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Empowering Young Girls in Pakistan through HPV Vaccination and Cervical Cancer Awareness

OPEN ACCESS

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Cervical cancer is a major public health challenge in Pakistan, with over 5,000 new cases and nearly 3,000 deaths each year, making it the third most common cancer among women and the second most frequent among those aged 15 to 44 [1, 2]. The disease is often diagnosed late, contributing to disproportionately high mortality compared to neighboring countries. Human papillomavirus (HPV) infection is the primary cause, with high-risk genotypes 16 and 18 responsible for nearly 90% of invasive cervical cancers, and recent data from Karachi show a prevalence of 16.7% among tested women [3, 4].

Despite being largely preventable through vaccination and early detection, cervical cancer in Pakistan remains neglected due to extremely low awareness, harmful misconceptions, lack of organized screening, and deep-rooted cultural stigma surrounding sexual and reproductive health. Many people wrongly believe that cervical cancer only affects women who are sexually active or have multiple partners, creating stigma that discourages open discussion and preventive care [5]. These cultural taboos and widespread opposition to addressing sexual and reproductive health leave countless women without access to life-saving knowledge and early detection. The silence and shame surrounding cervical cancer have allowed it to remain hidden, leaving Pakistani women disproportionately vulnerable to a disease that could otherwise be prevented or treated in time [6, 7].

In September 2025, Pakistan took a historic step by launching its first nationwide Human Papillomavirus (HPV) vaccination campaign, targeting 13 million girls aged 9 to 14 years. The vaccine is being provided free of charge through schools, health facilities, outreach sites, and mobile teams, with support from WHO, UNICEF, and Gavi. This initiative will not only protect young girls from cervical cancer a disease that claims thousands of lives each year, but also integrate HPV vaccination into routine immunization, ensuring protection for future generations [8].

This campaign is more than just a health intervention; it is an empowerment movement for women and girls. By protecting them early, we are giving them the right to a healthier future, free from a preventable disease. Families, teachers, and communities must come together to encourage every eligible girl to get vaccinated. With collective effort, Pakistan can break the silence around women's health, eliminate cervical cancer, and empower women to lead stronger, healthier lives. The way forward is clear to make screening services accessible, spread accurate information to every household, and create safe spaces where women can seek care without fear or stigma.

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Original Article

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Frequency of Intradialytic Complications among Patients of Maintenance Hemodialysis on Thrice Weekly

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ABSTRACT

Renal replacement therapy for ESRD includes hemodialysis, peritoneal dialysis, and transplantation, with hemodialysis being the most common. Over two million patients receive it annually. ESRD patients often have comorbidities like heart disease, vascular disease, and COPD, increasing their health risks. **Objectives:** To determine the frequency of intra-dialytic complications occurring in patients on maintenance hemodialysis. **Methods:** This cross-sectional study was conducted at the Nephrology Department of Sir Ganga Ram Hospital, Lahore. A total of 83 ESRD patients aged 15–70 years, undergoing thrice-weekly hemodialysis, were selected using non-probability consecutive sampling. Patients with acute renal failure, dementia, or unconsciousness were excluded. Dialysis was performed using Fresenius, Surdial, Toray, and Nipro machines, with complications monitored over two months. Data were recorded using a structured proforma and analyzed with SPSS version 25.0, with qualitative variables presented as frequencies and percentages and continuous variables as mean ± SD. Chi-square tests were applied, with statistical significance set at p≤0.050. **Results:** Among 83 patients (63.9% male, 63.9% >40 years), 60.2% had CKD for <5 years. Diabetes (65) and hypertension (29) were the leading causes. The most common complications were hypotension (28), nausea/vomiting (17), and cramping (11). There was no significant association among complications of CKD with age, gender, duration of disease and type of hemodialysis (p-value>0.050). **Conclusions:** Dialysis complications are common, with hypotension being the most frequent, followed by nausea, vomiting, hypertension, and muscle cramps. Diabetic patients are more vulnerable, emphasizing the need for better monitoring and preventive strategies to improve outcomes.

INTRODUCTION

The global prevalence of kidney diseases has risen to 11–13% over the past two decades, primarily due to the increasing burden of diabetes mellitus (DM), the leading cause worldwide. Other contributing factors include hypertension, glomerular diseases, renal stones, and excessive use of over-the-counter medications. End-stage renal disease (ESRD) is managed through renal replacement therapy (RRT), including dialysis hemodialysis or peritoneal dialysis and renal transplantation. Hemodialysis, a widely used treatment, enrolls over two million patients annually [1, 2]. Hemodialysis, crucial for end-stage renal disease, typically lasts 3–4 hours per session, conducted thrice weekly in developed countries and twice weekly in developing nations. Patients, often with comorbidities like ischemic heart disease, peripheral vascular disease, cerebrovascular disease, and COPD, face higher morbidity and mortality risks [3]. Despite its life-saving benefits, hemodialysis is generally safe, with a mortality rate of 1 in 75,000 treatments. However, complications arise, categorized as acute (occurring during or immediately after treatment) or chronic [4]. Hemodialysis complications arise from various factors related to equipment and patient conditions. Key factors include dialyzer type, conductivity, blood flow, ultrafiltration rate, anticoagulant use, and water contamination. Advances in technology have reduced

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these risks. Patient-related contributors include underlying disease, comorbidities, medications, weight gain during dialysis, and treatment frequency and duration [5, 6]. Hypotension, which is characterized by a decline in systolic blood pressure (SBP) greater than 20 mm Hg or a reduction in mean arterial pressure by 10 mmHg, stands as the most prevalent acute complication globally, with a reported incidence ranging from 25% to 55%. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative provides this definition. Additional complications encompass arrhythmias at a rate of 50%, while nausea and vomiting during and after the session occur in 15% of cases. Muscle cramps afflict 20% of individuals, followed by less frequent occurrences of headache, chest pain, back pain at 5%, and hypertension, fever, and chills due to dialyzer reaction [7, 8]. In a research endeavor, it was determined that hypotension emerged as the prevailing complication, accounting for 28.7% of cases, with nausea/vomiting following closely behind at 11.75%. Fever and muscle cramps were also observed as prominent symptoms, each representing 8.5% of occurrences [9]. The occurrence of end-stage renal disease (ESRD) in Pakistan amounts to 14.6%. In addition, given the escalating occurrence of chronic ailments, which are eventually associated with ESRD, it is imperative to assess the advantages and disadvantages of the available methods for managing this condition [10].

Although hemodialysis remains the most widely utilized renal replacement therapy for ESRD, intra-dialytic complications continue to contribute significantly to patient morbidity and reduced quality of life. Most available studies report variable frequencies of these complications, often derived from international populations with differing healthcare infrastructures and dialysis protocols. Local data from tertiary care centers in Pakistan, particularly regarding patients on thrice-weekly maintenance hemodialysis, remain limited. This gap in region-specific evidence necessitates a focused evaluation to better understand the burden and pattern of intra-dialytic complications in our setting. The primary objective of this investigation was to ascertain the diverse complications that frequently arise in the course of hemodialysis to facilitate the identification and implementation of preventive measures. This endeavor augments the understanding of hemodialysis complications among healthcare personnel and patients alike, aiding them in making informed decisions regarding treatment options. This study aimed to determine the frequency of intra-dialytic complications occurring in patients on maintenance hemodialysis at Sir Ganga Ram Hospital, Lahore.

METHODS

This cross-sectional study was conducted at the Nephrology Department of Sir Ganga Ram Hospital, Lahore, from July to December 2024, following synopsis approval (No:159-MD/ERC). A total of 83 participants were selected using non-probability consecutive sampling, based on a 95% confidence level, a 6% margin of error, and an estimated muscle cramp prevalence of 8.5% [7]. Patients aged 15 to 70 years with end-stage renal disease (ESRD), undergoing thrice-weekly acute hemodialysis, regardless of comorbidities or dialysis access site, were included. End-stage renal disease (ESRD) was defined as patients with a GFR <15 mL/min/1.73m^2 requiring hemodialysis initiation. Patients receiving hemodialysis due to acute renal failure or those with dementia or unconsciousness were excluded. Ethical approval was obtained before recruitment, and all use past tense participants were provided written informed consent. Demographic data (age, gender), cause of CKD, comorbidities, and baseline blood pressure were obtained from hospital medical records and verified with patients during interviews. Pre- and post-dialysis blood pressure values were recorded directly from dialysis session monitoring sheets maintained by nursing staff. The study population consisted of patients with a permanent vascular access (AV fistula), undergoing dialysis using a Fresenius hemodialysis machine. Dialysis-related complications were monitored over two months, with data recorded using a structured proforma. Statistical analysis was performed using SPSS version 25.0. Qualitative variables such as gender, ESRD cause, and type of hemodialysis were presented as frequencies and percentages, while continuous variables such as age and dialysis duration were expressed as mean ± standard deviation. Data were stratified by gender, age, type of hemodialysis, and dialysis duration to account for effect modifiers. Chi-square tests were applied for categorical variables, with statistical significance set at $p \leq 0.050$.

RESULTS

The study included 83 patients, with a majority (63.9%) being over the age of 40 years, while 36.1% were younger than 40 years. In terms of gender distribution, 63.9% of the patients were male, and 36.1% were female. The duration of disease varied, with 60.2% of patients having the condition for less than 5 years, while 39.8% had been affected for more than 5 years (Table 1).

Table 1: Demographic Features of Patients

Variables	Frequency (%)
Age	
<40	30 (36.1%)
>40	53 (63.9%)

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Gender	
Male	53 (63.9%)
Female	30 (36.1%)
Duration of Disease	
<5 Years	50 (60.2%)
>5 Years	33 (39.8%)

The most common causes of CKD among patients were diabetes mellitus, affecting 65 individuals, followed by hypertension, which was present in 29 patients. Other notable causes included obstructive nephropathy (17 patients) and polycystic kidney disease (PKD) (13 patients). Conditions such as glomerulonephritis and chronic pyelonephritis were observed in 10 patients each, while congenital or hereditary disorders were reported in 9 patients. Myeloma was the least common cause, affecting only 4 patients (Figure 1).

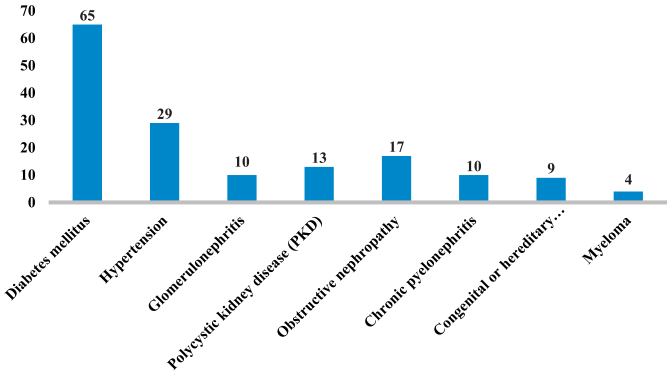

Figure 1: Causes of CKD among Patients

Complications varied among patients based on gender, age, and type of hemodialysis. Hypotension was the most frequently reported complication, occurring in 16 female and 12 male. Other common complications among male included nausea and vomiting (11 cases) and cramping (9 cases), while among female, hypotension (16 cases) was the most prominent issue (p-value=0.070). When analyzed by age groups, patients older than 40 years experienced a higher frequency of hypotension (20 cases) and nausea and vomiting (10 cases) compared to younger patients (8 and 7 cases, respectively) (p-value=0.615). Other complications were relatively evenly distributed between the two groups (p-value=0.900) (Table 2).

Table 2: Complications among Patients Based on Gender, Age, and Type of Hemodialysis

Variables	Hypotension	Cramping	Nausea/Vomiting	Backache	Chest Pain	Itching	Headache	Fever	p-Value
Gender									
Male (n=53)	12 (22.6%)	9 (17.0%)	11 (20.8%)	7 (13.2%)	4 (7.5%)	6 (11.3%)	3 (5.7%)	1 (1.9%)	0.070
Female (n=30)	16 (53.3%)	2 (6.7%)	6 (20.0%)	2 (6.7%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	
Age									
<40 Years (n=40)	8 (20.0%)	4 (10.0%)	7 (17.5%)	3 (7.5%)	5 (12.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	0.615
≥40 Years (n=43)	20 (46.5%)	7 (16.3%)	10 (23.3%)	6 (14.0%)	2 (4.7%)	4 (9.3%)	2 (4.7%)	2 (4.7%)	
Duration of Disease									
<5 Years (n=48)	13 (27.1%)	4 (8.3%)	7 (14.6%)	3 (6.3%)	3 (6.3%)	2 (4.2%)	0 (0.0%)	1 (2.1%)	0.914
≥5 Years (n=35)	15 (42.9%)	7 (20.0%)	10 (28.6%)	6 (17.1%)	4 (11.4%)	4 (11.4%)	3 (8.6%)	1 (2.9%)	

The distribution of blood pressure status was evaluated across three time points (pre- and post) in a sample of 83 participants. At baseline (pre_BP_1), 44.6% of participants were hypertensive (HTN) and 55.4% had normal blood pressure. Following the first intervention (post_BP_1), the proportion of hypertensive individuals increased to 50.6%, while those with normal blood pressure decreased to 49.4%. A similar distribution was observed in pre_BP2, with 50.6% hypertensive and 49.4% normal. However, in post_BP2, the proportion of hypertensive participants rose further to 59.0%, while normal readings dropped to 39.8%, and a small number (1.2%) were classified as having low blood pressure. In pre_BP3, hypertension was highest at 68.7%, with only 31.3% having normal readings. This percentage improved slightly in post_BP3, where 55.4% remained hypertensive and 44.6% had normal blood pressure (Table 3).

Table 3: Blood Pressure Status Across Time Points

Category	Pre_BP_1	Post_BP_1	Pre_BP2	Post_BP2	Pre_BP3	Post_BP3
HTN	37 (44.6%)	42 (50.6%)	42 (50.6%)	49 (59.0%)	57 (68.7%)	46 (55.4%)
NORMAL	46 (55.4%)	41 (49.4%)	41 (49.4%)	33 (39.8%)	26 (31.3%)	37 (44.6%)
LOW	–	–	–	1 (1.2%)	–	–
Total	83 (100%)	83 (100%)	83 (100%)	83 (100%)	83 (100%)	83 (100%)

Descriptive statistics for participants' weight across three time points revealed slight changes before and after each dialysis session. The mean pre-dialysis weight at the first time point was 61.67 kg, which increased to 65.87 kg post-dialysis. The second pre-dialysis weight showed a mean of 69.36 kg, while the post-dialysis mean was 59.69 kg. At the third time point, the mean pre-dialysis weight was 61.34 kg, with the post-dialysis mean again at 59.69 kg. Overall, the data indicate a modest reduction in weight following dialysis sessions, although some inconsistencies suggest the need for further data verification (Table 4).

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Table 4: Pre and Post Weight after Each Dialysis Session

Time Point	Mean ± SD
Before First Dialysis Session (Pre-Weight 1)	61.6 ± 74.0
After First Dialysis Session (Post-Weight 1)	65.86 ± 56.98
Before Second Dialysis Session (Pre-Weight 2)	69.36 ± 67.68
After Second Dialysis Session (Post-Weight 2)	59.69 ± 4.031
Before Third Dialysis Session (Pre-Weight 3)	61.34 ± 7.40
After Third Dialysis Session (Post-Weight 3)	59.69 ± 3.98

DISCUSSION

Renal replacement therapy (RRT) for end-stage renal disease (ESRD) includes hemodialysis, peritoneal dialysis, and renal transplantation. Hemodialysis is one of the most widely used treatments, with over two million patients receiving it annually [11]. ESRD patients often have comorbidities such as ischemic heart disease, peripheral vascular disease, cerebrovascular disease, and COPD, which heighten their morbidity and mortality risks [12]. Although hemodialysis is a life-saving and generally safe procedure, it is associated with acute complications that may arise during or immediately after sessions, as well as chronic complications over time. Therefore, the present study was conducted to determine the frequency of intradialytic complications occurring in patients on maintenance hemodialysis. This study included 83 patients, with 63.9% aged over 40 years and 63.9% male. Most (60.2%) had the condition for less than 5 years. A majority (68.7%) received bicarbonate-based hemodialysis. These findings were comparable with another study, which reported that among the 280 patients, 184 (65.7%) were male, indicating a predominance of men in the study population. The mean age was 47.9 ± 17.5 years, reflecting a broad age range. Overall, a male preponderance (69.1%) was observed, suggesting that men were more commonly affected by conditions necessitating dialysis [13]. The male predominance in our study aligns with previous findings, largely influenced by socioeconomic and cultural barriers that limit women's access to healthcare and result in skewed referral patterns [14]. Additionally, biological differences may contribute, as testosterone induces apoptosis in renal tubules, accelerating CKD progression in men, while estrogens offer renal protection, potentially delaying disease progression in women [15]. These factors collectively explain the higher prevalence of end-stage renal disease (ESRD) and dialysis dependence among men [16, 17]. In the current study, the leading causes of CKD were diabetes mellitus (65 patients) and hypertension (29 patients), followed by obstructive nephropathy (17) and PKD (13). Literature reports that CKD risk factors, categorized as initiating or perpetuating, include genetics, ethnicity, socioeconomic status, and age. The leading cause is diabetes mellitus, followed by glomerulonephritis, genetic disorders, medications, cardiovascular and multisystem diseases, urinary tract obstruction, infections, and AKI [18]. Studies have identified various CKD risk factors, including age, sex, ethnicity, family history, and socioeconomic status. Metabolic syndrome, dyslipidemia, and urinary albumin excretion contribute to disease progression, while nephrotoxins (NSAIDs, antibiotics, contrast agents) and primary kidney diseases (glomerulonephritis, PKD) increase susceptibility. Urinary disorders (obstruction, recurrent UTIs) and cardiovascular diseases further elevate risk. Diabetes mellitus remains the leading cause, and acute kidney disorders (AKD) can progress to CKD if untreated [19, 20]. In the current study, the reported complications included hypotension (28 cases), nausea and vomiting (17 cases), cramping (11 cases), backache (9 cases), chest pain (7 cases), itching (6 cases), fever (4 cases), and headache (3 cases). These findings correlate with previous research, which shows that hypotension is the most common complication in hemodialysis patients, affecting 28.7% of them due to fluid shifts and vascular instability. Other frequent issues include hypertension (17%) and nausea or vomiting (11.7%) [7], often linked to electrolyte imbalances and rapid fluid removal [21]. Additionally, backache and chest pain may arise from prolonged dialysis and cardiovascular stress. Recognizing these complications is vital for improving hemodialysis protocols and patient outcomes [22]. A comprehensive local study highlighted that hypertension emerged as the second most prevalent cause, afflicting 3.54% of the patient population examined [23]. In contrast, Mahmood *et al.* observed a strikingly lower prevalence of intradialytic hypertension, noting its occurrence in just 1% of patients [24]. These varying statistics underscore the complexities and discrepancies in hypertension prevalence among different patient groups undergoing treatment. Another study highlights the high prevalence of dialysis complications, with hypotension (10%) being the most common, followed by nausea/vomiting (5.24%), hypertension (5.06%), muscle cramps (4.71%), and headaches (4.54%). Less frequent issues (<3%) included back pain, chest pain, fever, chills, and itching. Notably, half of the complications occurred in diabetic patients, emphasizing their increased risk. While no deaths were directly linked to these events, vigilant monitoring and targeted care strategies are essential to improve patient outcomes [4, 25].

This study has certain limitations, including its single-center design and relatively small sample size, which may limit the generalizability of findings. The cross-sectional nature of the study also restricts the assessment of long-term outcomes and causal relationships. Additionally, variations in dialysis practices and patient compliance were not extensively explored. Future multicenter studies

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with larger sample sizes and longitudinal follow-up are recommended to better evaluate risk factors, preventive strategies, and the long-term impact of intra-dialytic complications on patient outcomes.

CONCLUSIONS

In conclusion, dialysis complications are prevalent, with hypotension being the most commonly experienced issue. Other frequent complications include nausea, vomiting, hypertension, muscle cramps, and headaches. Additionally, less common symptoms such as back pain, chest pain, fever, chills, and itching add to the discomfort of patients. Diabetic individuals tend to be more vulnerable to these complications, which emphasizes the importance of better monitoring and tailored management approaches. While no fatalities have been directly attributed to these complications, it remains crucial to refine dialysis protocols and implement preventive measures to improve patient safety and outcomes.

Authors' Contribution

Conceptualization: MSB
Methodology: MSB, SA[1], SA[2], SA[3], ZI, UA
Formal analysis: UA
Writing and Drafting: SA[2], SA[3]
Review and Editing: ZI, UA, MSB, SA[1], SA[2], SA[3]

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Celiac Disease Among Patients with Type 1 Diabetes Mellitus

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ABSTRACT

The prevalence of celiac disease (CD) in type-1 diabetes mellitus (T1DM) may vary depending on the region, genetic background, and screening practices. **Objectives:** To determine the frequency of CD in patients with T1DM. **Methods:** This cross-sectional study was conducted at the Outpatient Department and Pediatric Ward of Children's Hospital and Institute of Child Health, Multan, Pakistan, from February 2024 to July 2024. The inclusion criteria were children aged 2-18 years with type 1 diabetes mellitus (T1DM). Anti-transglutaminase assessment for the diagnosis of CD was performed, and it was deemed positive if the serum anti-tissue transglutaminase IgA antibody level was ≥100 IU/mL or the histopathology of the intestinal biopsy specimen was consistent with Marsh category 3 or higher. Data analysis was performed using IBM-SPSS Statistics, version 26.0. **Results:** The mean age was 9.03±3.6 years. There were 57(58.2%) children who were male. Fifty-two (53.1%) children belonged to middle-class families. A positive family history of T1DM, autoimmune thyroiditis, and CD was noted in 46 (46.9%), 10 (10.2%), and 6 (6.1%) cases, respectively. The diagnosis of CD was confirmed in 20 (20.4%) children with T1DM. There were 4 (20.0%) and 2 (10.0%) patients with positive CD who had a positive family history of autoimmune thyroiditis and CD, respectively. **Conclusions:** The frequency of celiac disease was high among children with type 1 diabetes mellitus. The utility of anti-tTG evaluation is a non-invasive diagnostic tool for the screening of CD and can be utilized for the early diagnosis of CD in children with T1DM.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an immune-related disease characterized by a deficiency or absence of the insulin hormone as a result of T-cell-mediated decay of β-cells of the pancreas [1, 2]. Recent epidemiological data reveal the incidence of T1DM is around 15/100,000 [3]. T1DM is associated with various autoimmune diseases, and it is believed that 15-30% of patients with T1DM also have an autoimmune thyroid disease, 5-10% have autoimmune gastritis, and 4-9% have celiac disease (CD) [4]. Data from the developed world have shown a very low prevalence of CD in T1DM [5]. CD is a disorder with an underlying genetic (the main involved gene is HLA-DQ2-8) and inflammatory etiology, resulting from an immune response to gluten present in barley, wheat, and rye, and when these are ingested, they alter the small intestine [6]. Both T1DM and CD share a strong genetic predisposition through HLA-DR3/DQ2 and HLA-DQ8 haplotypes, and these molecules present autoantigens to CD4+ T cells, leading to β-cell destruction in T1DM and gluten-driven intestinal inflammation in CD. This overlap explains their frequent coexistence and supports routine CD screening in T1DM patients [7]. The prevalence of CD is estimated to be around 0.5% in the general population [4]. CD is two times more prevalent among the female population, while the

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prevalence of CD in T1DM is 5-7 times higher [8]. Children with T1DM are at higher risk of autoimmune thyroiditis and also have an increased susceptibility to celiac disease, as both are influenced by environmental triggers, including HLA haplotypes. A study from the Islamic Republic of Iran done in 2013 to document the prevalence of CD as 6.8% in T1DM [9]. The elevated prevalence of CD among children is owing to an overlap in the genetic tendency of both disorders awarded by the HLA-DR3/DQ2-8 [2]. The typical presentation of CD consists chiefly of gastrointestinal symptoms related to malabsorption, e.g., loose stools, failure to gain weight, and height [10]. Children are screened for IgA and IgG anti-tissue transglutaminase (anti-tTG) antibodies present in serum, and diagnosis is usually confirmed by a small gut biopsy [11,12]. Data also show that underlying CD is related to a high risk of symptomatic high blood sugar and that the administration of a gluten-free diet (GFD) with normalization of the gut mucosa may decrease its frequency [13]. Researchers have highlighted the importance of diagnosing and managing CD in asymptomatic children with T1DM [14]. If unrecognized, the underlying CD in patients with T1DM may lead to erratic glucose control and poor linear growth (height and weight) due to ongoing malabsorption. The prevalence of CD in T1DM varies across regions due to genetic factors, dietary habits, and differences in screening protocols. In some areas, routine serological testing detects more cases, while selective or symptom-based screening leads to underdiagnosis. Given the lack of standardized local practices, this study aimed to determine the frequency of CD in children with T1DM to help guide early diagnosis and improve management strategies. Although celiac disease (CD) is recognized as a common autoimmune comorbidity in children with type 1 diabetes mellitus (T1DM), reported prevalence varies widely across regions due to differences in genetic background, environmental exposures, and screening strategies. In Pakistan, limited local data exist regarding the true burden of CD among pediatric T1DM patients, and routine screening practices are not standardized. This lack of region-specific evidence creates uncertainty in clinical decision-making and may lead to underdiagnosis. Therefore, determining the local frequency of CD in children with T1DM is essential to guide screening policies and optimize patient care. This study aims to provide valuable insights for clinicians, policymakers, and caregivers in tailoring care for children with T1DM who may also have CD. Therefore, this study aimed to determine the frequency of CD in children with T1DM.

METHODS

This cross-sectional study was conducted at the Outpatient Department and Pediatric Ward of Children's Hospital and Institute of Child Health, Multan, Pakistan, from February 2024 to July 2024. The study commenced after obtaining approval from the institutional ethical review committee (Letter No. ERC/2023/36). A sample size of 98 patients was calculated using the standard single-population proportion formula: $n=Z2\times p\times(1-p)/d2$; where Z = 1.96 (corresponding to a 95% confidence level), p=0.068 (expected prevalence of CD in T1DM = 6.8%) [9], and d = 0.05 (margin of error). The inclusion criteria were children of both genders, aged 2-18 years, with T1DM. The exclusion criteria were patients with other comorbidities, like other types of diabetes, chronic liver disease, chronic lung disease, tuberculosis, immunosuppressive disorders, congenital heart diseases, or hematological disorders. T1DM was labeled by the presence of any one or more of the following: i) fasting levels of plasma glucose≥126 mg/dL (7.0 mmol/L), ii) random levels of plasma glucose≥200 mg/dL (11.1 mmol/L), iii) HbA1c≥6.5% [2]. T1DM diagnosis was confirmed from existing medical records, where fasting glucose, random glucose, or HbA1c had already been performed at the time of initial diagnosis. Non-probability consecutive sampling technique was used. All of the study patients were subject to informed and written consent from their parents/guardians after they were informed of the objective, safety, and data secrecy. For children above 7 years of age, verbal assent was also sought in line with ethical guidelines for paediatric research. Once the patients were recruited, demographic data regarding age, gender, and duration of DM were recorded. A 5 ml venous blood sample was collected, and an anti-tTG assessment was done. If the index of suspicion was high and tTG was not suggestive, the patients underwent endoscopic intestinal biopsy, and specimens were sent for histopathology. The patients were classified as having CD, positive or negative. It was deemed positive if the serum anti-tissue transglutaminase IgA antibody level was≥100 IU/mL [5] or the histopathology of the intestinal biopsy specimen was consistent with Marsh category 3 or higher. The Marsh classification is a histopathological grading system for CD, ranging from early mucosal changes to advanced villous atrophy. Marsh I indicates increased intraepithelial lymphocytes, Marsh II adds crypt hyperplasia, while Marsh III (a–c) represents progressive villous atrophy of mild, moderate, or severe degree. A diagnosis of CD in this study was confirmed when biopsy findings were consistent with Marsh III or higher, reflecting clinically significant disease relevant to pediatric patients with T1DM. Age was grouped into early childhood (2–6 years), middle childhood (7–12 years), and adolescence (13–18 years). Socioeconomic status was classified based on monthly household income: low (<30,000 PKR), middle (30,000–70,000 PKR), and high (>70,000 PKR). Family history of T1DM or other autoimmune

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disorders (e.g., thyroid disease) was recorded as present or absent based on parental reporting. Data collection was carried out on a specific, predesigned proforma. Data was analyzed using "IBM-SPSS Statistics" version 26.0. The quantitative variables, which included age and duration of disease (T1DM), were presented as mean and standard deviation (SD), or median and interquartile range (IQR) (depending upon the normal distribution of data, checked by the Shapiro-Wilk test). For the qualitative variables such as gender, family history of T1DM (yes/no), family history of other autoimmune disorders, i.e., thyroid (yes/no), and the outcome, i.e., CD (yes/no), frequency and percentage were calculated. The effect modifiers like gender, age, socioeconomic status of the parents, age at diagnosis with T1DM, age at the time of diagnosis of CD, family history of T1DM, and family history of other autoimmune disorders, were dealt with through stratification. As the data were stratified with respect to CD status (present/absent), associations between categorical variables (e.g., gender, age groups, socioeconomic status, family history, and HbA1c categories) and CD were assessed using the chi-square / Fisher's exact test. A p-value ≤0.050 was considered statistically significant.

RESULTS

Of all 98 children, the mean age was 9.03±3.6 years, with ages ranging between 2.5 to 15 years. Male and female contributions were 57 (58.2%) and 41 (41.8%) children, respectively. In our study, the median duration of the disease (T1DM) was calculated to be 2 years (IQR: 2-5), with a minimum and maximum duration of 0.5 years and 8 years. There were 52 (53.1%) children who belonged to middle-class families. A positive family history of T1DM, autoimmune thyroiditis, and CD was noted in 46 (46.9%), 10 (10.2%), and 6 (6.1%) cases, respectively (Table 1).

Table 1: Characteristics of Patients (N=98)

Characteristics		Frequency (%)
Gender	Boys	41 (41.8%)
	Girls	57 (58.2%)
Age (years)	2-5	42 (42.9%)
	5-15	56 (57.1%)
Age at Diagnosis of T1DM (Years)	<5	32 (32.6%)
	5-10	53 (54.1%)
	>10	13 (13.3%)
Parental Socioeconomic Status	<30,000 PKR	35 (35.7%)
	30,000-70,000 PKR	52 (53.1%)
	>70,000 PKR	11 (11.2%)
Family History of Autoimmune T1DM	Yes	46 (46.9%)
	No	52 (53.1%)
Family History of Autoimmune Thyroiditis	Yes	10 (10.2%)
	No	88 (89.8%)
Family History of CD	Yes	6 (6.1%)
	No	92 (93.9%)
HbA1c (%)	≤7.5	31 (31.6%)
	>7.5	67 (68.4%)

When comparing children with and without CD, no statistically significant associations were observed with gender (65.0% vs. 56.4% females, p=0.487), age group (60.0% vs. 56.4% in 5–15 years, p=0.772), or age at T1DM diagnosis (70.0% vs. 50.0% for 5–10 years, p=0.232). Socioeconomic status also showed no significant association (p=0.412), though CD was more frequent in the middle-class group (65.0% vs. 50.0%). A positive family history of T1DM was less common in CD patients (30.0% vs. 51.3%, p=0.088), while family history of autoimmune thyroiditis was relatively higher (20.0% vs. 7.7%, p=0.104). Family history of CD showed no significant difference (10.0% vs. 5.1%, p=0.4175). Glycemic control measured by HbA1c also did not differ significantly (≤7.5%: 30.0% vs. 32.1%, p=0.860) (Table 2).

Table 2: Association of the Characteristics of Children with CD

Characteristics		Celiac Disease		p-Value
		Yes (n=20)	No (n=78)	
Gender	Boys	7 (35.0%)	34 (43.6%)	0.487
	Girls	13 (65.0%)	44 (56.4%)	
Age (Years)	2-5	8 (40.0%)	34 (43.6%)	0.772
	5-15	12 (60.0%)	44 (56.4%)	
Age at Diagnosis of	<5	5 (25.0%)	27 (34.6%)	0.232
	5-10	14 (70.0%)	39 (50.0%)	
	>10	1 (5.0%)	12 (15.4%)	
Socioeconomic Status (Rupees Per Month)	<30,000 PKR	6 (30.0%)	29 (37.2%)	0.412
	30,000-70,000 PKR	13 (65.0%)	39 (50.0%)	
	>70,000 PKR	1 (5.0%)	10 (12.8%)	
Family History of TIDM	Yes	6 (30.0%)	40 (51.3%)	0.088
	No	14 (70.0%)	38 (48.7%)	
Family History of Autoimmune Thyroiditis	Yes	4 (20.0%)	6 (7.7%)	0.104
	No	16 (80.0%)	72 (92.3%)	
Family History of CD	Yes	2 (10.0%)	4 (5.1%)	0.417
	No	18 (90.0%)	74 (94.9%)	
HbA1c (%)	≤7.5	6 (30.0%)	25 (32.1%)	0.860
	>7.5	14 (70.0%)	53 (67.9%)	

DISCUSSION

The frequency of celiac disease (CD) in T1DM in this study was 20.4%, which is considerably higher than global estimates. Craig *et al.*, analyzing 52,721 young T1DM patients across 3 continents, reported a biopsy-proven CD prevalence of 3.5% [15]. A recent meta-analysis by Karimzadhagh *et al.*, found that globally, about 1 in 16 individuals with T1DM are affected by CD, with a higher prevalence in Asia and the Middle East (≈1 in 12) [16]. Several factors may explain the comparatively higher frequency in

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this study. The selection bias cannot be ruled out, as this study was conducted at a tertiary care center where children with more severe or complicated diseases may be overrepresented. Regional genetic predisposition, particularly the high prevalence of HLA-DR3/DQ2 and DQ8 haplotypes in South Asian populations, may contribute to the increased risk. Environmental influences, such as dietary gluten exposure, early childhood infections, and differences in screening practices, may also play a role. These considerations highlight the need for routine and systematic screening for CD in children with T1DM, especially in regions with a potentially higher genetic and environmental risk. Early diagnosis and management can prevent complications like malabsorption, poor glycemic control, and impaired growth. The present findings contrast with those of Albatayneh *et al.*, who reported that among 138 patients, CD was positive in 6.5% [17]. Some researchers have reported that the occurrence of T1DM is rapidly rising in the pediatric age group, with a stated rise of 3% on an annual basis [18, 19]. So, with this rise, an overall rise in the prevalence of CD is also expected, which warrants measures for the timely identification and management of CD in this set of patients. CD is a female-dominant disorder and is almost three times more prevalent among the female population [19]. This study noted that the proportion of females in CD was 65.0% versus 56.4% without CD in T1DM. According to Wedrychowicz *et al.*, the occurrence of CD was significantly higher in girls (13.9%) than in boys (4.9%) with T1DM, and this correlates well with the present findings [20]. In this study, the mean age was 9.03±3.6 years in children with CD, which is relatively similar to what a recent study by Andari and colleagues reported as 8.28 years [21]. This study showed that the median duration of T1DM in children was 2 years, with a range of 6 months to 8 years. Honar *et al.*, demonstrated a significant association between disease duration and positive tTG findings, with the mean duration being markedly longer in antibody-positive patients (3.0 ± 0.8 years vs. 1.0 ± 0.4 years, p=0.04), suggesting that longer duration of T1DM increases the likelihood of developing CD [22]. Vajravelu *et al.*, in a large cohort of 9,180 patients with T1DM, reported that female gender and younger age at T1DM diagnosis were strong predictors of subsequent CD development, indicating robust associations with these demographic factors [23]. Unal *et al.*, analyzing 779 T1DM patients, revealed that serological evaluation and follow-up monitoring are advised instead of biopsy evaluation for the confirmation of CD [24]. Laitinen *et al.*, in a cohort study of 850 children aged up to 17 years, concluded that screening for CD should be done in every T1DM patient, as children who had screening for CD were less symptomatic than those who were tested after they had symptoms [25].

A study from Finland showed that the young patients with a +ve family history of other autoimmune disorders had a high level of islet cell auto-antibodies (p=0.003), and the HLA DR3 DQ2 haplotype in the children was linked with CD in the complete family (p<0.001), but not with a raised prevalence of immune diseases generally [26]. Routine screening for CD using anti-tTG in children with T1DM can enable early diagnosis, reducing complications associated with undiagnosed CD. Anti-tTG evaluation is a non-invasive, cost-effective tool that can be integrated into routine care for high-risk populations like T1DM patients. Early diagnosis and management of CD can improve growth, nutritional status, and overall quality of life in children with T1DM [24, 25]. The findings of this research support the need for standardized screening protocols for CD in T1DM patients, promoting better long-term health outcomes. Single-center study setting and a modest sample size were some of the limitations of this study, so our findings need further verification. Studies should also be planned to evaluate the clinical impact of CD on T1DM. As this was a cross-sectional study, causal relationships between T1DM and CD could not be established. A prospective cohort design would provide stronger evidence regarding temporal and causal associations, and future studies in this setting should consider such an approach.

This study has certain limitations, including its single-center design and relatively small sample size, which may restrict the generalizability of the findings. The cross-sectional nature also limits the ability to establish temporal or causal relationships between T1DM and CD. Additionally, long-term clinical outcomes following CD diagnosis were not assessed. Future multicenter, longitudinal studies with larger cohorts are needed to evaluate risk factors, monitor disease progression, and assess the impact of early CD screening on glycemic control and growth outcomes in children with T1DM.

CONCLUSIONS

The frequency of CD was high among children with T1DM. The utility of anti-tTG evaluation is a non-invasive diagnostic tool for the screening of CD and can be utilized for the early diagnosis of CD.

Authors' Contribution

Conceptualization: MJ
Methodology: ML, NQ, MI
Formal analysis: MJ, FJ
Writing and Drafting: MJ, MS, MF, MI, FJ
Review and Editing: MJ, MS, MF, MI, FJ, ML, NQ

All authors approved the final manuscript and take responsibility for the integrity of the work

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Conflicts of Interest

All the authors declare no conflict of interest.

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Polycystic Ovary Syndrome and Insulin Resistance: Comparative Analysis of Obese and Non-Obese Women in a Tertiary Care Setting Pakistan

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ABSTRACT

Polycystic ovarian syndrome is a widespread endocrine disease that is linked to insulin resistance, regardless of obesity. This correlation is especially pertinent to South-Asian groups, where culture and lifestyles could mediate the manifestation of diseases. **Objectives:** To evaluate the effect of obesity on insulin resistance in women with polycystic ovarian syndrome in a tertiary care setting in Lahore, Pakistan. **Methods:** An analytical cross-sectional study performed at Avicenna Hospital from May to December 2023. The sample size included 220 women with PCOS, with an equal number of obese and non-obese women. BMI, waist circumference, fasting glucose, and insulin level were measured as clinical and metabolic parameters. IR was assessed on the HOMA-IR with a cut-off of 2.5. Data were analyzed with logistic regression and associated statistical t-tests. All subjects gave written consent before the data collection. **Results:** Obese women had a much greater BMI, waist circumference, glucose, insulin, and HOMAIR scores (p=0.001). The prevalence of IR was 78% compared to 43% among the obese female versus the non-obese female. BMI was found to predict IR (OR over 3.4 with 95% interval in 2.1-5.5) and fasting glucose (OR over 1.5 with 95% interval in 1.1-2.3). The women were also obese and had an unfavorable lipid profile. **Conclusions:** Insulin resistance is common in both obese and non-obese women with polycystic ovarian syndrome, but it is higher in the obese group.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) has always remained among the most ubiquitous endocrine and metabolic disorders that bother women of childbearing age, with the prevalence rate of 6-10% being estimated worldwide. A group of clinical, biochemical, and ultrasonographic abnormalities, including menstrual irregularities, hyperandrogenic traits, which include hirsutism and acne, and the typical polycystic appearance of the ovaries, characterize the syndrome [1]. Although this disease is widespread, it is often underdiagnosed and covertly leads to a lack of treatment and a high likelihood of negative long-term outcomes [2]. The heterogeneity of its clinical presentation and inter-population variability underscores the importance of PCOS as a subject of international reproductive and metabolic health research [3]. In addition to reproductive consequences, PCOS bears a close relationship with a myriad of chronic illnesses, among them being obesity, type 2 diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease [4]. Metabolic syndrome is often observed in women diagnosed with PCOS and, as a result, it raises the cardiovascular risk of these individuals throughout their lives [5]. In addition, the psychological morbidities which are mostly encountered include depression, anxiety, and poor quality of life, again

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highlighting the multifaceted nature of the disorder burden [6]. These outcomes highlight the importance of an early diagnosis and its effective management through special approaches to women with PCOS. Insulin resistance (IR) represents one of the key aspects of the pathophysiology of PCOS as the main driver of its manifestations (both metabolic and reproductive) [7]. The effect of hyperinsulinemia is to stimulate ovarian androgen biosynthesis, which increases the clinical state of hyperandrogenism and ovulation in grime [8, 9]. Notably, IR is also not limited to adipose patients; it has been reported in a significant proportion of lean PCOS patients [10]. These findings accentuate both IR as a self-contained aspect of PCOS pathogenesis and as a determinant of increased complexity in the treatment of therapeutic control in the gamut of body mass index (BMI). Though studies have given significant attention to PCOS in Western and a few Asian populations, there is limited research on the relationship between PCOS and insulin resistance in Pakistani studies. The idea of native studies is that PCOS has no effect on the expression of the condition, and the intensity depends on socio-cultural factors, such as lifestyle habits, nutritional and individual predispositions [11]. The current literature, however, consists mostly of outdated information or literature that limits their studies to prevalence rates, omitting the metabolic variations that characterize obese and non-obese women [12]. Going by the increasing trends of obesity and type 2 diabetes in Pakistan, it is justified to examine a specific study of the interaction between adiposity and IR in the context of PCOS. The research determines whether obesity alone increases insulin resistance or whether lean women are equally susceptible, and this gives significant input in clinical decision-making and preventive measures. It is established that the expected results can inform health practitioners in putting in place contextually sensitive interventions to nutritious PCOS in Pakistani women to improve reproductive health outcomes, curb and reverse long-term cardiovascular risk.

Although insulin resistance is recognized as a central feature of PCOS, the extent to which obesity independently influences its prevalence and severity remains incompletely characterized in Pakistani women. Most local studies have focused primarily on overall prevalence rather than providing comparative metabolic profiling between obese and non-obese PCOS patients. Furthermore, region-specific data evaluating predictors of insulin resistance using standardized indices such as HOMA-IR are limited. This gap necessitates a focused comparative analysis to better inform screening strategies and individualized management in our population. This study aims to examine the similarities and differences in prevalence and severity of insulin resistance among PCOS-afflicted obese and non-obese women visiting a Lahore tertiary medical facility.

METHODS

A cross-sectional analytical study was conducted at Avicenna Hospital between May and December 2023 to examine the correlation between PCOS and insulin resistance and variations between obese and non-obese female. The data were collected at the Department of Obstetrics and Gynaecology, Avicenna Hospital, a tertiary care hospital affiliated with Avicenna Medical College, Lahore, Pakistan. The IRB of Avicenna Medical College, Lahore, was the institutional review board (IRB-38/3/23/AVC) that gave the wooden nod to the study protocol. All participants placed their informed consent in writing before the data collection, and patient information privacy was ensured to the utmost extent. The formula is presented as HOMA-IR = (Fasting Insulin (μU/mL) × Fasting Glucose (mmol/L)) / 22.5. A confidence level of 95% was applied for all analyses. Informed consent to the data collection was signed by all the participants. The anthropometric measurements were done by standardized methods: weight measured using a digital scale calibrated, height using a stadiometer and BMI calculated as kg/m2. Waist circumference was determined at the midline between the lower rib margin and the iliac crest with a non-stretchy tape. To reduce error, all measurements were repeated twice by one trained investigator and mean values were recorded. As one investigator performed all measurements, inter-rater reliability was not applicable; however, intra-rater consistency was maintained. The formula for calculating a single population proportion (Citation X) was used to get the sample size: n = (Z^2 * P(1-P)) / d^2. where: d = 0.05 (the acceptable margin of error), Z = 1.96 (the Z-score corresponding to a 95% CI), and P = 0.680 (the expected prevalence of insulin resistance in women with PCOS, based on a prior local study which indicated a prevalence of 68%). Using these parameters, the calculation yielded a minimum sample size of n = (1.96^2 * 0.68 * (1-0.68)) / 0.05^2, ≈ 334 participants. However, to account for potential non-response or missing data (estimated at 10%), the final target sample size was increased to 368 participants. This target was superseded by the logistical decision to use a convenience sampling frame of 220 participants (110 per group) to ensure equal group sizes for the obese and non-obese cohorts, acknowledging that this would affect the precision of the prevalence estimate. The calculation yielded a sample size of 220 participants, which was equally divided into two cohorts: obese women with PCOS (n=110) and non-obese women with PCOS (n=110). The use of the Shapiro-Wilk test to assess data normality has been explicitly stated to justify the application of parametric or non-parametric tests, fully

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addressing the statistical comments. The primary analysis to identify factors associated with insulin resistance (IR) was performed using logistic regression. Female aged between 18 and 35 years who reported irregular periods, clinical appearance of hyperandrogenism and ultrasound, proven polycystic appearance of the ovaries were eligible to be included. The inclusion criteria included: not pregnant, and not likely to have pre-existing endocrine or metabolic dysfunction (e.g. diabetes mellitus, thyroid disease, hyperprolactinemia, congenital adrenal hyperplasia), or other ovarian/uterine pathology. Clinical assessments were done effectively to collect data, using height, weight and waist circumference, spoken by only one trained investigator, to reduce inter-rater variability. The BMI was then computed, whereby the participants were either obese (BMI 30 or more) or were non-obese (BMI less than 30). A structured interview was used to gather demographic and medical histories. Laboratory tests included the analysis of glucose, insulin, and lipid profile using fasting (12 hours) of blood [13]. The diagnosis of polycystic ovary syndrome was based on the Rotterdam Criteria that requires the presence of two out of three the following characteristics: Oligo/ Anovulation - the frequent or no ovulation, Clinical and biochemical symptoms of hyperandrogenism - the presence of hirsutism, acne, or high levels of serum androgen, Polycystic ovarian morphology (PCOM) - the presence of numerous ovarian follicles or large ovarian size through the use of ultrasound. To maintain research integrity, participants with pre-existing endocrine or metabolic disorders such as diabetes mellitus, thyroid disorder, hyperprolactinemia, or congenital adrenal hyperplasia were excluded to ensure an accurate focus on the association between PCOS and insulin resistance. Data were collected through clinical evaluations, including measurement of height, weight, waist circumference, and BMI, to categorize participants as obese or non-obese. Patient interviews to gather demographic and medical information. Laboratory tests based on the blood samples collected after an overnight (approximately 12 hours) of fasting to determine fasting glucose and lipid profile. The insulin resistance level was estimated by means of the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index, and computed with the following formula: HOMA-IR Fasting Glucose (mmol/L) × Fasting Insulin (μU/mL)/22.5. An HOMA-IR score above 2.5 was taken to mean that there was insulin resistance. The analysis of data was done with SPSS version 29. Demographic and clinical characteristics information was summarized using descriptive statistics. The continuous variables such as BMI, fasting glucose, fasting insulin and HOMA-IR were presented in the form of means and standard deviations. The Shapiro-Wilk test was used to check on normality. Where normality was not satisfied, it was assumed that the results would be reported as median with interquartile range (IQR), and instead of an independent sample t-test, the non-parametric counterpart of the independent sample t-test, the Mann-Whitney U test, was employed. To analyze proportions in groups of categorical variables, e.g., the range of HOMA-IR, the Chi-square test was applied. There was a logistic regression analysis done to compare predictors of insulin resistance. Univariable logistic regression was used to calculate the unadjusted odds ratio (OR) and CI of 95%.

RESULTS

The study enrolled possibly 220 women, including 110 obese and 110 non-obese, who were diagnosed with polycystic ovary syndrome. Both groups are summarized in terms of demographic and clinical traits. The obese women were found to have considerably larger BMI and waist circumference compared to the women who were not found to be obese ($p<0.001$). The fasting glucose, fasting insulin and HOMA-IR levels were also high in the obese population. The findings revealed that the insulin resistance of the PCOS obese patients significantly increased. The BMI ($p<0.001$) and waist circumference ($p<0.001$) values of the obese woman were very large as compared to those of the non-obese women. Moreover, fasting glucose, fasting insulin and HOMA-IR scores were found to be significantly higher among the obese individuals as opposed to the non-obese ($p<0.001$). The prevalence was used to confirm the results that in obese women, there is a startling percentage, 78% (86 out of 110), who were shown to be insulin resistant, with the HOMA-IR score above 2.5. On the other hand, only 43% (47 of 110) non-obese women were insulin resistant, given in table 1.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristics	Obese Group (n=110)	Non-Obese Group (n=110)	p-Value
Age (Years)	27.7 ± 5.4	27.1 ± 5.2	0.430
BMI (kg/m^2)	32.8 ± 2.9	24.1 ± 2.3	<0.001*
Waist Circumference (cm)	91.3 ± 8.2	76.2 ± 6.5	<0.001*
Fasting Glucose (mmol/L)	5.6 ± 0.8	5.1 ± 0.6	0.020*
Fasting Insulin (μU/L)	18.5 ± 5.2	12.2 ± 3.8	<0.001*
HOMA-IR Score	4.6 ± 1.1	2.8 ± 0.7	<0.001*

Note: p≤0.050 shows a statistically significant difference

Logistic regression analysis revealed that BMI is a robust predictor of insulin resistance among PCOS women, with an odds ratio of 3.4 ($p<0.001$). Fasting glucose further revealed a notable association, with an odds ratio of 1.5 ($p=0.040$), indicating that higher fasting glucose levels indicate the likelihood of insulin resistance. The ORs with 95% CIs were calculated using logistic regression analysis. Univariable logistic regression was first conducted to

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obtain unadjusted ORs for individual predictors. Multivariable logistic regression was then applied to calculate adjusted ORs, accounting for potential confounding variables. The outcomes are illustrated in table 2.

Table 2: Logistic Regression Analysis of Factors Associated with Insulin Resistance

Variables	Unadjusted Odds Ratio (OR)	p-Value	Adjusted OR (95% CI)	p-Value
BMI	3.5 (2.1 – 5.5)*	<0.001*	3.3 (2.0 – 5.2)*	<0.001*
Age	1.2 (0.8 – 1.9)	0.320	1.1 (0.7 – 1.7)	0.380
Fasting Glucose	1.5 (1.1 – 2.3)*	0.040*	1.4 (1.0 – 2.1)*	0.048*

Note: *shows statistical significance at p<0.050. Unadjusted ORs derived from univariable logistic regression. Adjusted ORs were obtained from multivariable logistic regression, including BMI, age, and fasting glucose in the model

Analysis of metabolic parameters indicated significantly high levels of total cholesterol, triglycerides, and LDL cholesterol among obese women in comparison to their non-obese counterparts. Moreover, HDL cholesterol levels were lower in the obese group, indicating a more atherogenic lipid profile, as shown in table 3.

Table 3: Comparison of Metabolic Parameters between Obese and Non-Obese Women with PCOS

Metabolic Parameters	Obese Group (n=110)	Non-Obese Group (n=110)	p-Value
Total Cholesterol (mg/dl)	205.3 ± 30.4	185.7 ± 25.6	0.010
Triglycerides (mg/dl)	150.2 ± 35.8	110.4 ± 28.9	<0.001
HDL Cholesterol (mg/dl)	42.6 ± 6.7	55.1 ± 7.3	<0.001
LDL Cholesterol (mg/dl)	130.7 ± 20.9	105.3 ± 18.4	<0.001
Blood Pressure	130/85 ± 12/8	118/78 ± 10/7	<0.001

Note: p≤0.05 shows a statistically significant difference

Regarding insulin resistance severity, 40.9% of obese women exhibited moderate IR (HOMA-IR 4.0-5.9), and 14.5% showed severe IR (HOMA-IR ≥ 6.0). Conversely, only 9% of non-obese women showed moderate IR, while 1.8% exhibited severe IR. Notably, the majority of non-obese (57.3%) had no insulin resistance (HOMA-IR <2.5) compared to 21.8% in the obese group. These results on IR severity and obesity are shown in table 4.

Table 4: Severity of Insulin Resistance in Obese and Non-Obese Women with PCOS

HOMA-IR Range	Obese Group n (%)	Non-Obese Group n (%)	p-Value	Total n (%)
NO IR < 2.5	24 (21.8)	63 (57.3)	0.010	87 (39.5)
Mild (HOMA-IR 2.5-3.9)	25 (22.7)	35 (31.8)	<0.001	60 (27.3)
Moderate (HOMA-IR 4.0-5.9)	45 (40.9)	10 (9.1)	<0.001	55 (25.0)
Severe (HOMA-IR >6.0)	16 (14.5)	2 (1.8)	<0.001	18 (8.2)

Note: Data presented as frequency n (%). The overall p-value was obtained using the Chi-square test. The strength of the association between obesity status and insulin resistance severity was quantified using Cramer's V (V = 0.45), indicating a moderate effect size. *Statistically significant at p<0.050.

In summary, the results underscore significant differences in metabolic health and insulin resistance between obese and non-obese groups, reinforcing the crucial relationships between obesity, metabolic dysfunction and insulin resistance in PCOS women.

DISCUSSION

This study explored the relationship between IR and PCOS in obese and non-obese women [14]. The prevalence of IR was significantly higher among obese women (78%) than among non-obese women (43%). These findings reinforce the established role of obesity as a major contributor to IR in PCOS, while simultaneously confirming that lean women are also affected. The presence of IR in 43% of non-obese participants highlights the phenomenon of "lean PCOS". Lean women with PCOS may develop IR due to intrinsic factors such as genetic susceptibility, altered insulin signalling, or impaired pancreatic β-cell function, independent of obesity [15]. Importantly, lean PCOS is not a benign variant; it is associated with reproductive disturbances and metabolic abnormalities similar to those observed in obese PCOS. Therefore, routine metabolic screening is warranted in all women with PCOS, regardless of body mass index [16]. Our logistic regression analysis identified BMI as a strong predictor of IR (odds ratio 3.5), consistent with meta-analyses demonstrating BMI as a significant risk factor for metabolic dysfunction in PCOS [17]. Fasting glucose was also found to be an independent predictor of IR, underscoring that even mild glycemic elevations should not be overlooked in clinical practice. In terms of metabolic markers, obese women in our study had lower HDL cholesterol and higher LDL cholesterol, triglycerides, and total cholesterol compared with non-obese women. This adverse lipid profile is consistent with global and regional data linking PCOS to an elevated risk of cardiovascular disease [18]. In Pakistan, Tabassum *et al.* demonstrated a high prevalence of metabolic syndrome in PCOS [19], while Afridi *et al.* identified dyslipidemia and glucose intolerance among affected women [20]. Together, these findings highlight the urgent need for early metabolic risk assessment and lifestyle modification in Pakistani women with PCOS.

This study has certain limitations, including its single-center design, convenience sampling, and relatively modest sample size, which may limit the generalizability of the findings. The cross-sectional design also precludes establishing causal relationships between obesity and insulin resistance. Additionally, long-term metabolic outcomes and therapeutic responses were not assessed. Future multicenter longitudinal studies with larger cohorts are recommended to explore temporal metabolic changes, genetic influences, and the impact of early lifestyle or pharmacological interventions in both obese and lean women with PCOS.

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CONCLUSIONS

This study found that 78% of obese individuals and 43% of non-obese participants had insulin resistance, which is quite common in women with PCOS. The occurrence of IR in thin women highlights that metabolic dysfunction is not exclusively weight-dependent, even if obesity was found to be a substantial predictor. These results emphasize how crucial it is to regularly screen all polycystic ovarian syndrome-afflicted women for insulin resistance. A complete management strategy that includes metabolic monitoring, lifestyle change, and customized care should be implemented by clinicians. To lower long-term risks, including cardiovascular disease, infertility, and a lower quality of life linked to polycystic ovarian syndrome in Pakistan, public health initiatives must focus on raising awareness and implementing early intervention techniques.

Authors' Contribution

Conceptualization: ZG, GW
Methodology: ZG, GW
Formal analysis: ZG, GW
Writing and Drafting: ZG, GW
Review and Editing: ZG, GW

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Immediate Versus Delayed Percutaneous Coronary Intervention on Recovery and Complications in Diabetic Patients with Acute ST Segment Elevation Myocardial Infarction: A Cross-Sectional Study

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ABSTRACT

Acute STEMI in diabetic patients leads to worse outcomes, making timely PCI crucial. However, the optimal timing (immediate vs. delayed) of percutaneous coronary intervention (PCI) for long-term recovery and complications in diabetic individuals is still being investigated. **Objectives:** To compare recovery and complication rates in diabetic acute STEMI patients undergoing immediate versus delayed PCI. **Methods:** This analytical cross-sectional study was conducted at a tertiary care hospital in Peshawar, Pakistan (October 2024 to March 2025), and enrolled 296 adult diabetic STEMI patients (aged ≥18 years) requiring PCI. After informed consent, data on demographics, medical history, procedural details, and post-PCI outcomes were collected via a structured questionnaire. Participants were categorized into immediate and delayed PCI groups, with statistical analysis using descriptive statistics and Chi-square tests to compare outcomes. **Results:** A total of 296 diabetic STEMI patients were enrolled, with 32.1% undergoing immediate PCI and 67.9% delayed PCI. The mean age was 55.89 ± 11.57 years, and 77% had type 2 diabetes. The delayed PCI group included a higher percentage of male; however, this variation was not significant. Baseline LVEF did not differ significantly (immediate: 40.54 ± 6.49 vs. delayed: 41.33 ± 7.23, p>0.050). Both groups showed significant post-PCI LVEF improvement (immediate: 49.12 ± 7.10, delayed: 50.85 ± 6.80), but the intergroup difference remained non-significant. No statistically significant differences were observed in intra- or post-procedural complications between the groups. **Conclusions:** In diabetic STEMI patients, a slight clinical delay in PCI did not significantly impact functional recovery (LVEF improvement) or increase intra- and post-procedural complications when compared to immediate intervention.

INTRODUCTION

Acute Coronary Syndrome (ACS), encompassing unstable angina and myocardial infarction, is characterized by reduced myocardial perfusion, which significantly contributes to adverse cardiovascular events [1]. Globally, cardiovascular illnesses are the primary cause of mortality, with over 100,000 fatalities each year. The situation is similar in Pakistan, where nearly one in five adults is estimated to suffer from some form of cardiovascular disease [2]. According to the WHO, cardiovascular diseases (CVDs) will kill 23.6 million people by 2030, accounting for 7.4 million deaths in 2015. According to the American Heart Association, there is a heart attack every 40 seconds, a death every minute, and the annual costs amount to $200 billion [3]. Myocardial infarction (MI) is a critical coronary condition that can lead to sudden cardiac death. MI accounts for one-third to one-half of

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cardiovascular disease cases. One-third of MI cases present as ST-segment Elevation Myocardial Infarction, which requires immediate percutaneous coronary intervention [4]. Diabetes mellitus significantly increases the risk of coronary vascular disease, a leading cause of acute coronary syndromes [5]. Individuals with diabetes have a much higher likelihood of CAD, reported to be up to 10 times greater than that of the general population [6]. Patients with diabetes frequently present atypical clinical symptoms and face treatment delays during acute myocardial infarction, as they are at high risk for silent myocardial infarction [7]. Diabetes mellitus is associated with a significantly elevated risk of death and other sequelae, including stroke, deep sternal wound infections (DSWI), and renal failure. This cluster of comorbidities contributes to higher healthcare resource utilization, resulting in significantly greater healthcare expenditures compared to non-diabetic populations [8]. ST-segment elevation myocardial infarction represents a critical clinical presentation of coronary vascular disease, with outcomes influenced by left ventricular function, treatment strategies, and complications. However, timely reperfusion remains the most crucial factor [9]. Immediate primary percutaneous intervention is the gold standard for treating STEMI in diabetics [10]. Each thirty-minute delay in reperfusion is associated with an estimated one-year reduction in life expectancy [11, 12]. Diabetic patients with STEMI encounter unique pathophysiological and healing challenges that differentiate them from non-diabetic individuals, potentially impacting their recovery and complication rates post-PCI. Consequently, these patients who frequently undergo cardiovascular procedures experience reduced intervention efficacy and increased complication rates [13]. Nonetheless, PCI continues to provide substantial benefits for improving outcomes even after the golden time window [14]. Despite the consensus on timely reperfusion, the optimal timing for PCI is still debated in several areas. It is generally accepted that performing PCI within 12 hours of STEMI onset results in the best outcomes. In Pakistan, many individuals miss this ideal window due to elements such as incorrect diagnosis, geographic remoteness, and insufficient medical resources. Therefore, our research aims to compare the severity of complications, including adverse cardiovascular events, bleeding, and other procedure-related issues, between immediate and delayed percutaneous coronary intervention in individuals with acute coronary syndrome. Additionally, we assessed the difference in functional recovery between diabetic individuals who have Primary or Immediate or early PCI after acute STEMI and those who receive delayed PCI, as indicated by variations in left ventricular ejection fraction.

Despite the established benefits of timely PCI in STEMI patients, diabetic individuals often present with atypical symptoms, delayed hospital arrival, and higher risk of complications, making optimal intervention timing unclear. Limited local data exist comparing immediate versus delayed PCI specifically in diabetic populations, creating a gap in understanding how timing impacts recovery and complication rates. Addressing this gap is essential to guide individualized treatment strategies for high-risk diabetic STEMI patients. This study aims to compare recovery and complication rates in diabetic acute STEMI patients undergoing immediate versus delayed PCI.

METHODS

This analytical cross-sectional study was conducted at the Peshawar Institute of Cardiology, a tertiary care hospital located in Peshawar, Pakistan, for six months from October 2024 to March 2025. Ethical approval was obtained from the Institutional Review Board (IRB) of the Peshawar Institute of Cardiology, under reference number IRC/24/113. A total of 296 adult patients were assessed for eligibility. Participants eligible for inclusion were required to be aged 18 years or older, of either sex, and have a confirmed diagnosis of both acute ST-segment elevation myocardial infarction (STEMI) and diabetes mellitus. Exclusion criteria included individuals who declined to provide informed consent or those with severe renal impairment, chronic obstructive pulmonary disease (COPD), or chronic liver disease, as these conditions could potentially confound the outcomes of percutaneous coronary intervention (PCI) and subsequent recovery. Furthermore, patients with uncontrolled or severe comorbidities such as poorly managed hypertension or active systemic infections were excluded due to their potential to significantly affect treatment response and clinical prognosis. Missing data were addressed through real-time data validation and post-collection cross-verification. Cases with incomplete or poor-quality echocardiographic imaging data were excluded from the final analysis. For complication variables, cases with missing key information were excluded. The primary exposure variable was the timing of PCI, categorized as either immediate or delayed. Immediate PCI was defined as a door-to-balloon time of 90 minutes or less, while delayed PCI referred to a duration exceeding 90 minutes. Diabetes mellitus, a key inclusion criterion, was defined as severe hyperglycemia diagnosed before cardiac intervention and meeting at least one of the following: fasting plasma glucose ≥ 7.0 mmol/L or glycated haemoglobin (HbA1c) ≥ 6.5% [6]. The primary outcomes assessed were left ventricular ejection fraction (LVEF), measured via echocardiography both at admission and prior to discharge, and in-hospital mortality. Intra- and post-

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procedural complications were also evaluated. After obtaining informed consent, data were collected from individuals presenting to the Emergency Department with chest discomfort and requiring PCI for acute STEMI. A structured questionnaire was employed to gather demographic data, clinical presentation, diagnosis details, and procedural information. The questionnaire focused on PCI timing, procedural characteristics, and post-intervention outcomes, including echocardiographic findings and any complications. Following data collection, patients were divided into two groups based on PCI timing: immediate and delayed PCI. This stratification enabled a subgroup analysis specifically among diabetic patients with STEMI to examine differences in clinical characteristics and outcomes between the two groups. This structured analysis highlighted the potential impact of PCI timing on the treatment outcomes in diabetic STEMI patients. Sample size was determined using Open Epi software, based on the standard formula for proportion-based studies: $n = Z^2 \times p \times (1-p) / E^2$ [15]. Where Z represents the z-score for a 95% confidence level (1.96), p is the estimated prevalence (26% in this study), and E is the desired margin of error (5%). The calculated minimum sample size was 296 participants. A non-probability convenience sampling technique was employed due to practical constraints, including time limitations, restricted access to a broader patient pool, and the clinical setting. This method allowed for the inclusion of all eligible patients who were readily available during the data collection period. Data analysis was conducted using SPSS version 22.0. Descriptive statistics, including frequencies, percentages, means, and standard deviations, were utilized to summarize demographic and clinical characteristics. The Independent Samples t-test was applied to compare continuous variables (e.g., age) between groups, while the Chi-square test was used for categorical variables. Results were presented in tabular form to effectively illustrate variable distributions and highlight observed patterns through figures.

RESULTS

This study investigated the effect of Percutaneous Coronary Intervention timing on patient outcomes by comparing baseline characteristics, complications, and functional recovery between two groups: patients receiving immediate PCI and those undergoing delayed PCI. The demographic and clinical profiles of the two groups were broadly comparable. The average age of individuals in the immediate PCI group was 55.78 ± 10.85 years, while in the delayed PCI group, it was 55.94 ± 11.92 years (p=0.390). The PCI group that was delayed had a slightly higher ratio of male individuals, 65.7% vs. 60.0%, respectively, with no significant difference, with a p-value of 0.343. Notably, the frequency of hypertension was considerably greater in the delayed PCI group, 71.0% vs. 29.0%, with a significant difference (p<0.050). Other cardiovascular risk factors, including smoking status and diabetes mellitus, were comparable between the two groups (p>0.050) (Table 1).

Table 1: Baseline Characteristics

Variables	Immediate PCI (n=95)	Delayed PCI (n=201)	p-Value
Age and (Mean ± SD, Years)	55.78 ± 10.85	55.94 ± 11.92	0.390
Gender (Male)	57 (60.0%)	132 (65.7%)	0.343
Diabetes Type 1	27 (28.4%)	41 (20.4%)	0.126
Diabetes Type 2	68 (71.6%)	160 (79.6%)	0.126
Hypertension	65 (29.0%)	159 (71.0%)	0.046
Smoking	26 (30.6%)	59 (69.4%)	0.725

Continuous data were presented with mean and SD (±), while categorical data are reported as percentages (%)

The mean ejection fraction (EF) before percutaneous coronary intervention was nearly identical for both groups. The immediate PCI group had an EF of 40.54 ± 6.49 %, while the delayed PCI group recorded an EF of 41.33 ± 7.23 %. There was no discernible change in baseline left ventricular ejection fraction among the two groups (p>0.05). After PCI, both groups experienced improvements in EF. The immediate PCI group achieved an EF of 49.12 ± 7.10 %, while the delayed PCI group reached an EF of 50.85 ± 6.80 %. However, the p-value of 0.114 indicates that the difference in improvement in EF among the two groups was not statistically significant (Table 2).

Table 2: Left Ventricular Function (Functional Recovery)

Variables	Immediate PCI (n=95)	Delayed PCI (n=201)	p-Value
EF Before PCI (Mean ± SD)	40.54 ± 6.49	41.33 ± 7.23	>0.050
EF After PCI (Mean ± SD)	49.12 ± 7.10	50.85 ± 6.80	0.114

The findings illustrate the impact of Percutaneous Coronary Intervention timing on left ventricular ejection fraction (LVEF), comparing immediate versus delayed PCI (Figure 1).

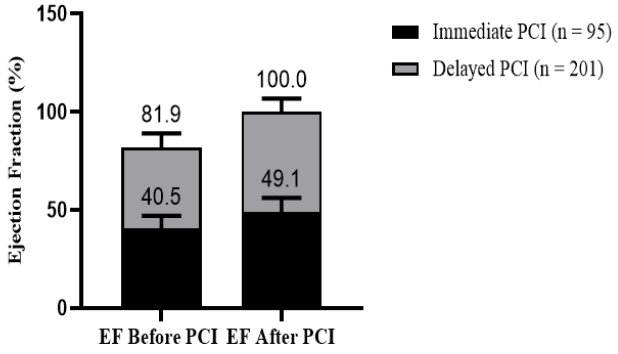

Figure 1: Impact of PCI Timing on Left Ventricular Function
EF=Ejection Fraction, PCI=Percutaneous Coronary Intervention, Continuous data is presented with mean and standard deviation (Mean ± SD%)

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The incidence of overall procedural complications was noticeably higher in the Delayed PCI subgroup (64.2%) compared to the Immediate PCI group (35.8%). Specific intra-procedural complications, including ventricular tachycardia, bradycardia, and arterial rupture, occurred more frequently in the Delayed PCI subgroup. Nevertheless, none of these comparisons reached statistical significance (p>0.050), indicating a lack of robust evidence supporting a difference among the groups. In terms of post-procedural complications, the rates were comparable in both groups, with each reporting an incidence of 20.1%. However, arrhythmias, heart failure, cardiogenic shock, and myocardial infarction are presented more commonly in the Delayed PCI group. Despite these observations, all P-values were > 0.050, suggesting no statistically significant differences among the groups. There was no reported mortality in either the immediate PCI group or the delayed PCI group (Table 3).

Table 3: Intra and Post-Procedure Complications

Variables	Immediate PCI (n=95)	Delayed PCI (n=201)	p-Value
Intra-Procedure Complications			
Overall Procedural Complications	19 (35.8%)	34 (64.2%)	0.518
Ventricular Tachycardia (VT)	2 (33.3%)	4 (66.7%)	0.739
Tachycardia	12 (41.4%)	17 (58.6%)	0.739
Bradycardia	1 (16.7%)	5 (83.3%)	0.739
Artery Rupture	3 (42.9%)	4 (57.1%)	0.739
Post-Procedure Complications			
Overall Post-Procedural Complications	16 (20.1%)	39 (20.1%)	0.597
Arrhythmia	2 (11.8%)	15 (88.2%)	0.227
Heart Failure	2 (25.0%)	6 (75.0%)	0.227
Cardiogenic Shock	3 (33.3%)	6 (66.7%)	0.227
Myocardial Infarction	7 (38.9%)	11 (61.1%)	0.227

Categorical data are reported as a percentage (%)

DISCUSSION

Despite advancements in primary percutaneous coronary intervention (PCI), the optimal timing of intervention for patients with ST-segment elevation myocardial infarction (STEMI), particularly in those with diabetes mellitus, remains a subject of ongoing debate. So the study evaluated the impact of PCI timing on outcomes by comparing baseline characteristics, complication rates, and recovery between immediate and delayed PCI groups. Baseline demographics, including mean age (55.78 ± 10.85 vs. 55.94 ± 11.92 years; p=0.390), were similar across groups, consistent with findings from a tertiary care hospital in South Punjab (mean age 53.51 ± 11.37) [16]. No significant differences were observed in intra-procedure complications (p=0.597), post-PCI recovery (p=0.114), or the incidence of complications such as arrhythmia, heart failure, and cardiogenic shock. Our findings align with the Korea Acute Myocardial Infarction Registry, which showed no increased long-term mortality in late presenters, despite higher in-hospital deaths (p=0.006). However, it contrasts with another report from the same registry showing significantly worse 180-day outcomes in late presenters (10.7% vs. 6.8%, p<0.001) [17]. Similarly, a Chinese study comparing early (3–14 days) vs. late (>14 days) PCI also reported no significant differences in major adverse events or strokes [13]. Contrasting results were observed in an Israeli retrospective study (2000–2021), where late presenters (>48 hours) experienced higher 30-day adverse cardiovascular events [18]. Supporting our findings, studies from GMCT Cardiology and Dr Kariadi General Hospital found no significant differences in major complications or myocardial recovery between early and late interventions [19, 20]. A systematic review further supports our results, finding no significant differences between immediate and delayed PCI regarding bleeding, re-intervention, mortality, ejection fraction, or major events in STEMI patients [21]. While the NHR study reported worse PCI outcomes in diabetics [8], the study found no significant association between diabetes and patient outcomes. Our findings contrast with studies from Iran and Denmark, which found delays associated with reduced LVEF and increased MI or heart failure risk, respectively [22, 23]. Similarly, a Kerala-based prospective study reported higher 1-year adverse events with delayed PCI [24], and a Multan-based study showed a significant correlation between early presentation and better EF (p=0.001) [24]. However, our data revealed no such association between PCI timing and EF. Several limitations must be acknowledged. First, the cross-sectional design precludes causal inference and limits our ability to assess long-term outcomes. Second, our sample was derived using convenience sampling from a single tertiary care centre, which may limit generalizability. Additionally, certain confounding variables, such as glycemic control levels, symptom-onset-to-balloon time, and pre-hospital delays, were not fully controlled, potentially influencing the results. Finally, echocardiographic assessments, although standardized, may vary based on operator interpretation, affecting LVEF measurements.

This study's cross-sectional design and single-center setting limit causal inference and generalizability. Additionally, factors such as glycemic control, pre-hospital delays, and operator variability in echocardiography were not fully controlled. Future multicenter longitudinal studies are warranted to evaluate long-term outcomes and to optimize PCI timing strategies tailored for diabetic patients with acute STEMI.

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CONCLUSIONS

Timely PCI in diabetic STEMI patients influences recovery outcomes. While delayed PCI showed slightly better improvement in left ventricular function, it did not significantly differ from immediate PCI in terms of complications or overall functional recovery. These findings suggest that PCI timing alone may not critically alter short-term clinical outcomes in this high-risk group, supporting a more individualized treatment approach.

Authors' Contribution

Conceptualization: BA
Methodology: MU, HU, BA, MA
Formal analysis: BA
Writing and Drafting: SG, SS
Review and Editing: SG, SS, MU, HU, BA, MA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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The Relationship Between Caffeine Consumption and Sleep Quality among Teenagers in Lahore, Pakistan

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ABSTRACT

Caffeine, a widely consumed stimulant, is prevalent among teenagers, particularly through beverages like tea, coffee, energy drinks, and soft drinks. As sleep is vital for physical and mental development in teenagers, increased caffeine intake may adversely affect their sleep quality. However, limited research exists on this association within the Pakistani context, particularly in urban centers. **Objectives:** To evaluate the relationship between caffeine consumption and sleep quality among teenagers in Lahore. **Methods:** An analytical cross-sectional study was conducted among 400 teenagers aged 13–19 years from selected schools and colleges in Lahore. Data were collected using a structured questionnaire that incorporated the Caffeine Consumption Questionnaire (CCQ) and the Pittsburgh Sleep Quality Index (PSQI). The CCQ assessed the frequency and quantity of caffeine intake, while the PSQI evaluated the participants' sleep quality. Participants were grouped based on caffeine consumption levels (low, moderate, high). Statistical analysis, including chi-square tests and logistic regression, was performed using SPSS to determine associations. **Results:** Many teens regularly consumed caffeine through tea or coffee, as revealed in our findings, which showed that 45.5% of teens consumed it daily and 31% consumed it frequently. The research showed that 68% of participants get poor sleep according to PSQI results, which indicates serious public health risks. **Conclusions:** The analysis revealed caffeine consumption led to poor sleep quality for teenagers according to research data.

INTRODUCTION

Caffeine is a natural stimulant found in beverages such as coffee, tea, energy drinks, and sodas, as well as in some foods, including chocolate. It is one of the most widely used psychoactive substances in the world and has found its way into the mainstream of many teens' drug use. The primary mechanism by which caffeine acts on the body is through its actions on the central nervous system; caffeine is an adenosine receptor antagonist [1]. Adenosine is a neurotransmitter which encourages sleep and relaxation in the body. Caffeine blocks adenosine receptors, making you feel less tired, experience greater alertness and an increase in overall energy. The stimulant effect of caffeine is why caffeine is often used by people wanting to stay awake and to help keep them focused. If caffeine is consumed, it is quickly absorbed into the bloodstream through the stomach and small intestine, and peaks in the

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blood in 30 -60 minutes. Caffeine gets into the bloodstream, and it binds to adenosine receptors in the brain, which are the main way that caffeine produces its effect. Normally, adenosine causes a sleep-promoting and drowsiness-promoting effect by slowing down nerve cell activity. But caffeine blocks these receptors, so the person doesn't become drowsy; instead, the caffeine is stimulating. This causes you to become more aware, to concentrate better, and, in most cases, to have an increased heart rate and blood pressure [2]. Caffeine provides these immediate benefits, but in large amounts, it can also have some rather dangerous effects on the body, particularly when consumed close to bedtime. Side effects of excessive caffeine include increased anxiety, jitteriness, digestive disturbances and palpitations. Additionally, caffeine overstimulated the body's systems, like the cardiovascular and nervous systems [3]. Continued caffeine overconsumption could eventually create problems like caffeine dependence, which can cause our bodies to become dependent on caffeine to achieve normal levels of alertness. Furthermore, they still find that regular high caffeine intake can lead to sleep disturbances, which could then turn into problems like insomnia or poor sleep quality. In contrast, sleep is a natural state of rest that is reversible and recurrent, which helps the body and mind recover and regenerate for overall health and well-being. Sleep also allows our body to go through various restoring processes like repairing muscles, consolidating our memory and boosting our immune system. Most of the body follows a circadian rhythm, which is an internal process that makes humans sleep at night and be awake during the day over a 24-hour period. Getting a proper sleep cycle helps when it comes to cognitive function, emotional regulation and physical health because it includes a crazy amount of deep sleep and light sleep stages [4]. Inadequate or poor sleep quality can lead to an array of health problems, from fatigue to mood disorders to impaired cognitive function, and a higher risk for chronic diseases. Caffeine, however, has a complicated relationship with sleep quality, and research has found that caffeine can break the natural sleep cycle when drunk close to bedtime or in high amounts. Caffeine is a stimulant and can override the way the body winds down at night by blocking the action of adenosine, the neurotransmitter that promotes sleep [5, 6]. Caffeine from various sources can have a particularly deleterious impact on sleep in teenagers, during a period of brain and body development. Competition for sleep in this group is already common: academic pressures, social activities, plus the normal biological shifts in circadian rhythms conspire against appropriate sleep. A combination with the effects of caffeine exacerbates sleep disturbance and produces negative effects, like anxiety, depression, lower academic performance and long-term health problems. With teenagers largely oblivious to the potentially harmful effects of too much caffeine, it's essential to learn how caffeine can detrimentally impact their sleep and wellness [7, 8]. Close to bedtime, caffeine can delay the onset of sleep and reduce the total duration and quality of deep restorative sleep. Consequently, people may find it hard to fall asleep, to sleep through to morning, or to spend the amount of time they need to in the rapid eye movement (REM) stage, vital for cognitive function and for good emotional health [9, 10]. For teenagers, especially, who are at a critical stage of physical and mental development and potentially more vulnerable to the negative effects of poor sleep, understanding the link between caffeine and sleep is important. So it's important to know how caffeine affects sleep quality in children and teens [11].

Despite growing global evidence linking caffeine intake with impaired sleep quality among adolescents, limited context-specific data are available from Pakistan, particularly in major urban centers such as Lahore. Cultural beverage patterns, increasing availability of energy drinks, and academic pressures may uniquely influence caffeine consumption behaviors in this population. However, few local studies have systematically examined both the quantity of caffeine intake and its measurable association with validated sleep quality indices. This gap highlights the need for region-specific evidence to inform adolescent health interventions and public awareness strategies. This study aims to evaluate the relationship between caffeine consumption and sleep quality among teenagers in Lahore.

METHODS

The study employed an analytical cross-sectional design to investigate the effects of caffeine consumption on sleep quality in teenagers. Ethical approval for the study was obtained from the Research Ethics Committee of the University of South Asia under IRB No: USA-RW/DR/2023/04/064. The study was conducted across Co-educational private schools and colleges in Lahore between October 2024 and April 2025, with informed consent obtained from all participants. Sample size was calculated using Cochran's formula for estimating a proportion in large populations, followed by the finite population correction when applicable [12]. A total of 400 participants, aged between 13 and 19 years, were gathered using a convenient sampling technique, chosen for its ease of access and consideration of time constraints. The study was carried out over a period of six months following the approval of the research protocol. In terms of sample selection, the inclusion criteria required participants to be teenagers within the specified age range, 13-19 years, who regularly consumed caffeine from sources such as coffee,

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tea, energy drinks, or chocolates. Participants with chronic illnesses, such as hypertension, or mental health disorders like depression and anxiety, were excluded to minimize confounding variables. Additionally, pregnant and lactating females, individuals with a history of psychiatric disorders, or those using psychoactive substances were also excluded. Data were collected using a structured questionnaire that incorporated the Caffeine Consumption Questionnaire (CCQ) and the Pittsburgh Sleep Quality Index (PSQI). The CCQ assessed the frequency and quantity of caffeine intake, while the PSQI evaluated the participants' sleep quality. The Caffeine Consumption Questionnaire (CCQ) categorizes caffeine intake into three levels based on the total score. A score between 5 and 8 points indicates low caffeine consumption, a score between 9 and 14 points reflects moderate caffeine consumption, while a score ranging from 15 to 20 points represents high caffeine consumption. Similarly, the Pittsburgh Sleep Quality Index (PSQI) is used to assess the quality of sleep and the severity of sleep difficulties. A score of 0 suggests no sleep difficulty, scores between 1 and 7 indicate mild sleep difficulty, scores between 8 and 14 reflect moderate sleep difficulty, and scores from 15 to 21 demonstrate severe sleep difficulty. Questionnaires were distributed to students in the selected institutions and completed under the supervision of the research team to ensure accuracy. Caffeine intake was not self-reported in milligrams by participants. It was assessed using the standardized Caffeine Consumption Questionnaire (CCQ), which includes predefined caffeine values (in mg) for various items. Participants selected their consumption frequency and calculated total intake by summing these values as per CCQ interpretation guidelines. For statistical analysis, IBM SPSS software version 27 was used. Quantitative variables were summarized using mean and standard deviation, while categorical data, such as caffeine intake levels, were expressed in frequencies and percentages. The Chi-square test was applied to examine the distribution of variables and determine associations between caffeine consumption and sleep quality.

RESULTS

This chapter presents the findings derived from the analysis of data collected from 400 teenagers across various educational institutes in Lahore, using the Caffeine Consumption Questionnaire (CCQ) and the Pittsburgh Sleep Quality Index (PSQI). The age of the participants was recorded to understand the demographic makeup of the sample. The study included 400 teenagers from Lahore. The participants were divided into two age groups: 13-15 years and 16-19 years. The results indicated a slightly higher representation of teenagers in the 16-19 years' age group (210 respondents, 52.5%) compared to the 13-15 years' age group (190 respondents, 47.5%), as mentioned in figure 1.

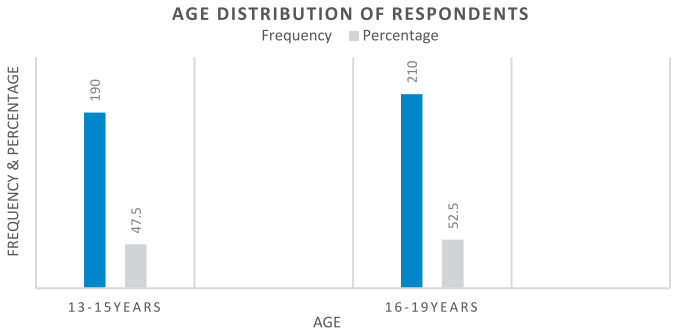

Figure 1: Age Distribution of Respondents

Participants were asked to estimate their total daily caffeine consumption in milligrams. The largest group of respondents (155 teenagers, 38.75%) estimated their daily caffeine intake to be between 100 and 200mg. 100 teenagers (25%) reported consuming 201-300mg, 95 teenagers (23.75%) consumed less than 100mg, and 50 teenagers (12.5%) reported consuming more than 300mg of caffeine daily. These estimations suggest that a considerable number of teenagers consume caffeine levels that may impact sleep, as mentioned in figure 2.

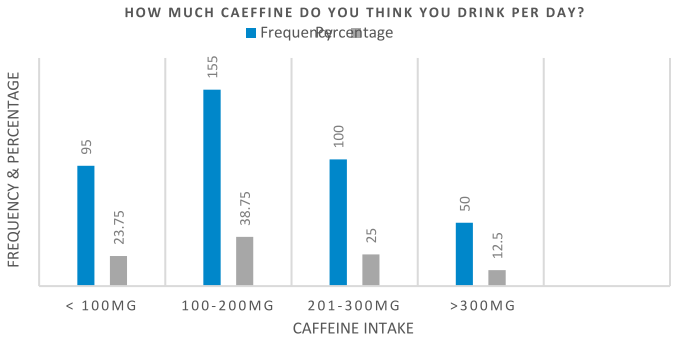

Figure 2: Caffeine Intake (mg/day)

Total scores from the Caffeine Consumption Questionnaire (CCQ) were calculated and categorized to provide an overall assessment of caffeine consumption levels. The results showed that the majority of teenagers (235 respondents, 58.75%) fell into the moderate caffeine consumption category. 90 respondents (22.5%) were categorized as low consumers, and 75 respondents (18.75%) as high consumers, indicating varied levels of caffeine dependence or habituation across the sample, as mentioned in figure 3.

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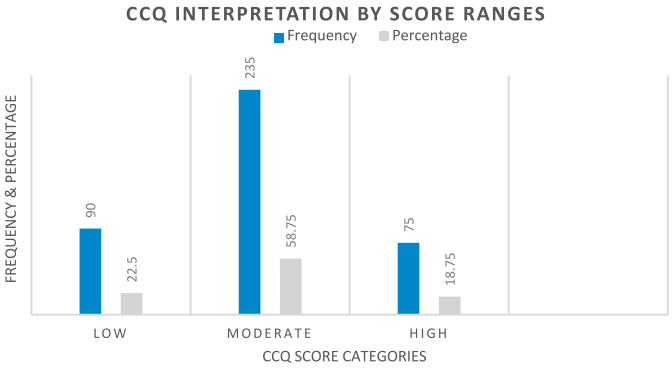

Figure 3: CCQ Interpretation by Score Ranges

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the overall sleep quality of the participants over the past month. According to the PSQI scores, 168 respondents (42%) had fair sleep quality. Poor sleep quality was reported by 130 respondents (32.5%), while 102 respondents (25.5%) reported good sleep quality. These findings highlight that a significant majority (74.5%) of the surveyed teenagers experienced sleep quality that was either fair or poor, as mentioned in figure 4.

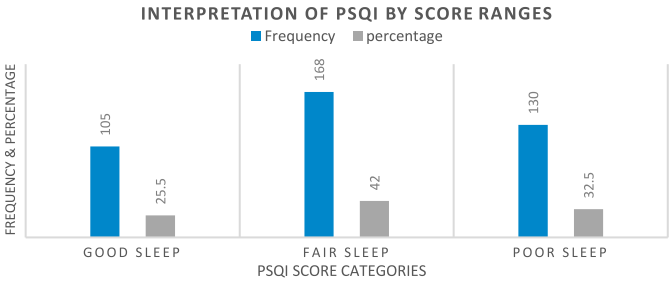

Figure 4: Interpretation of PSQI by Score Ranges

A Chi-square test was conducted to analyze the association between caffeine consumption levels (derived from CCQ scores and categorized as low, moderate, and high) and PSQI sleep quality categories (good, fair, and poor). The test result ($\chi^2 = 41.38$, df = 4, $p \leq 0.05$) indicated a statistically significant association. This suggests that the level of caffeine consumption among teenagers in Lahore is significantly related to their reported sleep quality. Teenagers with higher caffeine scores were more likely to report poor sleep quality. A Pearson correlation of r = +0.80 ($p \leq 0.05$) indicates a very strong positive linear relationship between caffeine intake and the sleep quality variable, as mentioned in table 1.

Table 1: Cross-tabulation and Correlation of Caffeine Score with PSQI Categories

Caffeine Level	Good Sleep	Fair Sleep	Poor Sleep	Total	p-Value	r
Low	55	25	10	90	≤0.05*	+0.8
Moderate	40	115	80	235		
High	7	28	40	75		

*indicates statistical significance at p≤0.050

DISCUSSION

The current research establishes that teenage residents of Lahore display poor sleep quality due to their caffeine intake. Research support suggests that the high prevalence of poor sleepers (68%) presents an increasing concern for public health throughout different regions. The research data matches scientific interpretations of caffeine because this stimulating substance blocks adenosine, which works as a neuromodulator to induce sleep [4, 5]. A relationship between daily caffeine intake and increased PSQI scores was found to be significant in this study, similar to Nasir *et al.* and Reichert *et al.* who reported the same pattern among adolescents and university students [13, 14]. This study extends previous research through its investigation of Lahore teenagers, even though little academic attention has been given to this relationship within this population. The analysis of when students consumed caffeine validates that it is essential to recognize both the amount consumed and the timing of consumption. The sleep quality of adolescents worsened when they used caffeine as a nighttime or evening beverage. The studies confirm that caffeine stays in the bloodstream for a long time, thus leading to delayed sleep onset and disrupted restful sleep periods [15, 16]. The rise of energy drinks as significant caffeine suppliers demands immediate attention because their advertisements target young people without control. Traditional beverages have fewer stimulants in them, so the disruptive sleep effect of energy drinks becomes stronger because they contain more caffeine and stimulants such as taurine and guarana. The research suggests that both parents and teenagers need strict regulation and awareness programs about the dangers that develop from excessive and frequent energy drink use [6, 8]. The survey results demonstrating high incidences of sleep complaints regarding falling asleep difficulty and nighttime disruptions, and daytime exhaustion, confirm how caffeine affects sleep at multiple levels. The sleep disturbances caused by caffeine intake affect more than basic sleeplessness because they disrupt both circadian rhythm function and hormone equilibrium. Public health experts express worry about findings which demonstrate how extended sleep problems in teenagers generate negative long-term consequences, including inferior academic achievements, higher anxiety-depression risks and obesity risks along with cardiovascular disease risks [17, 18]. Additionally, the results from this research indicate that caffeine impact and sleep troubles affect male and female in equivalent ratios, although Van der Linden *et al.* and Vézina-Im *et al.* established that female adolescents exhibit stronger effects. Additional studies need to analyze whether natural sexual differences combined with

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behavioural elements result in diverse sleep-related effects [19, 20]. The research contains certain restrictions in its methodology. The research design depends on historical data rather than following a timeline, so it restricts any conclusion about cause-and-effect relationships, and self-reported data can have inaccuracies due to recall memory issues. The established sleep assessment tool (PSQI), together with numerous study participants, contributes to the credibility of the analyzed data. Further research should integrate measurement tools such as actigraphy and polysomnography to confirm results while studying how physical activity, screen time, and dietary habits modify relationships between caffeine and sleep problems.

This study has certain limitations, including its cross-sectional design, which restricts causal inference, and reliance on self-reported data that may be subject to recall bias. The use of convenience sampling from selected private institutions may also limit generalizability to all adolescents in Lahore. Future research should adopt longitudinal designs, incorporate objective sleep assessment tools such as actigraphy, and include diverse educational and socioeconomic settings to better understand long-term effects and guide targeted public health interventions.

CONCLUSIONS

The research concluded that the majority of teenagers have poor sleep quality caused by excessive and mismanaged consumption of caffeine.

Authors' Contribution

Conceptualization: MI, RN
Methodology: MI, MH, AF, RN
Formal analysis: MI, NA
Writing and Drafting: MI, MH, AF, WN, RN, AA
Review and Editing: MI, MH, AF, WN, RN, AA, NA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Acute Complications in Hemodialysis: Frequency, Patterns, and Clinical Implications

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ABSTRACT

Chronic Kidney Disease (CKD) is a progressive and irreversible condition increasingly recognized as a global public health challenge. Hemodialysis, though life-sustaining, is frequently associated with acute complications that compromise patient outcomes and healthcare quality, especially in resource-limited settings. **Objectives:** To determine the frequency of acute complications during hemodialysis in patients with dialysis-dependent CKD at MTI Mardan Medical Complex, Mardan. **Methods:** This descriptive cross-sectional study was conducted from January to June 2025, involving 326 patients undergoing maintenance hemodialysis. Data were collected using a structured proforma documenting clinical and demographic characteristics, comorbidities, and intradialytic complications across multiple sessions. Standardized clinical definitions were applied to identify events such as hypotension (systolic BP drop ≥20 mmHg or <90 mmHg), hypoglycemia (RBS <70 mg/dL), and chest pain. The data were analyzed using SPSS version 20.0. **Results:** The mean age was 37.7 ± 12.1 years, with a male predominance (55.2%). The average duration of dialysis was 9.2 ± 5.1 months. Acute complications were observed in 41.7% of patients, with hypotension being the most frequently reported complication. **Conclusions:** Intra-dialytic complications are common in maintenance hemodialysis, with hypotension being the most prevalent. Enhanced monitoring, standardized protocols, and multicenter studies are warranted to reduce complication rates and improve patient care.

INTRODUCTION

Chronic kidney disease (CKD) is increasingly recognized as a systemic disorder rather than being confined to renal impairment alone. It affects multiple organ systems and significantly increases cardiovascular morbidity and mortality. Cardiovascular disease, including coronary artery disease, heart failure, arrhythmias, and sudden cardiac death, is the leading cause of death in CKD patients, with a risk up to tenfold higher than in the general population [1]. As CKD progresses and glomerular filtration rate (GFR) falls below 30mL/min/1.73m^2, disturbances in mineral metabolism emerge, marked by hyperphosphatemia, borderline or low serum calcium, and elevated parathyroid hormone (PTH) levels, collectively termed CKD–mineral and bone disorder (CKD–MBD) [2]. These changes manifest clinically as bone pain and muscular discomfort. Declining GFR also leads to anemia due to reduced erythropoietin production, contributing to symptoms such as exertional dyspnea, fatigue, and diminished quality of life [3]. When GFR drops below 15 mL/min/1.73 m^2, uremic complications, including anorexia,

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nausea, vomiting, dyspnea, weight loss, peripheral edema, acidosis, and cognitive impairment, become clinically significant [4]. At this advanced stage, conservative measures alone are insufficient, and renal replacement therapy (RRT) becomes necessary. Hemodialysis remains the most common modality for RRT worldwide due to its immediacy and broad clinician experience; however, it requires secure vascular access via catheters, arteriovenous fistulas, or grafts [5]. A pre-dialysis systolic blood pressure of at least 100 mmHg is typically required to ensure adequate treatment flow; whereas, hypotension is not a contraindication to peritoneal dialysis [6]. Despite its life-saving role, hemodialysis is associated with a spectrum of acute complications. These range from mild symptoms such as nausea and headache to more severe issues, including hypoglycemia, intradialytic hypotension or hypertension, hemolysis, allergic reactions, and even stroke [7]. Intradialytic hypotension, the most common complication affecting between 8% and 40% of sessions, is associated with increased cardiovascular events and mortality. It arises from excessive ultrafiltration, impaired cardiovascular compensatory mechanisms, and autonomic dysfunction, especially in elderly, diabetic, or dialysis-naïve individuals [8]. However, there exists a study gap in the regional literature documenting standardized, protocol-based evaluation of acute hemodialysis complications, especially in under-resourced healthcare settings like ours. Existing data lack uniformity in complication definitions, time points of monitoring, and interventions employed.

Despite the growing burden of CKD and the widespread use of maintenance hemodialysis in Pakistan, there is limited region-specific data systematically documenting the frequency and patterns of acute intradialytic complications. Most available literature originates from high-income settings, where standardized monitoring protocols and dialysis adequacy assessments differ significantly from resource-limited centers. Furthermore, inconsistencies in complication definitions and reporting methods make it difficult to compare outcomes across institutions. This gap highlights the need for locally generated evidence using clearly defined clinical criteria to better understand complication trends and inform targeted preventive strategies. This study aims to assess the frequency, patterns, and clinical implications of acute complications during maintenance hemodialysis among CKD patients at Mardan Medical Complex, Mardan.

METHODS

This descriptive cross-sectional study was conducted in the Nephrology Department of Mardan Medical Complex from January to June 2025 after obtaining ethical approval from the Bacha Khan Medical College and Mardan Medical Complex, Mardan, Pakistan (Ref No: 435/BKMC). Patients aged 15–70 years undergoing maintenance hemodialysis who provided informed consent were included, while those on peritoneal dialysis, receiving blood transfusions during dialysis, or presenting with pre-existing complications were excluded. A sample size of 326 was calculated using Cochran's formula for categorical data (p=30.4%, d=5%, Z=1.96), and non-probability consecutive sampling was employed [9]. Data were collected using a structured proforma recording demographic information, comorbidities (diabetes, hypertension, cardiovascular disease), and dialysis-related details, and patients were monitored during a single dialysis session for acute complications including hypotension (SBP <90 mmHg or a drop ≥20 mmHg with/without symptoms), headache, chest pain, nausea, vomiting, fever, muscle cramps, and hypoglycemia (RBS <70 mg/dL). Complications were documented by trained nursing staff and verified by the nephrologist, while preventive or corrective interventions (IV fluids, midodrine, dialysate temperature adjustment, ultrafiltration reduction) were provided as clinically indicated but not uniformly standardized, hence excluded from final analysis. Dialysis adequacy parameters (Kt/V or URR) were not recorded, although duration in months was noted. Data were analyzed using SPSS version 20.0 with descriptive statistics (means, standard deviations, frequencies), normality tested by Shapiro–Wilk, independent sample t-test applied for continuous variables, and Chi-square test for categorical variables, with a significance level set at $p \leq 0.050$.

RESULTS

The study results demonstrated the Distribution of demographic variables (age, gender, BMI) and clinical parameters (duration of dialysis, pre-dialysis systolic blood pressure, and diabetes status), along with the proportion of patients who experienced acute complications (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Patients Undergoing Hemodialysis (N = 326)

Variables		Frequency (%) / Mean ± SD
Mean Age (years)		37.7 ± 12.1
Gender	Male	180 (55.2%)
	Female	146 (44.8%)
Mean BMI (kg/m^2)		23.7 ± 5.17
Mean Duration of Dialysis (months)		12.6 ± 8.57
Mean Pre-Dialysis SBP (mmHg)		144.5 ± 29.8
Diabetes Mellitus		176 (53.9%)
Non-Diabetic		150 (46.1%)
Patients with Acute Complications		136 (41.7%)

The study showed the frequency of acute complications stratified by age, gender, duration of dialysis, BMI, systolic blood pressure, and diabetes status. Statistical significance ($p \leq 0.050$) is

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indicated by an asterisk (*), with intradialytic complications found to be significantly more common in older patients, diabetics, and those with lower BMI.

An independent sample t-test was applied for age; a Chi-square test was applied for other variables (Table 2).

Table 2: Association of Demographic and Clinical Risk Factors with Acute Complications in Hemodialysis Patients (n=326)

Risk Factor	Complication Rate (%)	p-Value
Age > 40 years	65.5	<0.001*
Age ≤ 40 years	28.5	<0.001*
Male	42.2	0.837
Female	41.1	0.837
>12 months dialysis	38.5	0.452
≤12 months dialysis	43.0	0.452
BMI > 25 kg/m^2	30.0	0.004*
BMI ≤ 25 kg/m^2	46.9	0.004*
SBP > 140 mmHg	35.7	0.056
SBP ≤ 140 mmHg	46.2	0.056
Diabetic	56.8	<0.001*
Non-Diabetic	24.0	<0.001*

Non-Diabetic24.0<0.001** p≤0.050 indicates statistical significance

The bar chart illustrates the distribution of acute intra-dialytic complications among 326 patients. Hypotension was the most frequently observed complication, affecting 34 patients, which accounts for 25.0% of all reported complications. Hypoglycemia followed as the second most common, with 21 instances (15.4%). Headache and Chest Pain occurred with similar frequencies, each at 18 cases (13.2%). Overall, 136 patients experienced at least one complication, representing 41.7% of the total patient group (Figure 1).

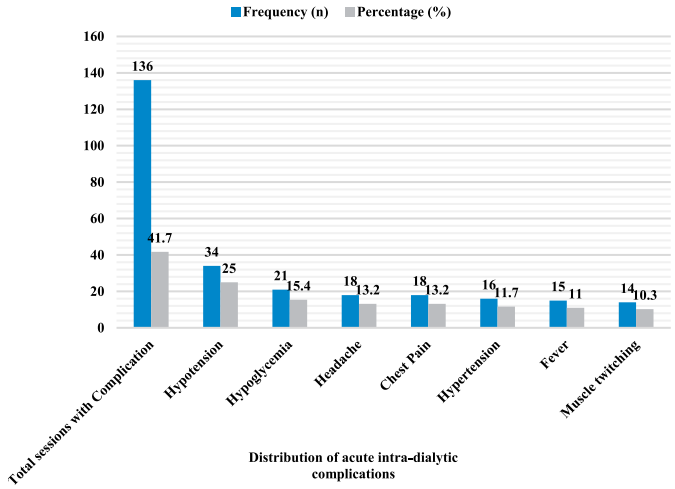

Figure 1: Distribution of Acute Intradialytic Complications Among 326 Patients

DISCUSSION

Chronic Kidney Disease (CKD) represents irreversible renal impairment associated with progressively worsening outcomes and systemic complications. Globally, diabetes mellitus and hypertension remain the leading causes of CKD, but nephrotoxic medications, recurrent infections, and urologic pathologies are increasingly being recognized as important contributors to renal decline [10, 11]. Additional etiologies include glomerulonephritis, interstitial nephritis, neoplasms, congenital anomalies, and obstructive uropathies [12]. Addressing the primary cause is essential to delay CKD progression and improve long-term prognosis [13]. CKD may remain clinically silent for years, particularly in cases of chronic glomerulonephritis or interstitial disease, but can also manifest as rapidly progressing renal failure, particularly in acute glomerular or obstructive pathologies [14]. Multiple studies report that most CKD patients are asymptomatic at the time of diagnosis, often identified during preoperative evaluations or anemia workups [15]. Given this, guidelines recommend annual screening for proteinuria and serum creatinine in diabetic patients above 40 years to enable early detection [16]. Proteinuria, in particular, is a reliable marker for both disease severity and prognosis [17]. CKD is stratified into five stages based on glomerular filtration rate (GFR), with stage G5 representing end-stage renal disease (ESRD), necessitating renal replacement therapy [18]. In Pakistan, hemodialysis remains the primary modality due to widespread availability and greater patient compliance compared to peritoneal dialysis [19]. Unfortunately, more than 95% of patients begin hemodialysis via temporary double-lumen catheters, often under emergency conditions [20]. Hemodialysis provides symptomatic relief, particularly from dyspnea, uremia, acidosis, and anorexia, but is also associated with various complications [21]. In the current study, acute intra-dialytic complications were observed in 41.7% of patients, a rate higher than seen in comparable international studies [22]. These complications, especially when frequent, contribute to reduced dialysis adherence, poor quality of life, and increased morbidity [23]. The most prevalent complication was intradialytic hypotension, which aligns with global findings and is often attributed to autonomic dysfunction, reduced cardiac reserve, and aggressive fluid removal strategies [24]. Our study showed that hypotension was more prevalent in patients with low BMI and in those with diabetes as the underlying cause of CKD, both of which are known risk factors for hemodynamic instability during dialysis. Interestingly, dialysis duration did not significantly affect complication frequency. Whether patients were on dialysis for less or more than 12 months, the incidence of acute complications remained

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comparable, suggesting that risk persists regardless of dialysis vintage. Gender also did not show a statistically significant correlation, with similar complication rates in males and females. Age, however, emerged as a significant factor. Patients older than 40 years had a higher incidence of complications, possibly due to increased vascular stiffness, subclinical atherosclerosis, and higher inflammatory markers typical of aging. Comorbidities such as coronary artery disease, osteoarthritis, and polypharmacy may further exacerbate this risk. Given these findings, routine pre-dialysis assessments should be intensified for diabetic patients and those above 40 years of age. Regular monitoring for early signs of intradialytic complications can guide timely interventions, improving patient safety and outcomes. Future prospective, multi-center studies are warranted to explore the pathophysiological links between aging, diabetes, and hemodialysis-associated complications to develop effective preventive strategies. Our study has several limitations. First, complications were recorded during a single dialysis session per patient, which may not fully represent their overall intradialytic experience. Second, although complications were defined using widely accepted clinical thresholds (e.g., systolic BP drop >20 mmHg for hypotension), a standardized documentation checklist was not used, which may have introduced variability in recognition or recording of events. Third, preventive or corrective measures such as fluid boluses, midodrine administration, or dialysate temperature adjustments were applied as per routine care but were not uniformly recorded or analyzed. Finally, dialysis adequacy indicators such as Kt/V or URR were not included, which might have influenced complication rates and limits our ability to correlate outcomes with session effectiveness.

This study has several limitations, including its single-center cross-sectional design and the assessment of complications during only one dialysis session per patient, which may not reflect longitudinal variability. The absence of standardized intervention documentation and dialysis adequacy parameters (Kt/V or URR) limits deeper outcome correlations. Additionally, non-probability sampling may affect generalizability. Future prospective multicenter studies incorporating repeated-session monitoring, standardized reporting protocols, and dialysis adequacy measures are recommended to strengthen causal inference and develop evidence-based preventive guidelines.

CONCLUSIONS

This study highlights that acute complications during hemodialysis are frequent, with intradialytic hypotension emerging as the most common event. Older age, diabetes mellitus, and low body mass index were identified as significant risk factors. These findings emphasize the need for careful pre-dialysis risk assessment and individualized management, particularly in high-risk patients. Strengthening early detection and timely intervention can improve safety and treatment outcomes. Larger multicenter studies are warranted to develop standardized preventive protocols and optimize care in dialysis populations.

Authors' Contribution

Conceptualization: MNS
Methodology: MWS, MM, YA
Formal analysis: ZU
Writing and Drafting: AK, MWS
Review and Editing: AK, MWS, MM, YA, MNS, ZU

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Epigenetic Regulation of the TLR7 Gene and Its Correlation with Immune Dysregulation in Post-COVID Syndrome

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ABSTRACT

Toll-like receptor 7(TLR7) is crucial for recognizing single-stranded viral RNA and initiating type I interferon signalling, which initiates antiviral immune responses. DNA methylation and other epigenetic controls may affect TLR7 expression and play a role in immune dysregulation in post-COVID syndrome. **Objectives:** To assess the association between immune dysregulation in people with post-COVID syndrome and epigenetic regulation of the TLR7 gene, specifically DNA methylation patterns. **Methods:** Patients with post-COVID-19 symptoms (≥12 weeks' post-infection) and age- and sex-matched recovered controls participated in a case-control study. The purpose of peripheral blood mononuclear cells (PBMCs) was to use bisulfite pyrosequencing to analyze the DNA methylation of TLR7 promoter CpG sites, to use qRT-PCR to quantify TLR7 mRNA, and to use flow cytometry to immunophenotype immune cell subsets and type I interferon (IFN-α) production. Analysis was done on statistical relationships among immune parameters, gene expression, and methylation status. **Results:** In comparison to controls, post-COVID patients showed notable changes in TLR7 promoter methylation patterns, with site-specific hypo- and hyper-methylation associated with corresponding changes in TLR7 expression. Anomalies in B-cell and plasmacytoid dendritic cell (pDC) profiles and dysregulated IFN-α levels were linked to aberrant expression, suggesting persistent innate immune activation. **Conclusions:** TLR7 epigenetic changes could be a factor in post-COVID-19 persistent immunological dysregulation. These results emphasize TLR7 methylation as a possible therapeutic target and biomarker. To confirm these correlations, more long-term research is needed.

INTRODUCTION

While most SARS-CoV-2 patients have mild to moderate illness and recover in a matter of weeks, a significant portion of patients continue to have a variety of chronic symptoms that persist for months after the acute phase of the virus. This condition is increasingly being referred to as post-COVID syndrome [1]. A range of neuropsychiatric, gastrointestinal, and musculoskeletal complaints are among the diverse clinical manifestations, which also include fatigue, cognitive impairment (also known as "brain fog"), dyspnea, myalgia, palpitations, and other symptoms [2, 3]. These symptoms can seriously reduce functional status and quality of life, adding to the strain on healthcare systems. There is growing evidence that the pathophysiology of post-COVID syndrome is largely influenced by persistent immune dysregulation [4]. Months after viral clearance, immune profiling studies have found

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persistent changes in both the innate and adaptive immune compartments, such as the growth of activated T cell subsets, dysregulation of B cell maturation, and the loss or malfunction of plasmacytoid dendritic cells (pDCs) [5]. Notably, some post-COVID patients continue to have elevated levels of pro-inflammatory cytokines, chemokines, and type I interferons (IFN-I), which is a sign of low-grade, chronic inflammation [6]. Neuro-inflammation, persistent tissue damage, and multi-system symptoms could all be caused by such immune changes. Toll-like receptor 7 (TLR7) is a pattern recognition receptor that is found in endosomal compartments and is specifically designed to recognize single-stranded RNA (ssRNA) from viruses, including coronaviruses [7]. Reports of TLR7 loss-of-function mutations resulting in severe COVID-19 in otherwise healthy young male highlight the crucial role of TLR7 in antiviral defence [8, 9]. Epigenetic mechanisms, which are heritable, reversible changes that do not change the underlying DNA sequence, have a significant impact on gene expression and are not only determined by genetic sequence [10]. A crucial epigenetic marker linked to transcriptional silencing is DNA methylation at cytosine residues within CpG dinucleotides, particularly in promoter regions [11]. While site-specific effects and interactions with other chromatin marks can result in more complex patterns of regulation, hypo-methylation generally correlates with gene activation [12]. According to research, SARS-CoV-2 infection causes extensive epigenomic reprogramming that impacts genes related to immune cell differentiation, cytokine signalling, and antiviral defence [13]. In both acute and convalescent COVID-19 patients, several studies have documented changed methylation profiles of innate immune receptors and signalling intermediates [14]. However, little is known about how TLR7 is epigenetically regulated in relation to post-COVID syndrome. Prolonged epigenetic changes may maintain aberrant immune signalling long after viral clearance, since TLR7 expression levels affect IFN-I responses and immune cell activation. Such signalling could function as a biomarker and therapeutic target if it is triggered or modulated by epigenetic modifications, specifically methylation changes in the TLR7 promoter. Research on autoimmune diseases has shown that TLR7 promoter methylation status is linked to immune phenotype and disease activity [15]. The immunological abnormalities associated with post-COVID syndrome are becoming more widely recognized, but the underlying molecular mechanisms are still not fully understood. The relationship between environmental triggers (SARS-CoV-2 infection) and long-lasting transcriptional alterations in immune genes can be convincingly explained by epigenetic regulation, especially DNA methylation. Since TLR7 plays a crucial role in antiviral sensing, can affect both innate and adaptive immunity, and is known to be involved in immune-mediated pathology when dysregulated, it is a biologically plausible candidate for such regulation. As far as we are aware, no previous study has thoroughly assessed the downstream immune cell and cytokine profiles, TLR7 promoter methylation, and gene expression in a post-COVID cohort. Identifying these connections may help clarify a potential mechanism of persistent immune activation and discover new biomarkers or treatment targets for post-COVID syndrome.

Despite increasing recognition of persistent immune dysregulation in post-COVID syndrome, the underlying molecular mechanisms driving prolonged innate immune activation remain poorly defined. While global epigenetic alterations have been described in acute and convalescent COVID-19, gene-specific epigenetic regulation of key antiviral receptors such as TLR7 has not been systematically explored in post-COVID cohorts. In particular, the relationship between TLR7 promoter methylation, transcriptional expression, and downstream immune functional responses has not been comprehensively evaluated. Addressing this gap may clarify whether epigenetic remodeling of TLR7 contributes to sustained interferon dysregulation in post-COVID syndrome. This study aimed to assess the association between immune dysregulation in people with post-COVID syndrome and epigenetic regulation of the TLR7 gene, specifically DNA methylation patterns.

METHODS

This case-control study investigated the association between immune dysregulation in post-COVID syndrome and epigenetic regulation of the TLR7 gene at Ziauddin Hospital from June 2022 to May 2023. The Institutional Review Board at Ziauddin University granted ethical approval (6560522BKBC), and before enrolment, each participant gave written informed consent. Eligibility was established by whether or not participants had persistent symptoms more than 12 weeks following laboratory-confirmed SARS-CoV-2 infection. Participants were selected using a consecutive sampling strategy. The control group consisted of people who had fully recovered and were matched by age and sex and did not have any lingering symptoms, while the post-COVID group was made up of people who were still experiencing symptoms. Originally, 40 participants per group were enrolled; however, power calculations were used to retrospectively justify the sample size's adequacy. A two-sided, two-sample t-test with α=0.05 and 80% power necessitates roughly 45 participants per group, according to previously published data that suggests an absolute mean methylation difference of ~8% at the TLR7 promoter with an SD of ~13% (Cohen's d≈0.62). To counteract this, we

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added more participants to make up for sample attrition and guarantee enough analysis samples for expression and methylation analyses. In addition, 62 samples are needed to detect correlations between TLR7 methylation and expression, with |r|=0.35 at 80% power and α=0.05. This was met within the sample size that was obtained after considering attrition. Every participant had 10–15 mL of peripheral venous blood drawn in EDTA tubes. Using density-gradient centrifugation, peripheral blood mononuclear cells (PBMCs) were separated. In order to measure site-specific DNA methylation within CpG-rich regions of the TLR7 promoter, genomic DNA was extracted, bisulfite converted using a commercial kit, and then amplified by PCR and pyrosequencing. TLR7 mRNA expression was assessed by quantitative real-time PCR (qRT-PCR) with GAPDH as the reference gene after total RNA was extracted and reverse-transcribed to cDNA. After staining PBMCs with fluorochrome-conjugated monoclonal antibodies against B cells and plasmacytoid dendritic cells (pDCs), flow cytometry was used to perform immune-profile analysis. Following stimulation with a TLR7 ligand, intracellular staining of IFN-α was used to evaluate functional cytokine responses. To ensure reproducibility, each assay was run in duplicate and included the proper quality controls for flow cytometry, gene expression, and DNA methylation. SPSS version 26 was used to perform statistical analyses (IBM Corp., Armonk, NY). Histogram inspection, Q–Q plots, and the Shapiro–Wilk test were used to assess the normality of continuous variables (such as methylation percentages, ΔCt or 2^-ΔCt expression values, and immune cell subset frequencies), and Levene's test was used to test for equality of variances. Welch's correction was used in cases where variances were unequal, and the independent-samples t-test was used to analyze normally distributed continuous variables with equal variances. The Mann–Whitney U test was used for variables that were not normally distributed. In correlation analyses, Spearman's rank correlation was used when assumptions were broken or the variables were ordinal, and Pearson's correlation when both variables satisfied the normality assumptions. To make the results easier to interpret, effect sizes (r^2) were computed in addition to correlation coefficients and p-values. Relative normality, heteroscedasticity, and collinearity checks were applied to all models to control for potential confounding variables like age, sex, and comorbidities (such as diabetes and hypertension). Adjusted coefficients with 95% confidence intervals (CIs) are the results of regression analysis. Using the Benjamini–Hochberg false discovery rate (FDR) method, p-values were modified for comparisons between multiple CpG sites.

RESULTS

There were 80 people enrolled, 40 of whom were in the control group and 40 of whom were in the post-COVID group. Major comorbidities, sex distribution, and age were similar between the two groups (Table 1).

Table 1: Participants' Baseline Characteristics in the Study

Variables	Post-COVID (n=40)	Control (n=40)	p-Value	Effect Size (95% CI)
Age, Years (mean ± SD)	45.2 ± 10.3	44.8 ± 9.9	0.820	d = 0.04 (−0.38 to 0.46)
Male, n (%)	22 (55.0%)	21 (52.5%)	0.820	OR = 1.10 (0.45–2.69)
Diabetes, n (%)	10 (25.0%)	8 (20.0%)	0.590	OR = 1.33 (0.47–3.77)
Hypertension, n (%)	12 (30.0%)	9 (22.5%)	0.450	OR = 1.47 (0.55–3.93)

When compared to controls, methylation analysis revealed that post-COVID participants had medium-to-large effect sizes and significantly higher methylation levels at the CpG1, CpG2, and CpG3 sites of the TLR7 promoter, On the other hand, the post-COVID group showed a significant decrease in TLR7 mRNA expression, with a large effect size (Table 2).

Table 2: Methylation Comparison of the TLR7 Promoter and TLR7 mRNA Expression Between Groups

Variables	Post-COVID (Mean ± SD)	Control (Mean ± SD)	Mean difference (95% CI)	p-Value	Cohen's d
Methylation Comparison of the TLR7 Promoter					
CpG1 (%)	12.8 ± 3.4	10.5 ± 2.8	2.3 (0.8–3.8)	0.003*	0.72
CpG2 (%)	15.6 ± 4.1	13.0 ± 3.5	2.6 (1.0–4.2)	0.001*	0.67
CpG3 (%)	14.9 ± 3.7	12.2 ± 3.3	2.7 (1.1–4.3)	0.002*	0.74
TLR7 mRNA Expression					
TLR7 Mrna (ΔCt)	1.82 ± 0.65	2.34 ± 0.71	−0.52 (−0.85 to −0.19)	0.002*	0.77

TLR7 expression showed a positive correlation with IFN-α response, which explained 20% of the variance, while methylation at CpG sites showed inverse associations with TLR7 mRNA expression, explaining 13–17% of the variance (Table 3).

Table 3: TLR7 Methylation, Expression, And IFN-A Response Correlations

Variables Compared	Correlation Coefficient (r)	r^2	95% CI for r	p-Value
CpG1 methylation vs TLR7 mRNA	−0.36	0.13	−0.58 to −0.08	0.012*
CpG2 methylation vs TLR7 mRNA	−0.41	0.17	−0.61 to −0.13	0.005*
CpG3 methylation vs TLR7 mRNA	−0.38	0.14	−0.59 to −0.10	0.009*
TLR7 mRNA vs IFN-α response	0.45	0.20	0.19 to 0.64	0.002*

Multivariable regression models that controlled for age, sex, and comorbidities verified that TLR7 expression independently predicted IFN-α response, while higher CpG methylation levels continued to be independently linked to lower TLR7 expression (Table 4).

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Table 4: Analysis of Relationships Using Multivariable Regression That Accounts for Comorbidities, Age, and Sex

Dependent Variables	Independent Variables	β (SE)	Adjusted β (95% CI)	p-Value
TLR7 mRNA (ΔCt)	CpG1 Methylation	−0.32 (0.09)	−0.30 (−0.46 to −0.14)	0.001*
TLR7 mRNA (ΔCt)	CpG2 Methylation	−0.28 (0.08)	−0.25 (−0.41 to −0.11)	0.002*
TLR7 mRNA (ΔCt)	CpG3 Methylation	−0.29 (0.08)	−0.26 (−0.42 to −0.12)	0.002*
IFN-α response	TLR7 mRNA (ΔCt)	0.45 (0.10)	0.42 (0.22 −0.62)	<0.001*

Findings significant differences were found in some populations when immune subsets from post-COVID individuals and healthy controls were compared. With a mean difference of −1.6% (95% CI: −2.7 to −0.5; p = 0.005; Cohen's d = 0.66), the post-COVID group had a significantly lower percentage of B cells ($CD19^+$) (8.5 ± 2.3%) than the controls (10.1 ± 2.5%), suggesting a moderate effect size. A large effect size was suggested by the significantly lower plasmacytoid dendritic cells (pDCs; $CD123^+CD303^+$) in post-COVID individuals (1.9 ± 0.7%) compared to controls (2.6 ± 0.8%), with a mean difference of −0.7% (95% CI: −1.1 to −0.3; p = 0.001; Cohen's d = 0.90). On the other hand, there was no significant difference in baseline IFN-α levels between post-COVID participants (42.5 ± 12.8 pg/mL) and controls (44.1 ± 13.2 pg/mL) (mean difference −1.6 pg/mL; 95% CI: −7.3 to 4.1; p = 0.570). However, the post-COVID group showed a significant impairment upon stimulation with the TLR7 ligand, producing significantly less IFN-α (198.6 ± 35.4 pg/mL) than the controls (235.2 ± 38.7 pg/mL). There was a significant impairment in TLR7-mediated interferon response among post-COVID individuals, as evidenced by the large effect size (Cohen's d = 0.98) and mean difference of −36.6 pg/mL (95% CI: −52.1 to −21.1; p<0.001) (Table 5).

Table 5: Comparison of Group-to-Group Immune Cell Subset Frequencies and Synthesis of IFN-α After TLR7 Ligand Activation

Variables	Post-COVID (n=40) (Mean ± SD)	Control (n=40) (Mean ± SD)	Mean Difference (95% CI)	p-Value	Cohen's d
Immune Subset (% of PBMCs)					
B cells ($CD19^+$)	8.5 ± 2.3	10.1 ± 2.5	−1.6 (−2.7 to −0.5)	0.005*	0.66
pDCs ($CD123^+CD303^+$)	1.9 ± 0.7	2.6 ± 0.8	−0.7 (−1.1 to −0.3)	0.001*	0.90
$CD4^+$ T cells	35.2 ± 6.5	36.0 ± 6.0	−0.8 (−3.9 to 2.3)	0.610	0.13
$CD8^+$ T cells	28.4 ± 5.8	27.9 ± 6.1	0.5 (−2.6 to 3.6)	0.740	0.08
Synthesis of IFN-α After TLR7 Ligand Activation					
IFN-α (pg/mL) Unstimulated	42.5 ± 12.8	44.1 ± 13.2	−1.6 (−7.3 to 4.1)	0.570	0.12
IFN-α (pg/mL) Stimulated	198.6 ± 35.4	235.2 ± 38.7	−36.6 (−52.1 to −21.1)	<0.001*	0.98

DISCUSSION

The study found that TLR7 promoter DNA methylation varies by site in patients with post-COVID syndrome: some CpG sites were hypermethylated, while others were hypomethylated. Thus, hypomethylation encourages transcriptional activation, while DNA methylation at promoter CpG islands inhibits gene expression [16]. Decreased TLR7 mRNA expression was significantly linked to these epigenetic changes. This delicate, site-specific regulation suggests intricate epigenetic control rather than a straightforward on/off mechanism. Decreased B cells, decreased plasmacytoid dendritic cells, and impaired IFN-α production were all indicators of immune dysregulation. This is consistent with TLR7's established function of identifying viral single-stranded RNA and inducing type I interferon reactions [17]. Significantly, TLR7 dysregulation has been linked to the pathophysiology of COVID-19, including sex-biased expression patterns and, in more severe cases, epigenetic changes [18]. Our findings add to this body of evidence by pointing to TLR7 epigenetic remodeling as a possible cause of immune activation that persists in the post-acute phase. Global DNA methylation studies in post-COVID cohorts have found long-lasting methylation changes across numerous genes and pathways, including those related to immune signalling, metabolic regulation, and accelerated epigenetic ageing [19, 20]. Therefore, our study's focus on TLR7 fits a broader pattern of host epigenetic alteration that may underlie long-COVID pathologies. More generally, reviews have demonstrated that the virus can modulate the host's epigenetic landscape, including DNA methylation, histone modifications, and chromatin remodeling to elude immune responses and spread inflammation [21]. Epigenetic modulation of TLR7 may impair IFN-α and disrupt innate immune cell homeostasis, contributing to persistent symptoms in post-COVID syndrome. This is consistent with evidence that delayed or dysregulated type I interferon responses are central to COVID severity and long-term sequelae. The association between TLR7 methylation/expression and immune cell dysregulation highlights a plausible mechanistic pathway. Two significant implications for clinical and translational research are highlighted in this study. First, the TLR7 promoter's methylation status at particular CpG sites may be a useful biomarker for determining who is at risk for

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long-term immune dysregulation in post-COVID syndrome. These biomarkers may help with risk assessment, early detection, and focused follow-up for patients who may experience long-term effects from SARS-CoV-2 infection. Second, our results imply that therapeutic targeting of epigenetic modifiers, like DNA methyltransferases or demethylation pathways, may be a new strategy for immune homeostasis restoration. Similar approaches could be investigated to manage immune dysregulation in patients with long-term COVID. Epigenetic therapies have already demonstrated promise in modifying immune responses in autoimmune and inflammatory conditions.

This study has certain limitations, including its single-center design and relatively modest sample size, which may limit the generalizability of the findings. The cross-sectional nature precludes assessment of temporal changes in TLR7 methylation and causality between epigenetic alterations and immune dysfunction. Additionally, other epigenetic mechanisms such as histone modifications and chromatin accessibility were not evaluated. Future longitudinal, multicenter studies with larger cohorts are needed to validate these findings, explore dynamic epigenetic changes over time, and assess the therapeutic potential of targeting TLR7-related epigenetic pathways in post-COVID syndrome.

CONCLUSIONS

This study concluded that different epigenetic changes in the TLR7 promoter region, including site-specific hypo- and hyper-methylation patterns, were present in people with post-COVID syndrome. These changes were strongly linked to abnormal TLR7 mRNA expression. These modifications were linked to dysregulated type I interferon production, aberrant B-cell and plasmacytoid dendritic cell profiles, and other findings that suggested innate immune dysregulation and persistent activation. The results show that TLR7 methylation alterations may be a biomarker for the persistence of the disease and a possible target for treatment. They may also be a factor in the long-term immune dysregulation seen in post-COVID syndrome. To verify these findings and investigate the clinical usefulness of TLR7 epigenetic profiling in post-COVID patient care, more longitudinal research with bigger cohorts is necessary.

Authors' Contribution

Conceptualization: BK, SKN
Methodology: BK, GMF
Formal analysis: AJ, HF
Writing and Drafting: SB, GMF
Review and Editing: SB, GMF, AJ, HF, BK, SKN

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Diagnostic Accuracy of MRCP for Detecting Choledocholithiasis in Patients with Obstructive Jaundice Keeping ERCP as Gold Standard

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ABSTRACT

Choledocholithiasis is a common cause of obstructive jaundice and may lead to serious complications if diagnosis or treatment is delayed. While ERCP is the gold standard for diagnosis and therapy, its invasive nature carries risks. MRCP offers a non-invasive alternative, but its accuracy may be influenced by clinical and technical factors. **Objectives:** To evaluate the diagnostic accuracy of MRCP in detecting choledocholithiasis using ERCP as the reference standard, and to assess the impact of stone size, location, number, and MRCP–ERCP interval. **Methods:** This analytical cross-sectional diagnostic accuracy study was conducted in the Department of Radiology, Bahawal Victoria Hospital, Bahawalpur (March 13, 2023, to March 12, 2024). A total of 271 patients with suspected choledocholithiasis underwent both MRCP and ERCP. Sensitivity, specificity, predictive values, overall accuracy, and Cohen's kappa were calculated with subgroup analyses by stone size, location, number, and MRCP–ERCP interval. **Results:** MRCP showed a sensitivity of 88.9% (95% CI: 83.5–92.7%), specificity of 67.0% (95% CI: 56.9–75.8%), PPV of 84.2% (95% CI: 78.4–88.7%), NPV of 75.3% (95% CI: 64.9–83.4%) and an overall accuracy of 81.5% (95% CI: 76.5–85.7%). Agreement with ERCP was moderate (Cohen's kappa = 0.55). Diagnostic performance was highest for stones measuring 5–10 mm, distally located stones, and when ERCP was performed within 3 days of MRCP. **Conclusions:** MRCP demonstrates good diagnostic accuracy and moderate agreement with ERCP, particularly for medium-sized distal stones and when ERCP is not delayed.

INTRODUCTION

Choledocholithiasis, or stones in the common bile duct, is a major cause of obstructive jaundice and may lead to ascending cholangitis, pancreatitis, or hepatic dysfunction if diagnosis is delayed [1]. Endoscopic Retrograde Cholangiopancreatography (ERCP) has long been the diagnostic and therapeutic gold standard, but its invasive nature carries risks such as pain, pancreatitis, bleeding, and perforation [2]. Magnetic Resonance Cholangiopancreatography (MRCP) provides detailed, non-invasive images of the biliary and pancreatic ducts without contrast or instrumentation and has emerged as a safe, robust tool for evaluating obstructive jaundice [3, 4]. Numerous studies report high diagnostic accuracy of MRCP for choledocholithiasis, with sensitivity and specificity frequently exceeding 90% [5–8]. Sherpa et al. noted an overall accuracy of 92.4% and identified choledocholithiasis as the most common benign cause of obstruction [6]. Isram et al. demonstrated sensitivity and specificity of 96.2% and 91.8%, supporting MRCP as a reliable prelude to therapeutic ERCP [9]. A 2025 tertiary-care study also reported sensitivity of 86.4% and specificity of 88% (AUC 0.864), reinforcing MRCP's role as a frontline modality [10]. Most prior studies assessed sensitivity and specificity in isolation, without considering clinical or technical factors that may influence MRCP performance. Our study addresses this gap by stratifying

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diagnostic accuracy by stone size, location, number, and MRCP–ERCP interval. Including one of the largest cohorts from a tertiary center in South Punjab, Pakistan, our work provides context-specific evidence on when MRCP is most reliable and where it may underperform, thereby enhancing its practical relevance for managing obstructive jaundice.

Although MRCP is widely regarded as a reliable non-invasive alternative to ERCP for diagnosing choledocholithiasis, reported diagnostic performance varies across studies and clinical settings. Most previous research has focused primarily on overall sensitivity and specificity, with limited evaluation of how stone size, anatomical location, number of stones, and timing between MRCP and ERCP influence diagnostic accuracy. Furthermore, context-specific data from tertiary care centers in South Punjab remain scarce. This gap highlights the need for a stratified analysis to better define the clinical scenarios in which MRCP performs optimally and where caution is warranted. This study aims to evaluate the diagnostic accuracy of MRCP in detecting choledocholithiasis using ERCP as the reference standard, and to assess the impact of stone size, location, number, and MRCP–ERCP interval.

METHODS

This analytical cross-sectional study was carried out in the Department of Radiology, Bahawal Victoria Hospital, Bahawalpur, from 13 March 2023 to 12 March 2024. Ethical approval was obtained (IRB No. 2079/DME/QAMC Bahawalpur), and written informed consent was obtained from all participants. Sample size was estimated for a diagnostic accuracy study using Buderer's method [11], which incorporates sensitivity (Se), specificity (Sp), and disease prevalence (Prev). For Sensitivity, $N(Se)=Z^2 \times Se \times (1-Se)/d^2 \times Prev$. For specificity, $N(Sp)=Z^2 \times Sp \times (1-Sp)/d^2 \times Prev$. With Z=1.96 (95% confidence), d=0.05, Se=0.881, and Sp=0.944 from Kumar *et al.* [12], and Prev=0.70 (70% expected prevalence), the calculations yielded N (Se)=230 and N (Sp)=271; the larger (271) was adopted as the final sample size. This ensured >80% power to estimate sensitivity and specificity with 5% precision. The formula was taken from Buderer NM [11]. Adults (≥18 years) with clinical and biochemical evidence of obstructive jaundice (raised bilirubin, ALP, GGT) undergoing both MRCP and ERCP within seven days were included. Exclusion criteria were prior biliary surgery, known hepatobiliary malignancy, inconclusive ERCP, or incomplete records. Demographics, presenting symptoms (jaundice, abdominal pain, fever, vomiting), and laboratory parameters (total/direct bilirubin, ALT, AST, ALP, GGT, WBC) were recorded. All examinations were performed on a 1.5 T MRI scanner with a standard hepatobiliary protocol. Axial and coronal T2-weighted SSFSE and respiratory-triggered 3D MRCP sequences were acquired (slice thickness 5 mm axial/coronal, 1.5 mm 3D; TR 2000–2500 ms; TE 600–800 ms; FOV 32–36 cm; matrix 256×256). Breath-hold or respiratory-triggered techniques were applied as tolerated; maximum-intensity projections were generated for uniform image review. MRCP findings (presence of stones, size, location, number) were interpreted independently by two radiologists blinded to ERCP results; ERCP by expert endoscopists served as the gold standard. Stone size was measured as the maximum short-axis diameter of the largest stone; number classified as single (1) or multiple (≥2); location as common hepatic duct, proximal CBD, or distal CBD. In multiple segments, the largest stone determined the location. Discrepancies were resolved by consensus. Data were analyzed using SPSS 26.0. Continuous variables were expressed as mean ± SD, categorical variables as frequencies/percentages. Diagnostic performance of MRCP was assessed with 2×2 tables against ERCP, calculating sensitivity, specificity, PPV, NPV, overall accuracy, and Cohen's kappa. Subgroup analyses evaluated performance by stone size (<5 mm, 5–10 mm, >10 mm), location (distal CBD, proximal CBD, common hepatic duct), number (single vs. multiple), and MRCP–ERCP interval (≤3 vs. >3 days). Chi-square test assessed differences; $p<0.05$ was considered significant.

RESULTS

A total of 271 patients were included. Baseline demographic and clinical characteristics are shown in Table 1. The mean age was 52.13 ± 16.21 years. There were 124 male (45.8%) and 147 female (54.2%). The most common presenting symptom was abdominal pain (234; 86.3%), followed by jaundice (207; 76.4%), vomiting (101; 37.3%), and fever (98; 36.2%) (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Participants (n=271)

Variables	n (%) or Mean ± SD
Age	
Years	52.13 ± 16.21
Gender	
Male	124 (45.8%)
Female	147 (54.2%)
Presenting Symptoms	
Jaundice	207 (76.4%)
Abdominal Pain	234 (86.3%)
Fever	98 (36.2%)
Vomiting	101 (37.3%)

Laboratory parameters of the study participants are summarized. The mean total bilirubin was 4.58 ± 1.20 mg/dL and direct bilirubin 2.54 ± 0.83 mg/dL. Mean ALT was 143.56 ± 64.26 U/L, AST 123.65 ± 58.17 U/L, ALP 452.38 ± 202.09 U/L, GGT 322.11 ± 167.86 U/L and WBC count 10.65 ± 3.18 × 10^3/µL (Table 2).

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Table 2: Laboratory Parameters of Study Participants (n=271)

Parameters	Mean ± SD
Total Bilirubin (mg/dL)	4.58 ± 1.20
Direct Bilirubin (mg/dL)	2.54 ± 0.83
ALT (U/L)	143.56 ± 64.26
AST (U/L)	123.65 ± 58.17
ALP (U/L)	452.38 ± 202.09
GGT (U/L)	322.11 ± 167.86
WBC Count (×10^3/µL)	10.65 ± 3.18

All 271 patients underwent both MRCP and ERCP for evaluation of suspected choledocholithiasis. According to ERCP findings, 180 patients (66.4%) had choledocholithiasis, while 91 patients (33.6%) did not. MRCP correctly identified 160 of the 180 ERCP-positive cases, yielding a sensitivity of 88.9% (95% CI: 83.5–92.7%). Among the 91 ERCP-negative cases, MRCP correctly reported 61 as negative, resulting in a specificity of 67.0% (95% CI: 56.9–75.8%). The positive predictive value was 84.2% (95% CI: 78.4–88.7%), while the negative predictive value was 75.3% (95% CI: 64.9–83.4%). The overall diagnostic accuracy was 81.5% (95% CI: 76.5–85.7%). Importantly, Cohen's kappa was 0.55 (95% CI: 0.45–0.65; p<0.05), indicating moderate agreement between MRCP and ERCP. These results confirm MRCP as a reasonably accurate and reliable non-invasive tool for detecting choledocholithiasis, particularly in confirming the presence of bile duct stones (Table 3).

Table 3: Cross-tabulation of MRCP Results Against ERCP (Gold Standard) for Diagnosing Choledocholithiasis (n=271)

ERCP Result (Gold Standard)	MRCP Negative	MRCP Positive	Total
Negative	61 (67.0%)	30 (33.0%)	91 (33.6%)
Positive	20 (11.1%)	160 (88.9%)	180 (66.4%)
Total	81 (29.9%)	190 (70.1%)	271 (100%)

Percentages are row-wise within the ERCP result.

Subgroup analysis of MRCP performance relative to ERCP revealed several clinically important trends. With respect to stone size, MRCP showed the highest diagnostic performance in the 5–10 mm subgroup, correctly identifying 85 true positives (66.4%) with only 6 false negatives (4.7%). Diagnostic accuracy was comparatively lower in the <5 mm group, with 30 true positives (50.0%) but 8 false negatives (13.3%) and 10 false positives (16.7%), reflecting the challenge of detecting very small stones. In the >10 mm group, MRCP demonstrated good performance with 45 true positives (54.2%) and only 6 false negatives (7.2%). For stone location, the highest diagnostic yield was observed in distal CBD stones, with 95 true positives (66.4%) and only 6 false negatives (4.2%). Performance declined slightly for proximal CBD stones (38 true positives, 55.1%; 7 false negatives, 10.1%) and common hepatic duct stones (27 true positives, 48.2%; 4 false negatives, 7.1%), indicating greater effectiveness in distal locations. When stratified by number of stones, MRCP was more accurate in patients with multiple stones, yielding 108 true positives (63.9%) and only 7 false negatives (4.1%). In the single stone subgroup, MRCP identified 72 true positives (59.0%) but missed 13 cases (10.7%), possibly due to subtle imaging findings when only one small stone is present. The MRCP–ERCP interval also significantly affected diagnostic accuracy. When ERCP was performed within ≤3 days of MRCP, 110 true positives (68.8%) were recorded, with only 6 false negatives (3.8%). However, when ERCP was delayed beyond 3 days, true positives declined to 90 (59.6%) and false negatives rose to 14 (9.3%), suggesting that stone migration, passage, or evolving biliary dynamics may reduce agreement when there is a longer interval. Overall, these subgroup findings confirm that MRCP is most reliable for detecting medium-sized, distally located, or multiple stones, and when ERCP is performed soon after MRCP. Greater caution is needed when interpreting MRCP results in patients with very small stones, more proximal locations, or longer imaging-to-intervention delays (Table 4).

Table 4: Diagnostic Performance of MRCP vs ERCP Stratified by Stone Characteristics and MRCP–ERCP Interval (n=271)

Subgroups	True -ve	False -ve	True -ve	False -ve	Total
<5 mm	30 (50.0%)	10 (16.7%)	12 (20.0%)	8 (13.3%)	60
5–10 mm	85 (66.4%)	12 (9.4%)	25 (19.5%)	6 (4.7%)	128
>10 mm	45 (54.2%)	8 (9.6%)	24 (28.9%)	6 (7.2%)	83
Distal CBD	95 (66.4%)	14 (9.8%)	28 (19.6%)	6 (4.2%)	143
Proximal CBD	38 (55.1%)	9 (13.0%)	15 (21.7%)	7 (10.1%)	69
Common Hepatic Duct	27 (48.2%)	7 (12.5%)	18 (32.1%)	4 (7.1%)	56
Single	72 (59.0%)	12 (9.8%)	25 (20.5%)	13 (10.7%)	122
Multiple	108 (63.9%)	18 (10.7%)	36 (21.3%)	7 (4.1%)	169
≤3 Days	110 (68.8%)	10 (6.2%)	34 (21.2%)	6 (3.8%)	160
>3 Days	90 (59.6%)	20 (13.2%)	27 (17.9%)	14 (9.3%)	151

Diagnostic Performance Indicators (with 95% CI): Sensitivity: 88.9% (95% CI: 83.5–92.7). Specificity: 67.0% (95% CI: 56.9–75.8). Positive Predictive Value (PPV): 84.2% (95% CI: 78.4–88.7). Negative Predictive Value (NPV): 75.3% (95% CI: 64.9–83.4). Overall Accuracy: 81.5% (95% CI: 76.5–85.7). Cohen's Kappa: 0.55 (95% CI: 0.45–0.65), p<0.05 (moderate agreement)

DISCUSSION

MRCP is now a widely accepted non-invasive modality for evaluating biliary and pancreatic pathologies. In this study, using ERCP as the gold standard, MRCP achieved a sensitivity of 88.9% (95% CI: 83.5–92.7%), specificity of 67.0% (95% CI: 56.9–75.8%), PPV 84.2% (95% CI: 78.4–88.7%), NPV 75.3% (95% CI: 64.9–83.4%) and an overall accuracy of 81.5% (95% CI: 76.5–85.7%), with

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moderate agreement (κ=0.55; p<0.05). Diagnostic performance was highest for stones 5–10 mm, distal CBD location, and when ERCP was performed within three days of MRCP, confirming MRCP's reliability while highlighting some limitations. Our results parallel recent reports of high diagnostic accuracy for MRCP. Kumar *et al.* found sensitivity and specificity of 88.1% and 94.4% [12], and Isram *et al.* found 96.2% and 91.8% [13]. Although our specificity was slightly lower, sensitivity and overall accuracy were comparable, supporting MRCP as a reliable non-invasive tool. Variation in specificity across studies may reflect imaging quality, expertise, and small filling defects mimicking sludge or air, causing false positives. Nayab *et al.* (87% sensitivity, 80% specificity) [14], Qaisar *et al.* (accuracy 90%, PPV 95.3%, NPV 76.9%) [15], Bilal *et al.* (accuracy 89.4%, sensitivity 83.3%, specificity 93.9%) [16] and Javaid *et al.* (accuracy 90.6%, sensitivity 95%, specificity 73.3%) [17] all demonstrate a pattern of high sensitivity with moderate–high specificity consistent with our findings. MRCP also showed better accuracy in multiple-stone cases, though overestimation may reduce specificity. Timing influenced performance: ERCP within three days yielded more true positives and fewer false negatives, while longer delays likely allowed stone migration or passage, reducing agreement. Tariq *et al.* also reported MRCP outperforming ultrasound (sensitivity 99%, specificity 94%) [18]. Varsha *et al.* (sensitivity 86.4%, specificity 88%, AUC 0.864) [19], Rashid *et al.* (accuracy 82%) [20], and Swaraj *et al.* (accuracy 94.8% vs. 48.9% for ultrasound) [21] further underscore MRCP's robustness and superiority to ultrasonography, especially where ERCP is unavailable or carries a higher risk.

This study has certain limitations, including its single-center design and cross-sectional nature, which may limit the generalizability of the findings and preclude assessment of long-term outcomes. Inter-observer variability in MRCP interpretation and potential interval changes such as spontaneous stone passage could also have influenced results. Additionally, advanced imaging techniques such as higher-field MRI (3T) were not evaluated. Future multicenter, prospective studies incorporating standardized imaging protocols and shorter MRCP–ERCP intervals are recommended to further refine diagnostic algorithms and optimize patient selection for therapeutic ERCP.

CONCLUSIONS

In conclusion, MRCP demonstrates high sensitivity and reasonably good specificity for the detection of choledocholithiasis, making it a reliable and non-invasive diagnostic tool in patients with obstructive jaundice. In this study, MRCP achieved an overall diagnostic accuracy of 81.5% with moderate agreement to ERCP (Cohen's kappa = 0.55), and performed best in detecting medium- to large-sized stones and those located in the distal common bile duct. Diagnostic accuracy was further enhanced when ERCP was performed within three days of MRCP, underscoring the importance of timely follow-up. Although limitations remain, particularly in detecting very small or proximally located stones, MRCP provides a valuable initial assessment that can guide further management.

Authors' Contribution

Conceptualization: KN
Methodology: KN
Formal analysis: KN, SN, FM
Writing and Drafting: SN
Review and Editing: SN, FM, KN

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Awareness of Keratoconus Among the Diagnosed Cases of Keratoconus in Patients Visiting Al Shifa Trust Eye Hospital

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ABSTRACT

Keratoconus is a chronic, progressive, non-inflammatory, usually bilateral corneal disorder that causes stromal thinning that leads to corneal apical protrusion, irregular astigmatism, and decreased vision. Its etiology is multifactorial, and it is important to determine its awareness and its association with non-genetic, environmental risk factors to prevent it. **Objectives:** To determine the level of awareness of keratoconus among the diagnosed cases of keratoconus. **Methods:** This descriptive cross-sectional study was conducted at Al Shifa Trust Eye Hospital in five months using a consecutive sampling technique. SPSS version 22.0 was used for Data Analysis. The Pearson's Chi-square test was utilized for cross-tabulation. **Results:** Out of 135 patients, it was seen that participants with a higher level of education (P value 0.0029) and those with positive family history had overall better knowledge about the disease and specific knowledge about eye rubbing as an aggravating factor of the disease (P value 0.00249). In conclusion, overall, 48.1% % had poor knowledge, 34.8% had fair, and only 17% had good knowledge regarding the disease. **Conclusions:** Despite keratoconus being more common in younger individuals who have internet access, patients still had poor knowledge of the disease. Different strategies can be devised to increase awareness and prevent its progression by eliminating the non-genetic, environmental risk factors, such as eye rubbing and discussing compliance regarding the use of topical anti-allergic medications and regular follow-up visits.

INTRODUCTION

Keratoconus is a chronic, progressive, non-inflammatory, usually bilateral corneal disorder that causes stromal thinning that leads to corneal apical protrusion, irregular astigmatism, and decreased vision [1]. Its onset is usually before puberty, and it stabilizes after the fourth decade of life [2]. There are multiple management options ranging from conservative management, e.g, use of spectacles and Rigid Gas permeable lenses, to Interventional, e.g, Corneal cross (CXL and penetrating keratoplasty (PKP) that cause visual rehabilitation. [3] Patients typically encounter blurred vision, distortion, and glare; as the majority are young, the disease significantly restricts daily activities and diminishes quality of life [4, 5]. Its etiology is multifactorial, having a genetic predisposition along with multiple risk factors such as atopy, persistent eye rubbing, and exposure to ultraviolet light [6, 7]. There are different levels of understanding among patients regarding disease pathogenesis, risk factors, progression, and treatment options [8, 9]. It is important to determine the awareness of the disease and its association with non-genetic, environmental risk factors so that an important cause of corneal blindness can be prevented [10]. A Study conducted in Jeddah, Kingdom of Saudi Arabia, in 2021, revealed that 63.3% of the participants had poor, 31.9% had

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fair, and 4.8% had good knowledge regarding the disease. Almost 75.8% of the study participants used to rub their eyes, and only one third knew the fact that eye rubbing may lead to keratoconus [11]. Another recent study conducted in Aseer Province, Saudi Arabia, in the year 2023 revealed that 85.74% of the participants had poor and 14.26 % had a good level of awareness [12]. Another study conducted in the year 2022, in Medina, revealed that almost 94.1% of the study participants had poor 5.9 % had good knowledge regarding the disease. 27.8% had known that keratoconus and a history of allergies might have a relationship, and most of them, i.e., 27.5% had relatives with KC as their primary source of information, hence highlighting the association of better knowledge with positive family history [10]. A Study conducted in China revealed that 71.9 % participants with advanced keratoconus gave a history of eye rubbing due to a lack of awareness [13]. A Study regarding the association of keratoconus with other ocular disorders was conducted in Layton Rehmat Ullah Benevolent Trust LRBT, and Sir Ganga Ram Hospital, Lahore, Pakistan, showing that 66 out of 110 patients gave a positive history of eye rubbing, although an association between this habit and disease progression has long been established [14, 15]. Keratoconus is a progressive disease that can be halted with early diagnosis and prompt management. Even after being clinically diagnosed, many patients have limited knowledge regarding their disease, its progression, exacerbating factors, treatment options, and preventive measures. This study hypothesizes that patients who have a family history and who have a higher education level have a better understanding of the disease. It is important to evaluate the patients' knowledge, to explore associations between their level of awareness and level of education, along with their family history, and to identify patient education gaps leading to regular follow-ups, improve compliance with the treatment, avoid harmful behaviors such as eye rubbing, and screen the family members with similar symptoms.

Although keratoconus is a progressive and potentially sight-threatening condition, existing literature primarily focuses on its clinical features and management rather than patients' awareness after diagnosis. Most awareness studies have been conducted in Middle Eastern populations, with limited region-specific data available from Pakistan, particularly from Rawalpindi. Furthermore, the relationship between patient education level, family history, and disease-specific knowledge among already diagnosed cases remains underexplored. Identifying these gaps is essential to design targeted educational interventions and prevent avoidable disease progression. This study aims to determine the level of awareness of keratoconus among diagnosed cases of keratoconus.

METHODS

This descriptive cross-sectional study was conducted at Al-Shifa Trust Eye Hospital for a duration of about 5 months, starting from 1/10/2024 to 1/3/2025. Ethical approval was obtained from the Ethical Review Committee of Al-Shifa Trust Eye Hospital, Rawalpindi (Ref. No: ERC-29/AST-24). Patients visiting the Cornea Department of the hospital for their follow-up checkup, who met the inclusion criteria, were recruited for the study. Informed consent was taken from the participants, and their confidentiality was ensured before the interview. A predesigned, pre-validated questionnaire was used that was amended according to our own population needs [12]. It was translated into the native language, Urdu, and then translated back into English to check for its validity by two other researchers. A pilot study was conducted on 15 participants to check the reliability of the questionnaire. Cronbach's alpha was calculated, which turned out to be 0.83; hence, the questionnaire was reliable. It contained three sections. The first section comprised three questions about personal details, including age, gender, and level of education. The second section contained four questions regarding the history of any allergies, types of allergies, treatment history, and family history of KC. The third section included ten questions about awareness regarding KC and its relation with allergies, recognition of eye rubbing as a risk factor, its complications, genetic predisposition, treatment options, and expectations from the treatment options. The responses were marked on a 5-point Likert scale. A single interviewer marked the responses to minimize the interviewer's bias. A sample size of 135 was calculated using the WHO calculator, with a 95% confidence interval, population proportion 14.26%, and absolute precision 6% [12]. Disease prevalence was taken as 5%, which is comparable in South Asia as well as the Middle East [12, 14]. All patients who were diagnosed with keratoconus for more than 6 months, were aged between 18 and 65, and had a K Max value > 48D on Galilei Scan topography were enrolled in the study. Patients with mental or verbal disability, those who could not fully comprehend the questions, had a language barrier, had no or less than a primary level of education, or who were eye care professionals, including ophthalmologists, ophthalmic nurses, optometrists, and opticians, were excluded. The responses were recorded on a 5-point Likert scale, and a total score was calculated. Data were analyzed using IBM SPSS version 22.0. The total score of awareness was calculated by adding the scores from each item of Section Three. Responses ranged from 1 point (strongly disagree) to 5 points (strongly agree), with higher scores indicating better knowledge. Scores were converted into percentages: <50%=poor, up to 70%=fair, and >70%=good knowledge [16]. Statistical analyses were performed using

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the Pearson Chi-Square test, with statistical significance set at p≤0.050.

RESULTS

About 135 participants were interviewed, and about 65.2% (n=88) were male, 71.9% (n=97) were aged from 18-30 years, 28.1 % had an education level below secondary level, and about 18.5 % had a higher level of education. About 56.3% had a history of allergies. Out of these, most of them had ocular allergy. 51.9 % had previously received any form of treatment (including CXL and keratoplasty), and 27.4 % had a positive family history of KC (Table 1).

Table 1: Demographic and Clinical Characteristics of Participants (n=135)

Variables	n (%)
Gender	
Male	88 (65.2)
Female	47 (34.8)
Age group (years)	
18–30	97 (71.9)
>30	38 (28.1)
Education level	
Below secondary	38 (28.1)
Intermediate	72 (53.3)
Higher	25 (18.5)
History of allergies	76 (56.3)
Ocular allergy (most common)	–
Previous treatment (CXL/keratoplasty)	70 (51.9)
Positive family history	37 (27.4)

Of 135 participants, only 10.4% had heard its name before their own diagnosis, while 89.6% did not. Approximately 41.5% recognized that keratoconus is actually corneal thinning. Specific knowledge about its association with allergy was noted by 40%. 41.5% claimed to know that it causes a permanent decrease in vision. Approximately 59.3% knew that eye rubbing worsens it and increases the complications, while 40.7% expressed uncertainty. Only 28.9% knew that it stabilizes with age. 18.5 %of the participants knew that it has a genetic predisposition (Table 2).

Table 2: Knowledge and awareness about keratoconus (n=135)

Q#	Questions	Response	Frequency (%)
Q1	Have you heard about KC before?	No	121 (89.6)
		Yes	14 (10.4)
Q2	Does KC mean corneal thinning?	Poor knowledge	79 (58.5)
		Good knowledge	56 (41.5)
Q3	Does KC have a relation with allergies?	No	81 (60.0)
		Yes	54 (40.0)
Q4	Does KC cause a permanent decrease in vision?	No	79 (58.5)
		Yes	56 (41.5)
Q5	Does eye rubbing worsen KC?	Poor knowledge	55 (40.7)
		Good knowledge	80 (59.3)
Q6	Does eye rubbing worsen complications of KC?	Poor knowledge	55 (40.7)
		Good knowledge	80 (59.3)
Q7	Does KC stabilize with age?	No	96 (71.1)
		Yes	39 (28.9)
Q8	Does KC have a genetic predisposition?	No	110 (81.5)
		Yes	25 (18.5)
Q9	CXL only stops the progression of KC and does not cure it?	No	51 (37.8)
		Yes	84 (62.2)
Q10	Knowledge regarding treatment options	Poor knowledge	82 (60.7)
		Good knowledge	53 (39.3)

Overall, 48.1% % had poor knowledge, 34.8% had fair, and only 17% had good knowledge regarding the disease (Figure 1).

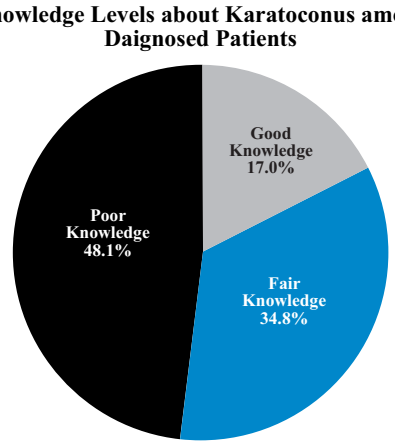

Figure 1: Knowledge Levels about Keratoconus among Diagnosed Patients

With dichotomization to Agree versus Disagree/Uncertain, education had a significant association with eye rubbing. The proportion of the participants who reported frequent eye rubbing as a preventable cause of keratoconus was 64.9% among those with secondary or higher education and 44.7% among those with below secondary education. This dissimilarity was statistically significant (χ^2 (1) =9.74, p=0.002)(Table 3).

Table 3: Association between Education Level and Knowledge Regarding Keratoconus (n=135)

Education level	Agree n (%)	Disagree/ Uncertain n (%)	Total n (%)
Below secondary	17 (44.7)	21 (55.3)	38 (28.1)
Secondary & above	63 (64.9)	34 (35.1)	97 (71.9)
Total	80 (59.3)	55 (40.7)	135 (100.0)

Chi-square test: $\chi^2(1) = 9.74$, p = 0.002.

Participants with a positive family history of keratoconus tend to know about its exacerbating effect with eye rubbing. The association was significant when analyzed across the full five categories (χ^2 (4)=11.97, p=0.018). This was lost when responses were collapsed in a 2×2 configuration and suggests that it is essential to maintain the original response distribution to capture subtle yet

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meaningful effects (Table 4).

Table 4: Association between Family History of Keratoconus and Knowledge about Eye Rubbing (n=135)

Family History	Strongly Disagree n (%)	Disagree n (%)	Don't Know n (%)	Agree n (%)	Strongly Agree n (%)	Total n (%)
Yes	13 (37.1)	0 (0.0)	0 (0.0)	8 (22.9)	14 (40.0)	35 (25.9)
No	19 (19.0)	17 (17.0)	6 (6.0)	18 (18.0)	40 (40.0)	100 (74.1)
Total	32 (23.7)	17 (12.6)	6 (4.4)	26 (19.3)	54 (40.0)	135 (100.0)

*Chi-square test: $\chi^2(4)=11.97$, p=0.018

DISCUSSION

The purpose of this study was to determine the awareness level of keratoconus among diagnosed patients who were coming to the outpatient department of Al Shifa Trust Eye Hospital on their follow-up visits. Regarding knowledge of their disease, overall, 51.8% had a satisfactory level of understanding, which included the participants who had fair (34.8%) and good knowledge (17%) of the disease. Only 40% knew the disease causes corneal thinning and weakness, leaving most unaware of its impact on their eyes. Only 40% linked it to allergies, and few knew its progressive, permanently blinding nature, which is an alarming gap. About 81.5% were aware that there is some association with family history. Specific knowledge regarding stabilization of the disease with progressing age was noted by only 28.9%, pointing to the cause of demanding CXL despite the stabilization of their disease due to age. Most of them acknowledged CXL as the treatment option, followed by spectacles, contact lenses, and surgery. Many participants (62.2%) knew that CXL halts disease progression rather than curing it permanently, but few believed otherwise. The study revealed that participants who had good knowledge were mostly younger patients, aged 18–30 years, who had a higher level of education and positive family history. A similar level of awareness was observed in a study conducted at Aseer province, showing 14.26% of participants having good knowledge of their disease [12]. Whereas a study conducted by Alamri *et al.* at Abha reported only 8.1% participants having satisfactory awareness, and more than 90% had poor awareness [17]. While Al Rashed et al. reported a good level of understanding (85.5%) regarding keratoconus among the Saudi population [18]. About 59.3% recognized eye rubbing as harmful, with educated participants and those with a family history showing better awareness of its sight-threatening impact. Alamri *et al.* reported that 57% of participants in Aseer province being aware of this preventable aggravating factor, which is comparable to our study [12, 19]. While Kordi *et al.* reported much lower numbers of aware participants (28.9%) in Medina [10]. Very few, only about 10% of the patients, had heard the name of the disease before their own diagnosis even those who had a positive family history which clearly exhibits that there is lack of overall awareness of keratoconus, and patients often assume it to be a usual refractive error [20]. This is the first study in Rawalpindi to assess keratoconus awareness through interviews, ensuring inclusion of those unable to complete questionnaires or lacking internet access. However, some limitations remain. Firstly, the questionnaire was administered only to participants who actually came for follow-up visits, so it can be assumed that those who knew the devastating nature of the disease were enrolled in the survey. Secondly, the questionnaire was undertaken from a single center hospital, which might lead to unequal distribution of participants; hence, the results cannot be generalized to the whole population of Pakistan. The study can be improved further by increasing the sample size and making it a multicenter study involving multiple centers across Pakistan.

This study has certain limitations, including its single-center design and relatively modest sample size, which may limit the generalizability of the findings to the broader Pakistani population. As participants were recruited during follow-up visits, individuals with better health-seeking behavior may have been overrepresented. Additionally, self-reported responses may introduce recall or response bias. Future multicenter studies with larger and more diverse populations are recommended to validate these findings and to evaluate the effectiveness of structured patient education programs in improving awareness and reducing modifiable risk factors such as eye rubbing. The study can be improved further by increasing the sample size and making it a multicenter study involving multiple centers across Pakistan.

CONCLUSIONS

Keratoconus is a chronic progressive disease and many patients, even after being clinically diagnosed, have limited knowledge regarding its progression, risk factors, treatment options and preventive measures. This study highlights the gaps between patient and health care providers so different strategies can be devised to increase regular follow ups, improve compliance to the treatment, avoid harmful behaviors such as eye rubbing and screen the family members with similar symptoms.

Authors' Contribution

Conceptualization: TA
Methodology: HGS, SFB, NY
Formal analysis: TA, FA, MAM
Writing and Drafting: TA
Review and Editing: TA, HGS, SFB, NY, FA, MAM

All authors approved the final manuscript and take responsibility for the integrity of the work

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Original Article

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Comparison of The Efficacy of Oral Versus Topical NSAIDs for Pain Relief in Osteoarthritis

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ABSTRACT

Osteoarthritis is a leading cause of chronic musculoskeletal pain worldwide, significantly impairing quality of life and increasing healthcare burden. Nonsteroidal anti-inflammatory drugs (NSAIDs), administered orally or topically, remain the mainstay of symptom management, though their relative efficacy and safety profiles require further evaluation. **Objectives:** To compare the efficacy of oral versus topical NSAIDs for pain relief in osteoarthritis. **Methods:** This quasi-experimental study was conducted at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period February 2025 to May 2025. 132 male and female patients aged more than 50 years diagnosed with osteoarthritis were assigned to topical (n=66) and oral NSAID (n=66) groups. Diclofenac gel and tablet diclofenac 50mg BD were administered for 4 weeks, respectively. Patients were evaluated for pain relief using the VAS score. **Results:** Mean age in topical versus oral NSAIDs was 64.73±8.25 years versus 66.55±9.606 years, respectively. Male participants were 41 (52.6%) and 37(47.4%) in topical and oral groups, respectively. 23(50.0%) had bilateral joint involvement in both groups. Pain relief was recorded in 25 patients (37.9%) with topical NSAIDs compared to 35 (53.1%) with oral NSAIDs (p-value 0.080). **Conclusions:** Statistically insignificant difference in pain relief was recorded with topical and oral NSAIDs in patients with chronic MSK pain of osteoarthritis. Though the proportion of pain relief was better with oral NSAIDs, the difference was statistically not significant.

INTRODUCTION

The leading knee condition worldwide is osteoarthritis (OA), which is also one of the main reasons for persistent pain brought on by musculoskeletal injuries [1]. The advancing age of human beings and the growing epidemic of obesity are expected to contribute to a rise in the proportion of persons with clinically significant OA. Given how quickly the frequency of an already prevalent illness is rising, it is likely that OA will continue to have an increasing influence on the nation's healthcare and health care systems in the years to come [2]. Even though it can be difficult to determine the prevalence and prevalence of osteoarthritis, new research indicates that the ailment has been increasing over the past ten years and affects a significant percentage of individuals globally [3]. Osteoarthritis frequently affects the hip and knee joint. Over the past couple of decades, the number of cases of this particular ailment has grown and is anticipated to keep growing, placing additional strain on health-related finances and lowering people's standard of living [4]. Numerous demographic variables are linked to osteoarthritis (OA), including repeated trauma, ongoing misuse and deterioration, elevated BMI, sex, heredity, and several metabolic, or hormonal problems have all been linked to an elevated risk [5]. The emergence of

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abnormalities and tiny erosions, together with inflammation of the cartilage in the joint, are preliminary indications of the disease process of OA. Higher type I and III collagen synthesis from the chondrocyte reaction leads to soft fragmentation, which in turn triggers the expulsion of intra-articular enzymes, which cause cartilage to eventually decline, destruction, and the development of subchondral cysts, throughout which contribute to joint inflammation and discomfort [6]. The goal of traditional medical management of osteoarthritis is to control its symptoms, and nonsteroidal anti-inflammatory medications (NSAIDs) are frequently used in this regard. Due to their painkiller and anti-inflammatory qualities, they are frequently used in musculoskeletal disorders. Opioids are also frequently used to treat persistent discomfort, which is frequently brought on by osteoarthritis [7]. A traditional NSAID that can be applied topically or taken orally, diclofenac, which reduces the production of prostaglandins, which are biochemical indicators linked to inflammation and painful sensations. 8 In addition to its analgesic and antipyretic properties, diclofenac is typically tolerated easily; nonetheless, oral treatment has been linked to significant cardiovascular and gastrointestinal concerns [8]. In a randomized controlled trial, overall pain relief was observed in 36.67% patients who were advised NSAIDs for pain relief in osteoarthritis, pain relief in the topical group was recorded in 28.0% and 51.6% patients with tablet diclofenac [9]. The use of topical application of diclofenac is consequently probably better to oral diclofenac for the relief of symptoms of OA in those individuals with GI, cardiac, and renal comorbidities, given that diclofenac is specifically intended to offer symptomatic managing of OA.

Although both oral and topical NSAIDs are widely used for the management of osteoarthritis pain, uncertainty remains regarding their comparative efficacy in routine clinical settings, particularly among elderly patients with comorbidities. Most available evidence is derived from randomized controlled trials conducted in controlled environments, with limited quasi-experimental or region-specific data from Pakistan. Furthermore, direct head-to-head comparisons of topical versus oral diclofenac using standardized pain assessment tools remain underreported locally. Addressing this gap is essential to guide evidence-based prescribing decisions in resource-limited settings. This study aims to provide medical professionals an understanding of recent research on this subject so they can make an informed decision when choosing between topical and oral diclofenac, particularly for the elderly and those who are at risk.

METHODS

This quasi-experimental study was carried out at the department of Rheumatology, Khyber Teaching Hospital department, Peshawar, during the period February 2025 to May 2025, after taking approval from the research review board of Khyber Medical College, Peshawar, Pakistan (Ref. No. 137/DME/KMC). Informed consent was obtained before enrollment in the study after explaining the study risks, benefits, and purpose. Participants were enrolled using a convenience sampling technique. Baseline clinical and socio-demographic data were collected. Participants aged 50 years or above diagnosed with osteoarthritis, complaining of knee joint pain (VAS>4), were enrolled. Patients with inflammatory joint disease, systemic disease, prior history of intra-articular steroid injection, infected joint, and traumatic injury to the knee were excluded. Osteoarthritis was confirmed when the patient was complaining of knee joint pain (VAS>4), and X-ray AP view of the joint shows narrowing of the knee joint space and formation of osteophytes. Efficacy was measured in terms of pain relief assessed after 4 weeks of treatment using the VAS score. The VAS score ranges from 0 to 10, with 0 representing no pain and 10 representing maximum pain. Generally, the score is interpreted as 0=no pain, 1 to 3=mild pain, 4 to 6= moderate pain, and 7 to 10 = severe pain. It is a globally adopted score for pain assessment in clinical studies, validated and endorsed [10]. Sample size was 132, (66 in each group), calculated using online Open Epi calculator using the formula $n = [(Z\alpha/2 + Z\beta)^2 \times (p0(1-p0) + p1(1-p1))] / (p1 - p0)^2$ taking anticipated proportion of pain relief with topical and oral NSAIDs as 28.0% and 51.6% respectively, 80.0% power of test and 95% confidence level [9]. Detailed history and clinical examination were performed for all patients. Following this, patients were assigned to two groups (A and B) in equal numbers through blocked randomization. Patients in group A received topical diclofenac, and group B received oral diclofenac. Topical diclofenac (1%) was administered four times per day, approximately 1gram of gel was gently applied on the affected knee cap and rubbed with hands softly for 2 to 3 minutes. The gel wasn't cleaned thereafter. Oral diclofenac was administered as a tablet in 50mg strength twice daily after a meal. Both groups were evaluated after 4 weeks for pain relief using a visual analogue scale. Data analysis was carried out using SPSS version 26.0. Continuous data were reported as means and standard deviation, and categorical data as frequencies and percentages. Pain relief in both groups was compared using the chi-square test at 5% significance level. Effect modifiers were controlled through stratification. Post-stratification chi-square test was applied at 5% significance level.

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RESULTS

Mean age in topical versus oral NSAIDs was 64.73±8.25 years versus 66.55±9.606 years, respectively and mean pain duration in the topical versus oral group was 7.70±2.578 versus 8.36±2.944 months (Table 1).

Table 1: Descriptive Statistics of Study Participants (N=132, 66 In Each Group)

Groups	Variables	Mean ± SD
Topical	Age (years)	64.73 ± 8.25
	BMI (kg/m^2)	24.92 ± 0.96
	Duration (months)	7.70 ± 2.57
Oral	Age (years)	66.55 ± 9.60
	BMI (kg/m^2)	25.32 ± 0.99

In terms of age distribution, 36 patients (52.9%) were aged below 65 years in the topical group compared to 32 (47.1%) in the oral group. Male participants were 41 (52.6%) and 37(47.4%) in topical and oral groups, respectively. 23(50.0%) had bilateral joint involvement in both groups (Table 2).

Table 2: Distribution of Study Participants According to Various Parameters (Total=32, Topical=66, Oral=66)

Variables	Category	Topical, N (%)	Oral, N (%)	Total, N (%)
Age (years)	≤ 65	36 (52.9)	32 (47.1)	68 (100.0)
	> 65	30 (46.9)	34 (53.1)	64 (100.0)
Gender	Male	41 (52.6)	37 (47.4)	78 (100.0)
	Female	25 (46.3)	29 (53.7)	54 (100.0)
BMI (kg/m^2)	≤ 24.0	16 (69.6)	7 (30.4)	23 (100.0)
	> 24.0	50 (45.9)	59 (54.1)	109 (100.0)
Pain Duration (months)	≤ 7	32 (56.1)	25 (43.9)	57 (100.0)
	> 7	34 (45.3)	41 (54.7)	75 (100.0)
Joint	Right	25 (58.1)	18 (41.9)	43 (100.0)
	Left	18 (41.9)	25 (58.1)	43 (100.0)
	Bilateral	23 (50.0)	23 (50.0)	46 (100.0)
Smoking	Yes	19 (41.3)	27 (58.7)	46 (100.0)
	No	47 (54.7)	39 (45.3)	86 (100.0)
Comorbidities	Hypertension	18 (39.1)	28 (60.9)	46 (100.0)
	Diabetes Mellitus (DM)	33 (52.4)	30 (47.6)	63 (100.0)
	Ischemic Heart Disease (IHD)	15 (65.2)	8 (34.8)	23 (100.0)

Comparison of pain relief in both groups showed that the chi-square p-value for the difference in pain relief was 0.080, which was statistically not significant (Table 3).

Table 3: Comparison of Pain Relief in Topical Versus Oral NSAIDs (Total=132, Topical=66, Oral=66)

Pain Relief	Topical, n (%)	Oral, n (%)	Total, n (%)	p-Value
Yes	25 (41.7)	35 (58.3)	60 (100.0)	0.080
No	41 (56.9)	31 (43.1)	72 (100.0)	
Total	66 (50.0)	66 (50.0)	132 (100.0)	

DISCUSSION

Chronic MSK pain is still a widespread issue, even with the latest advances in therapy. Substantial impairment may arise from prolonged MSK pain, which is frequently linked to decreased activity, insomnia, exhaustion, and mood swings. Patients with chronic pain may find themselves in a "vicious circle" of issues. Anxiety and depression brought on by the pain might exacerbate it [11, 12]. NSAIDs and other drugs, such as antidepressants, are among the many therapy options available for persistent MSK pain [13]. There are several ways to deliver NSAIDs, including topical, parenteral, rectal, and oral. Even though taking them by mouth is among the most often utilized methods, it can be linked to major adverse effects, including renal, cardiovascular, and gastrointestinal problems [14]. Numerous topical NSAID formulations, such as gels and transdermal patches, are accessible to address the issue with oral NSAIDs and are authorized for use for pain indications [15]. Diclofenac, when used topically, penetrates the subcutaneous tissue. A tiny lipophilic molecule, it has been demonstrated to diffuse quickly through the skin and to disperse into synovial fluid. When a dressing with occlusive qualities is employed, penetration is boosted and continues into the basal skin layers to a depth of 3–4 mm [16]. After many epicutaneous applications, diclofenac significantly penetrates the skeletal muscle directly. Within four weeks of starting medication, the impacts of the diclofenac sodium pill became noticeable in our research. After four weeks of therapy, the 100 mg diclofenac sodium pill also resulted in a greater decrease in the quantitative scale of evaluation for pain. A study revealed comparable outcomes with diclofenac SR tablets [17]. When the two categories in this research were evaluated for effectiveness, it was shown that local diclofenac gel was just as effective at lowering pain as daily tablets of diclofenac sodium (100 mg) at the end of four weeks. Final pain reduction in this trial was estimated to be 37.9% for the topical diclofenac gel group and 53.1% for the diclofenac tablet group. According to research, the greatest degree of patient perception of recovery was associated with a 50% decrease in the level of pain [18]. Despite a thorough review of the literature, no trials comparing the effects of topical and tablet forms of diclofenac sodium SR on chronic MSK pain have been identified. Comparing our findings with previous publications is therefore challenging. However, in many trials, topical and tablet forms of diclofenac sodium SR have been contrasted in terms of safety profile. In a previous study, the topical group produced analgesia comparable to oral diclofenac (100 mg) after the extraction of mandibular impacted third teeth, as assessed by VAS [19]. NSAIDs can effectively reduce chronic as well as acute

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pain when given locally. They lessen the inflammatory response and prevent the creation of prostaglandins. Topical and oral diclofenac sodium work similarly by inhibiting prostaglandin production, which accounts for their comparable effectiveness. According to a Previous study, the topically produced blood concentrations were lower than those obtained orally but lasted longer [20]. According to previous research, the absorbed dosage seems to be sufficient for therapeutic usage; however, the quantity of medication accessible for addressing the locations where it works is less compared to that taken orally [21]. The fact that the topical and oral diclofenac groups did not significantly vary in their pain relief scores at the end of four weeks was one of our study's key conclusions. By the time therapy ended, patients in both groups reported a general improvement in their overall condition for persistent MSK pain, both significantly. Research that involved individuals with rheumatoid arthritis and OA found similar results. In the transdermal diclofenac diethylamine group, 20% of patients had adverse medication responses, with 16% of those patients reporting local discomfort across the applied region. Except for 4% of patients experiencing abdominal burning, the transdermal diclofenac diethylamine patch was generally well tolerated. All of the negative medication responses, however, were modest in nature and went away with continuing use [22].

This study has certain limitations, including its single-center design, relatively short follow-up duration, and modest sample size, which may limit generalizability and assessment of long-term efficacy and safety. The quasi-experimental design may also introduce selection bias despite random allocation. Additionally, adverse events and cost-effectiveness were not comprehensively evaluated. Future multicenter, randomized controlled trials with longer follow-up periods are recommended to assess sustained pain control, safety profiles, and economic implications of oral versus topical NSAIDs in osteoarthritis management.

CONCLUSIONS

The present study showed that topical application of NSAIDs was as effective as oral NSAIDs in patients with chronic MSK pain of osteoarthritis. Though the proportion of pain relief was better with oral NSAIDs compared to locally applied NSAIDs, the difference in pain relief was statistically not significant. Further studies should be conducted to evaluate the long-term outcomes and adverse events, as well as cost assessment.

Authors' Contribution

Conceptualization: IUD
Methodology: N, HA, A
Formal analysis: AA, HA, UA
Writing and Drafting: AA, N, UA, AZ, AKM
Review and Editing: AA, N, UA, AZ, AKM, IUD, HA, A

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Association of Liver Enzymes with Thyroid Hormone Levels in Hyperthyroid Patients: A Cross-Sectional Study from a Tertiary Care Hospital

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ABSTRACT

Hyperthyroidism, characterized by the overproduction of thyroid hormones, may impact liver function. Understanding this relationship is essential for early identification and management of liver dysfunction in hyperthyroid patients. **Objectives:** To determine the association between thyroid hormone levels (TSH, T3, T4) and liver function tests (ALT, AST, ALP, bilirubin, and total protein) in patients with hyperthyroidism. **Methods:** This cross-sectional study was conducted from 28 July 2023 to 28 January 2024 at the Endocrinology OPD of Gulab Devi Hospital, Lahore. A total of 100 hyperthyroid patients were selected using non-probability sampling. Demographic data, thyroid profiles (T3, T4, TSH), and liver function tests (LFTs) were recorded. Data were analyzed by SPSS version 26.0 using descriptive statistics and Chi-square tests to assess associations. **Results:** Out of 100 hyperthyroid patients, 59 were female and 41 were male, with a mean age of 38.5 + 10.2 years. Elevated ALT was observed in 27% of patients, AST in 13%, ALP in 23%, bilirubin in 13%, and total protein in 11%. Chi-square analysis showed significant associations between TSH and ALT (p=0.028) and AST (p=0.017), as well as between T3 and ALP (p=0.031). No significant associations were found between T4 and any of the liver enzymes. **Conclusions:** A significant proportion of hyperthyroid patients showed abnormal LFTs, indicating a relationship between thyroid dysfunction and hepatic involvement. Further large-scale studies are recommended.

INTRODUCTION

Excessive secretion and release of thyroid hormones from the thyroid gland, leading to abnormally elevated blood levels, is called hyperthyroidism [1]. The hypothalamus produces thyroid-releasing hormone, which stimulates the pituitary gland to produce thyroid-stimulating hormone (TSH). This, in turn, stimulates the thyroid gland to produce thyroxine (T4) and triiodothyronine (T3). Increased thyroid hormone secretion inhibits the hypothalamus and pituitary from releasing thyroid-releasing hormone and TSH, respectively [2]. T3 is the biologically active thyroid hormone that binds to thyroid hormone receptors (TR), whereas T4 is a prohormone that must be transformed into T3 before signaling and biological activity can occur [3]. Excess thyroid hormone accelerates the body's metabolic processes, producing clinical manifestations such as tachycardia, weight loss, heat intolerance, muscle weakness, tremors, and sleep disturbances [4]. Beyond these systemic effects, hyperthyroidism also has profound implications for liver physiology and pathology. The liver is a crucial organ responsible for numerous functions related

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to metabolism, digestion, detoxification, storage, and the regulation of vital substances. It plays a dual role in thyroid physiology: it metabolizes thyroid hormones through glucuronidation, sulfation, and iodination [5], and at the same time, hepatic metabolic functions are dependent on adequate thyroid hormone levels. This bidirectional relationship makes the liver particularly vulnerable to thyroid dysfunction. In hyperthyroidism, excessive thyroid hormone increases basal metabolic rate and hepatic oxygen consumption, predisposing the perivenular regions of the liver to relative hypoxia and subsequent injury [6]. Other mechanisms include direct hepatotoxicity from hepatocyte anoxia, oxidative stress and free radical damage, breakdown of hepatic glycogen and proteins, and autoimmune-mediated liver injury. Furthermore, several studies indicate that excess T3 induces hepatocyte apoptosis through mitochondria-dependent pathways and activates death receptor-mediated signaling, thereby exacerbating liver dysfunction [7]. Recent evidence highlights that thyroid dysfunction not only alters liver enzyme patterns but may also contribute to the progression of chronic liver diseases and influence treatment outcomes [8]. However, data from local populations remain scarce, underscoring the need for region-specific studies to better understand the clinical significance of these biochemical alterations. The novelty of this study lies in its focus on a local patient population, where limited data are available regarding the biochemical alterations in hyperthyroidism. By characterizing these changes in liver enzyme patterns, the study provides region-specific evidence that may contribute to improved diagnostic evaluation and clinical management strategies.

Despite established evidence linking hyperthyroidism with alterations in liver function, data from local populations remain limited. Most existing studies are either conducted in other countries or focus on chronic thyroid disorders, with insufficient evaluation of newly diagnosed hyperthyroid patients. This lack of region-specific data makes it challenging to understand the true extent of hepatic involvement in hyperthyroidism in Pakistan, highlighting the need for targeted investigations. This study aims to ascertain the level of liver function tests in the serum of patients with hyperthyroidism and to investigate the relationship between liver damage and hyperthyroidism.

METHODS

This cross-sectional study was conducted over six months from 28 July 2023 to 28 January 2024 at the Endocrinology OPD of Gulab Devi Hospital. Ethical clearance was obtained from the Institutional Review Board (Ref. No. GPMI/AHS/IRB 15623), ensuring participant confidentiality and the right to withdraw without consequence. Informed consent was obtained in writing from all participants after explaining the procedure, purpose, risks, and benefits of the study. This study included a sample size of 100 people. 3ml serum of hyperthyroid patients was collected and processed for LFTs in the Pathology lab of Gulab Devi Hospital, Lahore. The sample size was calculated by using Cochran's formula [9].

$$n = \frac{Z^2 \frac{\alpha}{2} pq}{\rho^2}$$

n =sample size, P = prevalence, z = confidence, q = 1-p, ρ = margin of error. For this study, P was set at 55%, based on previous literature reporting that approximately 55% of hyperthyroid patients exhibit liver enzyme abnormalities. The margin of error (ρ) was set at 6%, with a 95% confidence interval. Using these values, the calculated sample size was approximately 264 participants. Due to the six-month duration of the study, during which informed consent, ethical approval, and patient data were collected, the sample size was limited to 100. This was influenced by the restricted availability of patients meeting the inclusion and exclusion criteria, as well as constraints in resources and time. Patients aged between 18-60 years of both genders, diagnosed with hyperthyroidism, were included. Patients below 18 or above 60 years of age, those with a history of alcoholism, chronic liver disease, and those with known hepatitis were excluded. The demographic data, such as age, gender, and marital status, were collected through a questionnaire and verified against hospital records. Blood samples (3 ml) were drawn from each patient to evaluate both liver function tests (LFTs) and thyroid hormone levels (TSH, T3, and T4). The analyses were performed using standard biochemical assays on the Micro Lab 400 instrument, which operates on the principle of spectrophotometry, at the Chemical Pathology Laboratory of Gulab Devi Hospital, Lahore. The reference (cut-off) values used to classify enzyme and hormone levels as high, normal, or low were as follows: ALT: 0–42 U/L, AST: 0–45 U/L, ALP: 44–147 U/L, total bilirubin: 0.1–1.1 mg/dL, total protein: 6.5–8.3 g/dL, TSH: 0.4–4.0 mIU/L, T3: 80–200 ng/dL, and T4: 5.0–12.0 µg/dL (10). These cut-off values were applied to categorize patient results and assess associations with thyroid hormone levels using Chi-square tests with significance at a p-value of <0.050 and descriptive statistics such as mean, median, mode, and standard deviation. The Chi-square test was chosen because it is appropriate for assessing the association between categorical variables, such as thyroid hormone levels and liver function test categories. Qualitative data was presented in the form of charts, and quantitative data was presented in the form of tables and graphs. All collected data were statistically analysed by using SPSS version 26.0.

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RESULTS

Out of 100 cases, 41% (n=41) were male and 59% (n=59) were female. A total of 21% (n=21) were aged 34–40 years. The mean age was 38.5 ± 10.2 years (range: 18–60 years). Most patients were married (87%, n = 87). The mean height was 5.51 ± 0.39 ft, and the mean weight was 66.39 ± 14.67 kg. The mean systolic blood pressure was 126.05 ± 14.9 mmHg, and the mean diastolic blood pressure was 90.14 ± 10.79 mmHg. A family history of hyperthyroidism was present in 25% (n=25), while 39% had a history of hypertension. The biochemical parameters were as follows: mean TSH 13.35 ± 6.02 mIU/L, mean T3 152.92 ± 40.26 ng/dL, mean T4 23.6 ± 10.60 µg/dL, mean AST 43.37 ± 35.68 U/L, mean ALP 127.70 ± 40.37 U/L, mean ALT 59.37 ± 45.00 U/L, mean total bilirubin 0.70 ± 0.30 mg/dL, and mean total protein 7.9 ± 0.8 g/dL (Table 1).

Table 1: Demographic, Clinical, and Biochemical Characteristics of Patients

Characteristics	Mean ± SD	Median	Mode
Age	38.5 ± 10.2	40	40
Height	5.51 ± 0.39	5.50	5.00
Weight	66.39 ± 14.67	65	60
Systolic BP	126.05 ± 14.9	120	120
Diastolic BP	90.14 ± 10.79	90	90
TSH	13.35 ± 6.02	11.5	10
T3	152.92 ± 40.26	111.6	94
T4	23.6 ± 10.60	10.7	7
AST	43.37 ± 35.68	25	18
ALP	127.70 ± 40.37	92	90
ALT	59.37 ± 45.00	28	27
Bilirubin	0.70 ± 0.3	0.60	0.50
Total Protein	7.9 ± 0.8	7.20	7.50

By applying the chi-square (χ^2) test between T3 and LFTs, a significant association was found between T3 and ALP (p=0.031). No significant associations were observed with ALT, AST, bilirubin, or total protein (p>0.050) (Table 2).

Table 2: Cross-tabulation of Tri-iodothyronine (T3) with LFTs

T3					χ^2	p-Value	Cramer's V
Parameters	Category	>180 (High)	<180 (Normal)	<60 (Low)			
AST	>45 (High)	3	8	2	2.334	0.311*	0.153
	<45 (Normal)	23	60	4			
ALP	>147 (High)	13	12	2	10.363	0.031*	0.231
	<147 (Normal)	13	54	4			
	<44 (Low)	0	2	0			
ALT	>42 (High)	9	15	3	3.218	0.200*	0.179
	<42 (Normal)	17	53	3			
Bilirubin	>1.1 (High)	4	7	2	3.182	0.528	0.165
	<1.1 (Normal)	22	60	4			
Total Protein	>8.3 (High)	2	9	0	1.376	0.502	0.117
	<8.3 (Normal)	24	59	6			

When the chi-square test was applied between TSH and LFTs, significant associations were observed with ALT (p=0.028) and AST (p=0.017). No significant associations were found with ALP, bilirubin, or total protein (p>0.050) (Table 3).

Table 3: Cross-Tabulation of Thyroid-Stimulating Hormone (TSH) With LFTs

Parameters		TSH			χ^2	p-Value	Cramer's V
		High	Normal	Low			
ALT	High	4	5	18	7.160	0.028*	0.268
	Normal	2	7	64			
AST	High	3	2	8	8.168	0.017*	0.286
	Normal	3	10	74			
ALP	High	2	3	22	0.591	0.964	0.054
	Normal	4	9	58			
	Low	0	0	2			
Bilirubin	High	2	2	9	2.812	0.590	0.119
	Normal	4	10	72			
	Low	0	0	1			
Total Protein	High	1	2	8	7.20	0.698	0.085
	Low	5	10	74			

No significant associations were observed between T4 and any LFT parameters (p>0.050). For parameters with small cell counts, ALP and bilirubin low categories (n=1–2), Fisher's exact test was applied instead of the chi-square test to ensure valid statistical inference

DISCUSSION

Thyroxine and triiodothyronine regulate hepatocyte metabolic rate and are required for appropriate organ growth, development, and function. In contrast, the liver is responsible for thyroid hormone metabolism and regulates its systemic effects [11]. The pituitary, heart, liver, and brain are all impacted by thyroid hormones T4, T3, and TSH [12]. In current study, we took 100 diagnosed hyperthyroid patients to check the association of elevated liver enzymes with hyperthyroidism. This study found significant associations between elevated TSH/T3 and liver enzymes ALT, AST, and ALP. In particular, the significant

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associations between TSH and ALT/AST may reflect the pathophysiological effect of thyroid dysfunction on hepatocellular metabolism. Excess thyroid hormones can increase hepatic oxygen demand, leading to oxidative stress and hepatocyte injury, which is commonly reflected in elevated transaminases [13]. While Hsieh *et al.* and Zhang *et al.* also observed a significant association between thyroid hormones and liver enzymes, their studies involved different patient populations and methodological approaches. Hsieh *et al.* focused on long-term thyroid dysfunction, whereas our study specifically examined newly diagnosed hyperthyroid patients. Similarly, Zhang *et al.* emphasized broader biochemical correlations, while we concentrated on liver enzyme elevation as a direct marker of hepatic involvement [14, 15]. At a biochemical level, hyperthyroidism may accelerate basal metabolic rate, contributing to increased oxygen consumption and oxidative stress in hepatocytes. This oxidative burden, together with altered lipid and carbohydrate metabolism, may play a role in liver cell stress and enzyme release [16]. Moreover, thyroid hormones influence bile acid synthesis and clearance, and their imbalance might impair bile flow, which could contribute to hepatocellular injury [17]. This link illustrates that thyroid diseases, including hypothyroidism and hyperthyroidism, are associated with alterations in liver function, potentially through raised metabolic rate and changes in liver enzyme activity. Such changes may be reflected in increased liver enzyme levels, suggesting possible liver involvement [18]. Interestingly, T3 was significantly associated with ALP, while TSH was not. This may be explained by the fact that T3 is the biologically active hormone directly influencing bone and hepatic enzyme regulation, whereas TSH acts indirectly through stimulation of the thyroid gland. Therefore, ALP elevations in hyperthyroidism may be more directly linked to circulating T3 levels than to TSH [19]. No correlation was observed between T4 and liver enzymes in our study. This may be because T4 is a prohormone requiring conversion to T3 to exert biological activity [20]. Furthermore, the relatively small sample size and categorization thresholds used could have reduced the statistical power to detect subtle associations with T4. Contrary to some studies, which showed no significant differences observed in ALT among patients with overt hyperthyroidism. No significant correlation was found between liver enzymes and thyroid profile in any study group [21]. Current research evaluated all possible relationships between abnormal metabolisms of liver metabolism and hyperthyroidism. This study assessed abnormal liver enzyme activity in relation to thyroid dysfunction in 100 people. Associations between thyroid profile and ALT/AST were significant, while no significant associations were found with Bilirubin, ALP, or Total Protein, which may be more indicative of chronic changes. This study used a non-probability sampling method, which may have introduced some bias and limited the generalizability of the results to the wider population. However, this approach was chosen due to constraints of time and resources, and strict adherence to methodological protocols and carefully applied inclusion and exclusion criteria were implemented, ensuring that the selected participants were representative of the study objectives.

This study was limited by a relatively small sample size and the use of non-probability sampling, which may affect the generalizability of results. Future research with larger, multicenter cohorts is needed to validate these findings and explore longitudinal changes in liver function among hyperthyroid patients. Additionally, mechanistic studies could further elucidate the pathways linking thyroid hormones to hepatic dysfunction.

CONCLUSIONS

In this study, significant associations were observed between elevated TSH and ALT/AST, and between T3 and ALP. These findings suggest that hyperthyroidism may be linked to selective liver enzyme abnormalities. Regular monitoring of liver function, particularly ALT, AST, and ALP, could help in early identification and management of potential hepatic involvement in hyperthyroid patients.

Authors' Contribution

Conceptualization: FJ, ARK
Methodology: FJ, ARK, HKS, MS, IA
Formal analysis: FJ, ARK, AR, MS
Writing and Drafting: FJ, ARK, HKS, AR, IA
Review and Editing: FJ, ARK, HKS, AR, IA, MS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Alveolar Bone Dimensions in Orthodontic Unilateral Impacted Canine Cases using Cone Beam Computed Tomography

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ABSTRACT

Impacted canines are due to missing laterals, crowding, or genetics. The alveolar bone that acts as a shock absorber distributes the masticatory forces to the underlying tissues. **Objectives:** To study the mean alveolar bone dimensions on the impaction and non-impaction side of Orthodontic unilateral impacted canine cases using CBCT. **Methods:** This descriptive cross-sectional research was organized at the Department of Orthodontics, CMH Lahore Medical College, where 165 patients were enrolled as per the selection criteria. Bucco-palatal width of the alveolar bone was measured at the level of the alveolar crest, while alveolar bone height was calculated from the alveolar crest to the nasal floor, on the impacted side. These were compared with corresponding alveolar bone dimensions on the non-impaction side, and the values were recorded. An independent samples t-test was used to find out whether any significant difference was present, and post-stratification. A p-value<0.050 was considered significant. **Results:** The mean age of the patients was 34.99 ± 14.69 years. There were 77 (46.7%) male and 88 (53.3%) female. On the impacted side, the mean width of alveolar bone was 6.58 ± 0.67 mm, and the mean height was 17.28 ± 0.67 mm. On the non-impacted side, the mean width and height of alveolar bone were 8.40 ± 0.96 mm and 19.01 ± 0.96 mm, respectively (p=0.001). **Conclusions:** The mean width and height of the alveolar bone on the impacted canine side were lower than the respective alveolar bone dimensions on the non-impacted side.

INTRODUCTION

Maxillary permanent canines are located at the angle of the mouth. They have a major role in maintaining the harmony and symmetry of occlusal relationships and facial aesthetics. Canines not only support facial muscles and lips but also have an important role, acting as guideposts in occlusion. The increased overbite of canines relieves premolars and molars from the exaggerated and adverse masticatory forces that occur during lateral excursive movements of the mandible [1]. Canine impaction is reported to occur in 3.5% of the population [2]. They are the second most commonly impacted teeth after wisdom teeth and are found twice as frequently in female as in male (2:1). Palatal canine impactions are two to three times more prevalent compared to buccal impactions (3:1) [3]. The most common reason for buccal canine impactions is a narrow maxillary arch or insufficient space. Whereas the genetic and guidance theories are the primary two hypothesis that have been put forth to explain the etiology of palatally displaced canines. According to the genetic theory, the primary cause of palatal canine impactions is

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genetic in origin. Guidance theory states that the root of the lateral incisors serves as a guide, and the canines emerge along its roots. Canine impaction may occur when the lateral incisor root is missing or malformed [4, 5]. Canine impactions may result in complications, including external or internal root resorption of the impacted and adjacent teeth [6], cyst formation, pain, infection, malpositioning of adjacent teeth resulting in loss of arch perimeter [3, 5], and reduction of alveolar bone dimensions [7, 8]. The alveolar bone provides anchorage to Sharpey's fibers, serving as shock absorbers, thus distributing the forces of mastication to the underlying tissues. Alveolar bone also supports the lips and skin around the mouth. Therefore, loss of alveolar bone may result in wrinkling of skin and lips around the mouth and loosening of adjacent and opposing teeth. Loss of alveolar bone is much more critical than apical root resorption for the remaining area of periodontal support. During the initial stages of root resorption and alveolar bone loss, 3mm apical root resorption is equivalent to 1mm crestal bone loss. Following bone loss of more than 2mm, 1mm of crestal bone loss is equivalent to 2mm of apical root resorption [9]. The center of resistance of teeth is also altered after bone loss, thus altering the forces required for the orthodontic movement. Thus, it is very important to make a timely diagnosis and treatment plan for canine impactions to prevent any irreversible harm to the involved teeth and the adjacent teeth. Diagnosis of impacted teeth can be confirmed via panoramic or periapical radiographs, but these techniques have their own shortcomings as they represent a 2-dimensional image of a 3-dimensional object. In addition to that, palatally displaced canines are often situated at the most curved part of the palate. Thus, it is difficult to avoid any distortion in radiographs in this area. To overcome these limitations, dentists have started using CBCT as it not only shows a 3-dimensional image of the impacted tooth and its precise location, but also the status of roots of adjacent teeth and the dimensions of alveolar bone [10]. According to a study conducted by Aditya Tadinada [8], the bucco-palatal width on the impacted side was 6.87 ± 1.08 mm, while on the non-impacted side, it was 8.70 ± 1.13mm. Alveolar bone height was 18.12 ± 2.28 mm and 19.49 ± 2.8 mm on the impacted and non-impacted side, respectively. This study has not been done in the Pakistani population in recent years. This study helps orthodontists in planning multidisciplinary treatment of impacted canines, improve arch symmetry, and prevent irreversible damage to impacted teeth, as well as neighboring teeth and alveolar bone.

Despite the critical role of alveolar bone in supporting teeth and facilitating orthodontic movement, recent data on alveolar bone dimensions in patients with unilateral impacted canines are limited, especially in the Pakistani population. Most prior studies either focused on small sample sizes or lacked comprehensive evaluation of both bucco-palatal width and vertical height. This gap hinders precise treatment planning and the prediction of potential complications, highlighting the need for updated, population-specific measurements. This study aims to measure the dimensions of the alveolar bone both in vertical and horizontal directions on the impaction and non-impaction side of the same patient using CBCT.

METHODS

This descriptive cross-sectional research was undertaken for six months, spanning from January 2022 to June 2022. The research protocol was approved by the Ethical Review Committee of the Institute of Dentistry, CMH Lahore Medical College (Case#.441/ERC/CMH/LMC). Participants provided informed consent to participate in this study. A total of 165 CBCT scans of patients with unilateral maxillary canine impactions, who were willing to undergo comprehensive orthodontic treatment, were evaluated. The sampling technique was a non-probability, consecutive sampling type. Sample size was calculated by the Open Epi sample size calculator, taking the mean alveolar bone height on the impacted side as 18.12 ± 2.38 mm [8], mean alveolar bone height on the non-impacted side as 19.49 ± 2.09 mm [8] and power of test as 80%. The calculated sample size was 84 (42 in each) at 95% confidence interval. To compensate for potential dropouts or image exclusions due to quality issues, the sample size was increased to 165. Impaction was characterized when the tooth failed to erupt after complete root formation or when the contralateral canine was fully erupted. Inclusion criteria were: 1-Patient with a palatally impacted canine in which the deciduous maxillary canine is not retained on the side of the canine impaction. 2- Full eruption of the canine on the other side. 3- No previous orthodontic treatment. 4- Patients 12-60 years old, both genders. Exclusion criteria involved: 1- CBCT scans showing any pathology. 2- Any systemic bone disease. 3- Craniofacial syndromes. The CBCT images were taken from a Promax 3D CBCT machine (Planmeca, Finland) with Romexis software. The CBCT scans were taken with orthodontic patients in the upright position, with the Frankfort horizontal plane parallel to the floor in maximum interdigitation. For the analysis of canine impaction cases, the CBCT images were saved as digital imaging and communications in medicine (DICOM) using Planmeca Romexis viewer 4.6.0.R CBCT software. Bucco-palatal width and height of alveolar bone were measured on the impaction side, and it was compared with alveolar bone dimensions on the non-impaction side. The first step involved panoramic reconstruction from CBCT. Then, two reference lines were drawn to orient researchers and

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calibrate measurements. The reference line A was drawn tangent to the crest of the alveolar bone in the panoramic reconstruction retrieved from the CBCT scan. The Reference line B was drawn perpendicular to reference line A, representing the ideal location of the long axis of the canine. The height of the alveolar bone was recorded as a distance from the nasal floor to the alveolar crest (reference line A). Alveolar Bone Width was recorded as the bucco-palatal distance of the alveolar crest, in millimetres, on a scale provided by CBCT.

To minimize measurement bias, reference line A (tangent to the alveolar crest) was standardized by visually identifying the consistently highest points of the crest (buccal and palatal) in the region of interest and drawing the line precisely tangent to them. Reference line B (perpendicular to A, representing ideal canine axis) was standardized by drawing it perpendicular (90 degrees using software tools) to reference line A, forming a consistent anatomical reference point (estimated center of the alveolar crest) within the impacted canine's expected position. The Planmeca Romexis software's calibrated scale was used for direct measurements, with reference lines guiding consistent measurement locations. This systematic approach aimed to ensure reliable and valid comparisons across all CBCT scans. Data analysis was performed by IBM SPSS Statistics version 27.0. Normality was checked by the Kolmogorov-Smirnov test. Mean ± standard deviation and median (1st quartile-3rd quartile) were presented for quantitative variables. Frequency and percentages were reported for qualitative variables. Since the data were not normally distributed, the independent sample t-test was not applicable. We utilized its non-parametric alternative. Hence, comparison of quantitative variables was done by the Mann-Whitney U test and the Wilcoxon signed-rank as appropriate. The p-values≤0.050 were considered significant.

RESULTS

The current study included 165 patients, of whom 53.3% were female. The median age of patients was 33(22-47) years, ranging from 12 years to 60 years. There were 72.7% of patients aged up to 45 years and 27.3% over 45 years. Among 165 patients, the left side was involved in 52.7% and the right side in 47.3% of patients. Whereas 47.3% were found with buccal and 52.7% with palatal sites. Detailed descriptive statistics of patient demographics and side and site are in table 1.

Table 1: Demographic and Clinical Profile of Study Participants (n=165)

Variables	Frequency (%)
Gender	
Male	77 (46.7%)
Female	88 (53.3%)
Age (Years)	
Median(Q1-Q3)	33 (22-47%)
Age Group	
≤45 Years	120 (72.7%)
>45 Years	45 (27.3%)
Site	
Buccal	78 (47.3%)
Palatal	87 (52.7%)

The median alveolar bone width at the impacted and non-impacted sides was 6.60 (6.00-7.20) mm and 8.40 (7.60-9.20) mm, respectively, while the median alveolar bone height at the impacted and non-impacted sides was 17.30 (16.70-17.90) mm and 19.00 (18.20-19.80), as shown in Table 2 (Figures 1 and 2).

Table 2: Descriptive Statistics for Alveolar Bone Width and Height

Variables	Min to Max	Mean ± SD	Median (Q1-Q3)
Alveolar Bone Width-Impacted Side (mm)	5.5 to 7.7	6.58 ± 0.67	6.60 (6.00-7.20)
Alveolar Bone Height-Impacted Side (mm)	16.2 to 18.4	17.28 ± 0.67	17.30 (16.70-17.90)
Alveolar Bone Width-Non Impacted Side (mm)	6.8 to 10.1	8.41 ± 0.96	8.40 (7.60-9.20)
Alveolar Bone Height Non Impacted Side (mm)	17.4 to 20.7	19.01 ± 0.96	19.00 (18.20-19.80)

Study discovered a significant difference in alveolar bone width-impacted side by gender (p=0.045). The findings provide a detailed comparison of alveolar bone width and height on the impacted and non-impacted sides (Table 3).

Table 3: Comparison of Alveolar Bone Width in Impacted and Non-Impacted Sides

Variables	Alveolar Bone Width (mm) Impacted Side			Alveolar Bone Width (mm) Non-Impacted Side		
	Mean ± SD	Median (Q1-Q3)	p-Value	Mean ± SD	Median (Q1-Q3)	p-Value
Gender						
Male	6.68 ± 0.63	6.70 (6.20-7.20)	0.045*	8.45 ± 0.97	8.50 (7.60-9.30)	0.543
Female	6.74 ± 0.69	6.40 (5.90-7.07)		8.36 ± 0.96	8.30 (7.50-9.17)	
Age Group						
≤45 Years	6.47 ± 0.64	6.40 (5.90-7.00)	0.572	8.47 ± 1.05	8.65 (7.42-9.40)	0.090
>45 Years	6.85 ± 0.67	7.00 (6.55-7.40)		8.21 ± 0.64	8.10 (7.80-8.60)	
Buccal	6.60 ± 0.70	6.60 (5.97-7.30)	0.001*	8.27 ± 1.01	8.05 (7.40-9.20)	0.120
Palatal	6.55 ± 0.64	6.50 (6.00-7.10)		8.52 ± 0.90	8.60 (7.80-9.30)	

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The Mann-Whitney U test was applied. p-value≤0.050 is considered significant. *Significant at 0.050 levels

The study also found a significant difference in alveolar bone height on the impacted side by gender (p=0.045). The findings provide a detailed comparison of alveolar bone width and height on the impacted and non-impacted sides (Table 4).

Table 4: Comparison of Alveolar Bone Height in Impacted and Non-Impacted Sides

Variables	Alveolar Bone Height Impacted Side			Alveolar Bone Height Non-Impacted Side		
	Mean ± SD	Median (IQR)	p-Value	Mean ± SD	Median (IQR)	p-Value
Gender						
Male	17.38 ± 0.63	17.40 (16.90-17.90)	0.045*	19.05 ± 0.97	19.10 (18.20-19.90)	0.543
Female	17.17±0.69	17.10 (16.60-17.77)		18.96 ± 0.96	18.90 (18.10-19.77)	
Age Group						
≤45 Years	17.17 ± 0.64	17.10 (16.60-17.70)	0.572	19.07 ± 1.05	19.25 (18.02-20.00)	0.090
>45 Years	17.55 ± 0.67	17.70 (17.25-18.10)		18.81 ± 0.64	18.70 (18.40-19.20)	

The Mann-Whitney U test was applied. p-value≤0.050 is considered significant. *Significant at 0.050 levels

Further findings show substantial differences in alveolar bone width and height between impacted and non-impacted sides (p<0.001) (Table 5).

Table 5: Comparison of Alveolar Bone Width and Height According to the Impacted and Non-Impacted Side

Variables	Mean ± SD	Median (Q1-Q3)	p-Value
Alveolar Bone Width-Impacted Side	6.58 ± 0.67	6.60 (6.00-7.20)	<0.001*
Alveolar Bone Width-Non-impacted Side	8.41 ± 0.96	8.40 (7.60-9.20)	
Alveolar Bone Height-Impacted Side	17.28 ± 0.67	17.30 (16.70-17.90)	<0.001*
Alveolar Bone Height-Non-impacted Side	19.01 ± 0.96	19.00 (18.20-19.80)	

The Wilcoxon signed-rank test was applied. p-value≤0.050 is considered as significant. *Significant at 0.050 levels

DISCUSSION

Canines are regarded as key elements of the upper and lower dental arches due to their vital role in establishing precise occlusion. However, canine impaction can affect the height and width of the alveolar bone, as the alveolar process develops in response to tooth eruption. Consequently, any deviation from normal tooth development and eruption necessitates careful examination [11]. Therefore, it is of crucial importance that timely diagnosis and treatment of impacted canines is made to avoid irreversible injury to the canine itself and its adjacent teeth. The purpose of our study was to examine the height and width of the alveolar bone on the affected and non-affected sides to understand the mechanical environment. This study helps orthodontists to plan and formulate a treatment plan that is minimally invasive and of decreased cost and treatment time. Timely intervention also decreases the psychological trauma to the patient. As CBCT has already been acknowledged as accurate in determining certain parameters, so it was used to investigate unilaterally impacted canine cases, whether buccal or palatal. CBCT investigations were also done to measure skeletal and dento-alveolar parameters of the maxilla [12]. The diagnostic technique preferred for the identification of tooth impaction is CBCT [13]. In comparison to any two-dimensional radiograph, it eliminates errors resulting from overlapping of structures, superimpositions, and blurring of images. Hence, we selected CBCT as the favored system for the evaluation of bone height and width due to its accuracy in assessing bone morphology and structure [14, 15]. Few studies were performed with the same approach, but they did not contain all the variables as in this study. According to our study, the alveolar bone dimensions were reduced on the impaction side with a mean width of alveolar bone of 6.58 ± 0.67 mm and a mean height of 17.28 ± 0.67mm. Whereas, the mean width of alveolar bone was measured 8.40 ± 0.96 mm, and the mean height was 19.01 ± 0.96 mm on the non-impacted side. Our research also revealed that unilateral impactions are more commonly found in female and are found more prevalent on the left side of the maxillary arch. These findings are consistent with those reported by other studies [16]. According to the results of a research by Elhamshary et al. the basal maxillary width in the control group was 63.63 ± 4.60mm, whereas in the unilaterally impacted canine group, the results showed decreased width with a value of 62.04 ± 3.38mm [17]. These results are similar to those found by Sadrhaghighi *et al.* in which alveolar thickness was less on the impacted side than on the non-impacted side when measured at 2mm height. Maxillary arch width was also significantly reduced on the impacted side [7]. Our study also demonstrated similar findings, revealing reduced alveolar bone dimensions on the impacted side compared to the non-impacted side. Another study by Sharhan et al. showed that both maxillary unilateral and bilateral canine impaction are associated with decreased maxillary dimension except arch depth [6]. A study done by Sar *et al.* on basal lateral width, inter-premolar width, and angulation of canines. They found that the mean basal lateral width of the impacted side was significantly reduced (p<0.050). On the impacted side, the inter-premolar width was similarly significantly decreased

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(p<0.050) [18]. More studies also had similar results to our research. A study done by Montes-Díaz *et al.* on unilateral impacted canines showed smaller angular and linear dento-skeletal measurements on the affected side in comparison to the non-affected side [19]. A study by Arvind *et al.* showed increased BMSA (Bone marrow surface area) in female, showing lesser bone density in female as compared to males. Whereas, BSA (Bone surface area) showed no gender variability. Dense alveolar bone microstructure was appreciated around impacted canines when compared to the non-impacted side, in contrast to completely erupted canines [20]. An advantage of the present study over previous ones is that it addressed a greater number of variables and also explored gender associations. The results of the normality test in the analysis showed normal distribution for their population.

However, a limitation of the study was a smaller sample size. Our study also showed a gender association, similar to this study. A significant gender wise difference was found. This might be due to a larger number of participants as compared to Arvind TR *et al.* study. Based on this study's results, early detection and treatment of impacted canines allow alveolar bone to develop properly. It also allows orthodontists to carry out tooth movement more efficiently, producing more aesthetic and efficient results. The positive and negative variation of results as compared to other studies might be due to changes in the research protocols. The sample in our study was collected from a single-center setting. The sample size was larger than that of other studies but was still within a moderate range. So it is suggested that in the future, further studies should be done with improved methodology.

CONCLUSIONS

CBCT imaging shows that the mean width and height of alveolar bone on the impacted canine side were lower than the respective alveolar bone dimensions on the non-impacted side.

Authors' Contribution

Conceptualization: EM
Methodology: EM, AR, MHR, MA, LA
Formal analysis: EM
Writing and Drafting: EM, AR, MHR, MA, LA, FY
Review and Editing: EM, AR, MHR, MA, LA, FY

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Impact of Diabetes on Short-Term Outcomes in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention (PCI)

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ABSTRACT

Diabetes mellitus is a major global health issue, significantly increasing the risk of morbidity and mortality, especially after myocardial infarction. **Objectives:** To assess the impact of diabetes on short-term outcomes in STEMI patients treated with primary PCI. **Methods:** This comparative cross-sectional study enrolled 200 patients undergoing elective coronary angiography at Shahida Islam Medical Complex, Lodhran, using non-probability consecutive sampling. Qualitative variables, such as gender and hypertension, were summarized as frequencies, while quantitative variables, including age, BMI, and HbA1c, were expressed as mean ± standard deviation (SD). Outcomes, including stroke, arrhythmia, renal failure, and mortality, were compared using the Chi-square test, whereas changes in serum creatinine were analyzed with independent t-tests. Statistical significance was set at $p < 0.05$. Data were collected using a structured proforma and analyzed using SPSS version 21.0. The combined effect of categorical variables was calculated and reported as risk ratios with 95% confidence intervals. **Results:** Diabetic patients were older and had a higher prevalence of hypertension, smoking, and prior ischemic heart disease (IHD). They showed significantly worse short-term outcomes, including higher rates of stroke (5.6%, p=0.040), renal failure (11.1%, p=0.020), and mortality (10.0%, p=0.030) compared to non-diabetics. **Conclusions:** There are worse short-term outcomes possibly related to diabetes mellitus in STEMI patients undergoing PCI, particularly for stroke, renal failure, and mortality. These findings highlight the need for aggressive management of diabetic patients presenting with STEMI.

INTRODUCTION

STEMI is a severe type of acute coronary syndrome. Overall, ACS is frequently a medical emergency, with primary percutaneous coronary intervention (PCI) a key treatment. Despite advances in PCI techniques, diabetes mellitus (DM) and poor. Glycaemic management continues to be an important risk factor.to achieve poor results after PCI. Primary PCI has been the preferred revascularization approach in patients with acute STEMI since it can facilitate rapid coronary perfusion and desirable clinical outcomes. However, patients with diabetes who undergo PCI tend to be predisposed to distinct challenges and unfavorable outcomes due to the intricate interplay between diabetes and heart conditions [1]. Diabetes mellitus is a chronic disorder that arises when the pancreas ceases insulin production or the body becomes resistant to the insulin it generates. It is a disease of macromolecule metabolism that impairs the body's capacity to produce or react to insulin, complicating the maintenance of normal blood glucose levels. An endocrine hormone released by the duct gland acts as a key, facilitating the entry of aldohexose from meals into cells for energy synthesis [2]. In the blood, all macromolecule meals are converted into aldohexose. endocrine aids aldohexose's cellular uptake. Sugar is transported from the blood into your cells via the endocrine system, where it may be stored or used for energy. Polygenic diseases are characterized by either an

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insufficient production of endocrine or an efficient use of the endocrine that is produced [3]. Damage to nerves, eyes, kidneys, and other organs may occur if polygenic disease-related elevated blood glucose goes untreated. The International Diabetes Federation statistics indicate a global rate of 537 million adults with diabetes in 2021, according to their data [4]. Diabetes was the 9th leading cause of death globally in 2020, killing over 2 million people annually as a direct consequence of diabetes and because of kidney disease [5]. Regional studies have shown that diabetes is a major determinant of PCI outcomes, with higher rates of adverse events. Additionally, global practices regarding the choice of vascular access sites differ significantly for diabetic patients [6]. The top five causes of death in the world include being overweight or obese, high blood pressure, smoking, high sugar levels, and lack of exercise. The rising population of obesity, the decrease in physical activity levels, and the ageing population are leading to the prevalence of diabetes mellitus. The prevalence of adult diabetes mellitus will increase to 4.4% in 2030 as compared to 2.8% in 2000 [5]. Not only that, but most cases would originate from the US, China, and India by 2030. Mortality and morbidity rates are greater among diabetics due to the increased risk of myocardial infarction, which is 2-4 times higher in this population. Men with diabetes have a fourfold increased risk, whereas women with the disease have an eightfold increased risk [7]. Globally, it is estimated that 415 million individuals have diabetes, with 91% of these cases being T2D, as reported by the IDF. The IDF forecasts 642 million additional diabetes cases by 2040, increasing the current worldwide prevalence to 2.8% [8]. The risk of atherosclerosis-related cardiovascular disorders, such as acute myocardial infarction (MI), is typically two times higher in those with DM [9]. Consequently, it is not uncommon for individuals with STEMI to also have DM. Only 17.5% of STEMI patients in our group had ever had diabetes. This number is in agreement with what other registries have found. Variables defined and the population of the study play a great role in the reported frequencies. As an illustration, based on recent data, the Polish Registry of Acute Coronary Syndromes (PL-ACS) identified 28.4% of the patients with acute coronary syndromes (ACS) to have diabetes [10]. This is significantly higher than the outcome that we reported in our research, since the ORPKI registry has not been gathering information about DM on cases diagnosed during hospital stays. Additionally, there are possibilities that the incidence of DM among STEMI patients is lower as compared to the entire group of patients with the diagnosis of ACS [11]. The total number of patients with STEMI who had PCI decreased in tandem with the number of individuals diagnosed with DM. Other primary-PCI networks also verified this slow but steady decline in STEMI patients. Several studies have shown that women have a higher increase in cardiovascular risk due to type 2 diabetes compared to males. Patients' prognoses after STEMI have been greatly improved by recent advancements in primary percutaneous coronary intervention (PPCI). Myocardial revascularisation and therapy have come a long way, but patients with DM and ACS still have a much greater death rate, particularly among women, than those without DM. Clinical trials seldom investigate variations in the progression of MI in individuals with diabetes mellitus, even though this population accounts for a sizable fraction of STEMI patients. Type 2 diabetes was identified in 5,346 (20.5%) STEMI patients, with a significantly greater prevalence in females (28% vs. 16.6%; P<0.001) compared to males. Among persons with DM, the proportion of females was higher (47.1% vs. 31.3%; P<0.001) than in those without the illness. Severe coronary atherosclerosis was significantly associated with the onset of type 2 diabetes. Ibanez *et al.* (2018) discovered that women with STEMI and type 2 diabetes had a markedly elevated risk of mortality both during hospitalization and within one year [12]. Major adverse cardiovascular events (MACE) occur at a much higher rate in diabetes individuals with diabetes compared to non-diabetic people when they present with STEMI. One possible link between the poorer prognosis in DM patients and prognostic indicators such as infarct size and the amount of reperfusion damage following PCI has been proposed. Enzymatic techniques or single-photon emission computed tomography were the major tools utilized in recent research to evaluate infarct size in both diabetic and non-diabetic individuals. Infarct size in diabetic individuals is comparable to or smaller in most of these investigations [13].

Despite advances in primary PCI, diabetic patients with STEMI continue to experience higher rates of adverse short-term outcomes, including stroke, renal failure, and mortality. Most regional studies are limited by small sample sizes or focus on single outcomes, and there is a lack of comprehensive data on multiple short-term complications in diabetic STEMI patients undergoing PCI in Pakistan. This study aims to address this gap by evaluating the impact of diabetes on a range of in-hospital outcomes. This study aimed to assess the impact of diabetes on short-term outcomes in STEMI patients treated with primary PCI.

METHODS

This comparative cross-sectional study was conducted between August 2024 and January 2025 at the Shahida Islam Medical Complex in Lodhran. Ethical approval (Ref. No. SIMC/ET.C/0042/24) was obtained from the institutional review board of the Shahida Islam Medical

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Complex in Lodhran. The study included 200 STEMI patients aged 40–70 years who underwent primary PCI, selected through non-probability consecutive sampling after providing written informed consent. Patients with steroid use or outside the age range were excluded. Participants were divided into Group A (diabetic) and Group B (non-diabetic). Data on demographic characteristics (age, sex, height, weight, BMI), risk factors (smoking, hypertension, diabetes, previous ischemic heart disease), laboratory parameters (HbA1c, fasting blood sugar, lipid profile, serum creatinine), and in-hospital outcomes (stroke, arrhythmia, renal failure, mortality) were collected using a structured proforma. Quantitative variables were expressed as mean ± standard deviation, median, and interquartile ranges, while qualitative variables were presented as frequencies and percentages. Group comparisons were performed using an independent sample t-test for quantitative variables and a chi-square test for qualitative outcomes, with p-values <0.050 considered statistically significant. Data were collected using a structured proforma and analyzed using SPSS version 21.0. The combined effect of categorical variables was calculated and reported as risk ratios with 95% confidence intervals.

RESULTS

The mean age diabetic 58.3 ± 8.4 and non-diabetic patients was 55.1 ± 9.2 years with statistically significant p-value 0.032, weight(kg), BMI (kg/m2), Serum Creatinine (mg/dL), HbA1c, fasting blood sugar (mg/dL) and LDL (mg/dL) showed statistically significant p-value as <0.050 except male gender and height(cm) were showed insignificant as p-value 0.540 and 0.078 respectively (Table 1).

Table 1: Comparison of Demographic Variables with respect to Research Groups

Variables	Diabetic (n=90)	Non-Diabetic (n=110)	p-Value
Age (years)	58.3 ± 8.4	55.1 ± 9.2	0.032
Male Gender, n (%)	60 (66.7%)	78 (70.9%)	0.540
Height (cm)	165.2 ± 7.1	167.4 ± 6.9	0.078
Weight (kg)	75.5 ± 11.0	71.3 ± 9.8	0.045
BMI (kg/m^2)	27.6 ± 3.5	25.4 ± 2.9	0.022
Serum Creatinine (mg/dL)	1.3 ± 0.4	1.1 ± 0.3	0.015
HbA1c (%)	8.2 ± 1.1	5.4 ± 0.5	<0.001
Fasting Blood Sugar (mg/dL)	142 ± 38	96 ± 14	<0.001
LDL (mg/dL)	120 ± 25	112 ± 22	0.054

*Cronbach's alpha for data reliability: 0.068

The smoker patients in diabetic groups 43(53.30%) compared with non-diabetic 55 (50%), with a statistically insignificant 0.0680. Hypertensive 72 (80%) and previous IHD was 30 (33.3%) with a significant difference between both groups as p-value 0.001 and 0.006, respectively (Table 2).

Table 2: Comparison Of Risk Factors with Respect to Research Groups

Characteristics	Diabetic (n=90)	Non-Diabetic (n=110)	p-Value
Smoking	48 (53.3%)	55 (50%)	0.680
Hypertension	72 (80%)	60 (54.5%)	0.001
Previous IHD	30 (33.3%)	18 (16.4%)	0.006

The stroke 5 (5.6%), renal failure 10 (11.1%), and mortality 9 (10%) showed statistically significant difference between diabetic and non-diabetic patients as p-value<0.050, while arrhythmia observed among both groups was insignificant, with a p-value of 0.080 (Table 3).

Table 3: Comparison of Outcomes Concerning Research Groups

Outcome	Diabetic (n=90)	Non-Diabetic (n=110)	p-Value
Stroke	5 (5.6%)	1 (0.9%)	0.040
Arrhythmia	12 (13.3%)	7 (6.4%)	0.080
Renal Failure	10 (11.1%)	3 (2.7%)	0.020
Mortality	9 (10%)	3 (2.7%)	0.030

Diabetic patients showed a higher risk of several adverse outcomes compared to non-diabetics. The risk of hypertension was 1.47 times higher in diabetics, indicating they were 47% more likely to have hypertension. Similarly, diabetics had a twofold increased likelihood of a prior history of ischemic heart disease (RR 2.03). Post-PCI, the risk of renal failure was over four times higher in diabetics (RR 4.07), and mortality was nearly four times higher (RR 3.67). The risk of stroke was also elevated (RR 6.11), although the wide confidence interval (0.73–51.11) reflects uncertainty due to the low number of events. While not statistically significant, there was a trend toward increased arrhythmia in diabetics (RR 2.10, p = 0.080). No notable difference was observed between groups for smoking (RR 1.07) (Table 4).

Table 4: Risk Analysis of Outcomes and Co-Morbidities

Characteristic/ Outcome	Diabetic (n=90)	Non-Diabetic (n=110)	Risk Ratio (RR)	95% Confidence Interval (CI)	p-Value
Hypertension	72 (80.0%)	60 (54.5%)	1.47	1.21 to 1.78	0.001
Previous IHD	30 (33.3%)	18 (16.4%)	2.03	1.21 to 3.42	0.006
Smoking	48 (53.3%)	55 (50.0%)	1.07	0.82 to 1.38	0.680
Short-Term Outcomes					
Stroke	5 (5.6%)	1 (0.9%)	6.11	0.73 to 51.11	0.040
Renal Failure	10 (11.1%)	3 (2.7%)	4.07	1.17 to 14.18	0.020
Mortality	9 (10.0%)	3 (2.7%)	3.67	1.03 to 13.04	0.030
Arrhythmia	12 (13.3%)	7 (6.4%)	2.19	0.86 to 5.11	0.080

DISCUSSION

Diabetes mellitus (DM) can result in a prothrombotic state, accompanied by platelet hypersensitivity, hypofibrinolysis, and coagulation disorders [14]. The present study findings reported a significant adverse impact of diabetes on in-hospital outcomes post-PCI. Diabetic patients exhibited a

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higher-risk profile, with significantly greater prevalence of hypertension (80% vs 54.5%) and prior ischemic heart disease, consistent with findings from other regional studies [15, 16]. Consistent with Karayiannides *et al.* diabetic patients were older, had higher BMI, and elevated serum creatinine, reflecting greater metabolic dysfunction and renal vulnerability. Previous studies have similarly reported higher prevalence of prior MI, PCI, multivessel disease, and lower rates of complete revascularization in diabetic STEMI patients [17]. Earlier research reported advanced age and renal impairment among diabetic STEMI patients undergoing PCI, highlighting their contribution to poorer myocardial reperfusion outcomes. Hypertension and prior ischemic heart disease were significantly more common among diabetics, corroborating the ISACS-TC Registry (2021), which emphasized the higher cardiovascular comorbidity burden in this population [19]. Stroke occurred in 5.6% of diabetics versus 0.9% of non-diabetics, indicating a six-fold increased risk, while arrhythmia rates were higher in diabetics but not statistically significant. Earlier researchers reported cerebrovascular risks in ACS patients with diabetes due to endothelial dysfunction, hypercoagulability, and proinflammatory states. Autonomic imbalance and ischemia-related myocardial scar may also explain increased arrhythmic events [20]. Renal failure was significantly more frequent in diabetics, likely reflecting baseline nephropathy and susceptibility to contrast-induced nephropathy, in line with earlier findings [21]. Mortality was notably higher in diabetics, consistent with the FAST-MI Registry 2021, which identified diabetes as a major predictor of 30-day mortality due to impaired myocardial healing, reduced collateral circulation, and systemic inflammation [22]. Follow-up studies also show a high occurrence of arrhythmias in STEMI patients regardless of diabetic status [23]. Risk ratio analysis further confirmed that diabetes significantly increases the likelihood of adverse short-term outcomes, particularly mortality, renal failure, and stroke, with risks more than tripled or quadrupled. These results mirror findings from Punjab-based and Rawalpindi registries, highlighting diabetes as a strong independent predictor of in-hospital complications, including cerebrovascular events and renal failure [23, 24]. Trends toward higher arrhythmia rates in diabetics, although not statistically significant, align with other regional studies [25]. This study reinforces that diabetes mellitus remains a significant predictor of adverse cardiovascular outcomes in STEMI patients undergoing primary PCI, even with modern interventional strategies. Overall, these findings underscore the urgent need for optimized management of diabetic patients with coronary artery disease in Pakistan. Enhanced preventive strategies, rigorous control of cardiovascular risk factors, and careful periprocedural management during PCI are essential to improve outcomes in this high-risk population. This study's strengths include its prospective comparative design and comprehensive analysis of multiple short-term outcomes.

However, limitations include the single-center scope, moderate sample size, and lack of long-term follow-up. Additionally, we did not assess medication adherence, glycemic control before admission, or procedural metrics, which could influence outcomes.

CONCLUSIONS

Diabetes mellitus significantly worsens the short-term prognosis of STEMI patients undergoing primary PCI, as evidenced by increased rates of stroke, renal failure, and in-hospital mortality. These findings highlight the importance of strict glycemic control before and after the procedure, proactive measures to preserve renal function such as hydration protocols and low-contrast techniques, vigilant neurological monitoring, and individualized pharmacotherapy and rehabilitation programs to optimize patient recovery and reduce complications.

Authors' Contribution

Conceptualization: HMM
Methodology: HMM, SEG
Formal analysis: HMM, ZI
Writing and Drafting: HMM, ZI
Review and Editing: HMM, ZI, SEG

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Assessment of Maxillary Premolar Root Position Within the Alveolar Bone Using Cone Beam Computed Tomography

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ABSTRACT

The location of maxillary premolars with respect to the alveolar bone and maxillary sinus is critical for treatments like extractions and implantation. CBCT imaging provides extensive information on root placement, sinus proximity, and buccal bone dimensions, enabling proper diagnosis and treatment planning. **Objectives:** To assess the position of the maxillary premolars' roots within the alveolar apparatus and their relationship to the maxillary sinus using cone-beam computed tomography. **Methods:** This is a cross-sectional descriptive study that included CBCT images of 105 patients with 411 maxillary premolars were viewed retrospectively over a period of six months. After obtaining permission from the institutional ethical review committee, each pair of premolars was observed on either side of the mouth. Each exhibited a distinct association between its root tip and the sinus floor, categorized into four different types. The roots were also variable in the alveolar housing and were either buccal, middle, or palatally placed with varying dimensions of buccal bone. **Results:** In our study, the majority of maxillary first premolars had roots positioned away from the sinus floor, with root angulation predominantly directed toward the buccal side. In contrast, most second premolars exhibited roots located close to or extending into the sinus floor, with their roots generally positioned centrally within the alveolar bone. **Conclusions:** Maxillary first premolars are mostly buccally placed with thinner associated buccal bone, whereas second premolars are more affected by sinus proximity during implant insertion operations. Given these specific anatomical obstacles, CBCT imaging is recommended for accurate diagnosis and effective implant design.

INTRODUCTION

Knowledge of the root position of any tooth within the alveolar housing is an important diagnostic parameter before instituting any treatment in the oral cavity [1]. The maxillary premolars, in particular, pose a clinical challenge during surgical procedures owing to their complex and variable root anatomy [2]. They also serve as transitional teeth as we go from anterior incisors to maxillary molars and, therefore, are often in close relation to the sinus in the maxilla [3]. The apposition of maxillary premolars to the floor of the maxillary sinus must be carefully assessed before performing any surgical procedures involving these teeth. Roots that are protruding or close to the maxillary sinus may increase the risk of perforation of the sinus membrane or facilitate the entry of foreign material into the cavity of the sinus. Implant placement in such situations requires maxillary sinus augmentation through a crestal approach or open surgery [4, 5]. Another important factor while placing dental implants is the buccal bone thickness, which is detrimental to both implant stability and esthetic outcome [6]. Chronic tooth loss results in

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alveolar bone resorption, where the buccal aspect demonstrates a more prominent presentation than the palatal [1, 6]. The subsequent thin buccal plate is more prone to fracture and results in fenestration or dehiscence-type defects that often require bone augmentation [7]. Buccal bone thickness is also important while instituting endodontic therapy, as a thin buccal bone at the apex can facilitate sinus tract formation [1]. Therefore, it is equally essential to determine how these teeth are positioned within the alveolar bone. For pre-surgical assessment of implant sites in the oral cavity, cone-beam computed tomography proves extremely beneficial [8]. While numerous studies have been conducted to evaluate the root position of maxillary posterior teeth relative to the maxillary sinus floor, limited data are available to precisely describe this relation in a specific ethnic population [9]. Although the anatomical relationships of premolars to the alveolar bone and maxillary sinus are well-documented in the literature, data specific to South Asian populations remain limited. This study addresses this gap and contributes population-specific insights.

While numerous studies have been conducted to evaluate the root position of maxillary posterior teeth relative to the maxillary sinus floor, limited data are available to precisely describe this relation in a specific ethnic population [9]. Although the anatomical relationships of premolars to the alveolar bone and maxillary sinus are well-documented in the literature, data specific to South Asian populations remain limited. Addressing this gap is essential to improve surgical planning, minimize complications, and optimize implant outcomes in this demographic.This study aimed to investigate how maxillary premolars relate to the sinus floor, their spatial location within the alveolus, and the subsequent proportions of the buccal bone in a selected Pakistani demographic.

METHODS

This cross-sectional descriptive study was conducted in the Department of Periodontology and Implantology at Lahore Medical and Dental College, Lahore, over six months (March–August 2024), after approval from the institutional review committee (Ref. No. LMDC: FD/5102/24). A total of 107 patients who had undergone CBCT examination for various reasons during the past five years (2020–2024) were included using the convenience non-probability sampling technique, and sample size was calculated using the WHO sample calculator formula with a 95% confidence interval, expected prevalence of 50% (p = 0.5), and precision of ±10% (d = 0.10). The final cohort consisted of 105 patients with a total of 411 premolars, and each participant had given consent for the use of their data for academic purposes. Inclusion criteria were patients aged 20–70 years who had undergone CBCT examination and had at least one premolar, while exclusion criteria included severe alveolar bone loss secondary to periodontal disease, periapical and sinus pathologies, history of orthodontic therapy, compromised image quality, artifacts, or prior surgical procedures. CBCT scans were performed using the Dentsply Sirona Galileo Comfort Plus machine at 90 kV, 12 mA, 16 seconds, with a voxel size of 150 µm and a field of view of 11 cm × 10 cm, and the obtained 2D images were processed into 3D models in Galileo software and viewed using Galaxis Galileos viewer. Each CBCT image was evaluated in a cross-sectional view to assess both maxillary premolars, their relationship with the maxillary sinus, root location in the alveolus, and buccal bone thickness. A single trained examiner recorded the sinus relationship according to Jung YH et al.'s classification [1] categorized as Type 0: root separate from sinus floor; Type 1: close contact between root and sinus floor; Type 2: sinus floor lying below the root apex without protrusion; and Type 3: root apex extending into the maxillary sinus cavity (Figure 1).

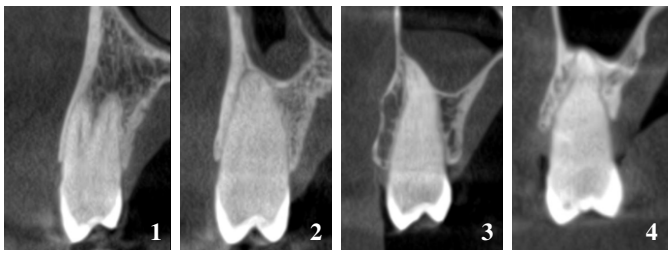

Figure 1: Classification of root–sinus relationship

The root position within the alveolar housing was also categorized according to Jung YH et al. [1], with Type A: buccal (root tip in the buccal third), Type B: middle (root tip centrally positioned), and Type C: palatal (root tip in the palatal third of the alveolar bone)(Figure 2).

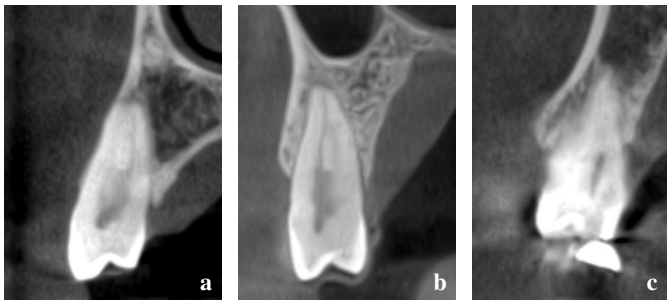

Figure 2: Classification of Root Position of Premolars in the Alveolar Bone

Buccal bone thickness was measured at two points, 1 mm below the alveolar crest and at the root apex, with a value of 0.00 assigned in cases of dehiscence/fenestration or bone thickness <0.1 mm (Figure 3).

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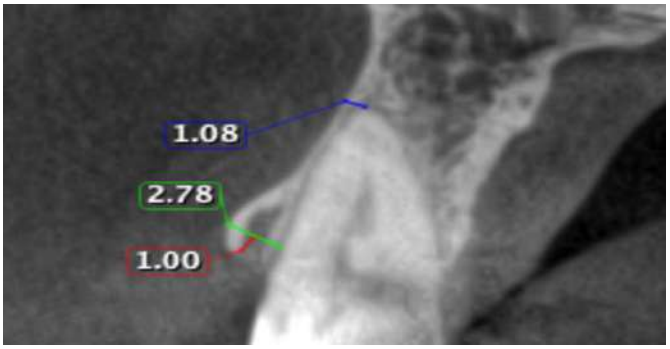

Figure 3: Measurements Taken at the Bone Crest (1mm Below) and at the Root Apex

A second trained examiner cross-checked all measurements, and discrepancies resulted in exclusion; thus, two patients were excluded, leaving 105 for analysis. Inter-examiner reliability was assessed on 20 cases, with an ICC of 0.89 for continuous data (good agreement) and Cohen's Kappa of 0.76 for categorical data (substantial agreement). The data were examined with SPSS version 22, which used descriptive statistics to categorize findings by age and gender. Correlation, Chi-square, and Games-Howell post-hoc tests were used, with p-values less than 0.05 indicating statistical significance.

RESULTS

In the present study, both CBCT imaging and the spatial relationship between maxillary premolars and maxillary sinus were used to assess the spatial relationship in this study. A total of 411 premolars were analyzed, had 206 first premolars and 205 second premolars (Table 1).

Table 1: Classification of Maxillary Premolars Based on Root–Sinus Relationship

Relationship with the sinus	First Premolar	Second Premolar
Type 0	171 (81.4%)	64 (30.5%)
Type 1	33 (15.7%)	93 (44.3%)
Type 2	2 (1%)	14 (6.7%)
Type 3	0 (0)	34 (16.2%)
Total	206	205

Most first premolars (Type A, 85%) were buccal in terms of their root position within the alveolar bone, whereas second premolars were most frequently centrally positioned (Type B, 50.5%). Palatal position (Type C) was rare in both premolar groups (Table 2).

Table 2: Localization of Maxillary Premolar Roots in the Alveolar Bone

Root Position	First Premolar	Second Premolar
A (Buccal)	179 (85%)	94 (44.8%)
B (Central)	22 (10.5%)	106 (50.5%)
C (Palatal)	5 (2.4%)	5 (2.4%)
Total	206	205

There were no statistically significant differences in first premolars when examining the relationship between root position and sinus relationship ($P > 0.050$). However, in second premolars, a significant association was observed ($P < 0.050$): Type 0 was mainly buccal (A), while Types 1, 2, and 3 were predominantly central (B) (Table 3).

Table 3: Association Between Root Positions of Maxillary Premolars and Their Sinus Relationship

Category	A	B	C	Total	p-Value
First Premolar					
Type 0	151 (88.3%)	16 (9.4%)	4 (2.3%)	171	0.183
Type 1	26 (78.8%)	6 (18.2%)	1 (3.0%)	33	
Type 2	2 (100%)	0 (0%)	0 (0%)	2	
Type 3	–	–	–	–	
Subtotal	179 (86.9%)	22 (10.5%)	5 (2.4%)	206	
Second Premolar					
Type 0	41 (64.1%)	19 (29.7%)	4 (6.2%)	64	0.001
Type 1	36 (38.7%)	56 (60.2%)	1 (1.1%)	93	
Type 2	3 (21.4%)	11 (78.6%)	0 (0%)	14	
Type 3	14 (41.2%)	20 (58.8%)	0 (0%)	34	
Subtotal	94 (44.8%)	106 (50.5%)	5 (2.4%)	205	

In terms of buccal bone thickness, first premolars consistently showed thinner bone than second premolars, particularly at the crest and apex. Buccally positioned roots (Type A) exhibited the thinnest dimensions compared with centrally or palatally placed roots (Table 4).

Table 4: Relationship Between Root Position and Buccal Bone Thickness in Maxillary Premolars

Root Position	First Premolar (1 mm below crest)	Second Premolar (1 mm below crest)	First Premolar (apex)	Second Premolar (apex)
A	0.74 ± 0.51	0.99 ± 0.66	0.64 ± 0.64	1.01 ± 0.67
B	1.76 ± 0.89	1.91 ± 0.91	2.30 ± 1.12	2.31 ± 1.10
C	2.30 ± 1.29	2.16 ± 1.07	1.42 ± 1.32	4.28 ± 2.55

When stratified by sinus relationship, premolars with Type 0 connection exhibited the thinnest buccal bone at the root apex. At the alveolar crest, most first premolars had <1 mm bone thickness, while second premolars exceeded 1 mm. The difference in buccal bone thickness at the apex between first and second premolars was statistically significant ($P<0.050$) (Table 5).

Table 5: Buccal Bone Thickness of Maxillary Premolars Based on Sinus Relationship

Relation with sinus	First Premolar (1 mm below crest)	Second Premolar (1 mm below crest)	p-Value	First Premolar (apex)	Second Premolar (apex)	p-Value
Type 0	0.88 ± 0.71	1.46 ± 0.99	0.065	0.84 ± 0.89	1.85 ± 1.59	0.037
Type 1	0.88 ± 0.69	1.58 ± 0.88		0.79 ± 0.84	1.80 ± 1.03	
Type 2	1.18 ± 0.01	2.09 ± 1.12		1.84 ± 0.35	1.93 ± 1.11	
Type 3	–	1.33 ± 0.77		–	1.44 ± 1.03	

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DISCUSSION

Gaining insight into the spatial relationship between the sinus and premolar roots is essential for clinicians, as it plays a critical role in the successful planning and execution of periapical surgeries, implant placements, and surgical endodontic treatments involving these teeth. Accurate knowledge of this anatomy helps minimize surgical risks and improve treatment outcomes [10]. The relationship between the maxillary posterior teeth and the maxillary sinus has been studied in several previous research works [11, 12]. However, little research has explored this relation in the maxillary premolars [1]. This study focused on studying these parameters in a specific ethnic population. In our study, most maxillary first premolars (81.4%) were Type 0, positioned away from the maxillary sinus, and none presented with a Type 3 relationship (protruding into the sinus). This finding coincides with previously reported data [13]. Moreover, in this study, the second premolars were mostly (44.3%) Type 1 with roots in contact with the sinus. A considerable amount of second premolar roots (16.2%) was also found to be Type 3 (protruding into the sinus), consistent with other CBCT-based studies [14]. The sagittal root position of teeth involved is an important factor to be addressed when planning and locating the dental implants in the maxillary premolar area [2]. This anatomical aspect is important in the realization of the ideal implant position and prevention of the complications caused by the involvement of cortical bone or sinuosity. In the current study, the proportion of first premolars that assumed a buccal position (which is Type A in the sagittal classification) was shown to be significant (around 85 percent). The second premolars, conversely, were most often found centrally in the alveolar housing, thus being Type B. These are in line with the data that have been published before [15]. Interestingly, Type C positioning, in which the apex of the root is placed nearer to the palatal cortical plate, was relatively fewer in the first and the second premolars. In our analysis, this arrangement was noted in very few, 2.4% of the analyzed premolars, which is not very common as compared to Types A and B. Lastly, the buccal bone thickness is another important factor to be considered during implant placement [8]. The alveolar bone undergoes significant remodeling after tooth extraction, and the resulting dimensional change is determined by the pre-extraction buccal bone thickness [16]. Teeth with a buccal bone thickness of less than 1 mm are more prone to vertical ridge resorption, posing a challenge to implant placement [17]. Several authors have studied this dimension in their previous studies [18-20]. We also examined buccal bone thickness at two levels: 1 mm below the alveolar crest and at the root apex. In the maxillary premolars, the first premolars demonstrated a thinner buccal plate compared with the second premolars, a finding consistent with previous work [21]. This difference reached statistical significance at the 1 mm subcrestal level ($p<0.05$), indicating a higher risk area for implant placement due to limited cortical support. At the apical level, bone dimensions are comparable in deeper regions between the two sites, with no statistically significant difference.

This study was limited by its cross-sectional design and a single-center sample, which may restrict generalizability. Future research could involve multicenter studies with larger sample sizes and explore three-dimensional bone quality assessments to further refine implant planning and enhance clinical outcomes for maxillary premolar treatments.

CONCLUSIONS

Maxillary premolars differ in position and bone structure: first premolars have thinner buccal bone and are more prone to post-extraction resorption, while second premolars more often protrude into the sinus. Careful CBCT assessment is recommended for treatment planning, with consideration given to bone grafting and a two-stage implant approach when necessary.

Authors' Contribution

Conceptualization: MUK
Methodology: MM, AD
Formal analysis: AD, UM, NK
Writing and Drafting: MM, UM, NAA, NK, MUK
Review and Editing: MM, UM, NAA, NK, MUK, AD

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Outcomes of the Primigravida with Engaged versus Unengaged Fetal Head at Term

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ABSTRACT

Engagement of the fetal head within the pelvis is an important clinical indicator during pregnancy. Such evaluation guides obstetric decision-making and optimizes maternal and neonatal care. **Objectives:** To compare the frequency of outcomes in primigravida women with engaged and unengaged fetal heads at term. **Methods:** This prospective cohort study was carried out in the Department of Obstetrics and Gynecology, Khyber Teaching Hospital, Peshawar, from January 2025 to June 2025. A total of 126 primigravida women were recruited. Data were analyzed using SPSS version 22.0, and relative risk (RR) was calculated for both groups. **Results:** Among the 126 participants, the mean maternal age was 28.71 ± 6.80 years (range: 18–42 years). The mean birth weight in the engaged group was 3.07 kg. A significant association was observed between fetal head engagement and delivery mode. The unengaged group showed a markedly higher cesarean section rate (63%) compared with the engaged group (21%), with a relative risk of 2.93. **Conclusions:** Primigravida women with unengaged fetal heads at term had a significantly greater likelihood of cesarean delivery compared with those with engaged heads.

INTRODUCTION

In several of the most close-ended case studies, head engagement has been associated with labor induction among most women, especially primigravidae who are more likely to experience complications (e.g, Labor dystocia) during labor because they do not possess experience birthing [1]. Fetal head engagement is when the biparietal diameter of the fetal skull descends into the pelvic inlet of the mothers. It is clinically significant in indicating that the pelvis is adequate for vaginal delivery. Labor begins with a series of progressive changes, including cervical dilation, thinning of the cervix, coordinated uterine contractions, and the descent of the fetal head. A key feature of this process is engagement, which occurs when the biparietal diameter of the fetal head successfully enters the pelvic inlet. In primigravida women, engagement is generally observed around the 38th week of pregnancy, though it may take place anytime between 38–42 weeks or during the active phase of the first stage of labor [2]. Traditionally, one had the idea in obstetrics that head engagement before term is an essential prerequisite for vaginal delivery in primigravidas. According to recent articles and clinical observation, it is common for fetal heads to not engage at term, while there may still exist an opportunity for vaginal delivery [3]. Nonetheless, its absence remains an extremely important clinical red flag, particularly in low-resource settings, as it may indicate

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cephalopelvic disproportion (CPD), malposition, or mechanical obstruction caused by the placenta or uterine anomalies [4, 5]. In these cases, the chances of encountering an urgent labour with fetal distress or cesarean delivery are extremely high. Labor in primigravida women tends to be more challenging than in multiparas, as the uterus is less efficient, with relatively hypotonic contractions, which leads to a prolonged latent or first stage of labor [6]. Dystocia, defined as difficult or abnormal labor, is frequently encountered in primigravidas, affecting nearly 37% of them, and is a leading indication for cesarean section [7, 8]. Labor abnormalities in general account for approximately 20% of obstetric complications [9]. In the context of Pakistan, where the maternal mortality ratio remains high (276 per 100,000 live births), understanding preventable causes of labor complications such as prolonged latent phase, obstructed labor, and unnecessary cesarean sections is imperative [10]. Monitoring fetal head engagement as shown in Figure 1, during antenatal visits and at the onset of labor, is a simple yet effective tool to predict labor outcomes, especially in primigravida women, who are inherently at higher risk due to their physiological and psychological inexperience [11]. Several studies have identified a significant association between unengaged fetal heads and operative deliveries. Earlier studies found that fetal head station at the onset of labor directly influences labor outcomes, with higher rates of cesarean observed in unengaged cases [12-14]. The risk of sepsis, perinatal asphyxia, and maternal exhaustion also increases when labor is prolonged due to fetal non-engagement [15]. Previous researchers highlighted that the engaged fetal head is associated with shorter labor duration and higher spontaneous vaginal delivery (SVD) rates [12, 16]. Dall'Asta et al. emphasized the predictive value of intrapartum ultrasound in estimating successful vaginal delivery in nulliparous women during the second stage of labor [17], while Ludvigsen et al. reported that head station at full cervical dilation significantly impacts second-stage duration [3]. These findings reinforce the clinical utility of head station monitoring at various labor stages. This research fills a severe knowledge gap in the literature by offering local evidence of the role of fetal head engagement in influencing labor outcomes in primigravida women in their term in the Pakistani context. There has been no previous research on the fetomaternal implications of fetal head engagement in this particular cohort, especially in an area with a heterogeneous ethnic and socio-economic make-up. Moreover, the difference in local obstetric care practices also creates the need to conduct region-specific studies to be in a better position to inform the labor management strategies. Through the target population of the Khyber Pakhtunkhwa, the proposed study will serve an important gap in knowledge as well as provide valuable information on how primigravida women can be managed during term. The results will prove priceless to clinicians and policymakers in improving maternal and fetal care, minimizing unnecessary cesarean deliveries, and enhancing labor outcomes in our local setting.

Despite the recognized importance of fetal head engagement in predicting labor outcomes, there is limited local data assessing its direct impact on delivery mode among primigravida women in Pakistan. Most existing studies are conducted in high-resource settings, with different obstetric practices and demographic characteristics, leaving a gap in evidence relevant to our population. This lack of context-specific data makes it challenging to develop tailored labor management strategies for primigravidas in low-resource settings. This study aims to compare the frequency of outcomes in primigravida with engaged versus unengaged fetal head at term.

METHODS

This prospective cohort study was conducted in the Department of Obstetrics and Gynecology, Khyber Teaching Hospital, Peshawar, over six months (January to June 2025), following synopsis approval. Ethical clearance was obtained from the Khyber Medical College, Peshawar (Ref. No: 611/DME/KMC), and written informed consent was taken from all participants. A total of 126 primigravida women, aged 18–40 years with term singleton pregnancies, were enrolled through non-probability purposive sampling. The required sample size was calculated using WHO software, with parameters set at a 95% confidence level, a 5% margin of error, and an expected NICU admission frequency of 9% [18]. Participants were classified into two groups according to abdominal examination findings on admission. Group A included 80 women with an engaged fetal head (≤2/5 of the head palpable per abdomen), whereas Group B comprised 46 women with an unengaged head (5/5 of the head palpable above the pelvic brim relative to the ischial spines). To ensure consistency, all examinations were carried out by senior postgraduate residents using a uniform protocol, verified by a consultant obstetrician, and confirmed by ultrasonography to validate inter-observer agreement. Women with macrosomia (estimated fetal weight >4 kg), skeletal abnormalities, non-cephalic presentations, intrauterine growth restriction (IUGR), placenta previa, multiple gestations, intrauterine fetal demise, prior uterine surgery, or evidence of fetal distress on cardiotocography (CTG) were excluded. Baseline variables such as maternal age, weight, gestational age, height, and BMI were recorded, along with fetal weight and labor duration. Participants were observed

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until delivery. Cesarean section under spinal anesthesia was performed if there was failure to progress, fetal distress, or abnormal CTG; otherwise, spontaneous vaginal delivery (SVD) was allowed. Data collection was carried out using a structured proforma, and analysis was performed with SPSS version 22.0. Continuous variables such as age, BMI, and labor duration were summarized using mean and standard deviation, whereas categorical variables like mode of delivery were presented as frequencies and percentages. To examine the relationship between fetal head engagement and cesarean delivery, 2×2 contingency tables were applied, and relative risk (RR) was calculated. An RR greater than 1 was interpreted as indicating a clinically meaningful increase in risk. Additional analyses were conducted by stratifying the data according to maternal age, fetal weight, gestational age, BMI, and duration of labor, with RR values recalculated within each subgroup to assess the likelihood of cesarean delivery.

RESULTS

The study included 126 primigravida women aged 18–40 years; 80 had engaged and 46 unengaged heads. Mean age was 28.7 years, with no significant age difference between groups (p=0.412).

Table 1: Comparison of Engaged and Unengaged Groups

Variables	Group	N	Mean ± SD	p-Value
Gestational Age (weeks)	Engaged	80	38.9 ± 1.10	0.049
	Unengaged	46	39.3 ± 1.4	0.049
BMI (kg/m^2)	Engaged	80	22.8 ± 3.20	0.065
	Unengaged	46	21.60 ± 2.9	0.065
Fetal Weight (kg)	Engaged	80	3.1 ± 0.45	0. 031
	Unengaged	46	2.95 ± 0.42	0.031
Duration of Labor (hrs)	Engaged	80	10.2 ± 1.5	0.048
	Unengaged	46	10.8 ± 1.4	0.048

The mode of delivery showed a statistically significant association with fetal head engagement. Women in the Unengaged group had a substantially higher rate of cesarean section compared to the Engaged group (p-value < 0.001)(Table 2).

Table 2: The Mode of Delivery for Engaged and Unengaged

Group	Engaged (N=80)	Unengaged (N=46)	Total (N=126)	p-Value	RR (95% CI)
C-Section	17 (21.3%)	29 (63.0%)	46 (36.5%)	<0.001	2.93
SVD	63 (78.7%)	17 (37.0%)	80 (63.5%)	–	–
Total	80 (100%)	46 (100%)	126 (100%)	–	–

When analyzing the mode of delivery by age stratification, cesarean rates were notably higher in younger women. Among women aged ≤25 years, 17 (73.9%) in the Unengaged group underwent cesarean section compared to 4 (16.7%) in the Engaged group. This suggests that younger age may be associated with an increased likelihood of cesarean section in unengaged cases, with a significant relative risk. When delivery outcomes were analyzed in relation to gestational age and length of labor, a statistically significant association was observed across both groups, except among women with gestational age < 39 weeks, where the difference was not statistically significant. Cesarean rates increased substantially with advancing gestational age, especially in the unengaged group, where 91.3% of women with gestational age >40 weeks underwent cesarean section, compared to only 4.2% in the engaged group (Table 3).

Table 3: Stratifications of Delivery Throughout Labour and Gestational Age, Fetal Weight, and BMI

Variables	Engaged (N=80)	Unengaged (N=46)	p-Value	RR (95% CI)
Duration of Labor (Hours)				
<10	52 (65%)	22 (48%)	0.028	2.8
>10	28 (35%)	24 (52%)	<0.001	3.5 (1.7, 7.3)
Mode of Delivery (<10 hours)				
C-section	11 (21.2%)	16 (72.7%)	–	–
SVD	41 (78.8%)	6 (27.3%)	–	–
Mode of Delivery (>10 hours)				
C-section	6 (21.4%)	14 (58.3%)	–	–
SVD	22 (78.6%)	10 (41.7%)	–	–
Gestational Age (weeks)				
<39 weeks: C-section	16 (30.2%)	10 (43.5%)	–	–
<39 weeks: SVD	37 (69.8%)	13 (56.5%)	–	–
>40 weeks: C-section	1 (3.7%)	21 (91.3%)	–	–
>40 weeks: SVD	26 (96.3%)	2 (8.7%)	–	–
Fetal Weight (kg)				
<2.5	10 (12.5%)	8 (17.4%)	0.014	NA
>2.5	70 (87.5%)	38 (82.6%)	0.002	2.6 (1.4, 4.8)
Mode of Delivery by Fetal Weight				
<2.5 kg: C-section	0 (0%)	4 (50%)	–	–
<2.5 kg: SVD	10 (100%)	4 (50%)	–	–
>2.5 kg: C-section	17 (24.3%)	27 (71%)	–	–
>2.5 kg: SVD	53 (75.7%)	11 (29%)	–	–
BMI (kg/m^2)				
<25	66 (82.5%)	43 (93.5%)	–	2.85
>25	14 (17.5%)	3 (6.5%)	0.245	3.3 (0.9, 11.9)
Mode of Delivery by BMI				
<25: C-section	13 (19.7%)	28 (65.1%)	–	–
<25: SVD	53 (80.3%)	15 (34.9%)	–	–
>25: C-section	4 (28.6%)	2 (66.7%)	–	–
>25: SVD	10 (71.4%)	1 (33.3%)	–	–
<39 weeks: C-section	16 (32.0%)	10 (43.5%)	–	–
<39 weeks: SVD	37 (69.8%)	13 (56.5%)	–	–
39–40 weeks C-section	3 (10.0%)	4 (30.8%)	–	–
39–40 weeks SVD	27 (90.0%	9 (69.2%)	–	–
>40 weeks: C-section	1 (4.2%)	21 (91.3%)	–	–
>40 weeks: SVD	23 (95.82%)	2 (8.7%)	–	–

Similarly, labor duration played a critical role. In women with labor lasting more than 10 hours, the cesarean rate

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was significantly higher in the unengaged group (58.3%) compared to the engaged group (21.4%), indicating that prolonged labor is associated with increased surgical intervention, particularly in cases with unengaged fetal heads. Fetal weight also influenced delivery outcomes. Women with fetal weight greater than 2.5 kg had a markedly higher likelihood of cesarean section, especially in the unengaged group (71%) compared to the engaged group (24.3%). This reflects that fetal macrosomia, in the absence of engagement, increases the risk of surgical delivery. Likewise, BMI >25 kg/m^2 was associated with increased cesarean rates in both groups. In the unengaged group, 66.7% of women with higher BMI underwent cesarean section compared to 28.6% in the engaged group. Although the sample size in the higher BMI category was smaller, the trend suggests that maternal weight and fetal size are important predictors of delivery outcomes. These findings collectively highlight that fetal head engagement, labor duration, gestational age, fetal weight, and maternal BMI are all significant contributors to the mode of delivery in primigravida women at term.

DISCUSSION

In primigravida women, fetal head engagement typically occurs by 38 weeks of gestation, with the majority achieving full engagement either before or during the first stage of labor, particularly between 38 and 42 weeks [17]. A persistently high fetal head position near term may indicate cephalopelvic disproportion (CPD) or mechanical obstruction, such as placental location, both of which are associated with abnormal labor progression [3, 18]. Delayed engagement at the onset of active labor has been correlated with an increased risk of cesarean delivery [19]. In our study, labor duration exceeded in more than half of the women, with a higher proportion of prolonged labor in the Unengaged group. Prolonged labor in unengaged women was associated with maladaptation of the presenting part, high station at onset, deflexed fetal head, early rupture of membranes, misalignment of uterine contractions, and ineffective uterine activity. The mode of delivery showed a marked difference between groups, with women in the Engaged group having a significantly lower cesarean section rate compared to the Unengaged group. In our cohort, cesarean sections in the Engaged group were primarily due to poor progress of labor and fetal distress, while in the Unengaged group, the most common indication remained fetal distress. The observed mean fetal birth weight was 3.07 kg in the Engaged group, consistent with prior studies reporting averages of 3.0–3.2 kg [7]. Our findings of a higher proportion of prolonged labor in the Unengaged group support earlier evidence that primigravidas with unengaged heads experience longer latent and active phases of labor [20]. Contributing factors for prolonged labor in unengaged women, such as maladaptation of the presenting part, high station at onset, and deflexed fetal head, align with mechanisms proposed in previous studies. The lower cesarean section rate in the Engaged group is also consistent with prior research [21, 22]. The Unengaged group had a cesarean rate of 64.4%, higher than rates reported in other studies, possibly due to higher rates of induction or augmentation and differences in institutional surgical protocols [23]. This study underscores the importance of individualized labor management protocols in low-resource settings like Pakistan, where maternal mortality remains high. Regular training of healthcare providers in accurate abdominal examination and labor monitoring, combined with patient education and preparedness, can improve fetomaternal outcomes. Further multi-centered studies with larger cohorts and real-time intrapartum monitoring (e.g., ultrasound-based assessments) are recommended to validate these findings and refine risk stratification protocols for primigravida women with high fetal head stations. Overall, the rate of surgical intervention was significantly higher among primigravida women presenting with an unengaged fetal head at term, highlighting the predictive value of head engagement for labor outcomes.

This study is limited by its single-center design and relatively small sample size, which may affect the generalizability of the findings. Future research should involve multi-center studies with larger cohorts and incorporate real-time intrapartum tools such as ultrasound to assess fetal head engagement dynamically. Such studies could refine risk stratification and improve labor management protocols, ultimately reducing unnecessary cesarean deliveries and enhancing maternal and neonatal outcomes in local settings.

CONCLUSIONS

In conclusion, the likelihood of cesarean delivery is considerably greater among primigravida women presenting with an unengaged fetal head at term. Early identification of fetal head engagement during antenatal visits can help guide labor management and potentially reduce unnecessary cesarean deliveries.

Authors' Contribution

Conceptualization: KAB
Methodology: KAB, SAB, SA
Formal analysis: SAB, SA
Writing and Drafting: NB, SAB, FSP, A, SA
Review and Editing: NB, SAB, FSP, A, SA, KAB

All authors approved the final manuscript and take responsibility for the integrity of the work

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Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Hypokalemia in Children with Acute Watery Diarrhea

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ABSTRACT

Acute watery diarrhea (AWD) remains a major cause of pediatric admissions, and electrolyte disturbances account for much of its morbidity. Hypokalemia is clinically important, yet its relationship with serum chloride is not consistently reported in hospital-based studies. **Objective:** To determine the frequency of hypokalemia among hospitalized children with AWD and examine its association with serum chloride categories and selected demographic and clinical factors. **Methods:** An analytical cross-sectional study was conducted on children aged 6 months to 12 years admitted with AWD. Data on demographics, clinical features, and laboratory parameters (serum potassium, sodium, chloride, bicarbonate, and acid-base status) were collected using a structured proforma. Hypokalemia was defined as serum potassium <3.5 mmol/L. Associations were assessed using the Chi-square test, with effect size reported as Cramér's V. **Results:** A total of 103 children were analyzed. Hypokalemia was present in 58.3% of cases. Serum chloride was the only variable significantly associated with hypokalemia ($\chi^2 = 6.66$, df = 2, p = 0.036; Cramér's V = 0.25). Hypokalemia was most frequent in hypochloremia (77.3%) and least frequent in hyperchloremia (30.0%). No significant associations were observed with age, sex, nutritional status, dehydration, sodium, bicarbonate, or categorical acid-base status. **Conclusions:** Hypokalemia is common in pediatric AWD and is significantly associated with serum chloride categories. Routine electrolyte testing that includes chloride, together with timely potassium correction and fluid planning, is essential to improve outcomes.

INTRODUCTION

Diarrheal disease is a leading cause of morbidity and mortality in children worldwide. According to the World Health Organization (2024), it is the third most common cause of death among children aged 1–59 months, accounting for hundreds of thousands of deaths annually and nearly 1.7 billion episodes of childhood diarrhea each year [1]. Despite improvements in case management, recent global estimates confirm that diarrheal disease remains responsible for more than one million deaths annually across all age groups, with the highest burden in children under five years of age [2]. Inequities in health-system performance also persist. A 2025 national analysis from India demonstrated wide variation in oral rehydration solution (ORS) coverage, underscoring gaps that contribute to preventable dehydration and electrolyte losses [3]. Electrolyte disturbances are among the most serious complications of acute gastroenteritis in children. Hypokalemia, sodium abnormalities, and chloride imbalances contribute to poor outcomes such as arrhythmias, ileus, and prolonged hospitalization. Recent international studies (2023–2025) emphasize that stool electrolyte composition, feeding practices, and fluid

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management play important roles in potassium and chloride balance, with rotavirus-positive cases often showing greater dehydration and more severe biochemical derangements [4-6]. Multi-country surveys from Africa and Asia also report high rates of electrolyte abnormalities in hospitalized children, reinforcing the value of routine laboratory profiling [7]. Evidence from Pakistan mirrors these findings. Single-center studies from Rawalakot and Karachi have reported frequent electrolyte disturbances in pediatric diarrhea, with hypokalemia being the most common abnormality and improving after appropriate rehydration [8]. More recent institutional data from Nowshera and other centers have confirmed that gastroenteritis is strongly linked with electrolyte shifts and renal stress, highlighting the need for proactive monitoring [9, 10]. Further Pakistani studies in 2024–2025 continue to describe specific abnormalities such as hypernatremia in children with gastroenteritis and correlations between electrolyte imbalance and clinical outcomes [11]. Despite this evidence, important gaps remain. Most datasets focus on sodium abnormalities, while chloride categories and their association with potassium status are less frequently analyzed, even though chloride physiology is closely linked with renal and gastrointestinal potassium handling. Moreover, effect sizes are rarely reported in local audits, which limits their clinical application in risk stratification. The aim is to generate evidence that can guide early testing, timely potassium replacement, and more effective fluid management strategies in similar clinical settings.

Despite numerous studies on electrolyte disturbances in pediatric diarrhea, most focus primarily on sodium and general potassium abnormalities, with limited attention to the role of serum chloride. Furthermore, local hospital-based data reporting the strength of association between chloride levels and hypokalemia remain scarce. This gap limits clinicians' ability to predict high-risk children and tailor timely potassium correction and fluid management. Addressing this gap is essential to improve evidence-based care for children with acute watery diarrhea. This study aimed to evaluate the frequency of hypokalemia in hospitalized children with AWD and examines its association with serum chloride categories as well as demographic and clinical factors.

METHODS

This analytical cross-sectional study was conducted in the Pediatric Department of Qazi Hussain Ahmad Medical Complex, Nowshera, for a period of 6 months from March 2025 to August 2025. The objective was to determine the frequency of hypokalemia in children presenting with acute watery diarrhea and to assess its association with demographic, clinical, and biochemical characteristics. Ethical approval was obtained from the Institutional Ethical Review Board of Nowshera Medical College, Nowshera (Ref. No. 511/IERB/NMC), and further approval of the synopsis was granted by the Research Evaluation Unit of the College of Physicians and Surgeons Pakistan (Ref. No. CPSP/REU/PED-2022-305-6858). Written informed consent was obtained from the parents or legal guardians of all participating children and written informed consent was obtained from the parents or legal guardians of all participating children, including those under 1 year of age. The required sample was estimated for a single proportion at 95% confidence using the standard formula $n = (Z^2 \times p \times (1 - p)) / d^2$. Here, Z = 1.96 (for 95% confidence), p=0.50 (maximum variability) [11], and d is the margin of error. Substituting these values gives If d = 0.05 (5%), n=384, If d = 0.07 (7%), n=196, and If d = 0.10 (10%), n=96. A margin of error of 10% to achieve a feasible yet statistically acceptable precision during the 6-month enrollment period, while retaining the conservative choice of p=0.50. The calculated minimum sample size of 96 was further increased to 103 to allow for possible exclusions or incomplete data, which became the final sample. Children aged between 6 months and 12 years who presented with acute watery diarrhea, defined as three or more loose or watery stools within 24 hours lasting not more than 14 days, were included. Exclusion criteria comprised children with persistent diarrhea of more than 14 days, those with chronic systemic illnesses such as renal or endocrine disorders, or those who had already received intravenous potassium supplementation before presentation. Data were collected using a structured proforma, which included demographic variables (age, gender, residence, nutritional status, and immunization history), clinical features (duration and frequency of diarrhea, presence of vomiting, fever, and dehydration status), and laboratory findings (serum potassium, sodium, chloride, bicarbonate, and acid–base status). The proforma used for data collection was pilot-tested on 10 patients to establish content validity, ensuring that all relevant demographic, clinical, and laboratory variables were clearly captured without ambiguity. To maintain reliability, pediatric residents received standardized training before the study began, and all assessments were carried out under the supervision of senior consultants. This process minimized observer variation and enhanced consistency in data recording across participants. Clinical evaluation was performed by trained pediatric residents under consultant supervision, while dehydration was graded as none, some, or severe according to World Health Organization (WHO) criteria. Nutritional status was assessed by anthropometric measurements and categorized as normal, underweight, or stunted/wasted. Blood samples were collected at admission under aseptic precautions and

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immediately transported to the hospital laboratory. Serum electrolytes (potassium, sodium, chloride, and bicarbonate) were analyzed using a Roche Cobas c311 fully automated chemistry analyzer based on ion-selective electrode (ISE) methodology. The analyzer was calibrated daily according to manufacturer guidelines, and two levels of internal quality control sera were run with each batch to ensure precision. Samples showing hemolysis were excluded to avoid spurious potassium values. Acid–base status was determined using an automated blood gas analyzer (ABL800 FLEX, Radiometer, Denmark) on arterial or venous samples, depending on availability. Data were analyzed using SPSS version 26.0. Categorical variables were summarized as frequencies and percentages, while the primary outcome variable was hypokalemia, categorized as present or absent. Associations between hypokalemia and predictor variables were assessed using the Chi-square test (or Fisher's exact test where required), and a p-value <0.050 was considered statistically significant. For significant associations, the effect size was calculated using Cramér's V to quantify the strength of the relationship.

RESULTS

Out of the 103 children included in the study, the majority (55.3%) were between 1 and 5 years of age, followed by infants below 1 year (31.1%), while only 13.6% were older than 5 years. Males represented 57.3% of the cohort, giving a male-to-female ratio of approximately 1.3:1. Rural residents constituted a higher proportion (62.1%) compared to urban children (37.9%). Nutritional assessment revealed that 41.7% of children had normal growth, whereas 32.0% were underweight and 26.2% were classified as stunted or wasted. Regarding immunization status, 65.0% of the children were fully immunized, while 35.0% had either an incomplete or no vaccination history (Table 1).

Table 1: Demographic Characteristics of Children with Acute Watery Diarrhea(n=103)

Variables	Category	Frequency (%)
Age Group	<1 Year	32 (31.1%)
	1–5 Years	57 (55.3%)
	>5 Years	14 (13.6%)
Gender	Male	59 (57.3%)
	Female	44 (42.7%)
Residence	Urban	39 (37.9%)
	Rural	64 (62.1%)
Nutritional Status	Normal	43 (41.7%)
	Underweight	33 (32.0%)
	Stunted/Wasted	27 (26.2%)
Immunization Status	Complete	67 (65.0%)
	Partial/None	36 (35.0%)

Among the 103 children, nearly half (47.6%) had diarrhea lasting 3–7 days, while 38.8% experienced symptoms for less than 3 days, and 13.6% had prolonged illness beyond 7 days. The majority (56.3%) passed stools 5–10 times per day, with 22.3% suffering from severe diarrhea (>10 times daily). Vomiting was reported in 63.1% of cases, and fever was noted in just over half of the children (52.4%). Dehydration assessment showed that 60.2% of children had some dehydration, 25.2% presented with severe dehydration, while only 14.6% had no signs of dehydration (Table 2).

Table 2: Clinical Characteristics of Children with Acute Watery Diarrhea(n=103)

Variables	Category	Frequency (%)
Duration of Diarrhea	<3 Days	40 (38.8%)
	3–7 Days	49 (47.6%)
	>7 Days	14 (13.6%)
Stool Frequency/Day	Mild (<5)	22 (21.4%)
	Moderate (5–10)	58 (56.3%)
	Severe (>10)	23 (22.3%)
Vomiting	Present	65 (63.1%)
	Absent	38 (36.9%)
Fever	Present	54 (52.4%)
	Absent	49 (47.6%)
Dehydration Status	None	15 (14.6%)
	Some	62 (60.2%)
	Severe	26 (25.2%)

More than half of the children (58.3%) demonstrated hypokalemia of varying severity, while only 41.7% had normal potassium levels. Hyponatremia was seen in one-fifth of the cohort (20.4%), with hypernatremia affecting 8.7%, whereas the majority (70.9%) maintained normal sodium values. Chloride levels showed a similar pattern, with 68.9% within the normal range, 21.4% below, and 9.7% above the reference interval. Bicarbonate was normal in 62.1% of cases, but almost one-third (32.0%) exhibited reduced levels suggestive of acidosis, while 5.8% had elevated values (Table 3).

Table 3: Biochemical Characteristics of Children with Acute Watery Diarrhea(n=103)

Variables	Category	Frequency (%)
Serum Potassium	Normal (>3.5 mmol/L)	43 (41.7%)
	Mild (3.0–3.4 mmol/L)	24 (23.3%)
	Moderate (2.5–2.9)	15 (14.6%)
	Severe (<2.5)	21 (20.4%)
Serum Sodium	Normal (135–145)	73 (70.9%)
	Hyponatremia (<135)	21 (20.4%)
	Hypernatremia (>145)	9 (8.7%)
Serum Chloride	Normal (98–107)	71 (68.9%)
	Hypochloremia (<98)	22 (21.4%)
	Hyperchloremia (>107)	10 (9.7%)

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Serum Bicarbonate	Normal (22–28)	64 (62.1%)
	Low (<22)	33 (32.0%)
	High (>28)	6 (5.8%)

In the present study, hypokalemia was observed across all demographic and clinical categories, but most comparisons did not reach statistical significance. Row percentages have been included in study to aid interpretation. Younger children under one year (68.8%) and those above five years (71.4%) showed a higher prevalence compared to the 1–5-year age group (49.1%), although the association between age and hypokalemia was not significant ($\chi^2 = 4.40$, p=0.111). Similarly, gender did not influence distribution, with comparable rates among females (61.4%) and males (55.9%) ($\chi^2 = 0.31$, p=0.580). Nutritional status showed a trend toward higher hypokalemia in children with normal growth (67.4%) compared to underweight (51.5%) and stunted/wasted children (51.9%), yet this difference was also not statistically significant ($\chi^2 = 2.56$, p=0.277). Duration of diarrhea and dehydration status followed expected patterns, with hypokalemia more frequent in prolonged illness and severe dehydration, but the results again did not achieve significance (p=0.451 and p=0.241, respectively).

Among biochemical parameters, serum sodium and bicarbonate levels were not significantly associated with hypokalemia. Children with hypernatremia (77.8%) tended to have more hypokalemia than those with normal (58.9%) or low sodium (47.6%), but this difference was not statistically significant ($\chi^2 = 2.40$, p=0.301). Likewise, bicarbonate levels did not demonstrate a meaningful pattern, with hypokalemia occurring in 62.5% of those with normal, 51.5% with low, and 50.0% with high bicarbonate levels ($\chi^2 = 1.26$, p=0.533). Acid–base status approached significance ($\chi^2 = 5.43$, p=0.066), with hypokalemia more frequent in children with normal status (68.4%) compared to those with metabolic acidosis (45.7%) or alkalosis (45.5%). The ony statistically significant association was found with serum chloride ($\chi^2 = 6.66$, df = 2, p=0.036, Cramér's V = 0.25), where hypochloremic children demonstrated the highest frequency of hypokalemia (77.3%), compared to 56.3% in those with normal chloride and just 30.0% in hyperchloremic children. This moderate effect size highlights chloride imbalance as an important determinant of potassium depletion in children with acute watery diarrhea (Table 4).

Table 4: Association of Hypokalemia with Demographic, Clinical, and Biochemical Variables (n=103)

Variables	Categories	Hypokalemia Present, n (%)	Hypokalemia Absent, n (%)	χ^2 (df), p-Value	Cramér's V
Age Group	<1 Year	22 (68.8%)	10 (31.2%)	4.40 (2), 0.111	–
	1–5 Years	28 (49.1%)	29 (50.9%)		
	>5 Years	10 (71.4%)	4 (28.6%)		
Gender	Male	33 (55.9%)	26 (44.1%)	0.31 (1), 0.580	–
	Female	27 (61.4%)	17 (38.6%)		
Nutritional Status	Normal	29 (67.4%)	14 (32.6%)	2.56 (2), 0.277	–
	Underweight	17 (51.5%)	16 (48.5%)		
	Stunted/Wasted	14 (51.9%)	13 (48.1%)		
Duration of Diarrhea	<3 Days	24 (60.0%)	16 (40.0%)	1.59 (2), 0.451	–
	3–7 Days	30 (61.2%)	19 (38.8%)		
	>7 Days	6 (42.9%)	8 (57.1%)		
Dehydration Status	None	10 (66.7%)	5 (33.3%)	2.85 (2), 0.241	–
	Some	32 (51.6%)	30 (48.4%)		
	Severe	18 (69.2%)	8 (30.8%)		
Serum Sodium	Normal	43 (58.9%)	30 (41.1%)	2.40 (2), 0.301	–
	Hyponatremia	10 (47.6%)	11 (52.4%)		
	Hypernatremia	7 (77.8%)	2 (22.2%)		
Serum Chloride	Normal	40 (56.3%)	31 (43.7%)	6.66 (2), 0.036	0.25
	Hypochloremia	17 (77.3%)	5 (22.7%)		
	Hyperchloremia	3 (30.0%)	7 (70.0%)		
Serum Bicarbonate	Normal	40 (62.5%)	24 (37.5%)	1.26 (2), 0.533	–
	Low	17 (51.5%)	16 (48.5%)		
	High	3 (50.0%)	3 (50.0%)		
Acid–Base Status	Normal	39 (68.4%)	18 (31.6%)	5.43 (2), 0.066	–
	Metabolic Acidosis	16 (45.7%)	19 (54.3%)		
	Metabolic Alkalosis	5 (45.5%)	6 (54.5%)		

Chi-square test applied. p<0.050 is considered statistically significant

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The clustered bar chart illustrates the distribution of hypokalemia according to serum chloride categories. Hypokalemia was most frequent among children with hypochloremia (77.3%), moderate among those with normal chloride (56.3%), and least frequent in hyperchloremic children (30.0%) (Figure 1).

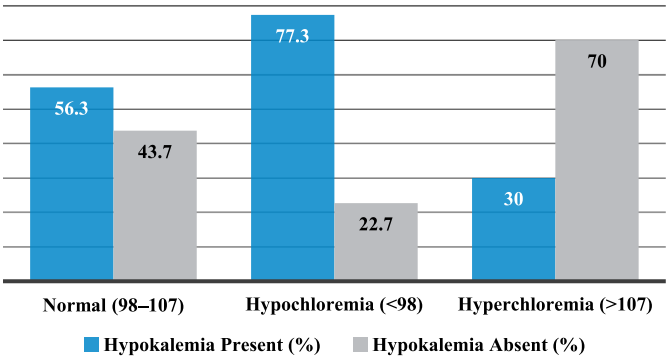

Figure 1: Association of Serum Chloride Levels with Hypokalemia in Children with Acute Watery Diarrhea (n=103)

DISCUSSION

This study found that hypokalemia was common in children with acute watery diarrhea (58.3%) and that potassium status varied significantly across serum-chloride categories: hypokalemia was most frequent with hypochloremia (77.3%) and least frequent with hyperchloremia (30.0%), with a moderate effect size (Cramér's V = 0.25). No statistically significant associations were observed with age, sex, nutritional status, duration of diarrhea, dehydration category, sodium, bicarbonate, or acid–base grouping. Findings on the overall burden of hypokalemia are broadly consistent with recent pediatric literature. Nasrin *et al.* 2024 reported hypokalemia in about 40% of children with acute diarrhea, confirming that potassium loss is a frequent complication [12]. The higher proportion in this study may reflect the wider age range and hospital-based sampling. In a tertiary African cohort, Eke *et al.* 2020 documented common electrolyte derangements with hypokalemia linked to mortality, evidence that underscores the clinical relevance of early potassium assessment and correction in settings like the one studied in our population [13]. Similarly, multi-centre data in southern Africa by Kinasha *et al.* 2025 associated electrolyte abnormalities with worse outcomes in children hospitalized for severe gastroenteritis, reinforcing the importance of routine electrolyte panels at admission [14]. More recent pediatric studies further reinforce the role of chloride imbalance in acute gastroenteritis. Khan *et al.* 2025 conducted a study in children aged 6 months to 3 years admitted with acute gastroenteritis at MTI DHQ Hospital, Dera Ismail Khan, Pakistan, and found that serum chloride levels were significantly elevated in children with more severe dehydration alongside potassium and sodium abnormalities [15]. The chlorid potassium signal observed here is physiologically coherent and mirrors contemporary reviews. Zaki and Shanbag describe how diarrheal bicarbonate loss typically produces normal anion-gap (hyperchloremic) metabolic acidosis, whereas chloride depletion (e.g., with vomiting or mixed fluid losses) favors metabolic alkalosis with renal potassium wasting [16]. Zieg *et al.* likewise emphasize the tight coupling of chloride and potassium handling in the gut and kidney [17]. Taken together, these sources explain why this study saw the highest hypokalemia frequency in hypochloremia and the lowest in hyperchloremia: chloride deficits promote kaliuresis, while hyperchloremia often accompanies acidosis without the same drive to renal potassium loss. The absence of significant associations between hypokalemia and bedside severity markers (dehydration grade, stool frequency, fever) accords with pediatric emergency observations that biochemical risk may be partly decoupled from clinical scores after early oral or intravenous rehydration. In a seasonal comparison, Saidian *et al.* found similar proportions of dehydration, hypernatremia, and hypokalemia across pre- and post-pandemic periods despite large shifts in admissions, an observation that helps contextualize why severity metrics did not map neatly to potassium status in this study [18]. Sodium and acid–base results also align with current syntheses. Zieg *et al.* and Alharbi *et al.* note that dysnatremias in pediatric gastroenteritis arise through mixed mechanisms (pathogen-specific stool electrolyte profiles, ORS composition, IV fluid type, and concurrent vomiting), which can obscure direct pairwise links with hypokalemia in cross-sectional snapshots such as this one [17, 19]. Likewise, trends without statistical significance for bicarbonate and categorical acid–base status in this study are unsurprising given timing effects (sampling after partial resuscitation) and the lower resolution of broad clinical categories compared with blood-gas-based classification. Regional evidence supports the local relevance of routine electrolyte testing. In Pakistani hospital cohorts, Ali *et al.* reported substantial electrolyte derangements with hypokalemia among children with acute malnutrition and diarrhea [20], and Chand *et al.* 2024 found electrolyte abnormalities in more than 90% of children with severe acute malnutrition, including hypokalemia in roughly 70% [21]. These reports strengthen the case concordant with this study's results for early electrolyte measurement (including chloride) and prompt potassium correction at admission. The strength of this study was a clear, statistically supported link between potassium status and chloride categories in AWD, indicating that chloride measurement can help flag

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children at the highest risk of hypokalemia even when standard bedside severity indicators and sodium or bicarbonate categories are unrevealing. Clinically, the results support early electrolyte testing (with attention to chloride), timely potassium replacement, and fluid strategies that avoid exacerbating chloride or potassium derangements.

This study was limited by its single-center design and the cross-sectional nature, which prevents causal inference regarding electrolyte changes over time. Blood-gas analyses and pathogen-specific data were not incorporated, and sampling occurred after initial fluid resuscitation in some cases. Future research should include multicenter cohorts with time-stamped electrolyte measurements, detailed pathogen profiling, and longitudinal follow-up to refine risk prediction and optimize fluid and potassium management strategies and incorporate blood-gas analysis, time-stamped sampling before and after fluids, and, where feasible, pathogen testing, to sharpen causal inference and guide protocolized correction strategies.

CONCLUSIONS

Hypokalemia was frequent among children with acute watery diarrhea. The only factor that showed a statistically significant association with hypokalemia was serum chloride, with the highest risk with hypochloremia and lowest with hyperchloremia, while age, sex, nutritional status, illness duration, dehydration, sodium, bicarbonate, and acid–base status were not significantly related. Clinically, early electrolyte testing (including chloride), timely potassium correction, and fluid plans that avoid worsening chloride or potassium imbalance should be routine. Future studies should incorporate blood-gas–based assessment and time-stamped sampling around fluid therapy to refine management.

Authors' Contribution

Conceptualization: TA
Methodology: TA, KA, IK, AI, SSAT, SJS
Formal analysis: KA, AI
Writing and Drafting: TA, KA, AI, SSAT, SJS
Review and Editing: TA, KA, AI, SSAT, SJS, IK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Carbapenem Resistance in the Pathogenic Gram-Negative Bacteria from Hyderabad, Sindh

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ABSTRACT

Carbapenems are β-lactam antibiotics and are often used as a last resort to treat infections caused by the β-lactamase-producing Gram-negative bacteria owing to their ability to withstand hydrolysis by many β-lactamase enzymes. However, the emergence of carbapenem resistance in these pathogens has already been reported. In order to avoid critical situations for public health, regular monitoring and reporting of carbapenem resistance is essential. **Objectives:** To determine the frequency of carbapenem-resistant Gram-negative pathogens circulating in Hyderabad, Sindh. **Methods:** This cross-sectional study was carried out for one year. The clinical samples were collected using a convenience sampling technique from patients suspected of bacterial infections. The bacterial isolates were subjected to identification based on their microscopic, cultural, and biochemical characteristics. Sensitivity of each type of Gram-negative pathogen to antibiotics was established in terms of Clinical Laboratory Standards Institute guidelines, with the use of the Kirby-Bauer disk diffusion technique. **Results:** 400 clinical samples were randomly selected and they were divided into urine (n=212), pus (n=85), blood (n=68), and other (n=35). Their microbiological processing resulted in the recovery of two hundred seventy-seven isolates of Gram-negative bacteria identified as *E. coli* (31.05%), *Enterobacter* spp. (24.19%), *Pseudomonas* spp. (16.25%), *Proteus* spp. (14.44%), *Klebsiella* spp. (10.11%), and others (3.96%). The frequency of carbapenem-resistant isolates varied among species, with the highest prevalence in *Pseudomonas* spp. demonstrating 20% being carbapenem-resistant isolates. **Conclusions:** Carbapenem resistance in pathogenic Gram-negative bacteria has emerged. The development of carbapenem resistance in these pathogens can be catastrophic for public health.

INTRODUCTION

Carbapenems, a subgroup of β-lactam antibiotics, act as cell wall inhibitors by restraining the biosynthesis of bacterial cell walls and are recognized as last-resort antibiotics for treating severe bacterial infections [1, 2]. Imipenem and meropenem are among the most broadly active carbapenem antibiotics available for systemic use in humans [3]. Carbapenems are typically resistant to hydrolysis by many beta-lactamase enzymes released by clinically significant bacterial pathogens. However, the emergence of carbapenem resistance (CR) in Gram-negative pathogenic bacteria such as *E. coli* and some species of *Acinetobacter*, *Klebsiella*, *Proteus*, and *Pseudomonas* genera has been reported in the last few years [4, 5], which has imposed a great public health concern worldwide by limiting treatment options for infections caused by CR-Gram-negative pathogenic bacteria. Consequently, infected patients face a high mortality rate. Additionally, the annual cost of combating these resistant bacterial infections has increased substantially worldwide [6, 7]. The carbapenem resistance in Gram-negative bacteria is mainly attributed to the conjugative plasmids, which can spread mobile genes that encode enzymes (carbapenemases) capable of hydrolyzing β-lactam agents, including carbapenems [8]. Among the

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clinically relevant carbapenemases, two types, namely K. *pneumoniae* carbapenemase (KPC) and Verona integron-encoded metallo-β-lactamase (VIM), are particularly prevalent. However, recently, oxacillinase-48 (OXA-48) and New Delhi metallo-β-lactamase-1 (NDM-1) have also become common [9]. Since the last decade, the isolation of CR-Gram-negative bacteria from clinical samples has been increasing, possibly due to the frequent usage of carbapenem antibiotics for treating bacterial infections. Consequently, CR-Gram-negative pathogenic bacteria have been listed in the critical priority pathogens group by the World Health Organization [10]. The epidemiological attributes of CR-Gram-negative pathogenic bacteria include multiple characteristics that show diversity and significantly vary by geographical region. Regular monitoring and surveillance of carbapenem resistance in Gram-negative pathogenic bacteria are suggested. The collected data have provided insights into the status of these clinically important antibiotics in terms of their effectiveness in treating infections associated with various Gram-negative bacteria.

Despite the growing global concern regarding carbapenem-resistant Gram-negative bacteria, region-specific surveillance data from interior Sindh, particularly Hyderabad, remain limited. Most available reports focus on national or tertiary-care urban centers, leaving a gap in localized epidemiological evidence needed to guide empirical therapy and antimicrobial stewardship strategies. The absence of updated regional resistance patterns may hinder timely clinical decision-making and infection control planning. Therefore, assessing the current frequency of carbapenem resistance in Gram-negative pathogens within this setting is essential. This study aimed to evaluate the frequency of CR in Gram-negative pathogenic bacteria from Hyderabad, Sindh, Pakistan.

METHODS

The study was conducted as a prospective and cross-sectional study in a period of one year (September 2021 to August 2022) at the Institute of Microbiology, University of Sindh, Jamshoro. The Institutional Bioethics Committee (IBC), University of Sindh, Jamshoro, Pakistan, was the source of the ethical approval through a letter with no. ORIC/SU/ 125. Cochran's sample size formula [11] was used to calculate sample size, ensuring a 95% level of confidence, a 5% margin of error and a 0.5 estimated proportion. Clinical specimens, including urine, blood, pus and pus swabs, vaginal swabs, tissue or wound aspirates, were collected from inpatients and outpatients visiting various diagnostic centers located in Hyderabad. Informed consent was obtained through verbal means directly via patients (or the guardian in the case of a minor), but no identifiable information has been shared, and the samples were gathered for diagnostic reasons. The standard convenience sampling method was used to collect the samples. The collected samples were immediately transported to the laboratory and processed on solid media (selective and differential), followed by incubating the inoculated plates at 37°C for 24 hours. The next day, the cultural characteristics were taken into account. Lactose-fermenting Gram-negative bacteria appeared pink while non-fermenters formed colorless to yellow colonies on the MacConkey agar. The isolates were further subjected to a Gram staining procedure and biochemical tests, including the Catalase test, Oxidase test, SIM test, Indole test, Citrate utilization test, Urease test, and Triple sugar iron test, to reveal their identity. Strains that did not exhibit the usual cultural and biochemical characteristics for their identification were further analyzed using commercially available API 20 E (Analytical Profile Index) strips. The API 20 E test was performed according to the manufacturer's recommendations (Biomerieux, USA). Briefly, 20 compartments on the API 20 E strip were loaded with the diluted test culture and covered with sterile oil. The strip was incubated in a moist tray overnight. The next day, the results were observed straight away for some tests, while other tests required the addition of specific reagents. The identification was determined using the API catalogue. Only one bacterial isolate was selected from each growth-positive sample, while co-infecting bacteria were excluded. AST of all isolates was performed using the Kirby-Bauer disc diffusion method [12] on Mueller-Hinton (MH) agar (Oxoid-UK) following Clinical and Laboratory Standards Institute(CLSI) guidelines [13]. Briefly, a lawn of the test cultures was prepared on the Muller-Hinton plates, followed by the deposition of commercially available antibiotic discs, including imipenem and meropenem. After incubation, the plates were observed for the inhibition zone. The size of the inhibition zone was measured, and the isolates were scored as resistant (R) or sensitive (S) to each of the antibiotics tested according to CLSI guidelines [13]. To test the quality of antibiotics, the E. coli ATCC 25922 strain was used. Statistical analysis of the given data was performed with the help of Microsoft Excel 2010 and SPSS version 26.0. The p-value was calculated by a Chi-square independence test, and a p-value of ≤0.05 was regarded as statistically significant.

RESULTS

The present study included 400 different types of clinical samples. The frequency of growth-positive clinical samples is given. The observed higher frequency of positive growth patterns reflects the targeted collection from suspected patients, consistent with the aim of the

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current research. Although some samples revealed mixed growth, one isolate per sample was included in the present study for identification and detection of the CR phenotype. The data has further indicated that among the growth-positive samples (n=316), a higher percentage was of urine specimens, followed by pus and blood specimens. In contrast, other specimens (ear swabs and body fluids) were less frequent. Notably, urinary tract infections (UTIs) caused by Gram-negative bacteria were significantly more prevalent than other infections (p-value<0.05). Moreover, a higher frequency of the clinical isolates (87.65%) appeared as Gram-negative bacteria with rod-shaped morphology when microscopic observations were done, while the remaining (12.35%) were Gram-positive bacteria. It was further observed that the highest frequency of Gram-negative isolates was recovered from urine samples (p-value<0.050), followed by blood and pus samples (Table 1).

Table 1: Percentage Distribution of Clinical Specimens

Clinical Samples	Gram-positive, n (%)	Gram-negative, n (%)	Total Growth Positive, n (%)
Urine	11 (28.2%)	171 (61.7%)*	182 (57.59%)*
Pus	25 (64.10%)	44 (15.9%)	69 (21.84%)
Blood	02 (5.13%)	43 (15.5%)	45 (14.24%)
Other	01 (2.57%)	19 (6.9%)	20 (6.33%)
Total	39 (100%)	277 (100%)	316 (100%)

*p-value<0.050

Further characterization of Gram-negative isolates showed that the rod-shaped bacilli were frequent among them, which included both lactose fermenters and lactose non-fermenters. The isolates identified as *E. coli*, *Enterobacter* spp., *Pseudomonas* spp., *Proteus* spp., Klebsiella spp., *Citrobacter* spp., *Salmonella* Typhi, and Xanthomonas maltophila were recovered with varying frequencies. The data indicated that the majority of isolates were responsible for causing UTIs in humans because these were obtained from urine samples. However, all *Salmonella* spp. isolated in this study were exclusively recovered from blood samples. This finding is consistent with the characterization of *S. Typhi,* which causes typhoid fever, an enteric fever primarily detected by the isolation of typhoidal *Salmonella* from human blood (Table 2).

Table 2: Percentage Distribution of the Gram-Negative Isolates

Type of Specimen	Lactose Fermenters, n=185 (66.79%)				Non-Lactose Fermenters, n=92 (33.21%)			
	E. coli	*Enterobacter* spp.	*Klebsiella* spp.	*Citrobacter* spp.	*Pro eus* spp.	*Pseudomonas* spp.	*Salmonella* Typhi	*Xanthomonas maltophilia*
Pus	6 (7.0%)	12 (17.9%)	4 (14.3%)	0 (0%)	15 (37.5%)	6 (13.3%)	0 (0%)	1 (100%)
Urine	64 (74.4%)	41 (61.2%)	24 (85.7%)	4 (100%)	21 (52.5%)	17 (37.8%)	0 (0%)	0 (0%)
Blood	8 (9.3%)	9 (13.4%)	0 (0%)	0 (0%)	3 (7.5%)	17 (37.8%)	6 (100%)	0 (0%)
Other	8 (9.3%)	5 (7.5%)	0 (0%)	0 (0%)	1 (2.5%)	5 (11.1%)	0 (0%)	0 (0%)
Total	86 (100%)	67 (100%)	28 (100%)	4 (100%)	40 (100%)	45 (100%)	6 (100%)	1 (100%)
% of Total Isolates	31.05%	24.19%	10.11%	1.44%	14.44%	16.25%	2.17%	0.35%

The representative result of antibiotic susceptibility testing for Gram-negative bacteria (E. coli) using the disc diffusion assay. No zone of inhibition against the antibiotic disc (Resistant), Zone of inhibition (Sensitive). Antibiotics tested were Amikacin (AK), Cephalosporins, Cefoperazone (CEF), Cefuroxime (CXM), Ciprofloxacin (CIP), Fosfomycin (FOS), Imipenem (IMP), and Meropenem (MEM). The antibiotic resistance profile of all common clinical isolates was determined against a panel of seven antibiotics from different classes of antibiotics, including carbapenems (Imipenem and meropenem). Information indicated that the *E. coli* isolates have become resistant to antibiotics, which are mostly used. Interestingly, the majority of the *E. coli* isolates were vulnerable to carbapenem antibiotics but resistant to cephalosporins and fluoroquinolone antibiotics. A particularly high resistance rate was observed against ciprofloxacin (Figure 1).

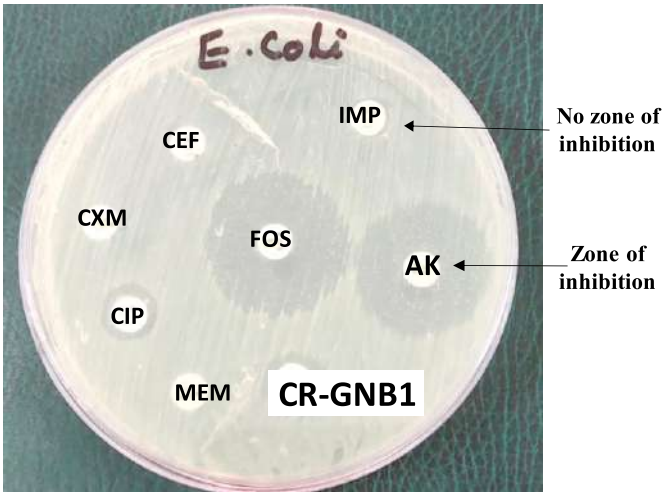

Figure 1: Antibiotic Susceptibility Testing for Gram-Negative Bacteria (*E. coli*) Using Disc Diffusion Assay

Additionally, *E. coli* isolates also showed resistance to the cephalosporin antibiotics used in the study. The CR was observed in 6.98% (n=6) of *E. coli* isolates, which is considered an emerging concern for public health. Notably,

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a higher degree of CR was observed among *Pseudomonas* spp. along with a higher level of resistance against cephalosporins such as cefuroxime and cefoperazone observed in *Pseudomonas* spp. Similarly, *Klebsiella* spp. were resistant particularly against ciprofloxacin, with 64.29% isolates. In addition, more than 50% of isolates showed resistance against both cephalosporins tested in this study. Regarding the carbapenems, 4 (14.29%) isolates showed resistance to meropenem and imipenem antibiotics. Similarly, a higher level of resistance against cephalosporins such as cefuroxime and cefoperazone was observed in Pseudomonas spp. Antibiotic susceptibility testing of *Enterobacter* spp. revealed that 46 (68.66%) were susceptible to cefuroxime, while 21 (31.34%) were resistant. Furthermore, resistance to ciprofloxacin was observed in more than 50% of isolates. Specifically, 7 (10.45%) of *Enterobacter* spp. were resistant to meropenem, a carbapenem antibiotic, indicating the emergence of CR in the Gram-negative pathogenic bacteria. AST of *Proteus* spp. isolates revealed that 31 (77.5%) were sensitive to cefuroxime and cefoperazone, while 9 (22.5%) were resistant. Additionally, resistance to ciprofloxacin was observed in 18 (45.0%) of the isolates. Furthermore, 6 (15.0%) of the *Proteus* spp. exhibited resistance to carbapenems. Overall, data showed that 32 out of 266 Gram-negative isolates tested were CR isolates.

Table 3: Antibiotic Susceptibility Profiles of Gram-Negative Bacteria Isolated from Various Clinical Samples

Clinical Isolates	*E. coli* n=86		*Enterobacter* spp. n=67		*Klebsiella* spp. n=28		*Proteus* spp. n=40		*Pseudomonas* spp. n=45	
Antibiotics	S, n (%)	R, n (%)	S, n (%)	R, n (%)	S, n (%)	R, n (%)	S, n (%)	R, n (%)	S, n (%)	R, n (%)
Amikacin	77 (89.53%)	9 (10.47%)	58 (86.57%)	9 (13.43%)	23 (82.14%)	5 (17.86%)	35 (87.5%)	5 (12.5%)	37 (82.22%)	8 (17.78%)
Cefoperazone	56 (65.11%)	30 (34.89%)	33 (49.25%)	34 (50.74%)	14 (50%)	14 (50%)	31 (77.5%)	9 (22.5%)	23 (51.11%)	22 (48.89%)
Cefuroxime	46 (53.49%)	40 (46.51%)	46 (68.66%)	21 (31.34%)	12 (42.86%)	16 (57.14%)	31 (77.5%)	9 (22.5%)	28 (62.22%)	17 (37.78%)
Ciprofloxacin	24 (27.90%)	62 (72.10%)	31 (46.26%)	36 (53.73%)	10 (35.71%)	18 (64.29%)	22 (55.0%)	18 (45.0%)	24 (53.33%)	21 (46.67%)
Fosfomycin	75 (87.20%)	11 (12.80%)	47 (70.15%)	20 (29.85%)	18 (64.29%)	10 (35.71%)	26 (65.0%)	14 (35.0%)	25 (55.56%)	20 (44.4%)
Imipenem	80 (93.02%)	6 (6.98%)	60 (89.55%)	7 (10.45%)	24 (85.71%)	4 (14.29%)	34 (85.0%)	6 (15.0%)	36 (80.0%)	9 (20.0%)
Meropenem	80 (93.02%)	6 (6.98%)	60 (89.55%)	7 (10.45%)	85.71 (24%)	4 (14.28%)	34 (85.0%)	6 (15.0%)	36 (80.0%)	9 (20.0%)

R=Resistant and S=Sensitive.

The percentage distribution of the CR-Gram-negative isolates is shown. In the current study, a chi-square test of independence was performed to determine whether the bacterial species and carbapenem resistance were significant; the results indicated the lack of a significant association (p-value>0.05) (Figure 2).

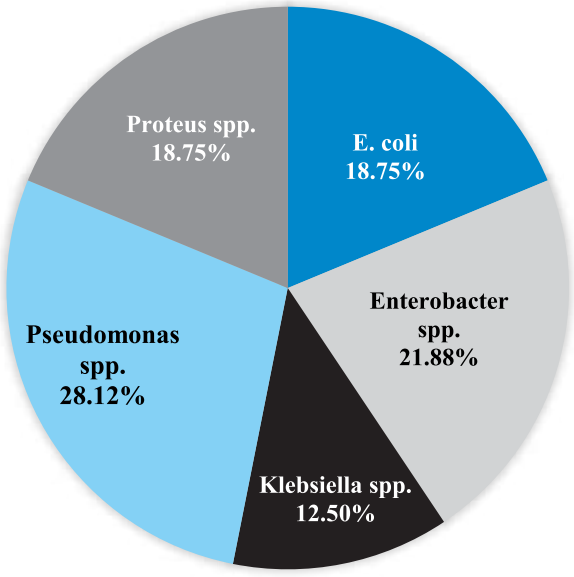

Figure 2: The Percentage Distribution of CR Gram-Negative Bacteria

DISCUSSION

Carbapenems are generally resistant to hydrolysis caused by clinically important β-lactamase enzymes, which are produced by Gram-negative bacteria. Therefore, the usage of carbapenems is commonly employed as a final resort antibiotic to treat infections that are brought about by the Gram-negative pathogens that produce β-lactamase. However, the acquisition of CR phenotype by the pathogens causes a challenging situation because of the lack of alternative treatment options for bacterial infections caused by CR Gram-negative pathogens. Consequently, CR has led to a dramatic increase in the death rate. The present study aimed to investigate carbapenem resistance developed by Gram-negative pathogens circulating in the study area. To realize the objective of the current study, firstly, Gram-negative pathogens were isolated among the patients who were suspected of bacterial infection. In our data, *E. coli* and the species of *Enterobacter*, *Klebsiella*, *Pseudomonas*, *Proteus*, and *Salmonella* were the most ubiquitous Gram-negative pathogens that cause different bacterial infections in humans in the study area. Our data has further highlighted that UTIs were more common than other bacterial infections. These findings are in agreement with the recent study, which has indicated an increased prevalence of UTIs across a wide range of bacterial infections worldwide [14]. Furthermore, *E. coli* remains the most prevalent causative agent of bacterial infections caused by Gram-negative

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bacteria [15]. Similarly, lactose-fermenting Gram-negative pathogens other than *E. coli* were also found to cause UTIs. Therefore, the development of antibiotic resistance in Gram-negative pathogens will contribute to the challenging public health concern. Furthermore, CR in *Proteus* spp. and *Pseudomonas* spp. presents a more concerning situation because the resistance mechanism causing the CR phenotype in these pathogens is comparatively less described. Moreover, AST results indicated that the majority of *E. coli* isolates have acquired resistance to ciprofloxacin and cephalosporin antibiotics, which are the common treatment options for *E. coli*-associated infections in humans. These findings are supported by a previous study that reported the higher frequency of ESBL producers among Gram-negative pathogenic bacteria [16]. Furthermore, the results suggested that *E. coli* isolates in this study exhibited high susceptibility to amikacin and carbapenem antibiotics, supported by the previous studies reporting minimal resistance against these antibiotics among clinical *E. coli* isolates [17]. However, the highest frequency of CR was observed in *Pseudomonas* spp. Overall, data show that CR is emerging in Gram-negative pathogens, which means that our last resort antibiotics are gradually failing to provide treatment for bacterial infections, thus limiting the antibiotic choices to treat infections associated with MDR-Gram-negative pathogens. Our data is consistent with recent reports from Pakistan showing an increasing trend of MDR in Gram-negative pathogens [18, 19]. Better monitoring and increased detectability of CR-Gram-negative pathogens underscore the fact that infections attributed to said pathogens are associated with serious morbidity and death [20]. In this regard, the current work explains the significance of researching the mechanisms of CR among Gram-negative pathogens found in the region of the current study. This could potentially facilitate the undetected spread of antibiotic-resistant pathogenic strains within our hospitals. Consequently, public health might experience a challenging situation sooner or later. Therefore, routine detection of these isolates should be prioritized. To achieve this, laboratories must possess the capacity to quickly identify these isolates, enabling the implementation of appropriate therapy to prevent antibiotic misuse or overuse. Furthermore, it is advisable to implement effective control measures to facilitate proper management and reduce the spread of these organisms.

This study was limited by its single-center design and reliance on phenotypic susceptibility testing without molecular characterization of carbapenemase genes. Additionally, the use of convenience sampling may restrict the generalizability of the findings to the wider population. Future studies should incorporate multicenter surveillance, molecular detection of resistance genes (such as blaKPC, blaNDM, and blaOXA-48), and long-term trend analysis to better understand transmission dynamics and support targeted antimicrobial stewardship interventions.

CONCLUSIONS

It was concluded that resistance against last-resort antibiotics like carbapenems has emerged in Gram-negative pathogens. Consequently, it is crucial to exercise prudent use of carbapenems and administer them appropriately.

Authors' Contribution

Conceptualization: MAI, SB, SAT
Methodology: MAI, SB, SAT, HD
Formal analysis: MAI, AAM, HD
Writing and Drafting: MAI
Review and Editing: MAI, AAM, HD, SB, SAT

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Excessive Screen Time and Its Emerging Health Hazards in Children of Female Health Care Professionals: A Descriptive Cross-Sectional Study

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ABSTRACT

Excessive screen time is a growing concern, particularly among children of working parents, including female health professionals. While digital devices are often used as convenient tools to manage childcare amidst demanding schedules, prolonged exposure poses risks to physical, cognitive, and emotional health. **Objectives:** To determine the prevalence and health hazards of excessive screen time in children of female health professionals. **Methods:** This descriptive cross-sectional study was conducted over six months, from January 2025 to July 2025, at the Combined Military Hospital, Lahore, Pakistan. A total of 195 children aged 4–15 years were included. Excessive screen time was defined as more than 2 hours per day. Data were collected using a validated questionnaire, and statistical analysis was performed using the chi-square test to determine associations, with a p-value <0.05 considered statistically significant. **Results:** Of the participants, 44.6% were obese, 47.7% had behavioral problems, 53.8% showed speech delays, and 49.2% reported sleep disturbances. Musculoskeletal pain (46.7%) and eye strain (44.6%) were also common. Excessive screen use was significantly associated with sleep and developmental delays. Chi-square test showed significant associations with behavioral issues and education level. **Conclusions:** Excessive screen time poses multiple health risks in children of female health professionals. Interventions through parental education, ergonomic guidance, and policy measures are needed to reduce these hazards.

INTRODUCTION

Screen time is a significant component of modern life for children, often referred to as 'digital natives,' who grow up surrounded by electronic media. Over the past five years, there has been a sharp increase in digital device ownership and usage among families. The easier availability of new technologies has been linked to a significant rise in children's average screen time engagement (such as smartphones and tablets). Regardless of the potential benefits of media exposure, inappropriate or excessive use of technology negatively influences children's general health [1-5]. Digital technical devices are electronic gadgets with screens that require digital signals to operate and emit radiation from the screens [6]. Tablets, laptops, desktops, cell phones, and monitors are some examples of more modern digital electronic devices. Screen time is spent using digital devices with screens [7, 8]. Female health professionals often have demanding work schedules, including irregular duty hours, long shifts, and on-call responsibilities. This can result in limited quality time spent with their children. The demanding nature of healthcare work can lead to physical and mental fatigue for female healthcare professionals. When they return home, they may have limited energy to engage in activities with their children, leading to the use of screens as a convenient

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means of entertainment. The irregular and unpredictable schedules of female health professionals may make it challenging to arrange consistent childcare. In the absence of alternative caregivers, children may spend more time with screens as a form of entertainment or companionship. The situation further deteriorated during the coronavirus disease (COVID-19) pandemic. Prolonged lockdowns and school closures led to a substantial increase in children's use of video games and social media, which often went unnoticed by parents. In many households, restrictions on screen time were relaxed to keep children occupied and manage their restlessness. In several cases, these limits disappeared altogether as digital devices, computers, tablets, and smartphones became central to both education and social interaction [9]. A study conducted in the United Kingdom revealed that 28% of children use electronic devices for almost three to four hours daily [10]. Prolonged exposure to artificial blue light from screens causes the light-sensitive cells in the eyes to create toxic compounds that degrade vision, cause blindness, and have other severe effects. In a study conducted at the University of Rome, 15.6% of primary school students, 39.5% of secondary school students, and 62.1% of high school students spent more than 10 hours a day on devices. Interestingly, even younger children experienced increased screen time. The strongest associations were found with computer use (94%), video games (86%), and mobile devices (83%), all of which consistently related to adverse sleep effects [11-13]. Excessive exposure to electronic media was linked to negative impacts on children's expressive vocabulary and language skills, as well as lower language scores and speech delays. Speech and language delays were noted in 28.4% of children who used media for more than three hours [14]. Another study conducted in Toronto showed that 42% children who had more than two hours of daily screen time and less than 11 hours of nighttime sleep at three years old faced nearly double the risk of being overweight or obese [15]. The prevalence of behavioral issues was significantly higher in children who were exposed to screens at an early age. Specifically, conduct problems were observed in 16.2% of children, learning problems in 24.2%, psychosomatic issues in 28.7%, and impulsive-hyperactive behavior in 19.9% Overall, 24% to 53% of children endorsed having musculoskeletal problems such as neck strain, shoulder and back pain while 12% to 55% had visual symptoms such as watering from eyes, refractive error and eye strain during and/or after electronic device use. Musculoskeletal and visual symptoms were approximately 1.8 to 3.0 times higher in secondary school students than in primary school students [16, 17].All these hazards in children are of great concern for parents, especially when both are working. Excessive screen time among children of female health professionals poses a growing concern due to its potential health hazards. However, most existing research has been conducted in Western or general parental populations, with little attention to children of female health professionals in South Asia. In Pakistan, although studies have examined patterns of screen use, there is no focused analysis on the health hazards in children of female health professionals, a group particularly vulnerable due to their mothers' demanding professional schedules.

Despite growing evidence on the adverse effects of excessive screen time on children, there is limited research focusing specifically on children of female health professionals in South Asia. This population is particularly vulnerable due to irregular maternal work schedules, high professional demands, and reliance on digital devices for childcare management. Current studies largely target Western populations or general parental groups, leaving a critical gap in understanding the prevalence and health consequences in this context. This study aimed to determine the prevalence and health hazards of excessive screen time in children of female health professionals.

METHODS

This cross-sectional study was conducted at the Combined Military Hospital, Medical College, and Institute of Dentistry, Lahore, over a period of six months, from January 2025 to July 2025. Ethical approval was granted by the Combined Military Hospital Ethical Review Committee (Ref. No: 108/ERC/CMH/LMC). Informed consent and written parental consent were obtained before participation. Children's data were anonymized, coded, and stored securely. A non-probability purposive sampling technique was employed to recruit 195 participants. The sample size was calculated at a 95% confidence level with a 5% margin of error, using an expected prevalence of behavioral problems of 24% (p=0.24). The single-proportion formula was applied: $n = (Z^2 \times p \times (1 - p)) / d^2$, where Z=1.96 for 95% confidence, p=0.24, and d=0.05. The calculated sample size was approximately 280 participants; however, due to feasibility constraints, 195 children were enrolled. The mothers of all enrolled children were educated healthcare professionals, including doctors, nurses, and allied health workers. Children aged 4–15 years who used digital devices for more than two hours daily and whose mothers were employed as doctors, nurses, or allied health professionals at CMH were included. Children already diagnosed with behavioral problems, visual defects, sleep disorders, musculoskeletal disorders, or speech problems, as well as those unwilling to participate, were excluded. Operationally, excessive screen time was defined as using digital devices for more than two hours daily. Health hazards were defined as

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follows: obesity was considered as BMI ≥95th percentile (CDC growth charts); sleep disorder as <10 hours/day in children <6 years or <9 hours/day in children ≥6 years. Mothers were asked direct questions regarding their child's behavior, including aggression, restlessness, difficulty sustaining attention, and hyperactivity. No standardized behavioral assessment tools (e.g., SDQ or CBCL) were used. Visual problems were assessed based on maternal reports of poor vision, squinting, or difficulty identifying colors. Although Snellen and Ishihara charts are standard ophthalmological tests, these were not administered in this study. Musculoskeletal disorders were assessed through maternal reports of frequent neck, back, or wrist pain in the child. No clinical examinations were performed. Maternal observations regarding delayed speech, unclear articulation, or stammering were also noted. Data were collected using a validated questionnaire (Cronbach's alpha=0.87) on screen use and associated health hazards. No clinical examinations or speech assessments were conducted as part of this cross-sectional survey. All outcome data were based on maternal subjective reporting through the questionnaire. Data analysis was conducted using SPSS version 26.0, with descriptive statistics presented as frequencies and percentages for qualitative data, and mean ± standard deviation for quantitative data.

RESULTS

Our collected data provides a comprehensive overview of the demographic and contextual characteristics of the participants. Among mothers, the most common age group was over 45 years (28.7%), followed by 36–45 years (25.1%), with smaller proportions in the 18–25 years (23.6%) and 26–35 years (22.6%) categories. Regarding professions, nurses made up the largest group (36.9%), followed by doctors (32.3%) and allied health professionals (30.8%). The children's age distribution showed the highest proportion in the 7–9 years group (27.7%), with other age groups 4–6 years (24.6%), 10–12 years (25.1%), and 13–15 years (22.6%)—being relatively evenly distributed. A slight majority of the children were male (53.3%) compared to females (46.7%). Education levels revealed that most children were in secondary education (39.5%), followed by primary (35.9%) and pre-school (24.6%). In terms of siblings, more children had no siblings (53.8%) compared to those who had siblings (46.2%). Device ownership among families highlighted laptops as the most commonly owned device (28.2%), followed by smartphones (26.2%), TVs (25.6%), and tablets (20.0%). This distribution reflects a diverse and balanced sample in terms of age, profession, and household resources (Table 1).

Table 1: Demographic Characteristics of the 195 Participating Mothers and Their Children (N=195)

Variables	Category	n (%)
Mother's Age (years)	18-25	46 (23.6)
	26-35	44 (22.6)
	36-45	49 (25.1)
	>45	56 (28.7)
Mother's Profession	Doctor	63 (32.3)
	Nurse	72 (36.9)
	Allied Health Professional	60 (30.8)
Child's Age (years)	4-6	48 (24.6)
	7-9	54 (27.7)
	10-12	49 (25.1)
	13-15	44 (22.6)
Child's Gender	Male	104 (53.3)
	Female	91 (46.7)
Child's Education Standard	Pre-school	48 (24.6)
	Primary	70 (35.9)
	Secondary	77 (39.5)
Siblings	Yes	90 (46.2)
	No	105 (53.8)
Devices Owned	Laptop	55 (28.2)
	Tablet	39 (20.0)
	TV	50 (25.6)
	Smartphone	51 (26.2)

Eye strain showed no significant associations with maternal or child characteristics, sibling presence, or device ownership. However, children whose mothers were doctors and those aged 4–6 years reported slightly higher frequencies of eye strain. Additionally, children who owned smartphones had a marginally higher frequency of eye strain (60.8%), though this did not reach statistical significance. Across all conditions, no single variable emerged as a consistent predictor (Table 2).

Table 2: Frequency of Health Hazards Associated with Excessive Screen Time (N=195)

Variables	Category	n (%)	95% CI
Sleep Disturbances	Yes	96 (49.2)	42.1 – 56.3
	No	99 (50.8)	43.7 – 57.9
Delayed Speech	Yes	105 (53.8)	46.7 – 60.8
	No	90 (46.2)	39.2 – 53.3
Obesity	Yes	87 (44.6)	37.6 – 51.7
	No	108 (55.4)	48.3 – 62.4
Behavioral Problems	Yes	93 (47.7)	40.7 – 54.8
	No	102 (52.3)	45.2 – 59.3
Musculoskeletal Pain	Yes	91 (46.7)	39.7 – 53.8
	No	104 (53.3)	46.2 – 60.3
Eye Strain	Yes	87 (44.6)	37.6 – 51.7
	No	108 (55.4)	48.3 – 62.4

However, trends suggest that a child's age, education level, and certain devices, such as smartphones and tablets, might influence specific outcomes, warranting further

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exploration. These findings underline the need for targeted interventions during early childhood and the potential impact of technology usage on child health and behavior (Table 3).

Table 3: Association of Potential Confounders with Screen-Time–Related Health Hazards

Confounders	Sleep Disturbances	Delayed Speech	Obesity	Behavioral Problems	Musculoskeletal Pain	Eye Strain
Mother's Age	0.871	0.311	0.754	0.786	0.783	0.826
Mother's Profession	0.260	0.869	0.784	0.358	0.419	0.589
Child's Age	0.551	0.653	0.328	0.013*	0.106	0.435
Child's Gender	0.605	0.565	0.908	0.206	0.659	0.686
Education Standard	0.836	0.606	0.480	0.030*	0.100	0.431
Siblings	0.842	0.191	0.965	0.550	0.249	0.965
Devices Owned	0.928 (F)	0.398 (F)	0.678 (F)	0.811 (F)	0.293 (F)	0.742 (F)

*(F) indicates Fisher's Exact test was applied due to expected cell counts <5. P<0.050=significant

DISCUSSION

This study highlights the significant health and developmental risks associated with excessive screen time among children of female health professionals, offering insights into a relatively underexplored population. Earlier studies found 42% of children with over two hours of daily screen use and less than 11 hours of sleep at age three faced nearly double the risk of being overweight or obese [15]. Screen time was also linked to conduct issues (16.2%), learning difficulties (24.2%), psychosomatic complaints (28.7%), and impulsive-hyperactive behaviors (19.9%) [16, 18]. By focusing on children of female healthcare professionals, this study provides novel insights into a group uniquely affected by irregular maternal work schedules and limited supervision, suggesting that professional commitments may inadvertently increase screen exposure, often substituting for direct parental interaction. This is particularly relevant during periods such as the COVID-19 pandemic, when digital devices became central to learning and recreation [19]. The type and manner of media use also influenced outcomes, with structured educational content offering benefits, whereas unregulated use was associated with sleep disturbances, musculoskeletal pain, eye strain, speech delays, and mental health concerns [20-22]. Previous research emphasizes balancing screen time with alternative activities [23], and our findings support the use of parental guidance, structured schedules, and outdoor play to mitigate screen-related harms. The high prevalence of eye strain (44.6%), musculoskeletal complaints (46.7%), and behavioral disturbances (47.7%) underscores the need for targeted interventions, including programs to help healthcare professionals balance work and childcare responsibilities, public awareness campaigns, and promotion of healthier screen habits [19, 22]. While this study provides context-specific insights, reliance on maternal self-reporting may introduce reporting bias, though validated questionnaires and operational definitions improve reliability. Future research should employ objective measures and longitudinal designs to confirm these findings. Overall, the results have practical implications for healthcare professionals, educators, and policymakers, highlighting the importance of parent education, regulated device use, school-based awareness sessions, and ergonomic training to promote healthier screen practices among children.

This study relied on maternal self-reports without objective clinical assessments, which may introduce reporting bias. Future research should incorporate standardized behavioral and clinical evaluations, larger sample sizes, and longitudinal designs to more accurately assess the long-term impact of excessive screen time. Additionally, intervention-based studies are needed to evaluate strategies that mitigate health risks and promote balanced digital use among children of working mothers.

CONCLUSIONS

Excessive screen time poses multiple health risks in children of female health professionals. Interventions through parental education, ergonomic guidance, and policy measures are needed to reduce these hazards.

Authors' Contribution

Conceptualization: FZ
Methodology: FZ, AC. FA
Formal analysis: FZ, AC, IF, BA
Writing and Drafting: FZ, AC, FA, QUA, IF, BA, TK
Review and Editing: FZ, AC, FA, QUA, IF, BA, TK

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

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Common Fetal Outcome among Women with Short Interpregnancy Interval

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ABSTRACT

The interpregnancy interval (IPI) is the time between the previous childbirth and the subsequent gestation. The short IPI is known for having adverse effects on fetal outcomes. **Objectives:** To investigate the association of short IPI ≤18 months. **Methods:** This cross-sectional study was conducted in the Obstetrics and Gynecology Department of Northwest General Hospital, Peshawar, and it lasted for more than six months. Participants were 126 women (15 to 45 years) with singleton pregnancies and IPI ≤ 18 months. Adverse outcomes, which include preterm birth, low birth weight, stillbirth, and early neonatal death, were analyzed using multivariable logistic regression. **Results:** 68(54%) women experienced at least one adverse fetal outcome, including low birth weight 27(21%), premature births 25(20%), stillbirths 11(9%), and early neonatal death 5(4%). Additionally, younger mothers (15 to 19 years) had the highest rates of preterm birth 7 35%) and low birth weight 6 28%). Multi variable logistic regression (confounding factors age, parity, education and residence) showed short IPI (<6 months) was strongly associated with early birth (aOR 8.62, 95% CI 1.53-48.51, p=0.014) and short IPI (6-11 months) also increased early birth risk (aOR 6.28, 95% CI 1.10-35.89, p=0.039). For underweight neonates, short IPI (6-11 months) had an elevated risk (aOR 7.22, 95% CI 1.90-27.47, p=0.004). Associations with stillbirth and neonatal death were not significant after adjustment. **Conclusions:** To reduce these risks, comprehensive family planning programs, maternal health education, and antenatal counselling on optimal birth spacing need to be prioritized in developing countries like Pakistan.

INTRODUCTION

The time between the previous childbirth and the subsequent gestation is known as the interpregnancy interval (IPI). According to earlier research, the short IPI of less than eighteen months was associated with unfavorable outcomes, which included premature birth, underweight neonates, stillbirth, and neonatal mortality [1-3]. A meta-analysis of sixty-seven settings that were conducted in various countries across the globe also revealed a similar association between short IPI and adverse fetal outcomes [4]. A previous systematic review and meta-analysis also found that an interpregnancy interval of <6 months is associated with negative fetal outcomes. This includes 40%, 61% and 26% higher risk of preterm birth, low birth weight, and small for gestational age, respectively, in the subsequent pregnancy. Short interpregnancy intervals up to 17 months were also associated with greater risks for these outcomes [5]. A recent study on the multiethnic Pakistani population also suggests that the optimal birth spacing reduces risks of perinatal and neonatal deaths [6]. A similar investigation in the Ethiopian population reveals that the percentage of premature and preterm birth is 10.4% and 25.9% in patients with short IPI, whereas with an optimal pregnancy interval, the percentage of preterm birth reduces to 2.9% [7].

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Another study conducted in Ethiopia compared the perinatal outcome in two groups (exposed and unexposed) of pregnant women based on their inter-pregnancy interval. The exposed group consists of women having an IPI<18 months, and the unexposed group consists of women having an IPI between 24 to 60 months. The results suggest the exposed group has a higher risk of adverse outcomes [8]. A short interpregnancy interval also adversely affects maternal health. It imposes the increased risk of diabetes and pregnancy in obese mothers [9]. It also increases the risk of maternal mortality, miscarriage, and induced abortion. In developing countries like Pakistan, social and cultural influences, along with low levels of maternal education, are the additional factors that lead to short IPI [4, 10]. Higher maternal education and better exposure to contraceptive counseling can improve postpartum contraceptive uptake. Younger maternal age and teenage pregnancy have repeatedly been linked to shorter birth spacing and worse perinatal outcomes. Socioeconomic disadvantage, high parity, and inadequate nutritional recovery are also crucial factors that can amplify the risk associated with short IPI [1, 2, 11, 12].

Although substantial international evidence links short interpregnancy interval (IPI) with adverse perinatal outcomes, context-specific data from tertiary care settings in Khyber Pakhtunkhwa remain limited. Many regional studies either combine maternal and fetal outcomes without stratified analysis or lack adjustment for key sociodemographic confounders. This limits the ability to determine the independent effect of short IPI on fetal outcomes within our population. Therefore, locally generated evidence is essential to guide targeted family planning strategies and obstetric care policies. This study aims to determine the frequency of adverse fetal outcomes associated with short interpregnancy intervals (IPI) and to evaluate their independent associations with maternal sociodemographic factors.

METHODS

This descriptive cross-sectional study was carried out in the Obstetrics and Gynecology Department of Northwest General Hospital and Research Center, Peshawar, Pakistan, over six months from 1st September 2023 to 20th March 2024, after obtaining ethical approval from the Northwest General Hospital and Research Center Institutional Review Board (Ref. No. IRB and EC/2023-GH/018) and from the College of Physicians and Surgeons Pakistan (Ref. No. CPSP/REU/OBG-2022-016-11507). A total of 126 women aged 15–45 years with single pregnancies and an interpregnancy interval (IPI) of less than 18 months were enrolled through consecutive non-probability sampling, with sample size calculated using OpenEpi software based on a 20% expected prevalence of short IPI, 95% confidence interval, and 7% error margin, conservatively derived from a meta-analysis reporting a pooled prevalence of 24.1% (95% CI 12.7–37.8%) [10]. Women with multiple pregnancies, diabetes mellitus (fasting blood glucose >126 mg/dL), active urogenital infections, or a history of cesarean section in their most recent delivery were excluded, while the inclusion criteria were an IPI of ≤18 months and presentation after 24 weeks of gestation. Data were collected through a structured proforma after obtaining informed consent in outpatient and emergency departments, with participants followed during routine antenatal visits until delivery; clinical examinations and ultrasound were performed to confirm eligibility. Data reliability was ensured by standardized training of collectors, use of calibrated weighing scales (LAICA BF-2025, Italy) and ultrasound machines (TOSHIBA TUS-X200, Japan), monthly calibration checks, cross-verification with antenatal and delivery records, refresher training, and periodic audits by senior obstetricians. Maternal and gestational age were quantitative variables, while categorical variables included parity, IPI category, residence, and education; outcome variables were premature birth, underweight neonates, stillbirth, and early neonatal death. Operational definitions included premature birth as delivery before 37 weeks, low birth weight as <2.5 kg, stillbirth as death of a viable fetus confirmed by absent cardiac activity on ultrasound, early neonatal death as death within the first week, and short IPI as pregnancy initiation within 18 months of a prior delivery. IPI months were categorized into four groups (Group 1: <6 months, Group 2: 6–11 months, Group 3: 12–17 months, and Group 4: ≥18 months [reference]). Continuous variables were summarized with mean and standard deviation, categorical variables with frequencies and percentages, and associations between short IPI and adverse outcomes were first assessed with crude logistic regression and then with multivariable models adjusted for maternal age, parity, education, and residence; results were reported as odds ratios (OR) with 95% confidence intervals and p-values, with p <0.050 considered significant. Participants were briefed on the study benefits and informed that participation was voluntary and withdrawal at any stage would not affect their medical care, while this study offers important insights on short IPI, its use of consecutive non-probability sampling may limit the generalizability of findings.

RESULTS

The baseline characteristics of the study sample are: the mean age of the study population is 27.02 years with a standard deviation of 5.35. Out of 126 patients, 29 (23%) were nulliparous, 57 (45.2%) primiparous, and 40 (31.7%) multiparous, and their mean gestational age was 36.52

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weeks with a standard deviation of 3.187 (Figure 1).

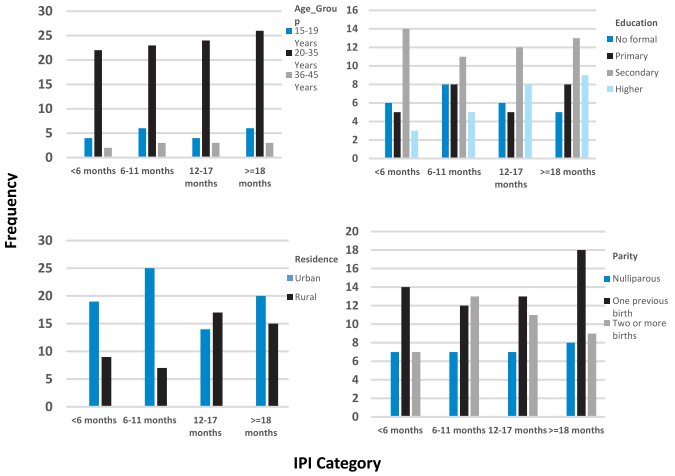

Figure 1: Characteristics of Study Population

Data were collected from patient enrollment until delivery for a comprehensive evaluation of fetal outcomes. A major portion of the study population, 68 (54%), experienced negative fetal outcomes, with the most common being low birth weight in 27 (21%) participants, followed by preterm birth in 25 (20%), stillbirth in 11 (9%), and early neonatal death in 5 (4%). To assess whether mother's age played a role in fetal outcomes, data were classified into three groups (Group 1: 15–19 years, Group 2: 20–35 years, Group 3: 36–45 years). The highest rates of adverse outcomes were observed in the youngest age group (Group 1: n = 20, 16%), where preterm birth (7, 35%) and low birth weight (6, 28%) were most common. The middle age group (Group 2: n = 95, 75%) also showed higher rates of adverse outcomes, including low birth weight (19, 20%) and preterm birth (17, 18%), while the oldest age group (Group 3: n = 11, 8%) had the lowest rates, with underweight neonates in 2 (18%) participants and preterm birth in 1 (9%). To evaluate how the duration of interpregnancy interval (IPI) affects fetal outcomes, participants were divided into four groups: Group 1 (<6 months), Group 2 (6–11 months), Group 3 (12–17 months), and Group 4 (≥18 months). To determine whether associations between short IPI and adverse outcomes were independent of maternal characteristics, multivariable logistic regression models were applied, including maternal age, parity, education level, and residence as covariates. Crude (unadjusted) and adjusted odds ratios (aOR) with 95% confidence intervals (CIs) were reported, model fit was examined using the Hosmer–Lemeshow test, and statistical significance was set at $p < 0.050$.

Table 1: Effect of Short IPI on Adverse Fetal Outcomes (Crude Vs Adjusted OR)

IPI (Months)		Frequency (%)	Crude OR	95% C.I.for EXP(B)		Adjusted OR	95% C.I. for EXP(B)		p-Value
				Lower	Upper		Lower	Upper	
Early Birth	< 6 (N=28)	9 (32.1%)	7.816	1.527	40.004	8.623	1.533	48.511	0.014
	6 – 11	8 (25%)	5.500	1.071	28.248	6.284	1.100	35.899	0.039
	12-17 (N=31)	6 (19.4%)	3.960	.736	21.302	4.490	.769	26.207	0.095
	>=18 (N=35) Reference	2 (5.7%)	–	–	–	–	–	–	0.104
Underweight Neonates	< 6 (N=28)	7 (25%)	2.000	.558	7.164	2.384	.604	9.409	0.215
	6 – 11	14 (43.8%)	4.667	1.439	15.134	7.215	1.895	27.471	0.004
	12-17 (N=31)	3 (9.7%)	.643	.140	2.943	.702	.146	3.384	0.660
	>=18 (N=35) Reference	5 (14.3%)	–	–	–	–	–	–	0.006
Still Birth	< 6 (N=28)	4 (14.3%)	1.778	.363	8.698	1.689	.322	8.872	0.536
	6 – 11	3 (9.4%)	1.103	.206	5.905	1.065	.184	6.167	0.944
	12-17 (N=31)	1 (3.2%)	.356	.035	3.608	.368	.035	3.885	0.405
	>=18 (N=35) Reference	3 (8.6%)	–	–	–	–	–	–	0.642
Early Neonatal Death	< 6 (N=28)	1 (3.6%)	1.259	.075	21.073	1.115	.060	20.612	0.942
	6 – 11	2 (6.3%)	2.267	.196	26.271	2.834	.197	40.814	0.444
	12-17 (N=31)	1 (3.2%)	1.133	.068	18.918	.850	.044	16.457	0.914
	>=18 (N=35) Reference	1 (2.9%)	–	–	–	–	–	–	0.803

After adjusting for potential confounding variables, the results showed that very short IPI (<12 months) remained strongly associated with early birth, with IPI <6 months showing markedly increased odds (Adjusted OR 8.62, 95% CI 1.53–48.51, p=0.014) and IPI 6–11 months also showing significantly higher odds (Adjusted OR 6.28, 95% CI 1.10–35.89, p=0.039) compared with IPI ≥18 months. For underweight neonates, IPI 6–11 months showed a substantial and statistically significant increase in risk (Adjusted OR 7.22, 95% CI 1.90–27.47, p=0.004), whereas IPI <6 months showed a non-significant trend (Adjusted OR 2.38, 95% CI 0.60–9.41, p=0.215). For stillbirth and early neonatal death, even very short IPI (<6 months) showed no statistically significant association (p>0.050) (Table 1).

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DISCUSSIONS

The baseline characteristics of participants are critical for understanding the study population. They ensure that the findings accurately reflect the demographic under investigation [5, 10]. A major portion of the study population experienced negative fetal outcomes. These adverse outcomes are preterm birth, low birth weight, stillbirth, and early neonatal death. The most common adverse outcome is low birth weight in 27 (21%) participants. Preterm birth in 25 (20%) participants is the second most occurring adverse outcome. Stillbirth in 11 (9%) participants and early neonatal death in 5 (4%) participants are also additional observed outcomes. These findings show a strong correlation between short IPI and neonatal complications. They emphasize the importance of optimal birth spacing for the better health of both newborns and mothers. Similar findings are also presented in previous studies that analyzed large metadata [1, 4, 11]. In Pakistan, Yousif *et al.* and Jameel *et al.* documented increased neonatal mortality and morbidities linked to short IPI [6, 12]. Brhane *et al.* and Jena *et al.* also reported increased preterm birth rates among Ethiopian women with short IPI [7, 8]. Maternal age also contributes to the risks associated with short IPI. Women of a younger age are at a higher risk of experiencing fetal complications. This study finds that women aged 15 to 19 years experienced the highest occurrence of premature birth (7, 35%) and underweight neonates (6, 28%). These trends show that maternal age also plays a crucial role in determining outcomes. Physiological weakness, underdeveloped reproductive systems, and socioeconomic factors challenge young mothers with higher risks of adverse fetal outcomes [13]. Studies conducted in India also confirm higher neonatal mortality and underweight neonates born to young mothers with short IPI [14]. Early marriage and poor family planning are also key drivers of short IPI in underdeveloped countries [15, 16]. For early birth outcomes, women with short IPI (<12 months) had markedly increased odds compared with those with IPI ≥18 months. For underweight neonates, the 6–11-month group showed a statistically significant increase in risk, whereas the IPI <6 months showed a non-significant trend. Crude estimates suggested elevated risks for stillbirth and neonatal death at shorter intervals, but these associations attenuated and were not statistically significant after adjustment. This suggests partial confounding by maternal sociodemographic factors. Overall, the pattern supports biological plausibility (nutritional depletion and incomplete recovery) and aligns with literature recommending longer spacing [5, 17-18]. The findings point to a particular vulnerability for preterm delivery and low birth weight when pregnancies are spaced under 12 months. Recent studies suggest that short IPI can be a detrimental factor for congenital anomalie. Environmental stressors such as air pollution further increase these risks [19]. These findings align with rates in other low-resource settings, and this study reinforces that an optimal IPI (≥18 months, ideally ≥24 months) substantially reduces the risk of adverse outcomes [20]. Although the current study effectively demonstrates the negative fetal outcomes of short IPI, it must be acknowledged that the limited sample size may hinder the generalization of the findings.

This study is limited by its single-center design, modest sample size, and use of consecutive non-probability sampling, which may restrict generalizability. Additionally, residual confounding from unmeasured factors such as maternal nutritional status and intercurrent infections cannot be excluded. Future multicenter prospective studies with larger samples and longer follow-up are recommended to validate these findings and to further explore biological and socioeconomic mechanisms underlying short IPI and adverse fetal outcomes.

CONCLUSIONS

This study effectively demonstrates that short IPI contributes to adverse fetal outcomes. These fetal complications are premature birth, underweight newborns, stillbirth, and early neonatal deaths. This study indicates that very short IPI, especially under 12 months, poses a significant risk for early birth and underweight neonates. Policies and clinical practice should reinforce family planning and postpartum contraceptive access to encourage optimal birth spacing (≥18 months). This study emphasizes the importance of enhancing maternal education and family planning in developing countries like Pakistan for mitigating the risks associated with short IPIs. It also recommends integrating postpartum family planning counseling into routine postnatal care and promoting community-level reproductive health education.

Authors' Contribution

Conceptualization: AUR
Methodology: AUR
Formal analysis: SJ
Writing and Drafting: AUR, SJ, FR
Review and Editing: AUR, SJ, FR

All authors approved the final manuscript and take responsibility for the integrity of the work

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Original Article

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Risk Factors Associated with Intrauterine Growth Restriction: A Case-Control Study

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ABSTRACT

Intrauterine growth restriction (IUGR) is a significant contributor to perinatal morbidity and mortality in low- and middle-income countries. **Objectives:** To determine maternal and clinical risk factors for IUGR among pregnant women at a tertiary care hospital in Karachi. **Methods:** This case-control study was conducted in the Department of Obstetrics and Gynecology, Kharadar General Hospital, from November 2023 to April 2024. A total of 188 women were enrolled, including 94 cases (women with IUGR) and 94 controls (women without IUGR). Data on sociodemographic characteristics, anemia, pregnancy-induced hypertension (PIH), thyroid dysfunction, and nutritional status were collected using predefined operational definitions. Logistic regression determined the independent risk factors. **Results:** The mean maternal age was 30.3 ± 4.2 years among cases and 29.3 ± 4.5 years among controls. Anemia and hypothyroidism were significantly associated with IUGR in multivariate analysis (aOR=4.23; 95% CI: 1.60–11.19; p=0.004 and aOR=6.04; 95% CI: 1.61–22.68; p=0.008, respectively). PIH showed significance in univariate analysis but lost significance after adjustment. Maternal underweight and hyperthyroidism were not independently associated with IUGR. **Conclusions:** Maternal anemia and hypothyroidism emerged as independent risk factors for IUGR, highlighting the need for routine screening and early interventions during pregnancy to improve neonatal outcomes.

INTRODUCTION

Increased perinatal morbidity and mortality are associated with intrauterine growth restriction (IUGR), which restricts the fetal growth potential. It is characterized by a birth weight below the 10th percentile for gestational age, affecting approximately 30 million infants worldwide each year, particularly in low- and middle-income countries [1, 2]. In Pakistan, IUGR contributes to an estimated 20–24% of live births, representing a significant cause of neonatal complications and mortality [3]. The etiology of IUGR differs between developed and developing regions. In high-income countries, placental insufficiency is a primary factor, whereas in resource-limited settings, maternal anemia, malnutrition, infections, and inadequate antenatal care are more prominent [4, 5]. Previous studies have also highlighted pregnancy-induced hypertension and thyroid dysfunction as major maternal contributors [6, 7]. These risk factors not only increase the likelihood of intrauterine growth restriction but also predispose affected infants to lifelong health consequences such as impaired neurodevelopment and metabolic disorders [8, 9]. As different studies highlighted the pool of risk factors, some factors like illiteracy, maternal mid-upper arm circumference <23, body mass index, altitude, small placental size, and small for gestational age are also known predictors of IUGR [10, 11].

Despite its importance, research on IUGR in Pakistan has largely focused on prevalence rather than determinants. Comprehensive data on maternal and clinical factors linked

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to intrauterine growth restriction (IUGR) in local populations are currently limited. Identifying such risk factors is essential for guiding obstetricians toward early diagnosis, preventive measures, and timely interventions. This study aims to assess maternal risk factors associated with IUGR and provide baseline data that may support national strategies to reduce perinatal morbidity and mortality.

METHODS

This case-control study was conducted in the Department of Obstetrics and Gynecology, Kharadar General Hospital, from November 2023 to April 2024, after obtaining ethical approval from the Hospital Ethical Review Committee (Ref. No. CPSP/REU/OBG-2022-207-11626). Written informed consent was taken from all participants. Pregnant women aged 18–45 years with more than 20 weeks of gestation attending the antenatal clinic were included, while those with multiple pregnancies, a history of renal failure or chronic liver disease, or unbooked status were excluded. The sample size was calculated using the WHO sample size calculator, based on the reported frequency of anemia among cases and controls (29.6% and 12.9%, respectively), with 80% power and a 95% confidence level, yielding a total of 188 participants (94 in each group). Non-probability consecutive sampling was applied to recruit both cases and controls. Participants were categorized into two groups: cases (women with intrauterine growth restriction, IUGR) and controls (women without IUGR). Baseline demographic and clinical data, including age, residence, family income, height, weight, BMI, parity, gravida, and number of children, were recorded on a predesigned proforma, and all patients were managed as per hospital protocols. Anemia, PIH, thyroid disorders, and maternal underweight were defined using standard clinical criteria. Data analysis in SPSS version 26 included descriptive statistics and binary logistic regression to identify IUGR-related factors. Variables with p <0.25 from univariate analysis were included in the model, showing no multicollinearity. Adjusted odds ratios with 95% confidence intervals were reported, considering confounders such as age, residence, income, parity, gravidity, and number of children, with significance set at p ≤0.050.

RESULTS

A total of 188 women participated in the study, consisting of 94 cases with Intrauterine Growth Restriction (IUGR) and 94 controls without IUGR. Both groups predominantly included women aged ≤30 years (53.2% in cases, 64.9% in controls), with no significant age difference (p=0.225). Income levels were similar, with 44.7% in both groups earning between 30,000 to 50,000 PKR (p=0.205). Urban residency was higher among both groups (62.8% cases, 69.1% controls), showing no significant difference (p=0.356). Notably, significant differences were observed in parity and gravidity: controls had a higher percentage of primigravida (46.8% vs. 27.7% in cases, p=0.007) and nulliparity (51.1% vs. 33% in cases, p=0.003) (Table 1).

Table 1: Baseline Characteristics of Patients According to Groups (N=188)

Variables	Groups	Case (with IUGR) N=94	Control (without IUGR) N=94	p-Value
Age Groups (Years)	≤ 30	50 (53.2%)	61 (64.9%)	0.225
	31–35	32 (34.0%)	22 (23.4%)	
	> 35	12 (12.8%)	11 (11.7%)	
Family Monthly Income (Rs)	< 30,000	27 (28.7%)	18 (19.1%)	0.205
	30,000–50,000	42 (44.7%)	42 (44.7%)	
	> 50,000	25 (26.6%)	34 (36.2%)	
Residence	Urban	59 (62.8%)	65 (69.1%)	0.356
	Rural	35 (37.2%)	29 (30.9%)	
Gravida	Primigravida	26 (27.7%)	44 (46.8%)	0.007
	Multigravida	68 (72.3%)	50 (53.2%)	
Parity	Nulliparous	31 (33.0%)	48 (51.1%)	0.003
	Primiparous	36 (38.3%)	36 (38.3%)	
	Multiparous	27 (28.7%)	10 (10.6%)	

Participants in both groups were similar in age, with no significant difference observed. However, controls had notably higher BMI and hemoglobin levels than cases, and both differences were statistically significant (p < 0.001) (Table 2).

Table 2: Descriptive Statistics of Study Patients According to Groups (N=188)

Variables	Cases (with IUGR)	Controls (without IUGR)	p-Value
Age (Years)	30.36 (±4.2)	29.31 (±4.53)	0.100
BMI (kg/m^2)	23.39 (±4.39)	28.66 (±5.57)	<0.001
Hemoglobin (g/dl)	10.37 (±1.89)	11.58 (±1.26)	<0.001
Family Income (Rs)	41,000 (±12,000)	46,000 (±12,700)	0.023

Anemia, underweight status, PIH, and thyroid dysfunction showed significant associations with intrauterine growth restriction (IUGR). Anemia was five times more common in IUGR cases than controls [OR=5.08; 95% CI: 2.71–10.41; p=0.005]. Underweight women had a threefold higher risk of IUGR [OR=3.24; 95% CI: 1.22–8.63; p=0.014]. PIH was also about three times more frequent among cases [OR=3.09; 95% CI: 1.29–7.39; p=0.009]. Thyroid dysfunction was significantly more prevalent in IUGR cases [OR=4.12; 95% CI: 2.19–7.76; p=0.005], with hypothyroidism showing a strong association [OR=13.97; 95% CI: 4.72–41.31; p=0.005], while hyperthyroidism showed no link (p=0.519) (Table 3).

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Table 3: Risk Factors Associated with Intrauterine Growth Restriction(N=188)

Variables	Category	Case (IUGR) (N=94)	Control (No IUGR) (N=94)	Total	p-Value	OR [95% CI]
Anemia	Yes	49 (52.1%)	16 (17.0%)	65	0.005	5.08 [2.71 – 10.41]
	No	45 (47.9%)	78 (83.0%)	123		
Underweight	Yes	17 (18.1%)	6 (6.4%)	23	0.014	3.24 [1.22 – 8.63]
	No	77 (81.9%)	88 (93.6%)	165		
Pregnancy-Induced Hypertension (PIH)	Yes	21 (22.3%)	8 (8.5%)	29	0.009	3.09 [1.29 – 7.39]
	No	73 (77.7%)	86 (91.5%)	159		
Thyroid Dysfunction	Yes	51 (54.3%)	21 (22.3%)	72	0.005	4.12 [2.19 – 7.76]
	No	43 (45.7%)	73 (77.7%)	116		
Hypo-thyroidism	Yes	36 (38.3%)	4 (4.3%)	40	0.005	13.97 [4.72 – 41.31]
	No	58 (61.7%)	90 (95.7%)	148		
Hyper-thyroidism	Yes	11 (11.7%)	14 (14.9%)	25	0.519	0.75 [0.33 – 1.77]
	No	83 (88.3%)	80 (85.1%)	163		

OR = Odds ratio, CI=Confidence Interval

Multivariate analysis identified anemia and hypothyroidism as significant predictors of IUGR after controlling for confounders, with adjusted odds ratios of 4.23 and 6.04, respectively. Thyroid dysfunction showed a marginal association, while factors such as underweight status, pregnancy-induced hypertension, age, gravida, and parity were not significantly linked to IUGR. The model achieved a 74.5% classification accuracy, correctly identifying IUGR status in most participants (Table 4).

Table 4: Multivariate Analysis Showing the Factors Associated with IUGR(N=188)

Variables	p-Values	Adjusted OR	95% CI for OR	
			Lower	Upper
Age Groups				
≤30	0.430	1.61	0.49	5.28
31–35	0.420	1.65	0.486	5.57
>35	–	Ref	–	–
Gravida				
Primigravida	0.890	0.89	0.159	5.02
Multigravida	–	Ref	–	–
Parity				
Nulliparous	0.070	0.18	0.027	1.18
Primiparous	0.130	0.45	0.162	1.26
Multiparous	–	Ref	–	–
Anemia				
Yes	0.004	4.23	1.60	11.19
No	–	Ref	–	–
Pregnancy-Induced Hypertension				
Yes	0.620	1.315	0.446	3.87
No	–	Ref	–	–
Thyroid Dysfunction				
Yes	0.068	2.24	0.942	5.32
No	–	Ref	–	–
Hypothyroidism				
Yes	0.008	6.04	1.61	22.68
No	–	Ref	–	–
Underweight				
Yes	0.990	0.992	0.261	3.77
No	–	Ref	–	–

Model Accuracy = 74.5% Ref= References, CI=Confidence Interval

DISCUSSION

Hypoxia, impaired neurodevelopment, and metabolic disorders later in life are among the negative neonatal outcomes that IUGR causes globally [12, 13]. The burden is particularly high in low- and middle-income countries, including Pakistan, where limited antenatal screening and nutritional deficiencies are common [14]. According to Sinha et al., the incidence of IUGR was 2.13%, with the majority of cases (48%) occurring in women aged 21–25 years. A separate case-control study reported that 51.9% of IUGR cases fell within the 21–25 age group, followed by 37.0% in the 26–30 age group, and 11.1% in women over 30 [15]. In the control group, the distribution was 40.7% (21–25 years), 48.2% (26–30 years), and 11.1% (>30 years). Several other studies have also identified younger maternal age as a significant risk factor for IUGR. In our study, anemia was found to be a strong independent risk factor for IUGR, with a fivefold higher likelihood among cases. These findings are consistent with previous reports highlighting anemia and antepartum hemorrhage as major contributing factors [16-19]. Hemoglobin deficiency reduces oxygen-carrying capacity, leading to chronic fetal hypoxia and growth restriction. We categorized thyroid dysfunction according to standard pregnancy-specific criteria. The significant association between hypothyroidism and IUGR in our study aligns with prior evidence that maternal thyroid insufficiency impairs placental and fetal development [20, 21]. The distinction between subclinical and overt hypothyroidism is important, as both conditions may increase the risk of adverse pregnancy outcomes, though overt hypothyroidism has a stronger effect on fetal growth restriction. Hypothyroidism remained significant in multivariate analysis, supporting prior evidence that maternal thyroid dysfunction interferes with placental and fetal metabolism, thereby increasing the risk of IUGR. However, some studies reported no association, possibly due to geographical variation [22]. Maternal underweight and hyperthyroidism were not associated with IUGR in multivariate analysis, although underweight status has been identified as a significant risk factor in other studies [17, 23]. Current findings suggest that nutritional and metabolic disturbances may exert their effects indirectly through anemia rather than BMI alone. In our study, the mean BMI was significantly higher among controls compared to cases, suggesting that maternal obesity may

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play a protective role against IUGR. Several studies have reported similar findings, indicating that higher maternal BMI is often associated with increased nutrient availability and placental growth, which may reduce the likelihood of restricted intrauterine growth [24, 25].

However, this does not imply that obesity is beneficial, as excessive maternal weight is independently linked to gestational diabetes, preeclampsia, and cesarean delivery. This study has certain limitations. First, as a single-center case-control study, the findings may not be generalizable to all populations. Second, definitions of IUGR vary across the literature, with some studies using <2 kg birth weight and others using <10th percentile for gestational age, which may introduce comparability bias. Third, only maternal clinical and biochemical factors were considered; fetal and placental parameters such as Doppler indices and congenital anomalies were not assessed. Fourth, the cross-sectional nature of measurements limited the ability to establish temporality between risk factors and IUGR. Lastly, although regression analysis was performed, residual confounding from unmeasured variables such as dietary intake, micronutrient supplementation, and socioeconomic influences cannot be fully excluded.

CONCLUSIONS

Intrauterine growth restriction remains a significant public health concern, particularly in low- and middle-income countries. This study identified maternal anemia and hypothyroidism as independent risk factors, underscoring the importance of routine screening and timely management during pregnancy. Early detection and treatment of these modifiable conditions, coupled with improved antenatal care and nutritional support, may reduce the burden of IUGR and improve neonatal outcomes. Future multicenter prospective studies incorporating both maternal and fetal factors are recommended to strengthen the evidence base and guide preventive strategies at the population level.

Authors' Contribution

Conceptualization: MA
Methodology: MM, MA
Formal analysis: SI
Writing and Drafting: SI
Review and Editing: SI, MM, MA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Prevalence, Severity, and Risk Factors of Neurodevelopmental Delay in Children with Cyanotic Versus Acyanotic CHD in Pakistan: A Cross-Sectional Study

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ABSTRACT

Children with congenital heart disease (CHD) are at increased risk of neurodevelopmental delay due to chronic hypoxemia and associated medical complexities. Measurement of this burden is critical in determining early intervention. **Objectives:** To compare the prevalence, severity, and risk factors of neurodevelopmental delay between cyanotic and acyanotic CHD in a Pakistani cohort. **Methods:** This cross-sectional study was conducted at the Department of Paediatric Cardiology, Quaid-e-Azam Medical College, Bahawalpur, from December 2023 to May 2025. A non-probability consecutive sample of 316 children, aged 6 months to 10 years, was recruited. Neurodevelopment was assessed using the Denver II and Ages & Stages Questionnaires-3 (ASQ-3), administered by trained assessors with inter-rater calibration. Cyanotic CHD and acyanotic CHD were verified by the use of echocardiography. **Results:** The mean age of participants was 4.2 ± 2.1 years; 178 (56.3%) were male. Developmental delay was identified in 186 children (58.9%), more frequent in cyanotic CHD (70.9%) than acyanotic CHD (46.8%) (χ^2=18.7, p<0.001). Cyanotic CHD (OR 2.83, 95% CI: 1.77–4.51), male sex (OR 1.52, 95% CI: 1.01–2.31), low oxygen saturation <85% (OR 3.21, 95% CI: 2.08–4.95), and age <5 years (OR 1.66, 95% CI: 1.11–2.49) were independent predictors. Lower oxygen saturation correlated with greater delay severity (Spearman's ρ=-0.46, p<0.001). **Conclusions:** Neurodevelopmental delay is very common in children with CHD, especially in cyanotic defects and hypoxemia. A routine developmental screening and early rehabilitation exercises may be necessary to prevent the long-term deficits.

INTRODUCTION

Congenital heart disease (CHD) is the most common birth defect in the world [1]. Many children with CHD also have problems with learning, movement, and behavior. In countries like Pakistan, the problem is worse because there are fewer doctors, less screening, and delays in treatment [2, 3]. Each year, about 40,000 babies in Pakistan are born with heart defects, but many are not diagnosed or treated in time [4]. Thanks to better surgeries, more children with CHD now survive [5]. But many still face long-term problems with school, thinking, motor skills, and emotions. Children with serious heart defects that reduce oxygen (like tetralogy of Fallot) are at higher risk of brain injury [6]. Even children with less severe defects (like holes in the heart) can have delays due to infections, poor growth, or surgery risks. Studies in South Asia show many children with CHD struggle with development, but results differ because research methods are not the same everywhere [7]. The mechanisms are multifactorial, involving hypoxaemia, impaired cerebral autoregulation, genetic syndromes, and operative factors

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such as cardiopulmonary bypass [8]. A growing body of literature has highlighted the heightened risk of school underachievement, reduced executive functioning, and increased psychosocial difficulties in these populations [9]. Nevertheless, substantial heterogeneity exists across studies in terms of methodology, neurodevelopmental assessment tools, and follow-up duration, limiting comparability and generalizability [10]. In Pakistan, there are few literature citations available about the neurodevelopmental outcomes of CHD, and whatever has been documented remains quite descriptive in nature. There is no comparative study in existence to identify the relative burden of neurodevelopmental delay of the various subgroups of the cyanotic and the acyanotic subgroups. International findings cannot be uncritically extrapolated to Pakistan, given differences in healthcare infrastructure, delayed diagnosis, and limited availability of rehabilitation services [11]. Domain-level analysis will be addressed in a prospective follow-up cohort. These locally relevant data will be used to provide information to conduct early screening activities, intervention at the appropriate stage, and development of individualized neurodevelopmental rehabilitation strategies in Pakistan.

Although neurodevelopmental impairment in children with congenital heart disease has been widely reported internationally, there is a scarcity of comparative data from Pakistan examining differences between cyanotic and acyanotic subtypes. Existing local studies remain largely descriptive and lack systematic assessment using validated developmental screening tools. Moreover, the contribution of modifiable clinical and socioeconomic risk factors has not been comprehensively evaluated in this population. This gap limits the development of evidence-based screening and rehabilitation pathways tailored to Pakistani children with CHD. This study aims to compare the prevalence of neurodevelopmental delay between cyanotic and acyanotic CHD, severity (number of ASQ-3 domains below cut-off), and to identify risk factors for delay.

METHODS

This cross-sectional study was conducted at the Department of Paediatric Cardiology from December 2023 to May 2025. The data were collected after obtaining an ethical clearance certificate from the IRB of the hospital (Ref. No. 2460/DME/QAMC). The data were collected after obtaining proper verbal consent from the parents/guardians of the child. The required sample was calculated for a single proportion using $n=Z^2p(1-p)/d^2$. An expected prevalence (p) of 0.25 for developmental delay in CHD was taken from Mussatto et al. [12]. With Z=1.96 and d=0.05, the base sample was n=288. A 10% inflation rate for non-response yielded a target of n=317. A total of 316 children were enrolled. The comparative analysis contrasted cyanotic vs acyanotic groups for the primary and secondary outcomes. Children between the ages of 6 months and 10 years with a confirmed diagnosis of cyanotic or acyanotic congenital heart disease were enrolled using a non-probability consecutive sampling method. Children with suspected chromosomal syndromes, significant extracardiac abnormalities, or disabling neurological diseases were excluded. Children's development was tested using two tools: ASQ-3 [13] and Denver II [14]. ASQ-3 checked communication, motor skills, problem-solving, and social skills. Denver II checked social skills, motor skills, language, and adaptation. Scores were compared with normal ranges for age. Low scores in ASQ-3 were marked for referral or follow-up. In Denver II, results were classified as normal, delay, caution, suspect, or untestable. The tests were done by trained pediatric staff who spoke English and Urdu. Parents filled out ASQ-3 forms in Urdu, and Denver II was also given in Urdu with demonstrations. Tests were carried out in a quiet clinic room. To ensure accuracy, some visits were double-checked by two staff members each month. Children with positive results were referred for further clinical evaluation. ASQ-3 was used as the main test, while Denver II confirmed delays. Laboratory measurements, including hemoglobin, hematocrit, and serum electrolytes, were performed on standardized automated analyzers (Sysmex XN-1000, Sysmex Corporation, Japan; and Cobas c 311, Roche Diagnostics, Germany). Internal quality control processes were provided on a daily basis following the manufacturer's guidelines, and external quality assurance was provided in the form of participation in proficiency schemes. Peripheral oxygen saturation was recorded using a validated pulse oximeter (Masimo Radical-7, Masimo Corporation, USA). Data were entered and analyzed in SPSS version 26.0 (IBM, USA). Continuous variables (SpO_2, hemoglobin, hematocrit, ferritin, age) were summarized as mean ± SD; categorical variables as n (%). Shapiro–Wilk tested normality (oxygen saturation: W=0.98, p=0.21), and Levene's test checked variance homogeneity before t-tests/ANOVA. Chi-square tested associations between categorical variables. Independent-samples t-tests were used for normal continuous data; Mann–Whitney for non-normal data. The main result was a low score in at least one ASQ-3 area. Extra results looked at how many areas were delayed and which skills were affected, such as talking, movement, problem-solving, or social skills. Denver II was used to confirm delays and guide referrals. Children with cyanotic and acyanotic heart disease were compared using statistical tests. Cyanotic versus acyanotic comparisons used χ^2 with risk difference, odds ratio, and 95% CI. Associations of SpO_2 and hematocrit with severity were assessed using

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Spearman's ρ with 95% CIs. Risk factors for delay were estimated with multivariable logistic regression, including cyanotic status, age, sex, SpO_2 (per 5% lower), hematocrit, ferritin, nutritional status, socioeconomic status, residence (rural/urban), consanguinity, and surgical history (repaired vs unrepaired; age at surgery). Missing data were minimal (<5%) and were handled through complete-case analysis without imputation.

RESULTS

A total of 316 children were included, of whom 178 (56.3%) were male. The average was 4.2 ±2.1years. Cyanotic congenital heart disease was present in 158 (50.0%) children, while the remaining 158 (50.0%) had acyanotic defects. Biochemical testing was done to confirm that cyanotic children had polycythaemia and also elevated haematocrit typical of chronic hypoxaemia. The serum ferritin levels were also decreased significantly in cyanotic children, and logistic regression confirmed the ferritin deficiency to be an independent prognostic factor of neurodevelopmental delay. Thyroid abnormalities occurred infrequently and were not significantly different between the groups, which suggests that endocrine disruption is not a primary cause in this cohort. Neurodevelopmental delay was common in the cohort and more frequent in cyanotic than acyanotic children. In multivariable analysis, cyanotic status and lower room-air SpO_2 were independently associated with delay. Higher hematocrit showed the expected positive association. After adjusting for age, sex, nutritional status, socioeconomic status, residence, consanguinity, and surgical history, these associations remained. Delay severity increased as SpO_2 decreased, and domain patterns were most pronounced for communication and gross motor. Full estimates with 95% confidence intervals are shown in the regression table. The results showed more developmental delay in children with cyanotic heart disease. Low iron levels and living in rural areas also played a role. Environmental exposures added to the burden. These patterns were similar to those of other low- and middle-income countries. This shows that the effects of congenital heart disease are not only heart-related. They also involve nutrition, social, and environmental factors (Table 1).

Table 1: Baseline Characteristics of Children with Cyanotic and Acyanotic CHD (N=316)

Variables	Cyanotic CHD (N=158)	Acyanotic CHD (N=158)
Age (years), mean ± SD	4.3 ± 2.2	4.1 ± 2.0
Oxygen saturation (%), mean ± SD	82.6 ± 7.4	95.2 ± 2.8
Haemoglobin (g/dL), mean ± SD	16.2 ± 2.3	12.1 ± 1.9
Ferritin (µg/L), median (IQR)	10.8 (7.1–15.4)	14.6 (10.3–20.7)
Hospitalisation days, median (IQR)	7 (5–11)	6 (4–9)
Sex: male, N (%)	90 (57.0)	88 (55.7)
Residence: rural, N (%)	102 (64.6)	80 (50.6)
Parental consanguinity, N (%)	116 (73.4)	88 (55.7)
Corrective surgery, N (%)	44 (27.8)	88 (55.7)
Cyanotic spells, N (%)	84 (53.2)	0 (0.0)

*Continuous data were checked with Shapiro–Wilk and summarized as mean ± SD (normal) or median (IQR) (non-normal). Between-group comparisons, when performed, used t-tests or Mann–Whitney U for continuous variables and chi-square/Fisher's exact for categorical variables.

The study showed the primary outcome (ASQ-3 "refer") by group, with effect size and minimal, focused inference (Table 2).

Table 2: Prevalence of Neurodevelopmental Delay (ASQ-3 "Refer") by CHD Group

Outcome	Cyanotic CHD (N=158)	Acyanotic CHD (N=158)	Effect size/test
Delay (≥1 domain below refers to cut-off), N (%)	112 (70.9)	74 (46.8)	χ^2=18.7, p<0.001; risk difference 24.1 percentage points; crude OR 2.76 (95% CI 1.74–4.40)
No delay, N (%)	46 (29.1)	84 (53.2)	–

*Primary outcome defined as ASQ-3 "refer" (≥1 domain below age-specific referral threshold). Group comparison by chi-square. Effect sizes shown as risk difference (cyanotic minus acyanotic) and crude odds ratio with 95% CI. Two-sided p<0.050 is considered significant.

The study demonstrated that independent predictors from the multivariable model aligned with the study aim; only clinically relevant, significant predictors are shown. Other covariates were entered, but were not significant (Table 3).

Table 3: Independent Predictors of Neurodevelopmental Delay (Multivariable Logistic Regression)

Predictor	Adjusted OR (95% CI)
Cyanotic CHD	2.83 (1.77–4.51)
Oxygen saturation <85%	3.21 (2.08–4.95)
Male sex	1.52 (1.01–2.31)
Age <5 years	1.66 (1.11–2.49)

Outcome: ASQ-3 "refer" (yes/no)

A significant negative correlation between oxygen saturation and developmental delay severity (r= -0.43, p<0.001) and a positive correlation between haematocrit and delay severity (ρ=0.39, p<0.001). Subgroup analysis further confirmed significant differences in oxygen saturation across categories of developmental delay (ANOVA, p <0.001) (Table 4).

Table 4: Correlation and Subgroup Analysis of Continuous and Developmental Variables

Variable Relationship	Correlation Coefficient	95% CI	p-Value
Oxygen saturation vs delay severity*	r = -0.43	-0.52 to -0.32	<0.001
Haematocrit vs delay severity†	ρ = 0.39	0.27 to 0.48	<0.001

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Ferritin vs delay severity†	ρ = -0.28	-0.38 to -0.16	0.002
Oxygen saturation across delay categories (ANOVA)$	F = 15.62	–	<0.001

*Pearson correlation for normally distributed variables; † Spearman correlation for non-normal variables; $ ANOVA used for subgroup comparison across >2 groups.

DISCUSSION

The results of this study showed that neurodevelopmental delay occurred considerably in children with cyanotic congenital heart disease as compared to the children with acyanotic lesions. The percentage concentration of oxygen in the blood, hemoglobin, and haematocrit was proved to vary significantly across the groups, with the cyanotic children having higher values of hypoxaemia and secondary polycythaemia. Serum ferritin depletion was also identified as an important correlate of developmental delay, and rural residence was found to independently predict adverse neurodevelopmental outcomes. The logistic regression also concluded that cyanotic congenital heart disease, living in the countryside, and ferritin insufficiency were the main predictors. These results are in line with sparse national data in Pakistan, where congenital heart disease has long been known to be a leading cause of morbidity in childhood, and its neurodevelopmental outcome has not been comprehensively characterised. Previous study reported developmental concerns in children with cyanotic lesions, but the outcomes were not systematically compared across subtypes [15]. Similarly, Vagha et al. demonstrated high rates of malnutrition and delayed developmental milestones among Pakistani children with complex congenital defects, though neurodevelopmental outcomes were not specifically analyzed [16]. The present study is therefore unique in that it quantitatively assesses neurodevelopmental delay of both cyanotic and acyanotic groups systematically, as well as to define the risk factors in the Pakistani setting. The number of children with developmental problems in this study is similar to reports from India and Nepal. In India, a study found that up to 45% of children had thinking and movement delays after heart surgery [17]. A study in Nepal showed that children with cyanotic heart disease were more likely to have developmental problems than those with acyanotic disease. This was linked to low oxygen and delays in surgery. These results are close to the findings of the current study, showing that low oxygen is a major factor for poor development. The difference in rates between studies may be due to access to surgery, follow-up time, and the tools used for testing. Worldwide, developmental problems in children with heart disease are well known. Hofer *et al.* reported that up to half of survivors had problems with memory, attention, or control of actions [18]. Studies in Europe and North America showed that early surgery lowers death rates but does not prevent delays. Children still had problems with language, motor skills, and spatial understanding. Al-Beltagi *et al.* confirmed that brain growth is delayed in newborns with severe heart disease, and problems begin before surgery as well as during and after it [19]. The current study adds to these findings in Pakistan, where late diagnosis, delays in surgery, poor nutrition, and environmental risks make the problem worse. The cause of these problems is clear. Chronic low oxygen in cyanotic disease reduces blood flow to the brain. Thick blood from polycythaemia also makes brain circulation worse. Both lead to poor brain function. Lack of nutrients, especially low iron, damages brain development by slowing myelination and chemical signals [20]. Social factors, such as parental relation by blood (consanguinity) and living in rural areas, also play a role. They affect access to healthcare and the stage at which the disease is diagnosed. This study has strengths. It is a comparative study, it uses well-tested screening tools, and it focuses on a population where little local data exists. It also highlights risk factors that can be changed, such as iron deficiency [21]. There were some important limitations. Individual areas like thinking and social skills were not studied. The study had a single focus, so results may not apply to all children. There was no long-term follow-up to see if problems continued into adolescence [22]. Using consecutive sampling could cause bias, even though the large sample made it more representative. More detailed psychological tests should have been used. Screening tools alone may have missed mild problems. The findings have important clinical meaning. Early checks for developmental delay should be part of routine heart care in Pakistan. Extra attention is needed for children with cyanotic defects, poor nutrition, or those living in rural areas [23]. Heart clinics should include developmental screening and refer children early for rehabilitation.

This study has certain limitations, including its single-center cross-sectional design, which precludes causal inference and may limit generalizability to other regions of Pakistan. Developmental assessment relied primarily on screening instruments rather than comprehensive neuropsychological batteries, potentially underestimating subtle deficits. Future multicenter longitudinal studies incorporating detailed cognitive testing and long-term follow-up into adolescence are warranted to better delineate developmental trajectories and evaluate the impact of early cardiac intervention and targeted rehabilitation strategies.

CONCLUSIONS

In conclusion, the research has presented information that neurodevelopmental delay is more prevalent in congenital heart disease with cyanosis in Pakistani children than in

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acyanotic. The independent predictors of developmental impairment were discovered to include ferritin deficiency, hypoxaemia, and rural residence, showing that a combination of factors has an influence of the developmental outcomes. The results add locally specific evidence that can help design clinical practice in the country and highlight the necessity of comprehensive cardiac and neurodevelopmental pathways of care in low-income settings.

Authors' Contribution

Conceptualization: IA
Methodology: MAZ, US
Formal analysis: FUR
Writing and Drafting: UM
Review and Editing: UM, FUR, MAZ, US, IA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Knowledge of Breast Cancer Screening and Protection Among Female Health Care Professionals of Federal Government Polyclinic Hospital, Islamabad, and its Allied Dispensaries

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ABSTRACT

Breast cancer is one of the leading causes of mortality among women globally, and Pakistan has the highest breast cancer prevalence in Asia. Despite the importance of early detection through screening and awareness, data on healthcare professionals' (HCPs) knowledge and practices in Pakistan are limited. **Objectives:** To evaluate the knowledge of breast cancer screening and protection among female HCPs at the Federal Government Polyclinic Hospital, Islamabad, and its allied dispensaries. Additionally, it sought to identify gaps in awareness and guide future interventions. **Methods:** A cross-sectional, descriptive study was conducted over six months at the Federal Government Polyclinic Hospital, Islamabad, and its allied dispensaries. A structured, self-administered questionnaire was distributed to 530 female HCPs, including physiotherapists, psychologists, administrative officers, doctors, nurses, and support staff. Data were analyzed using SPSS version 25.0. **Results:** The majority of participants were nurses (37.7%) and aged between 21 and 25 years (24.5%). A large proportion reported no family history of breast cancer (92.8%) and were non-smokers (89.8%). Knowledge regarding breast cancer symptoms, risk factors, and screening methods varied across different roles and educational levels, with junior doctors and postgraduates showing the highest knowledge levels. Despite this, gaps were identified in understanding protective measures and screening practices. **Conclusions:** While awareness of symptoms and risk factors was adequate, there were notable deficiencies in knowledge regarding protective practices and screening behavior. These gaps highlight the need for targeted educational interventions among female HCPs.

INTRODUCTION

Cancer is one of the main causes of death and a significant obstacle to increasing life expectancy worldwide. In 2019, the World Health Organization (WHO) estimated that cancer ranks first or second in 112 out of 183 nations for causing mortality before the age of 70, and third or fourth in another 23 countries. Pakistan has Asia's highest breast cancer incidence, with young women often diagnosed at advanced stages, making prognosis difficult. Annually, the absence of screening facilities leads to many deaths from breast cancer. In Pakistan, breast cancer was responsible for 11.7% (13,725) of all cancer-related deaths and 28.7% (25,928) of all new cases [1, 2]. The age-standardized cases of breast cancer in Pakistan are among the highest in Asia, with one in nine women currently at risk of the disease [3]. Numerous risk factors, such as positive family history, being obese, smoking, alcohol use, early menstruation, late menopause, sedentary lifestyle, hormone replacement treatment, and a history of breast cancer, interact

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intricately to cause breast cancer. Nursing history, physical exercise, and weight loss are factors associated with reduced probability of breast cancer. Having a first-degree relative with breast cancer increases a woman's lifetime risk of developing the disease by two to three times [4, 5]. Early breast cancer diagnosis is a crucial public health approach as it may enhance the probability of timely discovery of the disease and favorable outcomes, which will increase the odds of survival and the quality of life for women [6]. Breast Self-Examination (BSE) may be helpful in regions with limited assets to diagnose any aberrations in the breast, even though mammography is well-known and the most efficient diagnostic tool for early assessment of breast cancer [7]. This is because BSE gives women the chance to understand the physiology of their breasts [8]. Breast Self-Examination (BSE) may be helpful in regions with limited assets to diagnose any abnormalities in the breast [9]. When BCS is conducted by trained personnel, a better attitude is displayed [10]. Therefore, the HCWs' knowledge and abilities must be improved. By regularly evaluating the present awareness, perception, and obstacles regarding breast cancer screening programs, these factors can be addressed among the healthcare workers [11]. In Pakistan, where breast cancer incidence is rising, there is limited research on the awareness and practices of female HCPs [12]. Despite the critical role of healthcare professionals in promoting breast cancer awareness and screening, there is a lack of comprehensive data on their actual knowledge, attitudes, and practices within the Pakistani healthcare context, particularly among female staff at public sector institutions. The goal of this study is to assess the knowledge of breast cancer screening and protection among female health care professionals at the Department of Diagnostic Radiology, Federal Government Polyclinic Hospital, Islamabad, and its allied dispensaries.

Despite the rising burden of breast cancer in Pakistan and the critical role of healthcare professionals in promoting early detection, there remains a scarcity of institution-based data assessing their actual knowledge and screening practices. Most local studies have focused on the general population rather than healthcare workers, particularly female professionals working in public sector hospitals. Furthermore, discrepancies between awareness and practical implementation of screening behaviors remain underexplored. This gap highlights the need for a structured evaluation of breast cancer screening knowledge and protective practices among female healthcare professionals in Islamabad. Therefore, this study aims to evaluate the knowledge of breast cancer screening and protection among female HCPs at the Federal Government Polyclinic Hospital, Islamabad, and its allied dispensaries. Additionally, it sought to identify gaps in awareness and guide future interventions.

METHODS

This cross-sectional descriptive study was carried out at the Federal Government Polyclinic Hospital, Islamabad, and its affiliated dispensaries. The study was conducted over a period of six months, from August 2024 to January 2025, at the Department of Diagnostic Radiology, Federal Government Polyclinic Hospital, and its four allied dispensaries. Approval from the Institutional Ethical Review Board was obtained from the Federal Government Polyclinic Hospital, Islamabad (Ref. No. FGPC.1/12/2023/Ethical Committee) before the study. Verbal informed consent and willingness were obtained from the healthcare professionals through the survey. Anonymity was ensured to protect the individuals' identities and confidentiality. The inclusion criteria included female HCPs working at the Federal Government Polyclinic Hospital and its allied dispensaries. Male HCPs and individuals unwilling to participate were excluded. Data were collected using a structured, self-administered questionnaire designed to assess knowledge, attitudes, and practices related to breast cancer screening and protection. A sample size of 600 was planned using a standard sample size formula, with a 95% confidence level, an expected proportion of 0.5 (50%), and a 5% margin of error. This calculation also accounted for potential non-responses to ensure an adequate number of completed questionnaires for analysis. The study population comprised 163 female doctors, physiotherapists, psychologists, and administrative officers, 197 female nurses, and 170 female support healthcare staff. A total of 600 structured questionnaires were distributed; however, 530 participants were recruited in the research, selected through a non-probability consecutive sampling technique. The structured questionnaire was pre-tested for content validity and construct reliability among a sample of 30 healthcare professionals before the main study to ensure accuracy. A non-probability consecutive sampling technique was used in this study due to practical considerations, including limited access to participants, time constraints, and the structured work environment of healthcare professionals. This approach involved recruiting all eligible and available female healthcare professionals during the data collection period. The structured questionnaire comprised three sections: the first section focused on demographic details, the second section on knowledge of breast cancer, and the third section on screening practices, ways of protection, and awareness of the breast cancer screening center established at the Polyclinic Hospital. All documentation, record maintenance, and data analysis were carried out

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using SPSS version 25.0. Descriptive statistics were analyzed for variables. Statistical correlation was performed using ANOVA and t-tests. ANOVA was used to assess differences across multiple groups (e.g., by designation and education level), while t-tests were used for pairwise comparisons (e.g., between family history groups). Following significant ANOVA results, post-hoc comparisons were performed using Tukey's Honestly Significant Difference (HSD) test, with the significance level set at $p < 0.050$ to identify group differences.

RESULTS

A total of 530 health care professionals of the federal Government polyclinic hospital, Islamabad, participated in the study. The largest cohort of participants was from the age group 21-25 years. Most of the participants were single (N=290, 44.9%) and from Islamabad (N=396, 74.7%). (N=130, 24.5%). The majority of the respondents comprised nurses (N=200, 37.7%). The age of Puberty of most of the participants was between 13 and 15 years (N=344, 64.9%). A great number of samples comprised of graduates (N=248, 46. 8%). Most of the healthcare professionals reported no family History of Breast cancer (N=492, 92.8%) and no relative with a positive history of breast cancer (N=490, 92.5 %). Besides this, the maximum number of participants had no history of hormonal intake (N=496, 93.6%) and were non-smokers (N=476, 89.8%) with no history of breast surgery (N=514, 3.0%). The participants who were from Islamabad have more knowledge about the risk factors ($p>0.001$) and perform self-breast examination ($p<0.005$) (Table 1).

Table 1: Socio-Demographic Characteristics of Female Healthcare Professionals

Variables	Category	Frequency (%)
Age	Up to 20 years	32 (6.0%)
	21-25	130 (24.5%)
	26-30	124 (23.4%)
	31-35	76 (14.3%)
	36-40	48 (9.1%)
	41-45	40 (7.5%)
	46-50	32 (6.0%)
	51-55	32 (6.0%)
	56-60	10 (1.9%)
	Above 60	6 (1.1%)
Designation	Support Staff	30 (5.7%)
	Technicians	68 (12.8%)
	Nurse	200 (37.7%)
	Junior Doctor	102 (19.2%)
	Trainee Doctor	100 (18.9%)
	Consultant Doctor	30 (5.7%)
Marital Status	Married	290 (54.7%)
	Single	238 (44.9%)
	Divorced	2 (4%)
Residence	Islamabad	396 (74.7%)
	Outside Islamabad	134 (25.3%)
Age of Puberty	10-12 years	148 (27.9%)
	13-15 years	344 (64.9%)
	Above 15 years	38 (7.2%)
Age of Puberty	10-12 years	148 (27.9%)
	13-15 years	344 (64.9%)
	Above 15 years	38 (7.2%)
Qualification	Primary	10 (1.9%)
	Secondary	40 (7.5%)
	Higher Secondary	162 (30.6%)
	Graduate	248 (46.8%)
	Post Graduate	70 (13.2%)
Family History	No Family History of Breast Cancer	492 (92.8%)
	Positive Family History of Breast Cancer	38 (7.2%)
Relative to Breast Cancer	No relative with Breast Cancer	490 (92.5%)
	Mother	12 (2.3%)
	Sister	4 (8%)
	Maternal Aunt/Relative	10 (1.9%)
	Paternal Aunt/Relative	14 (2.6%)
Birth of a Child	No alive issue	294 (55.5%)
	One or More Births	236 (44.5%)
Age at Birth of 1st Child	Never Given Birth	262 (49.4%)
	Less than 20 years	42 (7.9%)
	20-30 years	204 (38.5%)
	30-40 years	22 (4.2%)
Hormonal Intake	No history of Hormonal Intake	496 (93.6%)
	Positive History of Hormonal Intake	34 (6.4%)
Smoking	Non-Smoker	476 (89.8%)
	Smoker	54 (10.2%)

The participants with positive family history best know the protection methods ($p<0.001$) and screening methods ($p<0.001$). Furthermore, the results indicated that the participants with no family history of breast cancer have greater knowledge about the self-breast examination($p<0.001$), and they know that breast cancer is curable ($p<0.050$) and perform self-breast examination($p<0.010$). Furthermore, they have visited the clinician for breast examination ($p<0.001$) and have done their ultrasounds ($p<0.001$) and mammograms ($p<0.001$) as compared to the participants with positive family history of breast cancer (Table 2).

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Table 2: Comparison of Breast Cancer Awareness and Practices Based on Family History Among Female HCPs

Variables	No Family History of Breast Cancer (Mean ± SD)	Positive Family History of Breast Cancer (Mean ± SD)	p-Value	t-Value (df)	Confidence Interval (95%)
How to protect oneself from it	1.77 ± 0.42	2.00 ± 0.00	<0.001	-3.34 (528)	-0.36 to -0.09
How can screening be done	2.56 ± 1.26	2.84 ± 1.00	0.001	-1.34 (528)	-0.69 to 0.13
Do you know about breast self-examination	1.13 ± 0.34	1.05 ± 0.23	0.001	1.45 (528)	-0.03 to 0.19
Is breast cancer curable	1.04 ± 0.18	1.00 ± 0.00	<0.001	1.19 (528)	-0.02 to 0.09
Do you do breast examination	1.29 ± 0.46	1.21 ± 0.41	0.010	1.10 (528)	-0.07 to 0.23
Have you ever been examined by a clinician	1.89 ± 0.31	1.74 ± 0.45	<0.001	2.93 (528)	0.05 to 0.26
Have you ever undergone a breast ultrasound	1.93 ± 0.25	1.84 ± 0.37	<0.001	2.00 (528)	0.00 to 0.17
Have you ever undergone a mammography	1.98 ± 0.13	1.79 ± 0.41	<0.001	7.04 (528)	0.14 to 0.25

The significant differences exist among health care professionals across different designations. Moreover, it illustrates that the Junior doctors have maximum knowledge about the symptoms of breast cancer and screening methods, while the Junior, Trainee, and Consultant doctors have almost equal knowledge about the strategies of protection from breast cancer as compared to others. Additionally, the trainee doctors and consultants have good information about the risk factors. Similarly, the trainee doctors know more about the age at which mammography has to be done. Furthermore, the technicians responded more positively to the question about the cure of breast cancer. Moreover, the consultants more frequently performed self-breast examination, and Trainee doctors have visited the clinician for breast examination as compared to other professionals (Table 3).

Table 3: Differences in Knowledge of Breast Cancer Screening and Protection Across Professional Designations

Variables	Support Staff Mean ± SD	Technician Mean ± SD	Nurse Mean ± SD	Junior Doctor Mean ± SD	Trainee Doctor Mean ± SD	Consultant Mean ± SD	F (5, 524)	p-Value	η^2	Post-Hoc Comparison
What do you know about the symptoms of breast cancer	2.20 ± 0.55	2.18 ± 0.71	2.27 ± 0.76	3.12 ± 0.84	2.88 ± 0.82	2.80 ± 0.55	25.64	<0.001	0.19	1 > 2 < 3 > 4 < 5 < 6
What are the risk factors	2.13 ± 0.82	1.91 ± 0.82	2.07 ± 0.85	2.90 ± 0.82	3.02 ± 0.86	3.00 ± 0.64	32.73	<0.001	0.24	1 < 2 > 3 < 4 < 5 > 6
How to protect one self from it	1.47 ± 0.51	1.68 ± 0.47	1.78 ± 0.42	1.88 ± 0.32	1.86 ± 0.35	1.87 ± 0.35	7.05	<0.001	0.06	1 < 2 < 3 < 4 > 5 < 6
How can screening be done	1.60 ± 0.97	2.06 ± 1.12	2.35 ± 1.35	3.14 ± 0.99	3.00 ± 1.08	3.00 ± 0.92	16.54	<0.001	0.13	1 < 2 < 3 < 4 > 5 = 6
Mammography is done at what age	2.27 ± 1.36	2.68 ± 1.44	3.07 ± 1.30	3.22 ± 0.94	3.26 ± 1.00	3.13 ± 1.22	4.86	<0.001	0.04	1 < 2 < 3 < 4 < 5 > 6
Is breast cancer curable	1.00 ± 0.00	1.12 ± 0.33	1.05 ± 0.22	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	5.25	<0.001	0.04	1 > 2 > 3 < 4 = 5 = 6
Frequency of breast self-examination	0.80 ± 1.13	1.44 ± 1.09	1.40 ± 1.07	1.33 ± 1.14	1.44 ± 1.16	2.33 ± 0.96	6.18	<0.001	0.06	1 < 2 > 3 < 4 > 5 < 6
Have you ever been examined by a clinician	1.87 ± 0.35	1.91 ± 0.28	1.89 ± 0.31	1.90 ± 0.29	1.92 ± 0.27	1.60 ± 0.49	5.33	<0.001	0.05	1 > 2 > 3 < 4 < 5 > 6

The results depict that post-graduates have more knowledge about the symptoms of breast cancer, while the graduates are well aware of the risk factors of breast cancer. Additionally, Graduates and post-graduates have greater and approximately equal knowledge about the protection strategies. Similarly, the postgraduates have sound knowledge about the screening methods, and the mammography age is higher in postgraduates and decreases with lower qualification levels. Moreover, the post-graduates are more concerned about breast self-examination, while the ratio of mammography is higher among the supporting staff. Furthermore, the consultants have argued more about why they have not undergone mammography (Table 4).

Table 4: Knowledge of Breast Cancer Screening and Practices Across Education Levels Among Female HCPs

Variables	Primary Mean ± SD	Secondary Mean ± SD	Higher Secondary Mean ± SD	Graduate Mean ± SD	Postgraduate Mean ± SD	F (5, 524)	p-Value	η^2	Post-Hoc Comparison
What do you know about symptoms of breast cancer	2.40 ± 0.52	1.95 ± 0.59	2.27 ± 0.80	2.77 ± 0.83	2.86 ± 0.77	18.24	<0.001	0.12	1 > 2 < 3 < 4 < 5
What are the risk factors	2.20 ± 0.78	1.75 ± 0.77	2.06 ± 0.85	2.74 ± 0.92	2.71 ± 0.88	22.72	<0.001	0.14	1 > 2 < 3 < 4 > 5
How to protect oneself from it	1.40 ± 0.52	1.40 ± 0.49	1.75 ± 0.43	1.87 ± 0.34	1.86 ± 0.35	16.32	<0.001	0.11	1 = 2 < 3 < 4 ≈ 5
How can screening be done	1.20 ± 0.42	1.60 ± 1.03	2.07 ± 1.18	3.00 ± 1.18	3.03 ± 0.88	30.78	<0.001	0.19	1 < 2, 3 < 4 < 5
Mammography is done at which age	1.60 ± 1.26	2.05 ± 1.38	2.94 ± 1.37	3.20 ± 1.03	3.49 ± 0.94	15.05	<0.001	0.10	1 < 2 < 3 < 4 < 5

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If yes, how frequently	1.00 ± 1.33	1.25 ± 1.15	1.28 ± 1.13	1.41 ± 1.06	1.91 ± 1.19	4.65	0.001	0.03	1 < 2 < 3 < 4 < 5
Have you ever undergone a mammography	2.00 ± 0.00	1.95 ± 0.22	1.98 ± 0.16	1.98 ± 0.13	1.91 ± 0.28	2.54	0.040	0.02	1 > 2 < 3 = 4 > 5
If not, why	1.60 ± 1.26	1.80 ± 1.74	1.52 ± 1.98	1.73 ± 2.00	2.60 ± 2.10	3.76	0.010	0.03	1 < 2 > 3 < 4 < 5

Additionally, the correlation analysis also proved that the knowledge about the symptoms of breast cancer has a significant negative correlation with the knowledge about self-breast examination and clinical breast examination. Moreover, a positive correlation exists between the knowledge and practice of self-breast examination (Table 5).

Table 5: Correlation Between Breast Cancer Knowledge Variables and Screening Practices

Variables	1	2	3	4	5	6	7	8	9	10	11	12
1. What do you know about symptoms of breast cancer	1	.58**	.32**	.42**	.16**	-.24**	-.25**	-.10*	-.08	-.06	-.04	.09*
2. What are the risk factors	-	1	.31**	.58**	.25**	-.22**	-.31**	-.17**	-.06	-.01	-.00	.05
3. How to protect oneself from it	-	-	1	.35**	.18**	-.33**	-.30**	-.11*	-.12**	.04	-.00	.07
4. How can screening be done	-	-	-	1	.22**	-.33**	-.31**	-.12**	-.19**	-.06	-.00	.05
5. Mammography is done at which age	-	-	-	-	1	-.16**	-.17**	-.12**	.05	-.04	-.12**	-.08
6. Do you know about self-breast examination	-	-	-	-	-	1	.49**	.17**	.35**	-.04	.07	.00
7. Do you know about clinical breast examination	-	-	-	-	-	-	1	.12**	.21**	.06	.07	-.08
8. Is breast cancer curable	-	-	-	-	-	-	-	1	.01	.00	.05	.03
9. Do you do self-breast examination	-	-	-	-	-	-	-	-	1	.18**	.15**	.06
10. Have you ever been examined by a clinician	-	-	-	-	-	-	-	-	-	1	.65**	.21**
11. Have you ever undergone a breast ultrasound	-	-	-	-	-	-	-	-	-	-	1	.28**
12. Have you ever undergone a mammography	-	-	-	-	-	-	-	-	-	-	-	1

*Ssignificance is indicated as: $p < 0.050 \rightarrow *$, $p < 0.010 \rightarrow **$

DISCUSSION

Breast cancer remains an important public health concern in Pakistan, with the highest incidence rate in Asia. The findings reveal several important aspects of the current state of knowledge and practices among female HCPs, which play a vital role in designing valuable interventions. The study found that the majority of participants were nurses (37.7%), followed by junior doctors (19.2%) and trainee doctors (18.9%). Most participants were aged 21–25 years (24.5%), and the majority were graduates (46.8%). These demographics show the composition of the healthcare workforce in the region and emphasize the need for targeted training programs, particularly for younger and less experienced HCPs. A significant finding was that 92.8% of participants reported no family history of breast cancer, and 92.5% had no relatives with breast cancer. This aligns with data available on breast cancer from the WHO 2024 [13], which states that having a family history of breast cancer raises the risk of getting the disease, even though the majority of women who receive a breast cancer diagnosis do not have a known family history of the condition. About 5–10% of instances of breast cancer are linked to a family history, making family history a significant contributing factor for the disease [14]. However, the study also revealed that participants who had a positive family history of breast cancer had better knowledge of protection methods and diagnostic techniques, revealing that self or family exposure to the disease may increase awareness levels. This aligns with previous researchers who reported that women were more likely to undergo mammography screenings if they had a family history of cancer, and their study demonstrated that family history is really important in determining women's knowledge of and involvement in breast cancer assessment. Women may be advised to prioritize and take part in routine screening tests if they have a family history of cancer. Self or family history of benign breast disease was substantially related to all screening practices [15]. According to previous research, breast cancer diagnostic practices like CBE and mammography are significantly positively correlated with a family history of cancer, and a history of breast diseases in oneself, friends, and peers [16]. The study identified significant differences in knowledge levels across different designations and education levels. Junior doctors and postgraduates demonstrated higher knowledge of breast cancer signs, contributing factors, and assessment methods compared to support staff and technicians. The study findings of earlier researchers showed limited female health workers' knowledge towards breast cancer, finding a negative attitude (16.1%) and a lack of knowledge about the signs and risk factors (48.6%) of breast cancer. Mammography screening was frequently hindered by concerns about radiation exposure (57%) and the stress of finding cancer (57.2%). Lack of knowledge of mammograms was found to be substantially correlated with age ($p=0.030$) and the category of healthcare workers (physicians: $p=0.016$). The study also revealed that

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participants from Islamabad had better knowledge of risk factors and had a higher likelihood of doing SBE than those from outside Islamabad [11]. This highlights the urban–rural divide in healthcare access and awareness. One of the most concerning findings was the low rate of self-breast examination (SBE) and clinical breast examination (CBE) among participants. Only a small percentage of participants reported performing SBE regularly, and even fewer had undergone CBE or mammography. Osei-Afriyie et al. explored that less than 50% of individuals underwent BSE, 10% underwent CBE, and 2.3% underwent mammography in the studied population [6]. Similarly, a study conducted in Bangladesh highlighted that despite relatively high awareness levels, the actual practice of breast cancer screening remained very limited [17]. Factors such as fear of diagnosis, perceived invulnerability, cultural beliefs, lack of time, or access to services may act as barriers, even when awareness is high. In line with our findings, research from Tanzania also demonstrated the effectiveness of clinical breast examination and fine-needle aspiration cytology as early detection tools in low-resource healthcare settings [18]. This is a serious situation because breast cancer is becoming more widespread in this region of the world. Correlation analysis revealed a positive relationship between knowledge of breast cancer symptoms and awareness of contributing factors, protection methods, and screening techniques. However, there was a negative correlation between knowledge of symptoms and the practice of SBE and CBE. This suggests that while HCPs may be aware of the importance of screening, they may not be applying this knowledge in practice. Interestingly, the results showed several inverse relationships between knowledge and screening practices. For instance, participants with greater awareness of breast cancer risk factors and symptoms did not consistently report higher rates of self-breast examination or clinical screening. This suggests a possible gap between knowledge and actual health-seeking behavior [19]. The value of concise, web-based learning activities tailored to address knowledge gaps in rapidly evolving fields like breast cancer, particularly for general oncologists who need to stay updated on the latest research and guidelines, must be highlighted. Such targeted educational tools can help nonspecialists remain informed and improve their practice in complex, fast-changing medical disciplines [20]. This study has limitations that should be accounted for when analyzing its outcomes. Firstly, it was conducted at a single hospital in Islamabad, which limits the generalizability of the results to other healthcare settings or regions in Pakistan. Secondly, the reliance on self-reported data can result in response bias, as participants may have overestimated their knowledge or practices.

This study has several limitations, including its single-center design and use of non-probability consecutive sampling, which may limit the generalizability of the findings to other healthcare settings in Pakistan. The reliance on self-reported responses introduces the possibility of reporting and social desirability bias. Additionally, the exclusion of male healthcare professionals restricts a comprehensive understanding of the broader healthcare workforce's role in breast cancer awareness and screening practices. Future research should incorporate multicenter studies with probability-based sampling, include both male and female healthcare professionals, and utilize objective assessment tools to provide a more comprehensive perspective on breast cancer screening knowledge and protective behaviors across the healthcare sector in Pakistan.

CONCLUSIONS

This study revealed that while female healthcare professionals at the Federal Government Polyclinic Hospital and its allied dispensaries demonstrated a reasonable level of awareness regarding the symptoms and risk factors of breast cancer, significant gaps remain in their knowledge and practices related to screening and protective measures. The findings highlight the need for targeted educational interventions and awareness programs to enhance early detection efforts and promote proactive screening behaviors. Strengthening knowledge among healthcare professionals is important not only for their personal health but also for their role in educating and influencing the wider community. Future research should explore the effectiveness of such interventions and aim to include broader healthcare settings for more generalizable outcomes.

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Authors' Contribution

Conceptualization: SS, JE
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Formal analysis: SS, JE, FJ, MB, AH
Writing and Drafting: SS, JE, FJ, MB, AH, AR, Z, R
Review and Editing: SS, JE, FJ, MB, AH, AR, Z, R

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Correlation of Carpal Tunnel Syndrome with Hand Grip Strength among Pregnant Females: A Cross-Sectional Study

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ABSTRACT

Pregnancy induces physiological changes, including hormonal fluctuations and fluid retention, which may affect musculoskeletal function. These factors can reduce hand grip strength (HGS) and increase susceptibility to Carpal Tunnel Syndrome (CTS), caused by median nerve compression. CTS symptoms, including pain, numbness, and weakness, may hinder daily activities. Early detection during pregnancy is crucial for timely intervention. **Objectives:** To determine the frequency of hand-grip weakness (HGW) among pregnant women and to evaluate its correlation with clinical signs of CTS. **Methods:** This analytical cross-sectional study was conducted with 292 pregnant women aged 18–45 years, recruited through non-probability purposive sampling from multiple Karachi hospitals. HGS was measured with a Camry EH101 dynamometer following ASHT protocol; CTS was assessed using Phalen's and Tinel's tests. Data were analyzed using descriptive statistics, Chi-square, t-tests, ANOVA, and correlation analysis. **Results:** HGW was observed in 92.8% of participants. Phalen's and Tinel's tests were positive in 62.0% and 56.5%, respectively, and both showed significant associations with weak grip ($p<0.001$). Correlation analysis confirmed positive associations (Phalen's $r=0.301$, Tinel's $r=0.264$, $p<0.001$). Mean grip strength was lower in the weak group (16.11 ± 3.59) than in the normal group (23.93 ± 2.56; $p<0.001$), with no significant trimester differences. **Conclusions:** HGS measurement is a simple, non-invasive screening tool for early detection of CTS in pregnancy. Routine incorporation into antenatal care may facilitate timely management and preserve maternal hand function. Longitudinal studies are recommended.

INTRODUCTION

Pregnancy induces physical, physiological, emotional, social, and musculoskeletal changes, often reducing quality of life [1, 2]. Organ systems undergo significant transformations, creating a distinct physiology [3]. Despite challenges, pregnancy offers physiological and emotional benefits, enhancing long-term well-being through hormonal shifts, healthier lifestyles, and reduced cancer risk [4]. Mental health also improves, strengthening relationships and building resilience [5]. Hormones during pregnancy and breastfeeding cause structural changes in the musculoskeletal system, essential for movement. A measurable marker of musculoskeletal health is Hand Grip Strength (HGS), a reliable indicator of overall health that reflects immune function, nutritional status, bone density, and muscle strength, especially relevant during pregnancy and postpartum. Hormonal variations like elevated estrogen and fluid retention contribute to reduced HGS, measured by a handgrip dynamometer. HGS strongly correlates with physical traits across age and gender. Reduced HGS in pregnant women has significant implications, impairing daily activities, underscoring the need to monitor maternal health [6, 7]. Carpal Tunnel

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Syndrome (CTS), common in pregnancy, involves median nerve compression due to hormonal changes, ligament laxity, or fluid retention [8, 9]. CTS causes pain, numbness, tingling, burning, reduced sensation, and disturbed sleep, affecting up to 70% of pregnant women, often after 30 weeks of gestation. Prolonged CTS can lead to thenar muscle atrophy, impairing hand function [10, 11]. Peripheral edema and fluid retention, common pregnancy conditions, exacerbate CTS symptoms. About 80% of pregnant women experience peripheral edema, often from hormonal fluid retention and reduced venous return [10]. Approximately 62% report fluid retention, worsening CTS symptoms [12, 13]. Relaxin secretion may also contribute by promoting fluid accumulation, decreasing blood flow to the median nerve, and thickening the carpal ligament, furthering nerve compression [14, 15]. Lumbrical muscles, essential for grip strength, are affected in CTS as finger flexion power decreases due to median nerve involvement [16, 17]. CTS symptoms typically intensify as pregnancy progresses, with studies showing a marked increase in the third trimester [18, 19]. Wrist pain patterns vary with parity and hormonal fluctuations. Evidence reveals 74.5% of pregnant women experience reduced grip strength in the dominant hand and 83.9% in the non-dominant hand. Compared to non-pregnant women, pregnant individuals show significantly diminished HGS, linked to higher body fat, parity, and hormonal changes [3, 6, 13]. Despite its prevalence, CTS often goes underdiagnosed; only 35% of symptomatic women seek medical care [20, 21]. Pregnancy can trigger first CTS episodes or worsen pre-existing symptoms, prompting medical consultation [14]. This underrecognition highlights the need for enhanced clinical awareness. This study focuses on HGS as a potential indicator of CTS in pregnancy, addressing a gap in the literature. By exploring this association, the study aims to support the development of simple, non-invasive screening protocols using HGS measurements for early CTS detection during prenatal care. Identifying grip weakness is crucial for recognizing contributing factors like hormonal shifts, edema, and altered biomechanics, aiding in enhanced care through interventions such as early screening, physical therapy, ergonomic modifications, and preventative strategies. Understanding the HGS-CTS relationship may improve clinical decision-making and prenatal care by enabling earlier treatment and symptom management. Currently, most literature on CTS in pregnancy emphasizes its symptoms, including pain, numbness, and tingling, while overlooking its direct effect on HGS [19]. This lack of focus limits a comprehensive understanding of the musculoskeletal impacts of pregnancy and their functional consequences. Pregnant women were chosen because hormonal changes, ligamentous laxity, and fluid retention during pregnancy increase intracarpal pressure and median nerve compression, making them especially vulnerable to CTS.

Although Carpal Tunnel Syndrome (CTS) is frequently reported during pregnancy, most existing literature primarily focuses on sensory symptoms such as pain, numbness, and tingling, with limited emphasis on its functional impact on hand grip strength (HGS). Moreover, local data examining the association between HGS and clinical CTS signs among pregnant women remain scarce. The lack of simple, objective screening indicators limits early identification and timely management of pregnancy-related CTS. Therefore, investigating HGS as a potential functional marker for CTS in pregnancy is essential to bridge this gap. This study aims to determine the frequency of hand grip weakness among pregnant women and to evaluate its correlation with clinical signs of Carpal Tunnel Syndrome.

METHODS

This analytical cross-sectional study was conducted from September 2024 to February 2025 at Dow University of Health and Sciences (Ojha Campus), Sindh Government Hospitals, and Al Tibri Medical College and Hospital. Ethical approval was obtained from the Institutional Review Board of the Sindh Institute of Physical Medicine and Rehabilitation, Karachi (Ref. No. SIPM&R/IRB/2024/50). The study used a non-probability purposive sampling method to recruit eligible pregnant women within the study timeframe. Exclusion criteria included comorbidities such as diabetes, hypertension, thyroid, cardiovascular, or neurological disorders (e.g., multiple sclerosis, Parkinson's), previous CTS diagnosis, limb or head injuries, rheumatoid arthritis, or gout. To reduce potential selection bias, participants were drawn from multiple hospitals across Karachi to enhance representativeness. A total of 292 pregnant women aged 18–45 years, in any trimester, and either primigravida or multigravida were enrolled after providing informed consent. The sample size was calculated using OpenEpi (Version 3.01), based on a reported 74.5% prevalence of hand grip weakness (HGW) among pregnant women, a 5% margin of error, and a 95% confidence interval, yielding approximately 292 participants [6]. Demographics, medical history, and assessments were recorded using a structured proforma. HGS was measured using a Camry EH 101 mechanical hand grip dynamometers. Participants, seated comfortably, gripped the device with maximal effort using their dominant hand. Arm and wrist positions were standardized according to the American Society of Hand Therapists (ASHT) protocol: shoulder adducted, elbow flexed at 90°, forearm neutral, and wrist in 0–30° extension. Three readings were taken with >30 seconds rest between each,

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and the mean was recorded in kilograms. Grip strength was classified as 'weak' or 'normal' based on age- and sex-matched reference values, with values below the 25th percentile considered weak [7]. CTS was assessed using Tinel's sign and Phalen's test [22]. For Tinel's sign, participants sat with forearms supported while the examiner tapped over the median nerve at the distal wrist crease; tingling in the fingers indicated a positive result. For Phalen's test, participants flexed their wrists fully by pressing the backs of their hands together for 60 seconds; paresthesia indicated a positive result. Reported sensitivity and specificity were 66%/94% for Tinel's sign and 78%/94% for Phalen's test [23]. Dependent variables were HGW and CTS, while independent variables included age, trimester, gestational age, and parity. Data analysis was performed using IBM SPSS Statistics Version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize data: means and standard deviations for continuous variables, and frequencies with percentages for categorical variables. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests; as data were normally distributed ($p > 0.050$), parametric tests (Independent t-test and one-way ANOVA) were applied. Chi-square tests examined associations between categorical variables, and Spearman's correlation assessed the relationship between grip strength and CTS signs, as Phalen's and Tinel's tests are binary categorical variables (Figure 1).

Age	Male (kg)			Female (kg)		
	Weak	Normal	Strong	Weak	Normal	Strong
10-11	<12.6	12.6-22.4	>22.4	<11.8	11.8-21.6	>21.6
12-13	<19.4	19.4-31.2	>31.2	<14.6	14.6-24.4	>24.4
14-15	<28.5	28.5-44.3	>44.3	<15.5	15.5-27.3	>27.3
16-17	<32.6	32.6-52.4	>52.4	<17.2	17.2-29.0	>29.0
18-19	<35.7	35.7-55.5	>55.5	<19.2	19.2-31.0	>31.0
20-24	<36.8	36.8-56.6	>56.6	<21.5	21.5-35.3	>35.3
25-29	<37.7	37.7-57.5	>57.5	<25.6	25.6-41.4	>41.4
30-34	<36.0	36.0-55.8	>55.8	<21.5	21.5-35.3	>35.3
35-39	<35.8	35.8-55.6	>55.6	<20.3	20.3-34.1	>34.1
40-44	<35.5	35.5-55.3	>55.3	<18.9	18.9-32.7	>32.7
45-49	<34.7	34.7-54.5	>54.5	<18.6	18.6-32.4	>32.4
50-54	<32.9	32.9-50.7	>50.7	<18.1	18.1-31.9	>31.9
55-59	<30.7	30.7-48.5	>48.5	<17.2	17.2-31.5	>31.5
60-64	<28.2	28.2-44.0	>44.0	<15.4	15.4-27.2	>27.2
70-99	<21.3	21.3-35.1	>35.1	<14.7	14.7-24.5	>24.5

Figure 1: Reference Values for Handgrip Dynamometer

RESULTS

A total of 292 participants were enrolled and included in the final analysis, with no dropouts, deaths, or missing data. All participants completed the study, and none were lost to follow-up. Group-wise classification was not applicable, as all participants were analyzed as a single. Normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, both of which indicated that the data were normally distributed ($p>0.050$), supporting the use of parametric statistical analyses for further evaluation. The following table summarizes the key demographic characteristics of the study participants. The total number of participants was 292. Among these, the majority of pregnant females were in the third trimester of pregnancy (47.6%). A larger proportion of the participants had experienced previous pregnancies (69.5%). Additionally, most participants were right-handed (93.5%) (Table 1).

Table 1: Demographic Characteristics of Study Participants (N=292)

Variables	Category	Frequency (%)
Trimester	First	56 (19.2%)
	Second	97 (33.2%)
	Third	139 (47.6%)
Gravida	Primigravida	89 (30.5%)
	Multigravida	203 (69.5%)
Hand dominance	Right-handed	273 (93.5%)
	Left-handed	19 (6.5%)
Total participants		292 (100%)

Among pregnant participants, the majority, 92.8% (n = 271), exhibited weak hand grip strength, whereas only 7.2% (n=21) demonstrated normal strength (Figure 2).

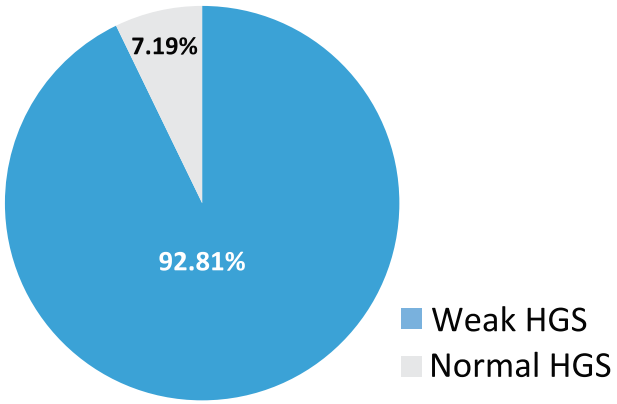

Figure 2: Frequency of HGW

Phalen's test, an indicator of CTS, was positive in 62.0% (n=181) of pregnant females and negative in 38.0% (n=111). Similarly, Tinel's sign was positive in 56.5% (n=165) and negative in 43.5% (n=127) (Figure 3).

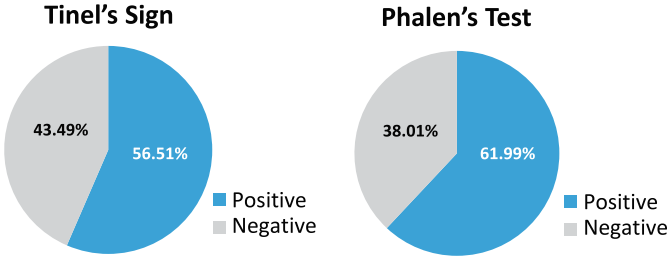

Figure 3: Frequencies of Tinel's Sign and Phalen's Test

Among participants, 92.8% (n=271) had weak hand grip strength, while 7.2% (n=21) demonstrated normal strength. Phalen's test was positive in 62.0% and Tinel's sign in 56.5% of participants. Chi-square analysis confirmed significant associations between weak hand grip strength and both Phalen's and Tinel's tests ($p<0.001$) (Table 2).

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Table 2: Association and Correlation Between Hand Grip Weakness and Clinical Tests for Carpal Tunnel Syndrome

Test	Group	Weak n (%)	Normal n (%)	Total n (%)	Pearson Chi-Square	p-Value
Phalen's Test	Positive	179 (98.9)	2 (1.1)	181 (100.0)	26.430	<0.001*
	Negative	92 (82.9)	19 (17.1)	111 (100.0)		
Tinel's Sign	Positive	163 (98.8)	2 (1.2)	165 (100.0)	20.323	<0.001*
	Negative	108 (85.0)	19 (15.0)	127 (100.0)		
Total		271 (92.8)	21 (7.2)	292 (100.0)	–	–

*Values marked with an asterisk (*) denote statistical significance at p ≤ 0.050

Spearman's correlation analysis demonstrated a positive association between hand grip strength (HGS) and CTS signs, with Phalen's test (r=0.301, p<0.001*) and Tinel's sign (r=0.264, p<0.001*) both showing significant correlations. Additionally, Phalen's and Tinel's tests were strongly correlated with each other (r=0.565, p<0.001*). Independent t-test analysis revealed that women with weak grip strength had significantly lower mean HGS compared to those with normal grip (16.11 ± 3.59 vs. 23.93 ± 2.56; p<0.001). However, one-way ANOVA indicated no statistically significant difference in mean HGS across pregnancy trimesters (p=0.258) (Table 3).

Table 3: Comparison of Hand Grip Strength Between Groups and Across Pregnancy Trimesters

Variables	Group	n (Mean ± SD)	Test Statistics	DF	p-Value
HGS (kg)	Weak grip	271 (16.11 ± 3.59)	t = -9.858	290	<0.001*
	Normal grip	21 (23.93 ± 2.56)			
Trimester	First	56 (17.17 ± 3.76)	F = 1.362	2, 289	0.258
	Second	97 (16.96 ± 3.92)			
	Third	139 (16.27 ± 4.22)			
Total		292 (16.67 ± 4.04)			

Values marked with an asterisk (*) indicate statistical significance at p≤0.050*

When comparing CTS indicators across trimesters, one-way ANOVA showed no significant differences for either Phalen's test (p=0.650) or Tinel's sign (p=0.843) (Table 4).

Table 4: Comparison of CTS Indicators Across Pregnancy Trimesters

Variables	Group	n (Mean ± SD)	Test Statistics	DF	p-Value
Phalen's Test	First trimester	56 (1.41 ± 0.50)	F = 0.432	2,289	0.650
	Second trimester	97 (1.40 ± 0.49)			
	Third trimester	139 (1.35 ± 0.48)			
	Total	292 (1.38 ± 0.49)			
Tinel's Sign	First trimester	56 (1.45 ± 0.50)	F = 0.171	2,289	0.843
	Second trimester	97 (1.45 ± 0.50)			
	Third trimester	139 (1.42 ± 0.50)			
	Total	292 (1.43 ± 0.50)			

DISCUSSION

In this study, participants were classified as CTS-positive if they demonstrated a positive result on either Phalen's test or Tinel's sign, consistent with established clinical criteria [23]. Pregnant women often have reduced HGS, with previous studies reporting that 74.5% of participants exhibited weak grip strength in their dominant hand [6]. This decline is largely due to physiological changes, including hormone imbalances and fluid retention, which increase ligament laxity and median nerve pressure, predisposing women to CTS [8, 9]. These changes intensify in the third trimester due to peak fluid retention and weight gain, exacerbating CTS symptoms and contributing to hand grip weakness [24]. Early detection and intervention are crucial. This study found a significant association between weak HGS and positive Phalen's test (62.0%) and Tinel's sign (56.5%), with a correlation of p<0.001, indicating that CTS may substantially contribute to grip weakness. Previous research has shown that CTS affects 31–62% of pregnant women, with symptom severity increasing in later trimesters [11, 16], underscoring the importance of integrating CTS screening into prenatal care to prevent long-term complications and support quality of life. However, no significant HGS differences were observed across trimesters in this study, diverging from some previous findings. Despite 47.6% of participants being in their third trimester, no trimester-based HGS variation emerged, suggesting that other factors, such as genetics or lifestyle, may influence grip strength and CTS risk. CTS is common in middle-aged and pregnant women, primarily due to hormonal changes and increased intracarpal pressure [8, 9]. Earlier studies have reported that sensory symptoms are more prevalent than motor symptoms, with the dominant hand more frequently affected. Pregnancy-related CTS (PRCTS) may worsen in the third trimester, causing pain, numbness, sleep disruption, and emotional distress. Yet, only 46% of symptomatic pregnant women reportedly seek medical help, and just 35% receive treatment, highlighting the need for education and timely care. Diagnostic methods such as Phalen's and Tinel's tests, with reported sensitivities of 78% and 66% and specificities of 94% and 64–80%, respectively, remain clinically valuable for CTS assessment [13, 20, 21]. Previous studies suggest that CTS progresses with pregnancy and is most prevalent in the third trimester [16, 17]. Other research supports CTS occurrence at any stage of pregnancy, unrelated to age or gestational month, aligning with our findings [25]. This indicates that fluid retention and hormonal shifts, rather than the gestational stage alone, may drive CTS. Some CTS symptoms may persist postpartum, warranting follow-up [20, 26]. Maintaining hand health positively impacts maternal well-being, as

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research links maternal happiness during pregnancy to reduced psychiatric risks and improved fetal development [27]. HGS reduction may serve as an early indicator of CTS and broader health decline, supporting its use as a low-cost, non-invasive screening tool during antenatal care, which also provides opportunities to address unhealthy behaviors [28]. Furthermore, literature supports physiotherapy for mild to moderate CTS, with wrist splinting and Kinesio taping proving effective for symptom management [29]. Kinesio taping has shown superior outcomes in pain reduction and grip strength improvement compared to splinting [30]. Addressing systemic health factors such as inflammation and nutrition may further enhance HGS and prevent CTS. Overall, integrating HGS testing into prenatal care, promoting physiotherapy, educating women on CTS, and conducting longitudinal studies including comparisons between primigravida and multigravida participants are recommended to improve management and understanding of pregnancy-related CTS.

This study has certain limitations, including its cross-sectional design, which restricts causal inference, and the use of non-probability purposive sampling, which may limit generalizability. CTS diagnosis relied solely on clinical tests without confirmatory electrodiagnostic studies, potentially affecting diagnostic precision. Future longitudinal multicenter studies incorporating nerve conduction studies and postpartum follow-up are recommended to better understand temporal relationships and long-term outcomes. Such research may further validate HGS as a reliable, non-invasive screening tool for early CTS detection during pregnancy.

CONCLUSIONS

This study confirms that handgrip weakness is common among pregnant women and strongly associated with clinical signs of CTS. These findings support the use of HGS as a prognostic indicator for early detection of CTS during pregnancy. Regular assessment during antenatal visits can help prevent functional impairment and improve quality of life.

Authors' Contribution

Conceptualization: AAS
Methodology: AN, YK, AW, HBA, SMO
Formal analysis: AN, YK, AW, HBA, SMO
Writing and Drafting: AAS, AN, YK, AW, HBA, SMO
Review and Editing: AAS, AN, YK, AW, HBA, SMO

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Association of Low Serum Ferritin Levels with Melasma: A Case-Control Study at a Tertiary Care Hospital

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ABSTRACT

Melasma is a common acquired hyperpigmentation disorder with multifactorial etiology, including hormonal influences, genetic predisposition, and environmental factors. Yet the relationship between serum ferritin levels and melasma remains unclear. **Objective:** To determine the association between low serum ferritin levels and melasma among patients presenting at a tertiary care hospital. **Methods:** This case-control study was conducted in the Department of Dermatology, Nishtar Hospital, Multan, from June 3, 2024, to December 2, 2024. A total of 114 participants were included, with 57 melasma cases and 57 age- and gender-matched controls. Serum ferritin levels were measured and compared between groups. Data were analyzed using SPSS version 23.0, with odds ratios (ORs) and p-values were calculated. **Results:** The mean age of participants was 24.67 ± 5.27 years and the mean BMI was 24.22 ± 2.17 kg/m^2. Low serum ferritin levels were significantly associated with melasma (p=0.002, OR=5.20). The association was stronger in males (p=0.002, OR=24.00), but not statistically significant in females (p=0.142, OR=2.81). Among participants with Fitzpatrick Skin Type III, the association was significant (p=0.001, OR=19.50), but not in those with Skin Type IV (p=0.490). A significant association was also observed in individuals older than 30 years (p=0.015, OR=2.66), and in non-obese participants (p=0.003, OR=4.85). **Conclusions:** This study demonstrates a strong association between low serum ferritin levels and melasma, particularly in male and individuals with Fitzpatrick Skin Type III, suggesting that iron storage depletion may play a role in melasma pathogenesis. Future studies should explore whether iron supplementation influences melasma severity or treatment outcomes.

INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder that primarily affects the face and carries a significant psychosocial impact. It is more prevalent in women and is influenced by multiple factors, including genetic predisposition, ultraviolet (UV) radiation, hormonal fluctuations, and oxidative stress [1]. Beyond these established causes, recent studies have explored the possible involvement of iron metabolism, particularly serum ferritin levels, in the pathogenesis of melasma [2, 3]. Ferritin, the primary intracellular iron-storage protein, is involved in regulating oxidative stress, inflammatory pathways, and melanogenesis [4]. Since iron is a cofactor for enzymes like tyrosinase, crucial in melanin biosynthesis, iron deficiency may impair normal pigment regulation [5]. Moreover, reduced serum ferritin levels may contribute to increased oxidative stress and inflammatory responses, both of which have been implicated in the development and exacerbation of melasma [6, 7]. A study evaluated the link between serum ferritin and melasma. For instance, some researchers have reported significantly lower serum ferritin, iron, and transferrin saturation levels in female melasma patients compared to healthy controls, which may indicate a potential role of iron storage depletion in melasma pathophysiology [8]. Another study found an inverse correlation between serum ferritin levels and melasma severity as assessed by the Melasma Area

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and Severity Index (MASI) [9]. However, not all evidence supports this association; some studies found no significant relationship, underscoring the need for further investigation [10]. The idea of correcting iron deficiency as an adjunct to standard melasma treatment has also been proposed. While a few reports suggest clinical improvement following iron supplementation, robust evidence from randomized controlled trials is still lacking [11–13].

Despite increasing interest in the role of iron metabolism in dermatological disorders, evidence regarding the association between serum ferritin levels and melasma remains inconsistent and limited, particularly in the Pakistani population. Most previous studies have focused on serum iron or anemia rather than ferritin as a marker of iron storage, and subgroup analyses based on gender, age, or skin type are scarce. This lack of localized and stratified data limits a clear understanding of whether iron depletion independently contributes to melasma pathogenesis. Therefore, further investigation is required to clarify this association in our setting. This study aims to investigate the association between low serum ferritin levels and melasma among patients presenting to a tertiary care hospital. By comparing ferritin levels between melasma patients and matched controls, we seek to clarify whether iron deficiency may play a contributory role in melasma development.

METHODS

This case-control study was conducted in the Department of Dermatology, Nishtar Hospital, Multan, from June 3, 2024, to December 2, 2024. A total of 114 patients were included in the study, with 57 cases (patients with melasma) and 57 controls (healthy individuals without melasma). The sample size was determined using EPI-Info software based on a melasma prevalence of 33% in cases and 9.8% in controls, with a 95% confidence interval [14]. The sampling technique employed was non-probability consecutive sampling. Written informed consent was taken from all the patients. The inclusion criteria for cases comprised male and female patients aged 18 to 45 years, having Fitzpatrick skin types III, IV, or V, and diagnosed with melasma for more than six months. The controls were also selected from both genders, aged 18 to 45 years, and having Fitzpatrick skin types III, IV, or V. Patients were excluded if they had been under melasma treatment within the last month, had a history of hirsutism or menstrual dysfunction, were pregnant, had Hepatitis C, or were using oral contraceptives. The study was approved by the institutional ethical committee, as shown by the reference number 7062. The subjects who met the inclusion criteria were selected from the outpatient department (OPD) of the Dermatology Department. All participants gave informed consent, and their anonymity was ensured. They were informed that the study posed no potential risks. Some of the control factors, including age, obesity, and skin type, were measured. All participants were requested to provide 3 ml of venous blood in a sterile tube for serum ferritin level determination, conducted in the hospital laboratory. The information was recorded in a pre-designed proforma. SPSS version 23.0 was used to analyze the data. Continuous variables such as age, serum ferritin levels, and BMI were summarized using mean and standard deviation. Categorical variables such as gender, obesity, skin type, and ferritin status were presented as frequencies and percentages. The odds ratios (OR) for the association between low serum ferritin levels and melasma were calculated, with values greater than 1 considered significant. Age, gender, skin type, and obesity were controlled as potential confounding factors through stratification. Ferritin levels were also analyzed after adjustment of ORs with post-stratification.

RESULTS

This study included a total of 114 participants, with a mean age of 24.67 ± 5.27 years and a mean body mass index (BMI) of 24.22 ± 2.17. The study demonstrates the association between low serum ferritin levels and melasma. Among the 57 melasma cases, 19 (33.3%) had low serum ferritin levels, compared to only 5 (8.8%) in the control group. In contrast, 38 (66.7%) melasma cases and 52 (91.2%) controls had normal ferritin levels. A statistically significant association was found between low serum ferritin levels and melasma (p=0.002). The odds ratio (5.20) indicates that individuals with low serum ferritin levels are approximately 5 times more likely to have melasma compared to those with normal ferritin levels (Table 1).

Table 1: Association of Low Serum Ferritin Levels with Melasma among Study Participants (n=114)

Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Yes (n=24, 21.1%)	19 (33.3%)	5 (8.8%)	5.20	0.002
No (n=90, 78.9%)	38 (66.7%)	52 (91.2%)		
Total	57 (100%)	57 (100%)		

This study presents the stratification of gender concerning low serum ferritin levels. Among male participants (n=32), 9 (28.1%) cases and only 1 (3.1%) control had low serum ferritin levels, with a statistically significant odds ratio of 24.00 (p=0.002). This finding suggests that males with low serum ferritin levels are 24 times more likely to develop melasma compared to those with normal ferritin levels. Conversely, among female participants (n=82), 10 (12.2%) cases and 4 (4.9%) controls had low serum ferritin levels, yielding an odds ratio of 2.81 (p=0.142), which was not statistically significant. These findings indicate that low serum ferritin levels are significantly associated with

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melasma in male but not in female. Results illustrate the stratification of age concerning low serum ferritin levels and melasma. Among participants up to 30 years old (n=92), 13 (14.1%) cases and 5 (5.4%) controls had low serum ferritin levels, with an odds ratio of 3.41 (p=0.036), indicating a statistically significant association. Among participants older than 30 years (n=22), 6 (27.3%) cases and 0 (0%) controls had low serum ferritin levels, with an odds ratio of 2.66 (p=0.015), which was also statistically significant. These findings suggest that low serum ferritin levels are significantly associated with melasma across different age groups, with a stronger association in individuals older than 30 years (Table 2).

Table 2: Stratification by Gender and Age

Variables	Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Gender					
Male (n=32)	Yes (n=10)	09 (28.1%)	01 (3.1%)	24.00	0.002
	No (n=22)	06 (18.8%)	16 (50.0%)		
Female (n=82)	Yes (n=14)	10 (12.2%)	04 (4.9%)	2.81	0.142
	No (n=68)	32 (39.0%)	36 (43.9%)		
Age Group					
Up to 30 Years (n=92)	Yes (n=18)	13 (14.1%)	5 (5.4%)	3.41	0.036
	No (n=74)	32 (34.8%)	42 (45.7%)		
More than 30 Years (n=22)	Yes (n=6)	6 (27.3%)	0 (0%)	2.66	0.015
	No (n=16)	6 (27.3%)	10 (45.4%)		

The findings present the stratification of skin type concerning low serum ferritin levels. Among participants with Fitzpatrick Skin Type III (n=64), 13 (20.3%) cases and 1 (1.6%) control had low serum ferritin levels, yielding a statistically significant odds ratio of 19.50 (p=0.001). This suggests that individuals with Skin Type III and low serum ferritin levels are 19.5 times more likely to have melasma than those with normal ferritin levels. In contrast, among participants with Fitzpatrick Skin Type IV (n=50), 6 (12.0%) cases and 4 (8.0%) controls had low serum ferritin levels, with an odds ratio of 1.83 (p=0.490), which was not statistically significant. These findings indicate that low serum ferritin levels are strongly associated with melasma in individuals with Skin Type III but not in those with Skin Type IV (Table 3).

Table 3: Stratification Concerning Skin Type

Skin Type	Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Type III (n=64)	Yes (n=14)	13 (20.3%)	1 (1.6%)	19.50	0.001
	No (n=50)	20 (31.2%)	30 (46.9%)		
Type IV (n=50)	Yes (n=10)	6 (12.0%)	4 (8.0%)	1.83	0.490
	No (n=40)	18 (36.0%)	22 (44.0%)		

The findings present the stratification of obesity concerning low serum ferritin levels. Among obese participants (n=7), 2 (28.6%) cases had low serum ferritin levels, whereas none of the controls had low levels. The odds ratio of 1.66 (p = 0.290) suggests no statistically significant association between obesity and low serum ferritin levels in melasma cases. Among non-obese participants (n=107), 17 (15.9%) cases and 5 (4.7%) controls had low serum ferritin levels, with a statistically significant odds ratio of 4.85 (p = 0.003). These findings indicate that low serum ferritin levels are significantly associated with melasma in non-obese individuals, but not in obese individuals (Table 4).

Table 4: Stratification Concerning Obesity

Obesity	Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Yes (n=7)	Yes (n=2)	2 (28.6%)	0 (0%)	1.66	0.290
	No (n=5)	3 (42.9%)	2 (28.6%)		
No (n=107)	Yes (n=22)	17 (15.9%)	5 (4.7%)	4.85	0.003
	No (n=85)	35 (32.7%)	50 (46.7%)		

DISCUSSION

This case-control study demonstrated a significant association between low serum ferritin levels and melasma. Participants with low ferritin were approximately five times more likely to have melasma (OR=5.20, p=0.002). This association was particularly marked in males (OR=24.00, p=0.002) but not statistically significant in female (OR=2.81, p=0.142). Stratified analysis further revealed significant associations among individuals over 30 years of age, non-obese individuals, and those with Fitzpatrick Skin Type III. These findings suggest that iron storage depletion may contribute to the pathogenesis of melasma, especially in certain subgroups. Our findings are in line with several previous studies. For instance, Goodarzi *et al.*, reported significantly lower serum ferritin and iron levels among melasma patients, supporting the link between iron metabolism and pigmentation disorders [14]. Similarly, Qazi *et al.*, observed an inverse correlation between serum ferritin and melasma severity, reinforcing the idea that diminished iron stores may exacerbate pigmentation [15]. However, contrasting evidence exists. Deshpande *et al.*, did not find a significant association between serum ferritin and melasma, and Behrangi et al., reported lower iron levels in melasma patients without statistical significance [16, 17]. Such discrepancies may reflect differences in sample sizes, ethnic backgrounds, sun exposure patterns, hormonal status, or dietary iron intake. Thus, while there is growing support for an association between iron deficiency and melasma, larger multicenter studies are needed to clarify these relationships. Prakash *et al.*, also found deranged iron profiles, including reduced ferritin levels, in 100% of melasma cases studied [18]. These results support the hypothesis that impaired iron storage could contribute to melasma development. Biologically, iron is a key cofactor for tyrosinase, the enzyme responsible for melanin

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production. Iron deficiency may impair tyrosinase activity, leading to altered melanogenesis and pigmentation abnormalities [19]. Furthermore, iron depletion increases oxidative stress by elevating reactive oxygen species (ROS), which can stimulate melanocyte activity and lead to hyperpigmentation [20]. Ferritin serves as a long-term storage form of iron, and its depletion can be an early marker of subclinical iron deficiency. Therefore, low ferritin levels may influence pigmentation even before serum iron levels drop [21]. An interesting aspect of our study is the significant association seen in males but not in female. This is consistent with the findings of Kiayani *et al.*, who found no link between iron deficiency anemia and melasma in women [21]. One possible explanation is that women, due to regular menstrual blood loss, are more physiologically adapted to lower iron levels. In men, however, a sudden or significant drop in iron stores may have a more noticeable effect on melanocyte function and pigmentation.

This study has certain limitations, including its single-center design, relatively small sample size, and use of non-probability sampling, which may limit generalizability. Additionally, serum ferritin was assessed at a single time point without evaluating other iron profile parameters or inflammatory markers that may influence ferritin levels. Future multicenter studies with larger cohorts, comprehensive iron profiling, and longitudinal follow-up are recommended to better elucidate causal relationships and to determine whether iron supplementation may improve melasma severity or treatment outcomes.

CONCLUSIONS

This study found a significant association between low serum ferritin levels and melasma, particularly in males, individuals older than 30 years, non-obese participants, and those with Fitzpatrick Skin Type III, suggesting that iron storage depletion may contribute to melasma pathogenesis. While previous studies have primarily focused on serum iron levels, our findings highlight the importance of ferritin as a long-term marker of iron status and its potential role in skin pigmentation regulation. The observed gender- and age-based differences indicate that iron metabolism may affect melasma development differently across populations, warranting further investigation. Given the potential role of iron deficiency in melasma, assessing serum ferritin levels in affected individuals could serve as a useful diagnostic and therapeutic consideration.

Authors' Contribution

Conceptualization: RT, MKS
Methodology: RT, MKS, AA, SB, CF
Formal analysis: RT, MKS, AA, SB, CF
Writing and Drafting: AA, SB, CF
Review and Editing: AA, SB, CF, RT, MKS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparison Between Visual and Radiographic Methods Using ICDAS Criteria in Permanent Molars for Detection of Occlusal and Proximal Caries – A Comparative Study

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ABSTRACT

Early detection of dental caries is critical for timely intervention and prevention of disease progression. The International Caries Detection and Assessment System (ICDAS) offers a standardized approach to evaluate caries through both visual and radiographic methods. **Objectives:** To compare between visual and radiographic methods using ICDAS criteria in permanent molars for detection of occlusal and proximal caries. **Methods:** This comparative cross-sectional study was conducted at Liaquat University of Medical and Health Sciences (LUMHS) after ethical approval, using non-probability consecutive sampling to recruit 378 patients. Individuals aged 16–35 years with fully erupted, clinically intact permanent molars and no signs of periodontal disease were included. Participants were assigned to Group A (occlusal caries) or Group B (proximal caries), with 189 in each group. Caries were assessed visually and radiographically using ICDAS criteria, with scores 1–2 indicating initial and 3–6 indicating advanced lesions. Two calibrated examiners performed the evaluations. **Results:** There were no statistically significant differences in baseline demographics between the occlusal and proximal caries groups. The mean age was comparable (25.9 ± 6.5 vs. 26.1 ± 6.2 years, p=0.753), as was gender distribution (p=0.752). When comparing diagnostic methods, no statistically significant differences were observed between visual and radiographic ICDAS assessments for detecting initial or advanced caries in either group (all p>0.050), indicating comparable diagnostic performance. **Conclusions:** Visual and radiographic methods based on the ICDAS system were equally effective in identifying occlusal and proximal carious lesions in permanent molars.

INTRODUCTION

Better quality information is ensured by using a standardized caries revelation method established on the finest available data. This helps practitioners make well-informed decisions on the optimal clinical treatment of dental caries at the individual and public health levels [1]. The International Caries Detection and Assessment System, or ICDAS, is a straightforward, rational, research backed method for detecting and evaluating dental caries that groups the phases of the disease according to histological activity and extent [2]. Since its launch in 2001, it has been widely accepted and used in the four fields of health services, clinical practice, education, and research, giving all parties involved a single vocabulary for staging dental cavities [3]. In order to enhance patient treatment and more accurately track caries development in research, it shifts the discipline distant from the oversimplified

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diagnosis of either visible decay or no apparent decay and toward a more thorough degree of assessment [4]. By using visually observed surface features, the ICDAS calculates the visual surface changes that correlate to the possible histological depth of carious lesions. Furthermore, it suggests the ICDAS radiographic grading system for a more thorough diagnosis, which groups lesions based on the degree of caries demineralization into enamel and dentin, shown by a radiolucency on the radiograph [5]. While radiography continues to be the most popular caries detection tool, clinical visual identification and evaluation of lesions on clean, dry teeth serves as the foundation for clinical appraisal of the carious lesion [6]. The bitewing method is intended to recognize proximal caries lesions that are invisible to the naked eye. According to recent research, radiographs are more sensitive than clinical examination when it comes to identifying proximal and occlusal lesions in dentin, determining the lesion's depth, and tracking its activity [6, 7]. The ICDAS uses radiography to categorize posterior tooth surfaces in different degrees based on progression. This classification system's high repeatability and accuracy provide more thorough information for managing, diagnosing, and planning dental decay [8, 9]. The null hypothesis was there is no significant difference between the visual and radiographic methods using ICDAS criteria in detecting occlusal and proximal caries in permanent molars.

Although both visual and radiographic approaches based on the ICDAS system are widely used for caries detection, uncertainty remains regarding their comparative diagnostic performance in routine clinical settings, particularly for occlusal and proximal surfaces of permanent molars. Most previous studies have been conducted in vitro or have relied on advanced imaging modalities such as micro-CT, limiting their direct applicability to everyday clinical practice. Furthermore, local data comparing these two modalities within a standardized ICDAS framework are scarce. This highlights the need for clinically relevant comparative research to guide evidence-based diagnostic decision-making. The objective of this study was to compare between visual and radiographic methods using ICDAS criteria in permanent molars for detection of occlusal and proximal caries.

METHODS

This comparative cross-sectional study was conducted from January 2023 to December 2023 in the Department of Operative Dentistry, Liaquat University of Medical and Health Sciences Jamshoro, Pakistan. After obtaining ethical approval from the ethical review board (Ref. No. LUMHS/REC/-05). The study employed a non-probability consecutive sampling technique. The sample size was calculated using an online sample size calculator (https://wnarifin.github.io/ssc/sskappa.html) based on an expected kappa value of 0.74 [10] between radiographic and visual ICDAS methods, assuming a caries prevalence of 29%[11], with 90% power and a 5% significance level. Although the calculated minimum required sample size was 39, all available cases (n = 378) were included to satisfy the assumption of normality. These patients were divided into two groups: Group A (occlusal caries) and Group B (proximal caries), with 189 participants in each group. The study included patients between 16 and 35 years of age, of either sex, who had fully erupted permanent molars with clinically intact occlusal and proximal surfaces, and no clinical signs of periodontal disease such as bleeding on probing, periodontal pocket depths greater than 3 mm, clinical attachment loss, or pathological tooth mobility. Only individuals who provided informed written consent were eligible. Patients were excluded if the target molars exhibited structural damage (e.g., fractures or excessive wear), had been restored with crowns or orthodontic appliances, or showed evidence of periodontal compromise. Additionally, individuals with systemic health conditions known to affect oral status, or those who declined participation or radiographic assessment, were not considered for inclusion. After taking the informed consent from patient, history, clinical examination investigations were performed and recorded on proforma. The radiographs were used to diagnose and examine the molars' proximal and occlusal surfaces. Caries detection in molars was performed visually using the International Caries Detection and Assessment System (ICDAS) criteria. Teeth were examined under artificial light after being cleaned (if necessary) to remove plaque or calculus, and then dried with compressed air to enhance visualization of enamel changes. A standard dental mirror and a ball-ended probe were used passively without exerting pressure to avoid causing cavitation. A quadrant-wise sequence was followed to ensure all molars were examined systematically. The ICDAS criteria were applied as follows: Score 0: Sound tooth surface; Score 1: First visual change in enamel; Score 2: Distinct visual change in enamel; Score 3: Localized enamel breakdown due to caries with no visible dentin; Score 4: Underlying dark shadow from dentin (with or without enamel breakdown); Score 5: Distinct cavity with visible dentin; Score 6: Extensive distinct cavity with visible dentin. For analytical purposes, initial caries lesions were defined as scores 1–2, while advanced lesions were categorized as scores 3–6 [12]. Both the occlusal and proximal surfaces were examined for bitewing caries using radiography. Radiographic imaging was performed using an X-linear system DC, with exposures ranging from 20 to 1000 milliseconds at 70 kVp and 7 mA. A digital sensor (Ateco, AT-301) captured the

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images within 3 seconds at 5.0V and 500 mA, with 12-bit per pixel digitization, and was connected via a USB 2.0 port to a PC or laptop. The images were printed on paper. Two examiners, previously calibrated for evaluating the radiographs using the ICDAS-recommended radiographic criteria. According to the radiographic ICDAS Caries ranking method, the identified lesions on radiographs were assigned a score, with 0–2 denoting early lesions and 3-6 indicating progressive lesions. Inter- and intra-observer reliability were assessed using kappa statistics, yielding values of 0.83 and 0.87, respectively. SPSS version 22.0 was used for statistical analysis. For qualitative variables like gender, tooth count, and tooth surface, frequency and percentage were computed. The age was either shown as a histogram or as a mean and standard deviation. The ICDAS criteria for optical and radiographic caries diagnosis in permanent molars were evaluated using the Chi-Square test. $p<0.050$ was the significance threshold.

RESULTS

There were no statistically significant differences in baseline demographic characteristics between the two groups. The mean age of participants in the occlusal caries group was 25.9 years (SD 6.5), and in the proximal caries group, it was 26.1 years (SD 6.2) ($p=0.753$, independent samples t-test). Gender distribution was also comparable between the groups, with males comprising 38.6% in the occlusal group and 40.2% in the proximal group, and females comprising 61.4% and 59.8%, respectively ($p=0.752$, χ^2 test)(Table 1).

Table 1: Comparison of Demographic Characteristics Between Group A (Occlusal Caries) and Group B (Proximal Caries)

Variables	Characteristics	Occlusal Caries	Proximal Caries	p-Value
Age (years)	–	25.9 ± 6.5 (range: 16–35)	26.1 ± 6.2 (range: 16–35)	0.753
Gender	Male	73 (38.6%)	76 (40.2%)	0.752
	Female	116 (61.4%)	113 (59.8%)	

*Independent samples t-test was used for age comparison; Chi-square test was used for gender distribution

The distribution of tooth location did not differ significantly between the occlusal and proximal caries groups (χ^2 test, $p=0.106$). In the occlusal caries group, mandibular molars were more frequently affected, with 61 teeth (32.1%) in the mandibular right quadrant and 60 teeth (31.6%) in the mandibular left. In contrast, the proximal caries group showed greater involvement of maxillary molars, particularly the maxillary left quadrant with 53 teeth (28.6%). In terms of tooth type, a statistically significant difference was observed (χ^2 test, $p=0.037$,). First molars were more frequently involved in both groups, but were significantly more common in the occlusal caries group (154 teeth, 81.1%) compared to the proximal caries group (137 teeth, 72.3%). Second molars were more often affected in the proximal caries group (52 teeth, 27.7%) than in the occlusal caries group (35 teeth, 18.9%)(Table 2).

Table 2: Distribution of Tooth Location and Type in Occlusal Caries and Proximal Caries Group (N=378)

Category	Subcategory	Occlusal Caries	Proximal Caries	p-Value
Tooth Location	Maxillary Right	33 (17.3%)	35 (18.4%)	0.106
	Maxillary Left	35 (18.9%)	53 (28.6%)	
	Mandibular Right	61 (32.1%)	51 (26.7%)	
	Mandibular Left	60 (31.6%)	50 (26.2%)	
Tooth Type	First Molar	154 (81.1%)	137 (72.3%)	0.037
	Second Molar	35 (18.9%)	52 (27.7%)	

The diagnostic comparison between visual and radiographic methods revealed no statistically significant differences in detecting initial or advanced caries in either group. In the occlusal caries group, initial lesions were identified in 6.3% of cases by visual examination compared to 4.8% via radiographic assessment ($p=0.622$), while advanced lesions were detected in 93.7% and 95.2% of cases, respectively. Similarly, in the proximal caries group, the visual method identified 5.3% of cases as initial caries versus 4.2% with radiographs ($p=0.624$), with advanced caries comprising the majority of cases in both modalities (94.7% visual vs 95.8% radiographic)(Table 3).

Table 3: Caries Diagnosis by Visual and Radiographic Methods in Both Groups (N=378)

Groups	Diagnosis Type	Visual, n (%)	Radiographic, n (%)	p-Value
Occlusal Caries Group (n=189)	Initial Caries	12 (6.3%)	9 (4.8%)	0.622
	Advanced Caries	177 (93.7%)	180 (95.2%)	
Proximal Caries Group (n=189)	Initial Caries	10 (5.3%)	8 (4.2%)	0.624
	Advanced Caries	179 (94.7%)	181 (95.8%)	

DISCUSSION

In vitro comparison of ICDAS visual vs. image-based ICDAS using micro-CT as the gold standard showed very similar diagnostic accuracy in molars (accuracy ≈ 0.83 vs 0.85), though both had limited specificity for caries needing operative treatment [13]. However, unlike that study, which used high-resolution micro-CT in a controlled laboratory setting, our study was conducted using conventional radiographs in a clinical environment. This shows the practical relevance of our findings, as they reflect real-world diagnostic conditions where micro-CT is not feasible. A previous in vitro study evaluated the reliability and accuracy of ICDAS and radiographs for detecting and estimating the depth of proximal lesions on directly visible surfaces of extracted primary and permanent teeth [14]. The findings indicated that ICDAS had higher intra- and inter-reproducibility ($\kappa > 0.9$ and > 0.85, respectively) compared to radiographs ($\kappa = 0.6$-0.8), and also demonstrated superior accuracy in estimating lesion

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depth, particularly for lesions confined to enamel or the outer third of dentine. The correlation for ICDAS with visual depth was ≥ 0.85, whereas for radiographs it was ≥ 0.45. In this study, most of the patients were female [116 (61.4%) and 113 (59.8%)] as compared to male patients [73 (38.6%) and 76 (40.2%)], with mean age of 25.9 ± 6.5 and 26.1 ± 6.2 years in Group A (Occlusal caries) and Group B (Proximal caries), respectively. Similar high female prevalence and mean age were observed, with 63% female patients having a mean age of 31 ± 17 years [15]. We observed a non-significant difference in how tooth quadrants were distributed between the two groups. However, occlusal caries was more frequently found in mandibular molars, affecting over 32% of cases, while proximal caries tended to involve the maxillary left quadrant more often. This pattern may reflect differences in anatomical accessibility, salivary flow, and plaque accumulation occlusal surfaces of mandibular molars are more exposed to masticatory forces and pit-and-fissure retention, making them more vulnerable to direct caries development [16, 17]. In contrast, the interproximal surfaces of maxillary molars, especially in the left quadrant, may be more difficult to clean effectively, leading to plaque retention and increased risk of proximal lesions [18]. When examining the types of teeth affected, a noticeable trend was found: occlusal caries was most commonly seen in the first permanent molars (81%), while proximal caries were more frequently detected in the second permanent molars (27.7%). This pattern may be explained by the fact that first molars erupt earlier and are exposed to the oral environment and thus cariogenic factors for a longer period, increasing their risk for occlusal surface breakdown [19]. On the other hand, the shape and contact points of the second molars can make them more prone to plaque accumulation between the teeth, especially if oral hygiene is not well maintained, leading to a higher risk of proximal caries [20]. The strength of this study lies in the meticulous matching of demographic variables, which was undertaken to minimize potential confounding factors. The application of the ICDAS classification system for both visual and radiographic assessments enhances diagnostic reliability and facilitates comparability with existing literature. Nevertheless, certain limitations must be acknowledged. The study relied solely on the ICDAS system without incorporating adjunctive caries detection technologies such as laser fluorescence or trans illumination, which may offer greater sensitivity, particularly in the detection of early proximal lesions. Furthermore, the absence of histological validation precludes definitive confirmation of diagnostic accuracy against established gold standards.

Despite its strengths, this study has certain limitations. Being a single-center cross-sectional study using non-probability sampling, the findings may not be generalizable to broader populations. Additionally, the absence of a histological or micro-CT gold standard limits the ability to determine true diagnostic accuracy, and advanced adjunctive technologies were not incorporated. Future multicenter studies incorporating gold standard validation methods and newer diagnostic tools are recommended to further evaluate sensitivity, specificity, and cost-effectiveness of ICDAS-based visual and radiographic assessments in diverse clinical settings.

CONCLUSIONS

In conclusion, this study found that visual and radiographic methods based on the ICDAS system were equally effective in identifying occlusal and proximal carious lesions in permanent molars. This suggests that both approaches can be reliably used in clinical practice for the detection of dental caries, offering flexibility in diagnostic decision-making depending on clinical circumstances and available resources.

Authors' Contribution

Conceptualization: VN, MM
Methodology: VN
Formal analysis: AAJ
Writing and Drafting: MM, MA, SM, SA
Review and Editing: MM, MA, SM, SA, VN, AAJ

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Evaluating the Predictive Validity of Objective Structured Clinical Examination (OSCE) Scores for Future Clinical Performance Among Final-Year Medical Students in Pakistan

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ABSTRACT

The Objective Structured Clinical Examination (OSCE) is widely used in medical education to assess students' clinical skills. However, its ability to predict future clinical performance, known as predictive validity, remains debated. **Objectives:** To evaluate the predictive validity of OSCE scores for subsequent clinical performance among final-year medical students. **Methods:** This retrospective cohort study was conducted at a tertiary medical college in Pakistan. Data were collected for 80 final-year MBBS students, including total OSCE scores and domain-wise performance. Subsequent clinical performance was assessed using clerkship scores in Internal Medicine and Surgery, along with Mini-CEX, DOPS, 360-degree evaluations, and supervisor ratings. Pearson's correlation and multiple linear regression were used to examine associations. **Results:** The mean OSCE score was 72.7 ± 7.8. Only the Internal Medicine Clerkship Score showed a statistically significant negative correlation with OSCE performance ($r = -0.224$, $p=0.046$). However, the effect size was small, and the clinical significance of this finding is questionable. The association may reflect random variation or unmeasured confounding and should be interpreted with caution. No other clinical outcomes showed significant correlations. Regression analysis revealed that none of the OSCE domains significantly predicted final clerkship scores. **Conclusions:** OSCE scores showed limited predictive value for subsequent clinical performance in this cohort. The results highlight the need to interpret statistically significant but weak associations with caution. Multimodal assessments combining OSCEs with workplace-based tools may offer a more comprehensive evaluation of clinical competence.

INTRODUCTION

The process of assessing clinical competence in undergraduate medical education has evolved significantly over recent decades [1]. As the focus shifts from traditional knowledge-based evaluations to performance-based assessments, institutions are increasingly adopting structured tools like the Objective Structured Clinical Examination (OSCE) to evaluate essential clinical skills [2]. The OSCE is designed to simulate real-life clinical scenarios in a controlled environment, allowing examiners to assess students' proficiency in history taking, physical

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examination, communication, clinical reasoning, and procedural tasks using standardized stations and checklists [3]. The widespread use of the OSCE is largely due to its perceived objectivity, reproducibility, and versatility in evaluating a broad range of clinical competencies [4]. It has become a cornerstone in many medical curricula globally and is often used as a high-stakes examination for promotion or graduation. While the OSCE offers a more structured and standardized alternative to traditional oral or long-case exams, concerns remain regarding its ability to predict how students perform in real clinical settings. Clinical competence in the workplace involves not only technical skill but also adaptability, time management, interpersonal communication, and professional judgment elements that may not be fully captured within the time-constrained, station-based format of an OSCE [5]. A key concept in evaluating the effectiveness of such assessments is predictive validity, which refers to the extent to which performance on an assessment (e.g., OSCE) can accurately forecast future performance in a related real-world context, such as clinical clerkships or postgraduate training. Previous research on the predictive validity of OSCEs has produced mixed results. Some studies have reported moderate correlations between OSCE performance and future clinical achievements, while others have found little to no association. These inconsistencies raise questions about whether OSCE performance can be reliably used to forecast students' clinical effectiveness during clerkships or postgraduate training [6, 7]. Additionally, much of the existing literature originates from high-income, Western academic settings, with relatively limited data from local or regional contexts in South Asia, where cultural, curricular, and assessment practices may differ significantly [8]. Despite the routine reliance on OSCEs in undergraduate medical education, there remains a lack of clear evidence regarding their ability to predict actual clinical performance across diverse clinical rotations and evaluative settings. This gap is particularly relevant in institutions where OSCEs are used as gatekeeping tools for advancement or licensure. Without sufficient evidence of predictive validity, there is a risk that assessment-driven decisions may not accurately reflect a student's real-world competence. By analyzing the relationship between OSCE scores and subsequent clerkship evaluations, this research aims to provide insight into the strengths and limitations of the OSCE as a predictive tool, offering data-driven recommendations for assessment practices in undergraduate medical education.

Despite the widespread use of OSCEs as high-stakes assessments in undergraduate medical education, evidence regarding their predictive validity for future clinical performance remains inconsistent, particularly in low- and middle-income countries. Most existing research originates from Western academic settings, with limited data from Pakistani medical institutions where curricular structures and workplace-based assessments may differ. Furthermore, few studies have examined domain-wise OSCE performance in relation to multiple clinical evaluation tools within the same cohort. This gap underscores the need for context-specific evidence to determine whether OSCE scores meaningfully predict real-world clinical competence. This study aims to evaluate whether OSCE scores correlate with and can predict future clinical performance among final-year medical students in a real clinical environment.

METHODS

This was a retrospective cohort study conducted among final-year medical students at Rawal Institute of Health Sciences, Islamabad. The study aimed to evaluate whether prior performance in the Objective Structured Clinical Examination (OSCE) could reliably predict subsequent clinical competence during clerkships. As the study utilized pre-existing institutional records to compare earlier OSCE scores with later clerkship outcomes, a retrospective design was considered methodologically appropriate. The study duration for 6 months from October 2024 to March 2025. Before data collection, ethical approval was obtained from the Institutional Review Board (IRB) of Rawal Institute of Health Sciences, under reference number RIHS/IRB/15/2024. Data were collected from April to October 2024. This approval confirmed adherence to institutional and ethical guidelines for human subject research. All participants provided written informed consent, and the principles of confidentiality, anonymity, and voluntary participation were strictly upheld throughout the study. A sample size of 80 students was determined based on anticipated effect sizes from prior literature [8], using a confidence level of 95% and statistical power of 80%. Non-probability consecutive sampling was used to include all eligible final-year MBBS students who had completed both the institutional OSCE and at least one full clerkship rotation. Inclusion criteria were final-year MBBS students enrolled in the current academic session, who had completed the institutional OSCE and undergone formal clinical clerkship evaluations in Internal Medicine and Surgery. Exclusion criteria were students who did not provide informed consent, those with incomplete data due to absenteeism or missing evaluations, and students with deferred or supplementary OSCE assessments. Data were collected in two distinct phases. OSCE scores were retrieved from the institutional examination department. The OSCE comprised multiple

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stations evaluating History Taking, Physical Examination, Communication Skills, Clinical Reasoning, and Procedural Skills. Each domain was scored independently using locally validated standardized rubrics, developed by a panel of senior clinical faculty and aligned with institutional learning objectives. These rubrics included detailed checklists with behavioural anchors and domain-specific criteria to minimize scoring subjectivity. Faculty assessors received prior training and participated in calibration exercises to ensure inter-rater reliability. Clinical performance data were obtained from clerkship evaluation forms and logbooks. The following outcomes were included: Final Clerkship Score (aggregated from Internal Medicine and Surgery), Individual Internal Medicine and Surgery Clerkship Scores, Mini-Clinical Evaluation Exercise (Mini-CEX), Directly Observed Procedural Skills (DOPS), Supervisor or Preceptor Ratings, 360-Degree Feedback Scores, Patient Interaction Ratings, and Post-OSCE Written Examination Scores. Mini-CEX and DOPS evaluations were scored out of 10 using institutionally approved rating forms. Two independent assessors conducted evaluations whenever possible, and discrepancies were resolved through consensus. Supervisor and peer feedback were collected using structured 360-degree feedback forms incorporating Likert-type response scales. All data were anonymized and double-entered into SPSS version 25 to minimize entry errors and ensure accuracy. To ensure content validity, OSCE stations were developed by experienced faculty and mapped against institutional curriculum objectives. Construct validity was established by designing stations to assess distinct clinical competencies, avoiding domain overlap. Internal consistency was confirmed through pilot testing, yielding an acceptable Cronbach's alpha ($\alpha > 0.70$). Inter-rater reliability was strengthened through assessor workshops and rubric alignment. Predictive validity was assessed by examining the strength and direction of associations between OSCE scores and subsequent clinical performance outcomes. Descriptive statistics (mean and standard deviation) were used for demographic and score summaries. Pearson's correlation coefficient (r) was used to evaluate associations between total OSCE scores and individual clinical outcomes. Multiple linear regression analysis was performed to determine whether any specific OSCE domain scores significantly predicted Final Clerkship Scores. A p-value of less than 0.050 was considered statistically significant.

RESULTS

The study included 80 final-year medical students. The mean age was 22.85 ± 1.15 years, with a nearly equal gender distribution: 41 male (51.2%) and 39 female (48.8%). All participants were enrolled in their final year of the MBBS program. Academic consistency was evident, with a mean cumulative GPA of 75.90 ± 6.13%, and the most recent professional exam scores averaged 75.47 ± 6.59%. Students achieved a mean total OSCE score of 72.70 ± 7.80 (out of 100). Among the component domains, the highest score was in Physical Examination (15.15 ± 1.46), followed by Communication Skills (14.67 ± 1.54) and History Taking (14.02 ± 2.25). Scores were relatively lower in Clinical Reasoning (12.78 ± 2.16) and Procedural Skills (13.37 ± 1.68). The post-OSCE written examination score was 72.26 ± 6.70%, closely aligned with the total OSCE score. While the OSCE was scored out of 100, each domain was scored independently on variable subscales and then standardized by the examination committee to compute the final composite OSCE score (Table 1).

Table 1: Demographic Characteristics of Medical Students, and Performance on OSCE Component (n=80)

Variables	Mean ± SD / n (%)
Age (years)	22.85 ± 1.15
Male	41 (51.2%)
Female	39 (48.8%)
Academic Year (Final)	80 (100%)
Cumulative GPA (%)	75.90 ± 6.13
Previous Exam Score (%)	75.47 ± 6.59
OSCE Component	
History Taking Score	14.02 ± 2.25
Physical Examination Score	15.15 ± 1.46
Communication Skills Score	14.67 ± 1.54
Clinical Reasoning Score	12.78 ± 2.16
Procedural Skills Score	13.37 ± 1.68
Total OSCE Score (/100)	72.70 ± 7.80
Post-OSCE Written Score (%)	72.26 ± 6.70

Clinical performance was assessed through clerkship scores and evaluator ratings. The Final Clerkship Score averaged 74.09 ± 6.68, with Internal Medicine at 77.48 ± 6.32, and Surgery at 75.11 ± 7.24. Additional evaluations were favorable: Supervisor Rating (8.22 ± 1.06), Mini-CEX (7.53 ± 1.10), DOPS (7.87 ± 0.93), 360-Degree Feedback (7.75 ± 0.90), and Patient Interaction Score (8.55 ± 1.07), all out of 10. Only the Internal Medicine Score showed a statistically significant negative correlation with OSCE score ($r = -0.224$, $p=0.046$). However, the effect size was small ($R^2 = 0.050$) and, according to Cohen's classification, represents a weak correlation. This suggests limited clinical relevance, and the finding should be interpreted cautiously, as it may reflect random variation or unmeasured confounders. No other correlations between OSCE and clinical variables were statistically significant ($p>0.050$) (Table 2).

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Table 2: Clinical Outcomes and Correlation with OSCE Score (n=80)

Clinical Outcome Variables	Mean ± SD	Pearson r	p-Value
Final Clerkship Score (%)	74.09 ± 6.68	−0.083	0.467
Internal Medicine Clerkship (%)	77.48 ± 6.32	−0.224	0.046
Surgery Clerkship (%)	75.11 ± 7.24	−0.122	0.281
Supervisor/Preceptor Rating (/10)	8.22 ± 1.06	−0.035	0.756
Mini-CEX Score (/10)	7.53 ± 1.10	0.006	0.959
DOPS Score (/10)	7.87 ± 0.93	0.120	0.287
360-Degree Feedback Score (/10)	7.75 ± 0.90	0.020	0.860
Patient Interaction Score (/10)	8.55 ± 1.07	0.033	0.770
Post-OSCE Written Score (%)	72.26 ± 6.70	0.058	0.611

To assess whether specific OSCE domains could predict overall clinical performance, a multiple linear regression model was constructed using the five OSCE components as independent variables and the Final Clerkship Score as the outcome. Pearson's correlation analysis revealed a statistically significant but weak negative correlation between the Total OSCE Score and the Internal Medicine Clerkship Score ($r = -0.224$, $p = 0.046$). According to Cohen's guidelines, this reflects a small effect size and likely lacks clinical relevance. The result may represent a Type I error due to random variation or uncontrolled confounding factors and should therefore be interpreted with caution. All other clinical outcomes showed non-significant correlations with OSCE scores, suggesting limited predictive value (Table 3).

Table 3: Multiple Linear Regression – OSCE Domains as Predictors of Final Clerkship Score (n=80)

Predictors	B Coefficient	Std. Error	t-Value	p-Value	95% CI (Lower, Upper)
Constant	82.70	14.69	5.63	<0.001	53.43, 111.96
History Taking Score	−0.263	0.345	−0.764	0.447	−0.951, 0.424
Physical Exam Score	−0.179	0.532	−0.337	0.737	−1.239, 0.880
Communication Skills	0.068	0.506	0.135	0.893	−0.940, 1.077
Clinical Reasoning Score	−0.027	0.359	−0.075	0.940	−0.743, 0.689
Procedural Skills Score	−0.213	0.459	−0.465	0.644	−1.128, 0.702

To evaluate the potential influence of gender and academic performance on assessment outcomes, subgroup analyses were performed using independent samples t-tests. Gender-wise comparisons showed that female students achieved a slightly higher mean OSCE score (73.56 ± 7.43) compared to male students (71.88 ± 8.15), but this difference was not statistically significant ($t = -0.963$, $p=0.339$). Similarly, in terms of Final Clerkship Scores, female students had a marginally higher mean (74.62 ± 7.64) than males (73.58 ± 5.68), yet the difference did not reach statistical significance ($t = -0.692$, $p=0.491$). These findings suggest that gender did not significantly impact either OSCE or clerkship performance in this cohort. GPA-based comparisons revealed a reverse trend. Students with a lower cumulative GPA (<75%) scored slightly higher on the OSCE (73.78 ± 7.50) than those with a higher GPA (≥75%), who averaged 71.81 ± 8.02. However, this difference was not statistically significant ($t = 1.125$, $p=0.264$). Final Clerkship Scores were also comparable between the low GPA (73.85 ± 7.28) and high GPA groups (74.29 ± 6.23), with no significant difference observed ($t = -0.291$, $p=0.772$). These results indicate that prior academic performance, as measured by GPA, did not predict OSCE or clerkship outcomes in a meaningful way (Table 4).

Table 4: Gender- and GPA-Based Comparison of OSCE and Final Clerkship Scores

Grouping Variables	Outcome Measure	Group	Mean ± SD	t-Value	p-Value
Gender	Total OSCE Score	Male	71.88 ± 8.15	−0.963	0.339
		Female	73.56 ± 7.43		
	Final Clerkship Score	Male	73.58 ± 5.68	−0.692	0.491
		Female	74.62 ± 7.64		
GPA Group	Total OSCE Score	Low GPA (<75%)	73.78 ± 7.50	1.125	0.264
		High GPA (≥75%)	71.81 ± 8.02		
	Final Clerkship Score	Low GPA (<75%)	73.85 ± 7.28	−0.291	0.772
		High GPA (≥75%)	74.29 ± 6.23		

A summary of the subgroup comparisons was presented. None of the differences observed across gender or GPA groupings reached statistical significance. The comparisons of OSCE scores by gender ($t(78) = -0.963$, $p=0.339$) and clerkship scores by gender ($t(78) = -0.692$, $p=0.491$) both yielded non-significant results, reinforcing that performance in both domains was independent of gender. Likewise, comparisons based on GPA showed no significant effect on OSCE scores ($t(78) = 1.125$, $p=0.264$) or clerkship scores ($t(78) = -0.291$, $p=0.772$). These findings provide further evidence that demographic and academic variables such as gender and GPA did not act as confounding factors in assessing clinical competence in this study (Table 5).

Table 5: Summary of Subgroup Analysis Results

Subgroup Comparison	Outcome Measure	Statistical Result	Interpretation
Gender vs. OSCE Score	$T(78) = -0.963$, $p=0.339$	Not significant (NS)	No significant difference
Gender vs. Clerkship Score	$T(78) = -0.692$, $p=0.491$	Not significant (NS)	No significant difference
GPA vs. OSCE Score	$T(78) = 1.125$, $p=0.264$	Not significant (NS)	No significant difference
GPA vs. Clerkship Score	$T(78) = -0.291$, $p=0.772$	Not significant (NS)	No significant difference

Scatter plot depicting the linear relationship between Internal Medicine Clerkship Scores and Total OSCE Scores. The line of best fit demonstrates a weak negative association ($R^2 = 0.050$), indicating that only 5% of the variance in OSCE scores is explained by performance in internal medicine. The trend is statistically significant but clinically negligible, with considerable data spread around the fit line (Table 5).

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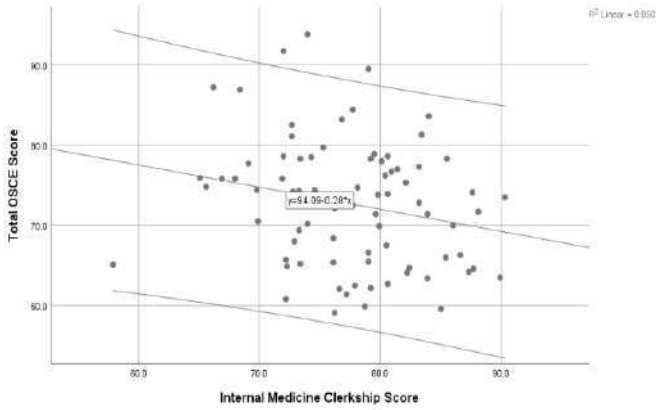

Figure 1: Linear Regression Between Internal Medicine Clerkship Scores and Total OSCE Scores

DISCUSSION

This study investigated whether OSCE scores could predict future clinical performance among final-year medical students. The analysis revealed a statistically significant but weak negative correlation between total OSCE scores and performance in the Internal Medicine clerkship. However, no such associations were observed for Surgery clerkship scores, Mini-CEX, DOPS, or other clinical evaluations. This suggests that while OSCEs serve as structured assessments of core skills, their ability to predict broader clinical competence in real-world settings appears limited. The weak inverse correlation with Internal Medicine performance warrants careful interpretation. One possible explanation may lie in the differences in assessment frameworks. OSCEs are standardized and time-constrained, while clerkship evaluations often reward adaptability, continuity of care, and interpersonal skills that are difficult to capture in a simulated environment. The weak inverse correlation with Internal Medicine clerkship performance, although statistically significant, is unlikely to have practical importance. Given the small effect size and borderline significance, this association may represent a chance finding (Type I error) or the influence of uncontrolled confounding factors such as assessor judgment, student motivation, or variability in clinical exposure. Therefore, this result should be interpreted with caution and not overemphasized. Furthermore, Internal Medicine often demands integrative reasoning, longitudinal patient care, and team-based decision-making domains less emphasized in traditional OSCE formats. The negative direction of correlation may also reflect a statistical artifact or unmeasured confounding, such as varying levels of student engagement, assessor subjectivity, or clinical exposure. Although prior literature often supports the formative value of OSCEs, its predictive utility remains a matter of controversy [9]. Nasiri *et al.* found that OSCE scores moderately predicted third-year clinical performance in a setting with integrated mentorship and longitudinal follow-up [10]. However, the contextual differences, including evaluation culture and curriculum structure, may explain the stronger alignment in that setting. Conversely, Dewan *et al.* Chang *et al.* and and Paynte *et al.* reported minimal associations between OSCEs and clerkship outcomes, consistent with our findings [11-13]. Moreover, studies by Dewan *et al.* and McGown *et al.* emphasized that OSCEs primarily assess discrete skills under observation but may not translate into performance in dynamic clinical environments [11, 14]. This supports the lack of association between domains such as Clinical Reasoning and real-world clerkship scores in our data. It is also possible that OSCE high-performers rely on structured preparation and checklist behaviors, while clerkship success often hinges on adaptability, communication, and professionalism traits harder to measure in OSCE stations. Some researchers advocate incorporating OSCEs into a broader competency-based assessment system [15-17]. Vhora et al. argued that while OSCEs demonstrate good inter-rater reliability, their summative use should be supplemented with workplace-based assessments [18]. Entrustable Professional Activities (EPAs), multisource feedback, and narrative clinical assessments may offer more valid insight into a student's readiness for clinical responsibilities [19, 20]. Overall, while the OSCE provides a valuable snapshot of student performance under controlled conditions, it cannot replace the depth and context provided by longitudinal clinical evaluations. Our findings support a shift toward multimodal assessment models that balance structured exams with authentic performance-based measures.

This study has several limitations, including its single-center retrospective design and relatively small sample size, which may limit generalizability. The reliance on institutional clerkship evaluations may also introduce assessor variability and unmeasured confounding factors influencing performance outcomes. Additionally, the follow-up period was limited to undergraduate clerkships without extending into internship or residency performance. Future multicenter longitudinal studies incorporating standardized workplace-based assessments and postgraduate outcomes are recommended to better clarify the long-term predictive value of OSCE scores.

CONCLUSIONS

In this single-institution study of 80 final-year medical students, OSCE scores demonstrated limited predictive validity for subsequent clinical performance. A weak negative correlation was observed between total OSCE scores and Internal Medicine clerkship outcomes, while no significant associations were found for Surgery clerkships,

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Mini-CEX, or DOPS. These findings suggest that OSCEs, although structured and standardized, may not adequately capture the complex competencies required in clinical environments. Future research should explore longitudinal, multisite studies and consider integrating OSCEs with entrustable professional activities and narrative workplace-based evaluations to better assess clinical readiness.

Authors' Contribution

Conceptualization: MA
Methodology: MA, ZA, BH, SA, HG
Formal analysis: ZA, SA, SS, HG
Writing and Drafting: MA, ZA, BH, SA, SS, HG
Review and Editing: MA, ZA, BH, SA, SS, HG

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Factors Affecting Clinical Learning of Undergraduate Nursing Students in Azad Jammu and Kashmir

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ABSTRACT

Nursing education encompasses both theoretical knowledge and clinical education, equipping nursing students for their future roles and enabling them to transition from dependency to independent practice. Thus, clinical education is considered integral and irreplaceable in training nursing professionals, allowing them to attain various educational objectives, including enhanced communication skills and critical thinking. **Objectives:** To identify factors affecting the clinical learning of undergraduate nursing students in Azad Jammu and Kashmir. **Methods:** This quantitative descriptive cross-sectional design study collected data through a census sampling technique from 286 undergraduate nursing students. Inclusion criteria focused on students who attend at least one complete course of clinical rotation; students who were on leave or not willing were excluded from the study. Data was collected by using structured questionnaires, and analysis was made by using SPSS 26 version. **Results:** The findings revealed the challenges, such as inadequate supervision (42.7%), time constraints for nursing staff (82.2%), and student hesitation due to fear of errors (75.9%). Factors include hospital collaboration (71%), educator support (74.7%), and patient reluctance (71.7%). Correlation analysis links these factors to demographics, including supervision type and study year. **Conclusions:** The study findings concluded that clinical learning in nursing students is influenced by supportive environments, clear objectives, and adequate preparation, while barriers like poor supervision, discrimination, and lack of resources. These factors must be addressed through improved educator-student ratios, better training, and collaboration with clinical staff.

INTRODUCTION

Nursing education blends theoretical instruction with hands-on experience to prepare students for independent practice [1]. Clinical education plays a crucial role in bridging the gap between classroom learning and real-life healthcare settings, offering opportunities for the development of communication, critical thinking, and decision-making skills [2]. Through clinical practice, students learn to apply theoretical concepts, uphold moral and ethical standards, and engage in evidence-based care. It also fosters teamwork, helping students to work effectively in multidisciplinary healthcare environments. This integration is vital for developing competent, empathetic, and safe practitioners. As such, clinical exposure is not supplementary but central to nursing education. Undergraduate nursing programs ensure clinical placements across diverse healthcare settings, each designed with specific learning objectives in mind [3]. Effective clinical education relies on clear goals, supportive guidance from instructors and staff, timely feedback, and student motivation [4]. Clinical learning environment also plays an important role by allowing students to apply theoretical knowledge in real-world settings [5]. It must align with the development of cognitive, psychomotor, and affective domains of learning.

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While theory enhances knowledge, clinical settings refine skills and professional behavior necessary for effective decision-making [6]. Therefore, a balanced approach involving both theoretical and practical components is essential for holistic nursing education. According to Hashemiparast *et al.* (2019), the learning environment, shaped by student-preceptor interactions and clinical dynamics, significantly impacts learning outcomes [7]. A supportive and engaging atmosphere, frequent student supervision, student-clinical educator ratio, and interpersonal relationships enhance student satisfaction and performance [8]. Nurse educators must ensure a positive clinical setting where students feel encouraged to learn, practice, and ask questions without hesitation [9]. Multiple factors influence clinical learning, including tutor supervision, resource availability, and individual student engagement [10,11]. Gemuhay *et al.* (2019) classify these as tutor-related (guidance and feedback), socio-economic (equipment and infrastructure), and individual (student motivation and effort). The effectiveness of clinical instructors and the integration of classroom and lab training with clinical practice are also vital. A well-maintained instructor-student ratio, ideally 1:12, ensures personalized mentorship and skill monitoring [12]. Additionally, elements like workload, number of available patients, and exposure time in departments further shape students' clinical experiences [13]. Proficiency and confidence in clinical skills developed during foundational nursing education are essential for competent nursing practice [14], yet students often underperform relative to their potential due to various challenges in clinical settings [6]. These challenges hinder effective clinical learning and lead to the production of inadequately prepared nurses, emphasizing the need to identify and address barriers to clinical competence. Real clinical environments, as opposed to simulated labs, play a critical role in cultivating clinical reasoning and practical skills [15]. While international research has examined factors influencing clinical learning, there remains a significant gap in the local context, where studies have been limited in scope, often focusing on diploma-level students or single institutions. There is a need for a broader investigation into diverse, context-specific factors affecting clinical education.

Although international literature has extensively explored factors influencing clinical learning environments, evidence from Azad Jammu and Kashmir remains scarce and fragmented. Most local studies have been limited to single institutions, diploma-level programs, or specific domains of clinical education, without comprehensively examining student-, educator-, hospital-, and patient-related factors together. This limited contextual evidence restricts the development of targeted strategies to enhance undergraduate nursing education in the region. Therefore, a broader investigation is required to identify context-specific determinants affecting clinical learning among undergraduate nursing students. This study aims to identify the factors affecting clinical learning of undergraduate nursing students in public and private nursing colleges of Azad Jammu and Kashmir.

METHODS

This quantitative descriptive cross-sectional design study was conducted from March 2023 to August 2023 at Shifa International Hospital, Islamabad. Ethical approval from the Institutional Review Board (Ref. No. 0176-23) of Shifa International Hospital, Islamabad. Participants were recruited through a census sampling, with a sample of 286. After obtaining informed written consent, participants were thoroughly briefed on the study's objectives, data collection procedures, and potential risks and benefits. Ethical considerations were strictly adhered to, ensuring participant autonomy, confidentiality, and informed consent throughout the study. Bachelor of Science in Nursing (BSN) students who attended at least one complete major nursing course clinical, who are 2nd year, 3rd year, and 4th year, were included in the study. Students who were not willing to participate in the study were excluded from the exclusion criteria. The maximum participants were from the State College of Nursing (institution A) that were 241(84.3%), and only 45 (15.7%) of participants were from Mohi-ud-Din College of Nursing (institution B). The reason for that disparity was that institution B was recently established, and only one class was fulfilling the inclusion criteria. Data were collected by the primary researcher using a validated and adapted structured questionnaire. After getting permission from the primary researcher few amendments were made, and calculated with a validity coefficient of 0.91, a reliability score of 0.87 (Cronbach's Alpha), and pilot-tested with 43 students. The questionnaire covered demographic information and 40 items related to factors influencing clinical learning covering five domains, including students' related factors, hospital-based factors, clinical educator-related factors, nursing colleges-based factors, and patients-related factors. Data analysis was conducted using SPSS version 26, and frequencies and percentages were employed for the categorical variables.

RESULTS

Out of 286 participants, 241 (84.3%) were from Institute A, 45 (15.7%) were from Nursing College B, and 241 (84.3%) were from Institute A. The largest group, 123 (43%), belonged to the third-year class (Table 1).

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Table 1: Participant Demographic Characteristics (N=286)

Demographic Characteristics	Frequency (%)
College of Nursing A	241 (84.3%)
College of Nursing B	45 (15.7%)
2nd year	122 (42.7%)
3rd year	123 (43%)
4th year	40 (14%)
Less than 20	249 (87.1)
21 – 25	36 (12.6)
26 and Above	01 (0.3%)
Single	284 (99.3%)
Married	02 (0.7%)
Muzaffarabad	71 (24.8%)
Mirpur	113 (39.5%)
Rawalakot	58 (20.3%)
Other than AJK	44 (15.4%)
Intermediate	259 (90.6%)
Bachelors	27 (9.4%)

During clinical practice, 122 participants (42.7%) reported no supervision, while 27 (9.4%) were supervised by clinical educators. Details are provided in the figure below (Figure 1).

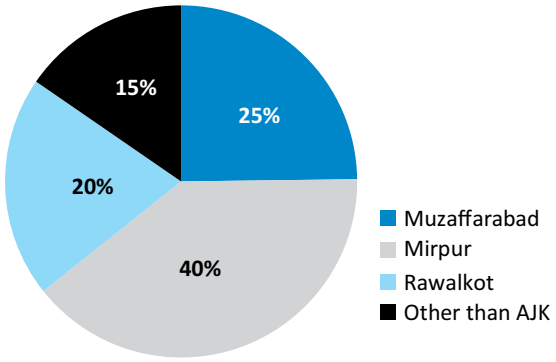

Figure 1: Clinical Practice Supervision

Clinical factors were categorized into hospital-based, clinical educator-related, nursing college-based, student-related, and patient-related constructs.

Hospital-based factors influencing clinical learning included learning opportunities, staff behavior, interprofessional collaboration, and available resources. While most students (71%) found collaboration beneficial, many (82.2%) felt nursing staff lacked time to support them, partly due to the high number of students from various departments. Most participants (71.1%) noted that patients were reluctant to receive care from students due to fear of mistakes, and 61.9% reported communication barriers. Additionally, 50% of students observed patient reluctance toward care from the opposite gender, with 19.2% uncertain (Table 2).

Table 2: Hospital and Patient-Related Factors Influencing Clinical Learning (N=286)

Sr. No.	Statements	Agree (%)	Uncertain (%)	Disagree (%)
01	The nursing staff does not have enough time to facilitate students' clinical learning due to the over burden of work.	235 (82.2%)	22 (7.7%)	29 (10.1%)
02	The presence of a large number of students from different health disciplines in the ward compromises the clinical learning of nursing students.	228 (79.7%)	30 (10.5%)	28 (9.7%)
03	Collaboration among clinical staff is helpful in promoting the clinical learning of nursing students.	203 (71.0%)	29 (10.1%)	54 (18.9%)
04	Discrimination against nursing students compared to students of other health disciplines by clinical staff/doctors in clinical areas is common.	197 (68.9%)	42 (14.7%)	47 (16.4%)
05	The clinical environment provides opportunities to meet the clinical learning needs of nursing students.	188 (65.8%)	52 (18.2%)	46 (16.1%)
06	The nursing staff is approachable when students require their help during clinical practice.	166 (58.0%)	59 (20.6%)	61 (21.4)
07	Nursing students are considered team members of healthcare workers in hospitals involved in patient care.	172 (60.1%)	52 (18.2%)	62 (21.6%%)
08	The clinical staff has a welcoming attitude towards students.	137 (47.7%)	76 (26.6%)	73 (25.5%)
09	Adequate opportunities are provided to perform clinical tasks during clinical practice.	136 (47.6%)	54 (18.9%)	96 (33.5%)
10	Patients are reluctant to receive any care from students due to fear of mistakes they might make.	205 (71.7%)	56 (19.6%)	25 (8.7%)
11	Adequate no. of patients is available to practice different nursing care skills.	187 (65.4%)	55 (19.2%)	44 (15.4%)
12	There are barriers to effective communication between students and patients.	177 (61.9%)	53 (18.55%)	56 (19.6%)
13	Students face religious or personal beliefs while attending the patients.	152 (53.2%)	38 (13.3%)	96 (33.5%)
14	Patients do not like to be attended to by the opposite gender.	109 (38.1%)	64 (22.4%)	113 (39.5%)

A majority of students (74.7%) recognized the importance of clinical supervision in their learning, though 65.4% felt clinical educators did not give enough time to each student. Despite this, over half of the participants acknowledged that educators were well-trained, respectful, and maintained supportive relationships with students (Table 3).

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Table 3: Clinical Educators' Related Factors

Sr. No.	Statements	Agree (%)	Uncertain (%)	Disagree (%)
01	Clinical supervision is helpful to promote clinical learning.	213 (74.5%)	21 (7.3%)	52 (18.2%)
02	Mutual respect between the instructor and students is maintained during clinical supe vision.	180 (62.9%)	37 (12.9%)	59 (24.1%)
03	Clinical educators are adequately trained for clinical teaching/ demonstration and facilitation.	174 (60.8%)	38 (13.3%)	74 (25.8%)
04	Instructors have a supportive relationship with students.	161 (56.3%)	41 (14.3%)	84 (29.3%)
05	Clinical educators guide students before sending them into the clinical area (pre-conference).	160 (56.0%)	47 (16.4%)	78 (27.3%)
06	Clinical educators take/give feedback after the completion of the clinical day (post-conference).	145 (50.7%)	52 (18.2%)	89 (31.1%)
07	Timely and constructive feedback is provided to the students to enhance clinical learning.	124 (43.3%)	47 (16.4%)	115 (40.2%)
08	Clinical educators encourage students to ask questions and discuss clinical assignments/ work.	120 (41.9%)	50 (17.5%)	116 (40.6%)
09	Clinical educators are readily available to assist students in their learning.	77 (26.9%)	42 (14.7%)	167 (58.4%)
10	The clinical educators provide sufficient time to each student.	46 (16.0%)	53 (18.5%)	187 (65.4%)

While 68.2% of participants felt theoretically prepared for clinical practice, many reported issues such as the improper student-to-instructor ratio (65.8%), inadequate clinical supervision (62.2%), and a lack of clinical conferences and seminars (60.9%) (Table 4).

Table 4: Nursing Colleges-Based Factors

Sr. No.	Statements	Agree (%)	Uncertain (%)	Disagree (%)
01	Students are prepared theoretically before starting clinical practice.	195 (68.2%)	41 (14.3%)	50 (17.4%)
02	The skills laboratories have enough equipment to meet the clinical needs of the students.	102 (35.6%)	53 (18.5%)	131 (45.8%)
03	All the students get equal opportunities to use the equipment during skills practice in the skills laboratories.	105 (36.7%)	41 (15.7%)	136 (47.5%)
04	Clinical conferences and seminars are arranged to promote students' clinical learning.	62 (21.7%)	50 (17.5%)	172 (60.9%)
05	One clinical educator is available for skill demonstration for 10-12 students in the clinical lab.	62 (19.2%)	36 (18.5%)	188 (65.8%)
06	The ratio of students and clinical instructors is 1:12, is available in the clinical area for guidance and supervision.	55 (19.2%)	53 (18.5%)	178 (62.2%)

Most participants (84.6%) agreed that continuous clinical supervision enhances learning, though 61.1% found it stressful. Many students reported challenges such as a lack of skill preparedness, fear of making mistakes, a theory-practice gap, and underreporting errors, while 88.2% highlighted the positive impact of peer support on clinical learning (Table 5).

Table 5: Students' Related Factors

Sr. No.	Statements	Agree (%)	Uncertain (%)	Disagree (%)
01	The positive support of classmates is supportive and positively influences clinical learning.	252 (88.2%)	8 (2.8%)	26 (9.0%)
02	Students learn better when they have continuous supervision during clinical practice.	242 (84.6%)	20 (7.0%)	24 (8.4%)
03	Students are hesitant to perform tasks/skills due to fear of making mistakes.	105 (75.9%)	36 (12.6%)	33 (11.5%)
04	Students are unable to apply theory to practice due to a lack of knowledge.	206 (72.1%)	18 (6.3%)	62 (21.6%)
05	Students are hesitant to report mistakes due to fear of punishment.	207 (72.4%)	24 (8.4%)	55 (19.2%)
06	Students are unable to perform tasks/skills accurately due to a lack of preparedness.	198 (69.3%)	34 (11.9%)	54 (18.8%)
07	Students are unable to demonstrate knowledge and kills due to a lack of confidence.	200 (69.9%)	39 (13.3%)	47 (16.4%)
08	While performing clinical tasks, continuous observation is stressful for students.	176 (61.6%)	47 (15.4%)	65 (22.7%)
09	Students are unable to communicate effectively with patients, clinical educators, and clinical staff.	122 (42.6%)	65 (22.7%)	99 (34.6%)

DISCUSSION

A marked gender disparity was observed, with no male students enrolled in the public institution and only six males in the private college. This contrasts with findings from Khyber Pakhtunkhwa (2022), where male enrollment predominated (73%) [16]. According to the World Health Organization (WHO), male nurses constitute only 18.55% of Pakistan's nursing workforce, well below the Pakistan Nursing Council's recommended 50:50 ratio, indicating a persistent gender imbalance [17]. A major issue identified was the inadequacy of clinical supervision, consistent with studies from Karachi (2024), Africa (2022), Japan (2019), and Pakistan (2019) [6,18-20]. Globally, inconsistent supervisory structures remain a concern, while the need for competent clinical educators has been underscored in recent studies [21-22]. A conducive CLE is essential for effective learning, as also reported previously [10]. In the current study, 56.8% of participants described their CLE as supportive, a higher proportion than in earlier Pakistani studies [23-24]. Positive staff collaboration (71%) was a strong facilitator of learning, consistent with earlier

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findings [25]. However, challenges such as limited staff approachability, discrimination (68.9%), and workload pressures mirrored findings from Tanzania and other international studies [11,26-28]. Overcrowded clinical placements (79.7%) further restricted practical exposure, aligning with previous research [29]. Theoretical preparation was generally adequate, with 68.2% of participants reporting being well-prepared before clinical practice. This contrasts with findings from Nigeria (2016) and Iran (2018) [30, 31]. Nonetheless, a significant theory–practice gap persists, reported by over 70% of students, consistent with recent studies [9,25]. Possible reasons include inadequate supervision, limited clinical conferences, and insufficiently aligned skill-lab experiences. A high educator–student ratio (1:12) also compromised supervision quality, echoing findings from Canada (2018) [32]. Continuous supervision was viewed as beneficial by most students (84.6%), though many found it stressful, similar to previous results [33]. This may be attributed to performance anxiety and fear of evaluation. Conversely, peer support was identified as a major enabler of clinical learning (88.2%), consistent with prior studies [30]. Communication barriers were another key concern, with 61.9% of students reporting difficulties in interacting with patients, largely due to language differences and patients' reluctance to be treated by students. Similar challenges have been documented in Pakistan (2016), England, and Kirkuk (2020) [22,34-35]. Such barriers hinder confidence-building and clinical competence.

This study has certain limitations, including its cross-sectional design, which limits causal interpretation, and data collection from only two institutions, potentially affecting generalizability. The use of self-reported questionnaires may also introduce response and social desirability bias. Future multicenter and mixed-method studies incorporating qualitative exploration are recommended to gain deeper insights into students' lived experiences and to evaluate interventional strategies aimed at improving supervision, institutional support, and clinical learning environments across diverse nursing institutions.

CONCLUSIONS

Various factors were identified in the current study that influence the process of clinical learning, including a supportive clinical environment, positive peer and educator relationships, clear objectives, and task preparedness. However, barriers such as high student-educator ratios, staff discrimination, inadequate resources, and fear of errors hinder learning. To enhance clinical learning, institutions should adopt recommended supervision ratios, hire qualified educators, equip skills labs, and collaborate with clinical staff. Future multi-centered and interventional studies are essential to explore experiences and evaluate strategies for improving nursing students' clinical learning. Due to time constrain study was kept limited to only two institutions by using a simple quantitative study technique.

Authors' Contribution

Conceptualization: SN, AZ, SI, BS
Methodology: SN
Formal analysis: SN, AZ, SI, BS
Writing and Drafting: SN, AZ, BS
Review and Editing: SN, AZ, BS, SN

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Case Study

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Outcome of Surgery for the Management of High Perianal Fistulae Using Elastic Seton

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ABSTRACT

High perianal fistulae are complex infections often originating from anal glands, requiring sphincter-preserving surgical approaches. Elastic seton offers controlled tract closure with reduced need for postoperative adjustments compared to traditional cutting setons. **Objectives:** To evaluate the outcomes of elastic seton in managing high perianal fistulae, focusing on pain, healing, hospital stay, and continence preservation. **Methods:** This descriptive case series was conducted from February 2025 to May 2025 at the Department of Surgery, Surgical Unit III, Sir Ganga Ram Hospital, Lahore. Forty-five patients with high perianal fistulae were enrolled using consecutive non-probability sampling. An elastic seton from a latex glove was placed under spinal anesthesia. Follow-ups at 1 week, 4 weeks, 3, and 6 months assessed pain (VAS), wound healing, complications, and analgesic use. Data were analyzed with SPSS v24.0 using Chi-square and ANOVA, with $p < 0.050$ significant. **Results:** Of the 45 patients (64.4% male; mean age 31.3 ± 8.4 years), the mean symptom duration was 11.8 ± 4.1 weeks, and average seton cut-through time was 6.3 ± 0.9 weeks. VAS scores significantly decreased from 5.13 (Week 1) to 0.40 (6 months) ($p < 0.001$). Complete wound healing occurred in 82.2% of patients, while complications declined from 42.2% to 17.8%. **Conclusion:** Elastic cutting seton with staged fistulotomy ensured safe, effective high anal fistula management with reduced pain, rapid healing, and preserved continence.

INTRODUCTION

Anal fistulae represent an abnormal communication between the anal canal and the perianal skin. The majority of perianal fistulae (PF) encountered in surgical practice are due to persistent infection of the anal glands located in the intersphincteric space, a concept known as the cryptoglandular hypothesis [1]. However, fistulae may also be associated with specific underlying conditions such as inflammatory bowel disease, Crohn's disease, tuberculosis, malignancy, actinomycosis, lymphogranuloma venereum, anal fissures, trauma, foreign bodies, previous radiation therapy, or surgical interventions [2]. Approximately 33% of patients who experience an anorectal abscess will subsequently develop a fistula [3]. PFs are more common in males, with a male-to-female ratio of 2:1, and typically occur between the ages of 30 and 50 years [4]. Diagnosis of PF involves a combination of clinical and radiological modalities including digital rectal examination, proctoscopy, anal manometry, fistulography, rectosigmoidoscopy, MRI, and CT scan to assess the anatomy and complexity of the tract [5]. Among the various classification systems proposed, the most widely accepted is Park's classification, which categorizes fistulae into four types: intersphincteric, trans-sphincteric, suprasphincteric, and extrasphincteric [6]. The intersphincteric type is the most common, accounting for about 45% of cases [7]. Surgery remains the mainstay of treatment for PF. The ideal surgical approach should eradicate the fistula tract while preserving

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sphincter function, minimizing recurrence, and preventing postoperative fecal incontinence [8]. Low and simple fistulae are typically managed with fistulotomy. However, complex and high fistulae often require sphincter-sparing techniques such as draining or cutting setons, advancement flaps, rerouting procedures, two-stage seton fistulotomy, fistulectomy with or without sphincter reconstruction, ligation of the intersphincteric fistula tract (LIFT), anal fistula plugs, and fibrin glue application [9, 10]. Recent studies have explored modifications to the cutting seton technique to improve outcomes and reduce complications. One such modification is the use of an elastic seton. Previous studies reported that an elastic material obtained from surgical gloves could serve as an effective seton with low recurrence and acceptable continence outcomes, with a mean hospital stay of 1.27 days and a general recovery rate of 93.9% [11]. A study on 128 patients concluded that the hybrid elastic seton allows for slow and stable sphincter division, preserving continence and eliminating the need for postoperative adjustment. Complete healing was achieved in 100% of cases within three months, and quality of life was significantly improved. [12]. Previous researches supported the use of elastic setons, finding them simple to use with satisfactory therapeutic outcomes. Healing time ranged from 14 days to 6 months (mean 4 months) [13]. Additionally, a study noted that 52.2% of patients experienced pain, and the mean duration of seton cut-through was 8 weeks (range: 5–11 weeks) [14]. Given the lack of local data, this study aims to evaluate the effectiveness of the elastic seton in managing high perianal fistulae in our population. Elastic seton, with its flexibility and consistent pressure, may reduce the need for postoperative adjustments, a major limitation of traditional cutting setons, while offering better outcomes in terms of continence preservation and patient comfort. This study is therefore designed to generate local evidence on surgical outcomes, focusing on postoperative pain, seton cut-through time, and hospital stay, as well as assessing feasibility, safety, and impact on quality of life. Although previous studies have reported favorable results, they were conducted in different healthcare settings that may not reflect our demographics, disease patterns, or surgical practices. Hence, evaluating elastic seton outcomes in our context is essential to guide clinical practice.

Despite advancements in surgical techniques for high perianal fistulae, postoperative pain, delayed healing, and risk of incontinence remain significant challenges. Most studies on elastic setons have been conducted in different populations and healthcare settings, with limited local data reflecting our demographic and clinical context. Therefore, there is a need to evaluate the effectiveness, safety, and patient-centered outcomes of elastic seton placement specifically in our population. This study aims to evaluate the outcomes of elastic seton in managing high perianal fistulae, focusing on pain, healing, hospital stay, and continence preservation.

METHODS

This descriptive case series was conducted at Surgical Unit I, Sir Ganga Ram Hospital, Lahore, over three months, from February 2025 to May 2025, after obtaining approval from the College of Physicians and Surgeons, Pakistan (Ref. No. CPSP/REU/SGR-2021-059-12970). Ethical approval (Ref. No 254-Research-Surgery/ERC) was obtained from the institutional review board of Fatima Jinnah Medical University, Lahore, and all participants provided written informed consent prior to inclusion. A total of 45 patients were enrolled using consecutive non-probability sampling. The sample size was calculated by using the WHO sample size calculator using a 95% confidence level, a 5% margin of error, and an expected frequency of fistula healing in patients as 97.6%, by using the formula: $n = \frac{Z^2 \cdot P \cdot (1-P)}{d^2}$ [15]. Patients included were aged above 15 years, of either gender, and presented with perianal sepsis/fistulae diagnosed through clinical examination and Pelvic MRI was performed on a 1.5 Tesla Siemens Magnetom Avanto (Siemens Healthcare, Erlangen, Germany) scanner using T1-weighted, T2-weighted, and STIR sequences in axial, coronal, and sagittal planes to delineate the primary tract and identify secondary extensions. Exclusion criteria included patients with known inflammatory bowel disease, tuberculosis, malignancy, actinomycosis, lymphogranuloma venereum, foreign body-related fistulae, anticoagulant or antiplatelet use, prior perineal trauma or obstetric sphincter injury, or those who were immunocompromised or malnourished. All surgeries were performed under spinal anesthesia in the lithotomy position after obtaining informed consent. High perianal fistula was confirmed through clinical and MRI findings. Examination under anesthesia (EUA) included digital rectal examination and proctoscopy. The digital examination was performed using a well-lubricated gloved finger to assess sphincter tone, tenderness, and internal opening, followed by rigid proctoscopy (St. Mark's proctoscope) to visualize the internal orifice and mucosal condition. A metal probe was gently introduced through the external opening to locate the tract and internal opening, avoiding false passage creation. The tract was excised up to the intersphincteric or suprasphincteric level, preserving the external sphincter. An elastic seton, prepared from a 2–3 mm latex strip cut from a sterile surgical glove, was passed through the tract and tied over the sphincter with minimal

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tension. Hemostasis was achieved, and the wound was packed with pyodine- and xylocaine-soaked gauze for eight hours before applying a pressure dressing. Postoperatively, patients were advised limited mobility for one week and daily SITZ baths. Medications included metronidazole (400 mg TID), ciprofloxacin (500 mg BID), diclofenac sodium (50 mg PRN), and omeprazole (40 mg OD). Patients were educated about wound care, expected discharge, and signs of complications such as fever, pain, or fecal incontinence. Follow-up visits were scheduled at 1 week, 4 weeks, 3 months, and 6 months. At each visit, symptoms, pain scores, wound healing, and postoperative complications were recorded using a structured follow-up form. Pain intensity was assessed using the Visual Analogue Scale (VAS), a validated 10-point scale where 0 indicates no pain and 10 represents the worst imaginable pain [16]. Patients also documented total analgesic use. Wound healing was assessed clinically at each visit based on the presence of healthy granulation tissue, absence of discharge, epithelialization of wound margins, and complete closure of the external opening. Postoperative complications, including infection, bleeding, fever, incontinence, recurrence, and delayed wound healing, were documented through clinical observation and patient reports. Recurrence was defined as persistent or recurrent drainage beyond six months of follow-up. Outcome measures included VAS scores at follow-ups, time to seton cut-through (weeks), and length of hospital stay (days). Data confidentiality was maintained throughout the study. Data were analyzed using SPSS v24.0. Qualitative variables such as gender, complications, and wound healing were reported as frequencies and percentages, while quantitative variables such as age, symptom duration, hospital stay, duration of symptoms, total analgesic consumption, and seton cut-through time were presented as mean ± SD. Fisher's exact test was applied to compare postoperative complications and wound healing while one-way ANOVA was used for pain at follow-ups, with a p-value <0.050 considered statistically significant.

RESULTS

Among 45 patients, 64.4% were male (n=29) and 35.6% were female (n=16). The mean age of the participants was 31.31 years (SD±8.35) (Table 1).

Table 1: Demographic Characteristics of the Study Participants

Variables	Category	N (%) / Mean±SD
Gender	Female	16 (35.6%)
	Male	29 (64.4%)
Age (years)	–	31.31 ± 8.35

The average duration of symptoms before treatment was 11.76 weeks (SD±4.07). On average, the time to seton cut-through was 6.31 weeks (SD±0.93). The mean total analgesic consumption was 853.78 mg (SD±91.31), while the average length of hospital stay was 2.51 days (SD±0.70) (Table 2).

Table 2: Clinical Characteristics and Treatment Outcomes (N=45)

Variables	Mean ± SD
Duration of Symptoms (weeks)	11.76 ± 4.07
Time to Seton Cut-through (weeks)	6.31 ± 0.93
Total Analgesic Consumption (mg)	853.78 ± 91.31
Length of Hospital Stay (days)	2.51 ± 0.70

The mean VAS score progressively decreased from Week 1 (5.13) to 6 Months (0.40), indicating significant pain reduction post-treatment. The ANOVA test showed a highly significant difference in pain scores over time ($F(3,176) = 280.73$, $p<0.001$), confirming that pain improvement was statistically significant across follow-ups (Table 3).

Table 3: Comparison of Mean ± SD VAS Scores During Follow-Up Visits Among Patients Treated for High Anal Fistula

Follow-Up Time Point	Mean ± SD	p-Value
Week 1	5.13 ± 1.14	<0.001
Week 4	3.22 ± 0.90	
3 Months	1.40 ± 0.50	
6 Months	0.40 ± 0.50	
Total	2.54 ± 1.98	

A significant trend was observed in wound healing progression over time ($p < 0.001$, Chi-square test for trend). Initially, at Week 1, only 8 patients (17.8%) had fully healed wounds, while 25 (55.6%) remained unhealed. By Week 4, the number of completely healed patients rose slightly to 10 (22.2%). Marked improvement was evident at the 3-month follow-up, where 28 patients (62.2%) achieved complete healing. At 6 Months, this figure further increased to 37 (82.2%), indicating continued and substantial recovery. Correspondingly, the number of patients with unhealed wounds declined steadily from 25 (Week 1) to just 3 by the 6-month. There was a statistically significant association between time and wound healing status (p-value<0.050) (Figure 1).

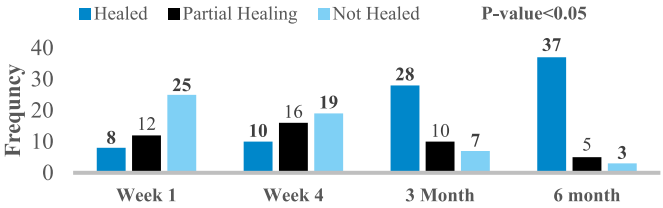

Figure 1: Weekly Follow-Up of Wound Healing Status Among Patients Over 6 Months (N=45 at Each Time Point)

Initially, in Week 1, 42.2% (n=19) of patients reported complications such as mild bleeding (n=5), pain (n=5), infection (n=5), and discharge (n=4), while 57.8% (n=26) had

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no complications. By Week 4, the proportion of patients without complications had slightly improved to 60% (n=27), and pain had become the most frequently reported issue (n=10), suggesting a transient peak in discomfort. At the 3-month follow-up, the majority of patients (64.4%, n = 29) were complication-free. Pain remained the most common complaint (n=14), but all other complications had resolved or significantly reduced. By 6 months, 82.2% (n=37) of patients reported no complications, with only minor reports of pain, infection, and discharge. There is a significant reduction in the frequency of complications over time, particularly from Week 1 to Month 6, indicating progressive wound healing and patient recovery. Pain showed a temporary increase at 3 months but eventually declined, while bleeding and infection resolved earlier in the follow-up period (Figure 2).

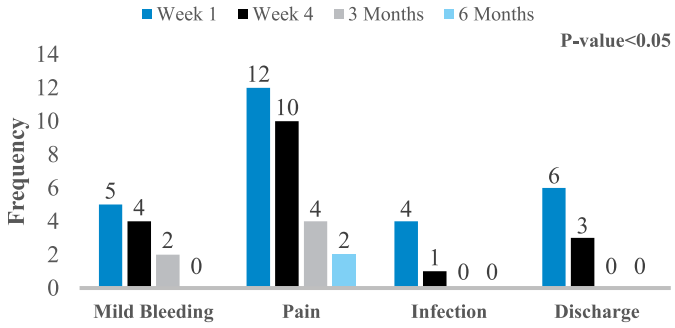

Figure 2: Frequency of Postoperative Complications Over Time

DISCUSSION

Anal fistula is a common sequela of anal abscess, with reported incidence rates ranging from 26% to 38%, meaning nearly one-third of patients with an abscess may eventually develop a chronic fistula requiring surgical treatment [17]. In the present study, the demographic distribution aligns with previous literature. Males comprised 64.4% (n=29) of the participants, while females accounted for 35.6% (n=16), reflecting the established male predominance in fistula-in-ano cases, where males are affected approximately twice as often as females [18]. The mean age of patients in our study was 31.31 years (SD ± 8.35), which is slightly younger than the commonly reported mean age of 40 years but still falls within the broader age range of 20 to 60 years [19]. These findings are consistent with existing epidemiological trends and highlight the relevance of age and gender in the clinical presentation of anal fistula. Anal fistula surgery aims to eliminate the tract, prevent recurrence, and preserve sphincter function. Setons, particularly in complex cases, aid drainage and minimize incontinence risk. In the current study, an elastic seton made from a 2–3 mm latex glove strip was tied with minimal tension, consistent with prior methods [20, 22]. In the current study, the average duration of symptoms was 11.76 weeks (SD ± 4.07), the mean time to seton cut-through was 6.31 weeks (SD ± 0.93), average analgesic consumption was 853.78 mg (SD ± 91.31), and the mean hospital stay was 2.51 days (SD ± 0.70), reflecting the feasibility and clinical effectiveness of this technique. Similarly, a previous study reported a 71% healing rate in the Seton group, along with lower complication rates (9%) and reduced fecal incontinence (4%) compared to fistulectomy [23]. These findings are consistent with the present results, reinforcing that elastic seton placement is a safe, cost-effective, and sphincter-preserving approach for managing complex anal fistulae. In the current study, a significant association was observed between time and wound healing status ($p<0.001$). Wound healing progressed steadily, with complete healing increasing from 17.8% at Week 1 to 82.2% at 6 months. This trend highlights the effectiveness of the treatment approach and the sustained improvement in wound resolution over time. Another study reported a notably higher healing rate of 97.6%, with a mean seton cut-through time of 8 weeks and complete wound closure achieved in approximately 9 weeks. Although 15.6% of patients experienced minor incontinence to flatus, there were no cases of fecal incontinence, and the recurrence rate was low at 2.4% [24]. These results highlight the efficacy of the cutting seton technique in promoting successful outcomes with minimal complications. Compared to the present study, which showed slightly longer healing times and lower incontinence rates, both findings collectively support the use of seton placement as an effective, sphincter-preserving treatment for complex anal fistulas.

The study has several limitations; it uses non-probability sampling, lacks a control group, depends on self-reported pain scores, and may experience losses in follow-up. Future research with larger, multicenter randomized trials is warranted to confirm these findings, assess long-term recurrence rates, and explore patient quality-of-life outcomes. Such studies could further refine elastic seton techniques and optimize postoperative care protocols.

CONCLUSIONS

The use of an elastic cutting seton with staged fistulotomy proved to be an effective and safe technique for managing high anal fistulae. The procedure resulted in a significant reduction in postoperative pain, progressive wound healing, and a marked decline in complication rates over six months of follow-up. Most patients achieved complete healing without notable functional impairment, indicating good sphincter preservation and favourable clinical outcomes. Overall, this method offers a reliable, minimally invasive, and reproducible approach for treating high perianal fistulae, with high healing rates and minimal

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morbidity when performed under careful surgical and postoperative supervision

Authors' Contribution

Conceptualization: TJ
Methodology: MI, MAJ, AN
Formal analysis: TJ, AN
Writing and Drafting: MI, MAJ, AN
Review and Editing: MI, MAJ, AN, TJ

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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The Impact of Reflective Writing on Empathy Development among Medical Students: A Systematic Review and Narrative Synthesis

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ABSTRACT

Empathy is central to patient-centered care but often declines during medical training. Reflective writing has emerged as a strategy to strengthen empathy by fostering emotional awareness, ethical reasoning, and self-reflection. **Objectives:** To evaluate the effectiveness of reflective writing in enhancing empathy among undergraduate medical students and identify features influencing its success. **Methods:** A systematic search of PubMed, ScienceDirect, ERIC, and Google Scholar (January 2020–July 2025) was conducted following PRISMA 2020 guidelines. Thirty-four records were identified, 4 duplicates removed, and 16 excluded during screening. Eighteen full texts were reviewed, and 15 studies met eligibility criteria. Eligible designs included qualitative, quantitative, and mixed-methods research; conceptual contributions with structured reflective models were also retained. Data on participants, interventions, reflective frameworks, and empathy measures were extracted. Risk of bias was assessed using adapted CASP and ROBINS-I criteria. **Results:** Of the 15 included studies, 3 demonstrated statistically significant empathy improvements using validated tools ($p<0.012$, $p=0.040$). One study showed no significant change, while 9 reported descriptive or thematic improvements, such as enhanced ethical reasoning and emotional engagement. Two studies provided anecdotal evidence, and 2 were theoretical. Risk-of-bias assessment indicated most studies were of moderate quality, limited by small samples, self-reported outcomes, and absence of controls. **Conclusion:** Reflective writing is a promising, low-cost educational tool for nurturing empathy in medical students, especially when structured, facilitated, and supported by feedback. Future studies should employ validated instruments, larger sample sizes, and longitudinal follow-up to confirm sustained effects.

INTRODUCTION

Empathy, the ability to understand and share the feelings of others, is fundamental to the physician-patient relationship and is consistently linked with improved diagnostic accuracy, treatment adherence, patient satisfaction, and professional well-being [1]. However, there is growing concern that empathy tends to decline during medical training, particularly in the clinical years, due to academic pressures, emotional fatigue, and the dominance of biomedical teaching models [2, 3]. To address this issue, medical educators worldwide have introduced reflective writing as a pedagogical tool that enables learners to process clinical experiences through

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introspective narrative. Structured reflection has been shown to foster critical thinking, enhance emotional resilience, and promote ethical awareness [4, 5]. In high-income countries, reflective writing is embedded into professionalism modules, narrative medicine curricula, and interdisciplinary humanities programs [6]. In contrast, evidence from low- and middle-income countries (LMICs) remains limited, with small-scale reports highlighting cultural stigma around emotional expression, limited faculty training, and curricular overload as common barriers [7, 8]. These challenges underline the need for context-sensitive strategies, but the primary scope of this review is global. The decision to restrict the review to studies published between 2020 and 2025 was deliberate, aiming to synthesize the most recent evidence and capture innovations that emerged in medical education following the COVID-19 pandemic, which accelerated the integration of reflective and humanities-based learning [9]. Against this backdrop, the present systematic review evaluates whether and how reflective writing contributes to empathy development among undergraduate medical students worldwide. By analyzing studies conducted across diverse cultural and educational settings, this review seeks to identify effective strategies, highlight methodological strengths and weaknesses, and offer recommendations for implementing reflective pedagogy in medical curricula.

Although reflective writing has been increasingly recognized as a tool to enhance empathy among medical students, existing evidence is limited by small sample sizes, heterogeneous interventions, and reliance on self-reported outcomes. Few studies systematically compare structured versus unstructured approaches, and longitudinal effects on sustained empathy remain unclear. This highlights a critical gap in understanding which reflective practices are most effective and under what educational conditions they maximize empathic development. The aim of this systematic review is to evaluate the effectiveness of reflective writing in enhancing empathy among undergraduate medical students, and to identify the features of interventions—such as structure, facilitation, and feedback that influence their success.

METHODS

This systematic review followed PRISMA 2020 guidelines to synthesize recent evidence on the role of reflective writing in enhancing empathy among undergraduate medical students. A comprehensive search was conducted in PubMed, ScienceDirect, ERIC, and Google Scholar (supplementary), using Boolean operators with the following PubMed string: ("reflective writing" OR "narrative writing" OR "journaling" OR "reflection") AND ("empathy" OR "empathic" OR "compassion") AND ("medical students" OR "undergraduate medical education"), with filters set to English-language studies published between January 2020 and July 2025; the first 200 results per query were reviewed for reproducibility. Eligible studies included original research involving undergraduate medical students where reflective writing (structured or unstructured) was the intervention and empathy was a measured outcome; conceptual papers and narrative reviews were also included if they presented structured reflective models (e.g., Gibbs, Kolb) or theoretical frameworks, which were classified separately as "theoretical evidence." Studies were excluded if they involved non-medical students, lacked a reflective writing component, did not assess empathy, were not in English, or lacked full-text availability. Screening was conducted at title/abstract and full-text stages, with data extracted on study design, participants, intervention structure, use of frameworks, facilitator involvement, feedback, comparison groups, empathy measures, timing, and outcomes. Study quality and risk of bias were evaluated using an adapted framework from ROBINS-I (for non-randomized studies) and CASP (for qualitative studies) across four domains: selection bias, measurement bias, confounding, and reporting bias, with narrative/conceptual papers assessed for transparency and theoretical coherence. Due to heterogeneity in design and outcomes, a narrative synthesis was undertaken, summarizing quantitative results through p-values or effect sizes and categorizing qualitative findings into themes such as emotional engagement, ethical reasoning, patient-centered communication, and professional identity development, with comparisons based on intervention features including reflective models, facilitator involvement, and feedback provision (Figure 1).

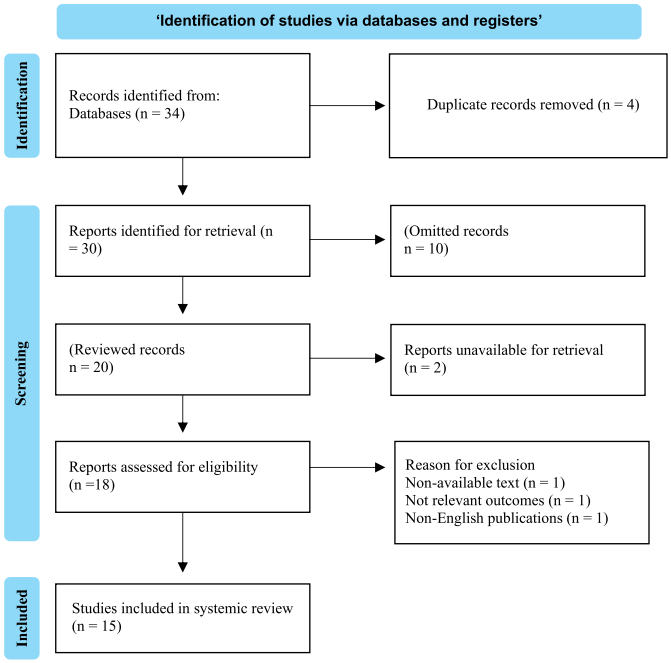

Figure 1: PRISMA 2020 Flow Diagram Illustrating the Process of Study Identification, Screening, and Inclusion

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RESULTS

Table 1 a summarizes the characteristics of the 15 studies published between 2020 and 2025 that examined the impact of reflective writing on empathy among medical students. The included studies were conducted across diverse geographical regions, including Asia, Europe, North America, and Africa, reflecting the global interest in empathy development. Study designs varied from interventional pre-post (n=1), experimental or quasi-experimental (n=3), mixed-methods (n=2), and longitudinal courses (n=1) to qualitative analyses (n=5) and conceptual/narrative contributions (n=3). Sample sizes ranged from 28 participants to 192 reflective essays, while some studies did not specify participant numbers. The participant groups included both preclinical (1st–2nd year) and clinical (final-year clerks, 3rd–6th year) students, demonstrating the integration of reflective writing across different stages of medical training. Most interventions were guided or structured, such as ethics vignettes, clinical exposure reflections, or visual arts–based activities. In contrast, free-form and creative writing approaches were explored in a smaller number of studies [11-13]. Notably, 10 of 15 studies (66%) incorporated facilitator involvement and feedback, while five relied on self-directed writing. The presence of facilitation and structured feedback appeared more frequently in studies reporting positive outcomes (Table 1).

Table 1: Characteristics of Included Studies (2020–2025)

Sr. No.	References	Country	Design	Sample Size (N)	Participants	Intervention	Facilitator/ Feedback
1	[10]	Taiwan	Qualitative	28	Medical students	Reflection on correctional school visits	No / No
2	[11]	Turkey	Qualitative	192 essays	5th-year students	Reflection on clinical year experiences	No / No
3	[12]	UK	Qualitative	Not reported	2nd-year students	Storytelling with patient educators	Yes / Yes
4	[13]	Spain	Longitudinal (3 years)	Not reported	4th–6th-year students	Professionalism course with reflection	Yes / Yes
5	[14]	UAE	Pre-post interventional	73	Final-year clerks	Free-form reflective writing during clerkship	None / No
6	[15]	Uganda	Narrative report	Not reported	Medical students	Creative writing, journaling	Yes / Yes
7	[16]	India	Qualitative	150	1st-year students	Guided reflective narratives post clinical exposure	Yes / Yes
8	[17]	USA	Mixed methods	128	1st-year students	Visual arts + reflective writing	Yes / Yes
9	[18]	India	Mixed methods	150	1st-year students	Ethics vignettes + guided reflection	Yes / Yes
10	[19]	USA	Experimental	Not reported	3rd-year students	Reflection rounds (4 sessions)	Yes / Yes
11	[20]	Russia	Quasi-experimental	60	Med students (English course)	Narrative writing (10–13 assignments)	Yes / Yes
12	[21]	Sweden	Qualitative	69 essays	Final-year students	Critical reflection essays	No / No
13	[22]	Ireland	Content analysis	80 essays	Undergrad psychiatry students	Graded reflective essays	Yes / Yes
14	[23]	Thailand	Narrative review	Not applicable	Medical students (general)	Reflection models	Encouraged / Yes

Not reported = Study did not specify participant number, not applicable = Conceptual/narrative review without participants. And Facilitator/Feedback = First entry = facilitator present (Yes/No), Second entry = feedback provided (Yes/No).

The study results showed the empathy-related outcomes and findings across the 15 included studies. Of these, 3 studies (20%) demonstrated statistically significant improvements in empathy scores using validated scales: Rezaei [17] ($p<0.012$), Menezes ($p=0.04$ [19]), and Torubarova ($p<0.050$ [20]). One study reported no statistically significant change (NS, $p>0.050$), though qualitative themes indicated emotional engagement [24]. Nine studies (60%) described descriptive or thematic improvements in empathy or related domains such as teamwork, ethical reasoning, and compassion; Donohoe quantified reflections, showing that 56% of essays demonstrated dialogic and 19% critical reflection [22]. Two studies provided anecdotal or narrative impressions without statistical analysis [12, 15]. Finally, 2 studies were conceptual/theoretical, emphasizing reflective models or poetic expression as strategies for empathy development [14, 23]. Taken together, the evidence base suggests that empathy gains were most robust when validated measurement tools were applied, but descriptive and thematic data consistently highlighted perceived improvements in empathic capacity, professional identity, and patient-centered attitudes (Table 2).

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Table 2: Empathy Outcomes and Findings (2020–2025)

Sr. No.	References	Empathy Measure	Timing	Main Outcome	Statistical Result	Risk of Bias
1	[10]	Reflective journals	Post	Gendered empathy patterns (♀ relational> ♂ practical)	Descriptive	Moderate
2	[11]	Thematic analysis of essays	Post	Empathy + stress themes	Descriptive (qualitative categories)	Moderate
3	[12]	Reflection essays	Post	↑ Compassion, ↑ engagement	Anecdotal	Moderate
4	[13]	Self-assessment + SP encounters	Multi-year (3 yrs)	↑ Empathy sustained	Significant (longitudinal trend, no p reported)	Moderate
5	[14]	Poetic reflection (conceptual)	N/A	Empathy enhancement suggested	Theoretical	Low
6	[15]	Creative journaling	N/A	↑ Self-awareness, ↑ empathy	Descriptive	Moderate
7	[16]	Not specified	Post	↑ Empathy, ↑ teamwork	Descriptive (student themes)	Moderate
8	[17]	Interpersonal Reactivity Index (IRI)	Pre/Post	↑ Perspective-taking	$p < 0.012$	Moderate
9	[18]	Custom rubric (Likert scale)	Post	↑ Ethical reasoning, ↑ empathy	Descriptive (Mean Likert > 4/5)	Moderate
10	[19]	Jefferson Scale of Empathy (JSE)	Pre/Post (clerkship)	↑ Empathy in intervention vs control	$p = 0.040$	Moderate
11	[20]	Empathy/Communication tolerance scale	Pre/Post (13 weeks)	↑ Empathy, ↑ communication tolerance	$p < 0.050$	Moderate
12	[21]	Critical reflection essays	Retrospective	Empathy preserved or ↑	Descriptive	Moderate
13	[22]	Reflection coding scale	Cross-sectional	56% dialogic, 19% critical reflections	Numerical descriptive	Moderate
14	[23]	Reflection models (review)	N/A	Supports empathy development	Theoretical	Low
15	[24]	Toronto Empathy Questionnaire	Pre/Post	No improvement in empathy	NS ($p > 0.050$)	Moderate

*NS = Not Significant ($p>0.050$), JSE = Jefferson Scale of Empathy, IRI = Interpersonal Reactivity Index, SP = Standardized Patients
Descriptive = Reported qualitatively or with descriptive scores/percentages (no inferential testing), Anecdotal = Narrative impressions without systematic analysis, Theoretical = Conceptual or framework-based evidence only

The majority of studies (12/15) were judged as having moderate overall risk of bias, largely due to limitations in study design, absence of control groups, reliance on self-reported empathy outcomes, and potential confounding from concurrent clinical experiences. Three studies were classified as low overall risk, this rating was qualified (*Low**), since conceptual/narrative studies did not lend themselves to traditional bias domains but were transparent in reporting [14, 23, 21]. One study showed a high risk of bias across selection, measurement, and confounding domains due to its narrative report format and lack of methodological detail. Measurement bias was low in studies using validated empathy tools [17, 19, 24], but high in conceptual and narrative works that relied on self-reflection without standardized tools. Confounding bias was commonly moderate, reflecting limited control for external factors such as prior exposure to communication skills training or clinical rotations.

Overall, the risk-of-bias profile demonstrates that while reflective writing shows promise, much of the evidence base rests on studies with moderate methodological rigor, emphasizing the need for future randomized controlled trials with standardized empathy measures and long-term follow-up (Table 3).

Table 3: Risk of Bias Assessment for Included Studies (2020–2025)

Sr. No.	References	Design	Selection Bias	Measurement Bias	Confounding	Reporting Bias	Overall Risk
1	[10]	Qualitative	Moderate	Moderate	Moderate	Low	Moderate
2	[11]	Qualitative	Low	Moderate	Moderate	Low	Moderate
3	[12]	Qualitative	Moderate	Moderate	High	Low	Moderate
4	[13]	Longitudinal	Low	Low	Moderate	Low	Moderate
5	[14]	Conceptual (essay)	Low	High	High	Low	Low*
6	[15]	Narrative report	High	High	High	Moderate	Moderate
7	[16]	Qualitative	Low	Moderate	Moderate	Low	Moderate
8	[17]	Mixed methods	Moderate	Low	Low	Low	Moderate
9	[19]	Experimental	Low	Low	Moderate	Low	Moderate
10	[20]	Quasi-experimental	Moderate	Moderate	Moderate	Low	Moderate
11	[21]	Qualitative	Low	Moderate	Moderate	Low	Moderate

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12	[22]	Content analysis	Low	Low	Moderate	Low	Moderate
13	[23]	Narrative review	Low	High	High	Low	Low*
14	[24]	Pre-post interventional	Moderate	Low	Moderate	Low	Moderate

*Selection bias = Representativeness of participant selection. Measurement bias = Use of validated empathy tools (low = validated tool, high = only self-report or unclear). Confounding = Adjustment for external factors (e.g., concurrent modules, clinical exposure, gender differences). Reporting bias = Completeness of outcome reporting.

DISCUSSION

This systematic review revealed that reflective writing, particularly when structured and supported, has a positive impact on the development of empathy among undergraduate medical students. The interventions varied in form, ranging from narrative reflections and journaling to guided essays and ethics-based vignettes. The outcomes collectively suggested improvements in students' ability to recognize emotions, engage compassionately, and reflect ethically on patient care. These findings were contextualized with recent 2025 studies outside the formal review window, cited to highlight convergent trends in medical education literature rather than as part of the systematic dataset. Earlier studies have shown that guided reflection significantly enhances empathic awareness, ethical reasoning, and patient-centered communication. This trend was mirrored by Ahmadpour and Shariati [24], who implemented Gibbs' reflective cycle in narrative writing and found measurable increases in empathy and communication skills among nursing students, and by Chan *et al.* [25], who observed that reflective writing mapped to ACGME competencies improved sensitivity toward interpersonal care. The value of structure and feedback was another recurrent theme. In this review, studies like Menezes *et al.* [19] and del Barrio *et al.* [13] showed statistically significant gains in empathy scores when reflection was embedded in structured educational settings. Comparable findings were reported by Mandal and Kundu [26], who demonstrated that rubrics enhanced emotional engagement, and by Artioli *et al.* [27], who confirmed that facilitator feedback amplified the depth of reflection. This review also showed that free-form reflections, while emotionally expressive, had mixed results in terms of measurable empathy gains. Earlier studies found no statistically significant improvements despite strong thematic insights into emotional awareness. Recent studies reported similar outcomes, where unstructured reflections lacked the consistency and depth seen in facilitated approaches [29, 30]. The influence of creative and humanities-based modalities was also noted. Previous studies described how poetry and journaling fostered emotional insight. This aligns with Malik *et al.* [31], who found that poetic reflection enhanced empathy by promoting emotional articulation among South Asian students, and with Rezaei *et al.* [17], who reported similar gains using visual prompts. Another notable theme was the role of cultural and gender variation. Hsu and Sung [10] reported gendered empathy patterns, which were further validated by McNally *et al.* [32], who found that sociocultural norms shaped empathetic narratives during debriefing sessions. Lastly, this review highlighted limitations in empirical rigor, including small sample sizes, absence of control groups, and inconsistent empathy measures. Similar limitations were reported by Imperato *et al.* [33] and Spaska *et al.* [34], who noted the difficulty of long-term evaluation, and by Zia *et al.* [35], who emphasized challenges in isolating reflection as the sole factor in improved interpersonal awareness. Limitations of this review itself should also be acknowledged. First, only English-language studies were included, which may have excluded relevant evidence published in other languages. Second, conceptual and narrative contributions were retained because of their theoretical value, but they lack empirical testing and should be interpreted cautiously. Third, due to heterogeneity in study designs, outcome measures, and reporting, a meta-analysis was not feasible, and a narrative synthesis was adopted instead. Taken together, the findings underscore the value of reflective writing as a pedagogical tool for enhancing empathy in medical education, particularly when thoughtfully designed, facilitated, and embedded within the curriculum. The evidence, both from this dataset and recent literature, strongly suggests that empathy is most likely to improve when reflective practices are intentional, supported, and evaluated using validated tools.

This review is constrained by methodological variability, including diverse study designs, inconsistent measurement tools, and moderate sample sizes, which limit the generalizability of findings. Future research should employ larger, multicenter cohorts, standardized empathy instruments, and longitudinal designs to evaluate sustained outcomes. Additionally, investigating culturally adapted and facilitated reflective frameworks can inform the integration of empathy-focused curricula across diverse medical education settings.

CONCLUSIONS

This review, enriched by recent contextual evidence, confirms that reflective writing, when well-structured, guided, and supported, plays a significant role in fostering empathy among medical students. The intervention is

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especially effective when based on established reflective models, embedded in clinical or humanities-based contexts, and coupled with facilitator feedback. However, methodological variability and limited long-term evaluation continue to constrain the evidence base. Future studies must prioritize methodological rigor by employing adequately powered sample sizes (ideally >100 participants per group), applying validated empathy instruments such as the Jefferson Scale of Empathy or Interpersonal Reactivity Index, and incorporating longitudinal follow-up of at least 6–12 months to evaluate the persistence of empathy gains. Until such evidence is available, reflective writing remains a promising, low-cost, and adaptable approach to nurturing empathy, a trait central to compassionate, patient-centered care.

Authors' Contribution

Conceptualization: SA
Methodology: S, BA, SS[1]
Formal analysis: S, SS[2]
Writing and Drafting: S, BA, SA, SS[1], SS[2], SF
Review and Editing: S, BA, SA, SS[1], SS[2], SF

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Association of Homocysteine Levels with Recurrent Pregnancy Loss: A Systematic Review

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ABSTRACT

Elevated homocysteine (Hcy) has been implicated in placental vascular dysfunction and adverse reproductive outcomes. **Objective:** To synthesize recent evidence on the association between Hcy levels and recurrent pregnancy loss (RPL), emphasizing methodological consistency and potential modifiers. **Methods:** Following PRISMA 2020, observational studies comparing Hcy in women with RPL versus controls were screened across PubMed, Scopus, and Cochrane. Reviews, pilots, case reports, abstracts, animal studies, and articles without quantitative Hcy data were excluded. Risk of bias was assessed using the Newcastle–Ottawa criteria; results were summarized with Synthesis Without Meta-analysis (SWiM). **Results:** Fourteen eligible studies across South Asia, the Middle East, Europe, and East Asia consistently reported higher Hcy among RPL cases, with typical mean differences ≈4–7 µmol/L and odds ratios ≈2–3, including studies adjusting for folate/B12 and MTHFR genotype. Heterogeneity stemmed from biospecimen type (serum/plasma), assay platform (HPLC vs immunoassay), fasting status, sampling time (preconception vs early pregnancy), and cut-offs (10–15 µmol/L). Emerging literature outside the included set supports endothelial mechanisms and gene nutrient interactions while highlighting reporting gaps and the need for interventional trials. **Conclusions:** Current evidence supports Hcy as a reproducible risk marker for RPL, plausibly mediated by endothelial and thrombo-inflammatory pathways and modified (but not fully explained) by folate/B12 status and genetic variants. Standardized measurement, rigorous adjustment, and randomized trials of targeted vitamin strategies are priorities.

INTRODUCTION

Recurrent pregnancy loss (RPL) affects 5% of couples and remains etiologically heterogeneous; endothelial dysfunction and microthrombosis are increasingly recognized contributors [1, 2]. Elevated Hcy is biologically plausible linked to endothelial injury, impaired trophoblast invasion, and dysregulated one-carbon metabolism [3, 4]. Recent data also connect adverse reproductive histories with later cardiometabolic and neurovascular sequelae through shared endothelial pathways, underscoring clinical relevance [5]. Contemporary studies associate higher maternal Hcy with miscarriage risk and subfertility, but variability in biospecimen, fasting protocols, assay methods, and cut-offs complicates comparability [6, 7]. Mechanistic work implicates Hcy metabolites in

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endothelial damage, yet few RPL studies measure vascular readouts in parallel. Moreover, gene nutrient interactions (e.g., folate-pathway variants) are inconsistently reported, and high-quality interventional data remain scarce [8]. A systematic synthesis focused on study-level methods (matrix, fasting, assay, thresholds) and adjustment for folate/B12 and MTHFR can clarify whether elevated Hcy is a robust signal rather than an artifact of measurement or confounding; mapping this against recent mechanistic and prognostic literature strengthens biological plausibility and translational potential [9].

Despite growing evidence linking elevated homocysteine to recurrent pregnancy loss (RPL), inconsistencies in study design, assay methods, and adjustment for confounders such as vitamin B12, folate status, and MTHFR polymorphisms limit the generalizability of current findings. Moreover, most studies are observational and region-specific, leaving a gap in understanding the mechanistic pathways and the potential impact of targeted interventions. Addressing these gaps is crucial to clarify the role of homocysteine as a predictive biomarker and therapeutic target in RPL. This study aims to summarize the direction and magnitude of association between Hcy and RPL across designs and regions, to describe sources of methodological heterogeneity, to review contemporary mechanistic, genetic, and prognostic evidence relevant to Hcy–RPL, and to outline priorities for standardization and trials.

METHODS

This systematic review was conducted in accordance with the PRISMA 2020 guidelines. A comprehensive search was carried out across three electronic databases: PubMed, Scopus, and the Cochrane Library, covering all publications from 2007 to March 2025. The search strategy used the following terms: ("homocysteine" OR "hyperhomocysteinemia") AND ("recurrent pregnancy loss" OR "recurrent miscarriage" OR "recurrent abortion"). In PubMed, controlled vocabulary (MeSH) terms were mapped alongside free-text keywords in titles and abstracts. In Scopus and Cochrane Library, equivalent free-text keywords and subject headings were used. Filters for human studies and female participants of reproductive age were applied where available, while no restrictions were set for publication year. Only studies published in the English language were included, while studies in other languages such as Chinese, Italian, Turkish, Spanish, Persian, and Arabic were excluded. Hence, only English-language articles were accepted. All identified records were imported into EndNote 21 (Clarivate Analytics) for reference management, and duplicate publications were removed using EndNote's duplicate detection tool. Studies were eligible if they reported original quantitative data on homocysteine levels in women with recurrent pregnancy loss (RPL) compared with controls, defined RPL as ≥2 or ≥3 consecutive miscarriages (regardless of gestational age), and included all study design like observational or experimental designs such as case-control, cross-sectional, cohort, and randomized studies etc. Although the inclusion criteria permitted all study designs such as case-control, cross-sectional, cohort, and randomized studies, during the full-text screening, no cross-sectional, cohort, or randomized experimental studies meeting the eligibility criteria were found. The available literature on homocysteine levels and recurrent pregnancy loss (RPL) is predominantly composed of case control designs, where women with RPL are compared with healthy controls. Cross-sectional or cohort studies addressing this association are either lacking or did not meet the required methodological standards (for example, not reporting homocysteine measurements, lacking control groups, or focusing on unrelated outcomes). Hence, only case–control studies were included in the final synthesis, which is consistent with most published reviews. The following were excluded: systematic reviews, scoping reviews, narrative reviews, case reports, pilot studies, conference abstracts, animal studies, and studies not reporting homocysteine measurements or lacking a control group. Articles with overlapping populations were carefully evaluated, and the most comprehensive dataset was retained. A total of 247 records were identified (PubMed n=91, Scopus n=80, Cochrane n=76). After removal of 32 duplicates, 215 unique records were screened by title and abstract. Of these, 126 were excluded as irrelevant. Full-text review was performed for 89 studies, of which 75 were excluded due to reasons such as not presenting quantitative data (n=22), being review or case report in nature (n=18), or involving the wrong population or outcome (n=35). Finally, 14 studies met the inclusion criteria and were incorporated into the qualitative synthesis. The selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

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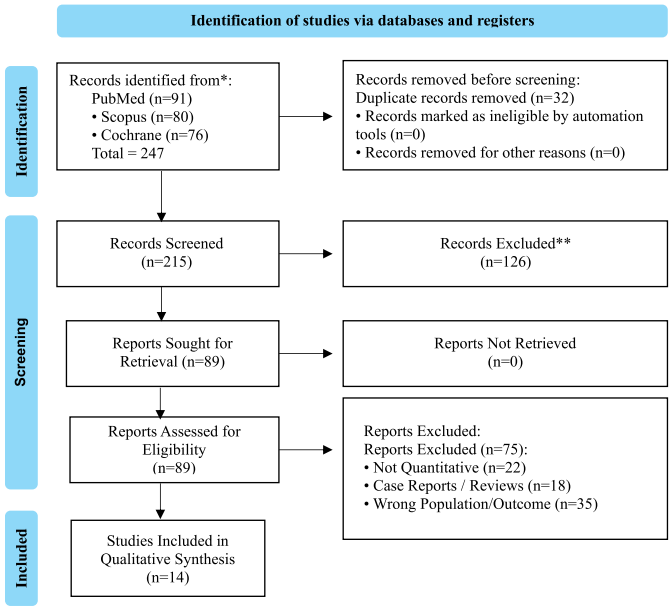

Figure 1: Selection Process in This Study

Data from the included studies were independently extracted by two reviewers using a standardized proforma. Extracted variables included: study characteristics (first author, year, country, study design, setting, and sample size), definition of RPL, demographic and clinical features of participants (age, BMI, vitamin supplementation, presence of thrombophilias), laboratory details (specimen type, fasting status, assay method, and cut-off values for hyperhomocysteinemia), and outcomes (mean homocysteine levels, odds ratios, confidence intervals, and adjustment for covariates). Where reported, subgroup data such as primary versus secondary RPL, MTHFR genotype status, and folate/vitamin B12 deficiency were also noted. The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates three domains: selection of participants (maximum 4 stars), comparability of cases and controls (maximum 2 stars), and ascertainment of exposure/outcome (maximum 3 stars). Studies achieving 7–9 stars were rated as low risk of bias, those with 5–6 stars as low–moderate risk, and those with <5 stars as moderate risk. Two reviewers conducted the appraisal independently, with disagreements resolved through discussion. A summary of NOS ratings was provided in Table X (Risk of Bias Assessment). Given the heterogeneity in study design, assay methods, and cut-off thresholds, a meta-analysis was not feasible. Instead, a qualitative synthesis without meta-analysis (SWiM) was conducted, focusing on direction of effect, consistency across studies, and subgroup analyses.

RESULTS

A total of 14 original case control or observational studies conducted between 2007 and 2025 were included. These studies originated from diverse geographic settings, including South Asia (Pakistan, India, Bangladesh), the Middle East (Egypt), Europe (Italy, Belgium), China, Türkiye, and Vietnam. Sample sizes varied considerably, ranging from 34 to 190 women in each group. Most studies defined recurrent pregnancy loss (RPL) as ≥2 consecutive miscarriages, while a few older studies applied the stricter definition of ≥3. Matching strategies also differed, with several studies age- or BMI-matching controls, while others recruited healthy parous women. This diversity highlights both the global recognition of homocysteine as a potential biomarker for RPL and the methodological heterogeneity across studies (Table 1).

Table 1: Characteristics of Included Studies

Sr. No.	References	Study Design	Setting	Sample Size (RPL / Controls)	RPL Definition	RPL Type	Matching/Selection
1	[10]	Case–control	Tertiary hospital, Karachi	62/62	≥2 consecutive	Mixed	Age-matched OPD controls
2	[11]	Case–control	Enam Med College	60/60	≥2	NR	Healthy parous controls
3	[12]	Case–control	Shaheed Suhrawardy/ BSMMU	34/34	≥2 unexplained	NR	Age & BMI matched
4	[13]	Case–control	Egyptian Hosp. Medicine network	60/60	≥3	NR	Hospital-based controls
5	[14]	Case–control	Univ. clinic	50/50 (approx.)	≥3 unexplained	NR	Non-pregnant healthy controls
6	[15]	Case–control	Fertility clinic	70/40	≥3	NR	Non-pregnant healthy controls
7	[16]	Prospective/Case–control (baseline + post -vit therapy)	Teaching hospital	50/50 (baseline)	≥2	NR	Consecutive cases; healthy controls
8	[17]	Observational	Regional OB-Gyn	80 40 (baseline)*	≥2	NR	Consecutive RPL; healthy controls
9	[18]	Case–control	Univ. hospital	86/86 (approx.)	≥2 unexplained	Mixed	Age-matched; detailed labs
10	[19]	Case–control	Tertiary center	120/120 (grouped)	≥2 (subset)	NR	Healthy controls; vitamins assessed
11	[20]	Case–control	Regional maternity hosp.	190/190 (approx.)	Early loss; URPL subset	NR	Controls matched; folate/B12/MTHFR
12	[21]	Case–control	National hospital	150/150	≥2 unexplained	NR	Frequency-matched

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13	[22]	Case-control	Teaching hospital	100/100	≥2	Mixed	Consecutive cases; age-matched
14	[23]	Experimental case-control	Academic center	60/60	≥2 unexplained	NR	Healthy parous controls

NR = Not reported; RPL = Recurrent Pregnancy Loss; OPD = Outpatient Department

Baseline characteristics were reported inconsistently across studies. Mean maternal age was comparable between RPL and control groups, typically ranging from 26 to 31 years, with only minor differences observed. Body mass index (BMI) was presented in some studies and showed no significant variation between groups, generally within the normal range (22–24 kg/m^2). Smoking status was rarely reported, which may reflect low prevalence in the studied populations or underreporting. Data on vitamin supplementation were sparse, though several studies documented folate and vitamin B12 deficiency rates. Most studies excluded participants with systemic conditions such as diabetes, hypertension, renal disease, thyroid dysfunction, or autoimmune disorders, aiming to minimize confounding. Overall, women with RPL were demographically similar to controls, suggesting that differences in outcomes were unlikely to be driven by baseline disparities (Table 2).

Table 2: Participant Characteristics at Baseline

References	Mean age (y)	BMI (kg/m^2)	Smoking (%)	Folic Acid/B-Vitamin Use (%)	Other Thrombophilias Reported	Exclusion Criteria Key Points
[10]	RPL: 27.6 ± 4.3; Controls: 26.9 ± 4.7	NR	NR	Reported folate/B12 deficiency prevalence; supplementation not routine	None screened beyond folate/B12	Excluded women with chronic illness, endocrine disorders
[11]	RPL: 28.3 ± 4.1; Controls: 27.7 ± 3.9	23.8 ± 2.9 vs 23.6 ± 3.0	NR	NR	NR	Excluded diabetes, HTN, renal disease
[12]	RPL: 27.5 ± 5.2; Controls: 26.8 ± 4.8	24.2 ± 3.1 vs 23.9 ± 2.8	NR	NR	NR	Excluded uterine anomalies, endocrine disorders
[13]	26.9 ± 4.2 vs 27.1 ± 3.9	NR	NR	Vit B12 measured; folate not always	Screened for B12 deficiency	Excluded systemic illness, infections, uterine anomalies
[14]	RPL: 31 ± 4; Controls: 30 ± 5	NR	NR	NR	Screened for antiphospholipid syndrome	Excluded thyroid, diabetes, known thrombophilia
[15]	~29 ± 5 (reported)	NR	NR	NR	B12/folate deficiency profiled	Excluded uterine malformations, systemic illness
[16]	27.4 ± 3.7 vs 26.5 ± 3.9	23.9 ± 2.8 vs 23.5 ± 2.7	NR	Folate/B12 supplementation group described	None other	Excluded thyroid, diabetes, PCOS structural uterine anomaly
[17]	28.0 ± 4.1 vs 27.5 ± 3.9	24.0 ± 2.6 vs 23.8 ± 2.9	NR	NR	NR	Excluded systemic disease, drug use
[18]	29.3 ± 4.9 vs 29.1 ± 4.7	22.8 ± 3.0 vs 22.6 ± 3.1	NR	Not on folate at baseline (confirmed)	Antiphospholipid, lupus, diabetes excluded	Excluded structural uterine anomalies, infections, endocrine disorders
[19]	28.7 ± 5.0 vs 29.0 ± 4.8	24.5 ± 3.2 vs 24.2 ± 3.1	NR	NR	NR	Excluded metabolic disease, thrombophilia
[20]	30.1 ± 4.6 vs 29.9 ± 4.4	22.7 ± 2.9 vs 22.5 ± 3.0	NR	Folate status measured	MTHFR, B12 deficiency noted	Excluded systemic illness, infection
[21]	28.9 ± 5.2 vs 28.5 ± 4.9	23.2 ± 3.0 vs 23.0 ± 2.8	NR	NR	Screened MTHFR genotypes	Excluded diabetes, HTN, lupus, uterine anomalies
[22]	27.6 ± 4.5 vs 27.2 ± 4.3	23.5 ± 2.8 vs 23.1 ± 2.7	NR	NR	NR	Excluded systemic illness, thyroid, PCOS
[23]	30.4 ± 4.2 vs 29.9 ± 4.0	22.1 ± 2.9 vs 22.0 ± 3.1	NR	NR	Screened vascular/ endothelial markers	Excluded thrombophilia, diabetes, smoking, obesity

RPL = Recurrent Pregnancy Loss; BMI = Body Mass Index; NR = Not reported; PCOS = Polycystic Ovary Syndrome; HTN = Hypertension; APLA = Antiphospholipid Antibody Syndrome

Methods of homocysteine assessment varied between studies. Most collected fasting plasma samples, though a few used serums. The majority employed high-performance liquid chromatography (HPLC), considered the gold standard, while others used ELISA or chemiluminescent immunoassays. Timing of sample collection was predominantly pre-conception, though two recent studies measured homocysteine during early pregnancy. Units were consistently reported in µmol/L, but cut-off values for defining hyperhomocysteinemia varied between 10 and 15 µmol/L. This methodological heterogeneity, particularly regarding assay type and cut-off thresholds, represents a potential source of variability in reported associations (Table 3).

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Table 3: Homocysteine Measurement Details

References	Specimen (Plasma/Serum)	Fasting Status	Assay Method	Timing (Pre-Conception / Pregnancy)	Units	Cut-Off Used (Elevated Hcy)
[10]	Plasma	Fasting (overnight)	ELISA kit	Pre-conception	µmol/L	≥15 µmol/L
[11]	Serum	Fasting	HPLC	Pre-conception	µmol/L	≥12 µmol/L
[12]	Serum	Fasting (8–10 h)	Chemiluminescence immunoassay	Pre-conception	µmol/L	≥12.44 µmol/L
[13]	Serum	Fasting (overnight)	ELISA (Shanghai Sunred kit)	Pre-conception	µmol/L	≥10.97 µmol/L
[14]	Plasma	Fasting	HPLC (fluorescence)	Pre-conception	µmol/L	>12 µmol/L
[15]	Serum	NR (likely fasting)	Spectrophotometric assay	Pre-conception	µmol/L	≥15 µmol/L
[16]	Plasma	Fasting (12 h)	HPLC	Pre-conception; post-therapy follow-up	µmol/L	≥15 µmol/L
[17]	Serum	Fasting (8 h)	Chemiluminescent microparticle immunoassay	Pre-conception	µmol/L	≥12 µmol/L
[18]	Plasma	Fasting (overnight)	HPLC	Pre-conception	µmol/L	≥12 µmol/L
[19]	Serum	Fasting (≥8 h)	Enzyme immunoassay (EIA)	Early pregnancy (≤12 w)	µmol/L	≥15 µmol/L
[20]	Plasma	Fasting	HPLC with fluorescence detection	Early pregnancy	µmol/L	≥12 µmol/L
[21]	Plasma	Fasting	LC-MS/MS	Pre-conception	µmol/L	≥10 µmol/L
[22]	Serum	NR (likely fasting)	Spectrophotometric enzymatic assay	Pre-conception	µmol/L	≥15 µmol/L
[23]	Plasma	Fasting	HPLC	Pre-conception	µmol/L	≥12 µmol/L

HPLC = High-Performance Liquid Chromatography; ELISA = Enzyme-Linked Immunosorbent Assay; LC-MS/MS = Liquid Chromatography–Mass Spectrometry/Mass Spectrometry; NR = Not reported; Hcy = Homocysteine

This review found that all fourteen included studies consistently demonstrated higher homocysteine levels among women with recurrent pregnancy loss compared to controls. The mean difference generally ranged between 4–7 µmol/L, and odds ratios indicated a two- to three-fold increased risk of RPL with elevated homocysteine. South Asian studies, including Afaq *et al.* and Sultana *et al.* and reported significant associations even after adjusting for nutritional deficiencies [10, 11], while Egyptian studies such as Abd-Ellatef *et al.* and Gaber *et al.* highlighted additional links with vitamin B12 deficiency [13. 15]. European and East Asian investigations, including Qi *et al.* and Que *et al.* confirmed that the association remained significant even after accounting for folate, vitamin B12, and MTHFR polymorphisms, with stronger effects observed in risk allele carriers [18, 21]. Notably, studies that differentiated between primary and secondary RPL, such as Ghaber *et al.* found elevated homocysteine in both subgroups [15]. Only Mukhopadhyay *et al.* assessed intervention, demonstrating a reduction in homocysteine following folate/B12 therapy, though pregnancy outcomes were not fully evaluated [16]. Collectively, these results indicate a robust and consistent association across diverse populations, independent of genetic or nutritional modifiers(Table 4).

Table 4: Main Outcomes and Subgroup Analyses: Association Between Homocysteine and Recurrent Pregnancy Loss

References	Group Hcy (RPL vs Control)	Effect Estimate	Adjustment (Covariates)	Subgroup Notes	Direction*
[10]	17.3 ± 3.4 vs 10.9 ± 2.8 µmol/L	OR 2.1 (1.2–3.8), p<0.010	Folate, B12	Effect persisted after adjustment	↑
[11]	15.6 ± 4.1 vs 11.3 ± 3.7	–, p<0.001	None	No subgroup analysis	↑
[12]	18.5 ± 4.6 vs 12.1 ± 3.9	OR 2.5 (1.3–4.7), p=0.002	Age, BMI	Effect stable across categories	↑
[13]	15.9 ± 1.1 vs 10.4 ± 0.9	–, p<0.001	B12 correlation	No subgroup data	↑
[14]	11.9 vs 8.4 (median)	–, p=0.010	Folate, B12	Excluded APLA/thyroid	↑
[15]	16.2 ± 2.7 vs 11.8 ± 2.2	–, p<0.001	B12, folate profiled	Higher Hcy in both primary & secondary RPL	↑
[16]	17.8 ± 4.2 vs 12.6 ± 3.1	RR 2.0 (1.1–3.5), p=0.010	Folate/B12 therapy	Hcy fell after supplementation	↑
[17]	16.7 ± 3.9 vs 11.1 ± 3.2	–, p<0.001	None	No subgroups	↑
[18]	15.4 ± 4.5 vs 10.8 ± 3.6	OR 1.9 (1.2–3.0), p<0.01	Folate, B12, MTHFR	Risk persisted across genotypes	↑
[19]	14.9 ± 3.2 vs 10.6 ± 2.7	–, p<0.001	None	Early loss subset consistent	↑
[20]	17.1 ± 4.0 vs 12.2 ± 3.5	OR 2.3 (1.5–3.6), p<0.001	Folate/B12, MTHFR	Effect stable across genotypes	↑
[21]	18.2 ± 4.8 vs 11.6 ± 3.9	OR 2.7 (1.6–4.5), p<0.001	Age, MTHFR	Stronger in risk allele carriers	↑
[22]	16.0 ± 3.7 vs 11.3 ± 3.0	–, p<0.001	None	No subgroup analysis	↑
[23]	12.7 ± 3.5 vs 10.1 ± 2.9	β=+2.3, p=0.020	Vascular markers	Examined endothelial function	↑

RPL = Recurrent Pregnancy Loss; OR = Odds Ratio; RR = Relative Risk; β = Regression Coefficient; Hcy = Homocysteine; MTHFR = Methylenetetrahydrofolate Reductase

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Only Mukhopadhyay *et al.* tested vitamin therapy, showing that folate/B12 supplementation reduced homocysteine levels, though pregnancy outcomes were not fully reported [16]. Other included studies profiled vitamin status but did not intervene, highlighting the lack of randomized evidence. Recent external trial has shown supplementation can improve outcomes, but such data were not captured in this review [25]. Most studies were rated low–moderate risk by the Newcastle–Ottawa criteria. Case/control definitions were clear, and assays consistent, but many lacked full adjustments for confounders (BMI, diet, smoking). More recent studies were stronger, adjusting for both folate/B12 and MTHFR genotype (Table 5).

Table 5: Risk of Bias Assessment using Newcastle–Ottawa Scale (NOS)

References	Selection (max 4)	Comparability (max 2)	Exposure / Outcome (max 3)	Total Score (max 9)	Risk of Bias
[10]	4	2	3	9	Low
[11]	3	2	2	7	Low–Moderate
[13]	3	1	2	6	Moderate
[14]	3	1	2	6	Moderate
[15]	3	1	2	6	Moderate
[16]	4	2	2	8	Low
[17]	3	1	2	6	Moderate
[18]	4	2	3	9	Low
[19]	3	1	2	6	Moderate
[20]	4	2	3	9	Low
[21]	4	2	3	9	Low
[22]	3	1	2	9	Moderate
[23]	4	2	3	6	Low

NOS = Newcastle–Ottawa Scale; Low risk (7–9 stars), Moderate risk (5–6 stars), High risk (<5 stars)

All 14 studies reported elevated homocysteine in RPL cases compared to controls. Where odds ratios were modeled, effect sizes ranged from 1.9–2.7. No study reported null or inverse findings, underscoring a consistent positive association across populations. Newer studies explicitly stated fasting duration, assay methods, and predefined cut-offs, while older ones often omitted these details. MTHFR genotyping was performed in only 3 studies. Handlings of missing data were rarely discussed, and conflict-of-interest declarations were more common post-2020.

DISCUSSION

This review found that across 14 original studies conducted between 2007 and March 2025, women with recurrent pregnancy loss (RPL) consistently had higher homocysteine levels compared with healthy controls. The association was strong and consistent, with odds ratios generally showing a two- to three-fold increased risk. These findings directly support the research question that elevated homocysteine is a significant biochemical marker associated with RPL. The observed pattern remained robust even after considering nutritional deficiencies and genetic factors such as MTHFR polymorphisms, suggesting that hyperhomocysteinemia may play an independent pathogenic role. Our study found that South Asian research consistently demonstrated elevated homocysteine among women with RPL, independent of folate or B12 deficiency [11, 17]. These findings suggest that both genetic and metabolic factors may contribute to elevated homocysteine in these populations. Comparable results were reported by Asanidze *et al.* in Georgia, who observed a strong correlation between high homocysteine and early miscarriage risk, particularly in women with polycystic ovarian syndrome (PCOS) [24]. This indicates that metabolic comorbidities such as PCOS could amplify the adverse reproductive effects of homocysteine. Similarly, Jawad *et al.* in Pakistan found that hyper-homocysteinemia was more pronounced in women with unexplained infertility and pregnancy loss, reinforcing the nutritional-genetic interaction observed in this review [26]. These comparisons strengthen the conclusion that hyper-homocysteinemia represents a common biochemical denominator across metabolic and reproductive disorders in South Asian women. Our study also included Middle Eastern evidence, which highlighted elevated homocysteine levels together with low vitamin B12. This dual pattern suggests that nutritional deficiency could potentiate the adverse vascular and oxidative effects of homocysteine [13, 15]. In accordance, Shibbl and Sharif demonstrated that Middle Eastern women with RPL had higher homocysteine and impaired endothelial function, implicating vascular pathways in addition to nutritional [27]. Conversely, Elagab *et al.* in Saudi Arabia observed that while hyperhomocysteinemia was common, it was not independently predictive after adjusting for obesity and hypertension, suggesting regional variation in confounder influence implying that the predictive value of this biomarker may vary depending on coexisting cardiometabolic risks [28]. Taken together, these studies highlight that homocysteine's role is most pronounced when metabolic or vascular health is already compromised. In European and East Asian cohorts, our review found that elevated homocysteine was consistently linked with RPL, even after accounting for nutritional and genetic factors [18, 21]. In support, Yang *et al.* in China reported that elevated homocysteine was associated with abnormal uterine artery Doppler indices in women with recurrent miscarriage, reinforcing vascular dysfunction as a mediator [29]. Similarly, Naim *et al.* linked hyperhomocysteinemia to endothelial activation and thrombotic risk in unexplained miscarriages [30]. Thus, the

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present findings align with growing evidence that endothelial impairment represents the principal pathway through which homocysteine contributes to pregnancy loss. Our study further showed that the association between homocysteine and RPL remained significant even after controlling for MTHFR polymorphisms and vitamin status, suggesting a gene nutrient interaction [18, 21]. External studies confirm this gene nutrient interaction: Li *et al.* reported that the combined presence of high homocysteine and MTHFR C677T mutation significantly increased miscarriage risk [23], while Jin *et al.* showed that dietary folate partially attenuated the association but did not eliminate risk [31]. In contrast, Asanidze *et al.* found the effect was substantially reduced after adjusting for folate levels, indicating regional heterogeneity in nutritional influence [24]. This comparison underscores that while genetic factors increase susceptibility, homocysteine acts as a final common metabolic pathway influencing placental function and vascular integrity. Our review included one interventional study, which found that folate and vitamin B12 supplementation reduced plasma homocysteine levels, although pregnancy outcomes were not fully reported [16]. Similarly, Bala *et al.* reported that combined folate and vitamin B12 therapy reduced miscarriage recurrence in women with hyperhomocysteinemia [32]. These comparisons highlight the gap between observational evidence and clinical trials, indicating that while biochemical improvement is achievable, its translation into reproductive benefit remains to be established. Future research should prioritize randomized studies to determine whether homocysteine-lowering therapy can effectively reduce miscarriage risk. Mechanistically, our study supports the concept that homocysteine contributes to miscarriage through oxidative stress, vascular dysfunction, and defective placentation. This interpretation is strengthened by experimental findings showing that hyperhomocysteinemia promotes endothelial oxidative injury and thrombotic changes [33, 34]. Qin *et al.* demonstrated that elevated homocysteine impairs trophoblast invasion and spiral artery remodeling, directly linking biochemical disruption to placental failure. These mechanistic insights provide biological plausibility to the associations observed in my review and emphasize that the effect is likely causal rather than coincidental [35]. Our findings confirm that elevated homocysteine is strongly and consistently associated with recurrent pregnancy loss across diverse populations and methodological settings. The relationship is biologically plausible, reinforced by mechanistic data, and appears to operate independently of vitamin deficiency. Homocysteine therefore represents both a diagnostic biomarker and a potential therapeutic target. Future prospective and interventional studies are essential to determine causality and to assess whether homocysteine-lowering interventions can improve pregnancy outcomes. Clinically, early screening and nutritional optimization may help reduce the recurrence risk in women with a history of pregnancy loss.

This review is limited by the predominance of case–control studies and variability in assay methods, cut-offs, and population characteristics, which restricts causal inference. Future research should focus on prospective and randomized trials, integrating biochemical, genetic, and vascular assessments, to establish causality and evaluate whether homocysteine-lowering interventions can effectively reduce RPL risk and improve pregnancy outcomes.

CONCLUSIONS

This review demonstrated that elevated homocysteine is consistently associated with recurrent pregnancy loss across diverse populations, with risk estimates remaining significant after adjustment for vitamin status and genetic polymorphisms. Comparisons with recent studies confirm that this association is mediated by both nutritional deficiencies and vascular-endothelial mechanisms, while also being influenced by comorbid conditions such as PCOS and metabolic disease. Interventional evidence suggests that folate and B12 supplementation can reduce homocysteine levels and potentially improve pregnancy outcomes, although randomized controlled trials remain scarce. Future research should integrate biochemical, genetic, and vascular assessments to clarify causality and to inform targeted preventive strategies.

Authors' Contribution

Conceptualization: RK
Methodology: NF, AA[1], AA[2]
Formal analysis: AA[1]
Writing and Drafting: RK, AM, SBS, NF, AA[2]
Review and Editing: RK, AM, SBS, NF, AA[1], AA[2]

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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