to the effect of age on tympanometric measurements when younger children are compared to older children with false positive results due to anatomical and physiological reasons [9, 10]. Another way of increasing the diagnostic accuracy is by using different tympanometric parameters including peak-compensated static acoustic admittance and tympanometric width [11]. Even with current advancements, there is little integration of tympanometry protocols and their results in clinical practice. Combining tympanometry with other tools like audiometry and otoscopy has been suggested to improve accuracy [12]. In addition, how new technologies like WBT contribute to OME detection remain unchecked [13]. This study seeks to determine the validity of tympanometric diagnosis of OME in children, using myringotomy as the gold standard. This review aimed to integrate pre-existing literature to give a thorough account of the impact and challenges posed by tympanometry and clinical practice.

The aim was to direct attention toward new opportunities for further studies.

METHODS

This was an observational cross sectional study carried out over a period of 18 months from January 2022 to June 2024 at the Ear, Nose and Throat (ENT) Department of Hayatabad Medical Complex Peshawar.The sample size was estimated based on a 60% expected prevalence of otitis media with effusion in the target population, using a standard method for single population proportion with a 95% confidence level and 5% margin of error.The prevalence value was derived from previously published data by Yeo SG *et al* [9].The initial calculated sample size was 147, which was increased to 157 to account for potential exclusions or incomplete data.Ethical approval was granted from Institutional Review Board (IRB) of HMC (Ref# 1605) and written consent was obtained from parents or guardians of all children involved in the study.Inclusion criteria were a diagnosis of chronic otitis media with effusion (lasting longer than three months) in children between the ages of two and twelve is made based on the absence of acute inflammatory symptoms (such as redness, bulging, or otorrhea) and otoscopic findings of a dull or retracted tympanic membrane, air-fluid level, or bubbles behind the tympanic membrane. Otoscopic examination was performed using a pneumatic otoscope to assess tympanic membrane mobility. Presence of tympanometric findings suggestive of ME (Type B tympanogram) were also taken into account prior to surgery. Children with ear congenital anomalies (such as associated otitis media with cleft palate), recent upper respiratory infections (within 2 weeks), chronic suppurative otitis media, a history of tympanostomy tube for drainage (within 6 months), or acute otitis media (defined by otoscopic examination revealing bulging, hyperemia, or purulent discharge) were excluded. This helped to guarantee that only individuals with simple, persistent middle ear effusions appropriate for tympanometric evaluation were included in the study. Tympanometric evaluations were performed with the Interacoustics AT235h middle ear analyzer, according to Jerger's classification (Type A, B or C). As per the manufacturer's guidelines, the device was calibrated every three months by certified biomedical engineers to ensure the reliability of the device. Moreover, before each patient testing session, audiologists conducted daily functional checks to ensure probe tone frequency and pressure pump functionality and probe seal integrity. Any anomalies identified on daily checks either triggered a recalibration, or a halt to test until rectified. For quality control purposes, random duplicate tympanometry tests were performed on a small subset of participants to check for machine-related inconsistencies. These actions minimized variability in tympanometric data in each session of the study period. Under general anaesthesia myringotomy was performed by experienced ENT surgeons, and intraoperatively the presence or absence of middle ear effusion was documented. The presence of middle ear effusion was identified at the time of surgery by visual inspection after myringotomy. The presence of effusion was defined as any type of effusion (serous, mucoid, or purulent) seen coming from the incision or aspirated from the middle ear. If none was identified during gentle suctioning, then the ear was characterized as being without effusion. The primary operating surgeon immediately recorded all intraoperative findings and these were independently verified by a second ENT surgeon to limit reporter bias.

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Therefore, all cases were classified in a standardized and objective way, ensuring reliability of the outcome in terms of middle ear status. Data were analyzed using SPSS version 25.0. Descriptive statistics such as means and standard deviations were calculated for continuous variables, while frequencies and percentages were reported for categorical variables. Diagnostic accuracy parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated using cross-tabulation of tympanometry results against myringotomy findings as the reference standard. Chi-square (χ^2) test was used to assess the statistical significance of the association between tympanometric findings and intraoperative myringotomy results. A p-value of ≤ 0.05 was considered statistically significant. Inter-rater reliability for myringotomy interpretation was assessed using Cohen's kappa coefficient.

RESULTS

This research assessed the validity of using tympanometry to detect otitis media with effusion (OME) in children, using myringotomy results as gold standard. One hundred and fifty-seven children aged between 2-12 years were analyzed. Tympanometry was found to have high diagnostic accuracy for the detection of OME. Proportion of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were determined and presented in summary in (Table 1).

Table 1: Diagnostic Accuracy of Tympanometry in detecting OME

Demographics	Value (%)	95% Confidence Interval (CI)
Sensitivity	92.5%	88.3 - 95.6
Specificity	85.7%	79.4 - 90.5
Positive Predictive Value (PPV)	89.2%	84.1 - 93.0
Negative Predictive Value (NPV)	90.1%	85.0 - 93.8
Overall Accuracy	89.8%	86.2 - 92.7

The frequencies of type A, B, and C tympanograms in the population studied are summarized in Table 2.Type B tympanograms, suggestive of OME, were seen in 112 children (71.3%).Type A was observed in 25 children (15.9%) and type C in 20 children (12.7%). Table-2

Table 2: Distribution of Tympanogram Types

Tympanogram Type	Frequency (%)
Type A (Normal)	25 (15.9%)
Type B (Flat)	112 (71.3%)
Type C (Negative Pressure)	20 (12.7%)

Tympanometry findings alongside myringotomy results are shown in Table 3.Myringotomy verified middle ear effusion in 120 children which is 76.4%. Within this group, 111 children presented with Type B tympanograms resulting in a true positive ratio of 92.5%. 9 cases (5.7%) were noticed with false positive results (Type B tympanogram without effusion). Table-3

Table 3: Comparison of Tympanometry Results with Myringotomy Findings

Tympanometry Result	Myringotomy Positive (N)	Myringotomy Negative (N)	Total (N)
Type B (Positive)	111	9	120
Type A/C (Negative)	9	28	37
Total	120	37	157

The association between the tympanometry results and myringotomy findings was evaluated using a chi-square test. The analysis showed significant association between results and findings (χ^2= 125.4, $p < 0.001$), confirming that the use of tympanometry as a diagnosis tool for OME in children is accurate. A sub group analysis was performed to determine the diagnostic accuracy of tympanometry in different age subgroups: 2-5 years, 6-8 years, and 9-12 years. The results are provided below in Table 4. Regular calibration of the tympanometry equipment and independent verification of intraoperative findings by two ENT surgeons ensured the reliability of the results. The inter-rater agreement for myringotomy findings was excellent (Cohen's kappa = 0.92).

Table 4: Diagnostic Accuracy of Tympanometry by Age Group

Age Group (Years)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
2-5	90.2%	82.4%	87.5%	86.3%	88.1%
6-8	93.1%	86.7%	90.8%	89.7%	90.5%
9-12	94.5%	88.9%	91.2%	92.1%	91.8%

DISCUSSION

This study's results show that tympanometry is an exact diagnostic method for the determination of otitis media with effusion (OME) in children, with a sensitivity of 92.5% and specificity of 85.7%.These results are in accordance with earlier studies that have assessed the accuracy of tympanometry against the 'gold standard' of myringotomy [14, 15]. For example, Torretta S *et al.*, reported a sensitivity of 90% and specificity of 80% for tympanometry in detecting OME and this is similar to these results [16].This also applies to Principi and Esposito where they found PPV of 85% for tympanometry [17].The accuracy of diagnosis using tympanometry in this study was high, because standard protocols were observed such as the use of calibrated instruments and qualified personnel.The classification of the tympanograms according to Jerger's criteria (Type A, B, and C) provided an understandable and reproducible framework for interpretation of results.Type B tympanograms (flat trace) are strongly associated with OME.This is in accordance with the findings of Suzuki HG *et al.*, who pointed out the usefulness of the width of the tympanometric peak and the value of peak-compensated static acoustic admittance for the diagnosis [18].Notable differences in accuracy have been reported in other

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studies, frequently as a result of differing study populations, equipment, and criteria for interpretation. To illustrate, Paul C *et al.*, emphasized that younger children are likely to have greater rates of false positives because of mid-ear anatomy and physiology [19]. The study was done in a single tertiary care facility which may not be representative of other areas and therefore is a confounding factor in the generalizability of the results. The exclusion of patients with congenital ear anomalies and those who had previous tympanostomy tube insertions also comes with selection bias. Further research should evaluate the accuracy of diagnosis of OME with more sophisticated tympanometric techniques like wideband tympanometry that was noted to be helpful in OME detection [20].Multicentric studies with different populations are also necessary to test the results to be more widely applied.Moreover, longitudinal studies evaluating the clinical outcomes for children with OME diagnosed through tympanometry will assist in understanding the consequences of using this clinical tool for diagnosis.

CONCLUSIONS

This study demonstrated that tympanometry is a valuable and effective tool for identifying otitis media with effusion (OME) in children. These findings emphasize the need for further validation of its clinical applicability across diverse populations and with improved wideband tympanometry techniques. Such research could enhance the accuracy of OME diagnosis and support better treatment strategies in pediatric care.

Authors Contribution

Conceptualization: MA, AN
Methodology: MA, HN
Formal analysis: MA, HN
Writing, review and editing: AN, HN
All authors have read and agreed to the published version of the manuscript

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Autopsy as a Teaching Methodology In Forensic Medicine: Students' Perspective

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ABSTRACT

Autopsy as a teaching tool has been historically accepted as a valued method for medical students but its usage has been reduced due to newer technologies being available. **Objective:** To assess the students opinions' on autopsy as a learning tool and their views on alternative teaching methods. **Methods:** A cross-sectional questionnaire-based study was conducted in 2024 at Rashid Latif Medical College. Prevalidated questionnaires were distributed among the third year MBBS students and participation was voluntary.115 complete questionnaires were analyzed by SPSS version 25.0. **Results:** All participants demonstrated an understanding of autopsy and considered its significance in medical education as a learning tool. 36.52% and 47.83% of the students considered videos and printed materials respectively as viable alternatives. However, 80.87% of students agreed that medical students should observe more autopsies for better understanding and appreciate their role in forensic and clinical correlation. **Conclusions:** Although students are aware of the potential benefits of autopsy, there is still a need to further emphasize its importance in this modern medical training. Without firsthand exposure, future doctors may struggle to explain procedures that have never been witnessed.

INTRODUCTION

The word "autopsy" originates from the Greek autopsia, meaning "the act of seeing for oneself". It can be simply defined as the examination of a deceased body, including its organs and structures. Autopsies are categorized into various types, but the medicolegal autopsy holds the most significance in forensic medicine. It involves a detailed examination of a dead body to determine the cause and manner of death [1]. Medicolegal autopsies play a crucial role in the administration of justice and are typically conducted in cases of suspicious or unexplained deaths as mandated by state laws and authorized legal authorities. Determination of the cause of death is not always straightforward upon opening the body. It is not a clearly defined physical entity but rather a concept subject to interpretations. A medico-legal autopsy requires meticulous descriptions, precise measurements and thorough documentation. Beyond its importance in the field of forensic medicine, the role of autopsy has evolved as a valuable teaching tool in medical education. It helps students understand the natural history of diseases and how they relate to clinical signs and symptoms [2]. For medical students it provides a unique opportunity to study human anatomy, observe disease processes and connect pathological findings with clinical scenarios. Autopsies

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also offer critical insights into diagnostic errors and often uncover previously undiagnosed conditions that contributed to a patient's death. Globally, autopsy is recognized as a valuable teaching tool for both undergraduate and postgraduate medical students. With a rich historical background, it has evolved into an essential component of medical education. By observing autopsies, students develop a deeper understanding of pathophysiological principles and enhance their ability to integrate pathology, physiology, and clinical findings. Additionally, forensic medicine remains the only subject that systemically investigates causes of natural deaths linking medical findings with legal considerations to aid in the pursuit of justice [3]. An autopsy is an important part of the forensic medicine curricula, offering students unparalleled opportunities to expand their understanding of human anatomy and pathology. It enables them to correlate findings with different manners of death-homicidal, suicidal, or accidental [4, 5]. Since medical students may end up working as forensic specialists and physicians, exposure to autoposies is crucial in preventing misinterpretations of autopsy findings [5]. However, recent discussions have questioned the effectiveness of autopsy as a teaching modality [4]. Digital resources and virtual simulations have been shown to be just as effective as traditional autopsies in imparting the necessary technical skills and anatomical knowledge. Nonetheless, autopsy remains essential for identifying errors, defining new diseases and pathological patterns, and guiding future research. When conducted meticulously, autopsies provide early insights into epidemics and disease causing agents [3]. Despite its advantages, the number of autopsies performed worldwide during medical school training has significantly declined. This decline may be attributed to the advancement of modern diagnostic techniques and the reluctance of families to consent to autopsies. The decreasing medical school autopsy rates pose a threat to the role of autopsy in medical education [6, 7]. Autopsy remains a cornerstone of problem-based learning and an essential method for correlating data from many sources helpful for imparting justice. However, it is often regarded as physically unpleasant and emotionally distressing, making it a challenging yet indispensable component of medical education [6]. In Pakistan, limited research has been conducted on medical students' perception of autopsy. The primary objective of this study is to evaluate how medical students who have studied forensic medicine perceive autopsy as a teaching modality. The current literature on the subject reviewed above generally favors students in support of the dissection process and acknowledges the value of technology-based learning, noting its capacity to foster professionalism, cooperation, and emotional resilience.

METHODS

A descriptive cross sectional study was conducted at Rashid Latif Medical College, Lahore, Pakistan involving 3rd year MBBS students during the academic year 2024 from March 2024 to September 2024. Ethical approval for this study was obtained from the Ethical Review Board of Rashid Latif Medical College (Reference no: IRB/2024/428). The participants had completed their 6-week rotation at Lahore General Hospital mortuary where they observed autopsies. A prevalidated questionnaire was distributed to the participants to assess their experience and opinions regarding autopsies. A prevalidated questionnaire was chosen to ensure the reliability and consistency of the data collected. Using a prevalidated tool offers several advantages—it minimizes measurement errors, ensures that the questions are interpreted uniformly by all respondents, and enhances the credibility of the study findings. Additionally, it allows for easier comparison with similar studies and saves time in the design and piloting phase, ensuring the focus remains on data collection and analysis. A sample size of 115 participants was calculated with a 90% confidence level (z=1.645), 7.7% margin of error, and by taking the prevalence of expected knowledge regarding medical should witness autopsies at 51.9% [8]. The following formula was used to calculate sample size $n=\frac{Z^2_{1-\alpha}P(1-P)}{d^2}$. Third year MBBS students who had completed their six week forensic medicine rotation were included in the study. Students who did not complete the full rotation or declined to participate were excluded from the study. A convience samlpling technique was used involving all eligible third year MBBS students who had completed their forensic medicine rotation during the academic year. Ethical considerations were carefully addressed in this study. Approval was obtained from the Institutional Review Board (IRB) of Rashid Latif Medical College before data collection. Participation in the study was entirely voluntary, and informed consent was obtained from all respondents. To maintain participant confidentiality, no personal identifiers were collected, and the questionnaires were anonymized. The data were securely stored and only accessible to the research team, ensuring that privacy and confidentiality were fully maintained throughout the study. Data entry and analysis were performed using SPSS version 25.0 with findings presented in tables and figures. Chi-square tests and Fisher's exact tests were used to assess correlations where needed with gender and the number of autopsies observed by the students. P values ≤ 0.05 was considered statistically significant.

RESULTS

A total of 120 third year MBBS students were invited to participate in the study, and 115 students (response rate 95.83%) completed the questionnaires. The cohort consisted of 65 females (56.52%) and 50 males (43.48%).

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The age distribution ranged from 20 to 25 years of age. The majority of the participants (59.13%) were age group of 22-23. The detailed age and gender distribution of the participants is presented in Table 1.

Table 1: Age and Gender distribution among students analysed using Chi square test

Age (Years)	Male Frequency (%)	Female Frequency (%)	Total Frequency (%)
20-21	17 (14.78%)	17 (14.78%)	41 (35.65%)
22-23	28 (24.35%)	28 (24.35%)	68 (59.13%)
24-25	5 (4.35%)	5 (4.35%)	6 (5.22%)
Total	50 (43.48%)	50 (43.48%)	115 (100%)

Among the study participants, 63 students (55%) of the respondents observed two autopsies while only 16 students (14%) attended more than three autopsies. Notably, 7 students (6%) did not witness any autopsy during their rotation as illustrated in the form of a graph. (Figure 1).

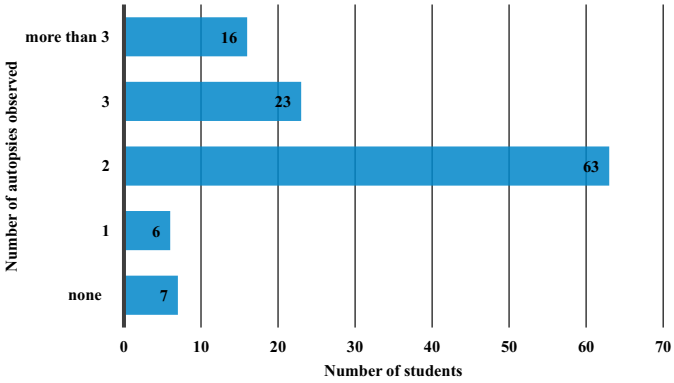

Figure 1: Number of Autopsies Observed by Students

Most participants (n=107, 93.04%) agreed that autopsy visits are effective and practical learning tools whereas 8 students (7%) disagreed. Similarly, 106 participants (92.17%) reported that their understanding of forensic medicine improved after attending the autopsy sessions. When asked about the overall experience, 95 students (82.61%) found these visits valuable and fulfilling, whereas 20 students (17.39%) did not share this sentiment. However, only 37 students (32.17%) indicated that these visits enhanced their interest in forensic medicine as a career option. Regarding alternative learning methods, 16 students (13.91%) considered autopsy visits a waste of time, and 55 students (47.83%) believed that forensics medicine could be effectively learned through textbooks. Additionally, 42 students (36.52%) suggested that video demonstrations could serve as a better alternative. A majority of participants (93 students, 80.87%) recommended that medical students should observe more autopsies as part of their curriculum. Additionally, 103 students (89.57%) recognized the importance of autopsy in the healthcare system and 89 students believed that the objectives and outcomes of autopsy-based learning were successfully achieved. Table 2 students suggests that medical students should watch more autopsies which helps the objective of this study.

Table 2: Overall Perception of Medical Students on Autopsy Visits and Their Educational Impact using Fisher Exact Test

S.No.	Demographics	Yes Frequency (%)	No Frequency (%)
Q1	Do you understand the meaning of the word Autopsy?	115 (100%)	0 (0%)
Q2	Do you think that autopsy visits are practical learning tool?	107 (93.04%)	8(6.96%)
Q3	Does your understanding of the subject get better after these visits?	106 (92.17%)	9 (7.83%)
Q4	Do you personally find these visit a valuable and fulfilling experience?	95 (82.61%)	20 (17.39%)
Q5	Do you think that these visits influence you to take interest in the subject as a career option?	37 (32.17%)	78 (67.83%)
Q6	Do the demonstrations at the autopsy supported your learning process?	98 (85.22%)	17 (14.78%)
Q7	Can you learn this topic from book without this exercise?	55 (47.83%)	60 (52.17%)
Q8	Do you think that videos can be a better alternative?	42 (36.52%)	73 (63.48%)
Q9	Was your time at these visits used effectively?	83 (72.17%)	32 (27.83%)
Q10	Would you suggest that medical students should watch more autopsies?	93 (80.87%)	22 (19.13%)
Q11	Is there any role of autopsy in health care system?	103 (89.57%)	12 (10.43%)
Q12	Do you think that objectives and outcomes of these visits are auspiciously achieved?	89(77.39%)	26 (22.61%)

The responses in Table 3 indicate both male and female students recognize the importance of autopsy visits as an effective learning tool, with over 90% agreeing with their practicality. However, fewer students believed these visits significantly influenced their career choices in forensic medicine. Notable a statistically significant difference (p=0.009) was observed in the suggestions that medical students should watch more autopsies with male students being more supportive of increased exposure compared to females. While most students acknowledge the role of autopsy in the health care system, opinions vary on whether videos could serve as an effective alternative

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Table 3: Perceptions of Medical Students on Autopsy Visits: A Gender-Based Comparison using Fisher Exact Test

S.No.	Questions	Genders	Yes Frequency (%)	No Frequency (%)	p-Value
Q1	Do you understand the meaning of the word Autopsy?	Male	50 (100%)	0	-
		Female	65 (100%)	0	
Q2	Do you think that autopsy visits are practical learning tool?	Male	46 (92%)	4 (8%)	0.726
		Female	61 (93.8%)	4 (6.2%)	
Q3	Does your understanding of the subject get better after these visits?	Male	46 (92%)	4 (8%)	1.000
		Female	60 (92.3%)	5 (7.7%)	
Q4	Do you personally find these visit a valuable and fulfilling experience?	Male	45 (90%)	5 (10%)	0.084
		Female	50 (76.9%)	15 (23.1%)	
Q5	Do you think that these visits influence you to take interest in the subject as a career option?	Male	20 (40%)	30 (60%)	0.158
		Female	17 (26.2%)	48 (73.8%)	
Q6	Do the demonstrations at the autopsy supported your learning process?	Male	46 (92%)	4 (8%)	0.111
		Female	52 (80%)	13 (20%)	
Q7	Can you learn this topic from book without this exercise?	Male	21 (42%)	29 (58%)	0.347
		Female	34 (52.3%)	31 (47.7%)	
Q8	Do you think that videos can be a better alternative?	Male	15 (30%)	35 (70%)	0.243
		Female	27 (41.5%)	38 (58.5%)	
Q9	Was your time at these visits used effectively?	Male	38 (76%)	12 (24%)	0.530
		Female	45 (69.2%)	20 (30.8%)	
Q10	Would you suggest that medical students should watch more autopsies?	Male	46 (92%)	4 (8%)	0.009
		Female	47 (72.3%)	18 (27.7%)	
Q11	Is there any role of autopsy in health care system?	Male	47 (94%)	3 (6%)	0.226
		Female	56 (86.2%)	9 (13.8%)	
Q12	Do you think that objectives and outcomes of these visits are auspiciously achieved?	Male	42 (84%)	8 (16%)	0.179
		Female	47 (72.3%)	18 (27.7%)	

DISCUSSION

Autopsies have long been recognized as the most reliable method for confirmation of diagnoses, playing an important role in medical education, legal and judicial proceedings, epidemiological studies, and understanding medical ambiguities and fallibilities. Their value in training medical students by providing hands-on experience, fostering critical thinking, and developing empathy has been well documented. Autopsies have been a vital component of medical education offering medical students valuable insights, abilities, and opportunities to cultivate compassion, understanding, and respect [3, 9]. Despite their historical significance, the prominence of autopsies in medical education has declined in recent decades. This decline can be attributed to several factors, including the lack of mortuary facilities in many private and public medical institutes resulting in limited student exposure [10]. Additionally, factors such as the constrained duration of forensic curricula, the decreasing number of hospital autopsies, advancement in diagnostic technology, and societal reservations regarding post-mortem examinations have contributed to this decline [3, 11]. The declining number of hospitals autopsies largely driven by improved diagnostics technologies and logistical barriers has significantly impacted hands-on learning opportunities for students. In addition to curricular change, the introduction of technological substitutes like movies and CD-ROMs, as well as current laws, have all led to a decrease in the use of autopsies as teaching tools. Similar trends have been reported in England, Wales, Canada, France, China, and Zambia, where postmortem examination rates have steadily declined [12, 13]. To counteract these, many institutions have adopted alternative teaching strategies such as virtual simulations, video demonstrations and case-based discussions to provide similar learning benefits in the absence of direct autopsy experience. In this study, all respondents demonstrated an understanding of the term "autopsy" which is essential for medical students. A clear comprehension of autopsy procedures not only strengthens their forensic knowledge but also equips future doctors to request postmortem examinations when necessary and to better address the concerns of bereaved families [3]. However, the limited exposure to autopsies may compromise students' depth of understanding in forensic medicine and reduce their preparedness to handle real-world medicolegal responsibilities. These findings revealed that approximately 54.78% of students observed two autopsies during their third year forensic medicine course while 14% had seen more than three autopsies. Only 6% of the students had not witnessed any autopsies. A plausible explanation for this limited exposure is the current curriculum structure, which allocates only 100 credit hours to the subject [14]. Encouragingly the majority of students recognized the significance of autopsies in the

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medical curriculum. In this study 93.04% of students suggested that medical students should observe more autopsies, a sentiment echoed in previous research by Ahmad et al., where 87% of participants felt that more autopsies should be observed to have a sound knowledge of the subject [15]. Students who witnessed more autopsies reported feeling more competent in forensic medicine, suggesting a positive corretaion between exposure and self-assessed competence. Furthermore, in the present study, 32.17% of students believed witnessing an autopsy enhanced the chance of pursuing forensic medicine as a career choice. While this was not a primary focus of the study, it raises an interesting question about whether early exposure to autopsies during preclinical years could positively influence career choices in forensic medicine. The component of the prompt does put into question the notion that witnessing an autopsy enhances the chance of pursuing forensic medicine as a career option. This supports the idea that the students perception of autopsies as meaningful learning tools may influence their interest in forensic careers. These findings are consistent with prior studies that medical students recognize the importance of autopsies in their education [8, 16]. Medical students widely recognize the usefulness of post-mortem examinations as a valuable educational tool. Several studies have reported similar sentiments among undergraduate students reinforcing the importance of incorporating autopsy-based learning into medical curricula [17, 18]. A survey conducted in Ohio found that 85% of participants believed autopsies should be an essential component of undergraduate medical education [19]. Teaching forensic medicine through autopsies is not only cost-effective but also enhances students' clinical and pathological understanding across various medical specialties [20]. Despite the decline in autopsy-based learning, forensic medicine students can refresh their clinical knowledge and pathological findings on the necessary steps in postmortem examination procedures through autopsy, which offers valuable learning opportunities [16, 17]. The findings of this study validate that students at Rashid Latif Medical College performed autopsies as an integral part of their education. To enhance medical students' understanding of autopsy and its clinical significance structured autopsy sessions should be integrated into a modular curriculum. This will bridge the gap between theoretical and practical applications. While this study does provide valuable insight but has a few limitations. Future studies with larger sample sizes and objective assessments of learning outcomes to better understand the educational impact of autopy will be more helpful. Given this consensus, further research should explore the long-term impact of autopsy exposure and should be made to reintegrate autopsy participation as a standard teaching method in medical curricula to maximize its educational benefits.

CONCLUSIONS

Despite the challenges facing autopsy education, its value as a teaching tool remains widely recognized. Integrating autopsies into medical curricula while addressing students' emotional and educational needs can enhance learning and prepare future doctors to navigate the complexities of death and disease. In countries like Pakistan, where violent fatalities are common, strengthening medicolegal frameworks and ensuring proper case referrals are important not only for delivering justice but also for accurate cause of death documentation. Improved collaboration between the medical and legal sectors can significantly enhance the effectiveness of forensic investigations and medical education alike.

Authors Contribution

Conceptualization: NY, SA
Methodology: NY, SA, HM
Formal analysis: NY, MAA, HM, KHS, RA
Writing, review and editing: MAA, MM, RA
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Role of Dexamethasone at the Surgical Site in The Control of Pain and Oedema in Management of Bilateral Mandibular Fractures Osteosynthesis Using the Split-Mouth Technique

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ABSTRACT

Osteosynthesis is a widely used technique for the treatment of fractures, ensuring stability in the healing process. This might cause postoperative pain, edema, trismus, infection, and reduced jaw mobility. **Objectives:** To assess the effectiveness of Dexamethasone in alleviating pain and oedema at the surgical site in patients undergoing bilateral mandibular fracture osteosynthesis using the split-mouth technique. **Methods:** A quasi-experimental study was conducted at the Pakistan Institute of Medical Sciences from 11th October 2023 to 10th August 2024, enrolling 30 participants with bilateral mandibular fractures.They were divided into two groups using the split-mouth technique, with 30 surgical sites in each group. Using a table of random numbers, surgical sites were assigned to Group A (study group), in which submucosal dexamethasone was administered after closure of the incision site, and Group B (control group), which did not receive submucosal dexamethasone. Postoperative pain and edema were evaluated at 24 hours, 72 hours, and one week postoperatively. **Results:** The mean age of the participants was 25.77 ± 8.274, with 73.3% being male. Group A experienced slightly reduced pain than group B (p s 0.005). After 24 hours and 1 week postoperatively, there were statistically significant differences in postoperative oedema among the two groups (p≤0.05), but not at 72 hours (p>0.05). **Conclusions:** It was concluded that dexamethasone can be used as an adjunct to improve postoperative outcomes in patients with mandibular fractures by decreasing pain and oedema.

INTRODUCTION

Once properly aligned, two or more bone fragments can be combined by a routine surgical process called osteosynthesis. It is important to use this technique to fix fractures and keep them stable while they recover [1]. Common osteosynthesis methods consist of metal plates and screws, intramedullary rods, and external fixation devices. Postoperative care is vital because patients often have pain, oedema, trismus, infection, and reduced jaw movements at the surgery site [2]. Clinicians have used a diversity of therapeutic methods, such as corticosteroids, acupuncture, cold therapy, low-level laser therapy, opioids, and nonsteroidal anti-inflammatory medications (NSAIDs) [3]. Predominantly, corticosteroids have gained notice for their capacity minimize problems and postoperative aftereffects in oral surgery [4, 5].According to the literature, these elements effectively decrease inflammation by interfering with several biological processes, such as leukocyte relocation, capillary dilatation, fibrin deposition, and edema [6].This action is best demonstrated by the synthetic cortisol complement dexamethasone, which has strong immunosuppressive and antiallergic properties.It is an important means in the

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postoperative care of patients having complex surgical procedures because of its ability to regulate inflammatory responses [7, 8]. Moreover, Dongol et al demonstrated the Dexamethasone group's oedema assessments were significantly lower (0.05 ± 1.2) than those of the control group (2.0 ± 0.85).3. 72 hours after surgery, the Dexamethasone group described significantly less pain and oedema as compared to the control group [2]. Additional study by Kishore *et al.*, reported that postoperative edema was much lower in the Dexamethasone group on the first day subsequently surgery, and 60–72% of cases had no swelling between the 4th and 7th days after surgery.On the other hand, all patients in the control group experienced edema, which generally went away in 9-12 days [9].The little information on Dexamethasone's effectiveness in lowering pain and swelling at surgical sites, especially in patients undergoing bilateral mandibular fracture osteosynthesis, supports the need to conduct this study in our local community in light of these positive findings.Despite the prevalence of osteosynthesis as a common surgical technique, there is a notable lack of comprehensive research addressing optimal management strategies for postoperative complications.Our study intends to close this knowledge gap and offer insightful information about the possible advantages of dexamethasone by examining its function in this particular setting.

This study aimed to assess how well dexamethasone works as an adjuvant medication to lessen postoperative pain and edema subsequent oral and maxillofacial operations. The ultimate goal of this study is to support better clinical practices with evidence, which will improve patient outcomes and satisfaction.

METHODS

A quasi-experimental study was conducted at the Department of Oral and Maxillofacial Surgery (OMFS) at the Pakistan Institute of Medical Sciences (PIMS) in Islamabad from October 11, 2023, to August 10, 2024, following approval by the Shaheed Zulfiqar Ali Bhutto Medical University ethical review board (No. F.1-1/2015/ERB/SZ ABMU/1064).The WHO sample calculator was used to calculate sample size with a significance level of 5% and a power of the test set at 90%. The anticipated population standard deviation is 1.025, and the expected mean difference between the groups is 2.0, with an anticipated population mean of 0.05 [3]. The sample size turned out to be 60 surgical sites, with 30 participants. This study used a split-mouth design, where individually participant's face was divided into two sections: the study side and the control side.The control group received conventional standard care, while the study side received the intervention that was being tested, as the injection of submucosal dexamethasone.This method successfully used each participant as their control, permitting the results of the two sides to be compared within the same individual. This concentrated variability improved the reliability of the results by enabling the study to account for individual factors that might affect the outcomes. The non-probability consecutive sampling technique was used to take in these patients, who ranged in age from 18 to 50 years and were of either gender and reported with bilateral mandibular fractures only. Individuals who were regarded as ASA II or ASA III and had accompanying fractures other than mandibular bone fractures that would have delayed their healing or surgical treatment were excluded from the study. By meeting these standards, the study population was sufficiently homogeneous to allow for the drawing of reliable findings about the effectiveness of treatment for bilateral mandibular fractures. Every patient who was hospitalized in the indoor facility to be operated through open reduction and internal fixation (ORIF) under general anesthesia was informed about the study participation before being the in the study, and their informed written agreement was obtained. A standardized form was used to collect demographic information such as age, gender, trauma source, trauma site, and trauma duration. A total of 30 Patients with bilateral mandibular fractures were divided using a table of random numbers into two groups, with 30 surgical sites in each group. Surgical sites were assigned Group A, in which submucosal Dexamethasone was administered after ORIF and closure of the incision site, and Group B, which did not receive submucosal dexamethasone.All patients underwent surgery performed by a single surgical team, following standard operating procedures. Group A patients received 8 mg of Dexamethasone [3] by submucosal infiltration at the surgical site following open reduction and internal fixation (ORIF) and primary closure of the incision site, whereas group B patients did not receive submucosal dexamethasone. Additionally, the duration of the operation (time from 1st incision to the last suture placed) and the period between trauma and surgery were recorded.The Visual Analogue Scale (VAS) is a well-validated, reliable, and widely used tool for assessing pain intensity.Studies confirm its validity and reliability in both acute and chronic pain settings, such as Delgado *et al.*, and Crossley KM *et al.*, reported excellent test-retest reliability with an intraclass correlation coefficient (ICC) of 0.49, and a validity score of 0.72, indicating consistent measurement over time [10, 11]. VAS is a 10-cm stripe with one side fixed, which was used to measure postoperative pain. A score of 0 denotes no pain, 1–3 mild, 4–6 moderate, 7–9 severe, and 10 the worst possible pain [12].To determine which side of the procedure caused more pain, patients were asked to record their possible experience level of pain on a line. Pain assessments were conducted postoperatively after 24 hours, 72 hours, and one week of surgery. The linear tape measurement method for assessing facial edema is a reliable and valid instrument, widely utilized in clinical research for postoperative swelling.Studies have indicated that tape measures of lengths between fixed facial

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landmarks yield good to outstanding reliability, with intraclass correlation coefficients (ICC) ranging from 0.66 to 0.95 depending on the anatomical site and evaluator consistency as reported by Chotipanich and Kongpit [12]. This point-to-point facial measurements demonstrated respectable precision and reproducibility, while neck circumference measures had ICCs ranging from 0.90 to 0.95, indicating strong reliability. In a similar vein, Dongol et al., objectively assessed postoperative edema using nine standardized facial lines measured in millimeters using a flexible tape, demonstrating the method's viability and sensitivity for identifying swelling changes [2], as shown in Figure 1.

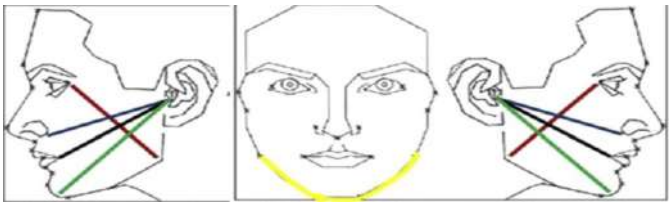

Figure 1: Linear Measurements of Postoperative Edema

Line 1 (Red): Beginning from the right lateral canthus to the right gonion.Line 2 (Blue): Beginning from the left lateral canthus to the left gonion. Line 3 (Green): Beginning from the right commissure of the lips to the right tragus. Line 4 (Purple): Beginning from the left commissure of the lips to the left tragus. Line 5 (Orange): Beginning from the midline of the chin to the right tragus. Line 6 (Yellow):Beginning from the midline of the chin to the left tragus.Line 7 (Cyan): Beginning from the right ala to the right tragus.Line 8 (Magenta): Beginning from the left ala to the left tragus. Line 9 (Black): Beginning from the left gonion to the right gonion.Three separate time intermissions were used to determine the level of postoperative oedema at 24 hours, 72 hours, and one week after surgery.The mean values gained from these assessments were computed.A thorough evaluation of surgical recovery is simplified by measuring each line, which offers important insights into how oedema evolves as per guidelines for measurement validated and published by Dongol A *et al.*, [2].The purpose of this comprehensive calculation is to offer valuable data concerning the effectiveness of dexamethasone in decreasing postoperative pain and oedema in individuals who have been reported with mandibular fractures bilaterally.The data were collected and interpreted using SPSS Version 27.0. Categorical variables like gender and pain level were shown via frequencies and percentages. Age, VAS pain scores, and postoperative oedema were amongst the numerical variables whose means and standard deviations were calculated.The study group was used to stratify the data.To assess the normality of quantitative data and confirm that the t-test was adequate, histograms, Q-Q plots, and the Shapiro-Wilk test were employed.The mean pain and oedema scores of two separate groups were compared using an independent sample t-test.A statistically significant p value of ≤0.05 proposed that there were significant differences between the two groups.This analysis provided insights into the effectiveness of Dexamethasone in managing postoperative complications like pain and edema in patients with bilateral mandibular fractures.

RESULTS

The data shows that majority of the patients reported in the department of OMFS were male (73.3%) with a mean age of 25.77 ± 8.274. The gender distribution is shown in Figure 2.

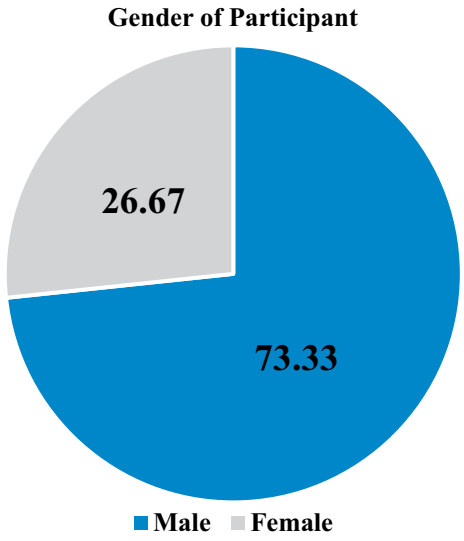

Figure 2: Gender Distribution of Study

The study represents the frequency and percentage of the Pain category based on the VAS score in either group after 24 hours, 72 hours, and one week postoperatively. There is slightly reduced post op pain among the patients in which dexamethasone was used compared to the control group B. The descriptive statistics of the study are shown in Table 1.

Table 1: Descriptive Statistics of Pain Category Based on VAS Score

Variables		Group-A Frequency (%)	Group B Frequency (%)	p-Value
VAS Pain After 24H Post-op	No Pain	0 (0.0%)	0 (0.0%)	<0.001*
	Mild Pain	0 (0.0%)	0 (0.0%)	
	Moderate Pain	0 (0.0%)	0 (0.0%)	
	Sever Pain	30 (100.0%)	15 (50.0%)	
	Worst Possible Pain	0 (0.0%)	15 (50.0%)	
	Total	30 (100.0%)	30 (100.0%)	
VAS Pain After 72H Post-op	No Pain	0 (0.0%)	0 (0.0%)	0.001*
	Mild Pain	09 (30.0%)	0 (0.0%)	
	Moderate Pain	16 (53.3%)	16 (53.3%)	
	Sever Pain	05 (16.7%)	14 (46.7%)	
	Worst Possible Pain	0 (0.0%)	0 (0.0%)	
	Total	30 (100.0%)	30 (100.0%)	

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VAS Pain After 1 Week Post-op	No Pain	18 (60.0%)	03 (10.0%)	<0.001*
	Mild Pain	11 (36.7%)	27 (90.0%)	
	Moderate Pain	01 (3.3%)	0 (0.0%)	
	Sever Pain	0 (0.0%)	0 (0.0%)	
	Worst Possible Pain	0 (0.0%)	0 (0.0%)	
	Total	30 (100.0%)	30 (100.0%)	

*Statistically significant

The study presents the mean and standard deviation of pain score and oedema with p-value after 24 hours, 72 hours, and one week postoperatively. The mean postoperative pain of the patients in group A was recorded as 7.90 ± 0.803, 4.80 ± 1.584, and 1.17 ± 1.020 after 24 hours, 72 hours, and after one week. Similarly, in group B mean postoperative pain was 9.90 ± 2.604, 6.34 ± 0.928, and 2.27 ± 0.907 after 24 hours, 72 hours, and one week postoperatively. Post stratification of the study outcome measured through independent sample t test shows a significant difference as p-value was <0.001*. The mean postoperative oedema of the patients in group A was recorded as 13.219 ± 1.042, 13.109 ± 0.905, and 11.466 ± 0.546 after 24 hours, 72 hours, and one week. Similarly, in group B mean postoperative oedema was 14.296 ± 1.094, 13.392 ± 1.005, and 11.851 ± 0.742 after 24 h, 72 h, and one week postoperatively. Post-stratification of the study outcome measured through independent sample t test shows a significant difference as p-value was <0.001* after 24h and 0.026* one week postoperatively, but this association was not significant after 72h postoperatively as p-value was 0.256, as given in Table 2.

Table 2: Descriptive Statistics of Independent Sample Test of the Study Outcomes Postoperatively

Variables		Group A	Group B	p-Value	Age of the Study Population
		Mean ± SD			
Vision Analog Scale Pain Score	Pain After 24H	7.90 ± 0.803	9.90 ± 2.604	<0.001*	25.77 ± 8.274
	Pain After 72H	4.80 ± 1.584	6.34 ± 0.928	<0.001*	
	Pain After 1 Week	1.17 ± 1.020	2.27 ± 0.907	<0.001*	
Oedema	Oedema After 24H	13.219 ± 1.042	14.296 ± 1.094	<0.001*	
	Oedema After 72H	13.109 ± 0.905	13.392 ± 1.005	0.256	
	Oedema After 1 Week	11.466 ± 0.546	11.851 ± 0.742	0.026*	

*Statistically significant

DISCUSSION

The anti-inflammatory qualities and proven safety of corticosteroids (also known as glucocorticoids) make them widely used. Cortisone, dexamethasone, prednisolone, and other substances are members of the glucocorticoid class. By blocking the chemotaxis of inflammatory mediators, these substances reduce vascular dilatation, fluid exudation, and cell turnover [14]. Due to its long half-life and rapid action, dexamethasone, a common glucocorticoid, is suggested for the majority of complex surgical operations, such as orthognathic surgery and open reduction internal fixation (ORIF) of facial fractures. Because of its prominence and mobility, the mandible is a common source of damage among facial bone fractures [15]. Oral and maxillofacial surgeons frequently prescribe corticosteroids to treat postoperative pain and edema. When assessing its effects on inflammation, tissue repair, and immunological function, clinical correlation is crucial [16]. The outcomes of this split-mouth randomized comparative study provide valuable information about how dexamethasone affects postoperative pain and oedema in individuals with bilateral mandibular fractures after open reduction and internal fixation. Thirty patients from 60 surgery sites participated in the study, and SPSS version 27.0 was used to analyze the data. The demographic profile of the patients showed that the majority were male (73.3%) with a mean age of 25.77 ±8.274, which is consistent with the typical age group involved in the road traffic accidents, Sports injuries, and physical assaults seeking oral and maxillofacial surgical management. This trend among the population was also reported by Wemambu et al., [17]. The gender distribution highlights the preponderance of male patients in the sample. The descriptive statistics reveal the frequency and percentage of pain categories based on the Visual Analog Scale (VAS) scores recorded at 24 hours, 72 hours, and one week postoperatively. From this, it is evident that patients who received dexamethasone (Group A) reported slightly reduced postoperative pain compared to the control group (Group B). The pain scores in Group A were consistently lower, suggesting that dexamethasone may have a beneficial effect in managing postoperative pain. This observation is further supported by the mean and standard deviation of pain. In Group A, the mean postoperative pain was 7.90 ± 0.803 at 24 hrs, 4.80 ± 1.584 at 72 hrs, and 1.17 ± 1.020 after one week. Conversely, Group B reported higher pain scores, with values of 9.90 ± 2.604, 6.34 ± 0.928, and 2.27 ± 0.907 at the corresponding time points. A significant difference in postoperative pain between the two groups was confirmed by an independent sample t-test; a p-value of ≤0.05 showed that dexamethasone significantly decreased pain in comparison to the control group. Mubeen et al., and Hashim et al., have reported similar reduction in post-operative pain after administration of dexamethasone [16, 18]. In addition to pain, the study also measured

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postoperative oedema, which is another critical outcome in post-surgical recovery. The mean oedema scores for Group A were 13.219 ± 1.042 at 24 hrs, 13.109 ± 0.905 at 72 hrs, and 11.466 ± 0.546 after one week. For Group B, the mean oedema scores were slightly higher at all time points: 14.296 ± 1.094, 13.392 ± 1.005, and 11.851 ± 0.742, respectively. Table 2 further presents statistical analysis that shows significant differences between the groups at 24 hrs and one week postoperatively, with p-values ≤0.05. However, at 72 hrs, no statistically significant difference was observed in oedema between the two groups (p-value ≥0.05). This proposes that dexamethasone, effectively reduced oedema in the initial postoperative period and remained effective one week after surgery. The role of dexamethasone in reducing oedema postoperatively was also investigated by Hashim *et al.*, Oksa *et al.*, and Genc et al., and they also concluded that it significantly reduces the postoperative oedema [18-20]. In another study reported by Rodrigues VP *et al.*, 100 participants between the ages of 18 and 40 were divided into 2 equal groups [21]. Fifty of these individuals (the Test group) received 4 mg of dexamethasone submucosally at the operating position before surgery. In the control group, however, no submucosal dexamethasone was administered. Both pain and facial edema were assessed, and while edema greatly decreased on the second postoperative day, which is inconsistent with our findings, pain significantly improved, which is in line with our research. Nair RB *et al.*, reported that participants who received dexamethasone 24 hrs and 72 hrs postoperatively experienced less edema [22]. The study also stated reduced pain score on the visual analog scale in dexamethasone group after 24 hours and 72 hours of operation compared to the control group [18]. These findings underscore the potential benefits of dexamethasone in managing postoperative pain and oedema in oral and maxillofacial surgery. The results suggest that dexamethasone can be a useful adjunct in improving patient recovery by reducing pain and swelling, particularly in the first 24 hours and 1 week after the surgery. The observed reduction in pain and oedema supports the use of dexamethasone as a standard adjunctive treatment in these types of surgeries. For confirmation of the long-term properties of dexamethasone and to examine its possible influence on other postoperative results, such as infection rates or functional recovery, more research with a bigger sample size and longer follow-up times would be helpful.

CONCLUSIONS

It was concluded that, based on the findings, dexamethasone is a supportive adjunctive drug for refining post-operative recovery. Its regular use in homologous surgical operations may improve patient outcomes and well-being due to the noticeable decrease in pain and edema. Dexamethasone should be a usual component of post-operative treatment regimens in light of these positive results. Patients may be happier and heal more quickly as a result of this approach.

Authors Contribution

Conceptualization: BP
Methodology: BP, RA, NUA, HU
Formal analysis: BP
Writing review and editing: MKS, MUF
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Risk Factors for Developmental Dysplasia of the Hip in Patients Presenting to a Tertiary Care Hospital

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ABSTRACT

Developmental dysplasia of the hip (DDH) involves abnormal hip joint development and is influenced by several perinatal risk factors. Early diagnosis is essential for optimal management. **Objective:** To evaluate the frequency of DDH-associated risk factors and their statistical associations. **Methods:** A cross-sectional study was conducted at Quaid-E-Azam Medical College, Bahawalpur, from January to August 2024. A total of 153 DDH patients were included. Risk factors such as gender, gestational age, birth weight, mode of delivery, breech presentation, oligohydramnios, multiple pregnancies, firstborn status, family history, and maternal complications were documented. Associations were analyzed using chi-square tests ($p<0.05$). **Results:** Of the 153 patients, 77 (50.3%) were male and 76 (49.7%) female. Term births were predominant (75.2%), and 19.6% had low birth weight. Breech presentation was seen in 13.7%, and oligohydramnios in 16.3%. Cesarean section accounted for 66.7% of deliveries, with no significant association with breech presentation (p=1.000). A significant association was found between multiple pregnancies and low birth weight, as all multiple births had low birth weight infants (p=0.000). No significant associations were found for gender, oligohydramnios, firstborn status, or family history. **Conclusions:** It was concluded that multiple pregnancies and resulting low birth weight showed a significant association with DDH. Other risk factors, including breech presentation and oligohydramnios, demonstrated no significant correlation. Focused DDH screening is recommended in infants from multiple gestations with low birth weight to ensure early detection and intervention.

INTRODUCTION

Developmental dysplasia of the hip (DDH) represents a continuum of structural abnormalities of the hip, ranging from mild instability to complete dislocation. If untreated, DDH can lead to serious, life-altering disorders, such as abnormal gait, chronic pain, and early-onset osteoarthritis. Therefore, early diagnosis and intervention targeting associated risk factors are crucial [1]. Multiple genetic, environmental, and perinatal factors influence the worldwide incidence of DDH. Previous studies consistently identify female gender as a risk factor, possibly due to estrogen-induced ligamentous laxity during intrauterine development [2, 3]. Breech presentation significantly increases DDH risk, as abnormal fetal hip positioning contributes to instability [4]. Additionally, a positive family history substantially raises DDH risk [5]. Macrosomia has also been implicated due to increased mechanical stress

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on the hip joint [6]. However, the role of prematurity remains controversial, with some evidence suggesting that reduced intrauterine forces in preterm infants may confer protection against DDH [7]. Cultural practices, including swaddling that restricts hip mobility, have been associated with higher DDH incidence, highlighting interactions between genetic susceptibility and environmental factors [8]. Technological advancements have improved diagnostic accuracy, with ultrasonographic screening outperforming traditional physical examination manoeuvres (e.g., Barlow and Ortolani manoeuvres), especially in mild dysplasia cases [9, 10]. Healthcare disparities further complicate DDH outcomes. Inequities in care access, socioeconomic status, and cultural barriers contribute to delayed diagnosis and suboptimal treatment outcomes. Consequently, targeted screening programs for high-risk populations are recommended despite some concerns regarding overtreatment [11, 12]. Although significant progress has been made in understanding DDH diagnosis and management, its precise etiopathogenesis remains unclear. Emerging genetic studies implicate multiple genes involved in connective tissue formation, osteogenesis, and chondrogenesis, with epigenetic modifications such as DNA methylation adding further complexity [12]. However, the prevalence and importance of specific DDH risk factors vary significantly across different populations, and local data are scarce. This study addresses this gap by assessing the frequency and associations of key DDH risk factors among patients presenting to a tertiary care hospital in Bahawalpur.

This study aims to identify the frequency of critical DDH risk factors and examine their associations within this specific regional context.

METHODS

This cross-sectional study was conducted at Quaid-E-Azam Medical College, Bahawalpur, from January 2024 to August 2024 after obtaining approval from the Institutional Review Board (IRB reference no. 2348/DME/QAMC Bahawalpur). The sample size was calculated using Open Epi software, assuming a 95% confidence interval, a 7% margin of error, and a reported prevalence of oligohydramnios (26.38%) among DDH patients from a previous study by Zeb et al., [13]. Consequently, a total of 153 patients were included. Written informed consent was obtained from parents or legal guardians before inclusion. Patients aged from birth up to 2 years (0–24 months) with a confirmed diagnosis of developmental dysplasia of the hip (DDH) were included. Patients older than 2 years or with incomplete medical records were excluded. Participants were recruited through non-probability consecutive sampling, involving patients who presented to the outpatient pediatric orthopedic clinic or those referred for specialized orthopedic consultation during the study period. Data collection involved structured interviews with parents or guardians, combined with a thorough review of hospital medical records to ensure accuracy. Prenatal risk factors documented included breech presentation (confirmed via medical records either in the last trimester or at delivery), oligohydramnios (documented through prenatal ultrasound reports), multiple pregnancies (confirmed through prenatal records), advanced maternal age (≥35 years), maternal complications (specifically gestational diabetes or preeclampsia documented in medical records), and a family history of hip disorders in first-degree relatives (documented through structured parental interviews). Detailed birth-related variables were also documented, including gender, mode of delivery (vaginal or cesarean), firstborn status, birth weight (low <2.5 kg, normal 2.5–4.0 kg, or high >4.0 kg), and gestational age (preterm: <37 weeks; term: ≥37 weeks). DDH diagnosis was confirmed clinically by two experienced pediatric orthopedic specialists using standardized manoeuvres (Barlow and Ortolani tests). Diagnoses were further validated by imaging studies hip ultrasound was performed for patients younger than 6 months using a Toshiba ultrasound machine (Model No UTSH19C), while plain radiographs (anteroposterior and frog-leg views) were obtained for patients aged 6 months or older using a Toshiba digital

RESULTS

A total of 153 patients diagnosed with DDH were included, with a balanced gender distribution of 77 males (50.3%) and 76 females (49.7%). The majority of patients were term births (75.2%), and over half of the patients had high birth weight (>4.0 kg, 53.6%). Cesarean sections were more frequent (66.7%) compared to vaginal deliveries (33.3%). Breech presentation occurred in 21 patients (13.7%), while oligohydramnios was present in 25 patients (16.3%). Firstborn status was noted in 51 patients (33.3%), and a positive family history of DDH was reported in 19 patients (12.4%). Multiple pregnancies were uncommon, occurring in 15 cases (9.8%), and advanced maternal age (≥35 years) was observed in 21 mothers (13.7%). Maternal complications, including gestational diabetes and preeclampsia, were documented in 30 mothers (19.6%) (Table 1).

Table 1: Frequency Distribution of Risk Factors for DDH in the Study Population (n=153)

Variables	Categories	Frequency (%)
Gender	Male	77 (50.3%)
	Female	76 (49.7%)
Gestational Age	Preterm	38 (24.8%)
	Term	115 (75.2%)
Birth Weight	Low (<2.5 kg)	30 (19.6%)
	Normal (2.5–4.0 kg)	41 (26.8%)
	High (>4.0 kg)	82 (53.6%)
Mode of Delivery	Vaginal	51 (33.3%)
	Cesarean	102 (66.7%)

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Firstborn Status	Firstborn	51 (33.3%)
	Not Firstborn	102 (66.7%)
Breech Presentation	No	132 (86.3%)
	Yes	21 (13.7%)
Oligohydramnios	No	128 (83.7%)
	Yes	25 (16.3%)
Multiple Pregnancy	No	138 (90.2%)
	Yes	15 (9.8%)
Family History of DDH	No	134 (87.6%)
	Yes	19 (12.4%)
Maternal Age Group	Advanced Age	21 (13.7%)
	Normal Age	(86.3%)
Maternal Complications	No	123 (80.4%)
	Yes	30 (19.6%)

In the analysis of breech presentation with various factors, no significant association was observed with mode of delivery (p=1.000; OR=1.00, 95% CI: 0.38–2.66) or gender (p=0.839; OR=1.10, 95% CI: 0.44–2.77), suggesting no meaningful relationship in this cohort. However, oligohydramnios (p<0.001; OR=0.03, 95% CI: 0.01–0.12), firstborn status (p=0.007; OR=0.25, 95% CI: 0.09–0.66), and family history of DDH (p<0.001; OR=0.02, 95% CI: 0.003–0.07) showed statistically significant associations with breech presentation. Despite their statistical significance, the wide confidence intervals indicate considerable uncertainty in the precision of these estimates, and the findings should be interpreted cautiously (Table 2).

Table 2: Association of Breech Presentation with Mode of Delivery, Gender, Oligohydramnios, Firstborn Status, and Family History of DDH

Variable	Category	Breech: No (n, %)	Breech: Yes (n, %)	p-value	Odds Ratio (95% CI)
Mode of Delivery	Vaginal Delivery	44 (33.3%)	7 (33.3%)	1.000	1.00 (0.38–2.66)
	Cesarean Delivery	88 (66.7%)	14 (66.7%)		
Gender	Male	66 (50.0%)	11 (52.4%)	0.839	1.10 (0.44–2.77)
	Female	66 (50.0%)	10 (47.6%)		
Oligohydramnios	No	110 (83.3%)	18 (85.7%)	0.784	0.03 (0.01–0.12)*
	Yes	22 (16.7%)	3 (14.3%)		
Firstborn Status	Firstborn	44 (33.3%)	7 (33.3%)	1.000	0.25 (0.09–0.66)*
	Not Firstborn	88 (66.7%)	14 (66.7%)		
Family History of DDH	No	115 (87.1%)	19 (90.5%)	0.665	0.02 (0.003–0.07)*
	Yes	17 (12.9%)	2 (9.5%)		

Note: *Indicates that, despite statistical significance, results must be interpreted cautiously due to wide confidence intervals suggesting low precision

A strong and statistically significant association was observed between multiple pregnancies and low birth weight (p<0.001; OR=246.0, 95% CI: 13.90–4354.80). All patients from multiple pregnancies had low birth weight. This finding underscores the relevance of multiple gestations as a significant predictor of low birth weight, a known risk factor for DDH. However, due to the wide confidence interval, validation through larger, multi-center studies is recommended (Table 3).

Table 3: Association Between Birth Weight and Multiple Pregnancy

Birth Weight	No Multiple Pregnancy: n (%)	Multiple Pregnancy: n (%)	Total	p-value	Odds Ratio (95% CI)
Low (<2.5 kg)	15 (10.9%)	15 (100.0%)	30 (19.6%)	<0.001	246.0 (13.90–4354.80)*
Normal (2.5–4.0 kg)	41 (29.7%)	0 (0.0%)	41 (26.8%)		
High (>4.0 kg)	82 (59.4%)	0 (0.0%)	82 (53.6%)		

Note: *Strong association, but due to wide confidence interval, validation in larger, multi-center studies is recommended.

DISCUSSION

DDH is a complex condition influenced by multiple prenatal, perinatal, and postnatal factors. Our findings align partially with existing literature, providing valuable insights into DDH epidemiology and highlighting certain population-specific and methodological differences that deserve attention. The gender distribution in our study showed near-equal representation, with males (50.3%) and females (49.7%). This contrasts markedly with previous reports indicating female predominance. Zeb *et al.*, Xiao *et al.*, and Kural *et al.*, consistently highlighted female sex as a significant risk factor due to increased ligamentous laxity from maternal estrogen exposure [13–15]. The absence of a clear female predominance in our study could result from local genetic factors, unique referral patterns, or sampling variations specific to our tertiary care setting. Further large-scale local studies are warranted to explore these differences. Breech presentation occurred in 13.7% of patients, comparable with previous findings by Zeb *et al.*, [13]. Although breech positioning is recognized as a mechanical risk factor due to abnormal fetal hip positioning

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[16], our study did not demonstrate a significant association between breech presentation and mode of delivery (p=1.000; OR = 1.00, 95% CI: 0.38–2.66).This non-significant finding could be attributed to routine cesarean deliveries for breech presentation at our institution, reducing variability and statistical power to detect meaningful differences.Additionally, our sample size, though sufficient for estimating frequencies, may lack the statistical power required to identify smaller effect sizes, necessitating caution in interpreting this result. Oligohydramnios was observed in 16.3% of our patients, consistent with previous reports (26.3%) [13, 17]. This condition restricts fetal movement, potentially independently contributing to abnormal hip development. While the statistical analysis showed a significant association between oligohydramnios and breech presentation, the wide confidence intervals (OR=0.03; 95% CI: 0.01–0.12) suggest uncertainty around the magnitude of the effect. This emphasizes the importance of targeted monitoring in pregnancies complicated by oligohydramnios, regardless of fetal presentation. A particularly strong association was observed between multiple pregnancies and low birth weight (p<0.001; OR=246.0, 95% CI: 13.90–4354.80). All multiple gestations in our study resulted in low birth weight infants, aligning with Kural *et al.*,'s findings [15].The magnitude of this association, though striking, comes with wide confidence intervals reflecting limited sample size.Validation through larger, multi-center studies would reinforce the clinical relevance of this association and guide targeted screening protocols. Firstborn status was noted in 33.3% of our cohort, in agreement with Ghaznavi *et al.*, [18]. Although theoretically, the tighter uterine environment in first pregnancies may restrict fetal movement, our study found no significant relationship between firstborn status and breech presentation (p=1.000; OR=0.25, 95% CI: 0.09–0.66). Given the wide confidence intervals and marginal significance, further larger-scale studies should explore this potential relationship more robustly. Family history of DDH was positive in 12.4% of cases, consistent with Hakim *et al.*, reported prevalence of 10.9% [19]. Current analysis revealed a statistically significant but uncertain association due to wide confidence intervals (OR=0.02, 95% CI: 0.003–0.07). This genetic predisposition highlights the necessity of careful monitoring and targeted ultrasonographic screening in infants with a positive family history. In conclusion, our results underscore the multifactorial nature of DDH, with multiple pregnancies and low birth weight emerging clearly as significant risk factors. Consistent with recommendations by Kuitunen *et al.*, universal ultrasound screening strategies have demonstrated effectiveness in reducing late DDH diagnosis [20]. Future multicentric studies with larger sample sizes and enhanced statistical power are recommended to clarify these associations and refine DDH screening protocols.

CONCLUSIONS

It was concluded that our findings revealed a strong and statistically significant association between multiple pregnancies and low birth weight among infants diagnosed with DDH. Conversely, breech presentation and mode of delivery did not demonstrate significant associations, potentially due to routine cesarean practices and limited statistical power. Additionally, oligohydramnios, firstborn status, gender, and family history showed either no association or uncertain associations requiring cautious interpretation due to wide confidence intervals. These results highlight the necessity of prioritizing targeted DDH screening for infants born from multiple pregnancies, particularly those with low birth weight. Further large-scale, multi-center studies are warranted to confirm these findings and clarify the roles of other potential risk factors.

Authors Contribution

Conceptualization: MS
Methodology: AMS, AUKK
Formal analysis: MS
Writing review and editing: MS, SARA, MSS, ZU, AGSK
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Correlation between Placenta Weight and Birth Weight at Full Term Pregnancy

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ABSTRACT

Placental pathology is a recognized factor contributing to perinatal adverse health outcomes, and it might be linked to the growth of the placenta, potentially being evaluated through indirect physical measurements. **Objective:** To examine the average weight of the placental tissue and its association with newborn weight. **Methods:** The study, conducted at Civil Hospital, Karachi, from October 2017 to February 2018, was a descriptive cross-sectional study. It enrolled 36 primigravida females with singleton pregnancies who delivered in the labor room.Placental weight and newborn weight were recorded at the time of delivery, and a structured questionnaire was completed for each participant. **Results:** The average age of participants was 25.5 years, with a typical pregnancy period of 38.8 weeks. Mean placental weight was 604 grams(range 500-670 grams), and mean fetal weight was 2958 grams(range 2500-3400 grams). A statistically significant positive correlation was found between placental weight and neonatal weight (Pearson's correlation at the 0.01 level), as well as between maternal age and placental weight (significant at the 0.05 level). **Conclusions:** This study establishes a reference range for placental and fetal weight in the Pakistani population and highlights the significant correlation between the two. Placental weight serves as a reliable indicator of fetal health, underlining the importance of monitoring placental development and assessing the placenta post-delivery to evaluate neonatal health.

INTRODUCTION

Placental pathology is a recognized factor contributing to perinatal adverse health outcomes, and it might be linked to the growth of the placenta, potentially being evaluated through indirect physical measurements. The current study, based on a cross-sectional study design aimed to examine the average weight of the placental tissue and its association with newborn weight [1]. The placenta has a crucial responsibility in supporting a healthy pregnancy through promoting the transfer of oxygen, macronutrients and micronutrients between the mother and the growing fetus thus maintaining a healthy pregnancy [2]. Although the placenta plays a critical role in eutherian pregnancy, it has not received the level of attention it truly warrants. Recent research highlights that the placenta is not only the primary organ for supplying essential substances to the growing fetus but also plays a critical role in modulating the endometrial intracellular environment, ensuring a successful pregnancy. Contrary to the traditional focus on maternal factors, growing evidence suggests that placental tissue cells and their secretory factors are pivotal to modulating the mother's immune response and promoting immunological system adaptation during

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pregnancy [3].The placenta performs a key function in regulating nutrient transfer to the developing embryo throughout gestation.Proper placental function is therefore crucial for ensuring normal fetal growth.One of the most prevalent pregnancy complications is fetal growth restriction, or Intrauterine Growth Restriction (IUGR), commonly associated with compromised placental function[4].Placental weight reflects the balance between fetal nutrient demand and placental nutrient supply, influencing birth weight outcomes[5].The development of the placenta is essential for fetal well-being. Placental weight is a marker of proper metabolism and healthy pregnancy.Thus, the placental weight reflects fetal growth and perinatal well-being [6-8].The typical weight of a trimmed term placenta is 510 g, with a diameter of 185mm, a thickness of 23 mm, and an average volume of 500ml. Additionally, weight of the placenta varies between 300g and 890g depending on birth weight, with a mean of 590± 82g [1].A low placental weight may indicate inadequate placentation, while a higher placental weight could result from diabetes in the mother or excessive weight gain during pregnancy. Both of these conditions are recognized as predisposing factors for unfavorable results for the mother and fetus, as well as potential long-term effects on the newborn [9].Increased weight of the placenta, or a higher placental weight relative to birth weight, has been associated with various negative consequences, including low Apgar scores, respiratory distress in newborns, perinatal loss, and cardiovascular fatalities in later life[10]. Placental weight shows a positive correlation with neonatal birth weight.However, the proportion of placental weight to neonatal birth weight decreases as the pregnancy duration increases.Therefore, extending pregnancy beyond term may negatively impact fetal health [11].Abnormalities in placental weight can indicate potential placental insufficiency or underlying pathological conditions, raising the risk of negative perinatal outcomes.Regular monitoring of placental weight and fetal growth throughout pregnancy can help identify high-risk cases and improve perinatal outcomes[12]. In a study conducted by Zhang K *et al.*, it was observed that gestational weight gain showed a significant correlation with both the weight and the volume of the placenta, with the connection being particularly noticeable in women who were classified as underweight or had normal weight before pregnancy[13]. Salavati *et al.*, (2019) found that greater placental weight at term is positively associated with higher bone mass and improved body composition in childhood [14]. Mayhew *et al.*, (2020) used stereology to reveal distinct placental morphological changes in pre-eclamptic pregnancies, especially when accompanied by fetal growth restriction [15].A research study by Janthanaphan M *et al.*, revealed that the mean placental to birth ratio was 17.08%, showing a slight decline with increasing gestational age [16]. It also identified a strong link between decreases in placental weight falling beneath the 10th percentile and associated fetal compromise [16]. In their Ukrainian research, Little RE *et al.*, determined that the placenta was readily accessible, provided consistent measurements, and by revealing a distinct aspect of fetal growth served as a valuable research tool [17].Disorders of the placenta are a well-recognized driver of perinatal and neonatal death and illness, often precipitating harmful outcomes for both mother and infant.Conducting a comprehensive placental evaluation, including gross inspection, microscopic analysis, immunohistochemical staining and, when indicated, genetic testing, is essential for detecting these pathologies. Fetal growth and thriving in utero rely critically on placental function[1].The placental weight serves as an indicator of placental efficiency. However, it is worth emphasizing that morphometric measurements of the placenta vary significantly across different regions, countries, and even within regions of the same country. The ethnic and ancestral backgrounds of both mother and fetus also contribute to these variations.This study aimed to assess the mean placental weight of term newborns and its association with birth weight at a tertiary care hospital in Karachi, Pakistan.This study was conducted at Civil Hospital Karachi, a setting where no previous research has focused on placental weight within the local population. By concentrating on this hospital, it was aimed to address the unique characteristics and health outcomes of the population living in Karachi.

The findings from this study provide meaningful understanding of the role of placental weight within the framework of neonatal health in this specific region, which has not been previously explored in detail.

METHODS

This study, designed as a prospective cross-sectional analysis, took place in the Department of Obstetrics and Gynecology, Unit-1 of Civil Hospital Karachi, between October 2017 and February 2018 following formal approval from the College of Physicians and Surgeons of Pakistan (Letter reference number: CPSP/REU/OBG-2016-183-7218). A sample size of 36 was determined using the WHO software [16]. Non-probability consecutive sampling techniques were employed. Females aged 18-30 years, booked, primigravida, having singleton pregnancies (confirmed by ultrasound scan at booking) with no comorbidities and a normal BMI (between 20-15 kg/m2) were included in this study. The decision to include only primigravida women with normal BMI was made to reduce potential confounding factors that could affect placental weight and neonatal outcomes. Primigravida women were chosen because first-time pregnancies may have different placental and fetal growth patterns compared to subsequent pregnancies, which could influence the

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results. Additionally, women with abnormal BMI (either underweight or overweight) were excluded, as abnormal BMI has been associated with increased risks of delivering small for Gestational Age (SGA) or Large for Gestational Age (LGA) babies, which could introduce variability into the analysis of placental weight and its association with birth outcomes. While this selective inclusion helps to control for known variables that may affect the outcomes of the study, it does restrict the applicability of the findings to the wider population. The results may be more applicable to primigravida women with a normal BMI, and further research including a more diverse sample of women, with varying BMI and parity, is necessary to explore how these factors influence placental weight in relation to perinatal outcomes in different populations. To ensure an accurate link between placental weight and neonatal outcomes, certain groups were excluded women from the study. Women who were unbooked, indicating possible socioeconomic disadvantage and limited access to prenatal care, as well as those with pre-existing conditions such as diabetes mellitus and hypertension or other chronic medical issues, were not included as these conditions can significantly affect placental function and fetal growth. Additionally, pregnancies classified as preterm or post term were excluded from the study to eliminate the potential impact of gestational age on placental weight and neonatal outcomes. This selection criteria helped control for confounding factors related to maternal health, nutritional and socioeconomic status, allowing for a more focused analysis of the interplay between placental weight and neonatal outcomes in the studied population. By excluding these factors, it was aimed to ensure that the study focused on a more homogenous group, minimizing the potential impact of these confounders on the relationship between placental weight and neonatal outcomes. This study primarily aimed to assess the correlation between placental mass and neonatal birth weight in full-term deliveries. Following approval from the CPSP, and the ethical review committee, data were collected. Consecutive booked patients presenting to the labour room and undergoing normal vaginal delivery or delivered by surgical assistance (vacuum vaginal delivery, forceps vaginal delivery or cesarean section) meeting the inclusion criteria were enrolled after taking an informed consent. Weight of newborn was taken immediately after birth on a standard set weight scale (with no zero error). Following delivery of the placenta, it was rinsed with water to eliminate blood clots and then weighed using the same scale. Data collection was conducted using a proforma to gather necessary information, including demographic variables such as maternal age, gestational age, weight, height, Body Mass Index (BMI), and outcomes such as neonatal weight and placental weight. All data were collected and entered by the primary investigator. SPSS software, version 21.0, was utilized for data entry and analysis. The mean ± SD was calculated for continuous variables such as maternal age, weight, height, BMI, gestational age, and the weight of the newborn and placenta. Frequency and percentage were computed for categorical variables, including newborn gender. To evaluate the association between placental weight and neonatal weight, Pearson's correlation coefficient was employed. Two-tailed testing was used to account for both positive and negative associations, as no specific direction of the relationship was hypothesized. Statistical significance was defined as a p-value of less than 0.05. Influencing factors, including maternal age, gender, gestational age, weight, height, BMI, and pregnancy duration, were adjusted using stratification. Post-stratification, the correlation coefficient was recalculated.

RESULTS

A sum of 36 primigravida females who met the requirements for inclusion were involved in the research. Table 1 summarized the mean values of the key variables in the study. The data includes 36 participants with no missing values. This table presents the mean, median, mode, standard deviation, and range for variables such as age, gravida (number of pregnancies), weight, height, BMI, gestational duration, placental weight, and fetal weight. Key observations include a mean age of 25.58 years, a mean BMI of 22.57, an average gestational duration of 38.86 weeks, and average placental and fetal weights of 604 grams and 2958.33 grams, respectively. The table highlighted the central tendency and spread of these variables, providing insight into the sample characteristics.

Table 1: Demographics of the Study Participants

Variable	N (Valid)	Missing	Mean ± SD	Median	Mode	Range
Age	36	0	25.58 ± 2.98	26.00	26.00	12.00
Gravida	36	0	1.00 ± 0.00	1.00	1.00	0.00
Weight (kg)	36	0	2.42 ± 0.55	2.00	2.00	2.00
Height (cm)	36	0	164.03 ± 5.52	165.00	165.00	29.00
BMI	36	0	22.57 ± 1.19	22.00	22.00	4.47
Duration (weeks)	36	0	38.86 ± 0.95	39.00	39.00	4.00

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Placenta Weight (g)	36	0	604.00 ± 39.17	605.00	600.00	170.00
Fetal Weight (g)	36	0	2958.33 ± 223.45	2950.00	2900.00	900.00

N=Number

A marked association was observed between placental weight and fetal size or weight, as determined by the Pearson correlation coefficient (at the 0.01 significance level) as demonstrated in Table 2.

Table 2: Association between placental, fetal weights and Age using Pearson Correlations

Variables	Placental Weight	Fetal Weight
Placenta Weight	Pearson Correlation	1
	Sig. (2-tailed)	-
	N	36
Fetal Weight	Pearson Correlation	0.602**
	Sig. (2-tailed)	0.000
	N	36
Age	Pearson Correlation	0.309*
	Sig. (2-tailed)	0.003
	N	36

* Correlation is significant at the 0.05 level (2-tailed)

Among the singleton pregnancies, 19 infants and 17 infants were males and females respectively. The average BMI of the patients was 22.56 kg/m2, with a strong positive link observed between the weight of the fetus, the weight of the placental and the BMI of the patient.

Figure 1 and 2 demonstrated the chorionic and the basal plate of the placenta and the photographs were taken during data collection.

Figure 1: Fetal Surface of a Term Placenta with Central Cord Insertion

DISCUSSION

The perinatal mortality rate, ranging from 63 to 92 per 1,000 births in two provinces of Pakistan, is notably high. A large proportion of births and neonatal deaths take place in household settings and go unrecorded. Despite the implementation of several effective child survival programs, their impact on perinatal health remains limited [18]. Placental weight is increasingly recognized as a key determinant of fetal development, neonatal outcomes, and long-term health. Hasegawa *et al.*, demonstrated that estimating placental weight using ultrasonography in the second trimester can serve as a valuable predictor of fetal growth, underscoring the clinical utility of prenatal imaging in early risk assessment [19]. Faupel-Badger *et al.*, found a significant association between increased placental weight and the risk of childhood obesity, suggesting that placental development may influence postnatal metabolic programming [20]. Similarly, Burton *et al.*, emphasized that disruptions in placental structure and function contribute to the developmental origins of chronic diseases, reinforcing the long-term implications of placental health [21]. In pregnancies affected by maternal obesity, O'Tierney-Ginn *et al.*, observed an increase in placental weight and alterations in fetal body composition, highlighting the placenta's role as a mediator between maternal metabolic status and fetal growth [22]. Heazell *et al.*, provided mechanistic insight by linking intrauterine growth restriction to increased placental apoptosis and altered angiogenic signaling, suggesting pathological remodeling of the placenta in response to suboptimal intrauterine conditions [23]. Moreover, Karayiannis *et al.*, reported that heavier placentas are associated with better neonatal anthropometric outcomes, while Jensen *et al.*, noted that an imbalanced placental-to-birth weight ratio may elevate the risk of neonatal complications [24, 25]. Finally, Abduljalil *et al.*, emphasized the importance of placental weight in predicting fetal drug and nutrient exposure, which has implications for both clinical pharmacology and personalized prenatal care [26]. A thorough examination of the placenta can uncover important pathological characteristics, such as hypoplasia, infarction, and retroplacental hemorrhage, which indicate maternal vascular mal-perfusion therefore, placental weight serves as a reliable indicator of placental function [27]. The primary role of the placenta is to supply oxygen and nutrients to the fetus, and its proper function is crucial for fetal health. It has been proposed that placental weight indicates the placenta's capacity to effectively deliver nutrients to the fetus. Although considerable attention has been given to understanding the placenta's role in fetal development, the significance of placental weight remains relatively unexplored [27]. While this study measures placental weight after delivery, the findings still have significant implications for clinical practice in predicting perinatal outcomes. The weight of the placenta after delivery can act as an effective indicator of its function during pregnancy, potentially identifying cases of placental insufficiency or abnormal fetal growth. By comparing placental weight to neonatal outcomes,

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clinicians can gain insights into possible complications related to fetal development, such as intrauterine growth restriction or other birth-related issues.This information may be useful for future pregnancies, allowing healthcare providers to monitor at-risk individuals more closely and take preventive measures when necessary.Additionally, the findings from this study may offer valuable contributions to the development of post-delivery guidelines for evaluating placental health, aiding in the management of long-term maternal and neonatal health. Although the study included a relatively small sample size of 36 participants, it is important to highlight that it was designed to detect key relationships between placental weight and neonatal outcomes, based on existing data and the WHO software for sample size calculation.However, a larger sample size would certainly increase the statistical power and reliability of the findings, making the results more generalizable to broader populations. Future research with a larger cohort is recommended to further strengthen the conclusions and better understand the relationships between placental weight and neonatal health outcomes.

CONCLUSIONS

This study established a reference range for placental and fetal weight in the Pakistani population and highlights the significant correlation between the two. Placental weight serves as a reliable indicator of fetal health, underlining the importance of monitoring placental development and assessing the placenta post-delivery to evaluate neonatal health.

Authors Contribution

Conceptualization: FNB
Methodology: SK
Formal analysis: ZAP
Writing, review and editing: ZM, FNB, RB, AI
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Association Between Meal Skipping and Premenstrual Syndrome Among Young Females

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ABSTRACT

Premenstrual syndrome (PMS) is the combination of physical, emotional, psychological and behavioural issues related to many symptoms. Due to which female are unable to perform their tasks. Somehow, PMS is linked with poor eating patterns and lifestyle.Modification in these things has seen lower prevalence in young female. **Objective:** To check the association between meal skipping and PMS in young females. **Methods:** A cross-sectional study was conducted among young female of the age group 18 to 30 at different educational institutions in Lahore. The target sample size of the study was 400 female.The data were gathered using a questionnaire sampling technique. A self-administered meal skipping questionnaire was used to check the dietary pattern, while the Premenstrual Syndrome Scale (PMSS) was used to examine the presence of PMS symptoms.After data collection, statistical analysis was done to find the results. **Results:** The p-value was 0.016, which was a significant level that indicates a positive association between PMS and meal skipping. Research revealed a significant link (p=0.016) between skipping meals and the severity of PMS symptoms, implying that dietary habits may influence symptom intensity. **Conclusions:** It was concluded that young adults, especially female, skip meals more frequently due to various reasons, which causes major health issues.It was seen that female who skip meals regularly have a more prominent association with premenstrual syndrome.

INTRODUCTION

Nutrition plays a major role throughout the life cycle, but it plays a crucial part in proper growth and development during the early years of life. That is why there is an increased demand in the adolescent phase due to body changes and the development of adult features. A healthy life is important for both male and female, but female nourished body is much more essential in later life stages [1]. A physically and mentally well woman is essential in building a healthy and fit generation, so they are required to consume all the necessary macro and micro nutrients, as in their later lives they have to give birth, for which more nutrients will be needed [2]. Menstruation occurs when a female hits their puberty age. It is defined as a periodic monthly cycle where there is blood discharge and cellular debris of the mucosal lining of the uterus in female. The normal and healthy length of menstruation is usually 21 to 35 days. Periods usually last for 2 to 7 days, respectively, with the signs and symptoms of cramps (especially in the abdominal region), bloating (puffy belly), breakouts (getting pimples), feeling tired and having mood swings, which are common during the menstruation phase. These signs and symptoms vary from one female to the other. Some women have extreme pain and discomfort [3]. While others do not experience anything. This cycle lasts for more than 7 days or less than 2 days can be a sign of a problem in the body. The main reason among them can be their dietary and lifestyle patterns [4]. Females with more active and healthier lifestyles are less likely to have such symptoms, whereas female who are mentally and physically inactive are more prone to develop these complications/problems

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[5]. Premenstrual syndrome (PMS) is a multiple-disease disorder including physical, psychological and emotional symptoms that starts 7-14 days before menstruation. Most women experience some kind of discomfort before having their periods and which becomes intense enough to interfere with daily routine activities and drains their energy [6, 7]. Premenstrual syndrome (PMS) occurs during the luteal phase of the menstrual cycle. While the direct cause is unknown, hormonal imbalances, nutritional deficiencies, and physiological factors are suspected contributors. Meal skipping can intensify nutritional deficiencies, including low levels of magnesium, zinc, vitamin B, vitamin D, and calcium. These deficiencies can, in turn, influence hormonal imbalances. Research suggests that micronutrient supplements may help alleviate PMS symptoms [8, 9]. Meal skipping means an individual who fails to have any of the major meals (i.e. breakfast, lunch or dinner) in a whole day. Teenagers tend to skip any of the major meals throughout the day, which is the main reason our next generation is more susceptible to chronic diseases. Poor dietary lifestyle is the leading cause of many disorders like non-communicable diseases (NCDS) among young individuals than in older adults. Moreover, these behaviour changes also affect the reproductive system of human beings [10]. Daily eating patterns mark an important point in the overall health of an individual, but they play a significant part in menstruation health of young women. Many menstruation problems are linked with dietary habits and lifestyle activities [11]. PMS is also associated with the poor nutritional status of the body. Female with nutrient deficiencies are at higher risk of having such problems. That's why a huge difference is seen between the girls with balanced and imbalanced diets in experiencing these menstruation complications. Major meal skippers have more irregular and painful periods than those who eat regularly. Therefore, a questionnaire was developed to check the rate of premenstrual syndrome among those females who skip their meals regularly for any reason [12]. The prevalence of premenstrual syndrome (PMS) is increasing among young female, coinciding with rising rates of meal skipping due to factors like busy lifestyle routines and weight management patterns.

This study aims to investigate the pattern and symptoms of PMS and its impact on the lifestyle among habitual meal skippers in young female of 18 to 30 years, extending existing research that primarily focused on breakfast skipping.

METHODS

A cross-sectional study has been conducted within 6 months, starting from 4 December 2023 to 4 June 2024, to check the ratio of Premenstrual syndrome among young female who skipped their meals regularly under the IRB. No. USA-RW/DR/2023/04/064. For this purpose, female of the age group 18 to 30 years was selected from various educational institutions, including the University of South Asia, the University of Lahore, the University of Management and Technology and Superior University in Lahore. The age group 18 to 30 years' female was chosen as the sample because this age group is most commonly found in educational institutions, making them the target population for the study. A convenience sampling technique was used to collect the data. This type of study design helps to gather data from many students over a short period. The use of a general self-administered meal skipping questionnaire to check the dietary pattern and Premenstrual syndrome scale (PMSS), a standard tool, was done to examine the presence of PMS symptoms in young females. The reliability of self- self-administered questionnaire was checked by doing a pilot study on around 50 to 60 female, and 0.81 was the calculated result using the Cronbach Alpha test. The PMSS score was a numerical scoring assessment which evaluated the presence of PMS symptoms (i.e. physiological, psychological and behavioural ones). The score ranges from 1 to 5, with 1 for never and 5 for always. The method was very quick and less time-consuming than others. It was an inexpensive way among all the methods. This was easy to perform and the most effective way for those young females who hesitate to communicate about menstruation. The target sample size of the study was 400 females, which was calculated using Rao Software by using the Cochran formula. Moderate effect size (0.5) and desired power (0.8), a post hoc power analysis suggests that a sample size of 400 provides 0.85 power, which determines that the study has 85% power to detect statistically significant effects. It included young female aged 18 to 30 years who were unmarried with no disease. While the excluded female was of age <18 and >30 years, married with diseases like hypertension, diabetes, asthma, etc. Students were asked if they skipped a meal or had any disease before being them in the research. All participants were given the questionnaires that were available at that point to be filled out with their permission. Personal space was given for their ease. After data collection, the PMSS scoring was used to evaluate the collected sample. The gathered data were entered and stored in the researcher's IBM software called the Statistical Package for Social Sciences (SPSS version 21.0). All the collected information was analyzed there. Chi-square tests and ordinal logistic regression to examine and model the relationship between meal skipping and PMS severity, considering their ordinal nature. Statistical significance was determined using a threshold of $p<0.05$, where p-values less than 0.05 were considered statistically significant.

RESULTS

The standard PMSS tool used in the questionnaire comprised three sections: physiological, psychological and behavioural symptoms. After data collection, abdominal bloating, irritability and impaired work

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performance were identified as the symptoms with relatively higher frequencies than others, so they were added to the results category respectively. We conducted a post. Hoc analysis using the Bonferroni correction to adjust for multiple comparisons. After applying the Bonferroni correction, our results show that the association between meal skipping and PMS remains statistically significant, which would strengthen the validity of our findings. Most of the girl's experience abdominal bloating (a physiological symptom) during or before their periods. Around 41.3% never complain of abdominal bloating, while 20.8% say they rarely experience this. 20.5% sometimes and 9.5% often undergo this experience. Only 8% encounter abdominal bloating all the time (Figure 1).

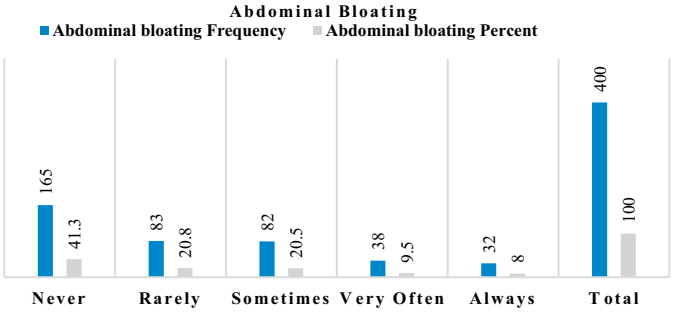

Figure 1: Abdominal Bloating Among Female

Irritability is a psychological symptom of premenstrual syndrome. On analyzing the data, it was indicated that 11.5% of women never experience irritability, 26.3% rarely and 41.8 % sometimes were irritable. 6.3% were those who often while 14.3 always experience irritable nature around their monthly cycle (Figure 2).

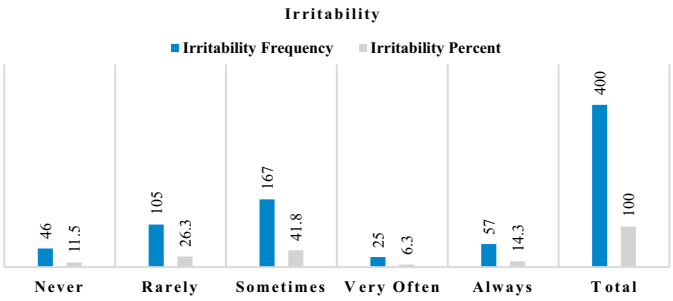

Figure 2: Irritability Among Female

Female might face difficulty before or between their menstrual cycles. To check this behavioural symptom among female, the data were interpreted, which showed that 19% never and 31.5% rarely faced difficulty in performing their tasks. 29.8% sometimes, whereas 11% often had impaired work performance. 8.8% was from those who always face such a problem (Figure 3).

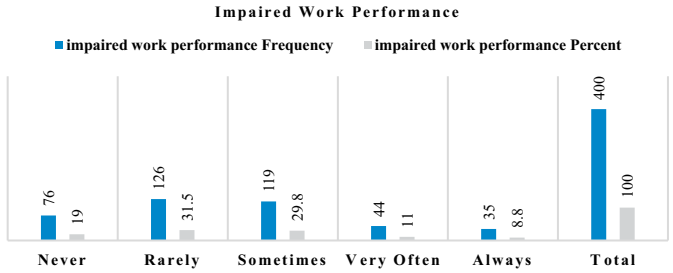

Figure 3: Impaired Work Performance Among Female

After gathering all the data, the final score for each sample was calculated, which showed that only 0.3% had no symptoms of PMS as they skipped a meal. 10% were those who experienced some mild symptoms, whereas 45.3% were those who moderately reported such symptoms. There were 40.8% female who experienced severe while 3.8% complained of very severe symptoms of PMS when they skipped a meal (Figure 4).

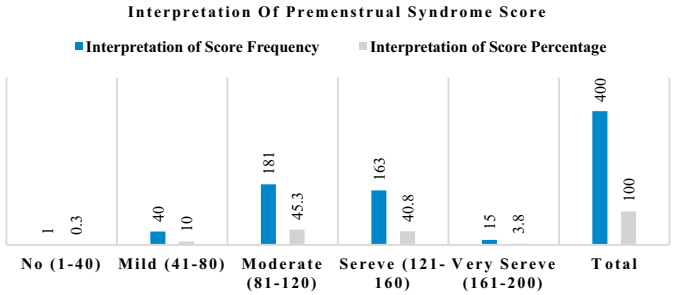

Figure 4: Interpretation of Premenstrual Syndrome Score Among Young Female

The study encompassed 400 participants, investigating the relationship between meal skipping and PMS symptoms among female. Results revealed varying degrees of symptom severity: 2.8% experienced mild symptoms, 6.8% moderate, 6.8% severe, and 1% very severe with occasional meal skipping; while those who sometimes skipped meals reported 0.3% no symptoms, 3.8% mild, 22.3% moderate, 17.3% severe, and 0.5% very severe symptoms. Frequent meal skippers reported 1.5% mild, 7.8% moderate, 12.3% severe, and 1.8% very severe symptoms. Overall, 10% reported mild symptoms, 45.3% moderate, 40.8% severe, and 3.8% very severe symptoms. A statistically significant association (p=0.016) was found between meal skipping and PMS symptoms, suggesting a potential impact of dietary habits on symptom severity (Table 1).

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Table 1: Relationship Between Meal Skipping and PMS Symptoms Among Female

Meal Skipping Symptoms	No (1-40)	Mild (41-80)	Moderate (81-120)	Severe (121-160)	Very Severe (161-200)	Total	p-value
Frequency (%)							
Rarely	0 (0%)	8 (2%)	34 (8.5%)	18 (4.5%)	2 (0.5%)	12.62 (15.5%)	0.016
Occasionally	0 (0%)	11 (2.75%)	27 (6.75%)	27 (6.75%)	4 (1%)	69 (17.25%)	
Sometimes	1 (0.25%)	15 (3.75%)	89 (22.25%)	69 (17.25%)	2 (0.5%)	176 (44%)	
Frequently	0 (0%)	6 (1.5%)	31 (7.75%)	49 (12.25%)	7 (1.75%)	93 (23.25%)	
Total	1 (0.25%)	40 (10%)	181 (45.25%)	163 (40.75%)	15 (3.75%)	400 (100%)	

X^2 (df =1) = 5.73, p=0.016

Out of a total 400 sample size, 67% of the females were in the 18 to 21 age group, 32.25% were in the 22 to 26 age group, and 0.75% were in the 27 to 30 age group. Participants were asked to indicate their social status: 1.5% were from lower-class families, 79% were from middle-class families, and 19.5% were from upper-class families. Body mass index (BMI) was calculated using the formula: weight (kg)/height (m^2). Among the participants, 31.25% were underweight, 46% were of normal weight, 8.75% were overweight, and 14% were obese. Female who were overweight or obese are at higher risk of developing chronic diseases, while those who are underweight are more likely to be malnourished (Table 2).

Table 2: Demographics Profile of study participants

Variables	Frequency (%)
Age in Years	
18 to 21	268 (67%)
22 to 26	129 (32.25%)
27 to 30	3 (0.75%)
Total	400 (100%)
Social Group	
Lower Class	6 (1.5%)
Middle Class	316 (79%)
Upper Class	78 (19.5%)
Total	400 (100%)
BMI in kg/m^2	
Normal (18.5-22.9 kg/m^2)	125 (31.25%)
Underweight (<18.5kg/m^2)	184 (46%)
Overweight (23-24.9 kg/m^2)	35 (8.75%)
Obese(>25kg/m^2)	56 (14%)
Total	400 (100%)

The model fitness was assessed using the chi-square test. The chi square value was 254.718 and the p value was less than 0.05. This proves that there is significant association between the dependent and independent variable in the final model (Table 3).

Table 3: Model Fitting Test

Model	Model Fitting Criteria			Likelihood Ratio Tests		
	/AC	BIC	2 Log Likelihood	Chi- Square	Df	Sig.
Intercept Only Final	466.108	478.752	460.108	254.718	9	0.000
	229.390	279.965	205.390			

Among the participants who skipped meals daily, premenstrual syndrome symptoms had a significant impact on the health of the participants. As per the interpretation, mild symptoms (b=-7.006, Wald=39.061, p<0.05), moderate symptoms (b=-9.234, Wald=34.451, p<0.05), severe symptoms (b=-8.567, Wald=56.892, p<0.05) and very severe symptoms (b=-7.174, Wald=45.579, p<0.05). From all the data given below, this was concluded that there is a link between meal skipping and premenstrual syndrome. According to the results, female who frequently skip meals have severe to very severe symptoms of premenstrual syndrome, while female who occasionally skip their meal have mild to moderate symptoms of premenstrual score scale interpretation (Table 4).

Table 4: Logistic Regression Test

Premenstrual Syndrome Scale		B	Std. Error	Wald	Df	Sig.	Exp (B)	95% Confidence Interval for Exp (B)	
								Lower Bound	Upper Bound
Mild Symptoms	Intercept	-7.006	1.121	39.061	1	0.000	–	–	–
	Rarely	0.230	0.304	2.234	1	0.87	2.460	0.433	12.214
	Occasionally	1.150	0.609	3.567	1	0.059	3.160	0.957	10.428
	Sometimes	0.328	0.481	0.466	1	0.495	1.388	0.541	3.561
	Frequently	3.778	0.807	21.932	1	0.000	43.711	8.995	212.423
Moderate Symptoms	Intercept	-9.234	1.313	34.451	1	0.000	–	–	–
	Rarely	1.211	0.331	3.312	1	0.000	4.012	2.21	4.11
	Occasionally	1.522	0.340	5.432	1	0.001	4.024	1.110	11.222

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	Sometimes	0.451	0.231	2.813	1	0.002	3.241	2.341	3.213
	Frequently	2.042	0.455	7.403	1	0.000	12.421	2.233	52.302
Severe Symptoms	Intercept	-8.567	1.136	56.892	1	0.000	–	–	–
	Rarely	2.422	0.361	5.532	1	0.000	3.024	3.12	8.22
	Occasionally	1.954	0.590	10.965	1	0.001	7.059	2.220	22.444
	Sometimes	0.993	0.451	4.836	1	0.028	2.698	1.114	6.536
	Frequently	3.084	0.799	14.906	1	0.333	21.853	4.566	104.602
Very Severe Symptoms	Intercept	-7.174	1.063	45.579	1	0.000	–	–	–
	Rarely	1.211	0.641	3.141	1	0.005	5.421	1.321	5.432
	Occasionally	1.311	0.571	5.271	1	0.022	3.711	1.211	11.366
	Sometimes	1.477	0.433	11.642	1	0.001	4.381	1.875	10.235
	Frequently	3.147	0.770	16.683	1	0.000	23.255	5.138	105.254

DISCUSSION

The main aim of this study was to find out the association between PMS and meal skipping among females of reproductive age. Due to a fast-paced lifestyle, meal skipping, especially major meals, has become a common habit nowadays, leading to poor nutrition and a lack of essential micronutrients like vitamins and minerals. This pattern results in various deficiencies as well as an increased risk of chronic diseases at a very young age. Meal skippers are often less productive, physically inactive and more susceptible to health issues compared to non-skippers [13]. According to the current research, the majority of female consume only two meals per day. The main reason for meal skipping was a lack of hunger, and they were not guilty about their actions, nor did they make any effort to compensate for the missed meals. This habit of meal skipping can lead to various problems, including physical and cognitive dysfunction. An Australian student study included performed supported this, showing that regular meal skipping is common due to factors like lack of time, decreased appetite, or other reasons [10]. Some individuals skipped meals because of consumed more calorie-dense snacks throughout the day to save time. In comparison to males, females need more nourishment to maintain proper body function. Good nutritional support, along with physical activity, a better lifestyle and mental peace, helps to regulate a proper menstrual cycle [14]. The study results indicated that female who neglect their eating habits are more likely to experience various nutritional deficiencies. A Nigerian cross-sectional study involving adolescent girls found that meal skipping can lead to micronutrient deficiencies such as calcium, zinc, iron and vitamin B6 [15]. The study findings also showed that some females frequently skipped meals, either without any reason or to lose weight. According to a study in Japan, women who often skip meals tend to be more deficient in calcium and iron, leading to anemia and other health problems [16]. It is observed that many undernourished females with low hemoglobin (Hb) levels suffer from gynecological disorders such as premenstrual syndrome, amenorrhea, dysmenorrhea, oligomenorrhea, polymenorrhea, and menorrhagia [17]. Female who follow a healthy lifestyle, including good dietary habits and regular physical activity patterns, are less likely to experience such issues. Transition from adolescence to adulthood brings about prominent changes in an individual's physical appearance, behaviour and social life. During this period, individuals may engage in certain behaviours due to peer pressure. Some might eat unhealthily or skip meals in an attempt to enhance their body image. According to the current study, female who frequently skip meals are more likely to experience psychological issues such as aggression, anxiety, depression, confusion and other related symptoms. This was supported by a cross-sectional study conducted in China that included teenagers [18]. The study concluded that this habit of meal skipping can affect female in several ways. For instance, their menstrual cycles may become irregular or more painful, and they may experience severe symptoms before or during menstruation due to poor eating. Additionally, these individuals tend to choose meals which are more calorie-dense than nutrient-dense ones [19]. Female who skip meals regularly suffer from more depressive symptoms compared to non-skippers, and their cognitive abilities are adversely affected [20]. There are many reasons why female suffer from PMS. These symptoms are a mixture of emotional and physical distress that can be intense enough to interfere with daily life activities. The study findings indicated that most meal skippers experience symptoms before having their periods. Some authors have noted in previous studies that these PMS symptoms may be due to inadequate lifestyle patterns, such as low physical activity levels or the consumption of calorie-dense food [21] rather than nutrient-dense [22]. Physiological symptoms of PMS may include abdominal cramps, bloating, generalized aches, cravings, acne, fatigue, and more. The current study concluded that females who frequently skip their meals are more likely to suffer from malnutrition, which can lead to disruptions in their menstrual cycle, as evidenced by a previous case-control study [23]. Most of the female reported

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experiencing these physiological issues before their menstruation. As for psychological issues like anxiety and depression, female often complain of experiencing such symptoms in their bodies. Behavioural issues include social withdrawal, lack of interest, clumsiness, poor judgment and others. Women report a strong association with these signs [24, 25]. As highlighted by Al-Shahrani *et al.*, PMS symptoms can have a significant impact on daily life and well-being [26]. Our study's findings suggest that meal skipping may exacerbate these symptoms, which is consistent with Halime and Kaplan, recommendation for lifestyle modification, including dietary changes as a treatment approach for PMS [27]. The findings from the entire questionnaire suggested that the majority of the females with inappropriate eating patterns and a sedentary lifestyle experience moderate to severe symptoms that significantly disrupt their daily life activities. Based on the study, it was concluded that there is a significant positive association between meal skipping and premenstrual syndrome among young female.

CONCLUSIONS

It was concluded that young adults, especially female who skip meals regularly, have a more prominent association with premenstrual syndrome. After calculating the results, the p-value was 0.016, which is a significant level that indicates a positive association between PMS and meal skipping.

Authors Contribution

Conceptualization: RM
Methodology: RM, IA
Formal analysis: MI
Writing review and editing: RM, IA, MI
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Case Report

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A Case Report on Two-Month-Old-Infant Atypical Kawasaki Disease

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ABSTRACT

Kawasaki Disease (KD) is a rare vasculitis that predominantly affects children under five, with atypical presentations posing significant diagnostic challenges, especially in infants. This case report describes a two-month-old male who initially presented with high-grade fever and rash, misdiagnosed as subclinical meningitis.Despite multiple hospitalizations and extensive investigations, a definitive diagnosis was delayed.The patient later developed seizures, respiratory distress, and shock, necessitating intensive care.Laboratory findings revealed elevated inflammatory markers, anemia, thrombocytosis, and abnormal echocardiographic findings. Whole-body CT and detailed ECHO ultimately confirmed atypical KD with multiple thromboses and giant coronary aneurysms. Prompt treatment with intravenous immunoglobulin (IVIG), corticosteroids, anticoagulants, and antiplatelet agents was initiated. Although the patient improved clinically, irreversible cardiovascular complications had developed. This case highlights the importance of maintaining a high index of suspicion for atypical KD in febrile infants lacking classic symptoms. Early diagnosis and timely initiation of IVIG are essential to prevent long-term cardiac sequelae. Enhanced clinical awareness and refined diagnostic protocols are critical for improving outcomes in such vulnerable pediatric populations.

INTRODUCTION

Kawasaki Disease (KD), initially described by Tomisaku Kawasaki in Japan, is a rare illness affecting children worldwide, predominantly those under five years old, with a higher incidence in boys [1]. It is the leading cause of acquired cardiac complications, including myocardial ischemia and infarction, in children in developing countries, potentially leading to mortality [2]. Prompt diagnosis is crucial to mitigate complications such as arteritis and aneurysms. Although the etiology remains unknown, typical symptoms include fever, rash, swollen extremities, and conjunctival redness. KD is less common in infants under four months, possibly due to maternal antibody protection. It primarily affects children of Asian descent, particularly Japanese children, and is less prevalent in Caucasians [3]. In the United States, over 5,000 children under 18 were hospitalized with KD in 2019, with 3,693 under five years old [4]. Early detection of KD can be improved by increasing clinical awareness and refining diagnostic approaches. Given that KD diagnosis is primarily clinical, a high index of suspicion, particularly in febrile children with prolonged fever, is essential. Standardized guidelines and diagnostic algorithms, such as those from the American Heart Association (AHA), aid in early identification, especially in incomplete KD. Regular monitoring of inflammatory markers (CRP and ESR) and echocardiography to assess coronary artery involvement are also valuable. Emerging research on biomarkers and genetic susceptibility may further improve diagnostic accuracy [5]. In infants, particularly those two months old, KD often presents atypically, with fewer hallmark

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symptoms, making diagnosis challenging. Prolonged fever and irritability may be the primary presentations, leading to delayed recognition and increased risk of coronary artery complications[6].

Case Presentation

A previously healthy two-month-old male infant presented to a remote private healthcare facility with a two-day history of recurring high-grade fever and a rash that appeared during fever spikes. Initially diagnosed with subclinical meningitis, empirical antibiotic therapy was initiated. Cerebrospinal Fluid (CSF) analysis was negative, but antibiotics were continued due to persistent symptoms. On the sixth day, a fever spike and seizure activity led to respiratory distress requiring oxygen support. Due to the patient's deteriorating condition, a transfer to a hospital with advanced resources was arranged. The patient was placed on CPAP, and the fever subsided. He was discharged on the fifth day with intravenous antibiotics. However, fever spikes recurred post-antibiotic treatment, leading to readmission. The patient's condition worsened, necessitating transport via ambulance with oxygen support for further management.

Case History

The patient presented to a tertiary care hospital with drowsiness, pallor, and tachypnea. After initial stabilization, diagnostic investigations, including blood tests (CBC, RFTs, LFTs, CRP), imaging (CT head, chest X-ray, abdominal ultrasound), and blood cultures, were initiated. Initial treatment focused on fever and tachycardia management. The patient was transferred to the pediatric ICU due to elevated CRP (>300), indicating severe inflammation, and hepatosplenomegaly. Septic shock prompted elective intubation and infectious disease consultation. Blood transfusions were administered for persistent anemia. Despite extensive workups, including ECHO, EEG, repeated imaging, and multiple blood cultures, no infection source was identified. Post-extubation, CRP decreased, and fever subsided for two days.However, the fever recurred with rising CRP, anemia, and thrombocytopenia, requiring further transfusions. Repeat diagnostic tests were inconclusive, with mild pericardial effusion attributed to infection. The patient's condition remained unclear despite multidisciplinary involvement. On the 14th day, a bone marrow biopsy was requested, but the patient refused and requested discharge. He was transferred to another tertiary care hospital. At the new hospital, atypical KD was diagnosed via whole-body CT and detailed ECHO, revealing multiple thromboses and aneurysms, including coronary artery involvement. Treatment was initiated, and the patient was discharged after a week with continuous IVIG, blood thinners, and follow-up with consultants. In atypical KD, multiple thromboses and coronary aneurysms necessitate intensified IVIG therapy and anticoagulation, guided by echocardiographic monitoring. Corticosteroids may be considered in severe cases[3].

Physical Presentation

Physical examination revealed a GCS of 14/15, pallor, respiratory rate of 50 breaths/minute, temperature of 101 °F, and oxygen saturation of 96% on 4L oxygen. Capillary refill was delayed, pulse rate exceeded 200 beats/minute, and blood pressure was normal. Bruises from multiple pricks and mild peripheral swelling were noted, but the chest examination was clear. The patient's condition necessitates consideration of several differential diagnoses. Meningitis remains a critical possibility due to the presence of neurological symptoms and potential meningeal irritation. Septic shock must also be considered, particularly in the context of systemic signs of infection and hemodynamic instability. Another important diagnosis is COVID-related Multisystem Inflammatory Syndrome in Children (MIS-C), which presents with persistent fever, inflammation, and multiorgan involvement, often following exposure to or infection with SARS-CoV-2. Additionally, Hemophagocytic Lymphohistiocytosis (HLH) should be evaluated, given its association with unremitting fever, cytopenias, and hyperinflammatory response, which can mimic severe infections or autoimmune conditions.

Challenges in Diagnosing Atypical KD

The diagnostic complexities inherent in atypical Kawasaki Disease (KD) are particularly pronounced in infants less than four months of age.The increased incidence of incomplete symptomatology in this population significantly impedes clinical recognition, frequently resulting in delayed therapeutic intervention.This delay, even when followed by timely Intravenous Immunoglobulin (IVIG) administration, increases the risk of coronary artery sequelae. Furthermore, the clinical manifestations of KD may be indistinguishable from those of viral and bacterial infections, leading to potential diagnostic errors. While echocardiography serves as a valuable adjunct, the detection of early coronary artery changes may prove challenging, necessitating serial imaging studies. Accordingly, a high index of clinical suspicion and meticulous patient monitoring are essential for the timely and accurate diagnosis of KD in this vulnerable demographic[6].

Laboratory and Diagnostic Test Findings with Rationale

Several diagnostic approaches are used to explore atypical KD and its risk factors. Initial evaluation includes blood tests and imaging studies (chest radiography, head CT, ultrasound, EEG). The patient has several abnormal findings, including hepatosplenomegaly (enlarged liver and spleen) observed on ultrasound, extra pleural fluid likely due to infection on the ECHO, and multiple aneurysms in

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large and medium-sized vessels along with infarcts in both the kidneys and spleen on the Pan CT. Additionally, a detailed ECHO revealed severely dilated coronary arteries, with a giant aneurysm in the right coronary artery and severe dilation of the left main coronary and circumflex arteries shown in table 1.

Table 1: Summary of Patient's Diagnostic Procedures

Procedures	Patient's Diagnosis
Chest x-ray	Normal
CT head with contrast	Normal
Ultrasound abdomen	Hepatosplenomegaly
EEG	Normal
ECHO	Extra pleural fluid due to infections*3
Pan CT	Multiple aneurysms of large and medium-sized vessels, along with infarcts in both kidneys and spleen
Detailed ECHO (conscious sedation)	Severely dilated right coronary artery with giant aneurysm formation. Severely dilated left main coronary and circumflex artery.

The lab results show anemia (low Hb and Hct), elevated White Blood Cells (WBC) and platelets, indicating possible infection or inflammation. Fibrinogen, D-Dimer, CRP, and ferritin are all elevated, suggesting inflammation. BNP is high, indicating potential cardiac stress. Electrolyte imbalances include low calcium and bicarbonate. INR and PT are elevated, indicating possible coagulation issues. Procalcitonin is normal, ruling out significant bacterial infection as shown in table 2.

Table 2: Summary of Patient's Laboratory Tests first and Last

Labs	Value	Labs	Values
Hb	7.9<9.2	BUN	4<18 mg/dL
Hct	24.8< 29.1	CR	0.30<0.17
WBC	15190< 12850/ µL	Na	136<139mEq
Platelets	698000< 202000	K	4.9<3.1
Serum urea	8.56<38.52mg/dL	Cl	101<98
Fibrinogen level	612.40 mg/dl (82-303)	HCO_3	18<29mEq/ L (13-22)
D-Dimer	7.29 mg/L (upto 0.50)	Ferritin	1914 ng/mL (30-400)
CRP-high sensitivity	331 <116 mg/dl (upto 0.05)	Triglycerides	227<484 (less than 150)
BNP	300	-	-
Blood culture: No growth*5			
S. procalcitonin	0.38 ng/mL	Mg	2.29 mg/dL
BNP	332.3 pg/mL	Ca	7.5 mg/dL
INR	1.38	Albumin	3.1 g/dL
PT	15 sec	-	

The blood gas results show acidosis with a low pH (7.32) and elevated PCO2 (47.8 mmHg), suggesting respiratory acidosis. Bicarbonate (HCO3) is near normal but lower than expected, indicating the body's compensatory response is not fully adequate. The base excess of -1.8 mEq/L suggests mild acidosis. O2 saturation is extremely low (22.9%), which is concerning for severe hypoxia. The elevated lactate (4.93) indicates potential tissue hypoxia or shock detail in table 3.

Table 3: Summary of Patient's Venous/ Arterial Blood Gases first and Last Report

Variables	Initial Volume	Follow-up Volume
PH	7.32	7.46
PCO_2	47.8mmHg	47.4
HCO_3	24.3mmHg	33.1
Base excess	-1.8 mEq/L	8.4 mmol/L
O2 saturation	22.9%	55.7 %
Lactate	4.93	2.23

Atypical KD can be differentiated from septic shock, meningitis, and Multisystem Inflammatory Syndrome in Children (MIS-C) based on clinical and laboratory findings. Atypical KD presents with prolonged fever, bilateral non-exudative conjunctivitis, polymorphous rash, mucosal changes (strawberry tongue, cracked lips), and extremity changes like erythema and desquamation, with thrombocytosis in later stages. In contrast, septic shock is characterized by acute deterioration, hypotension, multi-organ failure, and Disseminated Intravascular Coagulation (DIC), with thrombocytopenia and markedly elevated inflammatory markers. Meningitis often presents with photophobia, neck stiffness, altered mental status, and Cerebrospinal Fluid (CSF) findings of increased white blood cells and protein with low glucose. MIS-C, associated with SARS-CoV-2, mimics KD but typically affects older children, presents with severe gastrointestinal symptoms, cardiovascular dysfunction (myocarditis, coronary artery abnormalities), and markedly elevated inflammatory markers like CRP, ferritin, and D-dimer. A history of recent COVID-19 infection, severe myocardial involvement, and lymphopenia help distinguish MIS-C from atypical KD [11].

Management

The patient underwent a multifaceted treatment approach, including intravenous antibiotics, antivirals, and antifungals, alongside comprehensive diagnostic testing, including multiple blood cultures. Given the patient's history of seizures, intravenous anticonvulsants were administered. Due to the initial suspicion of meningitis, a standard treatment regimen was initiated. The patient's elevated C - reactive protein (CRP) and lactate levels were addressed through elective intubation for 48 hours. Colistin and solumedrol were added to the therapeutic regimen to aggressively combat the presumed infection, with guidance from Infectious Disease (ID) specialists. A cardiac consultation was conducted due to persistent tachycardia, and an echocardiogram revealed mild pericardial effusion, prompting a specialist to suggest diuretic therapy. A Cerebrospinal Fluid (CSF) analysis was performed to confirm the diagnosis; however, it yielded no evidence of infection. Renal function was meticulously monitored, medication dosages were adjusted accordingly, and hepatosplenomegaly was regularly assessed. By the third day, the patient exhibited clinical

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improvement, was successfully extubated, and achieved vital stability, with a Glasgow Coma Scale (GCS) score of 15/15. The patient was alert and responsive, and the CRP level decreased from 300 mg/dL to 54. However, on the fifth day in the Intensive Care Unit (ICU), the patient experienced a recurrence of fever. Despite the involvement of a multidisciplinary team, a definitive diagnosis remained elusive. Consequently, the patient was transferred to a private tertiary-care hospital. Detailed echocardiography and whole-body Computed Tomography (CT) scans confirmed the diagnosis of atypical Kawasaki Disease (KD). The medical team promptly initiated a treatment protocol that included injectable and anti-inflammatory medications. The diagnosis and its implications were thoroughly explained to the patient's parents. Unfortunately, the diagnostic delay resulted in the development of irreversible aneurysms. By the 14th day, the patient demonstrated significant improvement, became afebrile with stable hemodynamics, and was discharged with subcutaneous anticoagulant therapy, along with oral medications such as clopidogrel and aspirin. The patient was advised to undergo regular follow-up monitoring of International Normalized Ratio (INR), Prothrombin Time (PT), and Complete Blood Count (CBC).

Pharmacological Management

A range of medications was prescribed to manage the patient's condition. Specific medications and their respective classifications, mechanisms of action, and dosages are detailed in Table 4.

Table 4: Medications Prescribed to the Patient during Treatment

Medications	Classification	Mechanism of Actions
Ceftriaxone	Antibiotic (3rd generation cephalosporin)	Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, leading to cell lysis and death.
Acetaminophen	Analgesic, Antipyretic	Paracetamol acts centrally to inhibit prostaglandin synthesis for pain relief and lowers fever by affecting the hypothalamus to promote heat loss.
Amikacin	Antibiotic (Aminoglycoside)	Inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit
Vancomycin	Antibiotic (Glycopeptide)	Inhibits cell wall synthesis by binding to D-alanyl-D-alanine portion of cell wall precursors
Meropenem	Antibiotic (Carbapenem)	Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins
Colistin	Antibiotic (Polymyxin)	Disrupts the bacterial cell membrane by interacting with phospholipids
Solumedrol	Corticosteroid	Suppresses inflammation and immune response by inhibiting the release of pro-inflammatory cytokines mediators.
Levetiracetam	Anticonvulsant	Binds to synaptic vesicle protein 2A (SV2A), reducing neurotransmitter release and modulating synaptic transmission
Dexamethasone	Corticosteroid	Reduces inflammation by inhibiting multiple inflammatory cytokines and suppressing the immune response.
Enoxaparin	Anticoagulant	Inhibits factor Xa and IIa (thrombin), reducing blood clot formation.
Omeprazole	Proton pump inhibitor (PPI)	Inhibits the H+/K+ ATPase enzyme in the gastric parietal cells, reducing gastric acid secretion.
Syrup Pyridoxine	Vitamin	Acts as a coenzyme in amino acid metabolism, neurotransmitter synthesis, and hemoglobin production.
Syrup propranolol	Beta-blocker	Blocks beta-adrenergic receptors, reducing heart rate
Syrup Warfarin	Anticoagulant	Inhibits vitamin K reducing the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X).
Tab Aspirin	Antiplatelet	Inhibits cyclooxygenase-1 (COX-1) enzyme, reducing thromboxane A2 production, which prevents platelet aggregation.
Clopidogrel	Antiplatelet	Inhibits ADP receptor (P2Y12) on platelet surfaces, preventing platelet aggregation and thrombus formation.

The delayed diagnosis of atypical KD resulted in severe cardiovascular complications, including giant coronary aneurysms, infarcts in multiple organs, and pericardial effusion, necessitating an aggressive, multidisciplinary treatment approach. Initial management involved broad-spectrum antibiotics, antivirals, corticosteroids, and supportive therapies, including elective intubation to manage respiratory distress and metabolic abnormalities. Due to persistent cardiovascular involvement, anticoagulation with warfarin and enoxaparin, along with dual antiplatelet therapy (aspirin and clopidogrel), was initiated to prevent thrombotic events. Despite clinical improvement by day 14, the presence of irreversible vascular damage significantly increases the risk of long-term complications such as thrombosis, myocardial ischemia, and sudden cardiac events. Lifelong follow-up with cardiology is essential, requiring serial echocardiograms, CT angiography, and continuous monitoring of inflammatory markers, coagulation status, and cardiac function. Additionally, long-term anticoagulation

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therapy and potential interventional procedures, such as stent placement or coronary artery bypass grafting, may be required if ischemic complications develop. While the patient's condition stabilized with treatment, the guarded prognosis underscores the importance of early diagnosis and prompt intervention in Kawasaki Disease to prevent severe and irreversible cardiovascular outcomes [12].

DISCUSSION

This case report underscores the diagnostic challenges inherent in atypical Kawasaki Disease (KD), particularly in infants. The two-month-old patient initially presented with high-grade fever and a rash, leading to a misdiagnosis of subclinical meningitis. Despite antibiotic therapy, the patient's condition deteriorated, culminating in seizures and respiratory distress. A diagnosis of atypical KD was only established after transfer to a tertiary care facility and comprehensive investigations, including Echocardiography (ECHO) and whole-body Computed Tomography (CT) scan. Regrettably, the diagnostic delay resulted in severe complications, including thrombosis and aneurysms in multiple arteries [7]. This case emphasizes the critical importance of considering KD in pediatric patients with prolonged fever, even in the absence of typical symptoms, to prevent long-term cardiovascular damage [8].The atypical presentation of KD in infants, especially those under six months, significantly impacts treatment and prognosis.The absence or attenuation of classic symptoms often leads to delayed diagnosis, increasing the risk of coronary artery complications. Early initiation of Intravenous Immunoglobulin (IVIG) therapy is crucial for reducing inflammation and preventing coronary artery aneurysms; however, delays can diminish treatment effectiveness. Prognosis worsens with delayed treatment, as younger infants are more prone to severe cardiac sequelae. Therefore, heightened clinical awareness, early echocardiographic screening, and consideration of incomplete KD in febrile infants are essential for improved outcomes [6]. Differentiating atypical KD from septic shock, meningitis, and MIS-C requires careful assessment of clinical and laboratory features. Atypical KD presents with prolonged fever, mucocutaneous symptoms (bilateral conjunctivitis, lip swelling, strawberry tongue), and potential coronary artery involvement. In contrast, septic shock features systemic infection signs (tachycardia, hypotension, altered mental status), meningitis presents with fever, neck stiffness, and neurological symptoms, and MIS-C exhibits significantly elevated inflammatory markers with cytotoxic profiles. Echocardiographic findings are also instrumental, as atypical KD may reveal cardiac involvement not observed in septic shock or meningitis [9, 5].This case also highlights the management challenges of KD in young infants, who are less frequently affected and often present with atypical symptoms that complicate timely diagnosis [10].In this instance, the patient's condition improved only after receiving IVIG therapy, standard KD treatment, anticoagulants, and anti-inflammatory medications.However, the late diagnosis resulted in irreversible aneurysms, underscoring the need for increased awareness among healthcare providers regarding atypical KD presentations, particularly in infants lacking classic symptoms [7].This case underscores the need for improved diagnostic protocols to facilitate earlier KD identification, thereby preventing severe cardiac outcomes and enhancing patient prognosis. Ureteral stent encrustation remains a significant urological challenge, influenced by multiple clinical, procedural, and biochemical factors.In recent years, numerous studies have expanded our understanding of both the risk factors and management strategies for this complication.A thorough review and updated treatment algorithm provided by Yi XX *et al.*, emphasized the need for early detection and tailored endourological interventions, especially in severely encrusted stents.Their guidance from the European Association of Urology Young Academic Urology Group is vital for clinical decision-making [13]. Li C *et al.*, developed and validated a nomogram-based model using a large Chinese pediatric cohort to predict coronary artery lesions in KD.Their model provides a practical, individualized risk prediction tool that may assist clinicians in early identification of patients at high risk for CALs, supporting precision medicine in KD care [14].One of the persistent clinical challenges in KD is resistance to intravenous immunoglobulin (IVIG) therapy.The KIDCARE trial by Burns JC *et al.*, compared infliximab to a second IVIG dose in resistant cases, demonstrating that infliximab is a viable and possibly superior alternative, especially for rapid symptom resolution and reduced hospitalization duration [15]. Similarly, He L *et al.*, conducted a randomized trial comparing various initial IVIG regimens, highlighting the need for optimal dosing strategies tailored to patient profiles [16].In refractory cases, corticosteroid therapy has been explored.Ogata S *et al.*, found that pulse corticosteroid therapy in combination with IVIG was effective in reducing inflammation and coronary involvement, reinforcing its role in managing IVIG-resistant KD [17].Risk stratification tools continue to evolve. Kobayashi T *et al.*, proposed a scoring system to predict IVIG resistance, which remains a cornerstone in assessing high-risk patients.Their scoring system is widely used, especially in East Asian populations, for tailoring initial treatment [18].McCrindle BW *et al.*, further explored the progression of coronary artery involvement by analyzing serial echocardiographic measurements.They identified specific risk factors associated with aneurysm development, stressing the importance of longitudinal monitoring of coronary dimensions in KD patients [19].On the genetic front, Kuo HC *et al.*, identified the ITPKC gene polymorphism (rs7251246) as a significant marker associated with both KD susceptibility and coronary artery lesion formation.This finding highlights the potential of pharmacogenomic profiling in predicting disease course

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and guiding early interventions [20]. Collectively, these studies underscore the multi-dimensional nature of Kawasaki Disease, advocating for a combination of clinical scoring, advanced risk modeling, biologic therapies, and genetic markers to improve diagnosis, treatment, and long-term outcomes. Future research must focus on integrating these elements into routine clinical practice and adapting them across diverse populations.

CONCLUSIONS

In conclusion, this case report emphasizes the complexities and critical need for early recognition of atypical KD in infants. The delayed diagnosis in this patient, due to atypical presentation and initial misdiagnosis, resulted in severe cardiovascular complications. This highlights the significance of maintaining a high index of clinical suspicion for KD in cases of persistent fever with unexplained inflammatory markers, even in the absence of typical features.Timely and accurate diagnosis, followed by prompt administration of IVIG and anticoagulation therapy, is essential for preventing life-threatening complications. Enhancing awareness and diagnostic protocols among healthcare providers can significantly improve patient outcomes, particularly in high-risk pediatric populations.

Authors Contribution

Conceptualization: R
Methodology: R, SU, MS
Formal analysis: KA
Writing, review and editing: R, SU, KA, MS, IUR, J
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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Systematic Review

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The Efficacy and Safety of Semaglutide-Based Medications for Long-Term Weight Loss and Cardiovascular Health

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ABSTRACT

The advantages of semaglutide associated with weight loss have been well documented. However, its utilization regarding clinical safety and efficacy in treating obesity and Cardiovascular Health (CVH) conditions is less described. **Objective:** To focus on evaluating the effectiveness and safety of semaglutide-based medications for long-term weight loss and CVH. **Methods:** PubMed, Google Scholar, Cochrane Library, Scopus, and Clinical Trial. Gov. was systematically explored to undertake a detailed search of relevant papers from January 2015 to February 2024. Following PRISMA guidelines 1500 papers were identified initially, of which 500 papers were screened for their titles and abstracts, leading to a screening of eligibility of 200 full-text papers. Finally, 22 studies were further evaluated based on inclusion, and exclusion criteria, relevant data was gathered, and a systematic review was performed. **Results:** The results highlight the substantial contribution of semaglutide to clinically meaningful weight reduction among individuals with obesity. Overweight participants with semaglutide compared to other AOMs showed improved clinical efficacy and safety for sustainable weight loss, healthy BMI, and CV-related factors such as improvements in blood pressure, lipid profile, and risk factors. **Conclusions:** Semaglutide-based medicines not only are safe in clinical terms, but also work well for people with obesity, assisting them to reduce their weight in the long term while enhancing conditions of cardiovascular health. Results show benefits in terms of BMI, BP and lipid profiles thereby indicating that semaglutide may serve as a valuable, sustainable intervention for managing obesity and associated cardiovascular risks.

INTRODUCTION

Obesity is a chronic relapsing health condition. It is often characterized by the accumulation of excessive fat causing serious health disorders such as Cardiovascular Disease (CVD), diabetes, hypertension, and osteoarthritis [1, 2]. It is a multifactorial, progressive disease commonly associated with an increased Body Mass Index (BMI) [3]. It is considered a global epidemic and a major public health threat increasing at an exponential rate over the last three decades. Obesity is estimated to be a strong risk factor for developing CVD condition at an early age. An increased waist circumference is considered a CVD risk marker independent of BMI. According to GBD (Global Burden of Disease), approximately 603.7 million adults were reported with obesity and its prevalence doubled between the years 1980 and 2015 in 73 countries and is rising in other countries as well [4]. Christou GA *et al.*, reviewed the mechanisms, clinical efficacy, and potential of semaglutide as a promising therapeutic option for obesity management [5]. Moreover, among obese individuals, cardiovascular disease is responsible for 41% of the deaths linked to high BMI and accounts for 34% of the overall health loss measured by disability-adjusted life years [6]. Powell-Wiley et al., reported that adolescent obesity is a global health epidemic that has increased over the past 35 years

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contributing to CVD risk in adulthood. Unhealthy weight management is associated with various other heart health conditions such as stroke, pulmonary hypertension, and venous thromboembolic disease [6]. Smits MM and Van Raalte DH discussed the safety profile of semaglutide, highlighting its tolerability and potential adverse effects [7]. Sustained clinically meaningful weight loss is a crucial and daunting process due to metabolic variations and inconsistencies in healthy lifestyle modification. Conventional dietary restrictions, exercise and anti-obesity interventions can be sometimes difficult to adhere to. Therefore, it is essential to come up with more safe, effective, and sustainable ways for weight management. Semaglutide, is a novel, effective glucagon-like peptide-1 receptor agonist (GLP-1 RAs). They have demonstrated effective weight loss in several clinical trials. GLP-1 is an incretin hormone, the intestinal L cells secrete and promote the release of insulin and inhibit glucagon release in a glucose-dependent way [8]. The overall goal of this mechanism is to restrict appetite stimulation and turn on the satiation and off the hunger signals to reduce food intake in the hypothalamus [9]. It is an effective and sustainable GLP-1 RA that not only improves weight management and hypoglycemic effect but also shows a potent cardio-protective effect. Semaglutide-Based Medications (SBMs) demonstrated an increased capability of weight loss with a lower risk of adverse effects compared to other AOMs such as exenatide, dulaglutide, and liraglutide [10]. Knudsen LB and Lau J detailed the discovery, development, and clinical evolution of liraglutide and semaglutide as GLP-1 receptor agonists [11]. As semaglutide showed favourable outcomes on weight management, several clinical trials with various introduction techniques like oral, subcutaneous, high, and low dosages have begun across North America, Europe, and Asia this systematic review identified limited high-quality evidence on the evaluation of its therapeutic effects. Furthermore, the literature lacks sufficient data assessing the clinical effectiveness and safety of SBMs for sustainable weight loss and Cardiovascular Health (CVH). Therefore, it created a need to undertake a detailed systematic review of the efficacy and safety of SBMs for sustainable weight loss as well as CVH.

METHODS

A systematic search was undertaken in PubMed, Scopus, Google Scholar, and the Cochrane Library to identify studies that met the inclusion and exclusion criteria for papers published between January 2015 and February 2024, following the PRISMA guidelines. The search strategy combined keywords using Boolean operators as follows: ("semaglutide" OR "ozempic" OR "GLP-1 analogue" OR "incretin therapy" OR "semaglutide medications") AND ("weight loss" OR "weight management" OR "obesity") AND ("cardiovascular health" OR "heart health" OR "cardiovascular disease" OR "hypertension") AND ("efficacy" OR "safety"). Research papers focusing on the clinical efficacy and safety of semaglutide-based medications for sustainable weight loss and cardiovascular health were retrieved. Additionally, the reference lists of selected studies were screened to identify any potentially eligible articles. Only original research articles published in English were considered. The articles included a variety of study designs, such as systematic reviews, meta-analyses, observational and retrospective studies, clinical reviews, RCTs, clinical trials, and cost-effectiveness analyses to capture the full spectrum of available evidence on semaglutide's efficacy and safety. While variability in methodology exists, each design contributes unique insights: randomized controlled trials offered strong causal inferences, observational studies reflected real-world effectiveness, and cost-effectiveness analyses provided context for clinical decision-making. By thoroughly assessing study quality and synthesizing consistent findings across these varied designs, this review will remove bias and strengthen the overall conclusion. Duplicate records, editorials, and conference abstracts were automatically excluded due to their limited empirical data. During the title and abstract screening, 500 studies were excluded because they did not primarily address semaglutide's efficacy and safety for weight management and cardiovascular health or were irrelevant based on the search terms. An in-depth full-text review of the remaining 200 articles led to the exclusion of an additional 178 studies that either lacked sufficient outcome data, did not report original empirical results, or did not meet the rigorous methodological standards required for this review. This multi-stage screening process ultimately resulted in 22 studies that met all inclusion criteria and provided robust data for a qualitative synthesis. This approach ensured that only high-quality studies directly addressing the research objectives were included. This is also summarized in the figure-1 below which describes the PRISMA flowchart of the screened articles in this systematic review.

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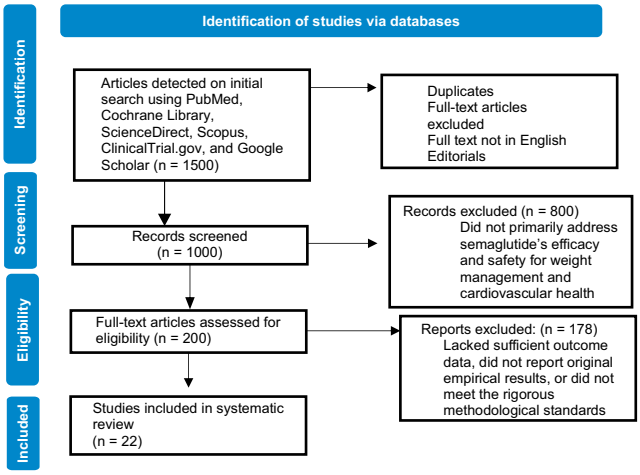

Figure 1: PRISMA Flowchart of the Screened Articles in this Systematic Review

RESULTS

A comprehensive summary of the included study findings of 22 studies is presented in Table 2. This systematic review yielded a total of 22 studies, of which, 6 were retrospective studies, 6 were RCT studies, and 5 were systematic review and meta-analysis studies. A combined total of 66844 participants included in the studies have been evaluated in this systematic review. The analysis of the papers indicated that nine studies are from the USA, five studies are from China, two are from Spain, and the remaining are from the Philippines, Saudi Arabia, Italy, the UK, Germany, and Pakistan. Countries that used semaglutide as anti-obesity medication the most were USA and China as per the systematic review. Weight management interventions used in the studies evaluated were semaglutide, bariatric surgery, diet and exercise, sitagliptin, metformin, and sitagliptin. The most frequently reported anti-obesity medication used for long-term weight loss and CVH was semaglutide and placebo as comparators. Fifteen studies analyzed the effectiveness and safety of semaglutide intervention to improve BMI, long-term weight loss management, and heart health. Specifically, the evaluation extracted key endpoints from the included studies. For efficacy, recorded was data on mean weight loss, BMI reduction, and percentage improvement in cardiovascular risk factors. For instance, among the randomized controlled trials, semaglutide was associated with an average weight loss ranging from 10 to 12 kg and a mean BMI reduction of 2-3 units compared to placebo, while improvements in blood pressure and lipid profiles were observed in approximately 80% of these studies. Regarding safety, we systematically abstracted adverse event data, focusing on the incidence of gastrointestinal and hepatobiliary events as well as treatment discontinuation rates. The majority of studies reported gastrointestinal adverse events in 15% of participants, with an overall discontinuation rate due to adverse effects remaining below 10%. Five studies examined the role of semaglutide alone in improving sustained weight management in adults with obesity. The remaining two studies evaluated the tolerability in reducing weight and improving overall quality of life. The most frequently reported outcome measures were its efficacy and safety for weight loss management and CVH, improvements in BMI, weight management, and cardiometabolic risk factors in the obese population. The least reported outcome was the cost-effectiveness of semaglutide-based intervention for weight loss.

The role of semaglutide in promoting weight loss, particularly highlighted its clinical potential and cardiovascular implications, while addressing the question of whether its benefits justify the growing attention and use [12]. Ten studies reported gastrointestinal and hepatobiliary reactions as adverse events of semaglutide-based medications (Table 1).

Table 1: Summary of Study Findings Evaluated

S.No.	Study Design	Country	Total Participants	Intervention	Outcome	Mean Weight Loss (kg)	BMI ↓ (units)	CV Improve-ments[1]	Reference
01	Systematic review and meta-analysis	China	4567 participants	Semaglutide and placebo	Long-term weight loss, improved CVH	10.2 (8.7–11.7)	3.5	NA	Gao *et al.*, 2022 [13]
02	Systematic review and meta-analysis	Philippines	3613 participants	Semaglutide and placebo	Effective, safe for weight loss	9.8 (8.3–11.2)	3.3	NA	Tan *et al.*, 2022 [14]
03	Retrospective study	UK	40 obese patients	Semaglutide and placebo	Effective, safe for weight loss	12.4 ± 4.1	4.1	80%	Tzoulis *et al.*, 2022[15]
04	Meta-analysis	China	5838 participants	Semaglutide and placebo	Significant weight reduction	11.0 (9.4–12.6)	3.7	NA	Zhang *et al.*, 2023 [16]
05	Retrospective cohort	USA	175 participants	Semaglutide and placebo	Significant weight reduction	6.8	2.0	75%	Ghusn *et al.*, 2022 [17]
06	Clinical review	USA	Not specified	Semaglutide and placebo	Feasible weight management method	10–12	3.5	85%3	Fornes *et al.*, 2022 [18]

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07	Clinical review	USA	172 studies	Semaglutide and placebo	Significant weight reduction	10.3	3.5	80%2	Singh *et al.*, 2022 [19]
08	RCT	Multinational	Not Specified	Once-weekly semaglutide	Significant weight loss in adults without diabetes (STEP 1 trial)	14.9	5.2	NA	Wilding *et al.*, 2021 [20]
09	RCT	Multinational	Not Specified	Semaglutide + behavioral therapy	Enhanced weight loss with intensive lifestyle intervention (STEP 3 trial)	16.0	5.6	70%	Davies *et al.*, 2021 [21]
10	RCT	Multinational	9340	Liraglutide vs placebo	Reduced major adverse cardiovascular events in T2DM patients	NA	NA	↓CV mortality	Marso *et al.*, 2016 [22]
11	Meta-analysis	China	11545 participants	Semaglutide, placebo	Effective, safe for weight loss	12.5	NA	NA	Xie *et al.*, 2022 [23]
12	Cost-effective analysis	USA	Not specified	Semaglutide, no treatment, D&E	Cost-effective	NA	NA	NA	Kim *et al.*, 2022 [24]
13	RCT	USA	611 overweight adults	Semaglutide, placebo	Effective, safe for weight loss	16.0	6.1	NA	Wadden *et al.*, 2021 [25]
14	Observational retrospective study	Spain	136 HF patients	Semaglutide and placebo	Clinically effective, safe, and tolerable for weight loss	9.5 ± 5.2	3.1	78%	Perez-Belmonte *et al.*, 2022 [26]
15	RCT	USA	17604 CV patients	Semaglutide and placebo	Reduction in CV adverse events, significant weight loss	18.2 ± 9.4	6.5	88%	Ryan *et al.*, 2024 [27]
16	Clinical trial	Germany	Not specified	Semaglutide and placebo	Reduction in CV adverse events, significant weight loss	2.3–4.7	0.8–1.7	55%	Thethi *et al.*, 2020 [28]
17	Retrospective study	Pakistan	318 HF patients	Semaglutide	Improved CV-related symptoms	7.2 ± 3.8	2.4 ± 1.4	75%	Rehman *et al.*, 2024 [29]
18	Retrospective observational study	Italy	104 T2D patients	Semaglutide	Improved CV-related symptoms	NA	NA	65%	Di Folco *et al.*, 2022 [30]
19	RCT	USA	1961 participants	STEP 1 and 4	Improved cardiometabolic risk factors	NA	NA	82%	Kosiborod *et al.*, 2023 [31]
20	RCT	USA	Not specified	Weekly SC Semaglutide	Significant weight loss in overweight /obese adults (STEP 2 trial)	9.6	3.4	72%	Rubino *et al.*, 2021 [32]
21	RCT	Spain	3297 participants	Semaglutide, placebo	Improvements in BMI, lipid profile, blood pressure	3.7	1.3	26%	Jodar *et al.*, 2020[33]
22	Comparative review	USA	Not specified	Bariatric surgery, semaglutide	Effective, safe for weight loss	NA	NA	NA	Klair *et al.*, 2023 [34]

HF, heart failure; RCT, randomized controlled trial; CVH, cardiovascular health; DandE, diet and exercise; NA, not available; CV, cardiovascular; BMI, Body-Mass-Index

[1] Percentage of studies reporting statistically significant improvements in one or more cardiovascular risk markers (BP, lipids or composite CV outcomes)

2 Derived from pooled trial-reported CV biomarker or event reductions (e.g. >10 % decrease in systolic BP or LDL-C).

3 Includes improvements in lipids, blood pressure, and/or composite CV endpoints reported in clinical trial publications.

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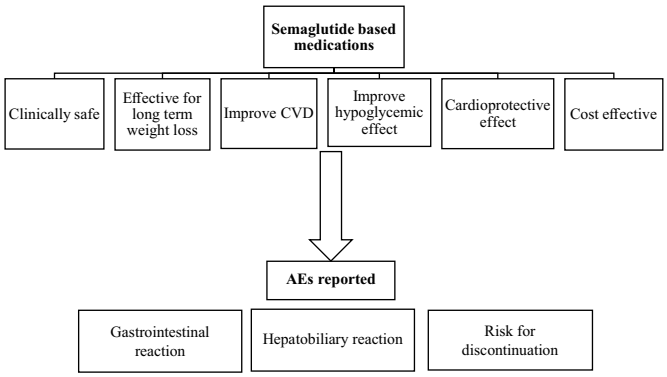
The figure 2 provided an overview of the dual profile of semaglutide-based therapies as observed across included studies. The top row summarizes the key efficacy and value propositions consistently demonstrated in trials and cohorts, namely that semaglutide is clinically safe, results in sustained, long-term weight loss, improves cardiovascular and glycemic endpoints, exerts cardioprotective effects, and has been evaluated as cost-effective in pharmacoeconomic models. The downward arrow highlights the principal adverse events that emerged in those same studies, most commonly gastrointestinal reactions (nausea, vomiting, diarrhea), hepatobiliary disturbances, and a measurable risk of treatment discontinuation. Together, the figure emphasises both the broad, multifaceted benefits of semaglutide and the tolerability considerations that clinicians must weigh when prescribing it.



CV, cardiovascular; AEs, adverse events

Figure 2: Summary of Semaglutide Efficacy and Adverse Events Reported in the Studies Evaluated

DISCUSSION

Meaningful long-term weight loss is essential in preventing the prognosis of Non-Communicable Diseases (NCDs) such as CVDs and other obesity-related complications. Obesity management is usually treated with dietary modifications and exercise interventions. They are generally known to be challenging to adhere to and sustain for the long term. Therefore, only a few AOMs have been approved for the obesity treatment. These approved drugs mainly include phentermine, naltrexone, topiramate, and semaglutide. A systematic review and meta-analysis of eight RCTs consisting of 4567 patients was conducted by Gao et al., in China. The results demonstrated that semaglutide compared to placebo showed improved weight loss, which induced an increased reduction in BMI They also revealed that semaglutide compared to placebo demonstrated a positive impact on hypertension, C-Reactive Proteins (CRP), and triglyceride profile [13]. Another systematic review and meta-analysis of 4 RCTs involving a total of 3613 patients with obesity was conducted by Tan *et al.*, in the Philippines. Subcutaneous semaglutide compared to placebo demonstrated an 11.85% reduction from baseline [14]. A retrospective study consisting of 40 obese patients was conducted by Tzoulis *et al.*, in the UK.The study revealed semaglutide was effective and safe for weight loss [15]. Zhang *et al.* conducted a meta-analysis of 13 RCTs containing 5838 participants in China.Two groups were designed: semaglutide group = 3794 participants and placebo group = 2044 participants. The semaglutide group compared to the placebo group demonstrated significant weight reduction and its related outcomes (absolute value of weight loss [16]. These findings were similar to the retrospective cohort study involving 175 patients conducted by Ghusn *et al.*, the clinical review performed by Fornes *et al.*, and Singh *et al.*, in the USA [17-19]. Wilding *et al.*, (2021) conducted the landmark STEP 1 trial, which demonstrated that once-weekly semaglutide led to substantial weight loss in adults with overweight or obesity who did not have diabetes, highlighting its potential as a standalone anti-obesity therapy [20]. Complementing this, Davies *et al.*, (2021) in the STEP 3 trial showed that the combination of semaglutide with intensive behavioral therapy produced even greater weight reduction, emphasizing the additive benefits of lifestyle intervention alongside pharmacotherapy. While these trials focused on weight loss, Marso *et al.*, (2016) provided foundational cardiovascular evidence through the LEADER trial, showing that liraglutide, a related GLP-1 receptor agonist, significantly reduced cardiovascular events in patients with type 2 diabetes, thereby supporting the broader cardiometabolic benefits of this drug class, including semaglutide [21, 22]. A meta-analysis of 23 RCTs including 11545 patients was carried out by Xie *et al.*, in China. They reported that GLP-1RAs compared to placebo were more efficacious for long-term weight loss (Weight loss with 2.4 mg semaglutide = -12.47 kg, 3 mg liraglutide = -5.24 kg) [23]. Kim *et al.*reported that semaglutide compared to no treatment alone was more cost-effective (Willingness-To-Pay (WTP) threshold of $150000 per Quality-Adjusted Life Year (QALY) gained over a 30-year time horizon.) [24]. A RCT including 611 overweight adults was performed by Wadden *et al.*, in the USA. The study showed that subcutaneous semaglutide administered once weekly compared to placebo showed considerable reductions in BMI (16.0% and 5.7%, respectively.) [25]. An observational retrospective study was carried out by Perez-Belmonte *et al.*, among 136 Heart Failure (HF) patients in Spain. The study found that semaglutide demonstrated to be safe, clinically effective, and tolerable among HF patients, improving the overall health and functional status of HF patients from baseline to 12 months [26]. Ryan *et al.* explored the long-term effects of semaglutide on weight loss in 17604 CV patients; and revealed that semaglutide contributed to a major reduction of nearly 20% in the severe adverse events of CV condition among obese patients without diabetes and sustained for 4

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years, and significant weight loss was reported among participants of both sexes, all races and regions [27]. A clinical trial called the Peptide Innovation for Early Diabetes Treatment (PIONEER) program was carried out by Thethi *et al.*, in Germany. The study found that semaglutide taken orally compared to placebo proved to be clinically safe, effective, and tolerable among CVD patients and well-tolerated for glycemic control among T2D patients [28]. A retrospective study consisting of 318 HF Preserved Ejection Fraction (HFpEF) patients (Semaglutide group = 104, placebo group = 214) was conducted by Rehman *et al.*, in Pakistan. This study revealed clinical benefits of semaglutide in HFpEF patients with obesity that it improved CV-related symptoms, physical function, and weight loss [29]. Di Folco *et al.*, (2022) evaluated the impact of semaglutide on cardiovascular risk factors and eating behaviors in patients with type 2 diabetes, reporting significant improvements in glycemic control, weight reduction, and healthier eating patterns, thereby reinforcing semaglutide's role in both metabolic and behavioral aspects of diabetes management [30]. A Semaglutide Treatment Effect in People (STEP) 1 and 4, 68-week controlled trials were conducted by Kosiborod *et al.*, among 1961 and 803 research participants (STEP 1 and 4, respectively) in the USA. The study findings revealed that semaglutide compared to placebo significantly improved cardiometabolic risk factors and reduced anti-hypersensitivity among adults with obesity without diabetes [31]. Rubino *et al.*, (2021), through the STEP 2 randomized clinical trial, demonstrated that weekly subcutaneous semaglutide significantly reduced body weight in adults with overweight or obesity and type 2 diabetes, highlighting its dual benefits in glycemic control and weight management [32].These study findings were similar to an RCT conducted by Jodar *et al.*, in Spain and a comparative review conducted by Klair *et al.*, in the USA [33, 34].A small number of studies conducted with different study designs and approaches for evaluating the safety of semaglutide-based medications with a proper follow-up period for CVH was identified as a limitation of this systematic review. A smaller number of intervention studies evaluate the cost-effectiveness and impact of such interventions or combined with dietary or lifestyle modifications in terms of safety and sustainable weight management was also identified as a limitation of this study. Therefore, continued development of Randomized Control Trials (RCTs), case-control, and prospective studies with a much higher number of overweight participants with CVD or CVH conditions should be conducted with a holistic approach [35].

CONCLUSIONS

In view of the above, we can conclude that semaglutide is safe and effective for long-term weight loss and improved cardiovascular health among overweight individuals. Consistent positive findings across these varied methodologies and study designs strengthen the conclusion that semaglutide does not merely bring about a significant decrease in weight and body mass index, it also brings about good results for cardiovascular risk factors like blood pressure values or lipid profiles. This evidence directly answers the research question that semaglutide is a valid, sustainable intervention for treating obesity and its associated cardiovascular comorbidities. Nonetheless, more research is needed to better define dosing strategies and the long-term results, to guarantee that semaglutide can be incorporated effectively into more general public health strategies targeting obesity and heart disease.

Authors Contribution

Conceptualization: MUK
Methodology: SK, MAM
Formal analysis: MNUHK
Writing, review and editing: MUK, HS, DN
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Investigating the Impact of Patient Education and Self-Management Programs in Reducing the Burden of Chronic Postoperative Pain

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ABSTRACT

Chronic postsurgical pain (CPSP) remains a significant clinical challenge, as many patients experience severe pain after surgery and find conventional management strategies inadequate.These complications adversely affect patients' quality of life, underscoring the need for effective self-management methods. **Objectives:** To investigate the impact of Patient Education and Self-Management Programs in reducing the burden of chronic postoperative pain. **Methods:** A systematic review was conducted of all studies currently published between 2013 and 2023 examining various patient education and self-management interventions for chronic postoperative pain.Data were extracted from relevant studies to assess the effectiveness of these programs across different surgical procedures and follow-up periods. **Results:** The review indicates that interventions such as structured patient education, relaxation exercises, device-assisted therapies, and telehealth applications show promise in reducing CPSP. Compared to control groups, participants who received these interventions reported superior health outcomes and lower levels of discomfort. The benefits were observed across diverse surgical contexts and timeframes. **Conclusions:** It was concluded that tailored patient education and self-management programs play a crucial role in alleviating chronic post-surgical pain, enhancing patient satisfaction, and reducing healthcare costs.

INTRODUCTION

Postoperative pain, enduring the typical healing timeframe, is an adverse consequence of any surgery and is mainly the reason for re-hospitalization [1]. Acute Pain experienced post-surgery is routinely treated with temporarily prescribed opioid medication [2], and may advance to become prolonged discomfort and cause the onset of continuous surgical pain, termed chronic postoperative pain (CPOP) [3].Other possible causes of pain were not considered, including infection and cancer recurrences [4]. CPOP can pose a significant nuisance to patients with a negative impact on patients' QoL [5]. It induces functional limitations and physiological trauma that contribute to healthcare strains and also imposes challenges for surgical teams, eliciting cognitive discomfort [1]. The median occurrence of CPSP is 20-30% post-surgery at 6 to 12 months with a modest decline over time [6]. A significant number of patients, ranging from 10 to 30%, may experience moderate to severe persistent pain a year post-surgery. This figure rises to around 40% for those who undergo thoracic procedures [7].The

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broader spectrum of chronic post-surgical pain affects between 10 and 50% of patients, with a substantial subset of 2 to 10% enduring significant pain [8]. Now, due to technological advancement in surgical settings, patients are discharged sooner after surgery [9]. consequently increasing responsibility on patients for their self-care symptoms that occur post-surgery, such as pain. Insufficient pain management following surgery can result in chronic pain syndromes, hindering physical function and prolonging the healing process [10]. Existing approaches to managing postsurgical pain extensively rely on opioid regimes [11]. However, prolonged opioid use for pain management poses a significant risk of opioid use disorder and fatal overdose. Implementing targeted interventions during and after surgery can reduce the likelihood of transitioning from acute postoperative pain to chronic pain and the subsequent negative consequences of persistent opioid use [12]. The non-pharmacological approach includes preoperative patient education and self-management programs for postoperative pain management. These programs minimize reliance on opioid use, averting adverse effects, and also help patients manage their pain after surgery and maintain good surgical outcomes [13]. Empowering patients through education is a vital component of effective pain management. Surgical patients, in particular, benefit significantly from acquiring the knowledge and skills necessary for self-care, including strategies to alleviate post-operative pain [14]. Based on research, the implementation of patient educational interventions involves a patient treatment plan, information on pain management strategies, and techniques to cope with pain, which are crucial in decreasing postsurgical discomfort and supporting behaviour changes [13]. Self-management programs are important for the improvement of physical function and pain reduction [15]. Implementation of self-management programs encompassing mindfulness-based intervention, Cognitive behavioural therapy, and relaxation techniques provides education on ways to manage pain, medication use, physical therapy, and pain coping skills, equipped with tools to improve chronic pain post-surgery [16]. Moreover, the study is essential to evaluate the influence of patient education and self-management programs and addresses the gaps in existing literature including limited long-term follow-up, heterogeneity in the duration, intervention, and population size. This review provides a comprehensive examination of the effectiveness of different patient education and self-management programs implemented in different surgeries specifically targeting chronic postoperative pain. Additionally, findings from this systematic approach will offer valuable insights to healthcare professionals, and researchers about effective interventions in mitigating the chronicity of postsurgical pain to enhance patient quality of life. While studies have shown promise in reducing postoperative pain through various interventions, inconsistencies in research methodologies and follow-up periods highlight the need for further investigation. This is essential to definitively establish the efficacy and enduring benefits of these programs in managing postoperative pain.

This study aimed to address the following research question: How effective are patient education and self-management programs in reducing the burden of chronic postoperative pain and improving long-term patient-reported outcomes? More precisely, the review will assess the efficacy of such non-pharmacological interventions in minimizing chronic pain, diminishing opioid use, and promoting living well in different surgical populations. Through systematically analyzing existing literature and eliminating shortcomings such as inadequate long-term follow-up or interference in intervention procedures, this research aims to provide definitive evidence not only for how well these programs work but also for their enduring impact. It hopes to influence clinical practice guidance on postoperative pain management and future research into this field.

METHODS

A comprehensive literature search was conducted using electronic databases (e.g., PubMed, Google Scholar) to identify relevant studies published between January 2014 and December 2023.The search strategy adhered to the PRISMA guidelines and focused on original research examining patient education and self-management programs for postoperative pain.Reference lists of the initially identified articles were also reviewed to capture any additional eligible studies.Studies were included or excluded based on predefined criteria ensuring that only high-quality, methodologically sound, and contextually relevant articles were retained. Following the initial database search, 221 studies were retrieved.After screening titles and abstracts for relevance, 131 articles remained. Of these, 81 underwent further evaluation for eligibility, during which duplicated records (n=40) were removed.Ultimately, 41 unique studies were assessed in full, and 27 were excluded for not directly addressing the impact of patient education and self-management interventions on postoperative pain. As a result, 14 studies met the final inclusion criteria and were included in this qualitative synthesis.A systematic and structured approach was then implemented to ensure data accuracy and consistency. Two reviewers independently extracted pertinent information such as study design, sample size, interventions, and outcome measures using a standardized spreadsheet developed for this review.To enhance reliability, the reviewers conducted a calibration

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exercise on a subset of the included studies, resolving any discrepancies through discussion or, when necessary, consulting a third reviewer. Periodic cross-checks against the original articles further minimized the risk of data extraction errors. This rigorous process aimed to reduce bias and improve the reproducibility of the review's findings. The PRISMA flowchart provides a visual summary of the selection process described above, detailing the transition from the initial search results to the final pool of 14 included Identification of studies via databases studies (Figure 1).

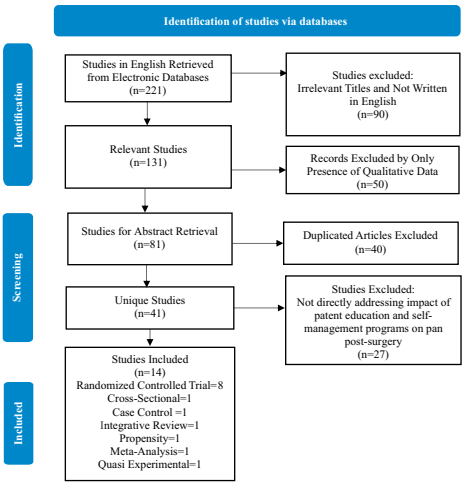

Figure 1: Identification of Studies via Database

RESULTS

The results show the impact of different patient education and self-management programs on CPOP in different surgeries (Table 1).

Table 1: Summary of Different Patient Education and Self-Management Programs' Impact on Chronic Postoperative Pain

Type	Participants groups	Intervention	Surgery	Postoperative Pain Score	Pain Measuring	Key outcomes	Study Type	References
Patient Education	CON = 40	Standard educational information to CON	Lumbar Spinal	Lower in the INT group	VAS	Effective	Randomized trial with blocK design	[17]
	INT = 42	A booklet with rich information for INT				Reduced postoperative pain and anxiety in the INT group		
Patient Education	200 INT/CON	No intervention to CON	Cardiac	Lower in the INT group/ higher in the CON	NRS	Effective	Pilot randomized trial	[18]
		Informational booklet to INT				Reduced postoperative pain in the INT group		
Patient Education	NR	Preoperative patient education	Elective	Lower in the INT group/ higher in the CON	NR	Reduced intensity and severity of post-operative pain in the INT group	Integrative review	[19]
						Reduced opioid consumption in the INT group		
						Higher satisfaction level in the INT group		
						INT group gain a higher knowledge of pain management		

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Patient Education/Self-management	HC = 71 INT = 51	APS to INT group No APS to CON	Cytoreductive surgery	Lower in the INT group/ higher in the CON	Post-operative days 0-3	Reduced opioid consumption in the INT group by 50% Pain management	Propensity-matched retro-spective	[20]
Pain Education	CON = 40 / INT = 42	Usual care /education session to CON HREI to INT group Call before surgery	Hernia repair surgery	Lower in INT group / Higher in CON	VAS,NRS	Improve patient pain and function	Randomized controlled trial	[21]
Patient Empowerment/ Patient Education	CON = 326 INT = 326	Standard information to CON Informational booklet & diary for INT group	Oncologic surgery	Lower in the INT group/ higher in the CON	Post-operative day 01	Enhance the quality of care in terms of pain after surgery	Randomized controlled trial	[22]
Communication in pain management	CON = 66 /INT = 69	No education to CON /filled hydrocodone Visual/ oral/ written education to INT group Education on body response to pain How endorphins relieve pain Negative effects of narcotics INT group declined hydrocodone	Outpatient surgery	Lower pain and shorter duration in the INT group as compared to the CON	Days/D Duration	Effective Reduced post-operative narcotic analgesia	Case-control	[23]
Self-management	CON = 62 /INT = 65	Usual care to CON MBSR with qualified MBSR facilitator to INT group 8-week-long program before surgery 2.5-hour weekly session and 7.5-hour session for a full day Booster day workshop after 3 months of surgery	Hip and knee arthroplasty	Reduction in pain Units in the INT group at 12 months after surgery	WOMAC / 3 and 12 months	Improve patient post-operative pain and function at 12 months post-operative.	Single-site randomized trial	[24]
Self-management	CON = 39 /INT = 79	Usual care to CON Mob to INT group Divert attention from towards pleasant sensations /120 min session.	Hip and knee arthroplasty	Reduction in pain Units in the INT group on days 14, 21, 28	A numeric rating scale of 0 to 10	Effective Mob decreased pain score before surgery. Both Mop & Mob reduced opioid use.	Single-site randomized trial	[25]
Self-management	CON/INT	Cognitive Behavioral Therapy	Arthroplasty	No difference at ≤12 months	NRS.VAS WOMAS	Improve the quality of life to some extent.	Systematic review and analysis	[26]
Self-management	60	Relaxation Exercise	Abdominal surgery	Reduced pain levels	VRS	Reduced pain levels after relaxation exercise 71.1% had less pain	Cross-sectional	[27]

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Self-management	CON = 26 /INT = 26	Novel device use / Navimed	Gynaecological	Higher	NR	Higher pain score on the device than reported to nurses 80% of patients found the device useful	Pro-spective-randomized	[28]
Patient Education/Self-management	CON = 99 /INT = 114	Telemedicine Day-to-day postoperative education for four weeks	Total knee replacement	Lower in the INT group	Pain at night Pain during activity Pain at rest	Deceased level of pain Improved mobilization	Multicenter randomized	[29]
Self-management	CON = 40 /INT = 40	Muscle relaxation technique	Abdominal surgery	Lower in the INT group	VAS	Reduced or absent pain intensity in the INT group	Quasi-experimental	[30]

Abbreviations: VAS, Visual Analog Scale; NRS, Numerical Rating Scale; INT, Intervention; CON, Control; NR, Numeric rating; MBSR, Mindfulness-based reduce stress; VRS, Verbal Rating Scale; Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC; NR, not reported

Findings contrast the two non-pharmacological intervention approaches evaluated in our review. The left panel of Patient Education encompasses perioperative education (timing and content of pain management information before and after surgery), medication management guidance, neuroscience education on pain mechanisms, collaborative goal-setting, scheduled follow-up contacts, coping-strategy training, e.g. breathing exercises, distraction techniques, and patient–provider communication skills. Whereas, the right panel of the Self-Management Program builds on education and goal setting by adding structured communication and emotional support, medication management review, cognitive behavioural therapy (CBT), mindfulness-based stress reduction (MBSR), relaxation techniques, use of monitoring or therapeutic devices, ongoing follow-up, and broader self-care approaches, e.g. tailored exercise or activity planning (Figure 2).

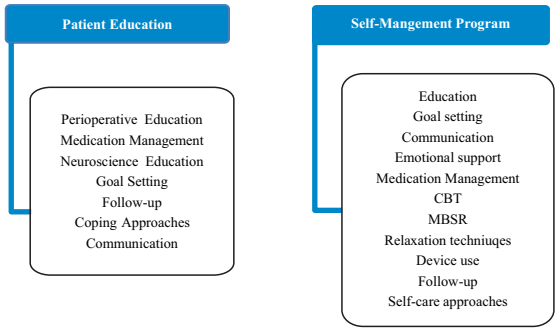

Figure 2: Components of the Patient Education and Self-Management Program Intervention

In Darville-Beneby *et al.*, study [13], postoperative pain outcomes were drawn from multiple primary studies that uniformly used validated patient-reported scales, chiefly the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS) administered at defined postoperative intervals, e.g., 24, 48, and 72 hours. A smaller number of studies also employed multidimensional instruments such as the Brief Pain Inventory (BPI) to capture both pain severity and its interference with function.A detailed literature review examined how effective patient education or self-management is in reducing chronic postoperative pain [17-30].These studies compared the effects on treatment groups who received specific interventions with those on control groups who had standard care.The main outcome measures included pain variables such as severity, duration and functional improvement. Additionally, almost all the studies adopted standardized tools for measuring pain levels, among them the Visual Analog Scale (VAS), the Numerical Rating Scale (NRS) and on a couple of occasions the Verbal Rating Scale (VRS) or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for various postoperative time points. VAS was used to monitor the change in pain intensity from baseline to postoperative follow-ups by multiple studies [17, 19, 22] and, within 48 hours in many cases, produced results that were at least markedly reduced. Only a small number of studies [20, 23, 29] have reported the use of NRS to quantify pain severity and improvements in functional mobility.These studies all found that their intervention groups reported lower pain scores.Less frequent were VRS- and WOMAC-compatible scenarios with outputs on pain perception or joint function [21, 24].When using these scales, subjects also demonstrated meaningful clinical improvement in the self-management intervention group.

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Six studies covering topics such as spinal surgery to cardiac surgery indicated that preoperative counseling, tailored written materials and regulated postoperative guidance (whether measured with VAS or NRS) made early postoperative pain significantly less severe for patients then continuing to need pain pills regularly elsewhere in their recovery program [17, 18, 19, 21, 22, 23].Six studies employing interventions such as Mindfulness-Based Stress Reduction (MBSR), Cognitive-Behavioural Therapy (CBT), telemedicine and relaxation exercises all indicate that pain scores (VAS or NRS) generally decline at various intervals [24, 25, 26, 27, 28, 30].MBSR has also been shown to provide benefits over a longer period, with sustained 12-month pain relief [24, 25].As for CBT, it works well in controlling the pain of the short term but has had mixed outcomes long term. In particular, it has been of benefit for abdominal surgery, with dropping pain scores and fewer analgesics prescribed [27, 30].Combined Approaches: Two studies mixed patient education with self-management strategies, and both reported significantly better pain control as well as functional results (NRS, WOMAC) when compared to allowing patients to follow their rehabilitation entirely on their own [20, 29].The authors measured pain using a self-administered questionnaire that captured patient-reported pain intensity via a Likert-type scale at multiple postoperative time points.This systematic review has interpreted these outcomes as valid subjective assessments of pain, consistent with similar studies, and has clarified this approach in the revised Results section.Many trials explicitly combined various interventions before surgery along with teachings on relaxation techniques, or they included follow-up care by telecommunication [21, 28].The result was that these measures typically yielded greater overall reductions in pain scores (VAS, NRS) and self-reported functionality for patients.Importantly, patients who received comprehensive, multimodal interventions typically followed the faster recovery trajectory and took fewer analgesics. In addition, quality of life comparisons were in favor of this group compared with those receiving only single interventions.These findings support the conclusion that multimodal strategies combining regard for psychological treatment (eg CBT, MBSR), patient education and extra technologies may offer better short- and long-term pain relief backed up by reliable clinical results. Overall, the results across these studies underscore the importance of using validated pain measurement tools to track improvements accurately, highlight the added value of self-management programs in postoperative care, and provide evidence that a multimodal approach yields significant benefits for chronic postoperative pain relief and enhanced patient outcomes.

DISCUSSION

The systematic review was conducted to assess the effectiveness of various interventions in mitigating chronic postoperative pain across different surgical procedures. A randomized controlled trial (RCT) by Lee *et al.*, explored the impact of patient education on postoperative pain and anxiety at Chung Shan Medical Hospital, Taiwan, between April and December 2012 [17]. The study compared the intervention and control groups undergoing spinal surgery.Standard information was provided to CON (n=42), whereas the Booklet, composed of information on spinal structure, type of spinal diseases, fusion surgery, and anesthesia) Before one day of surgery was provided to the INT group (n=40).The findings of the study reported positive results 30 min before surgery (t=3.45 and 2.30) in both groups and were highly significant pain reduction after one day of surgery (t=2.68 and 4.81, p<0.001) measured on the VAS scale.The results are similar to another randomized trial conducted by Sinderovsky *et al.*, in which a Booklet was given to the INT group to provide information on pain and no intervention was provided to the CON group (total = 200) who underwent cardiac surgery [18].The findings reported a reduction in the average 48-hour pain score in the INT group (NRS scale), the INT group (IQR 35-6.00) compared to the CON group (IQR 51.0-73.0; p<0.001). At the Australian College of Perioperative Nurses Australia, an integrative review was conducted encompassing 21 studies published after 2016 was executed by Adam *et al.*, to evaluate the patient education impact on postsurgical pain in elective surgery [19].The results of the study demonstrated the reduction in pain severity and intensity post-surgery in the intervention group using the NR scale, increased satisfaction, and knowledge of patients regarding pain management.This study also reported that the healthcare professional who had training in pain management effectively managed the patient's pain, and results comparable with the study of Bonkowski *et al.*, determined that continuous pain management training improved the nurse's ability to manage pain post-surgery [31].Sawhney *et al.*, designed and implemented a randomized controlled trial (RCT) that took place in Southern Ontario, Canada and assessed the impact of the Hernia Repair Education Intervention (HERI) on postoperative pain [21].Hernia repair is notorious for giving people lasting pain; up to 54% of patients still report moderate to severe discomfort 72 hours after their operations [32, 33].In this study, the control group (n=40) received standard verbal and written information about surgical procedures, postoperative care, and pain control. The intervention group received, in addition to this, a full, detailed booklet, a face-to-face teaching session and two further phone calls: one before surgery and another 24 hours after the operation. The results showed a significant reduction in the pain intensity in 2 days after surgery (POD-2) and less use of opioid analgesics in the intervention

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group than in the control group. Pain intensity was measured with the Numerical Rating Scale (NRS). A striking reduction in the worst movement-related 24-hour pain score was seen in the intervention group (4.7, p=0.0001) as compared to the control group (7.2). Although at 7 days' post-surgery, there were no significant differences in pain intensity between groups, most participants still reported their pain as mild or non-existent both at rest and on movement, indicating that effective implementation of this therapy takes effect over an extended period.At a hospital affiliated with an Australian university, Dowsey *et al.*, conducted a single randomized controlled trial between September 2017 and May 2018 [24].The primary objective was to find out how much an MBSR (Mindfulness-Based Stress Reduction) program can affect pain outcomes for patients who undergo hip and/or knee arthroplasty.A total of 127 patients who had both osteoarthritis and bilateral knee pain were chosen and then randomized into two groups by the regional medical ethics committee:An Intervention group (INT, n=65) and a Control group (CON). The INT group attended an eight-week MBSR program including weekly 2.5-hour sessions.Patients in the CON group received standard care.The primary measure for both groups was pain intensity, as assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-score.At 12 months, the INT group reported a significantly greater reduction in pain intensity when compared to the CON group (mean difference: -10.2 points, 95% confidence interval [CI] -1.3 to -19.2, p=0.025). A parallel group randomized controlled trial conducted by Hanley *et al.*, in an orthopaedic centre in Utah, evaluated the efficacy of Mindfulness-Based Stress Reduction (MBSR) in lowering chronic postoperative pain following hip and knee arthroplasty [25].Given that total joint arthroplasty is a common surgical procedure in the United States, often accompanied by prolonged postoperative pain and opioid use [34, 35], this study aimed to investigate an alternative approach to pain control.While the control group received standard care, the treatment group received an eight-session course of MBSR on mindfulness. The intervention began three weeks before surgery with mindfulness of breath (Mob) and before a two-hour preoperative education session on pain management, anesthesia options, drug treatment, and hypnosis therapy. The results of the study demonstrated that the use of MBSR in this population is practicable.In addition, they disclosed a movement in preoperative pain with Mob ($F_{2,89}=5.28$, p=0.007) and consequential decrease of postoperative pain using Mop ($F_{8,94}=3.21$, p=0.003) at 14, 21 and 28 days following the operation.A systematic review and meta-analysis conducted by Zhang *et al.*, in China investigated the efficacy of Cognitive Behavioural Therapy (CBT) in managing postoperative pain following arthroplasty [26]. By pooling data from nine randomized controlled trials, the study revealed a significant reduction in pain intensity, as measured by the CPS, NRS, and VAS scales, within the first three months' post-surgery in the CBT group compared to the control group.However, this effect was not sustained beyond 12 months.In a separate randomized controlled trial, Chen *et al.*, explored the impact of CBT on postoperative pain and psychological distress in elderly patients (aged 70 years and older) who underwent arthroplasty [36].While no significant difference in pain intensity was observed between the CBT and control groups, the CBT group exhibited reduced anxiety levels on the 7th and 14th postoperative days and decreased depression on the 3rd postoperative day.Topcu *et al.*, conducted a cross-sectional study to assess the effectiveness of relaxation exercises in mitigating postoperative pain in patients who underwent upper abdominal surgery [27].The study, conducted at Trakya University in Turkey, involved 60 participants who were asked to rate their pain levels using a verbal rating scale before and after performing relaxation exercises which resulted in a lowering of pain.The present systematic review has been constrained by small sample sizes, irregular and short periods of follow-up, and various intervention methodologies that change between studies. Hence, future research aimed at validating the effectiveness and benefits over time of patient education and self-management for CPSP needs to emphasize making the intervention techniques and study design standardized, targeting larger populations which may also be more diverse, while follow-up periods also aim to be longer.Overall, the findings of this review show that patient education, self-management programs and behavioural intervention (e.g., CBT, MBSR) can significantly reduce postoperative pain and associated psychological distress. This result is consistent with previous large-scale studies [26], which demonstrated that non-pharmacological methods are ideal for enhancing immediate pain relief in conjunction with standard care.At the same time, however, some studies differ as to whether these interventions cause lasting effects. For example, when Zhang *et al.*, [26] reported reduced efficacy 12 months later, other researchers like Dowsey *et al.*, [24] noted sustained improvements in pain outcomes at the one-year mark.This discrepancy shows that standard protocols and follow-up periods are necessary, as it can lead to mixed results if study design, sample characteristics, and specific components of each intervention differ.Additionally, the disparity in the magnitude of pain relief across studies [18, 21, 36] indicates that patient-specific factors, such as baseline health status, comorbidities or cultural influences, may moderate the effectiveness of these interventions.Taken together, these observations align with the broader literature that emphasizes a tailored, multifaceted approach to treatment approach to persistent post-operative pain. But they also underline the need for further larger clinical trials conducted with

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consistent methodology over extended periods so that the durability of such benefits can be clarified and any conflicting results in the present research resolved.

CONCLUSIONS

It was concluded that this systematic review demonstrates that a multimodal approach can be very effective for relieving chronic postoperative pain while at the same time enhancing clinical outcomes. A multimodal approach should combine preoperative patient education, and self-management programs including cognitive-behavioural therapy, mindfulness-based stress reduction, relaxation exercises, advanced device utilization and telehealth. Future research should include extended follow-up periods and explore innovative digital health tools to optimize long-term effectiveness and applicability in clinical practice.

Authors Contribution

Conceptualization: SA, ME
Methodology: MA, SS
Formal analysis: SH
Writing review and editing: MI, MB, SM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Effectiveness and Function of Dietary and Medical Iron Interventions in Treating Iron-Deficiency Anemia: A Systematic Review

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ABSTRACT

Iron-deficiency anaemia is a widespread nutritional disorder affecting individuals across all age groups, particularly children, pregnant women, and those with chronic illnesses. It arises due to insufficient dietary intake, impaired absorption, or increased iron loss, reducing haemoglobin and oxygen-carrying capacity. **Objectives:** To compare the effectiveness of dietary and medical iron interventions in preventing and treating iron-deficiency anaemia across different populations. **Methods:** A comprehensive search was conducted in PubMed, Scopus, Google Scholar, and Cochrane Library for studies published between 2017 and February 2025.Eligible studies included randomized controlled trials and clinical trials evaluating iron interventions in individuals with or at risk of iron-deficiency anaemia.Primary outcomes included changes in haemoglobin, serum ferritin, total body iron, and anaemia prevalence. **Results:** Both dietary and medical interventions were effective in improving iron status.Iron-fortified foods, micronutrient powders, and bioavailability enhancers such as vitamin C and probiotics were cost-effective for population-level prevention.Medical therapies, including oral and intravenous iron, provided rapid correction in individuals with moderate to severe anaemia. Adherence and long-term sustainability remained key challenges across both approaches. **Conclusions:** It was concluded that integrating dietary strategies with medical interventions offers the most effective approach for managing iron-deficiency anaemia.Future research should focus on enhancing adherence, improving iron bioavailability, and personalizing treatment based on individual needs.

INTRODUCTION

Iron-deficiency anaemia (IDA) is one of the most prevalent nutritional disorders globally, affecting millions across all age groups [1]. It remains a significant public health concern due to its wide-ranging impact on physical performance, cognitive development, maternal health, and productivity, especially among children, pregnant women, and individuals with chronic illnesses. IDA primarily arises from insufficient dietary iron intake, poor absorption, or increased iron loss, resulting in reduced haemoglobin production and impaired oxygen delivery to tissues [2]. The burden of IDA is particularly severe in low- and middle-income countries due to limited access to iron-rich foods, parasitic infections, and poor health infrastructure [3]. However, it also persists in high-income countries, especially among women of reproductive age, individuals with inflammatory bowel diseases, and those following restrictive diets [4]. Multiple intervention strategies exist, including dietary approaches such as iron fortification, micronutrient powders, and bioavailability enhancers (vitamin C, probiotics), and medical treatments like oral or

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intravenous iron therapy [5, 6]. While dietary strategies are generally affordable and suitable for public health programs, their effectiveness can be limited by inhibitors (e.g., phytates, calcium), poor compliance, and absorption variability [7]. On the other hand, medical interventions, particularly intravenous iron, offer rapid correction but are costly and invasive, with concerns over adherence and side effects. Despite the abundance of studies on individual interventions [8, 9], there is limited synthesis comparing the overall effectiveness of dietary and medical strategies across different populations and clinical contexts. This lack of comparative evidence presents a gap in guiding practical, context-specific decision-making for health providers and policymakers.

This study aims to critically assess and compare the effectiveness of dietary and medical iron interventions in improving iron status, identify challenges associated with each strategy, and evaluate their roles in prevention versus treatment across diverse populations.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and methodological rigor. The primary objective was to evaluate the effectiveness of dietary and medical iron interventions in treating iron-deficiency anaemia (IDA) across different populations. A comprehensive search of the literature was conducted using the following databases: PubMed, Scopus, Cochrane Library, and Google Scholar. The search was limited to original research articles published between January 2017 and February 2025 to ensure inclusion of the most recent and relevant studies on iron interventions. Keywords and MeSH terms included: "iron deficiency anaemia," "iron supplementation," "dietary iron intervention," "intravenous iron therapy," "fortified foods," "iron bioavailability," and "nutritional anaemia treatment." Boolean operators (AND/OR) were used to combine keywords and refine the search. Additionally, the reference lists of included studies were manually screened to identify other relevant articles. To ensure inclusion of high-quality and relevant studies, clear inclusion and exclusion criteria were established: Study Types: Randomized controlled trials (RCTs), cluster-RCTs, clinical trials, and open-label trials, Population: Individuals with diagnosed or at-risk IDA, including children, adolescents, pregnant women, adults, and elderly, Interventions, Dietary: Iron-fortified foods, micronutrient powders, lipid-based nutrient supplements, iron-rich diets, and probiotic-enhanced strategies, Medical: Oral iron supplementation (ferrous sulfate, bisglycinate) and intravenous iron therapies (ferric carboxymaltose, ferric derisomaltose, ferric citrate hydrate), Outcomes Measured: Haemoglobin, serum ferritin, total body iron, transferrin saturation, anomia prevalence, and bioavailability, Publication Period: Articles published between 2017 and March 2025 and Language: Only English-language studies were included. Study Type: Systematic reviews, meta-analyses, case reports, editorials, and animal/in-vitro studies, Population: Studies involving participants without iron deficiency or IDA, Intervention Focus: Studies evaluating iron supplementation for non-anaemia purposes (e.g., athletic performance) or combined with unrelated pharmaceutical treatments, Outcome Reporting: Studies without quantifiable outcomes related to iron status or reporting only short-term changes (<2 weeks) were excluded. All search results were imported into a reference manager, and duplicates were removed. Two reviewers independently screened the titles and abstracts of identified articles. Full texts of eligible studies were assessed in detail. Discrepancies were resolved through discussion, and if needed, a third reviewer was consulted for final decisions. Data were extracted using a standardized form. The following information was recorded: Author(s), year of publication, country, Study design and setting, Population (age group, gender), Type of intervention (dietary or medical), Dosage and duration, Outcomes assessed (e.g., haemoglobin, ferritin), Function of intervention (e.g., absorption enhancer, anaemia corrector), Role (prevention vs. treatment), Key findings. Studies were grouped into two categories: Dietary Interventions: Fortified foods, micronutrient powders, vitamin C-enhanced meals, probiotics and Medical Interventions: Oral iron tablets, intravenous iron infusions. The Cochrane Risk of Bias Tool was used to evaluate randomized trials. For non-randomized studies, the Newcastle-Ottawa Scale (NOS) was applied. Key quality indicators included: Adequate randomization and blinding. Transparent outcome reporting and definitions. Low attrition rates. Sufficient follow-up duration. Studies with low or moderate risk of bias were prioritized for final inclusion. Given the variability in study designs, populations, interventions, and outcome measures, a narrative synthesis approach was used. Studies were analyzed within their respective categories (dietary or medical) to identify overall trends, variations in effectiveness, influencing factors (adherence, baseline iron status), and potential limitations. In dietary interventions, the impact of iron enhancers (e.g., vitamin C, probiotics) and inhibitors (e.g., phytates, calcium) was discussed. For medical interventions, factors such as intravenous versus oral routes, dosage, and patient compliance were evaluated. The study selection process is illustrated in the PRISMA flow diagram, detailing

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identification, screening, eligibility, and inclusion stages (Figure 1).

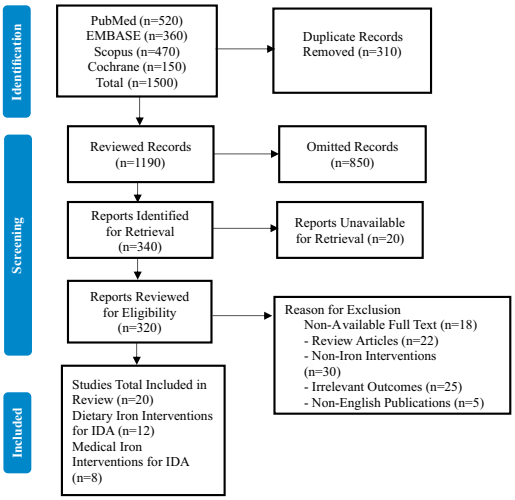

Figure 1: Prisma Flow Chart of Study Included

To enhance clarity and accessibility, the study provides a structured summary of the key characteristics of all included studies, including study design, setting, population, intervention type, outcome focus, and primary findings (Table 1).

Table 1: Study Characteristics of Included Articles

Sr. No.	References	Design	Country	Population	Intervention Type	Role	Main Outcome
1	[10]	Cluster-RCT	Bangladesh	Adolescent Girls	Fortified Lentils (Dietary)	Treatment	↓ Iron Deficiency
2	[11]	RCT	Thailand	Elderly	Rice Drink (Dietary)	Treatment	↑ Hemoglobin
3	[12]	RCT	Burkina Faso	Malnourished Children	Rutf (Dietary)	Treatment	↑ Iron, Persistent Anemia
4	[13]	RCT	India	Children	Mungbean + Guava (Dietary)	Treatment	↑ Hb, No Ferritin Gain
5	[14]	RCT	Thailand	Pregnant Women	Ferrous Bisglycinate (Medical)	Prevention	↑ Hb & Better Tolerance
6	[15]	RCT	Malawi	Malnourished Children	Soya-Maize RUTF (Dietary)	Treatment	↑ Iron Stores
7	[16]	Cluster-RCT	Kenya & Bangladesh	Infants	Lipid-Based Supplements (Dietary)	Prevention	Effective In Kenya Only
8	[17]	Cluster-RCT	China	Infants	Micronutrient Powder (Dietary)	Prevention	↑ Hb, No Cognitive Gain
9	[18]	RCT	Ethiopia	Adolescent Girls	Weekly Ifa (Medical)	Prevention	↑ Ferritin, Hb
10	[19]	RCT	Sweden	Pregnant Women	Probiotic + Iron (Dietary)	Prevention	↑ Absorption
11	[20]	Cluster-RCT	Ghana	Children	Fortified Powder (Dietary)	Prevention	↓ Anemia Prevalence
12	[21]	Clinical Trial	Italy	Celiac Women	High-Iron Diet (Dietary)	Treatment	Less Effective Than Oral Iron
13	[22]	RCT	Switzerland	Surgical Patients	IV Ferric Carboxymaltose (Medical)	Treatment	No Phosphate Effect
14	[23]	RCT	UK	HF Patients	IV Ferric Derisomaltose (Medical)	Treatment	↓ Infection -Related Admissions
15	[24]	Open-RCT	Japan	CKD Patients	Ferric Citrate Hydrate (Medical)	Treatment	↑ Iron, ↓ Platelets
16	[25]	RCT	International	HF Patients	IV Ferric Carboxymaltose (Medical)	Treatment	No Admission Reduction
17	[26]	RCT	International	HF Patients	IV Ferric Carboxymaltose (Medical)	Treatment	Effective at Hb ≥12 g/dL
18	[27]	RCT	Indonesia	HF Patients	Oral Ferrous Sulphate (Medical)	Treatment	↑ Hb and Function

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19	[28]	RCT	UK	HF Patients	IV Ferric Derisomaltose (Medical)	Treatment	↑ QoL, ↓ Admissions
20	[29]	RCT	Uganda	Pregnant Women	Iron + Folic Acid (Medical)	Prevention	↑ Hb, No Adherence Change

RESULTS

This review analyzed dietary and medical interventions for iron-deficiency anaemia (IDA), focusing on their effectiveness, role, and population-specific outcomes. Dietary strategies, including iron-fortified foods, micronutrient powders, and bioavailability enhancers, proved effective in improving iron status, especially for prevention in at-risk groups. Iron-fortified lentils and rice drinks improved haemoglobin and ferritin levels in adolescents and older adults, respectively. Co-fortification with vitamin C, such as mungbean dal with guava, enhanced absorption but had limited effects on iron stores, emphasizing the need for long-term strategies. Micronutrient powders and lipid-based nutrient supplements were moderately effective in infants and young children, though outcomes varied by region. For instance, lipid-based supplements reduced anaemia in Kenya but not in Bangladesh, likely due to baseline nutritional differences. Similarly, probiotic-supported interventions showed improved absorption in pregnant women, indicating improved gut health in iron bioavailability. Therapeutic foods like RUTF improved iron levels in malnourished children, though over half remained anaemic post-treatment, suggesting the need for combination strategies. A high-iron gluten-free diet improved iron stores in celiac patients but was less effective than oral supplementation. Overall, dietary approaches were cost-effective and suitable for population-level prevention, but their effectiveness depended on adherence, baseline iron status, and nutrient absorption. While dietary strategies offer preventive and treatment benefits, medical iron interventions are often necessary for individuals with moderate to severe iron deficiency anaemia. Findings summarize key studies examining intravenous (IV) iron therapies and oral iron supplementation(Table 2).

Table 2: Summary of Dietary Iron Interventions for IDA

Sr. no	References	Design	Population	Intervention	Outcome	Role	Key Finding
1	[10]	Cluster-RCT	Adolescent Girls	Fortified Lentils	↑ Ferritin	Treatment	57% Lower Iron Deficiency
2	[11]	RCT	Elderly	Rice Drink	↑ Hb	Treatment	↑ Hb by 0.6 G/dl
3	[12]	RCT	Malnourished Children	Rutf	↑ Hb, Ferritin	Treatment	55% Remained Anaemic
4	[13]	RCT	Children	Mungbean + Guava	↑ Hb	Treatment	No Change in Iron Stores
5	[14]	RCT	Pregnant Women	Ferrous Bisglycinate	↑ Hb, Ferritin	Prevention	Better Tolerated Than Fumarate
6	[15]	RCT	Malnourished Children	Soya-Maize Rutf	↑ Iron Stores	Treatment	More Effective Than Standard RUTF
7	[16]	Cluster-RCT	Infants	Lipid-Based Supplement	↓ Anemia	Prevention	Effective in Kenya, Not in Bangladesh
8	[17]	Cluster-RCT	Infants	Micronutrient Powder	↑ Hb	Prevention	No Cognitive Gain
9	[18]	RCT	Adolescent Girls	Weekly Iron-Folic Acid	↑ Hb, Ferritin	Prevention	↑ Hb By 0.9 G/Dl
10	[19]	RCT	Pregnant Women	Probiotic + Iron	↑ Absorption	Prevention	Enhanced Bioavailability
11	[20]	Cluster-RCT	Young Children	Fortified Powder	↓ Anemia	Prevention	Prevalence ↓ : from 42% to 27%
12	[21]	Clinical trial	Celiac Women	High-Iron Diet	↑ Ferritin	Treatment	Less Effective Than Oral Iron

Intravenous iron therapies provide a direct and rapid approach to correcting iron deficiency, particularly in clinical settings. Ferric carboxymaltose was evaluated in patients undergoing elective surgery, but results indicated that phosphate supplementation had no significant effect on treatment outcomes [22]. Ferric derisomaltose was studied in heart failure patients and was found to reduce the risk of first hospitalization due to infection, suggesting that correcting iron deficiency may have broader immune and health benefits beyond anaemia management [23]. In patients with anaemia due to chronic

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kidney disease and who are not yet dialysis-dependent, ferric citrate hydrate was equally capable of regulating iron homeostasis by increasing ferritin levels but showed a reduction in platelet counts [24]. Ferric carboxymaltose was assessed for its use in treating hospitalized heart failure patients with iron deficiency; no statistically significant reductions in hospitalizations occurred due to the intervention [25]. A different study showed that the use of ferric carboxymaltose was more effective in patients with haemoglobin levels of ≥12 g/dL, indicating that strategies for treatment should be patient-specific [26]. Iron deficiency anaemia is usually treated with iron supplementation through the oral route. Ferrous sulphate has recently been tested for its possible effect on functional capacity and haemoglobin levels in heart failure patients [27]. Ferric derisomaltose was evaluated in patients with chronic heart failure and iron deficiency, showing potential to reduce hospitalizations and improve quality of life [28]. In pregnant women, iron supplementation plays a critical role in preventing anaemia and supporting maternal and fetal health. Iron and folic acid supplementation using blister-packaged tablets was found to improve haemoglobin levels, though adherence rates did not significantly change [29]. This suggests that while medical interventions can be effective, ensuring compliance remains a challenge. Overall, medical interventions provide effective solutions for correcting iron deficiency, particularly in clinical populations with significant anaemia or comorbid conditions. However, the effectiveness of IV iron therapies appears to vary by patient characteristics, and oral iron supplements, while beneficial, require adherence strategies for long-term success. In summary, medical interventions offer targeted, rapid correction of IDA but require careful selection and adherence strategies. Dietary interventions are preventive and sustainable but need optimization for long-term impact (Table 3).

Table 3: Summary of Medical Iron Interventions for IDA

Sr. no	Author (Year)	Design	Population	Intervention	Outcome	Role	Key Finding
1	[22]	RCT	Surgical patients	IV ferric carboxymaltose	Hb, phosphate	Treatment	Phosphate had no added effect
2	[23]	RCT	Heart failure patients	IV ferric derisomaltose	↓ Hospitalizations	Treatment	Fewer infection -related admissions
3	[24]	Open-RCT	CKD patients	Ferric citrate hydrate	↑ Ferritin	Treatment	↓ Platelets, ↑ Iron
4	[25]	RCT	Heart failure	IV ferric carboxymaltose	Hospitalization	Treatment	No significant change
5	[26]	RCT	Heart failure	IV ferric carboxymaltose	↑ Hb	Treatment	Better in Hb ≥12 g/dL
6	[27]	RCT	HF patients	Oral ferrous sulfate	↑ Hb, function	Treatment	Improved capacity
7	[28]	RCT	HF with IDA	IV ferric derisomaltose	↓ CV risk	Treatment	Fewer admissions, ↑ QoL
8	[29]	RCT	Pregnant women	Iron + folic acid tabs	↑ Hb	Prevention	No adherence change

The systematic review categorizes iron interventions into dietary and medical approaches, both of which demonstrate effectiveness in treating or preventing iron-deficiency anaemia. Dietary interventions are highly accessible and suitable for preventive strategies, particularly when iron is combined with bioavailability enhancers like vitamin C and probiotics. However, medical interventions, such as IV iron and oral supplements, provide rapid correction of anaemia in clinical populations, particularly those with heart failure, kidney disease, or malabsorption disorders. A multifaceted approach, integrating both dietary and medical interventions, appears to be the most effective strategy in managing iron-deficiency anaemia across different populations. Future research should continue to explore bioavailability improvements, long-term adherence strategies, and personalized treatment approaches to optimize iron interventions worldwide.

DISCUSSION

Iron-deficiency anaemia (IDA) remains a major public health challenge, particularly among children, women, and individuals with chronic illnesses. This review evaluated both dietary and medical interventions, categorizing them by purpose (prevention vs. treatment) and method (dietary vs. medical), providing a clearer understanding of their respective roles. When compared with previous systematic reviews, this study builds on existing knowledge by categorizing interventions and assessing their effectiveness based on patient-specific factors, adherence, and long-term outcomes [30-32]. Dietary strategies proved effective, especially for preventing IDA in at-risk populations. Fortified foods and enhancers like vitamin C and probiotics consistently improved hemoglobin and ferritin levels. For example, Yunus *et al.*,

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and Lerttrakarnnon et al., showed that iron-fortified lentils and rice drinks enhanced iron status [10, 11]. These findings align with Hurrell *et al.*, who identified staple food fortification as a scalable solution [33].However, effects on iron stores were inconsistent.In Rani *et al.*, haemoglobin increased with mung-bean and guava, but ferritin did not [13].This supports Rajagukguk *et al.*, who noted vitamin C helps absorb non-heme iron but may not suffice in severe deficiency.Probiotic strategies also showed promise [34]. Micronutrient powders and lipid-based supplements had mixed results.Luo *et al.*, reported improved haemoglobin but no cognitive gains [17]. Similarly, Stewart *et al.*, found success in Kenya but not Bangladesh, suggesting regional nutrition affects outcomes [16]. Kangas *et al.*, noted that RUTF improved iron status, though anaemia persisted, echoing Imdad *et al.*, [12, 35]. While dietary interventions are affordable and scalable, success depends on adherence, bioavailability, and baseline iron levels. Medical therapies were more suitable for moderate-to-severe anaemia. IV iron therapies produced rapid results. Foley *et al.*, reported reduced hospitalizations in heart failure patients using ferric derisomaltose [23].However, Macdougall *et al.*, found no reduction in admissions [25], consistent with the AFFIRM-AHF trial, which emphasized appropriate patient selection [36]. Kaserer *et al.*, showed no added benefit from phosphate with IV ferric carboxymaltose [22]. Iolascon *et al.*, similarly, emphasized tailoring IV iron based on patient profile [37]. Oral iron improved haemoglobin and function, but adherence remains a barrier [27]. Byamugisha *et al.*, and Afolabi *et al.*, noted poor compliance, especially among pregnant women [29, 38]. While IV iron is fast and effective, it's costlier and invasive. Oral iron is more accessible but requires adherence strategies to ensure impact.

CONCLUSIONS

It was concluded that both dietary and medical iron interventions are effective in addressing iron-deficiency anaemia, each serving distinct roles. Dietary strategies, including fortified foods, micronutrient powders, and enhancers like vitamin C and probiotics, are sustainable and preventive, especially in community and public health settings. However, their effectiveness depends on long-term adherence and individual nutritional status. Medical interventions, particularly intravenous and oral iron therapies, are more appropriate for moderate to severe anaemia, offering rapid correction but requiring clinical monitoring and patient compliance. The findings support a complementary approach, where dietary and medical strategies are integrated based on population needs and anaemia severity. This dual-path strategy can improve outcomes, especially in resource-diverse settings.

Authors Contribution

Conceptualization: AA
Methodology: AA, NF
Formal analysis: MK, KS, NF, AS, SA
Writing review and editing: AA, AS, SA

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Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Iodine Levels and Thyroid Hormones in Pregnant Women and Neonatal Outcomes: A Systematic Review

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ABSTRACT

Iodine plays a vital role in the synthesis of thyroid hormones, which are essential for fetal growth and brain development. During pregnancy, maternal iodine needs to increase. Both deficiency and excess can impair maternal thyroid function and lead to complications such as hypothyroxinemia, fetal growth restriction, or thyroid dysfunction in the mother or child. **Objectives:** To assess the relationship between maternal iodine levels, thyroid function, and neonatal outcomes, and highlight the risks associated with both iodine deficiency and excess. **Methods:** A systematic search was conducted in PubMed, Web of Science, Scopus, Springer, and MDPI for studies published from 2021 to 2025. Inclusion criteria involved studies assessing iodine status (Urinary Iodine Concentration (UIC) or Serum Iodine Concentration (SIC), maternal thyroid function (TSH, FT4, FT3), and neonatal outcomes. Articles were screened using PRISMA guidelines. The risk of bias was assessed using the Newcastle-Ottawa Scale and Cochrane Risk of Bias Tool. Due to heterogeneity in methods and outcomes, results were narratively synthesized. **Results:** Ten studies were included. Iodine deficiency was consistently associated with low birth weight and disrupted thyroid hormone levels, while iodine excess particularly at levels ≥500 µg/L was linked to transient neonatal hyperthyrotropinemia. Environmental exposures such as endocrine-disrupting chemicals also influence maternal thyroid function. **Conclusions:** It was concluded that both iodine deficiency and excess pose risks to maternal and neonatal thyroid health. Routine monitoring and individualized supplementation based on regional dietary patterns and environmental exposures are recommended.

INTRODUCTION

Iodine is a critical micronutrient essential for the synthesis of thyroid hormones, which are vital for metabolic regulation, fetal growth, and neurological development [1]. During pregnancy, maternal iodine requirements increase significantly due to enhanced maternal thyroid hormone production, fetal thyroid development, and increased renal iodine clearance.Therefore, sufficient iodine intake is essential to maintain maternal thyroid health and ensure normal fetal development [2-4].Iodine deficiency during pregnancy has been associated with a range of adverse outcomes, including Maternal iodine deficiency can result in hypothyroxinemia, a condition characterized by low free thyroxine (FT4) levels despite normal TSH levels, which may impair fetal brain development, fetal growth restriction, and impaired neurodevelopment in children [5, 6]. In response to these risks, the World Health Organization (WHO) recommends an iodine intake of 250 µg/day during pregnancy [7].However, studies show that iodine intake varies across regions due to dietary habits, iodine fortification policies, and environmental factors.In iodine-

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deficient regions, subclinical hypothyroidism is more prevalent in pregnant women, contributing to developmental risks for the fetus [8, 9]. While the risks of iodine deficiency are well-established, emerging evidence suggests that excess iodine intake may also be harmful [10]. High maternal iodine levels can disrupt thyroid homeostasis, potentially leading to maternal hyperthyroidism or neonatal hypothyroidism Overconsumption from supplements or iodized salt can interfere with delicate maternal-fetal thyroid regulation. Thus, both insufficient and excessive iodine intake pose potential threats during pregnancy [11-13]. Despite the growing literature on this topic [14], there is still no global consensus on the optimal iodine concentration during pregnancy to ensure the best neonatal outcome Previous reviews have focused primarily on iodine deficiency; however, the effects of iodine excess and the influence of environmental factors such as endocrine-disrupting chemicals (EDCs) remain underexplored [15]. This systematic review aims to comprehensively evaluate the association between maternal iodine intake, thyroid function, and neonatal outcomes by synthesizing findings from recent literature. It further seeks to clarify the impacts of both deficiency and excess iodine intake, emphasizing the need for individualized iodine assessment and supplementation strategies in pregnant populations. Despite extensive research on iodine and pregnancy, even after considerable studies of iodine use in pregnancy, there remains controversy regarding the best concentration of maternal iodine that results in the optimal outcome for the newborn Some studies do emphasize the importance of iodine supplementation in the period of mild to moderate iodine deficiency, while others oppose the unconditional supplementation without prior evaluation of iodine status. Also, some recent studies of endocrine-disrupting chemicals (EDCs) exposure may view iodine metabolism during pregnancy in more complicated terms, which is already considered complex in the field of environmental health

This study aims to comprehensively evaluate the relationship regarding the levels of iodine consumed by mothers, thyroid function, and neonatal outcomes, synthesizing findings from recent studies. This review aims to offer informative recommendations on the ideal iodine intake during pregnancy by assessing both iodine deficiency and iodine excess and underscoring the need for tailored strategies concerning iodine supplementation and evaluation.

METHODS

This systematic review was conducted by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A structured search strategy was developed to identify studies evaluating maternal iodine levels and thyroid function about neonatal outcomes. Articles were retrieved from PubMed, Scopus, Web of Science, Springer Link, and MDPI, covering the period from January 2021 to February 2025. Both observational and interventional studies focusing on iodine status during pregnancy, maternal thyroid hormones, and infant health outcomes were considered. To maximize relevance and efficiency, the following keywords were used: "maternal iodine deficiency," "iodine levels," "thyroid function," "pregnant women," "neonatal outcomes," and the Me-SH term "Urinary Iodine Concentration (UIC)." Boolean operators AND and OR were applied to combine and refine searches. Additionally, the reference lists of included articles were screened to identify relevant studies not captured through database searches. Clear inclusion and exclusion criteria were defined to ensure relevance and quality. Inclusion Criteria: Studies published between 2021 and March 2025, peer-reviewed original research articles (excluding editorials, commentaries, and abstracts), studies assessing iodine levels in pregnant women via UIC or serum iodine concentration (SIC), studies evaluating maternal thyroid function (TSH, FT3, FT4, or thyroglobulin) and studies reporting neonatal outcomes (e.g., birth weight, preterm birth, stillbirth, neonatal thyroid function, or neurodevelopment). Exclusion Criteria: Studies not measuring iodine during pregnancy, studies on non-pregnant populations, articles with incomplete or unclear methodology for iodine measurement and case reports, reviews, meta-analyses, or animal studies. Two independent reviewers screened all titles and abstracts using the inclusion/exclusion criteria. Full texts of potentially eligible studies were then assessed. Discrepancies were resolved through discussion or by consulting a third reviewer. Extracted data included: author, year, study design, setting, sample size, gestational age at iodine assessment, iodine levels, measurement method, maternal thyroid parameters, neonatal outcomes, confounding variables, and key findings. The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for interventional studies. Studies were scored on selection bias, comparability, outcome assessment, and follow-up adequacy. Only studies with moderate to high methodological quality were included. Due to heterogeneity in study designs, iodine measurement methods, and outcomes, a narrative synthesis approach was adopted. Where applicable, studies were grouped by design or iodine assessment method to aid comparison. Special emphasis was placed on the relationship between iodine levels and maternal thyroid function and neonatal outcomes. Conflicting

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evidence, such as studies reporting no significant link between mild iodine deficiency and fetal outcomes, was noted and considered during synthesis (Figure 1).

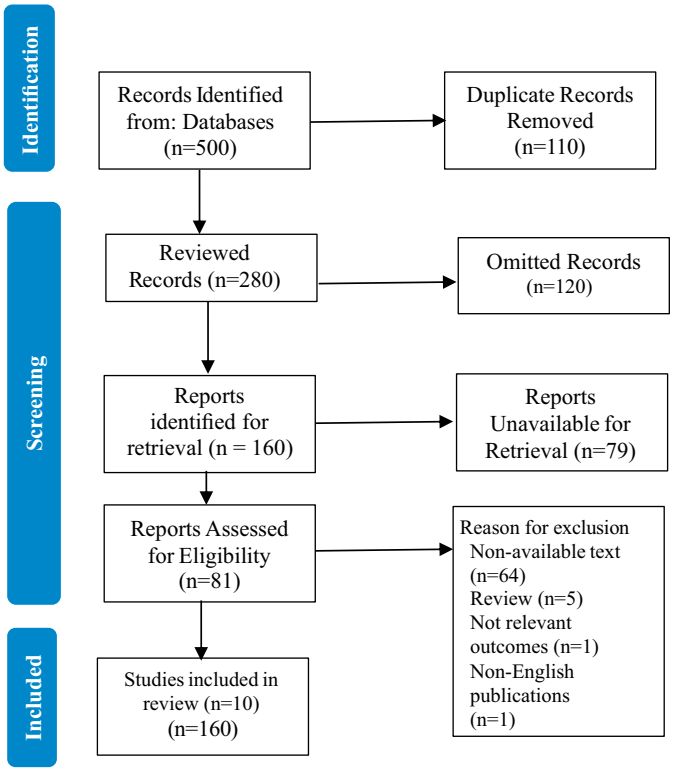

Figure 1: Selection Process of Studies Included in the Review

RESULTS

This systematic review includes ten studies that evaluated the relationship between maternal iodine intake, thyroid function, and neonatal outcomes.The studies varied in design, setting, and assessment methods, yet collectively they provide important insights into the dual risks of iodine deficiency and excess during pregnancy.Several studies emphasized the adverse effects of iodine deficiency on fetal development.For instance, Zha *et al.*, reported that lower urinary iodine concentration (UIC), adjusted by urinary creatinine, was significantly correlated with reduced maternal FT4 and increased TSH, contributing to a higher incidence of low birth weight (LBW) [16].Similarly, Liu *et al.*, found that lower serum iodine levels in early pregnancy were associated with decreased birth weight and increased maternal thyroid dysfunction [17].Fan *et al.*, added that maternal serum iodine concentrations influenced neonatal TSH levels, suggesting that maternal thyroid hormone fluctuations directly affect fetal thyroid regulation [1].These studies underline that iodine deficiency, even in mild to moderate forms, can impact fetal growth through disruption of maternal thyroid homeostasis.Study showed that exposure to phthalates endocrine-disrupting chemicals—may exacerbate thyroid hormone dysregulation in iodine-deficient regions.This highlights the potential influence of environmental toxins in altering thyroid function beyond iodine intake alone. Ovadia *et al.*, also reported that inadequate iodine intake was linked to isolated hypothyroxinemia and a higher risk of large-for-gestational-age (LGA) neonates, adding complexity to the narrative that both deficiency and excess can result in poor outcomes [18]. Conversely, studies such as Mathews *et al.*, and Rao *et al.*, discussed the effects of excessive iodine intake [19, 20].In both studies, high maternal iodine exposure specifically UIC levels ≥500 µg/L during the third trimester was associated with transient neonatal hyperthyrotropinemia.Although this condition normalized by 12 weeks postpartum, it highlights that excessive iodine can temporarily disrupt neonatal thyroid homeostasis.However, not all findings were consistent. Purdue-Smithe *et al.*, found no significant association between maternal iodine levels and the risk of stillbirth, suggesting that mild to moderate iodine deficiency may not always lead to adverse pregnancy outcomes [21].The overall evidence demonstrates that both insufficient and excessive iodine intake during pregnancy can adversely affect neonatal outcomes primarily through altered thyroid function.Bonell *et al.*, concluded that both low and high maternal iodine levels were linked to decreased birth weight and length [22].These outcomes emphasize the need for precise, region-specific monitoring of iodine intake in pregnant populations to prevent either extreme (Table 1).

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Table 1: Summary of Included Studies on Maternal Iodine Status, Thyroid Function, and Neonatal Outcomes

References	Study Design	Sample Size	Gestational Age (Weeks)	Iodine Levels (µg/L)	Thyroid Function (TSH, FT4, FT3)	Thyroid Dysfunction Prevalence (%)	Neonatal Outcomes	Confounders Adjusted	Key Findings
[16]	Observational Cohort	212	The second half of pregnancy	Group 1: <106.96; Group 2: 106.96–259.08; Group 3: >259.08	FT4↓, TSH↑	Not specified	Low birth weight	Not specified	Lower iodine levels linked to lower FT4, higher TSH; risk of LBW
[17]	Longitudinal Cohort	1,000	Early pregnancy	Median SIC: 60.3	FT4↓, TSH↑	Not specified	Lower birth weight	Age, BMI, education, parity, GWG	Low SIC linked to thyroid dysfunction and LBW
[1]	Prospective Cohort	559	All trimesters	Median SIC: 79.6	FT3↓, FT4↓, TSH↑	Not specified	Neonatal TSH levels	Age, gestational week, thyroid disorders	SIC influences maternal and neonatal thyroid hormones
[23]	Cross-Sectional	835	Not specified	Not directly measured	Altered thyroid hormones due to phthalates	Not specified	Birth weight changes	Age, education, smoking, SES	Pollution + iodine deficiency impact thyroid function and birth weight
[18]	Prospective Cohort	118	All trimesters	Median Tg: 16.5	Isolated hypothyroxinemia	OR = 3.4 (95% CI: 1.2–9.9)	LGA risk	Not specified	Iodine deficiency linked to hypothyroxinemia and LGA
[19]	Prospective Cohort	57	Not specified	Measured post-HSG	Neonatal TSH↑, FT4↓	No primary hypothyroidism	Altered thyroid markers	Not specified	High maternal iodine → altered neonatal thyroid levels
[24]	Prospective Cohort	202	Not specified	Dietary + UIC	Tg↑, Ft4 measured	Not specified	LGA	Age, BMI, parity, smoking	Tg >13 µg/L linked to LGA births (HR = 3.4)
[20]	Prospective Observational	400	Term neonates (≥37 wks)	UIC ≥500 µg/L	Neonatal TSH at birth, follow-up FT3/FT4	TSH ≥11 mIU/L in 12.2%	Transient hyperthyrotropinemia	Not specified	Excess iodine linked to temporary thyroid dysfunction in neonates
[21]	Nested Case-Control	448 (199 cases, 249 controls)	10–14 weeks	Q1: 0.1–6.5; Q2–3: 6.7–38.3; Q4: 38.3–228.3	Tg, TSH measured	Not specified	Stillbirth	Age, BMI, SES, smoking	No link between iodine and stillbirth in mildly deficient settings
[22]	Prospective Cohort	Not specified	Not specified	UIC	TSH, FT4	Not specified	BW, length, HC, Apgar	Age, BMI, smoking, education	Both low and high iodine are linked to poor birth outcomes

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DISCUSSION

The findings of this systematic review highlight the critical role of maternal iodine status in determining neonatal health outcomes.Both Zha *et al.*, and Liu *et al.*, reported significant associations between iodine deficiency and low birth weight, consistent with earlier literature linking inadequate maternal iodine to poor fetal growth and adverse pregnancy outcomes [16, 17].These results were supported by evidence that iodine deficiency may lead to maternal hypothyroxinemia, which impairs fetal brain and physical development. However, this view is not universally held; for example, researchers found no significant relationship between mild iodine deficiency and stillbirth, illustrating a key controversy in the field it was according to the previous systemic reviews [25-27].A review by Nazeri et al., emphasized the association between iodine intake and birth weight but noted a lack of consistent evidence linking mild iodine deficiency to neurocognitive impairments in children [28].This discrepancy underscores the need for well-designed longitudinal studies that examine both immediate and long-term consequences of maternal iodine intake [29].While iodine deficiency is widely recognized, this review also draws attention to the potential risks of iodine excess.Mathews *et al.*, and Rao *et al.*, identified high maternal iodine intake (UIC ≥ 500 µg/L) as a trigger for transient neonatal hyperthyrotropinemia [19, 20]. These findings align with previous work by Nazarpour *et al.*, who warned that excessive fetal exposure to iodine may impair thyroid function regulation [7].Although some studies suggest that neonatal thyroid disturbances may normalize postnatally, others caution that maternal overconsumption of iodine can increase the likelihood of persistent hypothyroidism in neonates [30, 31].This inconsistency supports the need for individualized monitoring of iodine intake during pregnancy. Beyond direct iodine intake, environmental and dietary factors also influence maternal thyroid function. Zha *et al.*, reported that phthalate exposure negatively affects iodine metabolism and maternal thyroid hormone levels [1]. Similar findings were echoed in other environmental health studies, which emphasize the vulnerability of iodine metabolism to endocrine-disrupting chemicals (EDCs) [32, 33].Additionally, many studies highlighted the influence of dietary iodine intake on maternal thyroglobulin levels and neonatal growth, aligning with evidence that food-based iodine alone is often insufficient to meet pregnancy demands [34, 35].In summary, this review supports prior research linking iodine status with neonatal outcomes, while also expanding on the dual risks of both deficiency and excess. Unlike earlier reviews that focused primarily on fetal neurodevelopment, this study incorporates additional outcomes such as birth weight and thyroid regulation, along with environmental interactions.Furthermore, while previous reviews have supported universal iodine supplementation policies, our findings emphasize the need for tailored strategies that account for regional dietary habits, environmental exposures, and individual maternal risk factors.

CONCLUSIONS

It was concluded that this systematic review highlights the importance of iodine status in maternal health and pregnancy outcomes. Both deficient and excess iodine levels can lead to thyroid complications and difficulties in neonatal health. The results suggest that routine monitoring of maternal iodine status and personalized supplementation based on regional needs should be prioritized. Future research should focus on establishing region-specific iodine intake thresholds and evaluating long-term outcomes through prospective cohort studies.

Authors Contribution

Conceptualization: SA
Methodology: MI, MIK
Formal analysis: OK, AI, UF
Writing review and editing: SA, MI, MIK, OK, AI, UF

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Conflicts of Interest

All the authors declare no conflict of interest.

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