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Chronic Respiratory Diseases: Innovations in Treatment and Management

OPEN ACCESS

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Chronic Respiratory Diseases (CRDs) include diseases of the airways and the lung and are among the major causes of morbidity and mortality worldwide. The major CRDs include asthma, chronic obstructive pulmonary disease (COPD), pulmonary sarcoidosis, pneumoconiosis and interstitial lung diseases (ILDs). The common symptoms of CRDs include wheezing, chest tightness, shortness of breath and cough [1]. These diseases affect millions of people across the globe and have significant impacts on patients' quality of life and healthcare.

Over the past few decades, however, improvement in the pharmacotherapy has provided a considerable progress. For example, biologics have given a new insight in the management of severe asthma by modulating certain inflammatory processes. Medications like omalizumab, dupilumab, and Mepolizumab are aimed at adjusting the immune response and significantly decrease the frequency of exacerbations and increase overall lung function.

In addition, innovations in the field of stem cell therapy and tissue engineering are targeted to repair or replace diseased lung tissue, thus, being aimed at treating the origin of the diseases rather than simply alleviating the symptoms. Furthermore, Nanoparticles can be orally given, intravenously injected or inhaled using nanoparticle aerosols. Nanoparticles can also be used in the molecular imaging of chronic lung diseases such as COPD.

Advanced inhalers, developed with sensors, can monitor the usage of medication and provide feedback in real-time to ensure compliance to prescriptions and other salient treatment plans. COPD pulmonary rehabilitation programs of exercise and education together with psychological support for individuals have been documented to enhance quality of life. The use of AI and a machine learning system has now moved to the ability to forecast disease exacerbations and provide individualized recommendations for treatment of CRDs.

As a result, people with COPD receive care through various healthcare professions like doctors, nurses, and physiotherapists, which may have diverse roles, such as prescribing medications, supporting their self-management or patient education, or delivering exercise training. The aim of an Integrated Disease Management (IDM) programme is that various aspects of care through which healthcare providers are working in coordination to deliver improved and optimum care to patients.

Similarly Advancements in the treatment of ILD are being conducted, and recently, some new FDA-approved drugs have been advised for the management of patients. Among these are Nintedanib is a tyrosine kinase inhibitor, Pirfenidone an anti-fibrotic and anti-thrombotic agent and Treprostinil is an analogue of prostacyclin. These drugs have opened a new path for the treatment of ILD and have improved the recovery outcomes of patients [2]. Rituximab has also been found to be effective in more than half of patients treated in a small prospective open-label trial of refractory pulmonary disease in sarcoidosis[3].

Overall, there is a renewed emphasis on CRD management as a burgeoning field. With the advancement in the research in the personalized, proactive and integrative strategy the efforts made will lay down new avenues of better health outcomes for millions of people suffering from the CRDs. The future of respiratory health is bright as it is a growing field that has no sign of discontinuing its steady development and pushing for the comforts and breakthroughs for many patients across the globe.

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Review Article

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Impact of Human Immunological Responses and Viral Genetic Diversity on Outbreak of Human Monkeypox Virus. A Comprehensive Literature Review Study

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ABSTRACT

Monkeypox was caused by Monkeypox Virus (MPXV) and can infect both humans and animals. An understanding of the interplay between host immunity and genetic diversity was necessary to understand the etiology and epidemiology of monkeypox disease. **Objective:** To clarify how genetic differences and host immune responses interact when a moneypox infection occurs. Furthermore, we also aim to provide insights into individual variability in illness outcomes and possible treatment targets by investigating how distinct genetic profiles affect immune system activation and efficacy. **Methods:** Recent research on monkeypox, concentrating on the immune response mechanisms of the host and genetic variables linked to virus vulnerability have thoroughly analyzed. For this purpose, the data were searched from various research engines such as google scholar, pubmed, medline etc., by using different key words i.e., monkeypox and host immunity, monkeypox and antibodies interactions, monkeypox outbreak, mnkeypox strains. **Conclusions:** The way a monkeypox infection progresses and turns out was greatly influenced by the interplay between host genetic differences and immunological responses. Public health initiatives and the creation of tailored treatment plans can both benefit from the identification of genetic markers linked to immunological response profiles and vulnerability.

INTRODUCTION

The causative agent of monkeypox is the Monkeypox Virus (MPXV), an orthopoxvirus being a part of the Poxviridae family of viruses [1]. The disease is referred to as "monkeypox" as MPXV was first discovered in 1958 in lab monkeys imported from Singapore [2]. It is more likely that rats and other tiny animals serve as the MPXV's natural hosts, nevertheless. Smallpox symptoms are similar to those of human monkeypox, but the former is less deadly [3]. In the 1970s, the MPXV virus was first found in humans in isolated cases throughout several African countries; however, during the next 20 years, the virus spread more broadly throughout Africa [4]. Two possible explanations of the present outbreak are the discontinuation of the smallpox vaccination program and waning immunity to

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smallpox in the general population [5]. Research has demonstrated that vaccination against smallpox confers immunity against monkeypox. During a nationwide smallpox vaccination effort that started 12 years before the commencement of data collecting, early research from Zaire in 1988 indicated that those who had gotten the immunization are around 85% less likely to experienced monkeypox than those who had not [6]. It was found in another study that those who had received the smallpox vaccination had decreased rates of long-term MPXV infection sequelae, severe problems and mortality. According to a recent study on 528 illnesses identified during this outbreak, only 9% of those ill had previously had a smallpox vaccination [7]. It's interesting to note that (MSM) have the highest number of infections associated with the recent outbreaks [8]. The virus that causes monkeypox is becoming more widespread in areas where it is not typically found. Monkeypox has unexpectedly and quickly spread too many different countries, which suggests that unreported transmission may have continued. The number of cases that are reported globally is steadily rising. At least twenty non-African nations, including the United Kingdom, Portugal, Spain, and Canada, had reported over 57662 probable or confirmed cases as of September [9]. Host Immunity to Monkeypox Virus: Innate and adaptive immune responses are both involved in host immunity to the monkeypox virus. The first line of defense is provided by the innate immune system, which does this by triggering inflammatory responses and using pattern recognition receptors to identify viral proteins. Controlling the early phases of infection depends on this first reaction. On the other hand, the adaptive immune system offers a more focused and durable defense [10]. It involves the production of antibodies by B cells that target the virus and T cells that are able to identify and eliminate infected cells. The creation of these particular antibodies and memory cells can be stimulated by vaccination, which results in more potent and long-lasting protection against monkeypox[11]. This is why vaccination is essential for improving adaptive immunity. The goal of continuous research into immune responses to monkeypox is to enhance comprehension and create more potent vaccinations and therapies[12]. Outbreak of Human Monkeypox Virus: The first confirmed case of the Human Monkeypox Virus (hMPXV) in the United Kingdom was reported on May 7, 2022, which heightened concerns about infectious diseases following the COVID-19 pandemic. On July 23, 2022, the World Health Organization (WHO) deemed the monkeypox epidemic a global public health emergency. Clade I denotes the Central African or Congo Basin clade, and clade II will henceforth be used to refer to the West African clade. The World Health Organization is thinking of changing the virus's name to prevent stigmatization. The risk of having recently contracted the monkeypox virus was higher in men (including those who are transgender [13]. The origin of the outbreak is unknown. What led to its spread? The current outbreak is becoming more severe, so we must pay close attention to the rate of person-to-person transmission. We'll be able to tell whether the virus has changed and whether the circulating strain will spread more easily or not. The monkeypox virus cannot be transmitted sexually, however, samples from the vagina or sperm may provide fresh insights on the virus's mechanisms of transmission. Appropriate viral strains, like the Ebola and monkeypox viruses, can proliferate due to alterations in forest settings. Genetic Diversity among Poxviruses: It remains an arduous scientific task to ascertain whether the genetic alterations in the monkeypox virus are the source of the most recent epidemics[14]. For example, compared to the MPXV strains prevalent before 2017, the strain circulating in the 2022 pandemic may have had more DNA insertions and deletions, which could have contributed to the present outbreak [15]. D209N, P722S, and M1741I are three nonsynonymous single nucleotide polymorphisms in surface glycoprotein B21R, a critical target for antibodies, which may increase the virus's transmissibility [16]. The Variola Virus (VARV) exclusively infects humans, in contrast to other growing zoonotic diseases caused by poxviruses that afflict a number of animal species, including cattle, rats, monkeys, and others. The most prevalent clinical symptom of the poxvirus is skin lesions [17]. Two key traits of poxviruses are their genetic diversity and host range [18]. The E3L-encoded protein inhibits both 2′-5′ oligo adenylate synthase and Protein Kinase R (PKR) [19, 20]. Monkeypox Virus (MPXV) strains exhibit genetic heterogeneity, with the majority of these strains falling into the West African and Congo Basin clades. The Congo Basin clade is typically linked to more severe sickness, indicating that these genetic changes impact the virus's pathogenicity. Differences in the genetic makeup of the virus influence its transmissibility, clinical consequences, and ability to elude the host immune response [21]. Since it aids in comprehending the behaviour of the virus and modifying interventions to address changing risks, monitoring these genetic variants is crucial for the development of effective vaccines and public health policies [22]. In a Chinese hamster ovary cell line, VACV replication was restricted after the poxvirus ANK protein was eliminated. CP77, also known as CHOhr, is a protein that has been proven to be a host range factor [23-28]. It is possible that other ANK proteins perform comparable roles, but further investigation is required to confirm this. The genes E3L, C7L, and m62r (part of the C7L family) contain the most diversity of poxvirus homologs. It is anticipated that poxviruses with distant relatives will have

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distinct genes necessary for their host range [29, 30]. Immunity Responses: Neutralizing Antibodies (NAbs) are the primary immunological mechanism via which cross-protection against VACV immunization is mediated [31]. Because of the large variation in strength sand the lack of understanding regarding the molecular pathways governing protection, the degree of efficacy is unknown. Following VACV inoculation via percutaneous injection, a wide range of serum antibody responses directed against different VACV antigenic determinants are triggered. The fact that the sera of immune persons show cross-neutralizing activity against MPXV, VARV, and VACV suggests that these individuals' sera contain different specificities of Abs [32-34]. Although, every orthopoxvirus exhibited a distinct pattern of recognition, it was found that they all shared neutralizing components through polyclonal antibody testing on rabbit immune serum [35]. A significant factor in disease prevention is the smallpox vaccine's induction of strong humoral reactions [36]. Methods to Detect Cross Reactive Antibodies: Antibodies that recognized various related antigens can be identified by using several critical methods for the detection of cross-reactive antibodies. A popular method for testing for antibodies against distinct but structurally similar antigens is the Enzyme-Linked Immunosorbent Assay (ELISA), which can be adjusted [37, 38]. A further technique is Western blotting, which uses size-based protein separation to identify cross-reactive antibodies by their unique binding patterns. Furthermore, assays for neutralization can evaluate an antibody's ability to suppress the activity of different viral strains. In order to create broad-spectrum vaccinations and comprehend immune responses to various infections, these methods are essential [39, 40]. Imunity Mediated Protection Against Monkeypox Infection: Research often use interactions between VACV and multiple orthopoxviruses to examine monkeypox immunity. Research [41-43] suggests that monocytes are the primary target of the poxviruses. The poxvirus antigen found in neutrophils and monocytes is thought to be one of the primary reasons of MPXV mortality [44]. The innate immune system of the body depends heavily on natural killer cells known as monocytes, which also have the power to modify the functioning of the adaptive immune response. The blood and lymph nodes of rhesus macaques infected with MPXV show a substantial increase in natural killer cell numbers [45, 46]. There exists a correlation between the intensity of infection and cytokine responses in animals infected with VARV. MPXV did not substantially activate genes controlled by NF-B and TNF even in infected mice. This makes sense because orthopoxviruses such as VARV contain genes that alter the TNF and NF-kB pathways [47, 48]. Innate Immune Response and Monkeypox Virus Invading: Despite long-standing knowledge of the virus, human immunity to MPXV infection remains unknown. Therefore, to determine the methods by which MPXV interacts with the host immune system, research employing orthopoxviruses identical to VACV are frequently used [49]. The ensuing sections address the potential defense mechanisms of the host against MPXV, in addition to the immunological evasion tactics the virus use during active infection. While certain viruses also target innate immune cells, these cells normally react to an active viral infection first. Poxviruses first target monocytes, according to a number of in vitro and in vivo investigations [50]. Susceptible monocytes are attached to the infection sites when cynomolgus macaques get MPXV infection, with the lungs revealing a large increase in CD14+ monocytes [51]. Additionally, it has been demonstrated that inflammatory murine monocytes that are CD45+CD11b+GR-1int allow VACV multiplication and may even carry the virus. Moreover, human primary M2-like macrophages are claimed to have enabled VACV proliferation and dispersion [52]. One study that revealed a correlation between low blood neutrophil counts and moribundity in animals infected with MPXV indirectly supported our results [53, 54]. Natural killer cells, like monocytes, are essential for innate immunity because they have the ability to steer the trajectory of the adaptive immune response [55]. IgM and IgG Responses: A vital part of the immune system's response to infections are the Immunoglobulin M (IgM) and Immunoglobulin G (IgG) responses and measuring these reactions is essential for understanding and diagnosing a wide range of illnesses [56-57]. When a new infection arises, IgM is usually the first antibody to be generated and is a sign of recent or acute exposure to a pathogen [58-59]. IL-15 can be triggered via type 1 IFN-independent mechanism by IL-15 complex treatment, and this treatment is enough to drive IFN-c expression and lymphocyte responses [60]. Natural killer cell depletion had no effect on virus titers in the early stages of acute LCMV infection or during persistent LCMV infection [61]. Aside from lateral flow testing in fast diagnostic settings, it can be found in the blood by assays like ELISA, which use particular antigens to capture IgM antibodies. IgG, on the other hand, supplies long-term immunity and signifies prior exposure to an infection that has been more thoroughly treated [62, 63]. It also manifests later and stays longer in the bloodstream. It is assessed with methods similar to those for measuring IgM, but frequently with a focus on determining the pathogen's chronicity or history of exposure[64-66]. Immunological status evaluation, treatment and vaccination techniques, and the identification of the infection phase all depend on both IgM and IgG responses [67-68]. In circumstances where the immune system is significantly impaired, the body's capacity to build a successful defence against

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opportunistic infections is hindered.A lower CD4+ T cell count puts a person at higher risk of developing a serious illness from MPXV. Because of this, they experience more severe symptoms of monkeypox, including widespread skin lesions, longer sickness, and higher morbidity [69]. B Cell and Antibodies Mediated Immunity: The earliest evidence of the significance of B cells and immunoglobulins against poxviruses came from the live VACV vaccine, which was employed in the successful worldwide immunization campaign to eradicate smallpox [70, 71]. Additionally, it was shown that Vaccinia Immune Globulin (VIG), which is made from vaccine serum, greatly reduced the risk of smallpox among close relatives of affected individuals96. Particular to VACV, B cell responses helped avoid a deadly MPXV infection in rhesus macaques. Moreover, epidemiological research has notably shown that the VACV vaccine provides defense against several poxviruses, such as MPXV [72]. Monoclonal antibodies (mAbs) have demonstrated great potential in the battle against the Monkeypox Virus (MPXV), providing focused therapeutic alternatives that improve the effectiveness of treatment [73, 74]. In order to neutralise the virus and stop it from infecting or multiplying in host cells, these antibodies are designed to attach only to MPXV proteins. Experimental and preclinical research has indicated that specific monoclonal antibodies can considerably lower viral loads and lessen the severity of the illness in those who are afflicted. Its excellent specificity, which reduces off-target effects and increases antiviral activity, is credited with its efficacy. For those who are at high risk or have been exposed, monoclonal antibodies can also quickly produce passive immunity and offer protection [75–78]. Yet, based on the particular mAbs utilised, when they are administered, and the virus strains that are in use, their efficacy may differ [60, 61]. Enhancing treatment regimens and increasing outcomes for people affected with monkeypox should be possible with the ongoing research on monoclonal antibody treatments against MPXV [79-81]. T Cell Mediated Immunity: HIV-1 infection that is not under control has a major negative effect on CD4+ T cell numbers and makes people far more susceptible to opportunistic infections, such as the Monkeypox Virus (MPXV) [82, 83]. Aided in the coordination of the immune response, HIV-1 targets and eliminates CD4+ T cells. These cells gradually diminish as the infection worsens, which reduces the immune system's capacity to combat infections.Considerably lower CD4+ T cell counts, which can occasionally fall below 200 cells/mm^3-a threshold suggestive of progressive immunosuppression and Acquired Immunodeficiency Syndrome (AIDS) are frequently observed in studies of HIV-1 positive people with poorly managed viral loads [83]. This is because their immune system is compromised and cannot effectively control the virus. It is important to manage HIV-1 efficiently to lower the risk of opportunistic infections, as demonstrated by the interaction between HIV-1-induced immunosuppression and MPXV infection. Compromised immune defences can aggravate the severity and consequences of viral diseases [84-87]. Monkeypox Strains, Their Virulence and Transmissibility: There are two subclades of the monkeypox virus: the Congo Basin and West African subclades. The severity of strains from the Congo Basin and West Africa varies with respect to human and monkey disease, with the former being more virulent in non-human primates. According to reports, smallpox and human monkeypox share many of the same clinical symptoms. The representative strains of the monkeypox virus from the Congo Basin, Zr-599, and West Africa, Liberia, are utilized [88-92]. According to the A-type inclusion body gene sequence, Zr-599, which was isolated from a patient in the Democratic Republic of the Congo, and Liberia, which was isolated from a patient who had human monkeypox in Liberia, are allocated to the Congo Basin and the West African clades, respectively. To produce the virus solution for the challenge experiments, Vero E6 cells infected with each strain of the monkeypox virus are disrupted in a sonicator (TITEC Ultra S Homogeniser UP-5) for 30 seconds at maximum power. This is followed by high-speed centrifugation (3500 r.p.m. for 5 minutes at 4°C). The plaque assay was used to calculate the virus's infectious dosage. As previously described, the whole suite of vaccinia virus proteins was used as an antigen in an ELISA assay to evaluate antibody levels specific to the virus [93-96]. Limited research data are available on Strain-Specific monkeypox vaccines, therefore, developing customized vaccines and treatments is hampered by the lack of information regarding the impact of various monkeypox vaccines clades on host immunity and vaccine efficacy. Inadequate data about genetic variation and insufficient data about how host genetic variables affect disease severity, and genetic variations in monkeypox vaccines may play a role in the pathogen's pathogenicity and immune evasion [97, 98]. Furthermore, inadequate infrastructure and resources are a problem in many monkeypox vaccines-affected areas, which affects the efficiency of outbreak response and management [99, 100]. Conduct Research Specific to Strains: To develop vaccines and treatments that are specifically targeted, investigate the immunological variations across MPXV clades and how they affect vaccination efficacy [101]. Examine Host Genetic variants: To gain a better understanding and control of the disease, investigate how host genetic variants impact exposure to and immune responses from MPXV. In order to better support epidemic response and prevention initiatives, strengthen public health infrastructure by investing in

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high-risk locations. Encourage Global Collaboration: To accomplish monkeypox vaccine research and guarantee successful disease control plans, exchange information and resources worldwide [102].

CONCLUSIONS

In summary, an examination of the monkeypox virus from the perspectives of genetic variation and host immunity reveals a complicated interaction that determines the severity of the disease and how long it takes to spread. The fate of monkeypox was largely determined by the immunological response, with individual heterogeneity affecting susceptibility and development. The wide range of clinical symptoms and difficulties in controlling outbreaks were attributed to genetic characteristics in both the virus and the host. As science progresses, combining knowledge from immunology and genetics will be essential for creating vaccines and tailored treatments that will eventually improve our capacity to contain and eradicate monkeypox. Further research into these areas will help us better understand monkeypox and develop response plans for new viral dangers in a world that was changing quickly.

Authors Contribution

Conceptualization: FH

Methodology: FH

Formal analysis: MUH

Writing, review and editing: IS, AQ, AH, SR

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

Conflicts of Interest

The authors declare no conflict of interest.

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Assessment of Pain and Functional Outcomes in Individuals with Patellofemoral Pain Syndrome

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ABSTRACT

Patellofemoral pain syndrome is a pathological condition of the patellofemoral joint characterized by knee pain in the peripatellar, anterior, and even retro patellar regions. Between 15% and 45% of persons in their 20s to 40s experience patellofemoral pain. **Objective:** To assess pain and functional outcomes in individuals with patellofemoral pain syndrome. **Methods:** At Mayo Hospital and the University of Lahore Teaching Hospital, 87 people enrolled in this cross-sectional study using a non-probability convenience sampling technique during the period of 20th January 2024 to 20th July 2024. Both male and female patients between ages of 20 to 40 years with a positive patellar grind test were included. The numeric pain rating scale and Kujala score were used for data collection to assess pain and functional outcomes respectively. Data were analyzed using IBM SPSS Statistics 25.0. All qualitative variables were shown as frequency and percentages; all quantitative data were provided as Mean ± S.D. **Results:** Mean age of participants was 30.68 ± 5.62 years. Out of 87 participants, there were 41 (47.1%) females and 46 (52.9%) males. The mean score of the Numeric Pain Rating Scale was 6.31 ± 1.56 and the Kujala score was 46.37 ± 10.36. Out of 87 participants, 6 (6.9%) had mild pain, 62 (71.3%) had moderate pain and 19 (21.8%) had severe pain. The NPRS and Kujala Score have a very weak correlation of 0.049 with a p-value of 0.655. **Conclusions:** It was concluded that this study had a significant impact of patellofemoral pain syndrome on pain and functional outcomes in affected individuals.

INTRODUCTION

Patellofemoral pain syndrome (PFPS) is a pathological condition of the patellofemoral joint characterized by knee flexion and extension-related pain in the peripatellar, anterior, and even retro-patellar regions (i.e., running, stair climbing, walking, and squatting [1]. Typical symptoms are joint crepitus during flexion motions and instability during loading activities [2]. PFPS, which affects 22.7% of the general population [3]. Between 15% and 45% of persons in their 20s to 40s experience patellofemoral discomfort; almost twice as many women as men experience this condition [4]. Some of the minor musculoskeletal disorders are untidy and affect many people; chronic knee pain or patella-femoral pain. As a 'silent' disease this can disable people in their homes, impair their daily activities, and lead to a very long shadow of gloom over their lives. Being musculoskeletal, it is common and causes pain in the

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knee's patellar (anteromedial) side. The patient may experience symptoms gradually, such as a steady increase in pain or sudden discomfort when squatting, sitting for extended periods, or climbing stairs [5]. The main dynamics are made up of numerous intertwined processes where the support for the development and maintenance of PFPS is based. The causes of this condition, which can be from biomechanically faulty movements to neuromuscular pathology, can be quite hidden, and as such require a team effort to manage. It also entails precisely assessing how effective the disease is and how much of an impact it has on a person's life as a whole. Some recent papers have tried to give a better understanding of this crucial question focused on the methodological strategies that allow evaluating the amount of pain and the limitations of functioning that result from it [6]. Complaints in individuals involve pain in or around the anterior knee region that is aggravated by weight-bearing exercise. Some patients have said that staying for long periods with the knee flexed can worsen pain or joint stiffness. Patients should state if they have a history of knee surgeries or injuries, how physical they are at present and if this has changed in any way [7]. Knee overuse syndrome is commonly associated with PFPS. Knee buckling is usually caused by quadriceps weakness or pain, which results in a transient reduction of muscle tone as opposed to intrinsic laxity of the knee joint [8]. The degree of pain variation across PFPS patients, if pain varies throughout distinct functional tasks, and whether asymptomatic controls exist during those tasks are yet unknown. Researchers discovered significant differences in pain levels during daily activities when comparing people with PFPS to those who are asymptomatic. Tasks as seemingly basic as crouching, climbing stairs, or prolonged sitting can cause intense pain for persons with PFPS, significantly limiting their ability to perform daily tasks [9]. All people who have knee pain should get a physical exam. It is not common for PFPS to have large joint effusions, erythema, or elevated temperature. It may indicate infection, severe trauma, or inflammatory arthritis. A meta-analysis revealed that the physical examination finding that was most sensitive for PFPS was pain when squatting, and the highest positive likelihood ratio was seen in a positive patellar tilt test. The study also looked at the effectiveness of routinely used physical examination tests in diagnosing PFPS. Female gender is a risk factor, as are activities like sprinting, crouching, and stair climbing. The study found that decreasing quadriceps strength increases the incidence of PFPS, possibly due to patellar instability. One of the many possible causes of patellar instability is a sprained knee. Another PFPS-related process is dynamic valgus. Dynamic valgus occurs when there is significant valgus or internal-external rotation causing the knee to collapse medially. As a result, the patella experiences more lateral stress, which contributes to poor tracking. Female athletes are more likely to have dynamic valgus, which could explain their increased prevalence of PFPS [10]. The femur's trochlea and patella are joined by the patellofemoral joint and play a crucial role in Patellofemoral pain syndrome. Anterior knee discomfort in outpatient settings is frequently caused by patellofemoral pain syndrome (PFPS) in youngsters and adults under the age of 60 [11]. The incidence in the United Kingdom is between 3% and 6%. Anterior knee pain or surrounding it is a hallmark of PFPS, which worsens with weight-bearing activity. PFPS pain can intensify with prolonged seated or stair-climbing. Pain felt when squatting is the most significant physical test finding. PFPS may be related to patellar mal-tracking. Patellar mal-tracking, or sideways translation, is more common in PFPS patients when they are in load-bearing postures like squatting [12]. Although PFPS is a clinical diagnosis, imaging can assist in excluding other possible causes of knee discomfort. If pain doesn't go away after 4 to 8 weeks of conservative therapy, imaging might be necessary. Osteoarthritis can be ruled out with simple radiography of the knee in persons over the age of 50, patellar fractures in trauma patients, and osteochondritis whether it appears from the physical assessment or the history. It can be quite helpful to have anterior-posterior, sideways, and sunrise/merchant views. Magnetic resonance imaging results of lesions in the bone marrow, excessive fat pad signal, and small abnormalities in the patellar cartilage do not suggest PFPS. Therefore, imaging is recommended for PFPS [13]. Healthcare practitioners now have a better understanding of the complexities of PFPS, allowing them to guide patients towards long-term rehabilitation. A multimodal approach that includes multiple interventions has been recognized as the most effective method for managing this condition and improving quality of life [14]. A comprehensive care strategy that includes concentrated physical therapy and exercises, as well as biomechanical anomalies and training regimen adjustments, can help persons with PFPS increase mobility, reduce pain, and restore independence. As musculoskeletal research develops, so will our understanding of PFPS, paving the way for more tailored and effective treatments. This is why patellofemoral pain syndrome, is an illness that decreases quality of life because of low functional capacity and pain that arises in the knee joint in young athletes. Therefore, it is crucial to quantify the extent of pain and limitation of function in a subject with PFPS to enable the design of adequate treatment and regimens. Those offering health care are likely to be in a position to deliver the rehabilitation programs that would address the various risks, and promote regaining strength and, in general well-being, through critiquing of such performances. In addition, this evaluation can also increase the existing body of knowledge regarding the effectiveness of different treatment approaches in the case of PFPS that will in the long run improve the compassion for PFPS patients.

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This study aimed to evaluate pain and functional status in participants with patellofemoral pain syndrome.

METHODS

A cross-sectional survey was done among participants attending Mayo Hospital Lahore, and the University of Lahore Teaching Hospital for the period of 20th January 2024 to 20th July 2024. Permission from the ethics committee of the University of Lahore Teaching Hospital was obtained before the start of this study (REC Number: 388/24) and (Reference Number: REC-UOL-/388/08/24). Before beginning the data collection process, informed consent was obtained. Religious and cultural factors were appropriately considered while gathering data. The total sample size calculated through the open epi tool was 87 using the formula n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)]. The % frequency of outcome factor in the population was 6% taken from a previous study [15]. Both male and female patients between the ages 20 to 40 years with a positive patellar grind test and anterior knee discomfort that has persisted for two to three months and is worsened by walking, climbing stairs, or spending extended amounts of time sitting were included in this study [16]. The participants with recently sustained trauma or fracture, acute illness, knee replacement, a tumour or infection surrounding the knee, rheumatoid arthritis, pregnancy, joint excessive mobility, any deformity, and disease of the patellar tendon were excluded. For the assessment of pain, a numeric pain rating scale was used. Extreme values on the Numeric Pain Rating Scale (NPRS) range from "no pain" to "severe pain," on a horizontal or vertical line of scale. The NPRS can be self-reported or given by a physician. The NPRS is a pain scale that ranges from zero (no pain) to ten (worst suffering). This scale has high reliability (0.84-0.92) and high validity (0.83=0.94). For the assessment of functional outcomes, the kujala score was used. Kujala score has high reliability (0.83-0.98) and validity (0.90-0.92). It has thirteen items that assess several elements of knee function, such as quadriceps strength, oedema, instability, and pain during exercises. Higher scores indicate improved knee function. Each item is scored, and the overall score runs from 0 to 100. Based on the total score, functional outcomes are classified as poor (0-49), fair (50-69), good (70-89), or outstanding (90-100), offering a thorough evaluation of how knee pain impacts everyday activities and overall knee health [17]. Data were analyzed by IBM SPSS Statistics 25.0. Whereas all qualitative factors were shown as frequency and percentages, all quantitative data were provided as Mean ± S.D. The correlation was measured by Pearson's correlation coefficient.

RESULTS

The mean score of numeric pain rating scale was 6.31 ± 1.56 and the mean kujala score was 46.37 ± 10.36. Descriptive statistics of pain and functional outcomes of participants are given in table 1.

Table 1: Descriptive Statistics of Pain and Functional Outcomes of Participants

Variables	Mean ± S.D
NPRS	6.31 ± 1.56
Kujala	46.37 ± 10.36

It showed that the mean age of participants was 30.68 ± 5.62 years. Out of 87 participants, 46 (52.9%) were male and 41 (47.1%) were female. The demographic profile of participants is given in table 2.

Table 2: Demographics of Participants

Variables		Mean ± S.D
Age (In Years)		30.68 ± 5.62
Gender n (%)	Male	46 (52.9%)
	Female	41 (47.1%)

Out of 87 participants, 6 (6.9%) had mild pain, 62 (71.3%) had moderate pain and 19 (21.8%) had severe pain. The pain categories of participants are shown in table 3.

Table 3: Pain Categories of Participants according to numeric pain rating scale

Variables	Mean ± S.D
Mild Pain	6 (6.9%)
Moderate Pain	62 (71.3%)
Severe Pain	19 (21.8%)
Total	87 (100.0%)

The NPRS and Kujala Score have a very weak, non-significant linear association, according to the Pearson correlation of 0.049 with a p-value of 0.655. The correlation of the NPRS and the Kujala Score is shown in table 4.

Table 4: Correlation of NPRS and Kujala Score

Correlations		Pain	Kujala Score Total
Pain	Pearson Correlation	1	0.049
	Sig. (2-tailed)	-	0.655
	N	87	87

DISCUSSION

Understanding the effects of patellofemoral pain syndrome (PFPS) and creating successful treatment plans need measuring the pain and functional outcomes in affected individuals. The present research comprised 87 participants with an average age of 30 years old. It also gives useful information on the degree of pain and the level of functional disability observed in PFPS. In the patients of the current study, the mean NPRS was 6. 31 ± 1. 56, which, according to the specified scale, can be considered as a moderate-severe amount of pain. This agrees with research that was conducted by Shabnam *et al.*, in which participants had NPRS scores of about 6. 5 patients of similar age to the patients in this study to confirm that pain

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levels represented in our sample are mean amongst PFPS patient population. Furthermore, our pain severity classification revealed that 6.9% of participants experienced light pain, 71.3% reported moderate pain, and 21.8% reported severe pain. These distributions indicate the significant pain burden that PFPS is associated with. The lower mean NPRS score of 5.2 reported by Greaves *et al.*, could have been due to variations in the sample characteristics, such as the inclusion of fewer severe cases or discrepancies in the length of symptoms. This gap highlights the potential influence of PFPS chronicity and patient selection factors on self-reported pain levels [18]. Patients in our study had an average Kujala score of 46.37 ± 10.36, suggesting significant functional impairment. Yanez *et al.*, discovered a mean Kujala score of around 48, which is consistent with our findings and suggests that our patients' functional limits were comparable. Our findings show that PFPS has a considerable impact on daily activities and overall knee function, as measured by the Kujala score, a comprehensive measure of knee function [19]. However, Prieto *et al.*, study found that Kujala scores were higher, averaging around 52. The higher functional outcomes found in this study could be attributed to a longer rehabilitation program, the use of patients with fewer severe symptoms, or variations in intervention strategies. These discrepancies illustrate the need to take into account each study's technique and environment when comparing functional outcomes [20]. In our study, the gender distribution was 47.1% female and 52.9% male. This is in contrast to other studies by Sanchis *et al.*, which discovered a higher prevalence of PFPS in females [21]. The nearly equal representation of our sample guarantees a gender-neutral assessment of functional results and discomfort. However, it's crucial to keep in mind that variations in gender about biomechanical elements, activity levels, and pain perception could affect how severe and persistent the PFPS is. The majority of our study subjects reported substantial discomfort, which is consistent with earlier research highlighting the chronic and debilitating nature of Patellofemoral pain syndrome. For example, our findings are comparable with those of Jayaseelan *et al.*, who discovered that a large proportion of PFPS patients experienced moderate to severe discomfort [22]. The large number of study participants who experienced moderate pain highlights the significant impact of PFPS on quality of life and the necessity for adequate pain management strategies. The NPRS and Kujala Score have a very weak, non-significant linear association, according to the Pearson correlation of 0.049 with a p-value of 0.655. This implies that there is no significant correlation between these two measures and that changes in pain intensity (as determined by NPRS) are not linked to modifications in functional outcomes (as determined by Kujala Score). The lack of correlation supports the theory that the Kujala Score and NPRS measure different aspects of knee health, with the latter measuring functional outcomes and the former focusing on pain severity. This may suggest that patients' stated pain levels on the NPRS are not indicative of or a predictor of their functional limits as determined by the Kujala Score.

CONCLUSIONS

It was concluded that this study had a significant impact of patellofemoral pain syndrome on pain levels and functional outcomes in affected individuals. The findings reveal moderate to severe pain and considerable functional impairment, emphasizing the chronic and debilitating nature of PFPS.

Authors Contribution

Conceptualization: AH,
Methodology: AH, WA, YM, AM, HMW
Formal analysis: AH, MKN, AZ
Writing review and editing: MA, AZ

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

Conflicts of Interest

The authors declare no conflict of interest.

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Comparing Absolute Eosinophil and Monocyte Counts in Critical and Non-Critical COVID-19 Patients

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ABSTRACT

Emerging evidence suggests that variations in immune cell counts, particularly absolute eosinophil and monocyte counts may be important in predicting the clinical course and severity of the disease in COVID-19 patients. **Objective:** To compare the absolute eosinophil and monocyte counts 'between critical and non-critical COVID-19 patients to elucidate potential associations with disease severity and prognosis. **Methods:** Between March 19th and June 6th, 2021, peripheral blood samples were taken from 26 'critical COVID-19 patients and 26 non-critical COVID-19 patients. Standard laboratory procedures were used to determine the immunological and haematological parameters for every participant. Whole blood samples were taken in ethylenediaminetetraacetic acid (EDTA) tubes and processed per the manufacturer's instructions using an automated haematology analyser (XN-1000, Sysmex, Japan). **Results:** Critical patients of COVID-19 exhibited significantly reduced absolute eosinophil, absolute monocyte, and lymphocyte count compared to non-critical patients. Additionally, critical patients were significantly older. However, there is no significant differences in the two groups' basophil counts, neutrophil counts, WBC counts, RBC counts, HCT percentage, HGB levels, MCH levels, MCV, MCHC levels, and MPV or platelet counts. **Conclusions:** Critical patients exhibited significantly reduced absolute eosinophil and monocyte counts suggesting a potentially weaker immune response in these subgroups. The significance of immune cell counts in assessing the severity of COVID-19 is highlighted by these results which may aid in developing targeted therapeutic interventions and prognostic indicators. Validating these results and clarifying their therapeutic significance will require more investigation.

INTRODUCTION

The COVID-19 pandemic, which has been attributed to the new coronavirus SARS-CoV-2, has posed challenges to healthcare systems worldwide [1]. Mild to severe dyspnoea and multi-system organ failure are the clinical manifestation of this viral respiratory illness [2]. those patients who were medically compromised or had advanced age were more prone to develop critical illness i.e. 'acute respiratory distress syndrome' (ARDS), cytokine storm, and 'systemic inflammatory response syndrome' (SIRS) which often necessitated 'intensive care unit (ICU) admission and mechanical ventilation' [3]. The severity and outcome of COVID-19 are determined in part by immunologic and hematologic variables [4]. These factors include numerous immune cells and inflammatory cells reflecting the immunity of host to viral infection following the inflammatory cascade [5, 6]. The 'absolute eosinophil count, absolute monocyte count, and absolute lymphocyte count' are important cells due to their significant role in modifying immunological responses and fighting viral infections [7]. Many investigations highlighted the importance of these factors in evaluating 'severity and prognosis of COVID-19' [8, 9]. Research conducted by Yang *et al.*, showed significantly lower absolute lymphocyte counts in 'critical COVID-19 patients as compared to non-

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critical patients' which suggested lymphopenia as an important prognostic indicator [1, 10]. Similarly, a study conducted by Qin C *et al.*, observed lower absolute monocyte counts in critical COVID-19 patients, indicating a possible link between monocyte impairment and severity of disease [10]. However, there are lack of studies on comparing the immunologic and hematologic factors of 'critical and non-critical COVID-19 patients' [11, 12]. By understanding the immunologic and hematologic factors linked with COVID-19 severity is important for revealing the primary mechanisms underlying severe COVID-19 and for recognizing therapies prognosis of disease.

This study aimed to distinguish the immunologic and hematologic factors between critical and non-critical COVID-19 patients by evaluating 'absolute eosinophil count', 'absolute monocyte count', and 'absolute lymphocyte count', along with other relevant factors.

METHODS

The study was conducted at two prominent hospitals in Peshawar, Rehman Medical Institute and Hayatabad Medical Complex between March 19th and June 6th, 2021. It was a prospective, cross-sectional observational study. The study enrolled a total of 52 participants, comprising 26 'critical patients and 26 non-critical patients', all diagnosed with COVID-19. The sample size was calculated by using mean ± SD of CD4/CD8. OpenEpi, Version 3, was used with 95% of Confidence Interval and Power of 80%, using values 2.24 ± 0.93 for non-critically ill and 3.38 ± 1.83 for critically ill people from Pallotto *et al* [12, 13]. The participants were carefully matched for age and gender distribution. Patients who were not very sick got outpatient care at the pulmonology clinic, whereas critical patients were admitted to isolation rooms or the intensive care unit. Exclusion criteria for participation in the study included individuals with pre-existing chronic conditions requiringe immunosuppressive therapy, active viral, autoimmune, or oncological diseases, and those who had received steroid treatment prior to blood sample collection. Upon obtaining informed written consent, demographic and clinical information was systematically recorded using a specifically designed questionnaire. Three milliliters of vein blood were drawn from every individual. and subjected to analysis for immunological and hematological parameters using a fully automated hematology analyzer (XN-1000, Sysmex, Japan). The analysis adhered to established guidelines for laboratory testing of suspected COVID-19 cases. The approval of this study was taken from the Institutional Research Ethical Board of IBMS KMU Peshawar with the reference no. KMU/IBMS/IRBE/10th Meeting/2024/1753-H. The statistical software SPSS Version 23.0 was utilized for data analysis, and descriptive statistics were employed to obtain the mean and standard deviation of numerical variables. The threshold for statistical significance was fixed at $p < 0.05$. The study findings were meticulously presented through tables, charts and graphs.

RESULTS

Critical patients were significantly older compared to non-critical patients (57.85 ± 11.66 versus 44.15 ± 14.74, p = 0.001). Critical patients had significantly reduced absolute monocyte counts compared to non- critical patients (0.36 ± 0.23 vs 0.63 ± 0.31, p = 0.01). Absolute basophil numbers did not significantly differ between critical and non-critical COVID-19 patients (p = 0.65; 0.02 ± 0.01 versus 0.01 ± 0.01). Absolute lymphocyte counts were substantially higher in non-critical patients (1.85 ± 0.97 versus 1.12 ± 0.74, p = 0.004) than in critical patients. Absolute neutrophil counts did not significantly differ between patients classified as critical and non-critical (6.24 ± 4.11 versus 8.17 ± 4.46, p = 0.112). Absolute white blood cell (WBC) counts did not significantly differ between patients classified as critical and non-critical (8.54 ± 3.83 versus 9.72 ± 4.57, p = 0.315). Between critical and non-critical patients, there was no statistically significant difference in absolute red blood cell (RBC) counts (4.90 ± 0.86 versus 4.99 ± 0.66, p = 0.681). Hematocrit (HCT) levels did not significantly differ between patients classified as critical and non-critical (42.27 ± 8.68 versus 44.09 ± 8.03, p = 0.436). Haemoglobin (HGB) levels did not significantly differ between patients classified as critical and non-critical (13.10 ± 2.12 versus 13.32 ± 1.83, p = 0.686). Between critical and non-critical patients, there were no appreciable variations in 'mean corpuscular haemoglobin' (MCH), 'mean corpuscular haemoglobin concentration' (MCHC), 'mean corpuscular volume' (MCV), or 'mean platelet volume' (MPV) ($p > 0.05$). Between patients classified as critical and non-critical, there was no statistically significant difference in platelet counts (268.73 ± 88.83 versus 243.15 ± 100.79, p = 0.336) (Table 1).

Table 1: Comparison of Immunological and Hematological Parameters between Critical and Non-Critical COVID Patients

Variables	Non-Critical Patients Mean ± SD	Critical Patients Mean ± SD	p-Value
Age (Years)	44.15 ± 14.74	57.85 ± 11.66	0.001
Absolute Basophil Count	0.02 ± 0.01	0.01 ± 0.01	0.65
Absolute Eosinophil Count	0.99 ± 0.13	0.09 ± 0.02	0.01
Absolute Lymphocyte Count	1.85 ± 0.97	1.12 ± 0.74	0.004
Absolute Monocytes Count	0.63 ± 0.31	0.36 ± 0.23	0.01
Absolute Neutrophil Count	6.24 ± 4.11	8.17 ± 4.46	0.112
Absolute WBC Count	8.54 ± 3.83	9.72 ± 4.57	0.315
Absolute RBC Count	4.90 ± 0.86	4.99 ± 0.66	0.681
HCT%	42.27 ± 8.68	44.09 ± 8.03	0.436
HGB (g/dL)	13.10 ± 2.12	13.32 ± 1.83	0.686
MCH (pg)	26.96 ± 3.33	26.97 ± 2.543	0.996
MCHC (g/dL)	31.55 ± 5.08	0.15 ± 3.07	0.233
MCV (fL)	86.07 ± 8.16	89.70 ± 7.79	0.107
MPV (fL)	11.87 ± 1.06	11.72 ± 0.87	0.579
Platelets Count	268.73 ± 88.83	243.15 ± 100.79	0.336

Note: P values ≤ 0.05 are considered significant

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Figure 1 shows the comparison of absolute monocyte and eosinophil counts between critical and non-critical COVID-19 patients. Critical patients exhibited significantly lower counts of both monocytes and eosinophils compared to non-critical patients. The data highlights the potential association between reduced immune cell counts and disease severity. Critical patients had significantly reduced absolute eosinophil counts compared to non-critical patients (0.09 ± 0.02 vs 0.99 ± 0.13 p = 0.01)(Figure 1).

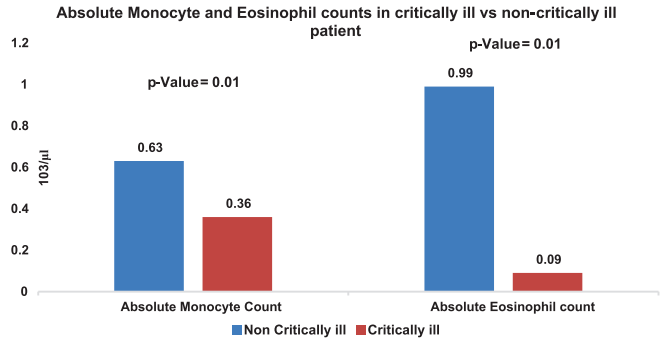

Figure 1: The Absolute Counts of Monocytes and Eosinophils in Critical Versus Non-Critical Patients

DISCUSSION

In the present investigation we found that critical patients were significantly older compared to non-critical patients (57.85 ± 11.66 versus 44.15 ± 14.74, p = 0.001). 'A retrospective study carried out by Tian R *et al.*, in 2020 from China also found that elderly patients were more serious when comparing to young patients [13]. A multicenter study conducted by another author from Egypt also found that older age critical patients were more effected [14]. In our study critical patients had significantly reduced absolute monocyte counts compared to non- critical patients (0.36 ± 0.23 vs 0.63 ± 0.31, p = 0.01). A study by Chinese researchers Zhang D *et al.*, in 2020 also discovered a decreased monocyte count in seriously ill COVID-19 patients [14]. In line with our findings, Shuang Qin *et al.*, in 2020 study discovered lower monocyte numbers in critically sick COVID-19 patients [15]. Our results revealed that the eosinophils count and critical and non-critical COVID 19 patients were significantly associated. A study conducted by Liu *et al.*, found the association between reduced eosinophils count and the severity of disease in COVID-19 patients. It was found that critical patients had more reduced eosinophil count than non-critical patients [16]. An investigation carried by researcher examined the immunologic features of reduced eosinophils in patients infected with COVID-19. They found that eosinophil reduction was associated with impaired T-cell responses and increased production of inflammatory cytokines which led to the formation of severe respiratory complications and systemic inflammation [17]. Additionally, eosinophil count in COVID-19 was evaluated in a systematic review conducted by Senthilnayagam B *et al.*, for its diagnostic and prognostic efficacy. This study showed the clinical importance of reduced eosinophils as a possible indicator of illness severity and mortality [18, 19]. Our investigation shows that Absolute lymphocyte counts were substantially higher in non-critical patients (1.85 ± 0.97 versus 1.12 ± 0.74, p = 0.004) than in critical patients. This study's findings contradicted to those of Javadi A *et al.*, in 2021, who discovered that severely ill patients had higher lymphocyte counts. In our study findings absolute neutrophil counts, absolute 'white blood cell' counts, 'red blood cell' counts, 'Hematocrit' levels Hemoglobin 'mean corpuscular hemoglobin', 'mean corpuscular hemoglobin concentration', 'mean corpuscular volume', or 'mean platelet volume' did not significantly differ between patients classified as critical and non-critical. Our results are consistent with the study carried out in 2021 by Javadi A *et al* [20].

CONCLUSIONS

In conclusion, the present investigation showed the association of immunologic and hematologic factors in COVID-19 by relating 'critical and non-critical patients. The analysis of absolute eosinophil count, absolute monocyte counts along with other relevant markers led us to their association with disease severity and clinical outcomes. By illuminating these associations, our results help in diagnosis, informing treatment plan and the developing targeted therapies to improve patient outcomes against COVID-19.

Authors Contribution

Conceptualization: YI,
Methodology: MOM, AM, YI
Formal analysis: YMY
Writing, review and editing: MQ, IK, YI

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

Conflicts of Interest

The authors declare no conflict of interest.

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Demographic and Clinical Features of Allergic Rhinitis Presenting at a Postgraduate Teaching Hospital

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ABSTRACT

Allergic rhinitis is a common disorder that affects millions worldwide and it represents a global concern. **Objective:** To determine the frequency of clinical variables, and demographic pattern of the allergic rhinitis patients in the otorhinolaryngology outpatient department in a Teaching Hospital. **Methods:** This cross-sectional study was conducted at the Department of Ear, Nose, and Throat of Kulsumbai Valik Site Postgraduate Teaching Hospital Karachi from 1st July 2022 to 31st December 2023. The study comprised allergic rhinitis patients. A total of 750 patients were included in this study after diagnosing allergic Rhinitis mentioned on their prescription. Data were collected properly on a predesigned questionnaire. Variables included age, gender, socioeconomic status, residence, sneezing, itching in the eye and nose, rhinorrhea, nasal discharge, bluish pale nasal mucosa (Nasal Congestion), edematous turbinate, and headache. Data were entered in SPSS software version 23.0 and analyzed. **Results:** The mean age of patients were 39 ± 13 years. Male were reported 447 (59.6%) and female patients were 303 (40.4%). 390 (52%) patients have resided in Industrial areas while 360 (48%) patients were in city areas. The most common symptom was nasal itching 522 (69.6%) followed by rhinorrhea 492 (65%) and nasal discharge 465(62%). **Conclusions:** It was concluded that allergic rhinitis patients presenting at the ENT outpatient department showed that males were commonly affected with the productive age group 59% of males suffered from Allergic Rhinitis. The most frequent and common symptom was nasal itching (69.6%) followed by rhinorrhea (65%) and nasal discharge(62%).

INTRODUCTION

Allergic Rhinitis (AR), sometimes referred to as Hay fever, is an inflammatory nasal illness caused by an allergic reaction to airborne allergens [1]. Allergic rhinitis (AR) is defined as an Ig E-mediated inflammatory reaction of the lining epithelium of the nose due to allergens [2]. The symptoms of this ailment include runny nose, itching, nasal congestion, and sneezing. People of all ages are affected by allergic rhinitis, which is one of the most common chronic respiratory illnesses in the world. Allergens that trigger an immune response are the primary cause of allergic rhinitis. Among the allergens that are commonly encountered include grass, weed, and tree pollen, dust mites, mold spores, and pet dander. Allergic rhinitis (AR) is a very common disorder that affects 400 million patients in the world. As its prevalence has increased but still it is usually undiagnosed. Severe allergic rhinitis rate is high in Africa and Latin America [3]. The rate of incidence of allergic rhinitis (AR) in children above 5 years was reported up to 17.2%. The peak age is between 24-29 months for the diagnosis (2.5%) [4]. The symptoms of allergic rhinitis can vary in intensity and include a runny nose, watery eyes, runny nose, itching of the nose, throat, or eyes. These

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symptoms may make it difficult to go about everyday activities and have a major negative influence on quality of life [5]. There are two types of allergic rhinitis: seasonal and permanent. Seasonal allergic rhinitis usually happens at certain seasons of the year when certain allergens, such as pollen, are more common. Conversely, mold, dust mites, and pet dander are common indoor allergens that cause perennial allergic rhinitis, which lasts all year. Non-pharmacological and pharmaceutical techniques are also possible to reduce symptoms of allergic rhinitis. One non-pharmacological strategy is to avoid allergens by utilizing air purifiers or staying indoors during seasons with high pollen counts. In severe instances, pharmacological alternatives include immunotherapy, nasal corticosteroids, decongestants, and antihistamines [6, 7]. Intranasal corticosteroid nasal spray is the first-line treatment for controlling the symptoms of allergic rhinitis [8]. Allergic rhinitis is a common disorder and affects up to 40%. In the past people considered Allergic rhinitis to be a localized disease of the nasal mucosa and nasal passages but now it is a component of airway disease and involved in the entire respiratory mucous membrane [9]. Allergic rhinitis imposes a heavy burden on the general population and produces a significant financial impact [10]. Surgery is typically regarded as a treatment option for allergic rhinitis when more conservative approaches and medicines are unable to relieve symptoms or when structural problems with the nasal passages are a contributing factor to symptoms. It's crucial to remember that surgical procedures are usually saved for particular circumstances and are not the primary line of therapy for allergic rhinitis. The following surgical procedures can be used to treat allergic rhinitis: including, Septoplasty, Turbinate Reduction, Sinus Surgery (ESS), Nasal Polypectomy and Laser Surgery [11]. It's crucial to note that surgery is not a cure for allergic rhinitis, and it may not eliminate the underlying allergic response. Allergic rhinitis is a chronic condition, and surgical interventions are typically reserved for specific cases where structural abnormalities or complications contribute to symptoms. While it might be difficult to completely avoid allergic rhinitis, there are steps you can take to lessen your exposure to allergens and manage your symptoms. These include utilizing air purifiers, keeping one's home tidy, and adhering to treatment regimens as directed [9, 10]. Probiotics are used nowadays for the treatment of allergic rhinitis and this may be beneficial, particularly for Bifidobacterium spp [12].

The study aimed to determine the clinical picture, demographic pattern and complications of allergic rhinitis in patients attending the otorhinolaryngology (ORL) outpatient department in a postgraduate teaching hospital.

METHODS

This was a cross-sectional study, conducted in the outpatient of the Department of Ear, Nose, and Throat (ENT) of Kulsumbai Valika Postgraduate Teaching Hospital Karachi from 1st July 2022 to 31st December 2023, after obtaining ethical approval from IRB (reference No. IRB/81/2022) and written consent was also taken from all participants for this study. The study subjects comprised patients with allergic rhinitis diagnosed by the consultant ENT specialist. All patients were advised for serum Ig-E for confirmation of diagnoses. Those patients who had raised serum Ig-E levels along with sneezing, rhinorrhea, and itching in eyes and nose were labelled as patients of "Allergic Rhinitis". A convenient sampling technique was used. The sample size was calculated by taking an expected proportion of allergic rhinitis as 48% [16], with 1% absolute precision and 95% Confidence Interval. After calculation sample size came 739 which was further enhanced to 750 for better precision and accuracy. A total of 750 patients of both genders were included randomly in the study with age ranges from 13 to 70 years who were identified with "Allergic rhinitis" and willing to participate in the study. Patients having Allergic fungal rhino sinusitis, Atrophic rhinitis, Vasomotor rhinitis, a history of nasal trauma, and a history of previous nasal surgeries were excluded from this study. Data were collected on a predesigned questionnaire. Demographic variables included age, gender, socioeconomic status, residence (Industrial area/City area), sneezing, itching in the eye and itching in the nose, rhinorrhea, nasal discharge, bluish pale nasal mucosa(nasal congestion), edematous turbinate and headache. Data were entered and analyzed by using SPSS software version 23.0. Quantitative variables like age were presented as mean and standard deviation. Categorical data were presented as percentages such as gender, socioeconomic status, and clinical features of allergic rhinitis.

RESULTS

This study included 750 study subjects having Allergic Rhinitis. The mean age of the study subjects was 39 ± 13 years, and the most common age group was 16 to 30 years. The most common symptom was nasal itching 522 (69.6%), followed by rhinorrhea 492 (65%) and nasal discharge 465 (62%). 303 (40.4%) patients were female and 447 (59.6%) were male i.e. male patients were more predominant (Figure 1).

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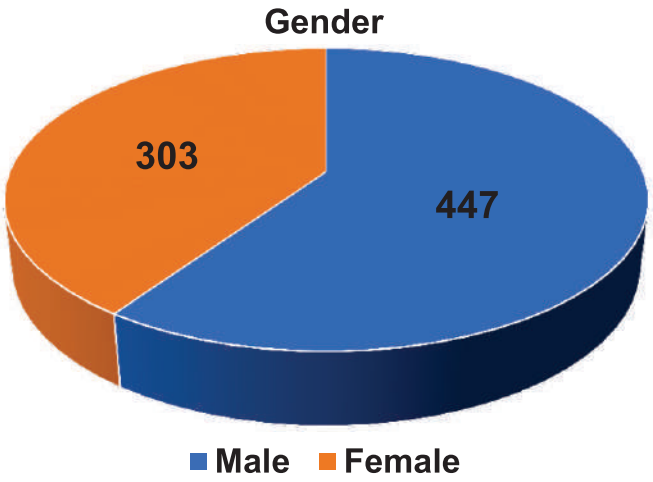

Figure 1: Gender Distribution in 750 Patients

The most common age group was 16-30 years and 220 (29.33%) patients were involved. In the study, 390 (52%) patients resided in the Industrial area, and 360 (48%) resided in the city area. Regarding socioeconomic status 650 (86.67%) were poor (Table 1).

Table 1: Demographic Characteristics of the Study Population

Variable	Frequency (%)
Age Groups	
Less than 16	111 (14.8%)
Between 16-30 Years	220 (29.33%)
Between 31-45 Years	110 (14.67%)
Between 46-60 Years	279 (37.2%)
Above 60 Years	30 (4%)
Residence	
Industrial Area	390 (52%)
City Area	360 (48%)
Socio Economic Status	
Poor	650 (86.67%)
Middle Class	100 (13.3%)

In the study, the clinical features of Allergic Rhinitis were analyzed. The total number of patients was 750. In nasal itching, 522 (69.6%) patients were recorded. For rhinorrhea, 492 (65.6%) patients were analyzed (Table 2).

Table 2: Clinical Features of Allergic Rhinitis (N=750)

Clinical Features	Frequency (%)
Nasal Itching	522 (69.6%)
Rhinorrhea	492 (65.6%)
Nasal Discharge	465 (62%)
Sneezing	387 (51.6%)
Bluish Pale Nasal Mucosa (Nasal Congestion)	294 (39.2%)
Headache	87 (11.6%)
Edematous Nasal Turbinate	72 (9.6%)
Eye Itching	66 (8.8%)

DISCUSSION

Allergic rhinitis is a response of the immune system to an allergen. Sneezing, itching and rhinorrhea are examples of allergic symptoms due to the release of these chemical substances. Subsequently, immune i.e. neutrophils, eosinophils and basophils penetrate the nasal mucosa, and their released chemical mediators trigger the inflammatory process. Thus, mast cells create the first response, which is then carried on by other inflammatory cells [13]. In current study, 750 patients had allergic rhinitis and the most common age group was 16-30 years, in which 220 patients were there i.e. 29.3%. Male patients were found more i.e. 447 (59.6%) patients while female patients were 303 (40.4%). Among study subjects, 390 (52%) patients resided in industrial areas, and 360 (48%) patients were from city areas. Regarding socioeconomic status 650 (86.67%) patients were poor and 100 (13.3%) patients belonged to the middle class. The most common symptom was nasal itching 522 (69.6%), followed by rhinorrhea 492 (65.6%) and nasal discharge 465 (62%). These findings are comparable to earlier research studies [14]. In a study, Appiah *et al.*, reported that in a hospital's ENT clinic, 10% of patients have allergic rhinitis and it was most prevalent in the 19–35-year-old age group. Compared to people living in the rural areas versus city areas, people in the city area experienced allergic rhinitis more. Sneezing was the primary complaint, while dust mites and sinusitis were the most prevalent comorbid conditions and triggers for allergic rhinitis, respectively. Male patients were 42% and female patients were 58%. The majority of them resided in city areas (67%). The majority 52% were between the ages of 19-35 years and the leading symptom was sneezing i.e. 25%, rhinorrhea 21%, headache 8% and nasal congestion 4% [14]. Ranjana *et al.*, reported that allergic rhinitis may affect all ages of patients and among them, 80% of patients were ≤20 years. female patients suffered more from allergic rhinitis as compared with male patients. Sneezing was 71.2%, nasal congestion was 51.9%, headache was 44.2%, rhinorrhea was 44.2% and nasal itching was 25.5% [15]. In a study in 2018, Adegbiji *et al.*, reported that 63% of patients were male and 37% were female. Among them, 42.3% were living in city areas. Sneezing was 58.5%, nasal congestion was 75.8%, itching in the nose was 53.22%, itching in the eye was 32.5%, edematous nasal mucosa was72.8%, turbinate enlargement was 67.2% and the headache was 52.8% in the study population [16]. In another study, Nur *et al.*, reported that the incidence of allergic rhinitis in children was 17.2% for the first 5 years of their life and 80% of allergic rhinitis symptoms develop, under the age of 20 years [17]. In a study, Zhang *et al.*, reported that the most common symptom in allergic rhinitis was sneezing i.e. 81.8%, rhinorrhea was 60.2% and nasal itching was 49.6%, nasal congestion was 54.9% and itching in eyes was 42.9% [18]. Kef K *et al.*, reported in a study that the mean age of patients was 20.71 ± 3.12 years and among them, 42.88% of patients were male and 57.12% of patients were female. The common symptom was

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sneezing i.e. 18.9%, nasal congestion 17.14%, itching in the nose 13.2%, Rhinorrhea 14.35%, itching in the eyes 11.24% and socioeconomic status showed 20.19% poor and 13.95% patients belonged to the middle class and p<0.053 which was significant [19]. In a study Ologe *et al.*, was reported that the mean age of patients was 38.5 ± 16.3 years and the most common symptom was sneezing i.e. 93% in allergic rhinitis patients and the p-value was <0.001[20].

CONCLUSIONS

It was concluded that allergic rhinitis is a common disease presenting at the outpatient Ear, Nose and Throat Department of a Postgraduate Teaching Hospital. This study showed that males were affected more as compared with females in the productive age group. The most frequent and common symptom was nasal itching followed by rhinorrhea and nasal discharge.

Authors Contribution

Conceptualization: THK
Methodology: MJM, TZS, MOKB
Formal analysis: AHR
Writing review and editing: MA

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

Conflicts of Interest

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Original Article

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Association Between Acute Ischemic Stroke and Raised Serum Gamma Glutamyl Transferase

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ABSTRACT

The serum gamma-glutamyl transferase level predicts the development of cardiovascular illnesses. Serum gamma-glutamyl transferase levels have been linked to atherosclerosis in several investigations, indicating that gamma-glutamyl transferase may be utilized as an early indicator of atherosclerosis. **Objective:** To determine the association between acute ischemic stroke and raised serum gamma-glutamyl transferase. **Methods:** After obtaining ethical approval, in this case-control study, 310 patients fulfilling the selection criteria were included from the Medical Emergency Department of, KEMU/ Affiliated hospital, Lahore from August 2022 to February 2023. Informed consent was obtained. After matching for age (40-80 years) and gender (both male and female), 155 controls enrolled preferably the accompanying healthy attendants of the patients and 155 cases i.e. ischemic stroke patients. Venous blood samples were obtained from cases at the time of presentation in the Emergency Department for serum gamma-glutamyl transferase (GGT). Data was collected in structured proforma. Data scrutiny was done using SPSS version 26.0. Mean and standard deviation were used for quantitative variables and frequency for qualitative data. Data were stratified for effect modifiers, and $p \leq 0.05$ was taken as significant. **Results:** In the current study, the frequency of raised GGT was found more among cases as compared to controls i.e. 74% vs 20%, $p<0.00001$ and OR calculated was 11.5. **Conclusions:** It was concluded that a considerable percentage of patients had raised gamma-glutamyl transferase at the time of presentation with acute ischemic stroke. These results emphasize the need to keep an eye on GGT levels in ischemic stroke patients as a possible stroke marker.

INTRODUCTION

Stroke/cerebral vascular accident (CVA) remains the primary cause of disability and death worldwide. Hemorrhagic and ischemic strokes are its two forms. Just 20% of strokes are hemorrhagic, caused by blood vessel rupture, while the majority of strokes 80% are ischemic, due to disruption in blood supply to the brain caused by atherosclerosis/thrombosis [1, 2]. The most significant risk factors for CVA include being male, smoking, dyslipidemias, advanced age, diabetes (DM) and hypertension (HTN). There are other risk factors as well [3, 4]. Clinicians may be able to identify patients who are more likely to have a stroke and schedule early preventive therapies with the aid of risk factor identification [1]. It has long been believed that raised gamma-glutamyl transferase (GGT) is a sign of alcohol consumption and hepatobiliary dysfunction [5]. Cellular membrane-bound

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GGT protein promotes intracellular uptake of peptides and amino acids. It is essential for extracellular glutathione that is produced during regular metabolic activities to be absorbed within the cell, shielding it from oxidative damage. To restore normal glutathione levels, production of GGT is stimulated when oxidative stress lowers intracellular glutathione levels. On the other hand, during times of elevated oxidative stress, increased requirement for glutathione combined with inadequate glutathione availability causes oxidative stress to negatively impact cells [6]. According to recent research, GGT actively participates in oxidative and inflammatory pathways that lead to atherosclerosis. Atherosclerosis, cardiovascular disease, and stroke are all facilitated by oxidative stress, which also causes vascular damage and endothelial dysfunction [7]. Serum GGT levels and frequency of stroke are positively correlated, according to numerous research [8-10]. It makes GGT an affordable and easy addition to the list of accessible tests beneficial in primarily stratifying patient risk. According to one recent study, raised GGT, is related to a higher risk of CVA, irrespective of liver disease [11]. Within 24 hours of presentation, patients with ischemic stroke had considerably higher GGT levels, according to another study [12]. Further supported by another study, that raised GGT was found to be a potential risk factor for stroke [13]. Despite the well-established risk factors for ischemic stroke, there remains a need for additional biomarkers that can enhance early risk stratification and improve clinical outcomes. Recent studies suggest that elevated GGT, which may also be implicated in atherosclerosis, is a key contributor to ischemic stroke. However, the potential of GGT as a predictive biomarker for AIS has not been fully explored.

This study aimed to address this gap by investigating the association between elevated serum GGT levels and acute ischemic stroke (AIS), to identify a novel marker that could facilitate earlier intervention and reduce the burden of stroke.

METHODS

This case-control study was done at the Emergency Department, of Mayo Hospital, Lahore over a six-month duration i.e. August 2022 to February 2023 after the acceptance of a proposal from Child Protection & Safeguarding Policy (CPSP) (Ref No: CPSP/REU/MED-2020-066-16551). 310 (155 in each group) selected via non-probability consecutive sampling and the sample size was calculated, by using a 5% significance level and 80% power of the study, the prevalence of raised GGT in groups with and without ischemic stroke was 28.8% vs 16.9% [11]. Data were collected in structured proforma containing background information. Patients 40-80 years of either gender presented with first ever episode of acute ischemic stroke as determined by history and CT scan within the last 24 hours (cases) and healthy attendants of patients without a history of cardiovascular disease (controls) Patients with recent surgery or trauma, any liver disease, those with history of alcoholic intake, creatinine >1.4 mg/ dl and with history of previous stroke were excluded. Venous blood samples were taken from cases and controls at presentation in emergency for Serum GGT. Patients with serum GGT level >27 IU/ ml were labelled as having raised GGT. Data were analyzed using SPSS version 26.0. Mean and SD were computed for quantitative variables and categorical variables were presented with frequency and percentage. OR calculated to check the association. Data stratified for effect modifiers age, gender, and DM. Post-stratification chi-square test calculated. Taking p-value<=0.05 is taken as significant.

RESULTS

There were more male patients in both groups i.e. 99 (64%) and 109 (70%) male vs 56 (36%) and 46 (30%) females in the case and control groups, respectively. In the case group, 50 (32%) patients and in the control group 23 (15%) were found to be diabetics. 35% were current smokers in the case and 19% in control group. 45% of cases and 22% among controls were found to have dyslipidemia. The mean age calculated was 55.41 + 9.17 years and 50.21 + 9.17 years among cases and controls, respectively and also exhibits that among cases 75 (48%) and in the control group 105 (68%) patients belong to age group <55 years and 80 (52%) in the case and 155 (100%) in control group belong to age >/=55 years (Table 1).

Table 1: Sociodemographic Characteristics of Study Groups

Variables	Case n=155	Control n=155
Age		
<55 years	75 (48%)	105 (68%)
>/=55 years	80 (52%)	50 (32%)
Total	155 (100%)	155 (100%)
Age (mean ± SD)	55.41 ± 9.17	50.21 ± 9.17
Gender		
Male	99 (64%)	109 (70%)
Female	56 (36%)	46 (30%)
Total	155 (100%)	155 (100%)
Diabetes Mellitus		
Yes	50 (32%)	23 (15%)
No	105 (68%)	132 (85%)
Total	155 (100%)	155 (100%)
Current Smokers		
Yes	55 (35%)	30 (19%)
No	100 (65%)	125 (81%)
Total	155 (100%)	155 (100%)
Current Smokers		
Yes	70 (45%)	35 (22%)
No	85 (55%)	120 (78%)
Total	155 (100%)	155 (100%)

The mean and SD of GGT i.e. 41.35 + 9.65 and 27.66 + 7.32 among cases and controls, p <0.0001 i.e. significant (Table 2).

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Table 2: Comparison of Descriptive Distribution of GGT Among Groups

GGT	Case n=155	Control n=155	p-value
Mean	41.35	27.66	<0.0001
SD	9.65	7.32	

The study showed a significantly raised frequency of raised GGT among cases as compared to controls i.e. 74% vs 20%, p<0.00001 and OR calculated was 11.5 (Table 3).

Table 3: Comparison of Frequency of Raised GGT among Case and Control Groups

Raised GGT	Case n=155	Control n=155	Total	p-value	Odds Ratio
Yes	115 (74%)	31 (20%)	146	<0.00001	11.5
No	40 (26%)	124 (80%)	164		
Total	155	155	310		

Data stratified for age, gender, and DM for raised GGT and compared among groups, showing statistically significant results i.e. p</= 0.05 for all stratified groups (Table 4).

Table 4: Data Stratification Concerning Effect Modifiers

DM	Raised GGT		p-value	Chi-Square
	Yes	No		
Yes				
Case	46	4	0.004	8.22
Control	15	8		
No				
Case	69	36	<0.00001	73.02
Control	16	116		
Age (Years)	Raised GGT		–	–
	Yes	No		
<55				
Case	40	35	<0.00001	41.85
Control	10	95		
>55				
Case	65	15	<0.00001	39.13
Control	13	37		
Gender	Raised GGT		–	–
	Yes	No		
Male				
Case	65	34	<0.00001	69.07
Control	11	98		
Female				
Case	50	6	<0.00001	42.31
Control	12	34		

DISCUSSION

According to the results of the current study, among cases 48% of patients and in the control group 68% of patients aged <55 years and 52% in case and 100% in control group aged >/=55 years. There were more male patients in both groups. In the case group 50 (32%) patients and in the control group 23 (15%) were found to be diabetic. 35% were current smokers in the case and 19% in the control group. 45% of cases and 22% among controls were found to have dyslipidemia. Furthermore, current results have shown significantly more frequency of raised GGT among cases as compared to controls i.e. 74% vs 20%, p<0.00001 and OR calculated was 11.5. Similar to the current study, one local study conducted has recently found to have high rates of hypertension (58%), dyslipidemia (26%), DM (34%), smoking (21%), ischemic heart disease (36%), obesity (19%), and other risk factors for stroke [14]. Previous studies have supported current study results, that increased frequency of raised GGT found in ischemic stroke patients, suggesting a possible relationship between GGT and cerebrovascular risk factors [15, 16]. In one previous study by Kalirawna *et al.*, unlike our results, no significant variance was found in age groups (p=0.741) or gender (p=0.1018) between case and controls. However, similar to our results, diabetes was notably higher in stroke patients compared to controls p=0.005 and an independent sample t-test revealed a significant difference in serum GGT levels between cases and controls [13]. According to current study results, GGT levels were found to be high among cases vs controls i.e. 41.35 + 9.65 vs 27.66 + 7.32urre, p<0.0001. Our results, further supported by another study by Ismail *et al.*, 2023, in which serum GGT level in case population noticed was 58.30 (U/L), and in the control group 17.48 (U/L) p-value<0.001 and implies increased level of serum GGT level in stroke patients [15]. Another Korean study by Lee *et al.*, found that higher serum GGT levels were found to be autonomously linked to the development of stroke in future [17]. According to a study by Gurbuzer *et al.*, patients with ischemic CVA with substantially greater regions of infarction had significantly higher mean GGT levels (p<0.05) [18]. However, the current study has not quantified the area of infarct. In another study by Korantzopoulos *et al.*, the proportion of ischemic CVA patients who showed up with elevated GGT levels (>27 IU/L) was higher than that of the control group. Individuals in the highest quartile of GGT levels had a 4.7-fold higher chance of having ischemic CVA (p<0.001) as compared to those in the lowest quartile. Even after adjusting for all possible confounding variables, this link held significance [19]. In contrast to the current study, however, Yang *et al.*, found that raised GGT levels in ischemic CVA patients were not linked with large-artery atherosclerosis stroke but with cardioembolic stroke [20]. However, in the current study, we have not studied the aetiology of ischemic stroke and have not divided our population to compare GGT levels. The current study has certain limitations, we have not studied stroke characteristics in detail, including infarct size. Further research will be needed in this area with a large sample size, including multi-centres to increase the generalizability of results.

CONCLUSIONS

It was concluded that higher GGT levels were found to be significantly associated with acute ischemic stroke as

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compared to the control group, reinforcing the relationship of raised GGT with acute ischemic stroke. This makes GGT, a potentially beneficial addition to an expanding panel of clinically available diagnostics that can be used to help with patient risk initialization.

Authors Contribution

Conceptualization: SK
Methodology: SK, QY, AJ, IUDYB, MUT, FR, UA, UH
Formal analysis: SK, WA, MQ
Writing review and editing: SK, QY, AJ, WA, IUDYB

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Antibiotic Resistance Patterns of *Pseudomonas aeruginosa* Bacterial Species Isolated from Various Clinical Samples

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ABSTRACT

Pseudomonas aeruginosa infections have become a real burden in healthcare settings, contributing substantially to nosocomial infections. The emergence of several drug-resistant strains was the major issue causing massive mortality. Multiple-drug resistant Pseudomonas aeruginosa isolates containing beta-lactamase were becoming more prevalent. **Objective:** To investigate and characterize the antibiotic resistance patterns of *Pseudomonas aeruginosa* isolated from different clinical samples. **Methods:** A total of 618 different clinical samples including blood, pus and urine samples were collected from the patients visiting Indus Medical College Hospital Tando Muhammad Khan, Sindh, Pakistan. All the clinical samples were processed for the isolation of bacterial species using specific culture media. The identification of *Pseudomonas aeruginosa* strains was achieved based on Gram's staining and certain biochemical tests including Cetrimide test. Moreover, antibiotic susceptibility testing was determined by Kirby-Bauer disc diffusion method. **Results:** A total of 452 bacterial strains were isolated and pure cultured from different clinical samples. Among these, 60.62% were Gram-negative and 25% of the total isolates were found to be *Pseudomonas aeruginosa* strains. Antibiotic sensitivity testing results revealed the highest resistance ratio of *Pseudomonas aeruginosa* strains against Ticarcillin (46.02%), while Colistin showed the lowest resistance (3.54%). Overall, 14.15% of the isolates of *Pseudomonas aeruginosa* strains were found to be multi-drug-resistant bacteria. **Conclusions:** The results of the present study reveal an increased ratio of antibiotic resistance particularly of Ticarcillin, piperacillin and imipenem in *Pseudomonas aeruginosa* isolated from various clinical samples.

INTRODUCTION

Pseudomonas aeruginosa are classified under the group of Gram-negative bacteria and are characterized with rod-shaped structure, aerobic in nature, motile and non-lactose fermenting bacteria [1]. The mucoid strains of *Pseudomonas aeruginosa* are encapsulated in a mucoid slime layer and produce extracellular polysaccharides that are primarily alginate polymers [2]. These bacteria are found in diverse environments including water, soil, plants and humans [3]. *Pseudomonas aeruginosa* is a versatile and opportunistic pathogen, capable of causing several types of infections, including cystic fibrosis, septicemia, and urinary tract infections especially in immunocompromised patients [4]. Mainly, Quorum Sensing (QS) system also known as communication system has been identified as a key factor in pathogenesis of *Pseudomonas aeruginosa* infections particularly in clinical isolates [5]. The characteristics of *Pseudomonas* species to grow at very low nutrient requirements and ability to withstand a vast array of physical parameters empowered these bacteria to prevail in different environments. Mainly, long-term infections caused by *Pseudomonas aeruginosa* have been associated with substantial mortality and morbidity rates. Irrespective of providing hygiene facilities and broad-spectrum antibiotics, the infections caused by

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Pseudomonas species are yet uncontrolled [6, 7]. Several *Pseudomonas aeruginosa* bacterial strains are reported to show resistance against a broad group of antibiotics [7]. With the widespread use of 3rd generation cephalosporins by the health practitioners, several isolates of *Pseudomonas aeruginosa* have become resistant to this class too [8].

Antibiotic resistance in *Pseudomonas aeruginosa* is mediated by the production of specific genes, genetic mutations and biofilm formation [4, 9]. These characteristics collectively contribute to the ability of this bacterium to evade antibiotic therapy. Additionally, overuse of antibiotics enhances the development of Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* strains leading to inadequate treatment and failure to combat this pathogen [10]. The elevated resistance ratio in *Pseudomonas aeruginosa* strains against a wide range of antibiotics poses a considerable threat causing community acquired and nosocomial infections [11, 12]. The studies on antibiotic sensitivity testing and occurrence ratio of *Pseudomonas* species in different regions world-wide would play a pivotal role in preventing such types of infections.

In view of these facts, the present study was carried out to investigate antibiotic resistance patterns of *Pseudomonas aeruginosa* isolated from various clinical sample at Indus medical college hospital, Tando Muhammad Khan (TMK), Sindh, Pakistan.

METHODS

This cross-sectional prospective study was carried out from January 2022 to December 2022 at the Research Laboratory, Institute of Microbiology, University of Sindh, Jamshoro, Pakistan. The study was approved by the Advanced Studies and Research Board (ASRB) of the University vide letter no ORIC/SU/872. A total of 618 patients suspected with bacterial infections visiting OPD at Indus medical college hospital, TMK, were registered for this study. This study only included patients who had not received antibiotic therapy, while those on antibiotic therapy were excluded. Notably, prior to collecting clinical samples, consent was obtained from all patients. Among the pathogenic bacteria, *Pseudomonas aeruginosa* was renowned for its extensive infectivity range and elevated resistance ratio against various antibiotics. Despite the significance of this issue, very limited studies have been conducted in TMK district, Sindh, Pakistan. In this regard, the present study underscores the necessity of investigating antibiotic resistance profiles of *Pseudomonas aeruginosa*, including the emergence of multi-drug-resistant strains, to suggest more effective treatment strategies in this region. Primarily, the clinical samples consisting of blood, pus and urine were brought and processed within three hours of the collection time at the research lab, Institute of Microbiology, University of Sindh, Pakistan. All the chemical reagents, culture media and antibiotic discs utilized in this study were procured from Oxoid Ltd. The isolation of bacteria was achieved using multiple culture media, including nutrient agar, CLED, MacConkey's agar, and cetrimide agar. The isolated bacterial strains were further sub-cultured using four-way culturing method in order to obtain pure cultures. The identification of the pure cultured strains particularly for *Pseudomonas aeruginosa* bacterial strains was carried out primarily based colony morphology and Gram's staining reaction followed by different biochemical tests including oxidase, indole, citrate and production of pigments [13]. Further, *Pseudomonas aeruginosa* strains were confirmed by cetrimide test. Antibiotic resistance testing was conducted using Kirby-Bauer disk diffusion method according to CLSI guidelines [14]. Antibiotic discs applied in this were listed as Piperacillin (100µg), Ticarcillin (TIC) (75µg), Piperacillin/Tazobactam (100/10µg), Ticarcillin/ Clavulanic acid (85µg), Cefepime (30µg), Ceftazidime (30µg), Imipenem (10µg). Gentamicin (10µg), Amikacin (30µg), Ciprofloxacin (5µg), Levofloxacin (30µg), Ofloxacin (5µg) and Colistin (5µg).

RESULTS

A total of 618 different clinical samples were collected from the patients registered under this study. Out of 618 clinical samples, 32.45% were blood, 38.33% pus samples and 29.22% were urine samples (Figure 1).

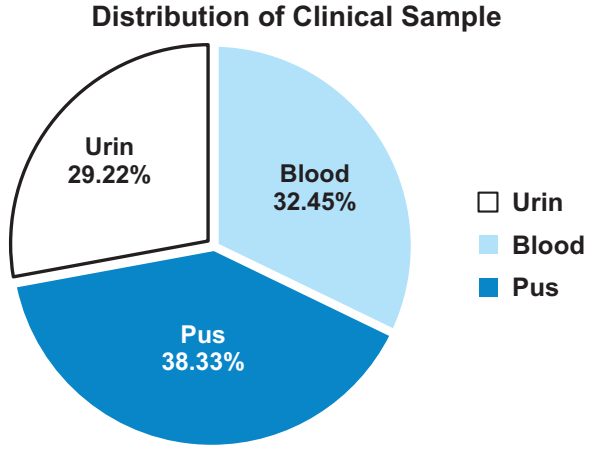

Figure 1: Distribution of Clinical Samples

Isolation frequency of the bacterial growth revealed 73.14% of the samples positive for growth with single and mixed colonies, while 26.86% of the clinical samples showed no growth. To avoid duplicates, only bacterial colonies with different colony morphologies were selected for further analysis. Gram's staining results showed 60.62% as Gram-negative and 39.38% Gram-positive bacterial species (Figure 2).

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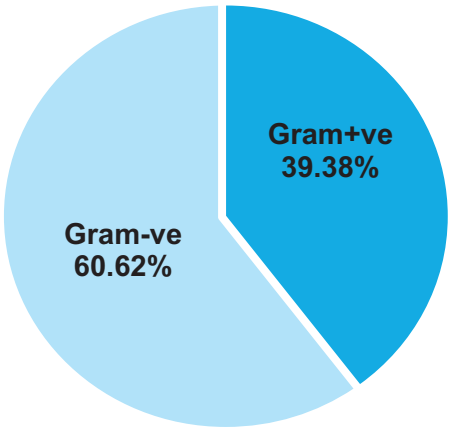

Figure 2: Results of Gram's Staining

Among the Gram-negative bacteria, 41.25 % (n=113) were identified as *Pseudomonas aeruginosa* strains, while 58.75% were other types of Gram-negative bacteria. In general, this study reveals the isolation and identification of 113 clinical isolates of *Pseudomonas aeruginosa* from various clinical samples collected from the patients suspected with bacterial infections. The isolation frequency of *Pseudomonas aeruginosa* was found highest in pus samples followed by blood and urine samples, respectively. All the *Pseudomonas aeruginosa* strains showed excellent growth on cetrimide agar medium with production of different pigments (Figure 3).

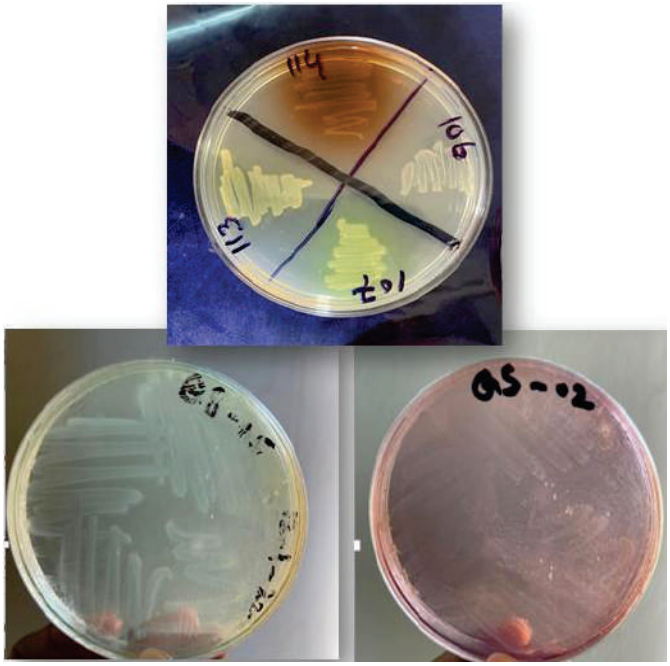

Figure 3: Pure Cultures of *Pseudomonas aeruginosa*

Biochemical identification of *Pseudomonas aeruginosa* strains revealed positive for oxidase, catalase, and citrate utilization test, while negative for indole and H2S (Figure 4). Moreover, all the *Pseudomonas aeruginosa* strains showed motility in both wet mount and SIM test.

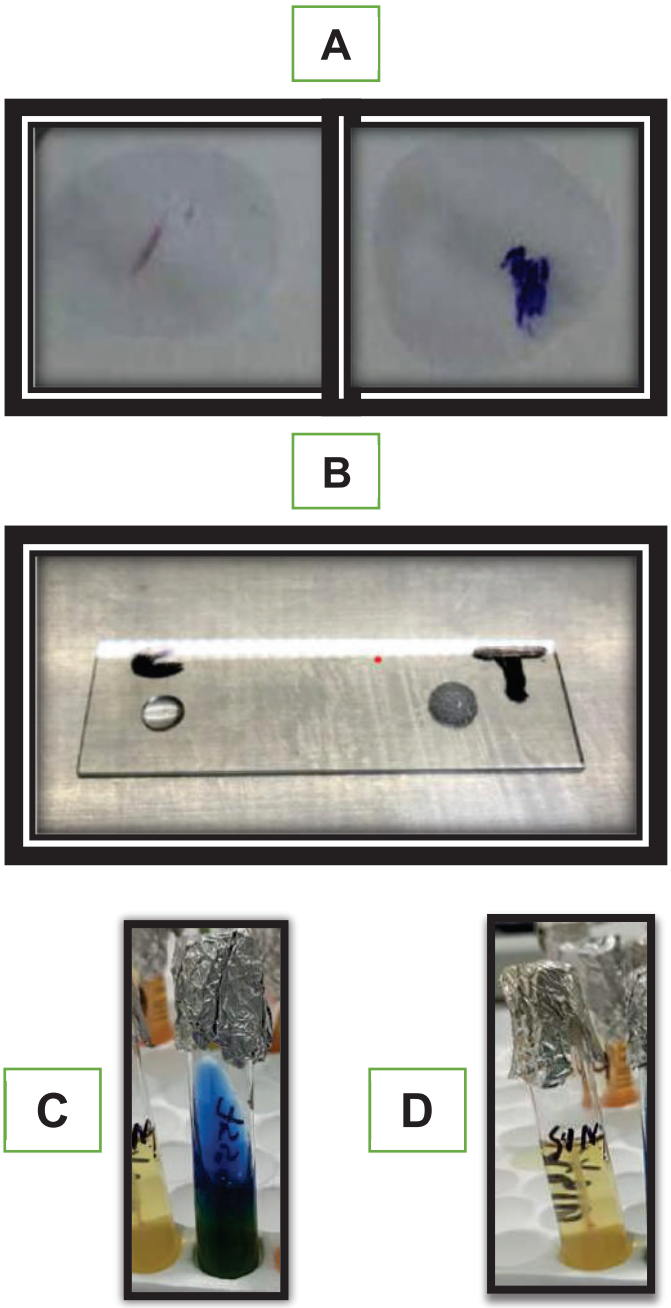

Figure 4: Biochemical Testing Results, Where "A" Shows Oxidase Test, "B" Catalase Test, "C" Citrate Utilization Test, and "D" Indicates SIM Test.

The antimicrobial resistance patterns of *Pseudomonas aeruginosa* isolates from clinical samples revealed the highest resistance ratio against Ticarcillin (46.02%), followed by Imipenem (39.83%) and Piperacillin (34.52%). The lowest resistance ratio was observed against Colistin (3.54%) followed by piperacillin/Tazobactam (13.28%), and Tic/Clavulanic acid (18.59%). *Pseudomonas aeruginosa* strains also exhibited resistance to various other antibiotics, including Ciprofloxacin (31.86%), Ofloxacin (30.09%), Gentamicin (23.99%), and Ceftazidime (23.01%), Amikacin (22.13%), Levofloxacin (20.36%) and Cefepime

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(19.45%) (Table 1). Overall, 14.15% of the *Pseudomonas aeruginosa* isolates were confirmed as MDR exhibited resistance to more than three antibiotics (Table 1).

Table 1: Demographic Details of study Participants

S. No.	Antibiotics	Concentration (µg)	Sensitive Zone Diameter/mm	Sensitive (%)	Resistance (%)
1	Amikacin (AK)	30 µg	≥14	77.87%	22.13%
2	Gentamicin (CN)	10 µg	≥12	76.10%	23.9%
3	Cefepime (FEP)	30 µg	≥12	80.53%	19.47%
4	Ceftazidime (CAZ)	30 µg	≥16	76.99%	23.01%
5	Ciprofloxacin (CIP)	5 µg	≥25	68.14%	31.86%
6	Levofloxacin (LEV)	30 µg	≥18	79.64%	20.36%
7	Ofloxacin (OFX)	5 µg	≥15	69.91%	30.09%
8	Piperacillin (PRL)	100 µg	≥21	65.48%	34.52%
9	Pip/Tazobactam (TZP)	100/10 µg	≥15	86.72%	13.28%
10	Ticarcillin (TIC)	75 µg	≥17	53.98%	46.02%
11	Ticarcillin Clavulanic acid (TIM)	85 µg	≥15	81.41%	18.59%
12	Imipenem (IMP)	10 µg	≥20	60.17%	39.83%
13	Colistin (CT)	5 µg	≥11	96.46%	3.54%

Disc diffusion method CLSI-M 100

DISCUSSION

Pseudomonas aeruginosa infections have become a real burden for nosocomial infections, especially in immunocompromised and critically ill patients. The emergence of several drug-resistant strains is the major issue causing massive mortality. Multiple-drug resistant *Pseudomonas aeruginosa* isolates containing beta-lactamase were becoming more prevalent. The present study was carried out to investigate antibiotic resistant patterns of *Pseudomonas aeruginosa* strains isolated from various clinical samples including blood, pus and urine samples. Overall, 618 patients suspected with bacterial infections with different age groups were registered in this study who visited OPD at Indus medical college hospital, TMK, Sindh, Pakistan. Antibiotic resistance patterns were observed using Kirby-Bauer disk diffusion method according to CLSI guidelines [14]. A total of thirteen different antibiotics were tested against clinical isolates of *Pseudomonas aeruginosa* strains either individually or in combination of another drug (two-drug combinations). This study has revealed the isolation and identification of 113 clinical isolates of *Pseudomonas aeruginosa* strains. The isolation frequency of *Pseudomonas aeruginosa* was found highest in pus samples as compared to blood and urine samples. Previously, several studies have also recovered the highest ratio of *Pseudomonas aeruginosa* from pus samples [15, 16]. The findings of this study were consistent with results of the earlier studies conducted worldwide. However, some studies have shown the highest prevalence of *Pseudomonas aeruginosa* from sputum and urine samples [3, 17]. The antimicrobial sensitivity testing results of *Pseudomonas aeruginosa* strains showed the highest resistance ratio against Ticarcillin (46.02%), Imipenem (39.83%) and Piperacillin (34.52%). While the lowest resistance ratio was recorded against Colistin (3.54%). Ticarcillin was found to be the least effective antibiotic against *Pseudomonas aeruginosa.* Previously, Odoi H *et al.*, also revealed same results showing Pseudomonas aeruginosa highly resistant to Ticarcillin [18]. Out of 113 *Pseudomonas aeruginosa* strains, 14.15% showed resistance against several antibiotics and thus revealed as MDR bacterial strains. However, this ratio of MDR was much lower than that reported by Ahmad S *et al.*, who reported 20% of MDR in clinical isolates of *Pseudomonas aeruginosa.* One of the studies has shown the highest resistance patterns to Gentamicin (65.5%) and another study has shown highest resistance ratio against Imipenem [15, 19, 20]. Moreover, a combination of two drugs such as piperacillin / Tazobactam indicated 13.28% resistance by *Pseudomonas aeruginosa* as to alone piperacillin (34.52%). Furthermore, *Pseudomonas aeruginosa* were also found highly sensitive against another combination of two drugs such as Ticarcillin / Clavulanic acid. These results suggest that the combination of two drugs may reduce the resistance ratio and increase the sensitivity among clinical isolates of *Pseudomonas aeruginosa* strains. Qayoom S *et al.*, has also shown the similar results with higher sensitivity of *Pseudomonas aeruginosa* strains against combination of piperacillin / Tazobactam and Ticarcillin / Clavulanic acid. Moreover, Pseudomonas aeruginosa isolates exhibited 23.01% resistance to ceftazidime (3rd generation cephalosporin) and 19.47% to cefepime (4th generation cephalosporin) [15]. Previously, two studies on *Pseudomonas aeruginosa* also recorded similar results against 3rd and 4th generation of cephalosporins [21, 22].

CONCLUSIONS

In conclusion, the present study revealed the resistance ratio exhibited by *Pseudomonas aeruginosa* strains isolated from different clinical samples. The highest resistance ratio was observed against Ticarcillin (46.02%), Imipenem (39.83%) and Piperacillin (34.52%). While the lowest resistance ratio was recorded against Colistin (3.54%). In addition, the combinations of two drugs such as Piperacillin/Tazobactam and Ticarcillin/Clavulanic acid demonstrated efficacy against *Pseudomonas aeruginosa* strains. The findings of the present study will be highly beneficial to identify the drug-resistant patterns in *Pseudomonas aeruginosa* strains in healthcare associated infections and will help the health professionals to suggest the proper antibiotic for the treatment of patients suffering from severe infections caused by *Pseudomonas aeruginosa* bacteria and to prevent the emergence of antibiotic resistance. Early recognition and implementation of infection management measures were critical for preventing the spread of drug-resistant pathogens.

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Authors Contribution

Conceptualization: QAS, AN
Methodology: QAS, AN, SAT, ASQ
Formal analysis: QAS, AN, NAB, FAK
Writing, review editing: QAS, AN, ASD, AP, ASQ

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Comparative Efficacy of Single-Dose versus Multiple-Dose Antibiotic Prophylaxis in Reducing Postoperative Infections in Elective Cesarean Deliveries

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ABSTRACT

Cesarean Sections (CS) were common surgeries that may lead to complications like endometritis and Surgical Site Infections (SSIs). While prophylactic antibiotics reduce these risks, the ideal dosing regimen remains debated. **Objective:** To evaluates whether a single or multiple-dose antibiotic regimen offers better protection against infections in patients undergoing planned cesarean sections. **Methods:** A six-month quasi-experimental study was conducted from October 1, 2020, to March 30, 2021, at Lady Reading Hospital in Peshawar. Eighty-two women scheduled for elective CS were assigned into two groups: one received a single 1g dose of intravenous cefazolin before surgery, and the other received the same initial dose followed by two additional doses every eight hours. Primary outcomes assessed were the incidence of endometritis and SSIs within 30 days post-surgery. **Results:** Postpartum infections were significantly lower in the multiple-dose group (4.9%) compared to the single-dose group (19.5%, p = 0.039). The multiple-dose group also had fewer SSIs (4.9% vs. 14.6%, p = 0.140) and no cases of endometritis (0% vs. 4.9%, p = 0.154), though these differences were not statistically significant. There were no significant differences in adverse drug reactions, hospital stay duration, or antibiotic resistance development between the groups. **Conclusions:** Multiple-dose antibiotic regimens may reduce infection rates in planned CS without increasing adverse effects or antibiotic resistance. Further studies were needed to confirm these findings and optimize prophylactic strategies.

INTRODUCTION

With a major share of all deliveries, Cesarean Sections (CS) are among the most often carried out surgical operations globally. Though it is somewhat common, cesarean birth has some hazards, especially in relation to postoperative infections [1]. Among the most important problems linked to cesarean births are Surgical Site Infections (SSIs) and endometritis, which raise mother morbidity, extend hospital stays, drive greater healthcare expenditures, and, in some cases, result in major long-term health implications [2]. Thus, a major emphasis in obstetric treatment is on preventing these infections. The main intervention in lowering the risk of postoperative infections in women undergoing cesarean sections is antibiotic prophylaxis [3]. Given before surgery, antibiotics are supposed to reduce the number of germs introduced during operation, therefore lowering the risk of endometritis and SSIs. Still under inquiry and discussion, however, is the ideal antibiotic prophylactic schedule especially in terms of dosage count [4]. Antibiotics given single doses before to surgery were the accepted method of treatment for infections historically. This method is based on the theory that maintaining the appropriate level

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of antibiotics in the body during the most probable period for an infection to develop usually during surgery and for a few hours following is sufficient to prevent infections from starting [5]. Because they are less likely to produce antibiotic resistance, simpler to administer, and less expensive, single dose preventive medications are superior. Conversely, new research indicates that delivering multiple doses of antibiotics over an extended period of time might help prevent endometritis and SSIs even more [6-8]. This lengthier schedule is required to provide continuous antibiotic therapy throughout the period after surgery. After the initial dosage loses part of its efficacy, this may help cure infections that can develop thereafter. Those who are overweight, diabetic, or have another illness that increases their susceptibility to infections might find this method particularly beneficial. Furthermore, some data point to multiple-dose strategies perhaps being more effective in preventing diseases brought on by less sensitive single-dose preventative bacteria [9-11]. The purpose of this research is to ascertain if it is safe and effective for women having planned cesarean sections to receive a single dose of antibiotic prophylaxis. The incidence of endometritis and SSIs were compared between the single and multiple-dose groups, and secondary outcomes such hospital stays, side effects, and antibiotic resistance were also examined.

The aim was to provide insightful information to help doctors manage pre- and post-cesarean care. To more effectively customize antibiotic usage, variables such as patient age, Body Mass Index (BMI), kind and timing of antibiotics, and pre-existing medical issues were taken into account. In order to enable a more individualized and efficient strategy to antibiotic administration in cesarean births, the results are anticipated to have an impact on clinical practice by assisting doctors in striking a balance between infection prevention and avoiding side effects and drug resistance.

METHODS

This quasi-experimental study was conducted at Lady Reading Hospital in Peshawar. The research spanned six months, from October 1, 2020, to March 30, 2021. The major objective of the trial was to determine if for women scheduled for a planned cesarean section, single or repeated doses of antibiotics were more safe and effective. Previous research showing variations in infection rates between single and multiple-dose antibiotic prophylaxis helped to determine the sample size. A minimum of 82 individuals were projected to be needed to find a clinically meaningful difference between the two groups using a significance threshold of 0.05 and a power of 0.80. For the single-dose group, this computation projected an expected infection rate of 20%; for the multiple-dose group, it projected 5% [12]. The research included 82 women booked for elective cesarean sections at Lady Reading Hospital. Simple random sampling let participants be chosen. Women between the ages of 18 and 40, who had a singleton pregnancy, and without any known antibiotics allergy were among the inclusion criteria. Women with past infections, immunocompromised states, or those who had taken antibiotics within 14 days before the cesarean delivery were excluded. One of two groups the single-dose or the multiple-dose group was allocated randomly to each participant. A computer-generated random number sequence was followed in randomizing. Thirty minutes before the surgical incision, women in the single-dose group got one gram of intravenous cefazolin. Women in the multiple-dosage group got an initial dose of intravenous cefazolin (1g) 30 minutes before the surgical incision, then extra doses every 8 hours for a total of three doses. Direct patient evaluations along with medical record reviews gathered the data. Within 30 days following the cesarean section, the main result was the frequency of postoperative infections including endometritis and Surgical Site Infections (SSIs). Additional effects included length of hospital stay, side effects from medications, and emergence of antibiotic resistance. Trained nurses and doctors oversaw postoperative surveillance. Daily during their hospital stay, patients were evaluated for symptoms of infection; they were followed up at the outpatient clinic at 7, 14, and 30 days following surgery. Every indication of an infection was recorded and handled using hospital guidelines. Endometritis was diagnosed based on clinical signs including uterine tenderness, fever, and abnormal vaginal discharge, confirmed by laboratory findings such as elevated white blood cell count and positive bacterial cultures. SPSS version 25.0 was used to examine data. The subjects' baseline features were compiled using descriptive statistics. Chi-square tests for categorical data and t-tests for Continuous variables let the two groups' incidence of postoperative infections and other outcomes were compared p-value less than 0.05 was considered statistically significant. The Lady Reading Hospital Ethics Committee authorized the research with approval vide Ref No 497/LRH/MTI. Before each subject was included into the research, informed permission was acquired from each one. Participants were guaranteed their freedom to withdraw from the research at any moment without affecting their medical treatment as well as their confidentiality of their data. Following this thorough approach, the research sought to give a thorough comparison of single vs. several doses of antibiotic prophylactic treatment in reducing postoperative infections in women having elective cesarean sections.

RESULTS

The research included 82 women in total and randomly divided them into either the single-dose or multiple-dose group 41 in each of the former categories. table 1 listed the

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individuals' baseline characteristics in general. The two groups had no appreciable variations in age, Body Mass Index (BMI), gestational age, or underlying medical problems, therefore guaranteeing comparability across groups.

Table 1: Baseline Characteristics of Participants(n=82)

Variables	Single-Dose Group Mean ± SD / N (%)	Multiple-Dose Group Mean ± SD / N (%)	p-Value
Age (Years)	29.5 ± 4.3	28.7 ± 4.8	0.487
BMI (Kg/m^2)	28.2 ± 3.5	27.9 ± 3.7	0.736
Gestational Age (Weeks)	38.1 ± 1.2	37.9 ± 1.3	0.491
Hypertension	5 (12.2%)	4 (9.8%)	0.729
Diabetes	3 (7.3%)	2 (4.9%)	0.645

Within 30 days following the cesarean section, the main result was the frequency of postoperative infections including endometritis and Surgical Site Infections (SSIs). With a p=0.039, the multiple-dose group had a far lower incidence of any postoperative infection than the single-dose group 4.9% vs. 19.5%. Although in the multiple-dose group the incidence of SSIs and endometritis separately was lower, these variations were not statistically significant (p=0.140 and p=0.154, respectively). Of the six SSIs in the single-dose group, four were superficial infections and two were deep incisional infections after further investigation. Both of the SSIs in the multiple-dose group were superficial. Among the instances of endometritis in the single-dose group, both affected women with extra risk factors including obesity and protracted labor before the cesarean surgery figure 1 provided the outcomes.

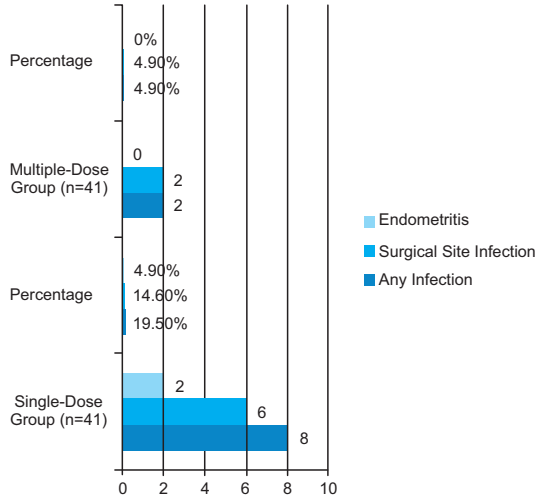

Figure 1: Incidence of Postoperative Infections

Secondary outcomes included the length of hospital stay, adverse drug reactions, and the development of antibiotic resistance. The mean length of hospital stay in the multiple-dose group was somewhat shorter than in the single-dose group (4.7 ± 1.1 days vs. 5.2 ± 1.4 days), this difference was not statistically significant (p=0.081). Especially, the most of the prolonged stays in the single-dose group were linked to SSIs, suggesting a possible therapeutic advantage from the multiple-dose schedule. The length of hospital stay was measured in days and was summarized in table 2.

Table 2: Comparison of Length of Hospital Stays In Different Dose Groups(n=82)

Length of Stay (Days)	Single-Dose Group Mean ± SD	Multiple-Dose Group Mean ± SD	p-Value
	5.2 ± 1.4	4.7 ± 1.1	0.487

With no appreciable difference between the single-dose and multiple-dose groups (p=0.645), both groups had low incidence of adverse medication responses. The most often occurring side effects were gastrointestinal ones; allergic responses came second; all of them were moderate and no antibiotic medication had to be stopped. Adverse drug reactions were monitored and were presented in figure 2.

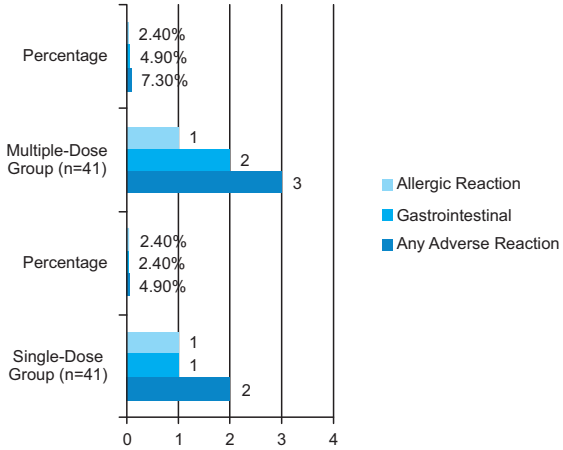

Figure 2: Adverse Drug Reactions in Different Dose Groups

The development of antibiotic resistance was assessed through culture and sensitivity tests for any isolated pathogens. In the single-dose group one instance showed evidence of antibiotic resistance; none in the multiple-dose group. Still, this variation lacked statistical significance p=0.313. The Methicillin-Resistant Staphylococcus Aureus (MRSA) found in the single-dose group underlined the need of ongoing monitoring and careful administration of antibiotics. The results were presented in figure 3.

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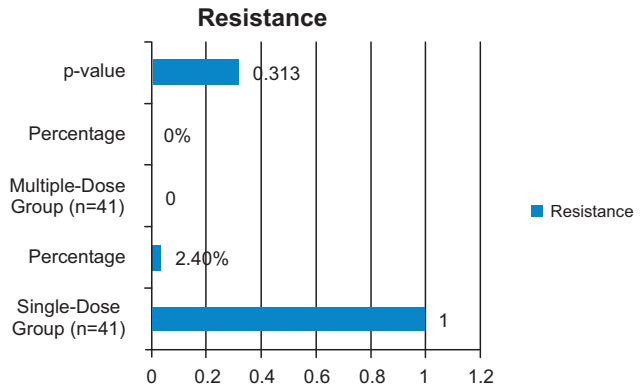

Figure 3: Antibiotic Resistance in Different Dose Groups

DISCUSSION

This study that in women undergoing elective cesarean sections, many doses of antibiotic prophylaxis were more beneficial than one dosage in lowering the general incidence of postoperative infections [13]. This result was consistent with several studies investigating the advantages of prolonged antibiotic prophylactic policies for surgical operations. Extended regimens of antibiotics, especially the addition of a secondary antibiotic to routine cephalosporin prophylactic treatments, greatly lower the frequency of post-cesarean infections compared to a single dose of cephalosporin alone, as previous studies have indicated [14]. Comparable to the declines seen in previous investigations, the drop in infection rates shown in this study (from 19.5% to 4.9%) supports the theory that extended antibiotic coverage can provide improved protection against postoperative infections [15]. Meta-analyses comparing single to multiple doses of antibiotic prophylaxis in cesarean births show that multiple doses significantly lower the incidence of endometritis and wound infections [16]. While the reduction in endometritis was not statistically significant in this sample, the decreased incidence of surgical site infections (14.6% in the single-dose group vs. 4.9% in the multiple-dose group) aligns with these findings [17]. However, concerns have been raised about the potential negative consequences and antibiotic resistance associated with multiple-dose schedules [18]. Although multiple doses may reduce infection rates, they have also been associated with an increased frequency of side effects and concerns about promoting antibiotic-resistant bacteria. In this study, there was no significant difference in adverse drug reactions between the two groups (4.9% in the single-dose group vs. 7.3% in the multiple-dose group) and no significant increase in antibiotic resistance, suggesting that the benefits of multiple-dose prophylaxis may outweigh these risks [19]. Clinically, the notable drop in general postoperative infections resulting from several doses of antibiotic prophylactic treatment has great ramifications. Adopting a multiple-dose schedule might help to improve patient outcomes and save healthcare expenditures related to treating surgical site infections and endometritis, which were the main causes of maternal morbidity [20]. Though not statistically significant, the somewhat shorter hospital stay noted in the multiple-dose group might possibly point to better recovery periods and less healthcare use. Particularly for people at increased risk of infection, including those with obesity, diabetes, or other comorbidities, these findings supported the use of multiple-dose antibiotic prophylactic programs. Existing clinical guidelines might be modified to include this strategy, therefore improving the quality of treatment for women having cesarean sections [21]. While this study provided valuable insights, it has limitations that should be acknowledged. The sample size of 82 women, though adequate for detecting differences in infection rates, may not fully capture the range of potential side effects or the long-term impact of antibiotic resistance.

CONCLUSIONS

This study shows that, compared to a single-dose schedule, many doses of antibiotic prophylaxis greatly lower the risk of postoperative infections in women undergoing elective cesarean sections. The results imply that without raising negative medication responses or antibiotic resistance, longer antibiotic coverage offers greater protection against surgical site infections and endometritis. Using multiple-dose prophylaxis in clinical settings might help to lower postoperative healthcare expenses and enhance mothers's health outcomes.

Authors Contribution

Conceptualization: A
Methodology: A, NU
Formal analysis: RZ, MS
Writing, review and editing: SG, NR, SS

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

Conflicts of Interest

The authors declare no conflict of interest.

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Paced QRS Duration as the Major Determinant of Pacing Induced Cardiomyopathy in Complete AV Block

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ABSTRACT

Patients with complete heart block often develop pacing-induced cardiomyopathy (PICM) after placement of a permanent pacemaker. **Objective:** To establish paced QRS duration as determinant of pacing induced cardiomyopathy in complete Atrioventricular (AV) block. **Methods:** This descriptive study included 115 male and female patients that had a permanent pacemaker implanted for complete AV block, at the department of Cardiology, Hayatabad Medical Complex, Peshawar, during the period 1st November 2023 till 30th June 2024. Patients were evaluated for the presence of PICM and subsequently grouped as PICM and non-PICM. Paced QRS duration in both groups was compared. **Results:** PICM was confirmed in 63 patients (54.8%) and 52 (45.2%) were non-PICM. Mean age in PICM group was 71.2 ± 8.7 years and 66.8 ± 9.5 years in non-PICM group. The mean paced QRS duration in PICM group was 200.5 ± 22.3 milliseconds and 168.3 ± 15.7milliseconds in non-PICM group (p value <0.001). **Conclusions:** Prolonged paced QRS duration was found as key indicator for predicting pacing induced cardiomyopathy in patients with permanent pacing for complete AV block.

INTRODUCTION

Pacing Induced Cardiomyopathy (PICM) is an issue that needs attention in patients having prolonged ventricular pacing on placement of a Permanent Pacemaker (PPM) for full AV block [1, 2]. Restoration of normal cardiac rhythm prevent negative hemodynamic consequences resulting from AV block but prolonged ventricular pacing has been shown to adversely affect cardiac structure and function eventually leading to PICM [3-5]. Risk stratification and prevention strategies are hampered by impenetrable complex factors which cause PICM [6]. The prolonged PR interval or QRS complex might be indicative of major dyssynchrony that can lead to dilated atria or ventricles as well as their poor contractility [7]. However other studies suggest that protracted pQRS may also be an additional marker for excessive dyssynchrony during ventricular contractions associated with damaging remodeling and dysfunction [8-10]. Nevertheless, there is still a lack of clarity on how development of PICM occurs due to pQRSd

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increase [11]. Thus, identification of variables influencing onset of PICM will provide evidence for optimizing patient care and outcomes in terms of clinical implications associated with this disease. The study focused on variables such as age, gender and baseline LVEF in the multivariate model because they have been shown to potentially influence the development of PICM. Multicollinearity was checked using Variance Inflation Factor (VIF), and all variables had acceptable VIF values (below 4), ensuring that multicollinearity did not affect the results.

Consequently, the present study aimed to investigate paced QRS duration as a predictor for PICM among patients with complete atrio-ventricular block following permanent pacemaker implantation. The current paper also explored how pQRSd can be utilized as a measure of risk stratification and target therapy in order to minimize adverse effects related to ventricular pacing on myocardial contractility.

METHODS

This descriptive study was carried at the department of Cardiology, Hayatabad Medical, Complex, Peshawar, during the period 1st November 2023 till 30th June 2024. Approval for the conduct of the study was granted vide no: 1638. A total of 115 male and female patients in the age range 20 to 90 years who underwent permanent pacing for complete AV block at the department of cardiology of the hospital were registered. Patients with prior history of cardiomyopathies, patients taking diuretics, beta blockers or digoxin, patients with history hyperthyroidism, patients with valvular heart disease and previous history of intervention for conduction abnormalities were excluded. Complete AV block was confirmed by the presence of clinical findings such as dizziness, palpitations and shortness of breath and ECG showing identifiable p waves with complete dissociation from QRS complex. Permanent pacemaker was small battery placed under the skin that generates and provides electrical impulses to the heart at regular intervals. Pacing induced cardiomyopathy was confirmed on echocardiography defined as ejection fraction 50.0% or below or sudden decline in ejection fraction by greater 10.0% from baseline after permanent pacemaker installation. Paced QRS duration was measured as the distance from the start of Q wave till the end of S wave on ECG recorded in milliseconds in patients with pacing. Normal value was 160.0 ± 18.0 milliseconds. Patients were recruited using non-probability consecutive sampling technique and sample size was calculated using WHO sample size calculator taking 31.5% anticipated prevalence of pacing induced cardiomyopathy in patients with pacing for complete AV block, 8.5% margin of error and 95% confidence level [4]. Patients were enrolled after taking permission from research review board of the institute. Informed consent was obtained from registered participants. Basic information and relevant medical records was retrieved from Electronic Health Records (EHRs). Baseline left ventricular ejection fraction was noted. An echocardiography was performed by consultant cardiologist. Left ventricular ejection fraction was compared with baseline values and presence of PICM was noted. Patients were subsequently grouped into (PICM) and (non-PICM) based on the presence or absence of PICM. An ECG was performed and paced QRS duration was noted in milliseconds by measuring the interval between the start of Q wave till the end of S wave. Paced QRS value more than 180 milliseconds was called prolonged paced QRS duration. Normality of continuous variables (e.g., LVEF, QRS duration) was tested using the Shapiro-Wilk test. Non-normally distributed data were reported as median and Interquartile Range (IQR) and compared using non-parametric tests (Mann-Whitney U). Potential confounders, such as the severity of heart conditions (e.g., history of coronary artery disease or myocardial infarction), pacemaker duration, and medication history (e.g., use of beta-blockers or diuretics), were adjusted for in the multivariate logistic regression model. Data analysis was done with SPSS version 22. Means ± standard deviation was used to characterize continuous variables and categorical data were presented as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test, and based on the results, parametric or non-parametric tests were applied accordingly. Continuous data were compared using independent sample t test and chi square test was applied to categorical data. Multivariate logistic regression analysis was conducted to evaluate the predictors of PICM while controlling for confounders such as age, gender, and baseline LVEF. ROC curve analysis was used to obtain the cut off value for paced QRS duration for predicting PICM. P value ≤0.05 was considered statistically significant.

RESULTS

A total of 115 patients were recruited. PICM was observed in 63 patients (54.8%) and 52 (45.2%) were non-PICM. Overall mean age of the participants was 68.5 ± 9.2 years. Mean age in PICM group was 71.2 ± 8.7 years and 66.8 ± 9.5 years in non-PICM group. Male to female ratio in both groups was 1: 1.25 and 1: 1.36 respectively. 15 (23.8%) had previous history of MI in PICM group and 12 patients (23.0%) had MI history. Baseline clinico-demographic characteristics of the patients were summarized in table 1.

Table 1: Patient Demographics and Baseline Clinical Characteristics (n=230)

Variables	Total (Mean ± SD) / N (%)	PICM (Mean ± SD) / N (%)	Non-PICM (Mean ± SD) / N (%)	p-Value
Age (Years)	68.5 ± 9.2	71.2 ± 8.7	66.8 ± 9.5	0.097*

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Gender				
Male	65 (56.5%)	35 (55.5%)	30 (57.7%)	
Female	50 (43.5%)	28 (44.5%)	22 (42.3%)	0.123**
Hypertension	82 (71.3%)	45 (71.4%)	37 (71.2%)	0.456**
Diabetes mellitus	38 (33.0%)	20 (31.7%)	18 (34.6%)	0.789**
Coronary artery disease	45 (39.1%)	22 (34.9%)	23 (44.2%)	0.234**
Previous myocardial infarction	27 (23.5%)	15 (23.8%)	12 (23.0%)	0.567**

**Independent sample t test*
***Chi square test*

Patient with PICM had a significantly lower mean (LVEF) than those without (49.8% vs. 58.7%, p = 0.001). The left ventricular end-diastolic and end-systolic diameters were similar between groups (p > 0.05) as reported in table 2.

Table 2: Baseline Echocardiographic Parameters (n=345)

Variables	Total (Mean ± SD)	PICM (Mean ± SD)	Non-PICM (Mean ± SD)	p-Value	Skewness value
LVEF (%)	55.2 ± 5.6	49.8 ± 6.35	58.7 ± 4.8	0.001	0.683
Left ventricular end-diastolic diameter (mm)	49.6 ± 3.2	0.8 ± 3.5	48.9 ± 2.9	0.234	0.198
Left ventricular end-systolic diameter (mm)	31.4 ± 2.9	33.1 ± 3.2	30.2 ± 2.5	0.456	0.031

The mean paced QRS duration (pQRSd) compared to non-PICM patients was significantly different (200.5 ms vs. 168.3 ms, p < 0.001). Patient with PICM had a considerably higher rate of right ventricular lead insertion at the apical position (82.8% vs. 66.1%, p = 0.123) as reported in table 3.

Table 3: Pacing Variables (n=345)

Variables	Total (Mean ± SD) / N (%)	PICM (Mean ± SD) / N (%)	Non-PICM (Mean ± SD) / N (%)	p-Value	Skewness value
Paced QRS Duration (ms)	180.6 ± 20.8	200.5±22.3	168.3 ± 15.7	<0.001	0.985
Right Ventricular Lead Location					
Apical	85 (73.9%)	48 (82.8%)	37 (66.1%)	0.1231	-
Septal	25 (21.7%)	2 (20.7%)	13 (23.2%)	0.456	
Other	5 (4.4%)	3 (5.2%)	2 (3.6%)	0.789	

As illustrated in table 4, Univariate logistic regression analysis demonstrated that paced QRS duration (OR: 1.15, 95% CI: 1.08–1.23, p < 0.001) and age (OR: 1.05, 95% CI: 1.01–1.10, p = 0.02) were significant predictors of PICM. Other variables like gender and hypertension were not significant in univariate analysis.

Table 4: Univariate and Multivariate Logistic Regression Analysis

Variables	Adjusted Odds Ratio (95% CI)	p-Value
Univariate Logistic Regression		
Paced QRS Duration	1.15 (1.08–1.23)	<0.001
Age	1.05 (1.01–1.10)	0.02
Multivariate Logistic Regression		
Paced QRS Duration	1.25 (1.12 - 1.39)	<0.001
Age	1.08 (1.02 - 1.15)	0.234
Gender (male)	1.17 (0.98 - 1.32)	0.567
Baseline LVEF	0.92 (0.86 - 0.98)	0.091

Logistic regression model analysis was constructed to determine the predictive ability of paced QRS duration with development of PICM, even after controlling for age, gender and baseline LVEF (adjusted odds ratio 1.25, 95% CI 1.12–1.39, p < 0.001). Variables of age, gender and baseline (LVEF) exhibited independent associations with PICM, which was not statistically significant. The ROC curve for paced QRS duration in predicting PICM had an area under the curve (AUC) of 0.78, indicating good predictive ability. A cutoff value of 180 milliseconds offered 75.0% sensitivity and 72.5% specificity as reported in table 5.

Table 5: ROC Curve Analysis for Paced QRS Duration

Variables	Area Under the Curve	Sensitivity	Specificity	Optimal Cutoff Value
Paced QRS Duration (ms)	0.78	75.0%	72.5%	180 ms

ROC Curve for Paced QRS Duration with a diagonal reference line, demonstrating the ability of paced QRS duration to predict pacing-induced cardiomyopathy (Figure 1).

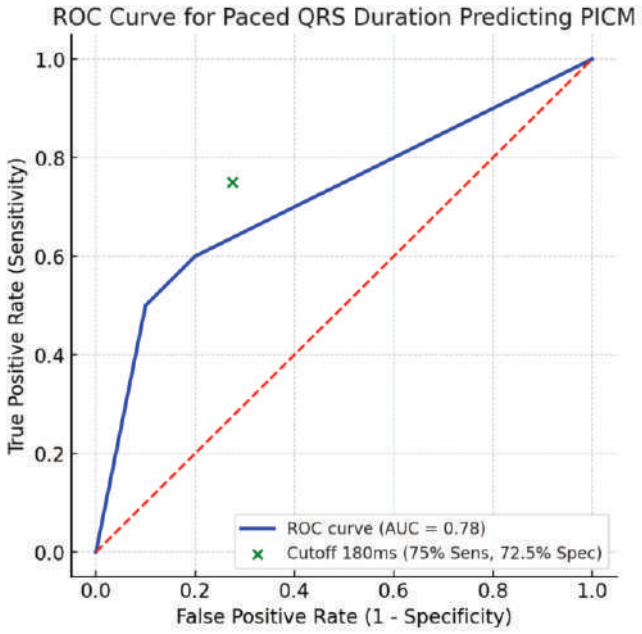

Figure 1: ROC Curve for Paced QRS Duration with Diagonal Reference Line

DISCUSSION

The present research, which included 115 patients diagnosed with complete AV block and received permanent pacemaker, provides important insights into the development of Pacing-Induced Cardiomyopathy (PICM). This data show that 54.8% of the patients acquired PICM during follow-up, which was consistent with prior studies by Ghosh A *et al.*, and Emerek K *et al.*, where PICM rates varied from 12% and 50% respectively, depending on the cohort and follow-up time [12, 13]. Differences in patient groups, PICM definitions, and follow-up durations were most likely to explain the discrepancy in these percentages. In this research, the mean age of patients

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was 68.5 ± 9.2 years. Those developing PICM were substantially older (71.2 years) than those who did not (66.8 years). This age difference was consistent with previous research, which suggests that advanced age was a risk factor for the development of PICM [14]. Older age was likely associated with a higher load of comorbidities and cardiac structural alterations that predispose individuals to PICM. these findings revealed a substantial difference in LVEF between patients with and without PICM (49.8% vs 58.7%, p=0.001). This result supports prior research by Cho and colleagues who found lower LVEF as both a predictor and a consequence of PICM [15]. A lower baseline LVEF indicates a fragile myocardial that may not withstand the dys-synchronous pacing associated with right ventricular pacing. The study found that patients with PICM had considerably longer mean pQRSd (200.5 ms) than those without PICM (168.3 ms, $p < 0.001$). Previous study has also identified extended pQRSd as a crucial element in the development of PICM, with comparable cut-off values of roughly 190 ms described as predictive [16]. This study's ROC curve analysis for pQRSd produced an area of 0.78, suggesting strong predictive power, and the discovered cutoff value of 180ms offered 75.0% sensitivity and 72.5% specificity, which was similar with previous research [14]. The PICM group had a greater rate of right ventricular lead insertion at the apical location (82.8%) than the non-PICM group (66.1%), although the difference was not statistically significant ($p = 0.123$). This result was consistent with previous findings of Weintraub WS *et al.*, and another study by Samaras K *et al.*, that apical pacing was related with worse remodeling and PICM than non-apical pacing locations [17, 18]. The independent correlation between the development of PICM and longer pQRSd, older age, and poorer baseline LVEF was validated by the multivariable analysis. Garcia, J. M. *et al.*, and Lee, H. *et al.*, showed that gender was not found to be a significant predictor [19, 20].

CONCLUSIONS

This study highlights the importance of paced QRS duration in predicting pacing induced cardiomyopathy in patients with complete AV block. Mean paced QRS complex in PICM group was longer than non-PICM group (200.5 ms vs. 168.3 ms, $p<0.001$). ROC curve analysis revealed 180.0milliseconds cut off for predicting PICM. The sensitivity and specificity obtained were 75.0% and 72.5% respectively. Demographics like age, gender and clinical parameters could not perform significantly effect in multivariate analysis.

Authors Contribution

Conceptualization: HT, YA, IUH, WS
Methodology: RK, HT
Formal analysis: RK, HT, TM, SK
Writing, review and editing: TM, IUH, WS, KNK
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Analyzing the Role of Mechanical Bowel Preparation on Surgical Outcomes in Colorectal Surgery

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ABSTRACT

Despite improved postoperative recovery from the use of minimally invasive procedures and enhanced recovery after surgery protocols in recent decades, colectomy is still associated with morbidity. Surgical site infections range from trivial wound infections to potentially deadly colonic anastomotic leaks. **Objectives:** To compare the outcome results regarding postoperative complications of Mechanical Bowel Preparation and Non-Medical Bowel Preparation groups in elective colorectal surgery at a Tertiary Care Hospital in Peshawar, Pakistan. **Methods:** The research was a quasi-experimental study. In this study, 210 patients were included; they were divided into 2 groups: Mechanical Bowel Preparation Group and the Non-Mechanical Bowel Preparation Group. Data were collected through electronic health records. The data were analysed using SPSS software version 26.0. Descriptive statistics, such as the Chi-Square test, were applied to the results. **Results:** There was no statistically significant difference regarding the surgical outcomes and the demographics between the Mechanical Bowel Preparation and Mechanical Bowel Preparation groups. The escalation of the surgical site infection looked lower when the Mechanical Bowel Preparation was not in use i.e 20 (19.05%) in the Mechanical Bowel Preparation group and 14 (13.33%) in the Non-Mechanical Bowel Preparation group, but it did not seem to be, statistically significant; p-value=0.261014. The anastomotic leak rates and intra-abdominal collection rates do not differ significantly between the two groups; p>0.05. **Conclusions:** It was concluded that there was no statistical significance between the groups of mechanical bowel preparation and non-mechanical bowel preparation concerning surgical site infections, anastomotic leakages, and other colorectal surgery complications.

INTRODUCTION

Patients undergoing colorectal resections were all treated with preoperative Mechanical Bowel Preparation (MBP) and/or preoperative oral antibiosis for many years. However, several other studies carried out in the late 1990s and early 2000s questioned the role of MBP [1]. Although postoperative recovery has improved over the last two decades with the introduction of minimally invasive surgery and implementation of enhanced recovery after surgery (ERAS), protocols, colectomy remains associated with morbidity. The most common form of such morbidity relates to surgical site infection (SSI). This can take the form of minor infections of the wounds, but also life-threatening colonic anastomotic leaks [2, 3]. By using MBP, the dissection is facilitated, and endoscopic review is possible. It will also lessen the volume of faeces and, hence, bacteria colonization, therefore reducing the chance of postoperative complications such as anastomotic leak and wound infection [4]. Anastomotic leak refers to the projection of faeces through the drainage opening or the incision in the wound from the site of the anastomosis [5]. In mechanical bowel preparation, laxatives or enemas are used to try and empty the colon before surgery in an attempt to improve safety and visibility [4, 6]. The benefits of MBP must be weighed against its detrimental effects

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concerning patient distress and electrolyte imbalance [7]. Mechanical bowel preparation before elective colorectal surgery has taken on a new focus. This is a burning issue now, one that's controversial not because the data are bad, but because the research in it has generated a wide range of outcomes [8]. It is no surprise that there isn't concurrence among international rules in the Asia Pacific Region, Europe, and America. Australian guidelines are one of the recent international guidelines recommended against the routine use of MBP during colonic surgery [9]. Mechanical bowel preparation is studied in great detail by the medical fraternity to achieve a balance between advantages and disadvantages to increase patient satisfaction while undergoing colorectal surgery. The current study will evaluate MBP in colorectal surgery at large and particularly in a tertiary care centre in Peshawar, Pakistan. Since this practice is age-old, MBP has been used extensively in this geographical region with the belief that it improves surgical outcomes. There is an absolute need to determine its real impact on surgical outcomes.

This study aimed to elucidate the worth of MBP in the local setup based on the peculiar demographics of patients' surgical practices and postoperative complications. Such an appraisal is essential in informing clinical decisions that will lead to effective patient care with potential revision of existing practices based on the evidence obtained.

METHODS

This quasi-experimental study was carried out at the Northwest General Hospital and Research Centre (II), Peshawar, Pakistan, a tertiary healthcare setting. Spanning from January to December 2023, the research focused on a detailed exam of patients undergoing elective colorectal surgical procedures. The study's protocol acquired approval from the Institutional Review Board and Ethical Committee (IRB&EC) of the Northwest School of Medicine, Peshawar (No: IRB&EC/2023-SM/070). The study's goals and objectives were explained to the participants, they received assurances about their confidentiality, and their consent was obtained. A general of 210 patients were carefully selected and randomly assigned into two classes: The Mechanical Bowel Preparation (MBP) Group and the Non-Mechanical Bowel Preparation (Non-MBP) Group, following particular standards. Randomization turned into the usage of a random number desk, where sufferers assigned odd numbers were located in the MBP Group and those with even numbers in the Non-MBP Group. Patients in the preparation group received oral MBP, reconstituted with two packs of polyethene glycol in a two-litre water solution, starting 12 to 16 hours pre-surgery, as scheduled. Blood pressure, hydration status, pulse rate, and electrolytes were monitored before and after preparation, and deficits, if any, were corrected. The patients were allowed only liquid diets till midnight of the evening before surgery. The unprepared patients were allowed a residue-free diet until midnight of the day preceding the day of surgery. Premedication included a tablet of diazepam 10 mg orally the night before surgery to allay anxiety and for sound sleep, and a tablet of ranitidine 150 mg the previous night with sips of water. In the perioperative, all patients in both cohorts were administered intravenous broad-spectrum antibiotics before the commencement of the surgical procedure. This included a 1 g injection of ceftriaxone and an injection of metronidazole at 500 mg dosage. Postoperatively this course of antibiotics was continued for another 72 hrs. The operating surgeon was also kept blind about the status of preparation of the patients to avoid any bias. Inclusion criteria included both male patients and female patients aged 18 years and above waiting to undergo elective colorectal surgeries for conditions like colorectal cancer, diverticular disease, inflammatory bowel disease, and other non-malignant diseases. The exclusion criteria were cases with incomplete data, patients who had received a colonoscopy within one week of surgery, those who refused or would not provide informed consent, those patients with renal failure defined as a serum creatinine >3 mg/dL, and those patients with obstructive symptoms that required more urgent intervention, such as emergency surgery cases. Also excluded from the study were patients with pre-existing hypertension, coronary artery disease, diabetes, immunodeficiency, coagulopathy, asthma and chronic obstructive pulmonary disease. The outcomes following surgery were judged by clinical (vital signs, physical examination findings, and drain outputs) as well as radiological assessment (ultrasonography and CT scans where necessary). The specific complications that had to be looked for especially included anastomotic leaks, intra-abdominal septic collections, and wound infections. Wound infection was defined as the requirement to reopen the incision wound partially or completely for drainage of accumulated fluids. Anastomotic leak was presumed where there was observable faecal drainage from abdominal drains or when a leak was confirmed by imaging techniques (Computed Tomography (CT) Scan; with contrast, indicated by the presence of extraluminal contrast material or fluid collections near the anastomosis). An abdominal or pelvic collection was defined as the presence of a collection seen on ultrasonography or computed tomography scans along with elevated temperature or total leukocyte count. The duration of postoperative hospital stay in days was also recorded very carefully. Data were extracted from (EHRs) electronic health records that were recorded by health professionals, covering a wide range of variables, including demographic data, comorbidities, nutritional status before surgery, surgical variables, and postoperative outcomes. The main factors analyzed were age, sex, body mass index

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(BMI), American Society of Anaesthesiologists (ASA) classification (Patients were categorized as ASA I, II, or III), surgical procedure type, operative duration, intraoperative blood loss (by measuring suction canister volumes, estimating blood-soaked sponges, and accounting for irrigation fluids), hospital stay duration, occurrences of postoperative complications, and SSI cases. The SPSS software version 26.0 was used to carry out the statistical analysis, where descriptive statistics summarized the demographics and surgical outcomes among the patients, and the chi-square test with a significance value of 0.05 was used to identify the independent predictors of postoperative complications and SSI. This gives a complete evaluation of factors affecting surgical outcomes.

RESULTS

In the current study, 210 patients scheduled for elective colorectal surgery were included. The average age was 58.4 ± 12.3 years in the MBP group and 60.1 ± 11.8 years in the Non-MBP group. One hundred three patients were male and 107 were female. The average BMI was slightly higher in the Non-MBP group with 28.3 kg/m^2 than in the MBP group with 27.8 kg/m^2. Both groups had a similar distribution across American Society of Anesthesiologists (ASA) classifications, with the majority being ASA II reflecting mild systemic disease with minimal impact on daily activities, ensuring similar baseline health conditions between the groups. The Non-MBP group has a slightly higher proportion of ASA III patients, who have more severe systemic disease (10.50% vs. 9.50% in the MBP group). This slight difference indicates a potentially marginally higher risk of complications in the non-MBP group, but the overall ASA classification is comparable, supporting an equitable comparison of surgical outcomes. Colorectal cancer was the main indication for surgery in both groups (Table 1).

Table 1: Demographic Data and Clinical Characteristics of Patients

Characteristic	Mechanical Bowel Preparation (MBP) Group (n=105)	Non-Mechanical Bowel Preparation (Non-MBP) Group (n=105)
Age (years), Mean ± SD	58.4 ± 12.3	60.1 ± 11.8
Sex (Male/ Female), n (%)	52 (49.50) / 53 (50.50)	51 (48.60) / 54 (51.40)
BMI (kg/m^2) Mean ± SD	27.8 ± 4.1	28.3 ± 4.2
American Society of Anaesthesiologists (ASA) Classification, n (%)		
ASA I	38 (36.20)	35 (33.30)
ASA II	57 (54.30)	59 (56.20)
ASA III	10 (9.50)	11 (10.50)
Indication for Surgery, n (%)		
Colorectal Cancer	65 (61.90)	59 (56.19)
Diverticular Disease	20 (19.05)	26 (24.76)
Inflammatory Bowel Disease	17 (16.19)	14 (13.33)
Benign Colorectal Conditions	3 (2.86)	6 (5.71)

The operative time, blood loss, and length of stay in the hospital are practically the same in both groups of patients. There was, however, a trend suggesting a decrease in surgical site infections in the group of patients receiving mechanical bowel preparation, albeit it was not statistically significant (Table 2).

Table 2: Surgical and Post-Operative Outcomes of Patients

Surgical Outcome Measure Mean ± SD	Mechanical Bowel Preparation (MBP) Group (n=105)	Non-Mechanical Bowel Preparation (Non-MBP) Group (n=105)
Operative Time (minutes)	185.50 ± 45.7	198.20 ± 49.1
Blood Loss (mL)	225 ± 85	210 ± 92
Length of Hospital Stay (days)	7.6 ± 2.1	7.2 ± 2.3
Postoperative Complications, n (%)		
Surgical Site Infection	20 (19.0%)	14 (13.3%)
Anastomotic Leak	10 (9.5%)	8 (7.6%)
Intra-Abdominal Collections	10 (9.5%)	8 (7.6%)
Extra-Abdominal Septic Complications	25 (23.8%)	23 (21.9%)

(Extra-abdominal septic complications: Chest infection, UTI, Septicaemia)

The SSI incidence was indicated in 19.05% or 20 of the 105 patients who belong to the MBP group, while it was 13.33% or 14 of 105 participants constituting the Non-MBP group, which has χ^2=1.2634 with the p-value of 0.261014. From this evidence, indeed, both groups did not show any significant difference in the development of SSI (Table 3).

Table 3: Comparison of Surgical Site Infection Occurrence Based on MBP Status

Surgical Site Infection	MBP Group n (%)	Non-MBP Group n (%)	Total n (%)	χ^2-value	p-value
Yes	20 (19.05)	14 (13.33)	34 (16.19)	1.2634	0.261014
No	85 (80.95)	91 (86.67)	176 (83.81)		
Total	105 (100)	105 (100)	210 (100)		

Whereas 9.50% (10 out of 105) participants suffered from leakage in the MBP group, 7.60% (8 out of 105) participants did so in the Non-MBP group, with the chi-square value being χ^2=0.2431 and the p-value was 0.622008, therefore the difference is not significant (Table 4).

Table 4: Anastomotic Leakage Rates Comparison Between Patients with and without MBP

Anastomotic Leakage	MBP Group n (%)	Non-MBP Group n (%)	Total n (%)	χ^2-value	p-value
Yes	10 (9.50)	8 (7.60)	18 (8.57)	0.2431	0.622008
No	95 (90.50)	97 (92.40)	192 (91.43)		
Total	105 (100)	105 (100)	210 (100)		

A total of 9.50% which is, 10/105, in the MBP group

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developed intra-abdominal collections. At the same time, 7.60% which is, 8/105 in the Non-MBP group did. $\chi 2$=0.2431, p-value 0.622008. Thus, no significant difference is demonstrated in the incidence of intra-abdominal collections between the two groups (Table 5).

Table 5: Occurrence of Intra-Abdominal Collections About Medical Bowel Preparation (MBP) Status

Intra-Abdominal Collections	MBP Group n (%)	Non-MBP Group n (%)	Total n (%)	χ^2-value	p-value
Yes	10 (9.50)	8 (7.60)	18 (8.57)		
No	95 (90.50)	97 (92.40)	192 (91.43)	0.2431	0.622008
Total	105 (100)	105 (100)	210 (100)		

Extra-abdominal septic complications in the MBP group, 23.80% or 25 of 105. In the Non-MBP group, however, 21.90% or 23 of 105 were affected. X^2=0.108, p=0.742404 There is no significant difference between the two groups in the occurrence of extra-abdominal septic complications (Table 6).

Table 5: Comparing the incidence of Extra-Abdominal Septic Complications Concerning the Implementation or Absence of Medical Bowel Preparation (MBP)

Extra-Abdominal Septic Complications	MBP Group n (%)	Non-MBP Group n (%)	Total n (%)	χ^2-value	p-value
Yes	25 (23.80)	23 (21.90)	48 (22.86)		
No	80 (76.20)	82 (78.10)	162 (77.14)	0.108	0.742404
Total	105 (100)	105 (100)	210 (100)		

(Extra-abdominal septic complications: Chest infection, UTI, Septicaemia)

DISCUSSION

The results of the present study indicated that the surgical site infections were less in the Non-MBP group (13.33%) than in the MBP group (19.05%), although not statistically significant (p=0.261014). This may infer that Non-MBP has some advantage in decreasing the risk of postoperative infections [10]. This is in contrast with the traditional reasoning for MBP: decreasing infection rates through a clean surgical field. The lack of statistical significance in the results suggests that there is room for debate over how much those reductions would, in practical medical terms, be considered important [11]. On the other hand, as shown in the anastomotic leak and intra-abdominal collections rates, p=0.622008, between MBP and non-MBP, there is no statistically significant difference between them. This proves that the occurrence of these two complications isn't dependent upon the performance or not performance of MBP [12]. The findings are not statistically valid, invalidating the old, recommended perception that MBP reduces the number of anastomotic leaks importantly and, in general, complications associated with surgery [13]. Discussion from the study of Ozturk *et al.*, reported that there was no significant association of MBP with the intraoperative visibility of the surgical site or easy surgery. However, MBP was found to have no beneficial positive effect on surgically operating patients with high BMI and undergoing these surgeries. Based on the findings, the authors do not advocate for the routine use of MBP before laparoscopic gynaecological surgeries [14]. The results from this study add to the continued debate and understanding of the performance of MBP in colorectal surgery. MBA recently became disputable as to how effective and useful it is now [15]. Wang *et al.*, Questioned the same widely held dogmas, arguing that patients would recover their gastrointestinal function more quickly after gynecologic malignancies surgery without prior MBP [16]. Further support for the theory that MBP does not significantly reduce Extra-abdominal septic complications is provided by the fact that no statistically significant differences exist, p=0.742404 [17]. The potential risks of MBP treatment concern patient discomfort, electrolyte imbalances, and dehydration, and are the most disputed subjects. The key takeaway is that despite no statistically significant differences in anastomotic leaks and other complications throughout the study, the balance between the projected benefits and drawbacks of MBP remains a critical consideration [18]. The new guidelines emphasize a personalized approach to preoperative care, considering factors such as the patient's overall health, the specifics of the surgical procedure, and any individual risk factors that might increase the likelihood of complications; this approach is reflected in the second-wave MBP, which is gaining traction in colorectal surgery [19, 20]. This prospective study is well-designed, minimizing bias and enhancing the reliability of the results. The thorough inclusion criteria encompass a large patient population, ensuring robust data. Additionally, blinding the operating surgeon helps prevent any potential biases that could arise during the procedures. However, there are two major limitations of this study: it is single-canter, and, hence generalizability of results might suffer as a result, while the relatively short duration of follow-up might not capture long-term complications or outcomes. Also, the exclusion of patients with some comorbidities, like atrial fibrillation, limits the application of findings to wider clinical populations.

CONCLUSIONS

This study concluded that the Non-Mechanical Bowel Preparation group had lower surgical site infections as compared with the Mechanical Bowel Preparation group; however, it was not statistically significant. Also, there wasn't any statistical significance for anastomotic leakages as well as other postoperative complications in both categories.

Authors Contribution

Conceptualization: MU, AAS, NSA, AAK, AK
Methodology: MU, AAS, NS, AK, SZ
Formal analysis: MU, AAS, SZ

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

Conflicts of Interest

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Cardiovascular Risk Factors Associated with Mitral Annular Calcification in a Non-Rheumatic Population

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ABSTRACT

Mitral Annular Calcification (MAC), cardiovascular disease marker was common in non-rheumatic populations but was frequently disregarded in clinical evaluations. **Objective:** To MAC and to assess effect of these factors on cardiac function in non-rheumatic adult population. **Methods:** From September 2022 to August 2023, we conducted this cross-sectional study at Cardiac Center, Pakistan institute of medical sciences Islamabad that included 182 adults aged 50 years and older. We evaluated the patient's clinical history, demographic data and echocardiographic and laboratory results. The association between the presence of MAC and cardiovascular risk factors (age, hypertension, diabetes, dyslipidemia, smoking, obesity and chronic renal disease) was analyzed using logistic regression. Echocardiographic data were used to provide insight into cardiac function. **Results:** The prevalence of MAC was substantially correlated with hypertension (OR = 2.30), diabetes (OR = 2.00), dyslipidemia (OR = 1.75) and obesity (OR = 1.07). Also, smoking demonstrated a significant correlation with MAC. In comparison to those without MAC, individuals with MAC exhibited substantially lower ejection fractions, increased left atrial diameters and impaired diastolic function, as indicated by cardiac function assessments. **Conclusions:** In non-rheumatic population, MAC was significantly associated with conventional cardiovascular risk factors, particularly hypertension and diabetes.

INTRODUCTION

In the chronic degenerative condition, Mitral Annular Calcification (MAC), calcium deposits in the fibrous base of the mitral valve leaflets characterize the disorder, mostly impacting non-rheumatic elderly population [1]. Imaging tools such as echocardiography can accidentally detect MAC, but now we know it's more of a warning sign of cardiovascular disease and death than a benign aberration [2]. Knowing what causes MAC in people who don't have rheumatoid arthritis is important since it could lead to better understanding of cardiovascular disease in general and how to treat it [3]. A complicated interaction of mechanical stress, lipid infiltration, and chronic inflammation characterizes the pathogenesis of MAC, much to the processes seen in atherosclerosis [4, 5]. Because of these similarities, scientists are looking for shared cardiovascular risk factors that could put people at risk for MAC. For instance, calcium deposition could be hastened when the mechanical strain on the mitral valve annulus rises from hypertension [6]. In a similar line, the calcification process and dyslipidemia, a disorder marked by either low high density lipoprotein (HDL) or greater low density lipoprotein (LDL) cholesterol levels, have been linked to oxidative alteration of lipids, which sets off inflammatory pathways [7, 8]. Advanced glycation end-products, encouraged by diabetes mellitus, help to produce increased inflammation and fibrosis inside the

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cardiac structure, so aggravating hyperglycemia and hence raising the risk. One other important risk factor, smoking aggravates calcific deposition by causing both systemic inflammation and oxidative stress [9, 10]. Furthermore, very important is Chronic Kidney Disease (CKD); the disturbance of calcium and phosphate balance in CKD usually results in arterial and valvular calcifications, therefore acting as the major risk factor for MAC [11]. Age and gender also have important influence; women and older persons have higher frequency. Consistent with noted rises in cardiovascular and osteoporotic risks among older women, this demographic pattern suggested that post-menopausal hormonal changes may distress calcium metabolism [12, 13]. Furthermore, new studies on genetic predispositions and biomarkers linked with MAC, such inflammatory cytokines and genetic polymorphisms, are ongoing [14]. In general, it is essential to comprehend MAC risk factors for non-rheumatic population in order to not only foresee the likelihood of developing this condition but also to situate it within the broader context of cardiovascular risk management [15].

The aim of this study was to find and evaluate cardiovascular risk factors for mitral annular calcification in the population free of rheumatoid arthritis and to determine their respective roles of these elements in the initiation of this condition.

METHODS

This cross-sectional study, spanning September 2022 to August 2023, took place in Pakistan Institute of Medical Sciences in Islamabad. All patients provided informed consent prior to their participation in the study. Without rheumatoid arthritis, researchers set out to investigate for cardiovascular risk factors linked to mitral annular calcification. The minimal necessary sample size for this study 182 participants was found by using of power analysis with 95% CI and 80% power with expected prevalence rates for MAC were 10% [16]. This study selected adults (50 and above) without rheumatoid arthritis from stratified random selection process as the representative sample. Originally stratified based on gender and age, population was then controlled for probable confounds by other factors. Volunteers were selected at random to provide sufficient representation of every stratum. The study excluded those having history of rheumatic heart disease, past heart valve surgery or any notable valvular abnormalities. Structured interviews and medical record reviews were implemented to accumulate comprehensive demographic and clinical data. Age, sex, smoking status, body mass index (BMI), history of hypertension, diabetes, dyslipidemia and chronic kidney disease were among the variables that were collected. Echocardiographic examinations were conducted by the cardiologists who were unaware of the clinical data of the participants, utilizing echocardiography machine (GE Vivid E95). The presence and extent of MAC were evaluated and documented. The echocardiographers implemented a particular protocol to quantify the girth of mitral annulus and to identify calcification points. In order to evaluate the levels of fasting glucose, total cholesterol, HDL, LDL cholesterol and triglycerides, blood samples were obtained following 12-hour fast. Serum creatinine levels were assessed to assess renal function and CKD-EPI equation was employed to estimate GFR. Data analysis were conducted using 25.0 version of SPSS software Descriptive statistics—which comprised frequencies and percentages summed demographic and clinical traits of the study participants. Chi-square tests examined categorical variables; independent sample t-tests assessed continuous variables across groups. Presenting findings of the regression analysis as odds ratios with 95% CIs and p-value less than 0.05 established statistical significance. Approved by the Institutional Review Board, Reference No F.3-1/2023(ERRB)/Chairman of Pakistan Institute of Medical Sciences, Islamabad, this study was carried out in compliance with ethical standards described in Declaration of Helsinki. All individuals gave written informed permission. Mitral Annular Calcification (MAC) is the buildup of calcium deposits around the mitral valve, which can impair valve function and lead to conditions like mitral regurgitation or stenosis (Figure 1).

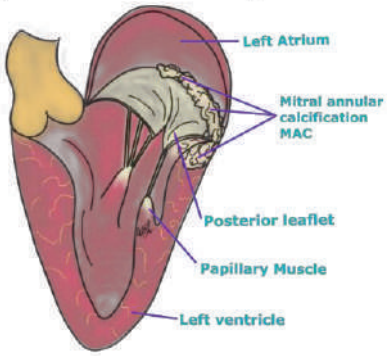

Figure 1: Mitral Annular Calcification (Source: https://www.mitraltherapies.com/mac)

RESULTS

The findings of our cross-sectional study, offered thorough examination of the cardiovascular risk factors, linked to mitral annular calcification in a non-rheumatic population. Demographic characteristics, clinical history, laboratory markers and echocardiographic parameters were evaluated in sample of 182 participants. In order to identify independent predictors of MAC and investigate potential interactions among various risk factors, multivariate logistic regression was implemented. The results demonstrated substantial correlations and provided unique perspective on the intricate relationship between systemic health conditions and development of MAC. They emphasized both modifiable and non-modifiable risk factors that contributed to the prevalence of MAC in the elderly population. The comparison between patients with

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and without MAC reveals several statistically significant differences. Patients with MAC were significantly older, with the mean age of 67.5 ± 8.9 years compared to 62.1 ± 10.2 years in those without MAC (p = 0.003). While the sex distribution was relatively balanced across both groups, with no significant difference in the proportion of males and females (p = 0.672), other health factors show notable differences. Patients with MAC have a higher mean BMI (29.4 ± 4.8 kg/m^2) compared to those without MAC (27.2 ± 5.5 kg/m^2), with a significant p-value of 0.015. Additionally, smoking status was more prevalent in MAC group (23.9%) compared to those without MAC (14.4%), with a p-value of 0.033. Hypertension was significantly more common in the MAC group (72.8% vs. 47.8%, p = 0.001), as was diabetes (51.1% vs. 27.8%, p = 0.001) and dyslipidemia (54.3% vs. 34.4%, p = 0.002). Chronic kidney disease also appears to be more prevalent in the MAC group (20.7% vs. 10%, p = 0.026). These findings suggested that patients with MAC tend to be older and have a higher prevalence of several cardiovascular risk factors compared to those without MAC (Table 1).

Table 1: Baseline Characteristics of Study Participants (n=364)

Variable	Total Mean ± SD / N (%)	With MAC Mean ± SD / N (%)	Without MAC Mean ± SD / N (%)	Chi-Square	p-value
Age (Years)	64.8 ± 9.7	67.5 ± 8.9	62.1 ± 10.2	8.76	0.003*
Male (%)	89 (48.9%)	46 (50%)	43 (47.8%)	0.18	0.672
Female (%)	93 (51.1%)	46 (50%)	47 (52.2%)		
Body Mass Index (Kg/m^2)	28.3 ± 5.2	29.4 ± 4.8	27.2 ± 5.5	5.87	0.015*
Smokers	35 (19.2%)	22 (23.9%)	13 (14.4%)	4.56	0.033*
Hypertension	110 (60.4%)	67 (72.8%)	43 (47.8%)	13.29	0.001*
Diabetes	72 (39.6%)	47 (51.1%)	25 (27.8%)	11.82	0.001*
Dyslipidemia	81 (44.5%)	50 (54.3%)	31 (34.4%)	9.56	0.002*
Chronic Kidney Disease	28 (15.4%)	19 (20.7%)	9 (10%)	4.98	0.026*

The analysis revealed that several factors were significantly associated with MAC. Each additional year of age increased the odds of having MAC by 6% (p<0.01). A higher BMI was also associated with increased odds of MAC, with each unit increase in BMI raising the odds by 8% (p<0.05). Hypertension more than doubled the odds of having MAC (OR: 2.29), while diabetes also significantly raised the odds by 2.03 (p<0.05). Dyslipidemia was found to increase the odds by 80% and chronic kidney disease was associated with the twofold increase in the odds of MAC (p<0.05). However, male sex and smoking status were not significantly associated with MAC, as indicated by their p-values of 0.432 and 0.116, respectively (Table 2).

Table 2: Logistic Regression Analysis of Risk Factors for Mitral Annular Calcification

Variables	Odds Ratio	95% CI	p-Value
Age (Per Year Increase)	1.06	1.03 - 1.09	0.001*
Male Sex	1.22	0.74 - 2.01	0.432
Body Mass Index	1.08	1.02 - 1.14	0.007*
Smoking Status	1.65	0.88 - 3.10	0.116
Hypertension	2.29	1.35 - 3.87	0.001*
Diabetes	2.03	1.23 - 3.36	0.006*
Dyslipidemia	1.80	1.09 - 2.96	0.022*
Chronic Kidney Disease	2.10	1.01 - 4.36	0.046*

The analysis of age groups revealed a significant association between age and presence of MAC (p<0.01), indicating that MAC was more common in older age groups. In the 50-59 years group, 26.1% of participants had MAC, while in the 60-69 years group, this percentage increased to 51.4%. Among participants aged 70-79 years, 75% were found to have MAC, making it the group with the highest prevalence. Interestingly, the prevalence dropped slightly to 53.8% in participants aged 80 years and older. Chi-Square test prevailed the likelihood of having MAC increases with age, particularly in those aged 70-79 years (Table 3). The analysis showed significant differences in laboratory markers between the MAC and non-MAC groups. Fasting glucose, total cholesterol, LDL cholesterol, and triglycerides were all significantly higher in the MAC group (p < 0.005), while HDL cholesterol was significantly lower in the MAC group. These results suggest that elevated glucose, cholesterol, and triglyceride levels, along with lower HDL, were associated with the presence of MAC (Table 3).

Table 3: Prevalence of Mitral Annular Calcification by Age Group

Age Groups	Total Participants	With MAC	MAC (%)	Chi-Square	p-value
50-59 Years	46	12	26.1	15.24	0.001*
60-69 Years	70	36	51.4		
70-79 Years	40	30	75.0		
80+ Years	26	14	53.8		

Chi-square test

Table 4 showed the correlation between Mitral Annular Calcification (MAC) and various laboratory markers, highlighting potential associations with cardiovascular risk factors (Table 4).

Table 4: Correlation of Mitral Annular Calcification with Laboratory Markers

Laboratory Marker	Mean Level in MAC Group	Mean Level in Non-MAC Group	T-Test	p-value
Fasting Glucose (mg/dL)	126.3	98.7	6.78	<0.001
Total Cholesterol (mg/dL)	205.5	187.9	3.92	0.001
LDL Cholesterol (mg/dL)	131.2	119.8	2.88	0.005
HDL Cholesterol (mg/dL)	40.2	45.1	-3.10	0.003
Triglycerides (mg/dL)	184.6	150.3	4.22	<0.001

The analysis of cardiac parameters showed significant differences between MAC and non-MAC groups. The ejection fraction was found to be significantly lower in MAC (58.9%) than non-MAC group (62.3%) (p<0.01). The left atrial diameter was significantly larger in the MAC group (38.4 mm) than in the non-MAC group (34.7 mm). Additionally, the mitral valve E/A ratio was significantly lower in the MAC group (0.9) compared to the non-MAC group (1.2) (p<0.01), indicating that patients with MAC had impaired diastolic function (Table 5).

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Table 5: Impact of Mitral Annular Calcification on Cardiac Function

Laboratory Marker	Mean Value in MAC Group	Mean Value in Non-MAC Group	T-Test	p-value
Ejection Fraction (%)	58.9	62.3	-3.55	0.001
Left Atrial Diameter (mm)	38.4	34.7	4.29	<0.001
Mitral Valve E/A Ratio	0.9	1.2	-5.62	<0.001

independent sample t test

Several noteworthy main and interaction effects linked to MAC were uncovered in the investigation. The odds increased by 5% for every year of age, indicating that age bear significant influence. An additional risk factor for MAC was a high BMI, with a 7% increase for every unit increase. The likelihood of MAC in hypertensive adults increased by 10% each year as they got older, according to an interaction effect and hypertension itself greatly raised the risks (OR: 2.30). The odds of MAC were twofold in people with diabetes and their risks were much higher for men due to an interaction effect ($p<0.05$). Dyslipidemia considerably raised the risks and an interaction with age revealed a 3% increase in odds per year ($p<0.05$), however smoking did not exhibit a significant interaction impact with BMI ($p=0.085$) (Table 6).

Table 6: Multivariate Analysis of Risk Factors and Interactions for Mitral Annular Calcification

Variables	Main Effects (Odds Ratio)	Interaction Effects	95% CI	p-value
Age (Per Year)	1.05	-	1.02 - 1.08	0.002
Male Sex	1.15	-	0.70 - 1.89	0.580
Body Mass Index	1.07	-	1.01 - 1.13	0.015
Hypertension	2.30	Age * Hypertension	1.50 - 3.50	<0.001
		1.10 per Year Increase	1.05 - 1.15	0.001
Diabetes	2.00	Diabetes * Sex	1.20 - 3.30	0.007
		1.50 if male	1.10 - 2.00	0.020
Smoking	1.60	Smoking * BMI	0.90 - 2.80	0.120
		1.05 per BMI unit	0.99 - 1.11	0.085
Dyslipidemia	1.75	Dyslipidemia * Age	1.00 - 2.50	0.048
		1.03 per year increase	1.00 - 1.06	0.040

independent sample t test

DISCUSSION

Current results were consistent with a research that established the correlation between presence of MAC and age, hypertension, diabetes, dyslipidemia, smoking and obesity, underscoring the multifactorial nature of this condition. In line with previous studies, our investigation confirmed that the incidence of MAC increases with age. Diel R *et al.*, in 2018 found that the likelihood of acquiring MAC rose somewhat with passing years. This finding was in line with other research suggesting that MAC was mostly an age-related degenerative process [17]. It was known that oxidative stress and systemic inflammation contribute to the calcification of cardiac tissues [18], which may explain the age-related increase. Hypertension was found to be a strong predictor of MAC in our investigation, outweighing other risk variables by a significant margin. This association was more pronounced in the elderly, suggesting that chronic hypertension may hasten mitral annulus calcification. These results were in line with those of Singh S *et al.*, in 2017, who discovered that persistently high blood pressure can cause structural changes in the heart, which could put people at risk for Myocardial Infarction (MAC) [19]. Additionally, MAC was substantially related with diabetes, especially in men. The presence of advanced glycation end-products, which play a role in calcification, was likely fostered by the chronic hyperglycemic environment [20, 21]. Differences in hormone levels, diabetes control strategies, and fat distribution patterns between the sexes were possible causes of the gender gap [22]. Dyslipidemia may have a role in atherosclerotic processes similar to those seen in valvular calcification, according to previous studies [23]. According to our findings, dyslipidemia was significantly linked to MAC. The interaction impact between age and dyslipidemia that our study found further emphasizes the significance of aggressive lipid control as part of preventive interventions for MAC in older populations. There was a correlation between smoking status, particularly being a current smoker, and the risk of MAC. Cigarette smoke induces inflammatory and oxidative activities, which may speed up the calcific processes within the mitral valve structure [24]. Curiously, it appears that there was a correlation between smoking and Body Mass Index (BMI), suggesting that smokers who were overweight may be at a higher risk. This highlights the need for specific initiatives to address this population. Obesity, as assessed by Body Mass Index (BMI), was another strong predictor of MAC. Chronic inflammation and elevated cardiac workload may play a role in the complex link between obesity and MAC [25]. In addition, there was a high correlation found between CKD and MAC, which was in line with the notion that CKD was linked to calcium-phosphate metabolism abnormalities, which in turn increase the risk of vascular and valvular calcifications [26]. From a clinical perspective, our findings about the impact of MAC on heart function were especially significant. Left atrial diameters were bigger, mitral valve E/A ratios were compromised, and ejection percentages were lowered in participants with MAC. Untreated cardiac dysfunction or heart failure could be a consequence of MAC, according to these echocardiographic findings. This lines up with what Kato Y *et al.*, in 2023 found, which was that valve calcification was associated with negative cardiac outcomes like reduced systolic and diastolic function [26]. Although our study shed light on the causes and effects of MAC, future studies should use longitudinal designs to better understand the correlations between risk variables and the progression of the disease.

CONCLUSIONS

Age, hypertension, diabetes, dyslipidemia, obesity and smoking were found to be significant predictors of mitral

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annular calcification in a non-rheumatic population, according to this study. It appears that hypertension and diabetes were major contributors to the development of MAC, since these two disorders showed the largest connections. Studies on diastolic function, left atrial diameter, and ejection fraction also showed that MAC significantly affects cardiac function. In light of these findings, it was clear that early intervention and control of cardiovascular risk factors were crucial for MAC prevention in order to lessen the likelihood of the condition's onset and the cardiac problems it might cause.

Authors Contribution

Conceptualization: MUR
Methodology: MF, AA[1], AR
Formal analysis: MI
Writing, review and editing: AA[2]

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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The New Spectrum of Plasmodium Vivax Malaria Severity: A Single-Center Experience

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ABSTRACT

Plasmodium vivax malaria, once considered a benign and self-limiting disease, has emerged as a significant public health concern, with increasing reports of severe and even fatal cases. **Objective:** To evaluate the clinical severity and complications associated with Plasmodium vivax malaria in patients in Peshawar. **Methods:** A descriptive cross-sectional study was conducted at Lady Reading Hospital, Peshawar, for about two months. A total of 160 patients diagnosed with Plasmodium vivax malaria were enrolled. Participants were divided into two groups based on platelet count. Laboratory tests, including complete blood count, liver function tests, and Renal Function Tests were performed. Data were analyzed using SPSS version 20.0 , An Independent sample t-test was used to assess the significant difference between the two groups with statistical significance set at $p<0.05$. **Results:** A total of 165 patients were included in the study. In the severe thrombocytopenia group (<100,000/µL), there were 23 cases of anemia, jaundice (n=25), acute renal failure (n=7), cerebral malaria (n=2), seizures (n=1) and hypoglycemia (n=1). In the less severe thrombocytopenia group (>100,000/µL), there were 14 cases of anemia, jaundice (n=17), and acute renal failure (n=2). The blood glucose level (p=0.37), systolic blood pressure (p=0.18) and pulse rate (p=0.21) revealed no significant differences between the two groups. **Conclusions:** It was concluded that severe thrombocytopenia in P. vivax malaria was associated with more severe clinical manifestations, with a few cases requiring transfusions. Patients with less severe thrombocytopenia had fewer complications.

INTRODUCTION

Malaria has impacted human populations since ancient times, causing significant morbidity and mortality in endemic regions. Malaria is caused by parasitic protozoa of the Plasmodium genus and is naturally transmitted to humans through the bite of female Anopheles mosquitoes carrying the parasites [1]. Despite advancements in medicine, malaria remains highly endemic in tropical, subtropical, and developing countries, and continues to be one of the leading causes of death globally, even though it is a treatable disease [2]. While Plasmodium falciparum is typically responsible for severe malaria cases, particularly in Africa, infections caused by Plasmodium vivax (P. vivax) have recently gained attention due to an increase in severe malaria cases linked to this species. P. vivax is widely distributed across Latin America, the Middle East, South Asia, Southeast Asia, and parts of Africa and Oceania [3]. The latest World Malaria Report documented 247 million malaria cases in 2021, a slight increase from 245 million in 2020. Malaria-related deaths decreased to 619,000 in 2021 compared to 625,000 in 2020 [4]. Malaria affects all blood components through mechanisms such as hemolysis, the host's inflammatory response, suppression of

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hematopoiesis, and sequestration of blood components in the spleen [5]. Although malaria is caused by five different Plasmodium species, P. falciparum is primarily responsible for severe complications, including acute renal failure, respiratory distress syndrome, cerebral malaria, and hematological and hemodynamic instability, occurring in about 1% of cases [1]. In 2018, Plasmodium spp. infections were estimated to result in 228 million malaria cases globally, with the African Region accounting for 213 million cases (93%), followed by the Southeast Asia Region (3.4%) and the Eastern Mediterranean Region (2.1%), leading to approximately 405,000 deaths. P. vivax infections were predominantly observed in the Southeast Asia Region, contributing to 53% of cases, with the majority (47%) occurring in India [6]. P. vivax causes an estimated 7 million cases annually [7]. Children younger than 5 years old made up 67% of the deaths, and the disease is still killing 1 child every 2 min [8]. Traditionally associated with mild tertian malaria, P. vivax has recently shown an increasing trend of life-threatening complications similar to those caused by P. falciparum [9]. Severe clinical manifestations of P. vivax malaria, such as acute kidney injury, splenic rupture, acute respiratory distress syndrome, and severe anemia, are being reported more frequently [1]. Several hypotheses have been proposed for the emergence of severe P. vivax cases, including platelet adherence to endothelial cells, triggered by tumor necrosis factor. Similar to P. falciparum, where platelets form bridges between red blood cells (RBCs) and endothelial cells, P. vivax-infected RBCs adhere to endothelial cells through mechanisms that resemble those seen in P. falciparum infections [10]. Given the high prevalence of Plasmodium vivax and the limited research on thrombocytopenia and its severe manifestations, this study was designed to explore the emerging trend of increased severity in Plasmodium vivax infections.

The study aims to explore the complications and clinical severity of Plasmodium Vivax malaria in Peshawar. By focusing on the complications associated with thrombocytopenia and other severe clinical outcomes, our study aims to fill a critical gap in the literature and provide valuable insights into the changing clinical profile of Plasmodium vivax malaria in the region. Understanding these trends is essential for improving clinical management and guiding public health strategies to address this evolving health concern.

METHODS

This descriptive longitudinal cross-sectional study was conducted at the Medical Teaching Institution (MTI), Lady Reading Hospital, Peshawar, from May to June 2024. Patients diagnosed with malaria via thick and thin smears, as well as immunochromatographic tests (ICT), were enrolled through non-probability random sampling. The sample size was calculated to be 160 using WHO's OpenEpi software, based on a prevalence rate of Plasmodium vivax in patients with severe malaria at 29.3%, with a 5% margin of error and a 95% confidence interval [1]. Informed written consent was obtained from all participants. Patients with mixed P. falciparum and P. vivax infections, as well as those with other conditions causing thrombocytopenia or severe systemic manifestations, such as sepsis, dengue fever, and chronic liver disease, were excluded. The participants were enrolled in the study after ethical approval from the Institutional Review Board of Lady Reading Hospital Peshawar (Ref. No: 131/LRH/MTI). Each patient underwent a thorough physical examination. Laboratory investigations, including complete blood count (CBC), were performed using Ruby cell-dyn Hematology analyzer, liver function tests (LFTs), blood glucose, and renal function tests were performed using Abbott Architect c4000, serum electrolytes were performed using EasyLyte Instrument, and chest X-rays, were performed. Selected patients also underwent specialized tests such as computed tomography (CT) brain scans and arterial blood gas (ABG) analysis. Thrombocytopenia was defined according to WHO criteria as a platelet count of fewer than 100,000 cells/mm^3, while anemia was defined as hemoglobin levels below 10 g/dL for women and below 12 g/dL for men. Respiratory distress was classified as an oxygen saturation of less than 94% on room air, acidotic breathing, or a respiratory rate greater than 32 breaths per minute [9]. Patients were divided into two groups based on their platelet count: Group A with a count of less than 100,000 cells/mm^3 and Group B with a count greater than 100,000 cells/mm3. Clinical history, examination findings, laboratory investigations, and complications were recorded for both groups via a performed proforma. The collected data were entered into Microsoft Excel 2020 and then imported into the Statistical Package for the Social Sciences (SPSS) version 20.0 for statistical analysis. Descriptive statistics, such as frequencies, and percentages were calculated for categorical variables such as gender, and clinical abnormalities while mean and standard deviation were used to summarize the quantitative variables such as Age, Blood glucose levels, Pulse rate and Systolic BP. For comparative analysis between the two groups (platelet count <100,000 cells/mm^3 and >100,000 cells/mm^3), an Independent sample t-test was used. Statistical significance was set at a p-value of less than 0.05. The results were presented in the form of tables and graphs, with a focus on highlighting significant clinical and laboratory differences between the two groups.

RESULTS

A total of 165 patients were enrolled in the study, patients

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were divided into two groups based on their platelet count: Group A (platelet count <100,000/µL) and Group B (platelet count >100,000/µL). Group A consisted of 67 patients (41.88%), while Group B had 83 patients (51.88%). In Group A, 39 patients (58.20%) were male, and 28 patients (41.80%) were female. Group B had 58 males (69.88%) and 25 females (30.12%). The average age of patients in Group A was 54 ± 8 years, while in Group B, it was 45 ± 6 years, indicating that patients in Group A were generally older. The mean blood glucose level was 111 ± 14 mg/dL in Group A and 116 ± 13 mg/dL in Group B, with no statistically significant difference (p=0.37) revealed by independent t-test. The average systolic blood pressure in Group A was 114 ± 11 mmHg, while in Group B, it was 118 ± 12 mmHg, also showing no significant difference (p=0.18). The average pulse rate in Group A was 100 ± 11 beats per minute, compared to 94 ± 9 beats per minute in Group B, with no significant difference between the groups (p=0.21) (Table 1).

Table 1: Demographic Characteristics of the Two Groups

Variable	Group A	Group B	p-value
Total Patients	67 (41.875%)	83 (51.875%)	–
Male	39 (58.20%)	58 (69.88%)	
Female	28 (41.80%)	25 (30.12%)	
Age (Years)	54 ± 8	45 ± 6	
Blood Glucose (gm⁄ dl)	111 ± 14	116 ± 13	0.37
BP Systolic (mmHg)	114 ± 11	118 ± 12	0.18
Pulse	100 ± 11	94 ± 9	0.21

Severe manifestations, including anemia, jaundice, renal failure, cerebral malaria, disseminated intravascular coagulation (DIC), and multi-organ failure, were more prevalent in Group-A (thrombocytopenia <100,000/µL) compared to Group B (>100,000/µL). In Group A, anemia (34.33%), jaundice (37.31%), and renal failure (10.45%) were more common, with additional cases of cerebral malaria, disseminated intravascular coagulation (DIC), and multi-organ failure, which was absent in Group-B. Group B exhibited fewer severe manifestations, with no cases of cerebral malaria, seizures, hypoglycemia, or multi-organ failure, suggesting a milder clinical course in patients with higher platelet counts (Table 2).

Table 2: Clinical Manifestations between the Two Groups

Variable	Group A	Group B
Anemia (HB<10 gm/dl)	23 (34.33%)	14 (16.86%)
Jaundice (Bilirubin>2 mg/dl)	25 (37.31%)	17 (20.48%)
Renal Failure (Creatinine>3mg/dl)	7 (10.45%)	2 (2.41%)
Cerebral Malaria (GCS<9/15)	2 (2.98%)	0 (0.00%)
Disseminated Intravascular Coagulation	1 (1.49%)	0 (0.00%)
Deranged Liver Enzymes (>3-fold elevation)	9 (13.43%)	3 (3.61%)
Leukocytosis (>11000/mm3)	3 (4.48%)	1 (1.20%)
Hypoglycemia	1 (1.49%)	0 (0.00%)
Multi-Organ Failure	3 (4.48%)	0 (0.00%)
Seizures	1 (1.49%)	0 (0.00%)

Some patients required various supportive interventions. In Group A, 4.47% (n=3) of patients needed blood transfusions, 1.49% (n=1) required platelet transfusions, 1.49% (n=1) ionotropic support, and mechanical ventilation in 1.49% (n=1). However, no patients in Group B required these interventions. Additionally, there were two deaths (2.98%) in Group A, while no deaths occurred in Group B. No patients in either group required hemodialysis. These findings highlight the more severe clinical course in Group A with lower platelet counts (Table 3).

Table 3: Supportive Care among the Participants of Both Groups

Supportive Care	Group A	Group B
Blood Transfusion	3 (4.47%)	0 (0.00%)
Platelet Transfusion	1 (1.49%)	0 (0.00%)
Ionotropic Support	1 (1.49%)	0 (0.00%)
Mechanical Ventilation	1 (1.49%)	0 (0.00%)
Hemodialysis	0 (0.00%)	0 (0.00%)
Deaths	2 (2.98%)	0 (0.00%)

DISCUSSION

Malaria presents with a wide range of signs and symptoms and its clinical course is dependent on several variables connected to both the host and the parasite. The illness spectrum advances from the stage of asymptomatic parasitemia to severe malaria, simple malaria, and in rare instances, fatal malaria [11]. With 305 million instances reported in the previous year, Pakistan too has a high illness burden. It is one of the malaria-endemic countries, meaning that practically everyone is susceptible to contracting the illness due to the extremely high risk of transmission. In Pakistan, P. vivax is more common than falciparum ranging from 71% to 80 % and other species of P. vivax are very rarely found [11]. Similar to falciparum, P. vivax was once believed to be a benign illness, but in recent years, more problematic and even fatal results have been reported. Notwithstanding minor variations, the ratio of falciparum malaria to P. vivax fell precipitously from 2.9:1 in 2010 to 0.6:1 in 2021, according to the 2022 World Malaria Report [12]. In our study, severe malarial manifestations were more common in Group A, which had more severe thrombocytopenia (<100,000/µL). This group included 23 patients (34.33%) with anemia, 25 patients (37.31%) with jaundice, 7 patients (10.45%) with acute renal failure, 2 patients (2.98%) with cerebral malaria, and 1 patient (1.49%) each with seizures and symptomatic hypoglycemia. Supportive treatments, such as blood transfusions and platelet transfusions, were required in three and one patient, respectively. Moreover, Group B (Platelets>100,000/µL), had 14 patients (16.86%) with anemia, 17 patients (20.48%) with jaundice, 2 patients (2.41%) with acute renal failure, 3 patients (3.61%) with deranged liver enzymes, and 1 patient (1.20%) with leukocytosis. No patients in this group exhibited cerebral malaria, seizures, or hypoglycemia, and none required supportive treatments. Our findings align with those of

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Humaira *et al.*, who conducted a study in the Sindh province of Pakistan, reporting severe manifestations in 54% of *P. vivax* patients, with jaundice present in 28% [13]. However, it should be noted that their study followed a major flood event. Zubairi *et al.*, reported an even higher severity rate, with severe *P. vivax* present in 79.9% of cases, a figure significantly higher than our findings [14]. Severe thrombocytopenia and neurological complications associated with *P. vivax* malaria were also noted in a study by Akhlaq *et al.*, conducted at Aga Khan University Hospital in Karachi [15]. In our study, severe anemia was the most common finding, observed in 34.33% of patients with severe thrombocytopenia and 16.86% of those with less severe thrombocytopenia. These results are comparable to those of Humaira *et al.*, who found anemia in 28% of *P. vivax* patients as the most frequent complication [13]. In New Delhi, an Indian study reported severe *P. vivax* malaria in 56% of patients [16]. Notably, jaundice (15%) and thrombocytopenia (65.5%) were also commonly observed as severe symptoms, with ARDS and renal impairment absent in that study. Doung MC and colleagues found severe *P. vivax* malaria in 10.5% of cases in Vietnam, which is lower than the severity observed in our study [17]. Similarly, in South Korea, Hyoung *et al.*, reported severe *P. vivax* in 21% of patients, a finding consistent with our results [18]. In Ethiopia, a study in children found severe *P. vivax* in 13.8% of cases [19]. This variation in severity across regions highlights the complex and evolving nature of *P. vivax* infections. Different studies from India have shown a wide range of severity, from 8.8% to 78.9% [20, 21]. We also reported two cases (2.98%) of cerebral malaria, which is unusual for *P. vivax*. These findings suggest that the clinical and biochemical spectrum of *P. vivax* has been changing, now resembling P. falciparum in its severity. This shift is concerning, particularly in countries like Pakistan and others in Asia, where *P. vivax* remains the predominant species. The mechanisms driving the increased severity of *P. vivax* infections are not fully understood, and there is a pressing need for further research into this alarming trend. A further large-scale study involving molecular and biochemical pathogenesis of the severity of the diseases is required to further elaborate on the factors leading to severity of the *P. vivax*. Every effort should be made to reduce the malaria burden. This was a single-center experience involving a small number of patients.

CONCLUSIONS

It was concluded that while uncomplicated *P. vivax* cases are still common, there is a notable rise in severe forms of the disease, characterized by complications such as anemia, jaundice, renal failure, and, in some cases, cerebral malaria. Patients with severe thrombocytopenia experienced more frequent and severe complications, including the need for blood and platelet transfusions, ionotropic support, and mechanical ventilation. Mortality was observed exclusively in this group. These findings emphasize the increasing severity of P. vivax malaria in endemic areas, highlighting the urgent need for preventive measures like mosquito control, repellents, and protective clothing to reduce transmission and severe disease outcomes.

Authors Contribution

Conceptualization: NI,
Methodology: NI, AAI, AG, SNM
Formal analysis: SNM
Writing review and editing: MH, FS, AG

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

Conflicts of Interest

The authors declare no conflict of interest.

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Attitudes Towards Learning Communication Skills Among University Nursing Students

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ABSTRACT

A major skill of nurses for achieving high-quality care is their ability to communicate effectively with patients, and this has been considered very valuable in the patient healing process. **Objectives:** To assess the learning attitudes of university nursing students towards communication skills and to find out the association of demographic characteristics of students with their attitude level. **Methods:** This cross-sectional analytical study design was conducted on 230 student nurses studying in a four-year Bachelor of Science in Nursing program. Permissions were obtained from the Ethical Review Committee and the Head of the Department for data collection. Data were collected via non-probability purposive sampling. Communication Skills Attitudes Scale was used to assess the attitude of university nursing students. Student's t-test and One-way analysis of variation were used to identify the differences in Positive Attitude Scores and Negative Attitude Scores between demographic variables. **Results:** Most of the study participants (77.4%) were male and 94% belonged to the age group 18-25 years. There was a significant difference in the Positive Attitude Score between gender and education of the students with p-values of 0.009 and 0.015 respectively. Furthermore, education level is the only variable that shows a significant association with a Negative Attitude Score with a p-value<0.0001. **Conclusions:** It was concluded that female students had more positive attitudes compared to their counterparts. Third-year students had a more positive attitude compared to other study years.

INTRODUCTION

A major skill of nurses for achieving high-quality care is their ability to communicate effectively with patients, and this has been considered very valuable in the patient healing process [1]. Communication helps to adhere to therapy, which increases the effectiveness of treatment in Primary Care [2]. The information and views of the nurses themselves may influence communication. The relationship between attitudes to communication was not explored in several studies [3]. Communication is the process of gathering and exchanging information among two or more individuals, vital for nurses in providing high quality safe, and secure medical care to patients. In addition, it is crucial that nurses can communicate their ideas and show them in practice [4]. The healthcare professional must be able to understand the roles and responsibilities of others, as well as their teamwork and communication skills in a complex environment. Inter-professional collaboration between all health and social care professionals, in particular doctors and nurses is essential to improving the safety and quality of treatment for patients. According to a literature review, communication failures between healthcare team members contribute significantly to the incidence of hospital side effects. By providing quality nursing care, patients feel satisfaction about the care they receive. Nurses demonstrated caring behaviours with competency

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and skills and also communicated effectively with patients. It helps in providing proper medical care and treatment by the nurses to their clients[5]. Nurses are not only providing specific tasks in routine but rather providing holistic care including all perspectives that are required by patients in their treatment. Furthermore, managing the queries of patient's families and decision-making in an emergency is also a requirement of nurses in their clinical areas. Effective communication is widely considered to be the basic principle of high-quality nursing care because healthcare workers play an integral part in relationships and interactions[6]. It is imperative to study the attitude of nursing students toward patient communication, to understand their beliefs and behavior. It is also a vital aspect of assessing the relevance of clinical care and healing. In addition, it is important to evaluate the attitude of students toward patient's communication, so they can better understand the behavior and be able to communicate effectively to achieve adequate communicative competence[7]. These skills are needed to provide safe nursing care, teamwork, healthcare and management for decision-making and problem-solving. The basic aspects of assessing patients' needs, enhancing the clinical skills of nurses and providing better care are part of communication skills. Research evidence showed the vital role of communication in many health outcomes relating to care, such as better use of quality healthcare services, improved client's attitude towards compliance, develop social backup or developments in therapeutic outcomes and prevention [8]. Limited research has been conducted in Pakistan related to identifying the attitude of student nurses at the university level towards communication. In addition, this study will not only identify nurses' attitudes about commutation but also its association with the demographic characteristics of the study participants.

The study aimed to assess the learning attitudes of university nursing students towards communication skills and to find out the association of demographic characteristics of students with their attitude level.

METHODS

This cross-sectional analytical study design was conducted on student nurses who were studying in Bachelor of Science in Nursing (BSN) programs. Data were collected via non-probability purposive sampling. This study was conducted at Jinnah College of Nursing, Sohail University from November 2022 to December 2022. Only students (of both genders) who were enrolled in the 4-year BSN program and had ages- between 18-35 years were part of this study. One-year diploma programs, Master's in nursing programs, and students who were enrolled in other programs (one-year speciality courses) were not part of this study. The sample size was calculated through OpenEpi software, by taking the 81.80% score for yes response of facial expression, with a confidence interval of 95% and a margin of error of 5%. The estimated sample was 229 participants[9], but the principal investigator took data from 230 participants for round figures. Data were collected from a self-administer demographic questionnaire form followed by 26-item questionnaires Communication Skills Attitudes Scale (CSAS). The scale was formerly designed by Rees et al., Positive Attitude Score (PAS) and Negative Attitude Score (NAS) have 13 items respectively: including items P4, P5, P7, P9, P10, P12, P 14, P16, P18, P21, P 23, P25 and the reversed score of items P22 for PAS and items N2, N3, N6, N8, N11, N13, N15, N17, N19, N20, N24, N26 and the reversed score of item N1 for NAS. The total score for both categories was from 13 minimums to 65 maximum scores. Permission was obtained from the Ethical Review Committee (ERC) (Protocol# 000245/22-22) of Sohail University and Permission from the Head of the Department (HOD) was also taken. Written informed consent was taken from all study participants. All scores were transferred into the statistical data analysis software R Studio. Descriptive statistics and inferential statistics were calculated for data analysis. Parametric tests, t-tests and one-way analysis of variation (ANOVA) were used to identify differences in PAS and NAS between demographic variables and the significance level was set as 5%.

RESULTS

This study was completed by 230 students. The mean value for PAS was 50.03 with an SD of 5.9 and the mean value for NAS was 45.40 with an SD of 7.16. The majority of the study students were male 77.4%. Out of 230 participants, 94% belong to the age group 18-25 years. This study shows that the most highlighted study year of the student is the 4th year (42.6%)(Table 1).

Table 1: Distribution of the Demographic Variables of the Study Participants(n=230)

Variables	Categories	Frequency (%)
Gender	Male	178 (77.4)
	Female	52 (22.6)
Age	18-25	216 (93.9)
	26-30	14 (6.1)
Marital Status	Single	206 (89.6)
	Married	24 (10.4)
Education	1st year	25 (10.9)
	2nd year	49 (21.3)
	3rd year	58 (25.2)
	4th year	98 (42.6)

Table 2 shows the comparison of positive attitudes towards learning communication skills between gender, age, marital status, and education. This table also shows similar comparisons for negative attitudes toward learning communication skills. Female students had more positive attitudes in comparison with their counterparts. There was

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no notable statistically significant difference in PAS between age groups and marital status of students. 3rd year students had a more positive attitude as compared to other study years. A significant difference was observed in PAS between gender and education of the students with probability values of 0.009 and 0.015 correspondingly. Table 2 exhibits that male students had slightly greater negative attitudes toward skills. However, 4th year students had a more negative attitude as compared to other study years. Education was the only variable where NAS significantly contrasted p-value <0.0001 ƒ*

Table 2: Comparisons of PAS and NAS Between Demographic Variables(n=230)

Variables	Categories	PAS			NAS		
		Mean	SD	p-value	Mean	SD	p-value
Gender	Male	49.8034	5.87733	0.009*	45.6910	7.04145	0.262 ₸
	Female	52.2500	5.91732		44.4231	7.55982	
Age	18-25	50.2870	5.87474	0.489	45.2546	7.00598	0.214 ₸
	26-30	51.4286	7.35594		47.7143	9.29374	
Marital Status	Single	50.3350	5.89083	0.873	45.2913	6.93613	0.574 ₸
	Married	50.5417	6.67884		46.3750	9.01116	
Education	1st year	50.9600	4.95379	0.015 ƒ*	39.7600	5.50212	<0.0001 ƒ*
	2nd year	48.5714	7.93725		42.8163	7.45451	
	3rd year	52.1724	4.58502		45.3276	7.71962	
	4th year	50.0204	5.52591		48.1837	5.63741	

*p-value < 0.05 considered as significant;
₸: P-value obtained from t-test
ƒ: p-value obtained using ANOVA

DISCUSSION

Attitude is one of the main elements which either increase or decrease the learning capabilities of the learner. Findings of a study conducted in Thailand by Kleebbua *et al.*, [9] evident that there is a relationship between attitude toward life on the learning outcome of students. This present study focuses on the assessment of the attitude of student nurses at the university level about learning communication skills and their association with various demographic characteristics. This study's findings highlighted that females have more positive attitudes towards communication skills compared to male participants. These findings were similar to the study conducted in Korea [10], which showed that female students had good scores compared with male students. Another study carried out by Jordon (2022) also evident that female students have better communication skills than male students [11]. This evidence shows that female students are more interested in learning communication in different parts of the world. This study evident that there is a significant difference in PAS between gender and the education of the students. These findings were opposed to a study conducted among medical students that showed no significant difference in gender with PAS [12]. Another study conducted on Pakistani medical students also highlighted that there was no significant association of gender with PAS [13]. In contrast, a study conducted in Slovenia evident that PAS is significantly associated with the education level of students [14]. The finding of this current study revealed that gender, age and marital status were the variables that showed no significant association with NAS. A study conducted on medical students in Pakistan brought similar findings, where gender was the variable that showed no association with NAS [15]. Another study conducted among medical students in Oranjested, Aruba showed similar findings [16]. The findings of this study evident that 3rd years students have a more positive attitude towards communication skills as compared to other classes. A study conducted in Iran in 2015 showed that students who were enrolled in higher semesters showed good communication skills [17]. In contrast, a study conducted on medical students in Pakistan (2018) showed that with the seniority of students, attitudes towards communication skills decline [14]. It was observed that the majority of the participants in this study were male. These findings were opposed by the studies conducted in Egypt [18] and Jordon, where the majority of the participants were female. This observation shows that enrollment of male nurses is higher in the field of nursing in our local context. Most of the participants in this study were in the age group of 18-25 years of age. A study conducted in the USA in 2021, showed that the mean age of the study participants was 22.77 years. Another study also had the mean age of the study participants in the same category. In contrast, a study conducted in Egypt showed the participant's ages were between 30-35 years [18]. This study finding revealed that more than ¾ of the participants were single. These findings were similar to a study conducted in Jordon [11] and USA 2019 [19] showed that most of the participants were unmarried. Most of the participants in this study were from the 4th year. Previous studies showed opposite findings, study conducted in 2023 showed most of the study participants were belong to 1st year in their study [18]. In addition, studies conducted in 2021 and Saudi Arabia in 2018 [20] showed that the highest number of participants were in their 3rd year of studies. One more study conducted in Slovakia (2017) showed that most of the participants were in the 2nd year of their study career [21].

CONCLUSIONS

It was concluded that female students had more positive attitudes as compared to their counterparts. Third-year students had a more positive attitude as compared to other study years. Male students had slightly greater negative attitudes toward learning communication skills.

Authors Contribution

Conceptualization: AA
Methodology: AA, SN

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

Conflicts of Interest

The authors declare no conflict of interest.

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Impact of Lifestyle and Demographic Factors on Diabetes-Associated Complications; A Cross-Sectional Study

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ABSTRACT

Globally, the prevalence of Diabetes Mellitus (DM), a leading cause of death and morbidity, is rising, adults with DM have the highest prevalence of chronic illness. This study pursuits to assess and evaluate the impact of life style and demographic factors that aggravates the diabetic complications. **Methods:** A cross-sectional study design was carried out in adult diabetic patients. The study was a nationally based study in Lahore, Pakistan, target population was Medical OPDs and Diabetic Care centers. Participants includes both gender with age 20 year to 70 years who's diagnosed with type 2 Diabetes Mellitus. The study variables include the demographic information, patient assessment, regarding the life style, face to face interview through self-structured questionnaire and anthropometric measurement were taken from every participant (weight, height). SPSS version 20.0 was used for data analysis. **Results:** The sample of this study consisted of 189 (51.1%) females and 181(48.9%) male respondents (N=370). The descriptive Statistics of gender of respondents giving standard deviation of 0.501 and variance of 0.251. As all the respondents are diabetic patients so while cross tabulating the gender with Obese scale 167 of the total population fall in normal weight scale, 110 are categorized as overweight and 33 as obese. The people with good knowledge about their life style impact on Diabetes complications were relatively less affected. **Conclusions:** The findings alert the medical practitioner informed the patients about the significance of impact of sedentary lifestyle on diabetic's complications. Regular screening for diabetic patient is necessary for the early detection of complications by skilled health professionals.

INTRODUCTION

Diabetes, a global health crisis, is projected to affect 552 million people by 2030, with a significant rise in developing nations like the Middle East [1]. It disrupts the body's metabolic system, leading to elevated blood sugar levels and requiring significant physical and mental resources to manage [2, 3]. Psychological implications, including grief stages, accompany the diagnosis, affecting both patients and their families. Studies reveal variations in depression prevalence among Diabetic patients based on factors like Diabetes type, demographics, and geographic location [4, 5]. All things considered; studies showed that 49% of Diabetes patients who were in really poor health were misdiagnosed at clinics that provided important medical care [6, 7]. Diabetes Mellitus is a widespread issue that has a serious financial impact on people and society structures. In 2012, Diabetes affected more than 9% of the population in America, with adults aged 20 and over having a prevalence rate of 12.3%. This amounted to 1.7 million

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people with Diabetes who had been diagnosed, with an additional 8 million suspected cases. In the US, Diabetes is the fifth most common cause of mortality. In 2010, Diabetes was listed as the primary cause of death in more than 69,000 death endorsements, a figure that is thought to be significantly underreported. Without a doubt, Diabetes Mellitus is a serious issue for overall health [8]. Insulin resistance references to cells' inability to successfully use endogenous insulin. The pancreas is so stressed as it tries to overcome this resistance by producing more insulin. Blood glucose levels rise because the pancreas can't meet the body's demands, and they continue to rise [9]. Diabetes patients are twice as likely to have mental health problems as the general population, and one in five of them reported feeling depressed, according to some current studies. One in five Americans over the age of 18 who have Diabetes, which affects 34.2 million people, is unaware of their condition [10, 11]. BDI-II, a tool for measuring depression, was used (BDI-II). 85 (61%) of the 140 patients with type II Diabetes were female, and 55 (39%) were male. The average age was 45.745 years. Eighty-four patients (60%) had severe depression when they first arrived. Women and widows had greater rates of depression than men. Diabetes patients have significant rates of depression, particularly women and widows. It is crucial to note that both for prevention and treatment of Diabetes, psychological care may be required [12]. In 2017, the Global Diabetes Alliance (IDF) estimated that Diabetes caused 4.0 million deaths worldwide, demonstrating the overall number of deaths directly or indirectly caused by the disease [13]. Even though T2DM and troublesome symptoms frequently coexist, 66% of individuals with the two illnesses are predicted to go untreated. This may result in a decline in glycemic control and an increase in Diabetes complications, which may make or break depression due to poor metabolic control and functional incapacity due to growing unforeseen problems [14]. Despite this, there is currently no evidence to support the previous finding that Diabetes and depression have a mutually reinforcing association. Complications and side effects of Diabetes. More specifically, it was shown that there is a strong correlation between sadness and Diabetes problems such retinopathy, nephropathy, neuropathy, and macro vascular issues. Patients with Diabetes who are also clinically depressed (as determined by self-report measures such as the BDI, CES-D, PHQ-9, or DSM-IV guidelines) are associated with a greater number of diabetic complications and side effects. More specifically, it was shown that there is a strong correlation between sadness and Diabetes problems such retinopathy, nephropathy, neuropathy, and macrovascular issues [15].

The objective of this study was to find the frequency of depression and quality of life in Diabetes Mellitus Type 2 and assess the knowledge can change the life, acceptance of disease and healthy lifestyle.

METHODS

A cross-sectional study design was carried out in adult diabetic patients. The study was a nationally based study in Lahore, Pakistan, the target population was Medical OPDs and Diabetic Care centers. Participants includes both gender with age 20 year to 70 year whose diagnosed with type 2 Diabetes Mellitus. The study was conducted between the time period of March 2021 to October 2021. The study variables include the demographic information, patient assessment, quality of life, face to face interview through self-structured questionnaire and anthropometric measurement were taken from every participant (weight, height). A self-structured questionnaire was used for the data collection. A face-to-face interview was conducted with patients and complete questionnaire and note their anthropometric measurements.

The necessary sample size to this still up in the air utilizing the accompanying equation:

$$N = \underline{2*[Z*\sqrt{2P^{-}(1-P^{-})} + Z\sqrt{P1(1-P1) + P2(1-P2)}]2}$$

Sample size (n) = [DEFF*NP (1-P)]/ [d2/ Z21-∂/2 *N-1) +P *(1-P)]

The sample size calculated through formula is 369 with 95% confidence level.

Organizational and ethical issues were discussed extensively with supervisors, and written consent was obtained from the university's Ethical Review Committee and hospital authorities. All of the participants provided written consent with an informed consent form. The identities of the participants were kept hidden throughout the study. The participants were informed that there are no potential drawbacks or dangers associated with the research methodology. Participants were informed that they could withdraw from the study at any time during the research. Participants remained anonymous, and all information and data collected remained private. After the data collection, data cleaning and data coding were performed. SPSS (Statistical package for the social sciences) version 20 was used for data analysis. Descriptive Statistics (Frequencies, %ages, means, median, standard deviation) were applied to summarize the data. Inferential statistics tests Chi-square test was applied. As inferential statistics to evaluate associations and difference between various independent and dependent variables. Chi-square tests was applied where association was desired b/w dependent and independent variable both being Categorical, this was used for almost all of the parameters. The level of significance set as $p<0.05$.

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RESULTS

A total of 370 diabetic patients consisted of 189 (51.1%) females and 181 (48.9%) male respondents. Half of the of the study participants were lie between the age of 30-49 years age group. The majority of the study participants were employed. About half of the study population had normal weight according to the obese scale defined by WHO (table 1).

Table 1: Demographic Characteristics of Study Participants

Variables	Category	Frequency (%)
Age	30 to 40	195 (52.7)
	40 to 50	158 (42.7)
	50 to 60	17 (4.6)
Occupation of Respondents	Unemployed	63 (17)
	Employed	206 (55.7)
	Retired	35 (9.5)
	Housewife/ Household	66 (17.8)
Obese Scale	Under Weight	60 (16.2)
	Normal Weight	167 (45.1)
	Over Weight	110 (29.7)
	Obese	33 (8.9)

Qualification was compared to the Affected lifestyle, people who were nil by qualification were 7% in number they did not bother rather they are affected or not. People who had middle qualification were 26% number are not affected by being diabetic. Additionally, masters were at highest number with 7% whose life were not affected thus it is claimed that not only the education could reduce the effect on life. The percentages of good literacy rate with middle and higher was 32.2% and 37.3% respectively with the percentage of 16.5% of illiterates. The employment details that about 206 of 370 sample size were employed with the percentage of 55.7% (figure 1).

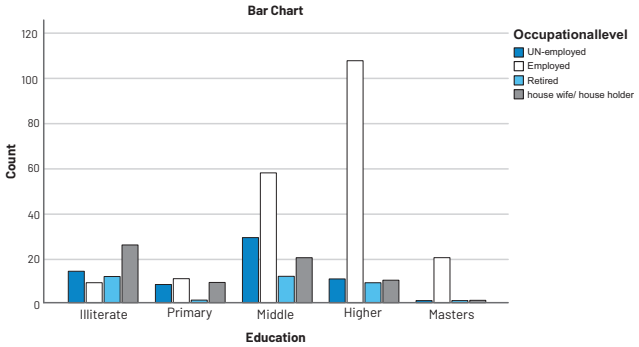

Figure 1: Education Status and Occupation Level

The lifestyle of the respondent was healthy with the percentage of 54.1% and 67.8% of the respondents with the history of Diabetes in family, 32.2% with no family history of Diabetes that means they developed later on. 84.1% of the population with this study indicated a close relationship with depression that effected their life rather they were studying or doing some kind of job. 61.4 % and 61.9% people are reported that their social life and physical life respectively is not affected by being diabetic, having enough knowledge, follow-up with diabetic centers, dietary management. Eating habits are the same with a little change that did not affect their lifestyle and responsible for anger or aggression being diabetic. Aggression/ depression being reported with standard deviation 0.470. The frequency of different health and psychological variables is given in table 2.

Table 2: Effect on Social and Physical life, Eating Habits, Aggression, Height, Weight, and Body Mass Index (BMI)

Variables	Mean ± SD
Weight (kg)	71.80 ± 10.136
Height (cm)	180.89 ± 68.718
BMI	23.4959 ± 5.19487
Obese Scale Record in Different Variables	2.31 ± .848
Effect on Social Life	0.848 ± 0.488
Effects on Physical Life	0.38 ± 0.486
Eating Habits	0.53 ± 0.50
Aggression	0.33 ± 0.47

The aggressive behavior towards the disease process related to its comorbidities and complication. Studies not only justify it with the knowledge of people of their disease process. Table 3 shows the frequency of the comorbidities associated with Diabetes. Hypertension had 30.8% association with Diabetes in the respondents. Different percentages were calculated that indicated that it varied from individual to individual. 13.2 % people got neuropathy complication of Diabetes.

Table 3: Prevalence of Comorbidities of Diabetes Mellitus Respondents

Variables	Frequency (%)
None	117 (31.6)
Hypertension	114 (30.8)
Congestive Heart Failure	32 (8.6)
Myocardial Infraction	3 (.8)
Peripheral Heart Disease	32 (8.6)
Hypertension; Peripheral Heart Disease	38 (10.3)
Hypertension; Congestive Heart Failure	19 (5.1)
Hypertension; Myocardial Infraction	15 (4.1)
Neuropathy	49 (13.2)
Total	370 (100.0)

This research also showed the relationship between the social/ physical life and associated complications with Diabetes that is retinopathy, nephropathy and neuropathy (table 4 and 5). The physical life and the social life were affected but not at that extent which was expected. People were well aware of their disease process. Upon asking about the cure of Diabetes and the motivational level to deal with Diabetes, the mean of 0.72 and 0.86 has been was shown respectively. The standard deviation of 0.804 and 0.351 respectively were revealed in this study.

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Table 4: Association of Social Life with Complications of Diabetes Mellitus

Complications of DM	x^2 value	df	p-value
Retinopathy	8.036	7	.329
Nephropathy	3.146	6	.790
Neuropathy	5.398	7	.612
None	12.803	5	.025

Table 5: Association of Physical Life with Complications of Diabetes Mellitus

Complications of DM	x^2 value	df	p-value
Retinopathy	6.359	7	.499
Nephropathy	9.582	6	.143
Neuropathy	1.404	7	.985
None	10.166	5	.071

DISCUSSION

With a percentage of between 54.1% and 67.8% of respondents reporting a family history of Diabetes, and 32.2% reporting no such history, the respondent's lifestyle is healthy. According to this report, 84.1% of the population experiences severe depression that has an impact on their lives whether they are at school or working. Nazar *et al.*, and their colleagues conducted research in Swat population incidence of DM is 56 % as compared to 37 % in rural areas. According to the findings of the Nazar *et al.*, older age groups had a greater incidence of Diabetes. The age groups 51-60, 61-70, and 71-80 years had the highest occurrence in both urban and rural areas [16]. Compared to another recent longitudinal research by Teigland and colleagues (47% and 38%), the prevalence rates of anxiety and depressive symptoms in this study (27.5% and 19.8%, respectively) are almost twice as low [17]. Our observed prevalence rate of depressive symptoms (19.8%) and the results of an earlier study on the epidemiology of depression in patients with type 2 Diabetes (19.1%) revealed results that are remarkably close [18]. Additionally, we discovered that more than 50% of Diabetes patients with anxiety symptoms also had depressive symptoms. This outcome was anticipated because anxiety-depression comorbidity has been discovered in a number of groups and symptoms of depression and anxiety frequently overlap [19, 20]. As diabetic patients, 37.6% of persons are regulating their diet. However, as shown by high HbA1c, FPG, and PPG, they had generally been permitted to deteriorate to glucose control levels considerably over target values. People with T2DM starting insulin have been found to have similar poor glycemic control across nations [21]. Due to their awareness, follow-up with diabetic centers, and nutritional management, 61.4% and 61.9% of persons say that having Diabetes has little impact on their social and physical lives, respectively. With a minor modification that had no impact on their way of life, their eating habits remained same, and Diabetes was to blame for any anger or aggressive behavior. With a standard deviation of 0.470 and a variance of 0.221, aggression and depression are reported. The comorbidities and complications of the illness process are related to its aggressive character. Studies support it in addition to people's understanding of their disease process. Notably, when compared to those who did not get DSME, 61.9% of interventions led to statistically significant and clinically meaningful improvements in A1C. Here, DSME participants experienced A1C reductions ranging from 0.1 to 2.50, while CG participants experienced changes between 1.5 and 1.7. A 0.9% decline in A1C was associated with a reduction of 25% in microvascular complications, 10% in Diabetes-related mortality, and 6% in all-cause mortality, according to Beckam *et al.*, and Lin *et al* [22, 23]. Associated comorbidities of Diabetes Mellitus included hypertension, which the respondents' 30.8% relationship with Diabetes. Different percentages are calculated to show how it varies from person to person. Diabetes-related neuropathy affected 13.2% of the population. 6.2% of people who were diagnosed with Diabetes Mellitus faced complications three or more. This study also demonstrates the link between comorbid conditions, such as retinopathy, nephropathy, and neuropathy, and the complications of Diabetes. It has been found that individuals with poor Diabetes control experience these problems. Although not to the amount that was anticipated, both the physical and social lives have been impacted. People were fully informed on how their illness worked.

CONCLUSIONS

A multitude of factors, such as diet—eating fruits and vegetables and avoiding fats and sweets—lack of exercise, inability to handle stress, or, to put it another way, improper life style management are among the risk factors for Diabetes complications. People will need to be trained and educated about self-care in order to prevent diabetic complications.

Authors Contribution

Conceptualization: MMA, SN[1], MSN, UH, SN[2], MJ, M
Methodology: MMA, SN[1], MSN, UH, SN[2], MJ, M
Formal analysis: MMA, SN[1], MSN, UH, SN[2], MJ, M
Writing-review and editing: MMA, SN[1], MSN, UH, SN[2], MJ,M

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

Conflicts of Interest

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Frequency of Dry Socket among Patients Undergoing Dental Extractions Presenting to A Teaching Hospital, Rawalpindi

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ABSTRACT

A dry socket, a painful post-extraction complication, occurs when the blood clot at the extraction site is dislodged or fails to form. Understanding its prevalence is crucial for improving outcomes in dental practices. **Objective:** To determine the frequency of dry sockets in patients undergoing dental extraction. **Methods:** A cross-sectional descriptive study was carried out and two customized questionnaires were filled out over three months. One questionnaire was for patients undergoing extractions and the other was filled for patients returning with dry sockets. The study included Pakistani individuals with permanent dentition while excluding non-Pakistani individuals, children with deciduous/mixed dentition, and severely immunocompromised patients. Chi-square and Fischer's exact tests were used to compare the frequency of dry sockets between gender and age groups. p-value of less than or equal to 0.05 was considered statistically significant. **Results:** Out of the 188 patients, 85 (45.2%) were males and 103 (54.8%) were females. Medically compromised patients comprised 24.5% of the study population. The overall incidence of dry sockets was 9.0%, with a slightly higher occurrence in females (9.7%), though the difference was not statistically significant (p-value=0.802). Smokers demonstrated a higher incidence of dry sockets (23.1%), which was also not statistically significant (p-value=0.099). Medically compromised patients experienced dry sockets at 17.4%, compared to 6.3% in healthy patients, suggesting a trend that did not reach statistical significance (p-value=0.363). **Conclusions:** It was concluded that identifying high-risk groups and promoting effective prevention and management techniques can reduce the incidence of dry sockets, leading to better outcomes and overall oral health.

INTRODUCTION

Dry socket, also known as alveolar osteitis, is a common post-extraction complication. It is caused due to acute inflammation of the alveolar bone of the extracted tooth and is characterized by severe pain, a dislodged clot leaving the socket empty [1]. The bone is exposed to the fluids in the oral cavity and bacteria. It takes about fourteen days for the connective tissue to cover the denuded bone and restore it to normal condition in which the bone is not exposed anymore. Till the time the healing process occurs, the exposed bone irritates resulting in pain [2]. As per recent previous literature, the ratio of occurrence of dry sockets has increased by 10% in physically fit individuals and up to 25% in patients with compromised immune systems. The occurrence of dry sockets has also been very commonly linked with the extraction of 3rd molars [3]. Recent advancements in the pathophysiology of dry sockets have paved the way for the development of several preventive approaches. For instance, the use of local antimicrobial agents like chlorhexidine has emerged as a promising strategy for decreasing the occurrence of dry sockets [4]. It works by lowering the growth of bacteria at the extraction, which helps in reducing the likelihood of infection and the subsequent breakdown of the blood clot [5]. These discoveries emphasize the critical role of

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integrating scientifically supported methods into everyday dental practices to improve patient results. Another emerging area of focus involves investigating how systemic health conditions contribute to the onset of dry sockets. Systemic conditions like diabetes and immunosuppression have been associated with higher chances of postoperative complications like dry socket [6]. Recognizing the connection between overall health and oral health is essential for crafting comprehensive treatment plans for individuals undergoing dental extractions. This holistic approach enables the customization of preventive and treatment measures to suit each patient's specific requirements, ultimately enhancing the quality of care provided. The risk factors associated with dry sockets include smoking (12%) as compared to non-smokers ratio (4%), surgical extractions (15%) as compared to non-surgical extractions (1.7%), single case extractions (13%) as compared to multiple extractions (5%). Risk factors for developing dry sockets include the use of oral contraceptives and also use of immediate irrigation of the socket with normal saline post-operatively. Post-operative socket bleeding is crucial as it promotes the formation of a blood clot, facilitating uncomplicated healing of the socket [7].

This study aims to determine the frequency of dry sockets in patients undergoing dental extraction in a teaching hospital in Rawalpindi

METHODS

A cross-sectional descriptive study was carried out at Margalla Dental Hospital, Rawalpindi from April 2023 to July 2023 for 3 months. The approval was taken from the ethical review committee (ref no. DN/193/23). The Inclusion criteria was the Pakistani population who have permanent dentition and the exclusion criteria were the Non-Pakistani population, children who have deciduous/mixed dentition, and extremely immunocompromised patients. The sample size taken for this study was 188 and the sampling technique used for this study was Non-probability convenience sampling. The sample size was calculated using Epi Info software, based on an expected dry socket prevalence of 5%, a 95% confidence interval, and a 5% margin of error. Approval of this study was taken from the ethical review committee of Margalla Dental College and informed consent of patients visiting the Oral Surgery Department, all the patients satisfying inclusion criteria were examined for the presence of Dry Sockets. A periapical radiograph was taken after the patient's consent only if conditions like a root left behind post-extraction, any chance of periapical lesion, a soft tissue lesion, food stagnation or any clinical symptoms associated with these conditions were examined. Two questionnaires were filled out over three months (Figure 1). One was for patients undergoing extraction of permanent teeth at the Oral and Maxilo-Facial Department, while the other was for those diagnosed with dry sockets during a postoperative visit within the study period. Data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0. The normal distribution of quantitative variables was checked using the Shapiro-Wilk test. Mean and standard deviation are calculated for quantitative variables while frequencies and percentages are given for qualitative variables. Chi-square tests were used to find the association between dry sockets and gender. Fisher's exact test was applied for smaller sample sizes. A p-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

This study included a total of 188 patients undergoing dental extractions, of which 85 (45.2%) were males and 103 (54.8%) were females. Among the participants, 46 (24.5%) had various medical ailments, classifying them as medically compromised, and 13 (6.9%) were identified as smokers (Table 1).

Table 1: Demographic and Clinical Characteristics

Category	Total Patients	Percentage
Total Patients	188	100%
Male	85	45.2%
Female	103	54.8%
Medically Compromised	46	24.5%
Smokers	13	6.9%

Dry socket was observed in 17 (9.0%) of the patients. The distribution of dry socket cases was slightly higher in females (10 out of 103, 9.7%) compared to males (7 out of 85, 8.2%), with a non-significant p-value of 0.802. Presenting complaints of the patients with dry sockets were pain and discomfort on the extracted side along with halitosis. Dry sockets were more frequent among smokers, affecting 3 out of 13 (23.1%), compared to non-smokers, where 14 out of 175 (8.0%) developed the condition. This difference, however, did not reach statistical significance (p-value=0.099). Of the 17 dry socket cases, 9 (52.9%) occurred in the maxillary region and 8 (47.1%) in the mandibular region. Notably, 16 cases were in the posterior region, with an equal split of 8 cases each in the maxillary and mandibular arches. Only 1 case was reported in the anterior region (Table 2).

Table 2: Incidence of Dry Socket by Subgroup and Statistical Significance

Subgroup	Total in Subgroup	Dry Socket Cases	Subgroup Percentage (%)	p-value (Test)
Smokers	13	3	23.1	0.099 (Fisher's exact)
Non-Smokers	175	14	8.0	
Healthy Patients	142	9	6.3	0.363 (Chi-Square)
Medically Compromised	46	8	17.64	

While not the focus of the current study, it is noteworthy to mention the incidence of dry sockets among medically

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compromised patients was 17.6% compared to the overall rate. However, this finding, along with the data for smokers, is provided for informational purposes and was not subjected to comparative analysis with healthy patients. Specifically, dry socket cases were slightly more prevalent in the maxillary region (52.9%) compared to the mandibular region (47.1%), with no significant gender-based variation. The p-values for all categories (maxillary, mandibular, anterior, and posterior teeth) were above 0.05, confirming the lack of statistically significant differences in dry socket occurrence by gender or tooth region. The distribution of dry socket cases showed no significant difference between males and females across maxillary, mandibular, anterior, and posterior teeth regions by the non-significant chi-square values ($p>0.05$) (Table 3).

Table 3: Incidence of Dry Socket by Gender and Location

Location	-	Male	Female	p-value
Incidence of Dry socket in maxillary teeth	Yes	3	6	0.733
	No	82	87	
Incidence of Dry socket in mandibular teeth	Yes	4	4	0.722
	No	81	96	

Two questionnaires were filled out over three months (Figure 1).

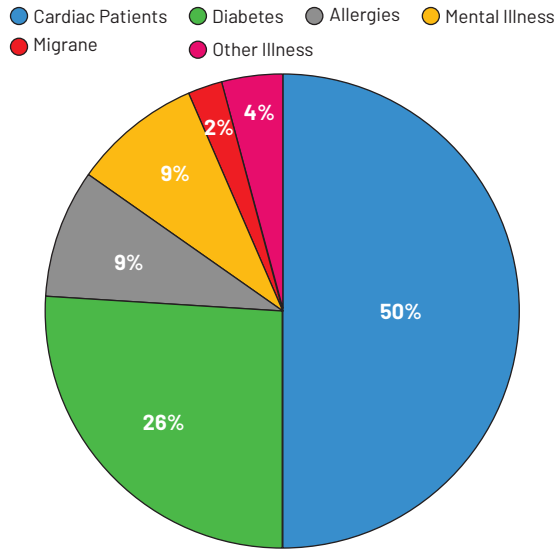

Figure 1: Distribution of Medically Compromised Patients

DISCUSSION

Alveolar osteitis is characterized by a disruption in the healing process at the extraction site before wound establishment, leading to mild to severe pain in the extraction region typically starting on the 2nd or 3rd day post-surgery, often accompanied by a foul smell and coloured discharge [8]. The occurrence of alveolar osteitis (dry socket) following a tooth extraction procedure has long been a concern for patients and dentists equally, particularly after mandibular third molar extraction [9]. Despite the use of common postoperative analgesics, a substantial proportion of patients, approximately 45%, require multiple postoperative visits before symptom resolution [10]. Historically, the frequency of alveolar osteitis has varied between 5% and 30% [11]. However, the current study recorded an incidence of 9% for all extractions conducted during the study period, which is lower than values reported in Iran, where the frequency of alveolar osteitis formation after surgical removal of mandibular impacted teeth was 23.45% [12]. Tobacco smoking has been extensively associated with various adverse effects, including negative outcomes in surgery [13]. Although smoking's adverse effects are well-documented in various surgical procedures, recent data on its influence on exodontia are scarce [14]. Alveolar osteitis developed in 23.1% of smokers, with no significant relationship identified. Similarly, a study in Bangladesh reported an insignificant relationship between smoking and the development of alveolar osteitis [15]. Localized tissue ischemia, possibly mediated by nicotine-induced vasoconstriction and platelet aggregation, may contribute to delayed wound healing and the formation of thrombotic microvascular occlusion [16]. Contrary to previous reports showing a strong female preponderance in alveolar osteitis occurrence, the current study did not find a significant gender association with the complication. However, a study in India in 2019 observed that females on oral contraceptive drugs had approximately twice the incidence of alveolar osteitis compared to females not on oral contraceptives and males [17]. A Study in Jordan study found that dry sockets occurred more frequently in mandibular extractions compared to maxillary extractions [18]. These findings are consistent with general observations that lower jaw extractions are more prone to developing dry sockets, likely due to factors such as denser bone and poorer vascular supply in the mandible. This aligns with general observations that lower jaw extractions are more prone to developing dry sockets due to factors such as denser bone and poorer vascular supply in the mandible. In the current study, the incidence was equal in both maxillary and mandibular teeth which aligns with the study done by Abdullah who also reported equal incidence between maxillary and mandibular teeth [19]. A local study on impacted 3rd molars in Kohat reported a 20.7% incidence of dry sockets, which is higher/lower than the findings presented, likely due to the focus on impacted 3rd molars in a local study done on impacted 3rd molar in Kohat found that 20.7% reported dry sockets which is higher as compared to this study considering cu t study was done on impacted 3rd molars [20]. In another study in Swat, khan found only 4% of patients complained about dry sockets. The incidence was high among males aged 20-30 and smokers had more prevalence [21]. A study in Karachi found a 3.3% incidence of dry sockets among patients visiting for extraction [22].

CONCLUSIONS

It was concluded that dry socket remains a common

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complication following tooth extractions, particularly among individuals with certain risk factors such as smoking, and complex surgical procedures. The data underscores the need for preventive strategies, including patient education on post-operative care and the implementation of best practices by dental professionals. By identifying high-risk groups and promoting effective prevention and management techniques, the incidence of dry sockets can be reduced, leading to better patient outcomes and overall oral health. Future research should continue to explore innovative approaches to prevention and treatment, aiming to minimize the occurrence and impact of this painful condition.

Authors Contribution

Conceptualization: NBK
Methodology: NBK, AA, MA
Formal analysis: KN
Writing review and editing: NBK, AA, AY, MA

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

Conflicts of Interest

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Electric Pulp Test Threshold Responses in Healthy Mature Permanent Teeth

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ABSTRACT

Electric pulp testers assess only the neural component of pulp sensibility in dental practice, while vascular status is evaluated with laser Doppler flowmeters and pulp oximeters, which are more reliable for determining vitality in traumatic teeth. **Objective:** To determine the accuracy of the electric pulp test in healthy mature permanent teeth. **Methods:** This cross-sectional study was conducted at the Liaquat University of Medical and Health Sciences Jamshoro by consecutive sampling on 220 participants aged 18-35, who had healthy, mature permanent central incisors, canines, first premolars, and first molars, with no history of cardiac pacemakers and metallic restorations. Teeth were isolated, dried, and tested with a COXO C-Pulse electric pulp tester using toothpaste as a conducting medium. Threshold responses were recorded at increasing currents, with each tooth tested twice to determine the mean value. Accuracy was assessed using additional metrics post-therapy. Chi-square tests were employed to compare accuracy across gender and age groups, with significance set at $p<0.05$. **Results:** The mean age of the patients was 25.55 ± 5.41 years. 132 (60%) subjects were female, 88 (40%) subjects were male in this study. Accuracy of the electric pulp test in healthy mature permanent teeth was detected in 181 (82.3%) subjects in this study. **Conclusions:** It was concluded that the electric pulp tester method seems to be a reliable way to evaluate how sensitive the live nerve tissue inside a tooth is for healthy permanent teeth that have fully formed.

INTRODUCTION

Accuracy refers to the degree to which the result of a measurement or test conforms to the true or accepted value. In the context of diagnostic tests like electric pulp testers (EPT), accuracy indicates how well the test correctly identifies or excludes the presence of a condition (e.g., pulp vitality) compared to a standard or reference method [1]. The health status of dental pulp cannot be determined only by clinical and radiological examination. To make a final diagnosis of pulp sensibility, a reliable diagnostic test is required along with a complete history of the patient [2]. An electric pulp test is used to determine the sensibility of the tooth. The tests that are used to evaluate the sensibility of pulp are all subjective and include heat tests, cold tests and EPT [3]. EPT are widely used devices in dental practice for assessing pulp sensibility [4]. An electric pulp tester assesses only the neural component of pulp while vascular status is assessed by a laser Doppler flowmeter and pulp oximeter which is reliable for the determination of vitality in traumatic teeth [5]. The sensibility of the pulp is determined by provoking sensory nerves by the movement of dentinal fluid or by generating action potential with electric current

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conduction [6]. The mechanism of action of EPT is to generate the electrical current to overcome enamel and dentine resistance that causes the excitation of myelinated A (Beta and Delta) fibers near the pulp-dentinal junction [7]. Sensibility test findings only show whether a pulp is likely to be vital or non-vital, not the health of the pulp. Simovic *et al.* studied the mean thresholds and reproducibility of EPT in maxillary and mandibular teeth which turned out to be statistically significant [8]. Eugene *et al.*, Studied the accuracy reliability and repeatability of the EPT with an accuracy of 97% [9].

This study aimed to determine the range of threshold responses in healthy dental pulps to evaluate the reproducibility and accuracy of the EPT. Thereby, the obtained data would be helpful for the dental community as well as for patients to adopt a better diagnostic tool and treatment planning in our local settings by identifying the pulpal status of teeth with accurate EPT. Gender differences may influence the sensory response thresholds, potentially affecting test results. Age is another crucial factor, as pulp sensitivity and response can vary with age due to physiological changes in the dental pulp and surrounding tissues.

METHODS

A cross-sectional study using non-probability consecutive sampling was conducted in the Outpatient Operative Dentistry Department of Liaquat University of Medical and Health Sciences Jamshoro, from January 2020 to December 2020. A sample size calculator (Sample Size Determination in Health Studies, WHO) was used to determine the sample size. By taking statistics of electric pulp test as 97% margin of error 2% and 95% confidence interval [9]. The calculated sample size came out as 220. Patients aged 18 to 35 years with healthy, mature permanent central incisors, canines, first premolars, and first molars in both arches and no pathology of pulpal disease, with no history of cardiac pacemakers or metallic restorations were included. The study was carried out after approval from the research and evaluation unit of the College of Physicians and Surgeons Pakistan (CPSP) (CPSP/REU/DSG-2017-166-2279). After reviewing the patient's complete history, patients satisfying the inclusion criteria were included in the study. Informed consent was taken from patients before including them in the research process. The procedure was explained to the patient before carrying out the test. Non-probability convenient sampling technique was applied. Each tooth to be tested was isolated using cotton rolls and dried with compressed air for 5 seconds, and electric pulp tester was applied according to the manufacturer's instructions and then threshold response was recorded using (COXO C-PULSE) electric pulp tester with a scale from 0 to 80 IA. The conducting medium was toothpaste, and the electrode tip was positioned on the enamel in the center of the buccal surface of the teeth. When a stimulus was administered to a tooth, the patients were asked to signal by raising their right hand whether they experienced any pain or feeling. The pulp tester was then used to record the reading for each tooth that corresponded to this threshold limit. The current increased at a rate of 1 uA s-1. Measurements were taken twice in a row for every canine, incisor, premolar and molar in the first and second appointments. Measurements were recorded twice consecutively for each canine, incisor, molar, and premolar. The mean value of these repeated measurements was then calculated. Data were analyzed by using SPSS version 24.0. Descriptive statistics were calculated for quantitative and qualitative variables. Mean and standard deviation were computed for continuous variables like age. Accuracy was compared concerning age, and gender using the chi-test at p-value≤0.05 as a significant level.

RESULTS

This research had 220 participants in total who met the inclusion criteria. The patient's average age was 25.55 ± 5.41 years. The age-related descriptive characteristics of the patient are shown in table 1.

Table 1: Descriptive Statistics of Patient's Age

Age (Years) n=220	
Range	16-35
Mean ± SD	25.55 ± 5.409

Distribution of gender was stated, where 132 (60%) subjects were female, 88 (40%) subjects were male in this study and this is shown in figure 1.

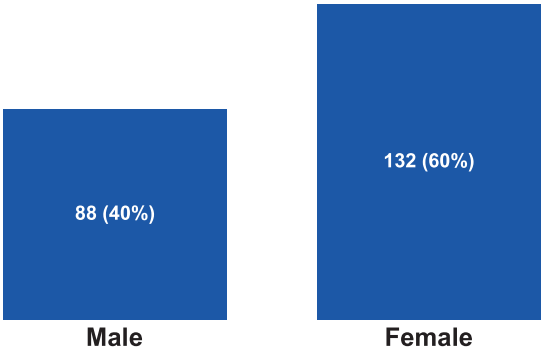

Figure 1: Distribution of Gender among study participants

Accuracy of EPT was detected in 181 (82.3%) subjects in this study. The distribution of outcome which is the accuracy of the Electric Pulp Test (EPT) in healthy mature permanent teeth was stated in figure 2.

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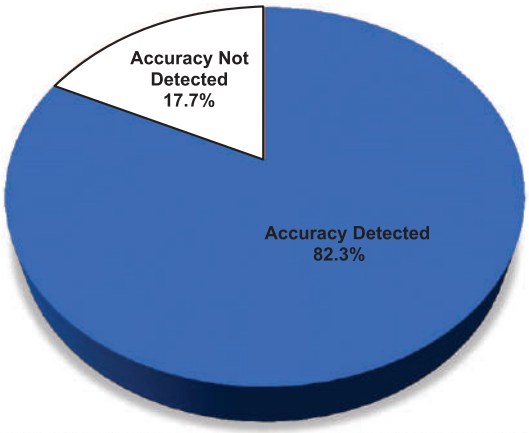

Figure 2: Distribution of Accuracy among study participants

Statistical analysis was done keeping a p-value<0.05 considered as significant. All variables showed a non-significant effect with a p-value>0.05. Stratification for outcome which is accuracy was done with effect modifiers age and gender in table 2.

Table 2: Stratification for Accuracy of EPT Concerning Gender and Age

Variable	Characteristic	Accuracy	Chi-Square Test	p-value
		No	Yes	
Gender	Female	22 (16.7%)	110 (83.3%)	0.255
	Male	17 (19.3%)	71 (80.7%)	
Age Group	16-25 Years	21 (19.1%)	89 (80.9%)	0.280
	More than 25 Years	18 (16.4%)	92 (83.6%)	

DISCUSSION

In this study, we confirmed the accuracy of electric pulp testing (EPT) in healthy mature permanent teeth, with results indicating an 82.3% detection rate of pulp sensitivity. This corresponds with previous research findings, suggesting that EPT is a reliable diagnostic tool in dental practice [10]. The mechanism by which EPT functions involves generating an electric current to stimulate nerve fibers within the dental pulp. Specifically, EPT targets the myelinated A-delta fibers located near the pulp-dentin junction. When a patient feels a sensation in response to this stimulus, it suggests the presence of vital, responsive pulp tissue. However, it is essential to note that EPT assesses only the neural component of the pulp, not the vascular status, which is crucial for a comprehensive evaluation of pulp vitality [11, 12]. Age and gender stratification in this study revealed no significant differences in EPT accuracy, consistent with findings from previous research. Tran *et al.*, [13] found that age and sex did not significantly affect the electrical response of human dental pulp, supporting the general applicability of EPT across different demographic groups. However, other studies have noted variations in EPT readings depending on tooth type, location, and size, indicating that these factors might influence EPT results to some extent [8, 14]. Despite its demonstrated accuracy, EPT has limitations that must be considered. Since it can take up to five years for the maximum number of myelinated fibres to reach the pulp-dentine border at the plexus of Rashkow in healthy immature teeth with incompletely formed roots that may be erupting, electric pulp tests are known to be unreliable in many cases and to produce false results [15]. Additionally, this is the time of apical root development. Patients with primary hyperthyroidism and teeth with pulp canal calcification (PCC) may have a higher sensory response threshold to EPT. While hypercalcaemia from hyperthyroidism may need twice as much current as is typically required to elicit a response from a clinically normal pulp, in the case of PCC, the sensory response may be entirely inhibited [16]. Because the pulp's sensory components may be disrupted for up to nine months during orthodontic treatment, false outcomes are also possible in teeth with healthy pulps. In a similar vein, newly traumatized teeth undergoing pulp repair could not react to EPT due to erroneous findings [17]. Additionally, the study underscored the importance of using EPT in conjunction with other diagnostic tools, such as thermal tests and radiographic evaluations, for a more comprehensive assessment of pulp health. This multi-modal approach is important because EPT alone cannot provide a complete picture of pulp vitality [18]. Techniques like laser Doppler flowmetry and pulp oximetry, which assess vascular status, offer more reliable information, particularly in cases of dental trauma [19, 20]. The findings of this study have significant implications for dental practice. They confirm that EPT is a valuable tool for assessing pulp sensitivity in healthy mature permanent teeth, but they also highlight the need for a nuanced approach that considers the limitations and potential inaccuracies of EPT. Dental practitioners should be aware of these factors and incorporate additional diagnostic methods to ensure accurate evaluations of pulp health.

CONCLUSIONS

It was concluded that the study found that the electric pulp tester (EPT) is a reliable method for assessing nerve sensitivity in fully formed, healthy permanent teeth, with an accuracy of about 82%. This supports previous research, confirming EPT's usefulness for dentists. The study highlights that while EPT is useful, it isn't flawless and can produce false negatives and positives. Therefore, dentists should use EPT alongside other tests to accurately assess tooth pulp health. The research shows EPT is effective but recommends combining it with other tests for a clearer assessment of tooth pulp health, leading to better treatment decisions and improved patient outcomes.

Authors Contribution

Conceptualization: RN
Methodology: SA, IA, AA
Formal analysis: HAZ

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Writing review and editing: AAM

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Significance of Modified Hodge Test in Carbapenemase Detection: A Brief Insight

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ABSTRACT

Neonatal sepsis is one of the leading causes of neonatal deaths. A. *baumannii-calcoaceticus* is the most notorious bacterial agent. Carbapenems are the most important antibiotics and modified Hodge Test is considered as important phenotypic method for observing Carbapenemase production. **Objective:** To evaluate the efficacy rate of Modified Hodge Test, for detection of Carbapenem resistance. **Methods:** A cross sectional study was conducted at department of pathology, Nishtar Medical University, Multan from August 2023 to September 2023. The blood samples of suspected cases of sepsis were collected and after isolation of *Acinetobacter baumannii* sensitivity of multiple antibiotics were checked by disc diffusion method. Carbapenem resistance was re-evaluated by Modified Hodge Test using Meropenem disc (10 µg). All data were entered and analyzed by SPSS version 23.0. **Results:** Total samples of neonatal sepsis were 182. 83 (45.6%) were culture positive for bacterial growth. Among the positive samples 26 (31.3%) were isolated as *Acinetobacter baumannii*. Kirby-Bauer disc diffusion method was used to check sensitivity of multiple antibiotics including Carbapenems. Out of 26 *Acinetobacter* isolated samples, 16 were found to be Carbapenem resistant by this method. Modified Hodge test was used to re-confirm Carbapenem resistance. Out of 16 Meropenem resistant cases this phenotypic test only detected 5 cases (31.25%). **Conclusions:** *Staphylococcus aureus* followed by *Acinetobacter baumannii* were isolated predominantly and Carbapenem resistance has markedly increased. In contrast to a study conducted in 2010 in Pakistan on MHT effectiveness where effectiveness of MHT for Carbapenemase detection was satisfactory, our results reveled that some other techniques should be introduced for Carbapenemase detection as Modified Hodge test did not give satisfactory results.

INTRODUCTION

Among various microorganisms involved in the several hospital-acquired infections *A. baumannii-calcoaceticus* is the most notorious bacterial agent. Major targets of this pathogen are those who are ill or have compromised immune system [1]. In tropical countries, long period existence of *Acinetobacter* pathogen at the multiple surfaces causes various outbreaks and infections mostly in ICUs [2]. There are multiple species of *Acinetobacter* but major pathogenic species is *Acinetobacter baumannii.* Hence, *A. baumannii* is frequently involved in most of the infectious diseases outbreaks [3]. Generally, these outbreaks are related to hospitals and water sources which create a challenging environment to put down pathogens as well as lessen the contamination in environment [4]. A. baumannii is a non-fermentative, and is the cause of several infections such as VAP, bacteremia, wound infection, UTI and several other nosocomial infections. The main concern of *A. baumannii* is its strong antimicrobial resistance. In ICU patients including those who undergo invasive procedures or encounter excessive broad-spectrum antibiotics, this Carbapenem Resistant *Acinetobacter baumannii* (CRAB) is associated with poor outcomes and high mortality (50%) as compared to those with bacteremia by other bacteria [5]. Neonatal sepsis is one of the leading causes of neonatal death [6]. In 2019, a study was conducted in which it was reported that the

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overall incidence of neonatal sepsis in Asian countries such as China, Thailand, Macau, and Malaysia was 26 per 1000 admissions [7, 8]. Hospital settings contain the flora which is highly resistant as many drugs are being introduced to patients and resistance is grossly increasing now a day. A. baumannii is among the bacteria which exhibited deadly resistance against multiple microorganisms. Various hospital acquired strains of *Acinetobacter* exhibit mechanisms of resistance including expression of β-lactamases, efflux pumping of antibiotic drug and alterations in cell-wall channels (porins) [9, 10]. Carbapenem and Cephalosporin resistances are associated to broad range of genetic matters. Among the transmissible oxacillinase, OXA-23-like was the most common. Additionally, the presence of ESBL was also found along in some isolates along with Carbapenemase [11]. Antibacterial drug resistance is an emerging issue. Currently, the first line therapies for suspected sepsis cases are engaging Piperacillin/Tazobactam and Amikacin [12]. However, when the empirical therapies consisting of first line drugs become unrewarding then Carbapenems are applied. In the most recent era, high Carbapenem resistance has left the clinicians with limited choices of antibiotics [13]. Carbapenems are the most important antibiotics as they can be used to treat severe infections. However, because of severe infection rates a serious public health threat has generated by the emergence of Carbapenem resistance [14]. This resistance mainly develops by the production of hydrolyzing enzymes (Carbapenemase). Uprising mortality rates due to Carbapenemase producing Carbapenem-resistant Enterobacteriaceae (CP-CRE) infection presents a great threat to population as compared to infections by non-CP-CRE. Moreover, high potential of Carbapenemase genes to get transferred by plasmids is an important factor [15]. CP-CRE is also less likely to be susceptible to other groups of antibiotics, including fluoroquinolone, polymyxins and aminoglycosides. Therefore, rapid and reliable detection of CP-CRE is great interest to streamline not only antibiotic treatment but also to minimize the spread of these bacteria both in health care facilities and in community [16]. Multiple methods are available for the detection CP-CRE, however Disk Diffusion Test and Modified Hodge Test are considered as important and accurate methods for the monitoring of Carbapenemase production. Thus, early and accurate identification of CP-CRE is extremely important not only for the treatment but for the control of spread and prevention of infections as well.

This study focused on the efficacy rate of Modified Hodge Test, for detection of carbapenem resistance.

METHODS

A cross sectional study was conducted at department of pathology, Nishtar Medical University, Multan from August 2023 to September 2023 and was approved by ethical review committee with a Ref. No. 13119/NMU. The sample size of the study was calculated by using online calculator openepi.com with 95% confidence level and p = 13.7% as expected proportion/anticipated frequency in population based study conducted by Nazir et al in 2019 [17]. Consent forms were available in the Neonatal ICU and parents/guardians were informed thoroughly about the study. After the approval of parents/guardians, blood samples of neonates were sent to laboratory with the filled history taking Performa and consent forms. According to the microbiological guidelines the blood samples of suspected cases of sepsis from neonatal ICU wards were collected by using aseptic techniques. Instantly, these samples were then transported to Microbiology lab for culture and sensitivity testing. As per microbiological protocols the samples were processed in VersaTREK Automated Microbial Detection System. The positive samples were next sub-cultured by streaking method on Blood agar and MacConkey agar. Cultured samples were further processed for biochemical testing. Genus Acinetobacter was distinguished on basis of gram staining and multiple biochemical tests. API 20E kits were used for reconfirmation of the species. Sensitivity of multiple antibiotics was checked by Disc Diffusion method. Antibiotic susceptibility testing was done following CLSI 2022 guidelines by using Kirby-Bauer disc diffusion method on Muller Hinton agar. Carbapenem resistance was also re-confirmed by Modified Hodge Test using Meropenem disc (10 µg). For that, 5ml saline was used to prepare 0.5 McFarland dilution of E. coli ATCC 25922. 0.5 ml of the 0.5 McFarland solutions was added dropwise to 4.5 ml of saline to make dilution of 1:10. A lawn of the dilution was streaked on Muller Hinton agar plate and allowed to dry for 3-5 minutes. 10ug Meropenem disc was placed in the middle of plate. Test organism was streaked from edge of disc to edge of plate. ATCC strain was also processed in same manner. The plate was incubated overnight at 37°C. Clover leaf pattern was observed at the corner junction of growth and streaked line. Efficacy of Modified Hodge test was interpreted in form of percentage for detection of Carbapenem resistance or Carbapenemase production. All data were entered and analysed by SPSS version 23.0.

RESULTS

Total samples of neonatal sepsis were 182. The mean age of neonates was 14.4 ± 6.39 days and majority 112 (61.5%) were male. Our study results showed that out of 182, 83 (45.6%) were culture positive for bacterial growth and 99 (54.4%) were culture negative. Among the positive samples 26 (31.3%) were isolated as *Acinetobacter baumannii*. Other isolated organisms include *Staphylococcus aureus* 29 (34.93%), *Enterobacter spp* 17 (20.48%), *Pseudomonas aeruginosa* 4 (4.81%), *E. coli* 3 (3.61%), *Klebsiella*

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pneumoniae 3 (3.61%) and *Citrobacter spp* 1 (1.2%). The specific isolated strains of *Acinetobacter* were evaluated for multiple variables. According to the data most affected gender was of males in neonatal sepsis. Gestational age showed that almost equal number of neonates fall in preterm (54.1%) and term (45.6%) categories. However, weight at birth had great impact on developing Acinetobacter associated neonatal sepsis as 86.8% were low birth weight (<2.5 kg) (Table 1).

Table 1: Demographic Details of Study Cases

S. No.	Variables	Frequency from Total Samples N (%)
Gender		
1	Male	112 (61.5)
2	Female	70 (38.5)
Gestational Age		
3	Preterm <37 Weeks	99 (54.1)
4	Term >37 Weeks	83 (45.6)
Age		
5	<7 Days (EOS)	99 (54.1)
6	7-29 Days (LOS)	83 (45.6)
Weight at Birth		
7	<2.5 Kg (Low)	158 (86.8)
8	>2.5 Kg (Normal)	24 (13.2)
Mode of Delivery		
9	C-Section	167 (91.8)
10	SVD (Normal)	15 (8.2)

Kirby Bauer disc diffusion method was used to check sensitivity of multiple antibiotics including Carbapenems. Out of 26 Acinetobacter isolated samples, 16 (61.53%) were found to be Carbapenem resistant. Modified Hodge test was used to re-confirm Carbapenem resistance. Out of 16 Meropenem resistant cases (confirmed by Disc Diffusion Method), this test only detected 5 cases (31.25%) (Table 2).

Table 2: Comparison of Disc Diffusion Method and Modified Hodge Test for Carbapenemase Detection

Number of Cases of *Acinetobacter baumannii*	Total Resistant *Acinetobacter* Cases N (%)	Disc Diffusion Method N (%)	Modified Hodge Test N (%)
	16 (100)	16 (100)	5 (31.25)

DISCUSSION

In our study Meropenem was resistant in 61.53% cases. In contrast to our study Gladstone *et al.*, from Vellore, India conducted a study in which they published 14% Carbapenem resistant Acinetobacter spp isolated from tracheal secretions samples [18, 19]. After that, in 2006 in New Delhi the prevalence of Carbapenem resistant Acinetobacter was found to be 35% [20]. Above studies showed upward trend in Carbapenem resistance pattern for Acinetobacter. In 1999, a surveillance study was conducted on Acinetobacter in which Amikacin 10%–51%, Piperacillin-Tazobactam 36%-75% and Imipenem 5%-19% were resistant [21]. In contrast to these results our study provided the data that Piperacillin-Tazobactam has less resistance i.e. 2% and Meropenem has become more resistant i.e. 61.53%. Amikacin was found to be at same resistance level of 30.76% which is in the range of former surveillance study i.e., 10%-51%. This high level resistance against multiple antibiotics has made Acinetobacter a popular and persistent hospital pathogen. The main cause of increased resistance to Carbapenems is excessive and unjustified use of Meropenem. Carbapenemase production was confirmed by Disc diffusion method and then reconfirmation was done by Modified Hodge test. According to study of Girlich D et al., and his co-workers worked on "Value of the Modified Hodge Test for detection of emerging Carbapenemase in Enterobacteriaceae", they found out that the sensitivity to MHT was 77.4% [22]. Among 35 Carbapenemase producing enterobacteriaceae 24 gave positive results and 11 gave negative results. They explained that addition of Zinc improved the sensitivity of MHT [23]. Unlike that, in our study 16 carbapenem resistant strains were isolated by disc diffusion method. Out of 16 resistant strains MHT (without Zinc addition) re-confirmed only 5 positive samples and 11 samples gave false negative results. The sensitivity was found to be 31.25% only.

CONCLUSIONS

In the region of South Punjab there is an increased trend of infections among neonates, especially by *Acinetobacter.* Empirical antibiotics are used as first line treatment. This study showed increased resistant trends of antibiotics. Results of this study are helpful in modifying the empirical treatment. Among multiple antibiotics the resistance to Carbapenem has markedly increased. The production of Carbapenemase has been detected by disc diffusion method and re-confirmed by Modified Hodge test. The results obtained from Modified Hodge test were not satisfactory. So introduction of the antibiotics to the neonates will be done by following the results from disc diffusion method.

Authors Contribution

Conceptualization: RI

Methodology: AJ, AN

Formal analysis: AZ

Writing-review and editing: MSJ, MJ

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

Conflicts of Interest

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Original Article

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Comparing the Student Learning Outcomes and Teaching Satisfaction of Conventional Lecture and Team-Based Learning Methods

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ABSTRACT

Students hesitate to pursue subjects like biochemistry and manifest a lack of participation and motivation during conventional lectures. However, team-based learning facilitates interactive learning through discussion and improves learning outcomes. **Objective:** To compare the student learning outcomes and teaching satisfaction from team-based learning and conventional learning among medical students. **Methods:** A prospective study was conducted in Rahbar Medical College from December 2023 to May 2024. A total of 100 undergraduate students aged from 19 to 22 years studying biochemistry course were selected for the study. A total of 16 classes were conducted for teaching biochemistry among which 8 were taught by conventional lecture method and the rest 8 were taught by team-based learning. Students were instructed to fill out a student satisfaction scale questionnaire consisting of 20 questions at the end of the last TBL session. **Results:** The mean score of conventional lectures was 11.85 ± 1.54 with a maximum score of 15.5 and minimum score of 10 out of 20. The highest score was obtained by group assessment readiness test i.e. 16.25 ± 1.05. The mean score of conventional and TBL methods was 14.10 ± 1.12, with a minimum score of 12.20, and a maximum score of 15.95 out of 20 (P=0.016). Overall satisfaction scores in females were higher than in males (p<0.001). The mean student satisfaction score was 81.27 ± 9.18. **Conclusions:** Team-based learning yields better learning outcomes and teaching satisfaction in medical students as compared to conventional lecture methods. These results were also improved in female students than in males.

INTRODUCTION

Cooperative learning is a type of learning which involves working with student groups to solve a common problem together [1]. This technique allows the learners to sharpen their communication skills, enhance social interaction, and foster group thinking. Team-based learning is a structured extension of cooperative learning that has been practiced effectively for decades and its incorporation in the medical field is increasing [2]. The goal of team-based learning is to improve cognitive learning by collaborating with the masses using personal expertise. Team-based learning involves three steps. Firstly, the students are encouraged to study and prepare to discuss their viewpoints. Secondly, students' cognitive ability regarding subjects studied earlier is calculated through individual and group readiness assessment tests by dividing students into groups for discussion among peers and instructors. Lastly, students are asked to present and discuss higher-level subjects with team members [3]. TBL facilitates interactive learning

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through discussion regarding principles and assessments. Laboratory medicine is often taught by conventional lectures where teachers deliver their knowledge regarding basic and professional topics. However, in this type of learning, the student outcomes depend upon the expertise of the instructor and limited information can be a hindrance to learning and satisfaction of pupils. In addition, this method does not encourage student participation and communication but it is inexpensive and faster than TBL. Critical thinking and behavioral skills are not polished through lectures which are important characteristics for a medical student. Some studies have been conducted to compare the student outcomes by team-based learning and other methods which reported increased student participation and engagement in TBL [4, 5]. In conventional learning, teachers use different teaching techniques to deliver limited information, leading to obstruction of quality education and student satisfaction [6]. However, most of these studies are conducted for subjects like pharmacology and neurology. But students hesitate to pursue subjects like biochemistry and manifest a lack of participation and motivation during conventional lectures. It was hypothesized that this lack of motivation and satisfaction is due to the teaching methods to deliver these subjects. Our study includes students studying biochemistry and the learning outcomes and satisfaction scores were compared between both genders which is a finding rarely reported in many studies comparing learning methods.

This study compared the student learning outcomes and teaching satisfaction from team-based learning and conventional learning among medical students.

METHODS

A prospective study was conducted in Rahbar Medical College from December 2023 to May 2024. A total of 100 undergraduate students aged from 19 to 22 years studying biochemistry course were selected for the study by consecutive sampling. The sample size was calculated by Daniel's formula keeping a 95% confidence interval, 50% population proportion, and 7% precision. Students inconsistent with attendance were excluded. All the student provided their consent to become a part of the study. The ethical committee of the medical college approved the study EC/IRB Ref.No.31. A total of 16 classes were conducted for teaching clinical biochemistry among which 8 were taught by conventional lecture method and the rest 8 were taught by team-based learning. The topics were divided into each method equally by keeping in view the volume of content and difficulty. The following topics were taught in lectures; gene transcription and translation, replication of DNA and post-transcriptional modifications. The topics covered in TBL were vitamins, enzymes and protein biosynthesis. The conventional lectures were delivered keeping in view the following: topics were divided according to students' convenience and time available in each lecture, an introductory summary of the topic was provided, maintenance of listeners' attention by good presentation and comprehension, and a conclusory summary at the end of each lecture. The content of the eight lectures was tested by a multiple-choice exam on the 9th lecture with questions of varied difficulty. For team-based learning, students were allocated to groups with 6-7 members, a manager, and a designated name. TBL was conducted in the following manner: individual readiness assessment tests were conducted with multiple choice questions from easy to increasing difficulty, group readiness assessment test was conducted in closed book exam, GRAT was checked and an appeal form for every mistake for each group was filled and lastly students were asked to fill a peer evaluation form. Students rated each group member with respect to their participation, preparation of the designated topic, cooperation, and inclusivity. For this purpose, the students assigned a score out of 100 to the team as a whole, mentioning the score of each member. The topic of the next lecture was summarized at the end of each lecture and students were recommended materials for self-study. To compare the student satisfaction between the two teaching methods, students were instructed to fill out a student satisfaction scale questionnaire consisting of 20 questions which could be answered by selecting from scoring options from 5 to 1 according to Likert scoring, with 5 being totally agree and 1 being totally disagree. This questionnaire was filled out at the end of the last team-based learning lecture. The validity of the scale was tested by asking teachers to rate the questions according to necessity/no necessity in the SSS and modifications required before presenting it to the students. A CVI score of 93% was achieved, which proved the validity of the scale [7]. The Cronbach's alpha coefficient was 0.957 for the calculation of external consistency and 0.918 for internal consistency with the split-half model. The student satisfaction score in each team-based learning session was calculated by the following formula [8]: A+C=D, ·:A= IRAT score, ·:C= P% x B, ·:B= adjusted peer evaluation score, ·:P= mean peer evaluation score, D= Total score. The average score of 8 TBL lectures was a total score. The final score of the biochemistry course was the mean score of both learning methods. All the data was analyzed by SPSS version 24. The normalcy of data was tested by the Kolmogorov-Smirnov test. Independent samples t-test was used to calculate the difference between two means and one-way analysis of variance was used to calculate the difference between more than two means. Pearson correlation test was used to evaluate the association between variates. The validity of the student satisfaction scale was tested by achieving internal and external consistency by calculating the intra-class correlation coefficient and Cronbach's alpha

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coefficient (with the Split-half model for internal consistency). A p-value less than 0.05 was considered significant.

RESULTS

The mean score of conventional lectures was 11.85 ± 1.54 with a maximum score of 15.5 and a minimum score of 10 out of 20. The highest score was obtained by GART i.e. 16.25 ± 1.05. The mean score of conventional and TBL methods was 14.10 ± 1.12, with a minimum score of 12.20 and a maximum score of 15.95 out of 20 (P=0.016). The scores of female students were significantly higher than male students (p<0.001). Overall satisfaction scores in females were higher than in males (p<0.001) (Table 1).

Table 1: Comparison of Mean Score of Each Method According to Student Gender (n=70)

Method	Mean Score (Mean ± SD)	Male (Mean ± SD)	Female (Mean ± SD)	p-Value
Lecturel	11.85 ± 1.54	11.44 ± 1.33	12.22 ± 1.35	0.071
ART	14.72 ± 1.55	13.42 ± 0.90	15.19 ± 1.83	0.001
GART	16.25 ± 1.05	14.88 ± 0.52	16.66 ± 1.28	0.001
Final	14.10 ± 1.12	13.09 ± 0.69	14.51 ± 0.89	0.001

Table 2 showed the subsequent student satisfaction scores in all eight sessions of team-based learning based on the results of individual and group readiness assessments. The results show that the scores increased with an increase in teaching sessions and the difference between the mean scores of both assessments was significant (p<0.001).

Table 2: Individual and Group Readiness Assessment Test Scores in 8 Sessions of TBL

Session	Individual Readiness Assessment Test Score	Group Readiness Assessment Test Score
1st	8.51	11.73
2nd	10.67	13.85
3rd	17.75	18.66
4th	13.12	15.71
5th	15.26	18.38
6th	17.82	16.14
7th	17.23	18.32
8th	18.07	18.72

*T-test was performed to compare scores

The mean student satisfaction score was 81.27 ± 9.18. This score was obtained by results from the SSS questionnaire at the end of the last TBL session (Table 3). Students answered questions on a Likert scale with 20 representing totally disagree (option 1) and 100 representing totally agree (option 5). Students obtained a score of 16.91 ± 1.22 (Max: 18.77, Min: 14.83) out of 20 in the last academic semester and this score was not associated with the mean TBL score (p= 0.385, r= -0.111) or extent of satisfaction (p=0.933, r= 0.015). However, the final lecture score and student average scores were significantly associated (p=0.001, r= 0.427).

Table 3: Student Satisfaction Score within 14 Days of Completion

Student Satisfaction	Mean ± SD	Min	Max	Range
TBL	81.27	9.18	65	33
Conventional Lectures	81.05	8.82	70	29

DISCUSSION

The current study was conducted to compare the student satisfaction scores in conventional lecture sessions and team-based learning. An increase in scores was seen from lectured learning to team-based learning. This growth can be due to effective self-study course preparation and collaborative working in team-based learning. Another study comparing student satisfaction in second-year neurology students taught using TBL with scores from the last academic year reported similar results [9]. The students showed improved learning outcomes after TBL and GART scores were higher than IRAT and traditional lecture scores. The present study also used the SSS scale to confirm the reliability and validity of the results of both methods. The questionnaire revealed 80% satisfaction with the TBL method than conventional teaching. The results comply with the study by Jafri that employed the SSS scale and reported considerably high satisfaction in the TBL sessions [8]. Although most of the previous studies assessed student outcomes by employing TBL in clinical courses, the results were similar to the present study [10-12]. Zaman A *et al.*, revealed significantly higher scores using TBL as an active learning method in biochemistry students than the passive learning method and the difference between both scores was significant in below-average students [13]. However, in the current study, no correlation between students' last year scores and TBL scores and satisfaction was noted. Therefore, the academic history of the student did not affect study scores or satisfaction. However, this correlation was prominent in conventional learning, implying that TBL improves learning outcomes irrespective of student caliber and a higher score in conventional learning can only be achieved if the student has a good academic background [14, 15]. The current study administered the two methods in the full semester to compare results effectively and maintain a balance between content covered and time management. Studies previously conducted usually record results for a limited time and teaching hours and mostly only observed results for TBL, but all of them agree on higher learning outcomes and satisfaction in active learning by TBL than traditional lectures [16-18]. With respect to gender, female students performed considerably better than male students in IRAT and GRAT evaluations of team-based learning, this difference was significant in results of conventional lectures. Along with improved outcomes, teaching satisfaction was also higher in females. Although there was limited literature available comparing learning outcomes by TBL in both genders, Das S *et al.*, and Aguillon

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SM *et al.*, studied first-year medical students taught by TBL which revealed greater student satisfaction in females but test results showed better performance in males as they achieved higher exam scores [19, 20]. This difference in results from these studies and the present study may be due to differences in study duration and course, however, more studies were needed to report consistent results. In the current study, an SSS scale consisted of 20 questions that could be answered on a Likert scale to express satisfaction with TBL and conventional teaching. A CVI of 93% was achieved after consulting teachers. A score of 80% proves the validity of the resource for assessment. The reliability of the questionnaire was tested by internal and external consistency which were both high in this study indicating reliable and consistent data. Results revealed improved knowledge of the course and confidence that led to highly reproducible results as the assessments could be completed twice within 14 days. Although the course content and difficulty of data were divided equally between the teaching methods, the difference in topics taught between the first and second half of the semester may be a limitation of this research. In addition, the small sample size of student included and bias through self-reported questionnaire may have influenced the results.

CONCLUSIONS

Team-based learning yields better learning outcomes and teaching satisfaction in medical students as compared to conventional lecture methods. These results were also improved in female students than in males.

Authors Contribution

Conceptualization: HAS
Methodology: ZHQ
Formal analysis: FNT, SIC
Writing, review and editing: MS, BTF, BF

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

Conflicts of Interest

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Original Article

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Prevalence and Patterns of Electrolyte Imbalance in Children Diagnosed with Acute Severe Malnutrition at a Nutritional Stabilization Center

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ABSTRACT

Malnutrition accounts for around 35% of all fatalities in Pakistan among children under five, making it the primary cause of childhood mortality in that country. The most severe type of malnutrition, known as severe acute malnutrition (SAM), was frequently linked to electrolyte abnormalities. The purpose of this study was to ascertain how frequently electrolyte imbalance occurred in children with SAM who were admitted to a tertiary care facility. **Objective:** To Determine the Prevalence and Patterns of Electrolyte Imbalance in Children Diagnosed with Acute Severe Malnutrition at a Nutritional Stabilization Center". **Methods:** A cross-sectional study was carried out in Nawabshah at the Department of Pediatrics, Peoples University of Medical and Health Sciences, from May 16 to August 15, 2024. This study comprised 92 patients with severe acute malnutrition, ranging in age from 2 to 60 months. Non purposive sampling technique was used for data collection. Children with secondary causes of wasting were excluded, including those with congenital heart disease, chronic renal or liver illness, TB, cancer, and hemolytic anaemia. Weight-for-height was calculated using measurements of weight, length, and height. When the weight-for-height ratio fell below the -3 standard deviation (SD), children were diagnosed with SAM. The lab received blood samples that were taken for serum electrolytes. The chi-square test was used for stratification, and descriptive statistics were computed. **Results:** Participants' average ages ranged from 23.63± 12.71 months. A total of 85 (93.4%) of the 92 SAM patients had an electrolyte imbalance. The prevalence of hypokalemia (70.08%), hypocalcemia (56.52%), hyponatremia (32.60%), and hypomagnesemia (28.26%), respectively. **Conclusions:** Children with SAM experience dyselectrolytemia both with and without problems. In all cases of SAM, serum electrolyte levels may need to be assessed in order to identify hyponatremia and hypokalemia in the absence of symptoms. This will facilitate the inpatient treatment triage process for patients with asymptomatic hyponatremia and hypokalemia.

INTRODUCTION

A lack of nutrients and energy causes malnutrition since the body needs both in order to grow and develop properly. Malnutrition can show up in a number of ways, including undernutrition, stunting, wasting, micronutrient deficiencies, and being overweight or obese as an adult [1]. Malnutrition plays a significant role in the burden of diseases that affect children and is a global public health concern. Malnutrition affects 50–150 million young children under the age of five globally. It is the primary cause of one-third of mortality among children under five [2]. Between 50 and 38 per cent of the world's wasted and stunted children reside in Pakistan [3]. In Pakistan, around 35% of deaths involving children under five are related to malnutrition. Malnutrition results in a number of anomalies in the body's electrolyte levels. The electrolyte imbalances involving sodium, potassium, bicarbonate, and water are the most prevalent ones. When a child is malnourished and edematous, their body water content rises along with extracellular sodium retention. However, in most cases, their serum sodium level falls, concealing their salt overload. The accompanying diarrhea may be the reason for these low levels. Because of low muscle mass and

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decreased consumption, total body potassium can drop by up to 25% in cases of overt malnutrition [4].

Children who are underweight frequently suffer electrolyte abnormalities. When diarrheal illnesses are present, electrolyte imbalance increases the risk of death in children [5]. Low serum sodium levels cover up the sodium overload in extremely malnourished, edematous children. [6, 7]. Hypokalemia frequently manifests as paralytic ileus, hypotonia, apathy, and cardiac arrhythmias. Clinical signs of hypocalcemia are frequently modest. However, if hypomagnesemia also exists, hypocalcemia can cause deadly convulsions in young infants [8]. Children who are undernourished are more vulnerable to electrolyte balance-related illnesses and deaths. The results of this study will be useful in estimating the degree of electrolyte imbalance in kids with SAM, and more research can be done for a more thorough examination.

The purpose of this study was to determine the Prevalence and Patterns of Electrolyte Imbalance in Children Diagnosed with Acute Severe Malnutrition at a Nutritional Stabilization Center." .This will allow treatment strategies to be developed expeditiously and prevent potentially devastating outcomes for these children.

METHODS

A cross-sectional study was carried out in Nawabshah at the Department of Pediatrics, Peoples University of Medical and Health Sciences, from May 16 to August 15, 2024. Peoples University of Medical and Health Sciences ethical board approved the study. The IRB approval number is PUMHSW/SBA/PVC/ERC/25/2024. The parents or guardians of the admitted patients provided written approval. This study comprised 92 patients with severe acute malnutrition, ranging in age from 2 to 60 months. WHO Sample size calculator was used to calculate sample size. A sample size of 92 children was calculated at a prevalence of 93% taken from a similar study [3]. Non purposive sampling technique was used for data collection. Children with secondary causes of wasting were excluded, including those with congenital heart disease, chronic renal or liver illness, TB, cancer, and hemolytic anaemia. Based on the diagnosis provided by the history, physical examination, and relevant test results, the secondary reasons were ruled out. The chief researcher created a self-made questionnaire, which the stabilization center's skilled nursing staff completed. Age, gender, and name were the demographic information gathered. A sample of blood approximately 2 milliliters was taken from patients in the Stabilization Center ward, which was forwarded to the pathology department. Serum calcium and magnesium levels were measured using a fully automated chemistry analyzer Beckman Coulter AU-680, which operates on the principle of spectrophotometry, while sodium and potassium analysis was carried out using the patient's serum on a fully automated Electrolyte Analyzer Diestro 103 AP, which operates on the principle of ion selective electrode (ISE). The pathology department's lab technicians conducted the biochemical evaluation, and the nurses documented the results on the questionnaire. The Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used to analyze the collected data. For quantitative variables including age, serum concentrations of Na, K, Ca, and Mg, and the length of SAM, mean ± SD was computed. The frequency of electrolyte imbalance in children with SAM was determined to be a qualitative variable. Additionally, distinct frequencies and percentages were computed for hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia.

RESULTS

Our analysis showed that 93.5% of children had electrolyte imbalances. A total of 51 (59.3%) males and 35 (40.7%) female children had electrolyte imbalance (p-value 0.004). Most of the children 63 (68.5%) with electrolyte imbalance were below the age of 24 months. The duration of SAM was not significantly related with electrolyte imbalance. Most of the parents were illiterate or had a primary education whose children had electrolyte imbalance (Table 1).

Table 1: Demographic Data (n=92)

Variables	Electrolyte Imbalance N (%)			p-value
	Yes	No	Total	
Gender				
Male	51 (59.3%)	6 (100%)	57 (62%)	0.004
Female	35 (40.7%)	0 (0%)	35 (38%)	
Age (Months)				
≤24 Months	60 (69.8%)	3 (50%)	63 (68.5%)	0.152
>24 Months	26 (30.2%)	3 (50%)	29 (31.5%)	
Duration of SAM (Days)				
≤30	43 (50%)	3 (50%)	46 (50%)	1.000
>30	43 (50%)	3 (50%)	46 (50%)	
Educational Status of Parents				
Illiterate	33 (38.4%)	0 (0%)	33 (35.9%)	0.001
Primary	34 (39.5%)	6 (100%)	40 (43.5%)	
Secondary	15 (17.6%)	0 (0%)	15 (16.8%)	
Intermediate or Above	4 (4.5%)	0 (0)	4 (3.8%)	

Of the 92 children, 38% (n = 35) were female and 62% (n = 57) were male. The children were 23.63 months old on average, and SAM lasted 46.13 days on average. The average serum values of Na, K, Ca and Mg (Table 2).

Table 2: Serum Electrolyte Means and Standard Deviations (n = 92)

Variables (mEq/l)	Mean ± SD	Range
Serum Sodium	134.65 ± 5.27	127.0-145.0
Serum Potassium	2.75 ± 0.796	1.6-4.7
Serum Calcium	7.60 ± 1.02	6.0-9.6
Serum Magnesium	1.91 ± 0.41	0.8-3.2

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According to our data, 93.4% of children exhibited electrolyte abnormalities. The majority of the children (70.08%) had hypokalemia, while 56.52%, 32.60%, and 28.26% had hypocalcemia, hyponatremia, and hypomagnesemia, respectively (Table 3).

Table 3: Distribution of Electrolyte Imbalance Frequency (n= 92)

Variables	N (%)
Hyponatremia	30 (32.60%)
Hypokalemia	70 (70.08%)
Hypocalcemia	50 (56.52%)
Hypomagnesemia	26 (28.26%)

DISCUSSION

Malnutrition frequently results in electrolyte abnormalities, which continue to be a significant health issue in underdeveloped countries. Serum electrolyte levels in malnutrition reflect the concentration of electrolytes in the blood rather than the total body content. Parents who lack literacy were ignorant of the balance needed for their child to grow normally. Thus, an improper diet deficient in vital nutrients leads to an imbalance in serum electrolytes. In the current study, of the 92 children, 38% (n = 35) were female and 62% (n = 57) were male. According to our data, 93.4% of kids exhibited electrolyte abnormalities. The majority of the children (70.08%) had hypokalemia, while 56.52%, 32.60% and 28.26% had hypocalcemia, hyponatremia and hypomagnesemia, respectively. A total of 93.5% of children with SAM who were hospitalized also had electrolyte imbalances, according to Raza M *et al.*, The most prevalent electrolyte problem was found to be hypokalemia, which affected 79.9% of the patients [3]. According to Laghari GS *et al.*, Group B consisted of 46 malnourished children without diarrhea, while Group A included 54 malnourished children with diarrhea. Out of 79 children, 43 (79%) had hyponatremia (serum sodium <135 meq/l), with 27 of these cases occurring in Group B (p<0.0001). Regarding hypokalemia (serum potassium <3.5 meq/l), 27 malnourished children from Group A were affected, compared to 10 from Group B [5]. In a research conducted in India, hyponatremia was the most often found electrolyte abnormalities among the 60 SAM children who were enrolled (21–35%), followed by hypokalemia (18–30%) and hypocalcemia (15–25%). Thirteen (21.6%) individuals had metabolic acidosis, four (6.7%) had hypoglycemia, and two (3.3%) had metabolic alkalosis [9]. In a different study, by Ashok E *et al.*, Thirteen cases (20.0%) had hypocalcaemia, twenty-one cases (28.0%) had hypokalaemia, and three cases (4.0%) had hypopatremia. Thirty had elevated creatinine (40.0%) and 34 had elevated urea (44.0%). Of the 19, (25.3%) with random blood sugar, hypoglycemia was found [10]. Ali S *et al.*, conducted a study on children having severe acute malnutrition. The cases were 2.4 ± 3.13 years old on average. Male children made up 84 (62.6%) of the total, while girls made up 50 (37.3%). 57 patients (42.5%) had hypokalemia [11]. In a research by Meena *et al.*, dyselectrolytemia was found in 94.0% of the 100 children with complex SAM. The SAM children with the majority of co-morbidities had subnormal sodium levels (128–135 mEq/L) and normal potassium levels (368–4.34 mEq/L) at the time of admission. The mean potassium level was 4.17 ± 1.03 mEq/L and the mean sodium level was 131.82 ± 6.66 mEq/L in children with complex SAM. The average potassium level and sodium level of the children in the control group were 4.14 ± 1.11 mEq/L and 135.90 ± 4.26 mEq/L, respectively [12]. To determine how frequently hypokalemia occurs in children with severe acute malnutrition, ur Rehman M *et al.*, did a study. A total of 44 (45.8%) of the 96 patients were male and 52 (54.2%) were female. It was 20.65 ± 11.961 months on average. Overall 50 (52.1%) children had no electrolyte imbalance while 46 (47.9%) children had hypokalemia. Children's gender and age groups were taken into consideration while analyzing the prevalence of hypokalemia, and the p-values were 0.973 and 0.176, respectively [13]. According to a study by Khan S *et al.*, in total, 100 children suffering from severe acute malnutrition were a part of this study. There were 40 (40%) females and 60 (60%) males; the mean age was 23.65 months. Diarrhea was seen in 66% of the patients. 23 children (23%) and 28 children (28%) had hypokalemia and hyponatremia, respectively. The relative means for potassium and sodium were 3.06 (+1.7517) and 138.96 (8.692). Magnesium and calcium had respective means ± SD of 2.23 (2.38) and 8.51 (1.58) [14]. A local study reported that Group B consisted of 36 malnourished patients without diarrhea, while Group A included 64 malnourished patients, also without diarrhea. Serum electrolyte levels were tested in both groups, and the results were statistically analyzed. Hypokalemia was observed in 40 patients (62.5%) from Group A and 8 patients (22.22%) from Group B (p<0.001). Similarly, hyponatremia was present in 17 patients (26.56%) from Group A and 5 patients (13.88%) from Group B (p<0.001). Additionally, low serum bicarbonate levels were found in 41 patients (64%) from Group A and 15 patients (41.66%) from Group B (p<0.001) [15]. According to a study by Zulqarnain A *et al.*, patients who had severe acute malnutrition and diarrhea had hyponatremia in 28 (31.1%), hypokalemia in 55 (61.1%), and hypocalcemia in 12. (13.3%) of the patients [16]. Of the 113 SAM children involved in an international study, 42 did not have any issues, and 71 had. Serum potassium was measured at 4.29 ± 0.75 meq/L, sodium at 134.58 ± 5.45 meq/L, and chloride at 103.31 ± 7.16 meq/L on average. Of the children, 7.1% had hypokalemia and 43.4% had hyponatremia. The mean serum electrolyte values and the frequency of hyponatremia and hypokalemia did not differ statistically significantly across the groups [17]. An Indian study revealed that on day one, 72% of children had hyponatremia, while 6% exhibited hypernatremia. By day three, the hyponatremia rate dropped to 60%, and by day eight, hypernatremia decreased to 4%. Approximately 68% of the children maintained normal sodium levels. Between day 1 and day 8, there was a significant improvement in mean sodium

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levels, reaching an average of 135.8 ± 9.9 on day eight. Hypokalemia was most prevalent on day one, affecting 38% of patients. On day three, 28% had hyperkalemia, and by day eight, 80% of the children had normal potassium levels. The mean potassium levels also significantly improved, reaching 5.5 ± 1.24 by day eight [18]. Overall 53 patients (66%) in a local study reported having diarrhea for 1-3 days, with a mean duration of 3.2 ± 1.7 days. Ten patients (12.5%) showed no electrolyte imbalance, while 26 patients (32.5%) and 44 patients (55%), respectively, had hyponatremia and hypokalaemia. Hyperkalaemia and hypernatremia were absent in every subject [19]. In comparison to children who were not malnourished, children with edematous malnutrition had higher rates of pneumonia (P = 0.04), acute gastroenteritis (P < 0.001), hyponatremia (P = 0.04), metabolic acidosis (P = 0.005) and hypocalcemia (P = 0.006) [20]. An indian study, they looked at children between the ages of six and 59 months. The average age of admitted patients was 24.18 months, or almost 24 months. At the time of admission, the most common median age was almost one year (13 months). The relationship between serum potassium and sodium and the survival of SAM was shown to be statistically significant in their investigation [21]. In a different Indian study, 77 (64.17%) SAM children who had diarrhea also had dysnatremia, with 76 of them having hyponatremia (63.33%) and 2 cases having hypernatremia. For both diarrheal and non-diarrheal SAM patients, there was no statistically significant difference associated with hyponatremia (P value of 0.09) [22]. The mean age of all cases in a local study was 35.84±14.36 months, with a minimum and maximum age ranging from 6 to 60 months. There were 60 (41.7%) female cases and 84 (58.3%) male cases. Serum potassium levels were 3.20 ± 1.33 mmol/L and sodium levels were 134.82 ± 8.63 mmol/L on average. The incidence and percentage of hyponatremia and hypokalemia, respectively, were 47 (32.6%) and 86 (59.7%), based on the operational criteria [23].

CONCLUSIONS

Children with SAM experience dyselectrolytemia both with and without problems. In all cases of SAM, serum electrolyte levels may need to be assessed in order to identify hyponatremia and hypokalemia in the absence of symptoms. This will facilitate the inpatient treatment triage process for patients with asymptomatic hyponatremia and hypokalemia.

Authors Contribution

Conceptualization: MNC
Methodology: A
Formal analysis: HNB
Writing, review and editing: A, MAS, AHR, N, SC

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

Conflicts of Interest

The authors declare no conflict of interest.

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Radio-Histopathological Spectrum of Ovarian Specimens Following Cystectomy

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ABSTRACT

Ovarian cysts can be benign or malignant and requires accurate diagnosis for efficient treatment. **Objective:** To characterize the radiological and histopathological spectrum of ovarian specimens following cystectomy. **Methods:** This retrospective study was conducted at Pakistan Atomic Energy Commission General Hospital, Islamabad from 1st April 2022 to 31st December 2022. Eighty patient's samples from cystectomy patients who were suffering from ovarian cysts were included. Each patient underwent radiological examination before ovarian cystectomy through laparoscopic surgery except two cases of urgent laparotomy. Gross histopathological specimen examination was conducted. The data were analysed using SPSS version 26.0, wherein p value <. 0.05 was considered as significant. **Results:** The mean age of the patients enrolled in this study was 35.5 ± 5.9 years. Hemorrhagic cysts were having a reticular pattern of internal echoes with soli appearing area with concave margins and no internal flow, while endometrioma cysts were having homogenous low level internal echoes with non-solid component and tiny echogenic foci in the walls. While within the neoplastic cysts 4/8 werehaving cystic external surface and 1/8 presented with ovarian mass.The surface epithelial tumor presented of 2 cases with carcinoma detection on histopathology slides while in the germ cell tumor 1 cases each of strumaovarii, dysgerminoma and mixed germ cell tumor was observed. **Conclusions:** Surface epithelial tumors were the most common category of ovarian tumors and majority of the cysts were benign cystadenomas. Radiological imaging provides a precise non-invasive tool for categorizing various ovarian cysts and histopathological findings further confirms the exact category of tumors.

INTRODUCTION

Ovarian cystectomy, the surgical removal of cysts from the ovary, is a pivotal procedure in gynaecological practice, addressing both benign and potentially malignant conditions [1]. Ovarian cystectomy is a critical procedure for both diagnostic and therapeutic purposes. The worldwide prevalence of ovarian cyst is reported as 8% and 18% between premenopausal and postmenopausal females depending upon their genetic, creed and geographical life style. There is a wide variance between the exact prevalence of ovarian cyst among females all over the globe. Cyst of ovaries are many time filled with fluid which are mostly developing on or within the ovaries and can range from benign, asymptomatic growths to complex, potentially malignant tumors [1, 2]. While many ovarian cysts resolve on their own, others may cause significant symptoms such as pelvic pain, bloating, and irregular menstrual cycles, necessitating surgical intervention [3]. The decision to perform an ovarian cystectomy is influenced by factors including the size and type of the cyst, the patient's age, symptoms, and overall health, as well as concerns about malignancy. This procedure not only alleviates discomfort and prevents complications like cyst rupture or torsion but also facilitates histopathological examination to rule out cancer [3, 4]. Accurate diagnosis and effective treatment planning hinge on the integration of histopathological and radiological findings [5].

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Histopathological examination involves the microscopic analysis of excised tissue, providing critical insights into the cellular and structural characteristics of ovarian cysts [6]. Meanwhile, radiological imaging, including ultrasound, MRI, and CT scans, plays a crucial role in the preoperative evaluation by delineating the size, location, and morphological features of the cysts [7, 8]. By understanding the significance of correlating histopathological and radiological findings, healthcare professionals can improve patient outcomes, ensuring that benign and malignant conditions are appropriately identified and treated and the fact that understanding an ovarian cyst is highly critical in its treatment therefore requiring a precise identification method. Radiological imaging and histopathological finding can be an efficient method of ovarian cyst diagnosis [8]. The correlation between these diagnostic modalities is essential for validating the initial imaging assessments and ensuring a comprehensive understanding of the cystic lesions. This synergistic approach not only enhances diagnostic precision but also informs clinical decision-making, ultimately improving patient management and outcomes [9, 10]. This importance of correlating histopathological and radiological findings in ovarian cystectomy specimens, emphasizing their complementary roles and the benefits of an integrated diagnostic strategy. It will also highlight the strengths and limitations of each approach and discuss their synergistic role in the diagnostic process.

The present study aimed to determine the radiological and histopathological correction findings in pre and post ovarian cysts. This research provided significant information and data on radiological diagnostic accuracy of various ovarian cysts especially complex ones will provide a screening method and assisted in deciding which patients need biopsy correlation and further treatment. In addition to this the current study will benefit in providing histopathological diagnosis aids knowing the exact incidence of various entities as well as other epidemiological features, also early diagnosis leads to better management.

METHODS

This retrospective study was conducted at Pakistan Atomic Energy Commission General Hospital, Islamabad from1st April 2022 to 31st December 2022 vide letter no. PGHI-IRB (Dme)-RCD-06-038. The study was ethically cleared from the review committee before its initiation and enrolment of participants. A total of 80 samples from cystectomy patients were included. The sample size was generated by applying the cystectomy prevalence as 28% and 95% confidence interval, 5% margin of error with 80% power of test [4]. A written consent was taken from each patent for its participation in the study. The inclusion criteria included those who were suffering from ovarian cysts having any suspicion of cancerous or benign tumor in the ovaries in it requiring the removal of the cyst. The age of the patients was between 20-55 years. Patients suffering from metastasis, autoimmune disease or complications related with diabetes, hypertension were not included. Any sample that was not sent via surgical excision was excluded from the study. Autolyzed-specimen were excluded whereas resected ovarian cysts samples were included in the study. Each patient underwent radiological examination through pelvic USG, CT scan, MRI, testing before ovarian cystectomy. The radiological analysis was done to accurately identify the location and size of tumor. This further assisted in understanding the case and resulted in precise planning required during surgery. The ultrasound features which suspected malignancy or any form of nodule as well as pelvic mass and ascites were referred to the oncologist. All cysts larger than 10 cm were taken a suspicion for malignancy. Other featured included high Doppler flow with colour, irregularities, solid or other wose papillary with ascites present. Laparoscopic procedure was opted for cystectomy in all patients except two who underwent criticality and required laparotomy. A minute camera with light at the top was inserted through a small incision in the abdomen, providing a view of the pelvic and reproductive organs of the patients. Two other small incisions were made for surgical tools to insert and drain. The ovarian cysts were removed through the incision. A well-structured questionnaire was designed to record the patient's demographic details, radiological imaging data, specimen type and diagnosis. A gross histopathological specimen examination was conducted about its size concerning external and mucosal surface, size as well as wall thickening. Acquired specimens were corrected in buffered-neutral formalin for 12-24 hours and further submitted for processing. Post routine paraffin processing, a section of 3–5 µm was taken and stained by H and E staining protocol. The histopathological results post-cystectomy was analysed for accuracy. Data were analysed by using SPSS version 26.0 wherein the results interpretations were performed through mean ± SD for quantitative variables while percentages and frequencies were used for qualitative variable analysis. Chi square tool was used for results analysis with a p-Value <0.05 as significant.

RESULTS

The mean age of the patients enrolled in this study was 35.5 ± 5.9 years, which majority of the patients between the age group of 31-45 years. The radiological assessment was mainly conducted by Doppler sonography followed by CT scan and MRI scan if required. Various types of cysts were identified based on sonographic imaging. Haemorrhagic cysts were having a reticular pattern of internal echoes with soli appearing area with concave margins and no internal flow, while endometrium cysts were having

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homogenous low level internal echoes with non-solid component and tiny echogenic foci in the walls. The dermoid cysts had focal /diffuse hyperechoic component with lines and dots. There was an area of acoustic shadowing with no internal flow (Figure 1).

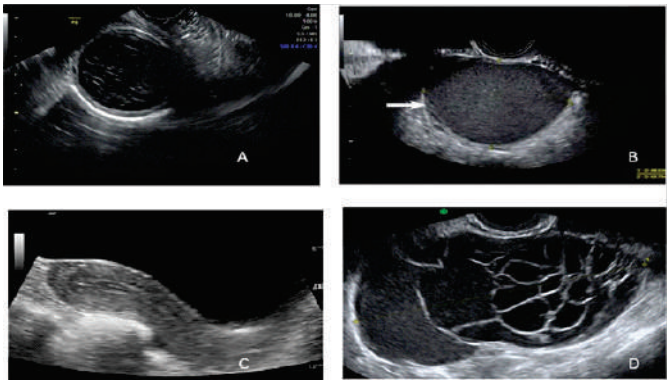

Figure 1: A: Hemorrhagic Ovarian Cyst, B: Endometrioma Ovarian Cyst C: Demoid Ovarian Cyst D: Bengin Mucinous Cystadenoma

The laterality of the non-neoplastic cyst had shown that cysts was identified as 50% (40/80) as left while 43.75% (35/80) as right side with majority having an external cystic surface while solid cut surface was identified in 9 cases (p value 0.033)(Table 1).

Table 1: The Non-Neoplastic Cysts Characteristics (n=80)

Variables	N (%)	p-Value
Laterally		
Left	40 (50%)	0.212
Right	35 (43.7%)	
Bilateral	5 (6.3%)	
External Surface		
Cystic	67 (83.7%)	0.032
Unremarkable	13 (16.3%)	
Cut Surface		
Cystic	60 (75%)	0.012
Solid	9 (11.3%)	
Unremarkable	11 (13.7%)	

While within the neoplastic cysts there were 8 which were malignant with 50% (4/8) having cystic external surface and 12.5% (1/8) presented with ovarian mass (Table 2).

Table 2: Neoplastic Cyst Characteristics (n=80)

External Surface	Benign	Malignant	p-Value
Cystic	44	4	0.022
Unremarkable	27	3	0.043
Ovarian Mass	1	1	-

The various type of tumors identified showed that bilaterality was presented in 3 germ cell tumor while 1 sex cord stromal tumor (p value 0.002)(Table 3).

Table 3: Association of Tumor Type with Bilaterality

Tumor Type	Bilaterality	Number
Sex Cord Stromal	1	2
Germ Cell	3	12
Surface Epithelial	4	28
Other (Metastatic)	-	2

The surface epithelial tumor, figure 2 presented presence of 2 cases with carcinoma detection on histopathology slides while in the germ cell tumor 1 cases each of strumaovarii, dysgerminoma and mixed germ cell tumor was observed (Figure 2).

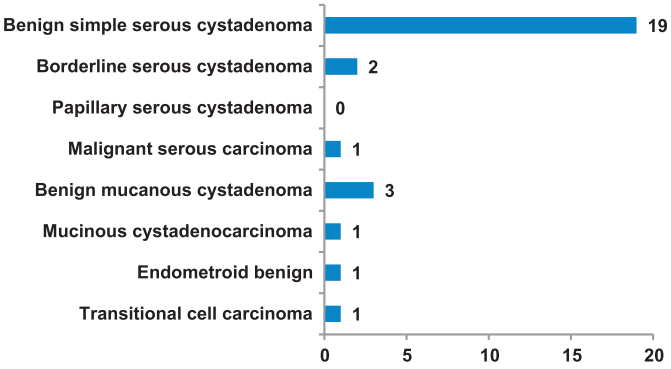

Figure 2: Histopathological Finding with Surface Epithelial Tumor

Within Germ Cell Tumor cases of teratoma, mixed germ cell tumor, dysgerminoma and struma ovarri in figure 3.

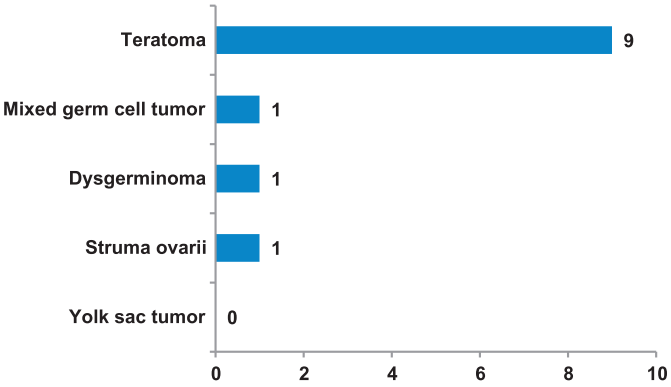

Figure 3: Histopathological Finding with Germ Cell Tumor

Within the Sex cord stromal tumor one each case of metastatic tumor and fibrothecoma was presented in figure 4.

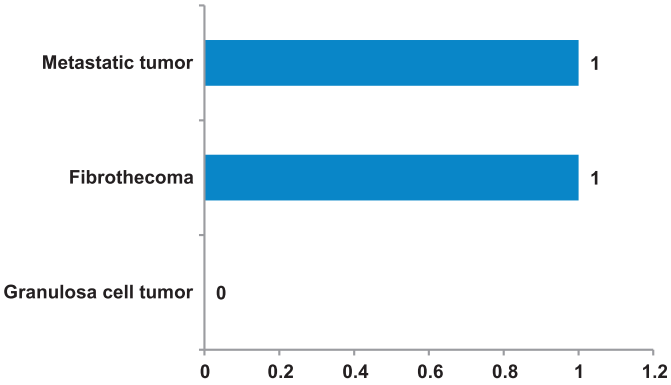

Figure 4: Histopathological Findings of Sex Cord Stromal Tumor

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DISCUSSION

Ovarian lesions present the most challenging issue in today's gynecological practice due to their late diagnosis and diverse morphologies. The mortality rate with ovarian tumors was even higher than the combined mortality rate of cervical and endometrial cancers [11, 12]. Our study focused on the histopathological and radiological correction of findings in ovarian cystectomy specimens which hold great clinical significance for improving treatment, prognosis, and disease management. In the present study, ovarian tumors were categorized based on WHO classification: into neoplastic and non-neoplastic groups. The neoplastic lesions were further divided into benign and malignant categories. This research revealed that the common cause of non-neoplastic ovarian lesions was benign cystadenoma, followed by corpus luteal cysts. The findings of the present study were similar with the studies of Mannan R *et al.*, and Prakash A *et al* [13, 14]. Mannan R *et al.*, indicated that out of 145 cases examined, 75 were non-neoplastic and the remaining 70 were neoplastic [13]. This indicates a remarkably high prevalence of follicular cysts. Similarly, in a study by Prakash A *et al.*, follicular cysts were the predominant non-neoplastic lesions at 45.5%, followed by orpus luteum cysts at 25% [14]. The study by Gaikwad SL *et al.*, found that corpus luteal cysts were the common non-neoplastic lesion [12]. The present study has the similar findings which correlated with the previously reported data. In this study, surface epithelial tumors were the most common neoplastic lesions of the ovary, while metastatic tumors were the least frequent. Tejani AS *et al.*, stated that they encountered surface epithelial tumors most frequently (63%), followed by germ cell tumors (29%) out of 258 cases [15]. Additionally, Wetterwald L *et al.*, found that 70.2% of cases were surface epithelial tumors [16]. In a study conducted by Kipp B *et al.*, revealed that 67.9% of all tumorsaccounted for surface epithelial tumors and 73% of the malignant group [17]. The distribution of sex cord-stromal tumors was very low at 5.3%. According to literature, endometrioid ovarian carcinoma makes up 10-25% of ovarian carcinomas. Consistent with our findings, previous studies have also indicated that among surface epithelial tumors, benignserous cystadenoma was most common[18-22].

CONCLUSIONS

Surface epithelial tumors were the most common category of ovarian tumors and majority of the cysts were benign cystadenomas. Radiological imaging provides a precise non-invasive tool for categorizing various ovarian cysts and histopathological findings further confirms the exact category of tumors.

Authors Contribution

Conceptualization: NK
Methodology: NK, HK, SG, SY, FBN, AK
Formal analysis: NK
Writing, review and editing: NK, HK, SG, SY, FBN, AK

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

An Exploratory Study on Integrative Management of Irritable Bowel Syndrome with Constipation (IBS-C)

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ABSTRACT

Irritable Bowel Syndrome (IBS) was complicated disorder that results in pain and change in bowel habits. The major contributing factors to the onset and detoriation include stress and gastrointestinal problem. The women between 20 to 40 years were most commonly involved. The prevalence varies among countries that was affected by diet and diagnostic criteria. **Objective:** Compairing the efficacy of Mebeverine, Polyethylene Glycol with the combination therapy of Mebeverine and Polyethylene Glycol in Irritable Bowel Syndrome associated with Constipation. **Methods:** The comparative analytical study was conducted at the National Medical Centre, Karachi, and approved by the Ethical Review Committee of Bahria University Health Science Campus. Participants aged 15-50 with IBS were selected to reflect the target population. Observational data were collected based on the treatments they naturally received: Mebeverine, Polyethylene glycol, or a combination. Pain and constipation status were recorded at baseline (day 0) and after 24 days, analyzing the effectiveness of the treatments as they were administered in routine care settings. **Results:** The demographic data mentioned comparable age, weight, height, and gender distribution across the three groups. Constipation and pain status before and after varied considerably across the investigation time. There was substantial improvements by day 24 from the baseline in the combination therapy. **Conclusions:** The combination of Mebeverine and Polyethylene glycol reveals in managing IBS, with prominent improvements in constipation severity over the research duration. This highlights the importance of multimodal treatment methods in addressing the varied symptoms of IBS and enhancing the quality of life.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a complicated condition involving the intestines. It is defined by changes in bowel habits and associated pain that is disturbing everyday life and ability to work normally . Multiple factors were involved that contribute to the onset of IBS, including impaired gastrointestinal movement, excessive bacterial presence, visceral sensitivity, changes in gut microbiota, impaired nutrient absorption, and inflammation [2]. Moreover, psychological factors like stress might worsen the severity of IBS symptoms [3]. This disorder normally affects more women than men, with onset frequently occurring between ages 20 and 29 years [4, 5]. The prevalence of irritable bowel syndrome (IBS) differs considerably between countries due to differences in dietary patterns, cultural influences, and diagnostic methodologies. Globally, the occurrence of IBS differs, influenced in part by the diagnostic criteria applied [6]. A meta-analysis mentioned 57 eligible studies, IBS prevalence was 9.2% using Rome III criteria and 3.8% with Rome IV criteria. IBS with mixed bowel habits was most common with Rome III, while IBS with diarrhea was most common with Rome IV. The prevalence of IBS was higher in women, and significant variability in prevalence was observed between countries, suggesting Rome IV criteria may be less suitable for broad

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epidemiological surveys [4]. While the nationwide prevalence of irritable bowel syndrome (IBS) in Pakistan is still unknown, a study conducted in the outpatient departments of internal medicine units at tertiary care hospitals across various cities found the prevalence of IBS in the general population to be 33.2% [7]. The categorization of lirrtable Bowel Syndrome (IBS) is based on stool pattern, distinguishing between diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), or undefined (IBS-U) [8]. This syndrome significantly impacts sufferers' professional and social lives, often leading to a notable decline in quality of life (QoL). This condition can cause debilitating symptoms such as abdominal pain, bloating, and altered bowel habits, which frequently hinder daily activities and social interactions. Studies indicate that patients with IBS may experience anxiety, depression, and social withdrawal due to the unpredictability and discomfort associated with their symptoms [9]. The pathophysiology of irritable bowel syndrome (IBS) is multifaceted and increasingly recognized as involving various biological and psychosocial factors rather than being purely psychological. Key contributors include genetic predispositions, environmental influences, and gut-specific disturbances. The condition is characterized by visceral hypersensitivity, leading to heightened pain perception, as well as motility issues that can result in symptoms like abdominal discomfort, diarrhea, or constipation [10]. Recognizing IBS as a spectrum disorder with overlapping features suggests a comprehensive approach to diagnosis and treatment, taking into account genetic predisposition, dietary factors, gut microbiota, and dysfunction in the gut-brain axis [2]. The management of Irritable Bowel Syndrome (IBS) has gained global attention due to the limited success of single-agent treatments. Treatment strategies for IBS-C may include both non-pharmacological and pharmacological interventions, tailored to individual symptoms. An evolving method includes combining pharmacological agents from diverse classes to widely address symptom [11]. This investigation aimed to integrate first line drug with agents from diverse classes, such as antispasmodics, to bridge this gap. Antispasmodics, such as Mebeverine, deliver a safe selection, regardless of the indistinct mechanism of action. Mebeverine's numerous actions, as well as reducing ion permeability and blocking noradrenaline reuptake, contribute to its efficacy in managing IBS-related abdominal distress. It acts by relaxing gut muscles, making it a chosen treatment for IBS patients with major pain, as per present strategies [12]. Polyethylene Glycol (PEG), or macrogol, is a non-absorbable polymer marginally absorbed in the gastrointestinal tract. Large daily doses of PEG solution have revealed effectiveness in the management of fecal impaction and severe constipation. As an osmotic laxative, PEG's efficiency differs with dosage, with low adverse effects and increase tolerability. Its inert nature approves marginal impact on the movement of other substances in the gastrointestinal tract [13].

The aim of this study was to investigate the efficacy of combining Mebeverine and Polyethylene glycol in managing symptoms of irritable bowel syndrome with constipation (IBS-C) over a 24-day period, compared to monotherapy with either medication alone.

METHODS

This comparative analytical study was conducted as part of MPhil research at Bahria University Health Science Campus. Ethical approval was granted by the Ethical Review Committee of Bahria University Health Science Campus (Ref No: FRC/BUMD 14/2021-Pharm-108, ERC 81/2021). The study took place at the National Medical Centre in Karachi from December 2021 to June 2022, with consent obtained from the director and head of the institution. Participants aged 15-50 years were recruited and randomly assigned to one of three groups. Informed consent was obtained in both Urdu and English. A total of 162 participants completed the study, with assessments conducted at baseline (day 0) and after 24 days [14]. Based on the calculations, the total sample size of 162 participants was required, with an equal number of exposed and unexposed individuals to achieve 80% power at a 95% confidence level. The study included patients with type 1 and type 2 constipation, identified using the Bristol Stool Chart, who reported mild to severe pain according to the Visual Analog Scale. Participants of any gender or ethnicity who consented to the study were eligible. Prior to enrollment, participants underwent evaluations including medical history, physical examination, hematological tests, stool analysis, and blood tests for glucose and thyroid profiles. Exclusion criteria included previous use of any relevant treatments or interventions, as well as the presence of co-morbid conditions such as coronary artery disease, cardiac failure, chronic obstructive pulmonary disease, hypothyroidism, gluten hypersensitivity, diabetes, or malignancy. Data collection involved assessing participants' symptoms and responses through questionnaires at baseline and after 24 days. Group I received oral Mebeverine 135 mg twice daily, Group II received Polyethylene glycol 3350 once daily, and Group III received both treatments. Data from the questionnaires were entered into Microsoft Excel for descriptive analysis and analyzed using SPSS version 25.0. Descriptive statistics included mean, standard deviation, frequencies, and proportions. One-way ANOVA was used for numerical data, while Pearson's Chi-square tests were applied to categorical data. Reliability analysis using Cronbach's alpha showed high internal consistency for the constipation scale ($\alpha = 0.883$).

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RESULTS

In the study, a total of 162 patients suffering from irritable bowel syndrome (IBS) were surveyed. The demographic characteristics of patients across the three treatment groups (Groups I, II, and III) were comparable, as indicated by mean age, weight, height, and gender distribution. There were no statistically significant differences observed among the groups for age (p = 0.168), weight (p = 0.348), height (p = 0.795), or gender distribution (p = 0.974) as demonstrated in Table 1.

Table 1: Demographics of Patients in Groups I, II and III

Variables	Group I Mean ± SD / N (%)	Group II Mean ± SD / N (%)	Group III Mean ± SD / N (%)	p-Value
Age (Years)	30.28 ± 10.31	33.89 ± 9.91	32.56 ± 9.74	0.168[a]
Weight (Kg)	70.85 ± 12.90	67.56 ± 10.11	68.57 ± 12.86	0.348[a]
Height (m)	1.62 ± 0.10	1.62 ± 0.11	1.63 ± 0.11	0.795[a]
Gender				
Female	33 (61.1%)	34 (63.0%)	33 (61.1%)	0.974[a]
Male	21 (38.9%)	20 (37.0%)	21 (38.9%)	

Group I – recieved Mebeverine, Group II – received Polyethylene glycol, Group III – received Mebeverine + Polyethylene glycol δ
Age, Height and Weight One-way ANOVA,
Gender – chi square test
[a] – non-significant p-value > 0.05

In table 2 at day 0, a considerable proportion of patients in all three groups experienced severe constipation, ranging from 66.7% to 72.2%. However, there were no significant differences observed among the groups regarding the severity of constipation at baseline (p = 0.815). On the 24th day, constipation showed varying degrees of improvement across the three groups. In Group I, constipation remained unchanged in 21 (38.9%) participants, while in Group II, only 1 (1.9%) participant experienced no change, and in Group III, none reported unchanged constipation. Moderately relieved constipation was observed in 30 (55.6%) participants in Group I, 21 (38.9%) in Group II, and 4 (7.4%) in Group III. Significantly relieved constipation was reported by 3 (5.6%) participants in Group I, 32 (59.3%) in Group II, and 50 (92.6%) in Group III. These differences in constipation status on the 24th day were statistically significant across the three groups (p < 0.001).

Table 2: Constipation Status at Days 0 and 24 in IBS Patients

Variables	Group I N (%)	Group II N (%)	Group III N (%)	p-Value
Constipation (Day 0)				
Mild	18 (33.3%)	16 (29.6%)	15 (27.8%)	0.815[a]
Severe	36 (66.7%)	38 (70.4%)	39 (72.2%)	
Constipation (Day 24)				
Unchanged	21 (38.9%)	1 (1.9%)	0 (0.0%)	<0.001**
Moderately Relieved	30 (55.6%)	21 (38.9%)	4 (7.4%)	
Significantly Relieved	3 (5.6%)	32 (59.3%)	50 (92.6%)	

Group I – recieved Mebeverine, Group II – received Polyethylene glycol, Group III – received Mebeverine + Polyethylene glycol δ
Chi square test
[a] – non-significant p-value > 0.05, * – significant p-value < 0.05

In table 3, at day 0, the distribution of pain severity, as assessed by the Visual Analogue Scale (VAS), showed similar patterns across all three groups. The majority of patients reported moderate to severe pain, with proportions ranging from 53.7% to 70.4%. However, there were no significant differences observed among the groups regarding pain severity at baseline (p = 0.781). On day 24, there were notable changes in pain severity across the groups. In Group I, a considerable proportion of patients reported no pain (57.4%), while in Group II, fewer patients reported no pain (11.1%). Interestingly, in Group III, the vast majority of patients (87.0%) reported no pain. Conversely, the proportion of patients reporting severe pain decreased significantly in all groups, with the most substantial reduction observed in Group III. These differences in pain severity on day 24 were statistically significant across the three groups (p < 0.001).

Table 3: Pain Severity on Visual Analogue Scale (VAS) at Day 0 and Day 24 in IBS-C Patients

Variables	Group I N (%)	Group II N (%)	Group III N (%)	p-Value
VAS Day 0				
No Pain	2 (3.7%)	2 (3.7%)	2 (3.7%)	0.781[a]
Slight	13 (24.1%)	11 (20.4%)	8 (14.8%)	
Moderate	29 (53.7%)	26 (48.1%)	27 (50.0%)	
Severe	10 (18.5%)	15 (27.8%)	17 (31.5%)	
VAS Day 24				
No Pain	31 (57.4%)	6 (11.1%)	47 (87.0%)	<0.001*
Slight	23 (42.6%)	18 (33.3%)	7 (13.0%)	
Moderate	0 (0.0%)	29 (53.7%)	0 (0.0%)	
Severe	0 (0.0%)	1 (1.9%)	0 (0.0%)	

Group I – recieved Mebeverine, Group II – received Polyethylene glycol, Group III – received Mebeverine + Polyethylene glycol,
Chi square test
[a] – non-significant p-value > 0.05, * – significant p-value < 0.05

DISCUSSION

The investigation involved patients diagnosed with Irritable Bowel Syndrome (IBS) and concurrent constipation, between an age ranges from 15 to 50 years. This distribution of age in this study revealed a higher incidence of IBS among younger age groups with a mean age between 30 to 34 years. Similarly, a study conducted in Vietnam indicated a mean patient age of 36 years [15]. Particularly, investigation from Norway underscored a substantial occurrence of IBS among the younger population, with age below 40 years [16]. The greater incidence of Irritable Bowel Syndrome (IBS) among younger in this study and previous may be accredited to lifestyle stressors, dietary habits, and hormonal variations during adolescence and early adulthood. In this study, most of the participants (62%) were female, whereas 38% were male. Similar findings were witnessed in a European study, where 62% were female [17]. Moreover, investigation in Saudi Arabia

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revealed a higher prevalence of IBS among females, however the exact reason for this gender difference remains indistinct [18]. The current study showed the effectiveness of Mebeverine, Polyethylene glycol, and their combination in treating IBS symptoms over 24 days was assessed. Patients were grouped based on their natural treatment regimens: Mebeverine alone, Polyethylene glycol alone, or a combination of both. At the end of the 24-day period, significant improvement in pain severity, as measured by the Visual Analog Scale (VAS), was observed primarily in the group receiving combination therapy. This finding suggests that while each treatment individually had an impact, the combined approach may offer enhanced relief for IBS symptoms in a real-world clinical setting. A study conducted with 200 IBS patients, the effects of Mebeverine in pain management was evaluated. While pain scores showed no change at baseline, a notable decrease was observed by day 28 in the Mebeverine group. Additionally, PAC-QOL scores improved significantly from 91.54% to 53.52% by day 28 [19]. However, antispasmodics, a diverse medication class with various mechanisms, require comprehensive investigation for reliable recommendations. Despite its common prescription for IBS patients, meta-analyses in 2010 and 2012 found no clear effectiveness of mebeverine, contrasting with cumin sofouf, which showed statistically superior results in reducing IBS symptoms [20]. Moreover, a meta-analysis examined the effectiveness of Mebeverine in managing multiple symptoms associated with Irritable Bowel Syndrome (IBS). Incorporating twenty-two studies and approximately 1052 participants, the analysis revealed a significant reduction in pain (P-values ranging from <0.05 to <0.001), consistent with this study findings [12]. Another comparable study conducted at Tanta University's Gastroenterology Department involved 50 outpatients divided into two groups: one receiving Mebeverine alone and the other Mebeverine combined with Pentoxifylline. Both groups showed a significant decrease in Numeric Pain Rating Scale scores (P<0.0001) after three months. Contradictory to this findings, another study in India assessing the efficacy of 200mg controlled release Mebeverine revealed non-significant results (P-value 0.615). Despite expectations, this formulation did not alleviate severe symptoms, as indicated by bowel movement frequency, severity of abdominal cramps, and IBS quality of life score [21]. In this study, a notable proportion of patients across all groups experienced severe constipation at baseline, with no significant differences observed among them ($p = 0.815$). However, by the 24th day, significant improvements in constipation were evident in Group II and Group III exhibiting the most substantial relief compared to Groups I ($p < 0.001$). These findings highlight the efficacy of polyethylene glycol and combination therapy in alleviating constipation symptoms.

In Europe, Polyethylene glycol 3350 plus electrolytes (PEG3350+E) was the primary treatment for Chronic Constipation (CC), boasting superior efficacy and long-term tolerability compared to other laxatives [22]. A randomized clinical trial on children with functional constipation revealed significant stool consistency improvements with both single and divided doses of Polyethylene Glycol (PEG), corroborating this study's outcomes [23]. Furthermore, a meta-analysis emphasized the preference for Polyethylene Glycol (PEG) in irritable bowel syndrome with constipation (IBS-C) due to its favorable side effect profile and efficacy in reducing spontaneous bowel movements versus placebo, aligning with this study's findings on combination therapy efficacy [24]. The disparity in results between this adult-focused combination therapy study and the pediatric longitudinal study may be because of the differences in patient age, treatment protocols, and follow-up duration, indicating the need for tailored approaches in managing IBS across age groups. This study highlighted the complexity of treating Irritable Bowel Syndrome (IBS), underlining the effectiveness of combination therapies like Mebeverine and Polyethylene glycol in improving symptoms, particularly pain and constipation.

CONCLUSIONS

In conclusion, Mebeverine, Polyethylene glycol, and their combination therapy all showed positive results in managing IBS symptoms. Among these, combination therapy demonstrated the most promising outcomes, with notable improvements in symptom relief due to the synergistic effects of the combined treatments. The importance of personalized treatment approaches tailored to individual patient needs. Continued research was essential to refine therapeutic strategies and enhance outcomes for IBS patients, ultimately aiming to improve their quality of life through a better understanding of effective treatment modalities.

Authors Contribution

Conceptualization: ISR
Methodology: WY, MSAJ
Formal analysis: UZ
Writing, review and editing: SJI, SZ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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The Impact of Endometriosis Diagnosis on Women's Mental Health-A Cross-Sectional Study

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ABSTRACT

Endometriosis is a chronic condition where tissue similar to endometrium grows outside the uterus. It affects the social and psychological life of women. **Objective:** To evaluate the impact of endometriosis diagnosis on women's mental health. **Methods:** In this cross-sectional study basal data, Endometriosis Health Profile (EHP-30) statuses, and Hospital Anxiety and Depression scale scores were collected from 200 sub-fertile women who were sampled using a non-probability sampling technique. Frequency distribution and chi-square (X^2) analysis were performed using IBM SPSS® version 26.0. **Results:** Out of 200 sub-fertile women 28 (14%) had endometriosis. Positive endometriosis significantly correlated with age (0.09<0.1). The endometriosis-related health statuses significantly correlated with anxiety and depression with two-sided asymptomatic significances of 0.007(<0.05) and 0.000(<0.05) respectively. The highest prevalence of severe anxiety and depression was present in women with bad possible health profiles related to endometriosis. **Conclusions:** It was concluded that endometriosis aggravates with age and its positive diagnosis has a strong negative impact on the social and psychological health of the patients.

INTRODUCTION

Endometriosis is a chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterus. It affects approximately 10% of women of reproductive age worldwide [1]. Endometriosis is a condition characterized by dysmenorrhea, menorrhagia, and dyspareunia, as well as severe pelvic pain, menstrual difficulties, difficulty walking, ovarian pain, bloating, diarrhoea, cramps, nausea, vomiting, anal pain, painful urinary tract symptoms, fainting, sciatica during menstruation, and right chest pain [2, 3]. It is also linked to sub-fertility or infertility, where women struggle to conceive due to the presence of endometrial polyps, fibroids, and PCOS. Retrograde menstruation, where endometrial cells flow back through fallopian tubes, is a major factor contributing to endometriosis [4]. Endometriosis causes significant psychological distress in

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women, including anxiety, depression, and reduced self-esteem due to fertility uncertainty, and management challenges [5]. Chronic pain, sexual dysfunction, and fertility issues associated with endometriosis can lead to decreased sexual satisfaction, communication difficulties, and relationship dissatisfaction [6]. Social support systems in Pakistan play a crucial role in addressing the challenges of endometriosis, with the laparoscopic diagnosis affecting 16.8-55% of women with infertility [7]. Endometriosis negatively impacts women, causing pain, psychological effects, and future uncertainty due to recurrent surgeries and prolonged medical treatment [8]. The physical impact was linked to symptoms, unfavourable therapeutic side effects, and physical changes, causing many individuals to struggle with daily activities like walking and exercising [9]. Reduced sex frequency, avoiding sex due to pain or bleeding, and lack of orgasm can cause frustration and strained relationships, leading to some couples' divorces due to misunderstanding [10]. Healthcare practitioners can give early diagnosis, and suitable management options, enhance patient care, and contribute to evidence-based decision-making by evaluating the prevalence of endometriosis in this specific group. Understanding the socio-psychological effects of endometriosis will also allow for the development of targeted interventions, support mechanisms, and counselling services to address these women's mental health and well-being, thereby improving their overall treatment experience and reproductive outcomes [11]. Teens' primary concern is education, with two-thirds of women experiencing academic performance issues, including time away from school, decreased productivity, and missed work opportunities due to endometriosis [12]. Endometriosis affects roughly 10-15% of women of reproductive age, according to prior research; the socio-psychological effects of endometriosis on women have been inadequately explored [13]. However, due to a lack of study in this group, the real prevalence of endometriosis among women having diagnostic laparoscopy for infertility remains unknown. It is difficult to appropriately identify and manage endometriosis in women seeking reproductive therapy without a firm awareness of its prevalence [14].

This research aimed to assess the socio-psychological effects of endometriosis on women having sub-fertility conducted at Arif Memorial Teaching Hospital in Lahore.

METHODS

The study incorporated a structured questionnaire and patient medical histories for data on endometriosis with informed consent. Demographic factors such as age, weight, height, waist, monthly income, marriage duration, ethnicity, family system, education, and working condition; medical history on alcohol consumption, smoking, abortion, previous surgeries and accidents; and menstruation-related analysis of irregularity, pain, duration, and bleeding patterns were measured. The demographic factors were quantitative variables while the rest of the measured variables were qualitative. Endometriosis Health Profile-30 (EHP-30) and the Hospital Anxiety and Depression Scale (HADS) tools were used to investigate the objectives. The EHP-30 assesses pain control, emotional well-being, social support, and sexual function, with scores ranging from 0 to 100. The scale findings were divided into four categories, (0-25) worst possible health status, (26-50) bad possible health status (51-75) good possible health status and (76-100) better possible health status. The HADS, a widely used scale, assesses anxiety and depression symptoms in patient's endometriosis, with scores ranging from normal to severe. This scale was divided into four categories for anxiety and depression normal (0-7), mild (8-10), moderate (11-15) and severe (16-21) [15, 16]. Data were analyzed using IBM SPSS® version 26.0. Descriptive statistics of the demographic, medical history, and menstruation-related factors were performed followed by the Pearson chi-square analysis of endometriosis with age and weight. A Chi-square association test was also applied between EHP and HADS anxiety and EHP and HADS depression. The study received approval from The University of Lahore and hospital Institutional Review Boards (IRBs) (research ethical committee, REC-UOL-/130/08/23).

RESULTS

The proportion of respondents with clinically diagnosed positive endometriosis was analyzed. It accounts for 14% of our study respondents among 200 sub-fertile women (Figure 1).

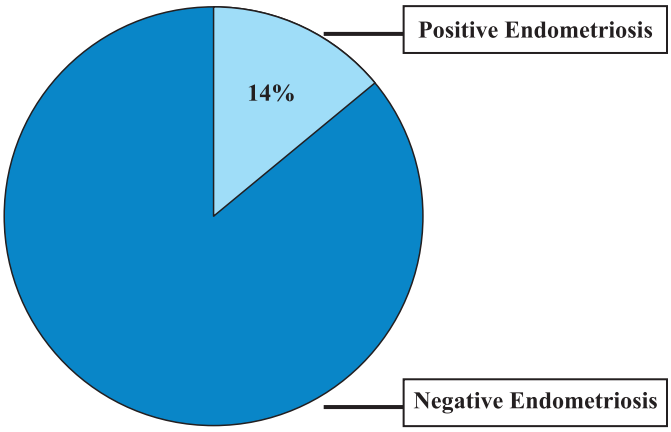

Figure 1: Proportion of Women with Clinically Diagnosed Endometriosis

A major proportion of the sub-fertile women were between 30-39 years (64%), while none were below 19 years of age. The major 58% proportion of sub-fertile women belonged

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to the weight range of 61-80kg. Women with a weight range of 61-80 kg are more prone to sub-fertility as supported by our study statistics of 58%. The highest proportion of sub-fertile women were more than average height (53%). In our study, 131 out of 200 sub-fertile women had a waist size of 88. A maximum number of sub-fertile women resided in nuclear family systems (53.5%) and played the roles of housewives (51.5%). 49% of the sub-fertile women were graduates and those with 1-5 years of marriage were sub-fertile (80.5%) (Table 1).

Table 1: Socio-Demographic Analysis of Sub-Fertile Women

Socio-Demographic Factors		Frequency (%)
Age (Years)	Below 19	0
	20-29	49 (24.5)
	30-39	128 (64)
	40-49	23 (11.5)
Weight (kg)	<40	-
	41-60	57 (28.5)
	61-80	116 (58)
	81-100	26 (13)
	>100	1 (0.5)
Height Foot' Inches"	4-4.5	2 (1)
	4.6-5	85 (42.5)
	5.1-5.5	1 (0.5)
	5.6-6	106 (53)
	>6	6 (3)
Waist	<88	45 (22.5)
	88	131 (65.5)
	>88	24 (12)
Ethnicity	Punjabi	198 (99)
	Prefer Not to Say	2 (1)
Family System	Joint	93 (46.5)
	Nuclear	107 (53.5)
Education	Primary	-
	Higher Secondary	76 (38)
	Graduate	98 (49)
	Post Graduate	26 (13)
Working Condition	Private Jobs	79 (39.5)
	Government Jobs	17 (8.5)
	Housewives	104 (51.5)
Monthly Income (Rs.)	<30k	2 (1)
	31k-60k	58 (29)
	61k-90k	109 (54.5)
	>90k	-
Marriage Duration (years)	1-5	161 (80.5)
	6-10	21 (10.5)
	11-15	16 (8)
	16-20	2 (1)

A general health status analysis of sub-fertile women was done which concluded that 57% of the women were in a good state of health; only 3.5% used to smoke and 2% consumed alcohol. There had been no previous abortions, surgeries, or accidents in 81.5%, 90.5%, and 87.5% of the sub-fertile women (Table 2).

Table 2: Medical History Analysis of Sub-Fertile Women

Medical History		Frequency (%)
Abortion	Yes	37 (18.5)
	No	163 (81.5)
Smoking	Yes	7 (3.5)
	Quitted	8 (4)
	Sometime	8 (4)
	No	177 (88.5)
Alcohol Consumption	Yes	4 (2)
	No	194 (97)
	Quitted	2 (1)
Previous Surgeries	Yes	12 (6)
	No	181 (90.5)
	Don't know	7 (3.5)
Previous Accidents	Yes	20 (10)
	No	175 (87.5)
	Don't know	5 (2.5)

The factors associated with the menstruation cycle of sub-fertile women are often assessed for predisposition to endometriosis. The majority of women were not undergoing any hormonal therapy (83.5%). There was menstruation regularity, slight pain, and normal bleeding patterns in 73.5%, 52% 64% of the sub-fertile women (Table 3).

Table 3: Menstruation-Related Analysis of Sub-Fertile Women

Menstruation-Related Conditions		Frequency (%)
Menstruation Irregularity	Yes	53 (26.5)
	No	147 (73.5)
Menstruation Pain	No	75 (37.5)
	Slight Pain	104 (52)
	Heavy Pain	21 (10.5)
	Light	35 (17.5)
Bleeding Patterns	Normal	124 (62)
	Heavy	41 (20.5)
	<3	22 (11)
Duration of Menstruation (Days)	3	15 (7.5)
	3-7	163 (81.5)
	>7	-

Table 4 indicates the chi-square cross-tabulation of endometriosis with age and weight. Frequency distribution shows that among the sub-fertile females with positive endometriosis, four were 30-39 years old and weighed around 41-60 Kgs. Person-associated p-value determines a correlation between age and positive endometriosis (0.0907<0.1) (Table 4).

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Table 4: Cross-Tabulation Analysis of Positive Endometriosis with Age and Weight

Variables		Endometriosis		Total (n)	Pearson Chi-Square Value	p-value
		Positive (%)	Negative (%)			
Age	20-29	12.5	87.5	8	2.758[a]	0.097
	30-39	20	80	20		
Total		17.8	82.1	28		
Weight	41-60	30.7	69.3	13	0.219[a]	0.640
	61-80	6.6	93.3	15		
Total		17.8	82.1	28		

The study reveals that individuals with normal anxiety are predominantly in the 'normal' or 'good health' category (11.1%), with minor representation in the 'bad possible health' category (7.4%). Mild anxiety is found in 'Better Possible Health Status' (3.7%), 'Bad Possible Health' (3.7%), and 'Worse Possible Health Status' (7.4%). Moderate anxiety is most common in the 'Bad Possible Health' group (11.1%), while severe anxiety is most frequently observed in the 'Bad Possible Health' (37%) and 'Worse Possible Health Status' (14.8%) groups, indicating a strong link between severe anxiety and poorer health conditions, highlighting a significant relationship between these mental health conditions and health status. Depression is most prevalent in individuals with 'Normal or Good Health' (11.1%); mild depression is found in 'Better Possible Health Status' (3.7%) and 'Bad Possible Health' (7.4%). Moderate depression is mostly found in 'Bad Possible Health' (7.4%), and severe depression is high in 'Bad Possible Health' (40.7%) and 'Worse Possible Health Status' (25.9%). This highlights a significant relationship between mental health conditions and health status (Table 5).

Table 5: Cross Tabulation Frequency Analysis of EHP Categories and HADS Anxiety and Depression

Variables		Endometriosis Health Profile (EHP)					
		Better Possible Health (%)	Normal or Good health (%)	Bad possible health (%)	Worse possible health (%)	Total (%)	Pearson X^2 (p-value)
HADS Anxiety	Normal	0	11.1	7.4	0	18.5	22.802 (0.007)
	Mild	3.7	0	3.7	7.4	14.8	
	Moderate	0	0	11.1	3.7	14.8	
	Severe	0	0	37	14.8	51.8	
Total		3.7	11.1	59.2	25.9	100	
HADS Depression	Normal	0	11.1	3.7	0	14.8	30.141 (0.000)
	Mild	3.7	0	7.4	0	11.1	
	Moderate	0	0	7.4	0	7.4	
	Severe	0	0	40.7	25.9	66.6	
Total		3.7	11.1	59.2	25.9	100	

DISCUSSION

The study reveals that endometriosis is a complex clinical issue with symptoms overlapping with other disorders, mistaking them for menstrual pain. Out of 200 sub-fertile women, 28 (14%) were positive for endometriosis after being diagnosed with laparoscopy and 16% were diagnosed positively for endometriosis after pelvic ultrasound and laparoscopy [17, 18]. In the two studies which comprised 169 and 100 women with primary infertility, the highest frequency (57% and 55.9%) belonged to the age group 20-30 years which contradicts the findings of this study i.e. 64% sub-fertile women aged 30-39 years [17, 19]. Marriage duration was also assessed with 61.5% of sub-fertile women being married for 2-4 years which aligns with the frequency of 80.5% being married for 1-5 years [17]. It is deduced from this study that 51.5% of sub-fertile women are housewives; this is supported by the 58% highest prevalence of housewives being sub-fertile. The study conducted by Ahmed et al., also assesses the menstruation cycle related to sub-fertility. Menstruation cycle, amount of loss, and dysmenorrhea were analyzed which are equivalent to menstruation irregularity, bleeding patterns, and menstruation pain in this study. The frequency distributions of these factors in both studies are highest for the same categories [19]. A study conducted in 2024 concluded that infertile women with no pain (predisposition of endometriosis) had higher income and higher education levels than fertile women; this supports the findings of this study which inferred that 54.5% of sub-fertile women earned more than ninety thousand rupees and 51.5% were graduates. Moreover, 83.5% of the women with primary infertility in this study underwent no hormonal therapy which complements the findings of the cross-sectional study where 80% of the women using hormonal therapy had no association with infertility [20]. The conducted study analyzed that severe anxiety (37%) and depression (40.7%) were present in women with bad possible health category of EHP-30; this lines up with the under-discussion study results in which worst scores for depression and anxiety were seen in women with both pain and infertility [21]. In a systematic review which assessed the impact of endometriosis on depressive and anxiety symptoms and quality of life, HADS was used in 22.2% of the 18 included studies; while EHP-30 was used as an assessment tool in 28.6% of the 28 included studies. In all of the studies that incorporated HADS-d and HADS-a scales significantly strong associations were declared between anxiety, depression, endometriosis, and quality of sleep. Similarly, in all the studies that utilized EHP-30 the QOL scores indicated endometriosis-related depression, dysmenorrhea, dyspareunia, acyclic pain, and fatigue [21]. This study is the first of its kind where associations between EHP-30 and HADS-a and EHP-30 and HADS-d were statistically analyzed resulting in significant Pearson p-values of 0.007 and 0.000 respectively.

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CONCLUSIONS

It was concluded that endometriosis aggravates with age and its positive diagnosis has a strong negative impact on the social and psychological health of the patients. Women with bad possible health status related to endometriosis will have severe anxiety and depression. It is advised to health clinicians and women, in general, to work on the early diagnosis and treatment of endometriosis before it interferes with the social and psychological health of the women.

Authors Contribution

Conceptualization: SH
Methodology: SH, MS
Formal analysis: NA, AT
Writing review and editing: MS, ZA, HT, AM, NS, AT

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

Conflicts of Interest

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Perceptions for Utilization of Artificial Intelligence among Early Pediatric Rehabilitation Practitioners: A Survey in Pakistan

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ABSTRACT

Integration of Artificial Intelligence in clinical medicine is rapidly expanding, driven by advancements in computing and extensive datasets. Artificial Intelligence is primarily utilized to design diagnostic tools for numerous medical conditions. **Objective:** To assess perceptions of using Artificial Intelligence among early pediatric rehabilitation practitioners in Pakistan. **Methods:** A cross-sectional online survey was conducted from November 2023 to April 2024, targeting young Masters students of Physical Therapy specializing in Pediatric Care and early pediatric therapists across Pakistan. Nonprobability convenience sampling was utilized. Participants were recruited through mailing lists and social media platforms. The anonymous survey collected demographic data and explored participants' knowledge, expected benefits, fears, and practices regarding Artificial Intelligence using a structured questionnaire. Descriptive statistics were employed for data analysis. **Results:** A total of 120 participants, with a mean age of 26 years and 70% female representation, completed the survey. Approximately 39.1% had received Artificial Intelligence training during their medical education, and 48.3% had utilized Artificial Intelligence tools during their learning. Key findings included 93.3% believing that Artificial Intelligence will enhance medical training and 60.8% agreeing that Artificial Intelligence will improve healthcare access. Despite positive attitudes towards AI, 54.1% had not utilized AI in their practice, indicating a need for further professional education. **Conclusions:** It was concluded that the study highlights a generally positive perception of Artificial Intelligence among novice pediatric rehabilitation practitioners in Pakistan but underscores the need for comprehensive AI education and training.

INTRODUCTION

Artificial intelligence (AI) inventor Marvin Minsky coined AI as "the science of making machines accomplish tasks that would typically necessitate human intelligence" [1]. Integration of AI tools is quickly increasing in clinical medicine, simplified by the extensive accessibility of strong processors and wide-ranging datasets [2]. AI has chiefly been employed in formulating diagnostic tools across various medical circumstances [3]. For example, by employing image recognition methods like convolutional neural networks, AI helps in the detection of fractures on X-rays [4], diabetic retinopathy on digital fundus images [5], skin cancer [6], and hereditary diseases on facial images [7]. Other than convolutional neural networks, AI-driven diagnostic applications comprise enhancing autism diagnosis [8], recognizing child abuse from medical archives [9], and using natural language processing methods to support clinicians in detecting uncommon disorders [10]. AI also has applications in non-diagnostic areas, supporting chronic illness management like diabetes [11], decision-making, hospital monitoring processes, drug discovery pipelines, and surgical robotics [12]. AI-based healthcare gadgets display potential but

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hinge on complex geometric practices and ideas, thereby suggesting both high outlooks and hesitations among practitioners. Several studies have investigated into the information, attitudes, and practices (KAP) of young healthcare professionals toward AI. Sit et al. executed an internet survey among four hundred and eighty-four medical student population in the UK via social media, exploring their knowledge, attitude and practices towards AI and its possible strong impact on selecting radiology as a speciality [13]. Though some students expressed reluctance to specialize in radiology due to AI concerns, the majority recognized AI's importance in medicine and believed AI training would benefit their careers. In France, Lai et al., conducted a qualitative survey focusing on AI perceptions among diverse healthcare stakeholders, revealing varying perspectives across professionals, industrial partners, regulatory agencies, and researchers. While healthcare professionals prioritized patient care and safety, industrial partners viewed AI as a significant breakthrough despite challenges in accessing health data. Researchers hoped for a smoother transition from AI research to practice [14]. Similarly, insights from international surveys that have been conducted among pediatric rehabilitation specialists shed light on their perceptions and utilization of AI in pediatric care. These specialists, while recognizing the potential of AI in improving pediatric rehabilitation outcomes, expressed concerns regarding data privacy, access to AI tools, and the need for further training to effectively integrate AI into practice. Their perspectives contribute valuable visions into the barriers and opportunities related to AI adoption in pediatric healthcare. While existing studies have explored AI perceptions among various healthcare specialities, none have specifically targeted young pediatric allied healthcare professionals in Pakistan.

This study aimed to conduct an online survey to gauge allied healthcare pediatricians' KAP towards AI, aiming to fill this research gap and provide unique insights into AI utilization in pediatric healthcare in Pakistan.

METHODS

This cross-sectional online study targeted young Masters students of Physical Therapy specializing in Pediatric care and novice pediatric therapists from across Pakistan. The study objective is to explore their perceptions, knowledge, and applications of artificial intelligence (AI) in pediatric rehabilitation. An online survey was conducted from November 2023 to April 2024, participants were recruited using several regional and nationwide emailing lists and media platforms. The study was designed to include new professionals registered on various Facebook pages and groups such as "Young Physiotherapist," "Physiotherapy in Pakistan" and specific pediatric rehabilitation promotion groups. Therapists between the age group of 24 to 34 were recruited in the study. The survey was anonymous, and only individuals identified as pediatric therapists were eligible for participation. Though there were no stringent age parameters, the majority of participants belonged to young physician groups, typically Master residents and fellows. The online survey form, formulated and administered through Google Forms, comprised several sections. The initial questions collected demographic data such as age, gender, faculty, experience level, and any further training. The survey was then organized into four portions: (1) information about AI, (2) probable benefits of AI, (3) uncertainties toward AI, and (4) practices about AI. Answers to closed queries were collected using a 5-point Likert scale, with choices extending from disagree to agree. Questions expecting numerical entries provided ranges of probable scores. Social media groups and emailing lists received a distinct form, and answer files were combined for analysis. Partial replies were included in the analysis, and it was not required to answer all survey questions. Descriptive statistics, including means, medians, and percentages, were used for data analysis. All analyses were conducted using SPSS Version 23.0 software. Participation in the survey was voluntary, and informed consent was considered obtained upon completion of the questionnaire. Participant responses were anonymized, and individuals had the right to view and omit their replies. Due to the anonymous nature of the questionnaire, duplicate responses were unlikely.

RESULTS

One hundred and twenty individuals participated in the survey. 70% of the sample constituted female pediatric novice therapists. Respondents' mean age was 26.2 years. Socio demographic characteristics are shown in table 1.

Table 1: Socio-Demographic Characteristics of Participants

Characteristics	Values
Age (Mean, SD)	26.2 (5.2)
Gender	
Male	43
Female	77
Working Place	
Private Clinic	48 (40%)
Special School	34 (28.3%)
Hospital	12 (10%)
Others	26 (21.6%)

A significant majority, 93.3%, believed that AI would enhance medical training, indicating strong confidence in its potential. When it came to gathering information from patients, opinions were more mixed; 51% affirmed AI's ability to improve this process, while 19.1% disagreed and 29.1% remained neutral. Similarly, nearly half of the respondents (48.3%) thought AI would assist in analyzing

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medical data, although 16.6% did not share this view, and 35% were neutral. In terms of improving healthcare access, 60.8% of participants supported the idea that AI could make a positive impact, while only 12.5% opposed it. The responses regarding AI's role in enhancing patient compliance with treatment and follow-up showed greater variability, with 35% believing it could help, 26.6% disagreeing, and 38.3% remaining neutral. Finally, for the question of whether AI would aid in accessing patient data to provide the most appropriate therapeutic options, 48.3% agreed, 14.1% disagreed, and 37.5% were neutral. Overall, the data reflected strong support for AI's potential benefits in medical training and healthcare access, while opinions were more divided on its effectiveness in patient compliance and information gathering. Survey responses regarding the perceived benefits of AI in healthcare across five key areas are summarized in table 2.

Table 2: Responses Regarding Benefits of AI

Question	Frequency (%)
Do you believe AI will enhance medical training?	
Yes	112 (93.3%)
No	6 (5.0%)
Neutral	2 (1.6%)
Do you think AI will improve the process of gathering information from patients?	
Yes	62 (51%)
No	23 (19.1%)
Neutral	35 (29.1%)
Do you think AI will assist in analyzing medical data?	
Yes	58 (48.3%)
No	20 (16.6%)
Neutral	42 (35.0%)
Do you believe AI will improve healthcare access?	
Yes	73 (60.8%)
No	15 (12.5%)
Neutral	32 (26.6%)
Can AI enhance patient compliance with treatment and follow-up?	
Yes	42 (35.0%)
No	32 (26.6%)
Neutral	46 (38.3%)

A minority, 39.1%, reported having received AI training during their medical college education, while 60.8% indicated they had not. Regarding the utilization of AI tools during their learning, 48.3% affirmed that they had used such tools, whereas 51.6% had not. In terms of practical application, 45.8% stated they had utilized AI in their practice, while 54.1% had not. When asked whether specific AI training should be provided to healthcare practitioners, a significant majority of 70% agreed, indicating strong support for enhanced training. Additionally, 61.6% believed that the ethical challenges associated with AI use should be part of the education for healthcare practitioners, while 38.3% disagreed. Overall, the data reflected a clear recognition of the importance of AI training and education on ethical issues among healthcare professionals, despite a lack of widespread training and tool utilization in their current practices. the descriptive statistics regarding the experiences and opinions of medical practitioners concerning AI training and its application in healthcare and these are shown in table 3.

Table 3: Responses Regarding Practices of AI

Question	Frequency (%)
Have you received AI training during your medical college?	
Yes	47 (39.1%)
No	73 (60.8%)
Have you utilized AI tools during your learning?	
Yes	58 (48.3%)
No	62 (51.6%)
Have you utilized AI in your practice?	
Yes	55 (45.8%)
No	65 (54.1%)
Do you believe specific AI training should be given to healthcare practitioners?	
Yes	84 (70.0%)
No	36 (30.0%)
Do you believe the ethical challenges associated with AI use should be educated to health care practitioners?	
Yes	74 (61.6%)
No	46 (38.3%)
Total	120 (100%)

Confidence in the reliability of AI systems was mixed, with 36.6% expressing confidence, 43.3% lacking it, and 20% neutral. A majority (54.1%) thought over-relying on AI could lead to negative consequences in decision-making, whereas opinions on AI's impact on job security varied; 28.3% were concerned, 42.5% were not, and 29.1% were neutral. Overall, the data reflected significant apprehension regarding ethical issues and potential negative outcomes associated with AI, alongside mixed feelings about its reliability and job security implications. 50% of respondents believed AI decision-making in healthcare raised ethical concerns, while 14.1% disagreed and 35.8% remained neutral and these observations are shown in table 4.

Table 4: Uncertainties Towards AI

Question	Frequency (%)
Do you believe that AI decision-making in healthcare raises ethical concerns?	
Yes	60 (50%)
No	17 (14.1%)
Neutral	43 (35.8%)
Are you confident that current testing methods ensure the reliability of AI systems in critical applications?	
Yes	44 (36.6%)
No	52 (43.3%)

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Neutral	24 (20%)
Do you think over-relying on AI could lead to negative consequences in decision-making processes?	
Yes	65 (54.1%)
No	32 (26.6%)
Neutral	23 (19.1%)
Are you concerned that AI will significantly impact job security in various industries?	
Yes	34 (28.3%)
No	51 (42.5%)
Neutral	35 (29.1%)

Four key barriers to implementing AI in healthcare were illustrated. It identified a gap in knowledge among practitioners, highlighting their lack of understanding of AI technologies. Additionally, it pointed out the lack of data, which hindered the effectiveness of AI tools. The attitudes of healthcare professionals were also noted, as their perceptions could influence their willingness to adopt AI. Lastly, the figure addressed the cost burden associated with implementing AI solutions, which could deter investment from healthcare facilities. A model was proposed on the reasons for decreased AI adoption amongst pediatric rehabilitation specialists in Pakistan as shown in figure 1.

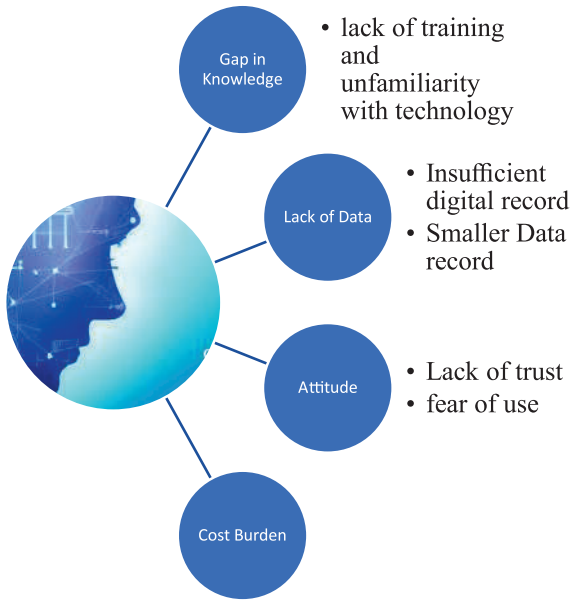

Figure 1: Sources of Decreased Utilization of AI in Pakistan

DISCUSSION

The objective of this study was to ascertain the level of knowledge that Pakistani pediatric rehabilitation specialists have about AI and various types of realities, as well as to evaluate their awareness and practical use of AI. With rapid advancements being made in the field of AI, it is becoming increasingly common for this technology to support the digital transformation of healthcare and provide evidence-based care [15]. Globally, this shift towards integrating AI into healthcare necessitates understanding the extent to which pediatric rehabilitation specialists are knowledgeable about, aware of, and practicing with AI, as they are the conduits through which this technology is introduced to patients. On a national level in Pakistan, a developing country lagging in the implementation of AI in healthcare [16], understanding the relationship between medical consultants and AI can shed light on narrowing the educational, research, and clinical gaps of AI between Pakistan and the developed world. The study's participant demographic was about 35% female and 65% male, which is in line with previous research. Fewer people wished to remain anonymous about their gender. The participants' average age was 32.0 years, which is comparable to the findings of other studies. Although slightly higher than in studies conducted in other developing countries like Iran and India, 39.1% of the participants indicated they had taken courses or training related to AI [17]. Despite this, the percentage is still low, indicating a significant need for AI-related education within Pakistan's medical landscape. 95.5% of participants reported using the Internet every day, and 97.7% of participants said they had a smartphone or tablet, indicating that medical consultants have extensive access to the Internet. Similar studies did not measure this parameter, probably because they assumed that most medical practitioners had access to this kind of equipment. The majority of participants (60.5%) said they were comfortable utilizing or working with computers and other devices, indicating a fundamental understanding of and ability to use such technology. Other studies—possibly because they are more relevant to the goal—did not ask about levels of fundamental technological competence instead focusing exclusively on issues regarding artificial intelligence. It is crucial to comprehend technical affinity in a country like Pakistan, where it is not possible to make the same assumptions about this metric as in developed states. Medical consultants have a strong technical background, which influences the national conversation regarding AI. Mixed responses regarding the analysis of medical data (48.3% yes, 35% neutral) and patient compliance (35% yes, 38.3% neutral) suggest a need for more detailed education on the specific capabilities and applications of AI in these areas. These findings align with previous studies indicating that even though healthcare experts recognize the strength of AI, they also express concerns about its practical implementation and efficacy in certain aspects of patient care. The majority of respondents stated they either agree or strongly agree with the concept that AI will provide an advantage in accessing patient information (51%) and had an overall

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optimistic or very confident view about the usage of AI in medicine and enhanced medical training (93.3%). This idea is communal across other research, signifying that Pakistan is parallel to other countries based on attitude towards AI in health care [18]. A common concern about AI is its positive strength to adhere patients to treatment plans [19]. However, 26.6% of participants disagreed that AI enhances patient compliance with treatment and follow-up, a belief common in participants of other studies. At the same time, 54.1% of participants agreed with the notion that they didn't utilize AI in their practice, suggesting that despite favourable opinions about AI, more professional knowledge is needed before clinical implementation. The findings of the current study highlight the significance of integrating AI education into the medical curriculum for novice pediatric rehabilitation practitioners. Given the swift developments in AI and its growing role in healthcare, it is crucial to equip practitioners with the necessary skills and knowledge to effectively utilize AI tools [20]. This includes not only technical training but also education on the ethical implications of AI, which is essential for ensuring responsible and effective use of technology in patient care. Moreover, addressing the concerns and neutrality expressed by participants regarding specific applications of AI, such as data analysis and patient compliance, could foster greater acceptance and confidence in AI tools. Providing practical examples and case studies demonstrating the successful implementation of AI in these areas may help bridge the gap between theoretical knowledge and practical application.

CONCLUSIONS

It was concluded that while there is a generally positive attitude towards the benefits of AI, there is also a clear need for enhanced education and training.

Authors Contribution

Conceptualization: Ss[1]
Methodology: SS[1], SR, SQ, SS[2]
Formal analysis: R, SS[2]
Writing review and editing: SS[1], SAA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Management of Symptomatic Gallstones in Pregnancy

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ABSTRACT

Gallstones, also known as cholelithiasis, are crystalline forms that occur in the gallbladder or biliary tract. Pregnancy causes various physiological changes that raise the chance of gallstone formation, which can lead to difficulties for both the mother and the fetus. **Objective:** To examine the safety and outcomes of conventional and interventional treatment in pregnant women with symptomatic gallstones. **Methods:** The study was longitudinal study. This study was conducted in Khairpur Medical College Civil Hospital Khairpur Mirs. The duration of this study was one Year, from Jan 2023 to Dec 2023. A total number of participant was (N=250) in this study. The age of participants was 18-35 years. There were included two treatment conventional and interventional. **Results:** The mean age of patients was 35.5 years. This study included 250 patients, had experienced gallstone symptoms. The intervention treatment group had the most participants (76%), followed by the conservative treatment group (24%). The cholecystitis participants had conservative treatment (76.3%), followed by laparoscopic treatment (53.3%). The majority participants was (66.6%) got laparoscopic therapy in the second trimester and indicate significant outcomes as compared to third trimester. The pregnant women was experienced no mortality, miscarriage during intervention therapy. **Conclusions:** This study supported prior findings that laparoscopic cholecystectomy can be performed safely during pregnancy, particularly in the second trimester. However, the third trimester brings additional obstacles, as seen by the higher prevalence of open cholecystectomy.

INTRODUCTION

Gallstones affect up to 20% of adults worldwide. The presence of gallstones does not warrant therapy, as the majority of people with stones are asymptomatic. However, roughly 25% develop symptoms and/or difficulties and are thus classified as having gallstone disease, for which the gold standard therapy is (laparoscopic) cholecystectomy (gallbladder removal) [1]. Gallstones, which originate in the gallbladder or biliary tract, are classified according to their location and composition. These stones form inside the gallbladder itself. They can range in size and quantity, from microscopic gravel-like particles to huge stones that can fill the gallbladder [2]. These stones can occur in a variety of locations in the biliary tract, including the bile ducts outside the gallbladder. Stones in the biliary tract may include: Choledocholithiasis, and Mirizzi. Gallstone pancreatitis had stones that clog the pancreatic duct, producing pancreatitis [3]. During pregnancy, maternal physiology changes significantly in order to support the developing fetus. These changes are necessary for the health of both the mother and the baby, but they can also predispose the mother to certain diseases or situations that necessitate medical intervention. During pregnancy, progesterone and estrogen hormone levels rise significantly to support fetal growth and development. They also have an impact on numerous bodily systems, such as the cardiovascular and gastrointestinal. The fetus and placenta have higher metabolic demands, thus the heart pumps more blood to fulfill them. Blood volume

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grows dramatically to meet the needs of the developing fetus and to compensate for blood loss after birth [4]. Accusations of Cholecystitis and Pancreatitis: turning into cholelithiasis challenge in antepartum, where immediate diagnoses of gallstones other affiliated complications needed for pregestationormsg. The diagnosis in time can result in complications that put both mother and baby at high risk. Untreated inflammation and infection can lead to gallbladder perforation. Perforation in patients with established acute cholecystitis results in Biliary Peritonitis (BP) where bile and infected contents escape into the abdominal cavity [5]. Peritonitis Perforation is a common cause of the extensive inflammation in peritoneum known as. This is a life threatening condition and it needs medical attention as fast as you can get. Weakened stomach aggravation, feveright case with infection. In physics throughout the pregnancy and postpartum periods, the occurrence of extreme had a triggering effect. This results in a state of physiologic stress and systemic inflammation that might lead to preterm delivery. Critically unwell mothers with severe maternal issues and systemic inflammatory reactions have a higher chance of their conceptus not surviving. Intrauterine infections and placental insufficiency, among other things, can all lead to fetal death. Furthermore, untreated gallstone symptoms can lead to extreme diseases such as sepsis and peritonitis [6, 7]. As a result, the risk of postpartum mortality in the present case is related to gallstone pain. Postpartum deaths due to these two illnesses underscore the significance of prompt detection and therapy. When pregnant, gallbladder pain can present specific issues, especially if it occurs in the third trimester. The third trimester is generally avoided for surgery because by this time, the rising uterus may crowd the operation site, making the operation more risky and pushing the date of prospective delivery even sooner [8]. Even though it may be hard sometimes, emergent surgical intervention can be necessary if there are severe complications such as cholecystitis, biliary colic or gallstone pancreatitis. It requires constant monitoring of the fetus to identify and manage any signs of distress. It is necessary to ensure that the placement is correct and it does not compress the inferior vena cava, limiting the venous return and cardiac output. When there is need, it is safe to perform surgery at the emergent/critical levels. The worst outcomes tend to occur if surgical intervention is delayed. Unfortunately, semi-urgent circumstances are rare with pregnant women suffering from symptomatic gallbladder disease [9, 10]. The surgical treatment of gallbladder disease in pregnancy specifically during the first trimester has its challenges and associated risk. Since no clinical reports exist on the efficacy and safety of such therapies, this was a cross-sectional studies inquiry whose goal was to appraise the consequences of surgery in pregnant women with symptomatic gallstones.

This study aimed to examine the safety and outcomes of conventional and interventional treatment in pregnant women with symptomatic gallstones.

METHODS

The study was longitudinal study. This investigation was carried out in Khairpur Medical College Civil Hospital Khairpur Mirs. The trial lasted six months, from Jan 2023 to Dec 2023. There were a total of 250 pregnant participants that attended various hospital wards. Participants were 26.5 years old. The gallstone symptoms were examined using the hospital's database to validate the woman's pregnancy. Inclusion criteria was pregnant women, with gallstone symptoms, and participant underwent surgical intervention. Exclusion criteria was non-pregnant women and participant underwent non-surgical intervention. The sample size formula was: $n=(P1-P2)2(Z\alpha/2+Z\beta)2\cdot[P1(1-P1)+P2(1-P2)]$. Where: n = required sample size per group, $Z\alpha/2$ = Z value corresponding to the desired level of significance (e.g., 1.96 for 5% significance). $Z\beta$ = Z value corresponding to the desired power (e.g., 0.84 for 80% power). P1 = expected proportion of success in the Conservative group was (0.70) 70%. P2 = expected proportion of success in the Intervention group was (0.50) 50%. Convenience sampling technique was used. Following stratification, participants were randomly assigned to either the conservative treatment group (n=190) or the intervention treatment group (n=60). The patient's demographics, clinical state, and laboratory findings were all reported at the time of presentation. Consent was taken from the patients. This study was validated following a permission letter from the Hospital's Ethics Committee (KMC/RERC/72). The data were statistically analyzed using chi-square tests by SPSS version 23.0. Standard deviation, mean, numerical frequencies, and percentages (%) were used to display data. There was statistical significance among the variables (p-value < 0.05).

RESULTS

This study included 250 patients had experienced gallstone symptoms. The intervention treatment group had the most participants (76%), followed by the conservative treatment group (24%). The average age of the patients was 26.5 ±4.91 years. The majority of pregnant women with gallstone symptoms (56%) were in their second trimester, with 24% in their third trimester. Table 1 showed that the majority of participants were overweight (56%), with (44%) being normal weight.

Table 1: Baseline Variables of study variables (n=250)

Variables	Total Number of Participants N (%) / (Mean ± SD)
Age	
18 -35 Years	26.5 ± 4.91

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Trimester	
First	60 (24%)
Second	140 (56%)
Third	50 (20%)
Body Mass Index (BMI)	
Normal Weight	110 (44%)
Over-weight	140 (56%)
Treatment Management	
Conservative	190 (76%)
Intervention	60 (24%)

According to these findings, the majority of cholecystitis patients had conservative treatment (76.3%), who were getting conservative care. This diagnosis was made in 32 patients (53.3%) who had undergone laparoscopic cholecystectomy in the interventional group. After an open cholecystectomy, (50%) participants experienced acute cholecystitis. P-value = 0.001 shows that there was a statistically significant difference in the frequency of acute cholecystitis between the interventional and conservative groups. 15 patients (8%) are being treated conservatively. 10% participants was in any laparoscopic cholecystectomy patients. 20 (30%) individuals who had an open cholecystectomy. Patients receiving open cholecystectomy were shown to have a higher incidence of acute cholangitis (P-value = 0.001), indicating a statistically significant difference between the groups. In the conservative group, there were 16% participants observed and 10% who had a laparoscopic cholecystectomy. 20% participants were noticed in cholecystectomy who had an open procedure. P-value = 0.0519 shows that there are notable variations between the treatment groups, as showed in table 2.

Table 2: Conservative vs Interventional Treatment (n=250)

Diagnosis	Conservative Treatment N (%)	Intervention Treatment Cholecystectomy N (%)		p-Value
		Laparoscopic (40)	Open (20)	
Acute Cholecystitis	145 (76.3%)	32 (53.3%)	10 (50%)	0.0519
Acute Cholangitis	15 (8%)	4 (10%)	6 (30%)	
Acute Pancreatitis	30 (16%)	4 (10%)	4 (20%)	

According to these findings, in the first trimester, Open cholecystectomy is less common (15%) but laparoscopic cholecystectomy is more prevalent (25%). In the second trimester, laparoscopic cholecystectomy is the most common procedure (62.5%), indicating that this is the method of choice. In the Third Trimester is a noticeable increase in open cholecystectomy (75%), suggesting a trend toward open surgery in later stages of pregnancy. Chi-square value is the 12.52, and the p-value is 0.0019. We reject the null hypothesis because the p-value (0.0019) is smaller than the conventional significance limit of 0.05. The distribution of open and laparoscopic cholecystectomy types across the trimesters in the intervention treatment group differs statistically significantly. This implies that there is a strong correlation between the kind of cholecystectomy (open vs. laparoscopic) and the trimester in which the procedure is done. To be more precise, laparoscopic cholecystectomy is more common in the first and second trimesters, but open cholecystectomy is significantly more common in the third trimester, as showed in table 3.

Table 3: Laparoscopic vs. Open Treatment across Trimesters in the Intervention Treatment Group (n=60)

Variables	Intervention Treatment Cholecystectomy N (%)		Chi-Square	p-Value
Trimester	Laparoscopic	Open		
First	10 (25%)	3 (15%)	12.52	0.0019
Second	25 (62.5%)	2 (10%)		
Third	5 (12.5%)	15 (75%)		

According to these findings, 21 participants was experienced problems. For the complications where no cases were observed in the laparoscopic group (miscarriage, bleeding, infection), indicating that these complications did not occur in the laparoscopic treatment group, see table 4.

Table 4: Maternal complication following Laparoscopic vs. Open Cholecystectomy during Pregnancy (n=21)

Variables	Number of Patients N (%)		p-Value
Complications	Laparoscopic Treatment	Open Surgery Treatment	
Preterm Labor	1 (25%)	6 (32%)	0.5991
Miscarriage	0 (0%)	1 (5.2%)	0.745
Bleeding	0 (0%)	4 (21%)	0.4815
Infection	0 (0%)	3 (16%)	0.553
Postoperative Pain	1 (25%)	5 (26.3%)	0.491

DISCUSSION

Pregnant women go through a number of physiological changes that might lead to the formation of gallstones. Gallstone formation is influenced by hormonal variables, changes in bile composition, and biliary system abnormalities. During pregnancy, estrogen levels rise, which may contribute to high bile cholesterol levels. Elevated cholesterol levels in the bile can cause cholesterol gallstone formation. Progesterone relaxes smooth muscles, including those of the gallbladder. Bile stasis is caused by reduced gallbladder movement, allowing cholesterol crystals to form and mature into stones [11]. In the current study, 250 pregnant women were identified as having gallstone symptoms. The majority of pregnant women experiencing gallstone symptoms were in the trimester. This shows that physiological and hormonal changes during this time play a significant role in the development or aggravation of gallstone symptoms [12]. Furthermore, being overweight increases the likelihood of getting gallstone symptoms during pregnancy, while normal-weight persons are not immune to this risk. This demonstrates the multidimensional nature of gallstone formation during pregnancy, which includes both physiological changes caused by pregnancy and pre-

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existing variables such as body weight. This is almost similar with the other studies. In the previous studies to found that, gallstone was formed in the second and third trimester [13, 14]. The majority of subjects with cholecystitis were treated conservatively. This shows that non-surgical treatments, including as antibiotics, pain relief, and dietary changes, are frequently successful for this disease throughout pregnancy. A considerable number of cholecystitis cases required laparoscopic intervention, demonstrating that while conservative care is frequently tried first, many cases eventually require surgical treatment to cure symptoms or prevent complications [15, 16]. The majority of patients are first managed conservatively, but a considerable percentage require laparoscopic surgery, which strikes a balance between non-invasive and minimally invasive treatments. Because of its potential severity and complications, acute cholangitis frequently demands more aggressive treatment, with a strong dependence on open surgery. Acute pancreatitis is typically treated conservatively, but surgical intervention is occasionally required, necessitating a case-by-case evaluation to decide the best course of action. In the previous studies to similar that, cholecystitis, cholangitis and acute pancreatitis was found during pregnancy [17, 18]. Based on the information supplied, we may assess the distribution of cholecystectomy interventions (both laparoscopic and open surgery) over the three trimesters of pregnancy. Interventions are uncommon in the first trimester, probably due to fears about the hazards of surgery during early pregnancy. The majority of laparoscopic cholecystectomies occur during the second trimester. This is most likely due to the relative safety of doing surgery during this era as opposed to the first and third trimesters. The third trimester has a higher frequency of open cholecystectomy than the previous trimesters. This could be related to the difficulties of performing laparoscopic treatments as the pregnancy continues, necessitating open surgery in more demanding cases. In the previous studies to found that, cholecystectomy interventions was similar during pregnancy [19, 20]. According to the research, conservative treatment is related with a higher risk of mortality, miscarriage, and low birth weight than cholecystectomy. There have been no recorded incidences of mortality or miscarriage with cholecystectomy treatment, and the prevalence of low birth weight is lower than with conservative treatment. Similar studies in the past discovered that cholecystectomy procedures were comparable during pregnancy. The findings point to a significant correlation between the kind of cholecystectomy and the pregnant trimester, with open cholecystectomy being preferred in the third trimester and laparoscopic cholecystectomy preferred in the first two. Clinical aspects like safety, practicality, and risk factors related to each surgical procedure at various stages of pregnancy may be reflected in this [21].

CONCLUSIONS

In the intervention group, the method of cholecystectomy performed (laparoscopic vs. open) differs considerably between the trimesters, with open surgery being performed more frequently in the third trimester and laparoscopic surgery more frequently in the first two. This strong correlation suggests that the decision-making process about surgery for cholecystectomy during pregnancy is influenced by the timing of the trimester. Therefore, these findings support that surgery is relatively safer for the mother and the fetus when the gastric stones are treated surgically during pregnancy.

Authors Contribution

Conceptualization: ZH
Methodology: AB, S[2]
Formal analysis: ZA, AH
Writing, review and editing: S[1]

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

Conflicts of Interest

The authors declare no conflict of interest.

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Correlation Between Complexity of Coronary Lesions and Delta High-sensitivity Troponin (hs-cTn) I Levels in Patients of Non-ST Elevation Myocardial Infarction

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ABSTRACT

Non-ST Elevation Myocardial Infarction is a critical condition where early identification of myocardial injury is essential for risk stratification and treatment. High-sensitivity cardiac troponin I (hs-cTnI) is a well-established biomarker for detecting myocardial damage. **Objective:** To assess the association between Syntax scores and initial significant delta hs-cTnI in patients who had been hospitalized with Non-ST Elevation Myocardial Infarction. **Methods:** Observational cohort study from January 2022 to December 2022 involving a total of one hundred and fifty patients admitted at Hayatabad Medical Complex Peshawar. hs-cTnI on admission and at 1, 2 hours and between (6h-12 h) post-admission daily was measured. Coronary lesion complexity was assessed with Syntax scores according to the results of coronary angiography. Statistical Analysis of data was performed using Pearson correlation to analyze the association between syntax scores delta hs-cTnI levels. **Results:** SYNTAX scores were correlated with Δhs-cTnI levels at all-time points, and the strongest correlation was found 6-12 hours post-admission (r=0.78). The syntax score had a mean value of 24.11 ± 14.74, and hs-cTnI levels increased over time to reflect the extent of myocardial injury. **Conclusions:** It was concluded that in Non-ST Elevation Myocardial Infarction patients, Syntax scores demonstrating more complex coronary lesions are related to higher delta hs-cTnI levels. This value highlights the use of hs-cTnI as a biomarker to evaluate the severity of myocardial injury and direct clinical decision-making in Non-ST Elevation Myocardial Infarction. Delta hs-cTnI measurements in diagnostic and risk stratification algorithms may lead to enhanced early identification of disease with improved outcomes.

INTRODUCTION

Non-ST Elevation Myocardial Infarction (NSTEMI) is a cardiac condition that is characterized by the absence of ST-segment elevation on electrocardiograms, without discharges myocardial necrosis markers such as High-sensitivity cardiac troponin I (hs-cTnI). The complexity of coronary lesions in NSTEMI patients and their association with significant elevations in delta hs-cTn I are coming into increasing prominence as important topics for study. The diagnosis and assessment of risk in acute coronary syndrome (ACS) have been revolutionized by high-sensitivity cardiac troponins such as hs-cTnI and High-sensitivity cardiac Troponin T (hs-cTnT), which have even greater sensitivity and prognostic value than conventional assays [1-3]. Thus, high-sensitivity troponin assays can detect myocardial injury sooner and better delineate the severity as well as prognosis of NSTEMI. High-sensitivity troponins have been shown to detect other conditions beyond MI and are strong predictors of future adverse cardiovascular events. The consequence of this increased sensitivity, however, is a decreased specificity including in patients with comorbidities that may also increase troponin levels independent of acute coronary syndromes

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[4-6]. Coronary lesion complexity, quantified by coronary angiography and other methods is related to hs-cTn levels. However, larger more complicated lesions usually are related to higher levels of hs-cTn, which probably represents a greater amount of myocardial damage. Such a relationship, that myocardial infarction without ST-segment elevation (NSTEMI) presentations are expected to be more reliably assessed for prognosis and most appropriate treatment strategies by thorough coronary evaluation [7, 8]. Early and accurate detection of hs-cTn changes, particularly delta hs-cTn I am important for the diagnosis and risk stratification of NSTEMI. Research has shown that the highest percentage of early rises in hs-cTn is tightly linked with a negative prognosis for morbidity and mortality, particularly heart failure (HoF) or major adverse cardiovascular events (MACE). This underscores the importance of early and frequent hs-cTn measurements for risk assessment into diagnosis [8, 9]. To use hs-cTn assays in clinical practice, clinicians should carefully evaluate the type of assay used and correlate it with the patient's context. To more quickly exclude and confirm NSTEMI, the ESC recommends a 0/1-h algorithm that has worked well across backgrounds other than issues with comorbidities or atypical presentations [10-12]. Use of hs-cTn in NSTEMI Recent studies refining practice. This could result, for example in operating characteristics such as sensitivity and specificity being improved by optimizing cutoff values for hs-cTn leading to a reduction of futile interventions or hospitalizations at the same time [13]. In addition, new generation hs-cTn assays are being designed to further improve diagnostic precision and prognostic value [14, 15]. How the complexity of coronary lesions correlates with delta hs-cTn I levels in NSTEMI patients may provide more information for accurate diagnosis, risk stratification and patient prognosis. Toward this end, high-sensitivity troponin assays (particularly hs-cTnI) are invaluable tools to be used wisely but not without recognition of the ongoing research and clinical vigilance that will continue until their potential benefits are finally realized in conjunction with all limitations addressed.

This study aims to assess the association between Syntax scores and initial significant delta hs-cTnI in patients who had been hospitalized with Non-ST Elevation Myocardial Infarction.

METHODS

An observational cohort study was conducted and sampling technique used in this study was convenience sampling. Patients admitted to the Hayatabad Medical Complex, Peshawar, with a confirmed diagnosis of NSTEMI during the study period (January 2022 to December 2022) were consecutively enrolled. The study protocol was approved by the Institutional Review Board of Hayatabad Medical Complex, Peshawar (Reference number: 1025), and informed consent was obtained from all participants before their inclusion in the study, adhering to ethical standards and the Declaration of Helsinki. A total of 150 patients presenting with NSTEMI were included in the study. The inclusion criteria required patients to be 18 years or older, with a diagnosis of NSTEMI confirmed through clinical assessment, electrocardiogram (ECG) changes, and elevated hs-cTnI levels. Additionally, all participants were required to provide informed consent. Exclusion criteria applied to patients with STEMI, those with chronic kidney disease stage IV or higher, and individuals with other conditions that could lead to elevated troponin levels, such as myocarditis or pulmonary embolism. Clinical data collected included demographic information such as age, gender, and medical history, along with risk factors like hypertension, diabetes mellitus, smoking status, and previous history of coronary artery disease. Clinical presentation details, including symptom onset, duration, and type of chest pain, were also recorded. Laboratory measurements involved blood samples collected on admission, as well as at 1 hour, 2 hours, and 6-12 hours post-admission, to assess hs-cTnI levels using the Abbott Architect STAT hs-cTnI assay, with the 99th percentile upper reference limit for a healthy population used for interpretation. All patients underwent coronary angiography within 24 hours of admission, and the complexity of coronary lesions was assessed using the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score, which evaluates the extent and severity of coronary artery disease based on anatomical criteria. To properly cite references for sample size calculations and justify your methods, you can use relevant sources from literature focused on statistical analysis and sample size determination for correlation studies, specifically in clinical research. Below are a few potential sources you can use, along with a short description of their relevance: The sample size for this study was calculated based on the primary outcome of the correlation between coronary lesion complexity (SYNTAX score) and delta hs-cTnI levels. A power analysis was conducted to ensure an adequate sample size for detecting a significant correlation. Using a power of 80% (1-β=0.80) and an alpha level of 0.05 (two-tailed), we assumed a moderate effect size (r=0.30) based on previous studies . According to standard sample size calculation formulas for correlation studies , the resulting sample size required to detect a significant correlation was 138 patients. To account for potential dropouts and incomplete data, the final sample size was increased to 150 patients. Data Analysis Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), while categorical variables were presented as frequencies and percentages. Pearson or Spearman correlation coefficients were used to examine

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the relationship between SYNTAX scores and delta hs-cTnI levels, depending on data distribution, with statistical significance set at a p-value below 0.05. SPSS version 25.0 (IBM) was utilized for data analysis. To ensure accuracy and reproducibility, all laboratory measurements were performed in duplicate, and data entry and statistical analyses were independently verified by researchers to minimize errors.

RESULTS

The patient population had a mean age of approximately 60 years (59.91 ± 11.75 years), with the majority being male (65%). The prevalence of hypertension, diabetes mellitus, smoking, and previous coronary artery disease (CAD) was 57%, 71%, 36%, and 51%, respectively (Table 1).

Table 1: Demographic Characteristics of Patients (n=150)

Parameter	Mean ± SD	Frequency (%)
Age (Years)	59.91 ± 11.75	-
Gender	-	Male: 65%
Hypertension	-	57%
Diabetes	-	71%
Smoking	-	36%
Previous CAD	-	51%

The hs-cTnI levels showed a significant increase over time, from admission to 6-12 hours post-admission. On admission, the mean hs-cTnI level was 27.34 ng/L, which increased to 111.53 ng/L at 6-12 hours post-admission (Table 2).

Table 2: High-sensitivity Troponin I Levels (ng/L) (n=150)

Time Point	Mean ± SD	Minimum	Maximum
Admission	27.34 ± 14.32	0.12	49.97
1 Hour	54.96 ± 27.56	10.02	99.67
2 Hours	87.44 ± 38.78	20.13	148.72
6-12 Hours	111.53 ± 46.29	31.54	198.87

The hs-cTnI levels showed a significant increase over time, from admission to 6-12 hours post-admission. On admission, the mean hs-cTnI level was 27.34 ng/L, which increased to 111.53 ng/L at 6-12 hours post-admission (Figure 1).

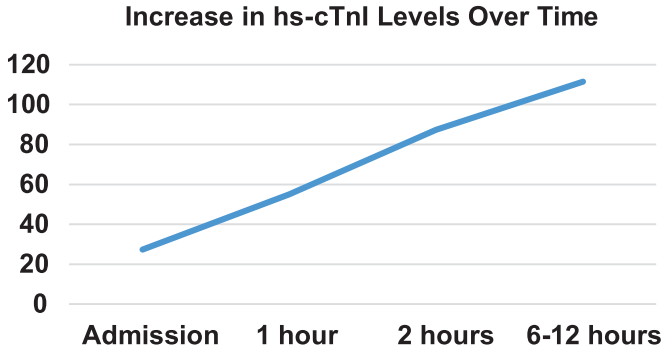

Figure 1: Increase in hs-cTnI Levels Over Time

The complexity of coronary lesions, as assessed by the SYNTAX score, indicated a wide range of lesion complexities among the patients. The mean SYNTAX score was 24.11 ± 14.74 (Table 3).

Table 3: SYNTAX Scores (n=150)

Parameter	Value
Mean ± SD	24.11 ± 14.74
Minimum	0
Maximum	49

The correlation between SYNTAX scores and delta hs-cTnI levels was examined at various time points, and p-values were calculated to determine the statistical significance of the observed correlations. A significant positive correlation was found between the complexity of coronary lesions (SYNTAX score) and delta hs-cTnI levels at all-time points, with the strongest correlation observed at 6-12 hours post-admission (r=0.78, p<0.001) (Table 4).

Table 4: Correlation Between SYNTAX Scores and Delta hs-cTnI Levels (n=150)

Time Point	Correlation Coefficient	p-value
Delta hs-cTnI 1 Hour	0.65	<0.001
Delta hs-cTnI 2 Hours	0.72	<0.001
Delta hs-cTnI 6-12 Hours	0.78	<0.001

The correlation between SYNTAX scores and delta hs-cTnI levels was examined at various time points, and p-values were calculated to determine the statistical significance of the observed correlations (Figure 2).

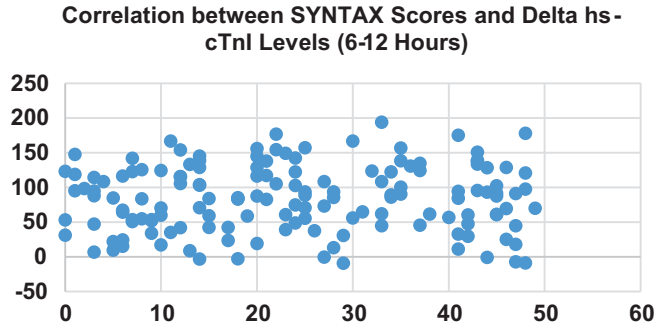

Figure 2: Correlation Between Delta hs-cTnI 6-12hr and SYNTAX Score

The relationship between hs-cTnI levels and patient characteristics, including age, smoking status, and diabetes status, was analyzed using Pearson correlation tests. The correlation between age and hs-cTnI levels at admission (r=0.005) and 6-12 hours (r=-0.034) was negligible, indicating no significant relationship between age and troponin levels. Smoking status demonstrated a weak negative correlation with hs-cTnI levels at admission (r=-0.039) and a weak positive correlation at 6-12 hours (r=0.012), suggesting minimal influence of smoking on troponin levels. Similarly, diabetes status showed a weak positive correlation with hs-cTnI levels at admission (r=0.117) and 6-12 hours (r=0.074), though the association was not strong enough to be considered clinically significant (Table 5).

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Table 5: Correlation Between Patient Characteristics and hs-cTnI Levels (n=150)

Variable	Correlation with hs-cTnI at Admission	Correlation with hs-c TnI at 6-12 Hours
Age	0.005	-0.034
Smoking Status	-0.039	0.012
Diabetes Status	0.117	0.074

DISCUSSION

This study aimed to assess the complexity of coronary lesions and significantly higher levels of hs-cTnI in patients at the time of admission in NSTEMI patients. Conclusion The functional relationship between the delta hs-cTn1 levels at different time points (1 h, 2 h and 6-12 h post-admission) following PCI for significant CAD predicted by SYNTAX scores that assess coronary lesion complexity is optimistically moderate to strong. This was particularly strong between 6 and up to 12 hours. Overall, these results imply that the higher complexity of coronary lesions is accompanied by a more pronounced increase in hs-cTnI levels, demonstrating the advantage of using it to evaluate myocardial injury severity in NSTEMI patients. Our results are consistent with many recent investigations of the analytical and prognostic importance of hs-cTnI in ACS, including NSTEMI. The early diagnosis and risk assessment of ACS have greatly benefited from high-sensitivity cardiac troponin assays. A study by Hussein et al., (2023) confirmed that hs-cTn assays can decrease the time required for a precise diagnosis of myocardial infarction (MI), including NSTEMI, to less than two hours [14]. Another study highlighted the high diagnostic value of hs-cTnI in differentiating STEMI from NSTEMI, supporting our findings on the importance of early and repeated measurements [18]. Hussein *et al.,* (2023) demonstrated that higher levels of troponin I are connected with the degree of coronary artery damage in NSTEMI patients, similar to our findings that show a correlation between SYNTAX scores and delta hs-cTnI levels [14]. Al-assaf et al., (2021) also found that higher hs-cTnI levels are associated with more severe coronary artery disease, emphasizing the role of hs-cTnI in risk stratification and management of NSTEMI patients [13]. The use of delta hs-cTnI levels for early diagnosis and risk assessment is well supported by the literature. Studies have shown that changes in hs-cTnI levels over time can effectively rule out or confirm NSTEMI, guiding timely interventions. In a study conducted to evaluate the real-time application of 0 h/1-hour algorithm with hs-cTnI in the Japanese population, the performance achieving high safety and efficacy for rapid ruling-in/out suspected NSTEMI cases by use of this approach has been validated [18]. The notable correlation of SYNTAX scores with delta hs-cTnI levels intimates the prospective role of hs-cTnI as a useful biomarker for evaluating CAD severity in NSTEMI patients. Identification of hs-cTnI levels associated with complex coronary lesions and thus, complexity prediction at the time of admission may guide relevant decisions on invasive procedures among patients with NSTEMI [19]. In addition, the implementation of delta hs-cTnI eases an on-the-fly examination of ongoing myocardial damage and megascopic efficiency of therapeutic manoeuvres. This is in agreement with new guidelines and evidence on hs-cTn combined with history; clinical findings, and other diagnostics [20].

CONCLUSIONS

It was concluded that the complexity of coronary lesions is importantly associated with the early significant delta hs-cTnI levels in NSTEMI patients, which have been provided by our study as an additional piece for understanding potential mechanisms that explain their high predictive role. These results support hs-cTnI as an essential marker of myocardial damage in NSTEMI and for clinical use. The use of delta hs-cTnI in diagnostic algorithms can support the early identification and risk stratification of patients with NSTEMI, thereby improving patient care.

Authors Contribution

Conceptualization: MHA, MAW
Methodology: MHA, MAW
Formal analysis: ND, MT, SN, SKM
Writing review and editing: MHA, MAW

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Association of Shock Index and Modified Shock Index with Mortality Rate in Emergency Department Trauma Patient

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ABSTRACT

At the emergency room, triage was used to determine which patients were more seriously injured and in need of urgent care. Trauma remains one of the primary causes of morbidity and death even with the use of modern triage techniques. **Objective:** To find out the relationship between trauma patients' 48-hour mortality and the shock index and modified shock index at Emergency Departments (EDs). **Methods:** A study was conducted in the Emergency Ward of Ziauddin University Hospital, focusing on patients aged 18-65 who sustained trauma. The study involved 50 trauma patients admitted to a Level I trauma center. Data were collected on heart rate, blood pressure, and shock indices at the time of admission. A shock index cut-off value of 0.9 was used to determine its association with patient outcomes. Data collection involved patients visiting the emergency department, with informed consent obtained. SPSS version 21.0 was used for analysis. **Results:** The study involved 50 patients, with 25 in each exposed and unexposed group. Exposed patients had a higher average age, higher heart rates, and lower blood pressure. Road traffic accidents were the leading trauma mechanism in both groups. Open wounds were more common in exposed patients. Most exposed patients received intravenous fluids and inotropic support. Patients with a Shock Index ≥ 1 and a Modified Shock Index ≥ 1.3 had higher mortality rates. **Conclusions:** The study revealed a significant link between medical mortality in older adults and bruises in emergency departments, indicating that SI and Modified SI were effective markers for severity assessment.

INTRODUCTION

Trauma is the third most common cause of death overall and the leading cause of mortality with a significant economic burden in the world, especially for those between the ages of 1 to 44 years [1]. Elderly trauma patients often present with multiple system injuries, significantly increasing their mortality risk, as evidenced by a 24% overall mortality rate in the studied population [2]. Following most trauma, an accurate assessment of a patient's state of shock is necessary to properly treat the patient and lessen the seriousness of their diseases [3]. Triage systems prioritize patients based on urgency, ensuring timely monitoring and intervention for those with critical conditions, while also facilitating departmental organization and evaluation [4]. Regardless of present triage processes, trauma remains the most prevalent cause of morbidity and mortality. Most healthcare facilities rely on experienced nurses or medical residents to perform this triage. Patients are usually triaged based on their age, presenting history, symptoms, level of consciousness, and apparent extent of the injury [5]. In different retrospective investigations, clinical variables such as Heart Rate (HR) Pulse Oxymetry (PR), Blood Pressure (BP), Shock Index (SI)

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and Modified Shock Index(MSI)are analyzed to estimate the extent of critical patients at a hospital emergency room [5, 6]. The Shock Index (SI), measured as Heart Rate (HR) divided by Systolic Blood Pressure (SBP), is an indicator of hemodynamic stability and is important for determining mortality and extent of injury in trauma patients [7]. This approach is superior to SBP and HR in predicting blood loss. SI provides high reliability among observers when used on patients with multiple injuries [8, 9]. SI is useful in clinical settings as it only requires SBP and HR values for calculation. Pre-hospital SI is beneficial for trauma patients, according to numerous research studies. It also helps in early identification of patients who may appear stable but are at risk of decompensation [6, 9]. Because the Shock Index does not include Diastolic Blood Pressure (DBP), Liu YC et al., developed a Modified Shock Index (MSI) to account for the influence of Diastolic Blood Pressure (DBP) on the Shock Index. MSI accurately represents stroke volume and systemic vascular resistance, while SI excludes DBP. They found that patients with high heart rates, low SBP, and low DBP had a higher risk of emergency death. However, they found an insignificant relationship between SI and emergency deaths in patients with a SI of 0.5-0.9 [5]. Comparing the predictive values of SI and MSI for in-hospital mortality in 9860 adult trauma patients, Singh A et al., found that MSI was a more accurate predictor of mortality. MSI is easily quantifiable prior to hospitalization [10]. These indices are particularly important in emergency settings, where rapid, accurate assessments can guide timely interventions and improve patient outcomes.

Thus, the goal of the study was to determine how trauma patients at Emergency Departments (EDs) correlate with shock index and modified shock index, in terms of 48-hour mortality.

METHODS

The study was conducted on trauma cases in the Emergency Ward of Ziauddin University Hospital. Shock indices were applied to each trauma patient, and based on these indices, patients were categorized into exposed and non-exposed groups. This cohort study took place over six months, from April 1, 2019, to September 30, 2019, using a non-probability consecutive sampling method. The approval was taken from ethical review committee of Ziauddin University (Reference Code: 0591118AZEMD). Inclusion criteria included patients of both genders, aged 18-65 years, who sustained trauma. Exclusion criteria were isolated traumatic brain injuries, patients dead on presentation, those with metabolic syndromes or hypertension, pregnant females, and patients in shock due to non-trauma causes like burns, food poisoning, or medication toxicity. This study involved calculating the sample size using WHO sample size calculator, based on an article's statistics indicating a 59.5% death rate in the exposed group and a 3.1% death rate in the non-exposed group [11]. The calculated sample size was 13 participants per group, totaling 26, with a 95% confidence interval and 80% study power. To account for potential data loss, the sample size was increased to 25 per group, making a total of 50 participants. Data collection was approved post-synopsis, involving trauma patients visiting the emergency department, with informed consent obtained from parents or guardians. Patient demographics and vital signs were recorded on a predesigned proforma. Heart rate was measured using a standard Electrocardiogram (ECG), and blood pressure was measured using an automated sphygmomanometer, both calibrated according to hospital protocols. Patients with SI > 0.9, MSI < 0.7 or > 1.3, while those with SI < 0.9, MSI 0.7-1.3 were in the non-exposed group. All variables were measured hourly, except for the shock index, which was assessed every six hours. During monitoring, if any parameter exceeded its cut-off limit, the value was recorded for further evaluation. The study's endpoints included admission to a ward/ICU, discharge home, continued emergency care, or in-hospital mortality. Admitted patients were monitored for 48 hours using their MR/reference number, while discharged patients were followed up for 48 hours through the contact number provided on the emergency form. Bias in this study was minimized by applying strict inclusion and exclusion criteria. Data analysis was performed using SPSS version 21.0. Qualitative variables were analyzed for frequency and percentage, while quantitative variables were reported as mean ± SD. To compare mortality rates between exposed and non-exposed groups over time, the Chi-Square Test was employed. Multivariate logistic regression was used to assess the association between clinical variables heart rate, blood pressure, shock index, and modified shock index, with a significance level set at $p \leq 0.05$.

RESULTS

A total of 50 patients were included in the study with 25 patients in each exposed and unexposed group. Table 1 exhibited patient demographics, including male (56% exposed, 52% unexposed) and female (44% exposed, 48% unexposed). Exposed patients had a higher average age (48.32 years) than unexposed patients (38.44 years). Exposed patients also have significantly higher heart rates (mean 133.40 beats/min), as well as lower systolic (mean 71.08 mmHg) and diastolic blood pressure (mean 47.40 mmHg) than unexposed patients.

Table 1: Descriptive Statistics of the Patient (n=50)

Variables	Exposed N (%)	Unexposed N (%)	Results (p-Value)
Male	14 (56%)	13 (52%)	0.774
Female	11 (44%)	12 (48%)	
Age (Years)	48.32	38.44	0.016
	10.89	13.61	

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Heart Rate (Beats/Min)	133.40	90.16	<0.05
	14.66	20.72	
Systolic Blood Pressure (mmHg)	71.08	117.12	<0.05
	12.40	22.81	
Diastolic Blood Pressure (mmHg)	47.40	74.16	<0.05
	8.77	15.34	

Note: SD = Standard Deviation
Gender Distribution and Age: chi-square test.
Heart Rate (Beats/Min), Systolic Blood Pressure (mmHg) Diastolic Blood Pressure (mmHg): Independent t-test.

Table 2 presented the frequency distribution of various clinical variables in shock patients. Road traffic accidents were the leading trauma mechanism in both exposed (80%) and unexposed (60%) groups. Open wounds were more common in exposed patients (72%) compared to unexposed patients (36%). A significant majority of exposed patients received intravenous fluids (96%) and inotropic support (96%) compared to unexposed patients (36% and 20%, respectively). The in-hospital mortality within 48 hours was substantially higher in exposed patients (72%) compared to unexposed patients (12%).

Table 2: Frequency Distribution of Variables in Shock Patients (n=50)

Variables	Category	Exposed N (%)	Unexposed N (%)
Trauma Mechanism	Road Traffic Accident	20 (80%)	15 (60%)
	Fall	4 (16%)	9 (36%)
	Other	1 (4%)	1 (4%)
Wound Type	Closed	7 (28%)	16 (64%)
	Open	18 (72%)	9 (36%)
Intravenous Fluid	Yes	24 (96%)	9 (36%)
	No	1 (4%)	16 (64%)
Inotropic Support	Yes	24 (96%)	5 (20%)
	No	1 (4%)	20 (80%)
48 Hour In-Hospital Mortality	Yes	18 (72%)	3 (12%)
	No	7 (28%)	22 (88%)

Note: Percentages were calculated based on the total number of individuals in each group (n=25).

Table 3 showed the 48-hour in-hospital mortality rates according to Shock Index and Modified Shock Index. A significant association was observed, with higher mortality rates in patients with a Shock Index ≥ 1 (73.1%) and a Modified Shock Index ≥ 1.3 (73.1%) compared to those with lower indices (8.3%). The chi-square p-values for both indices were 0.000, indicating strong statistical significance ($p < 0.05$).

Table 3: Frequency Distribution of Outcomes within 48 Hours Based on Shock Index and Modified Shock Index in Exposed and Unexposed Groups

Index	Category	Exposed N (%)	Unexposed N (%)	Total	p-Value[(a)]
Shock Index	<1	2 (8.3%)	22 (91.7%)	24	0.000*
	≥1	19 (73.1%)	7 (26.9%)	26	
	Total	21	29	50	
Modified Shock Index	<1.3	2 (8.3%)	22 (91.7%)	24	0.000*
	≥1.3	19 (73.1%)	7 (26.9%)	26	
	Total	21	29	50	

Note: Percentages were calculated based on the total number of individuals in each category.
(a): Chi-square test
(*)Statistically significant result (p-value < 0.05)

In Table 4 the multivariate logistic regression analysis demonstrated that patients with a heart rate greater than 120 bpm, systolic blood pressure below 90 mmHg, and diastolic blood pressure below 60 mmHg had increased odds of 48-hour in-hospital mortality. Both Shock Index ≥ 1 and Modified Shock Index ≥ 1.3 were strong predictors of mortality.

Table 4: Multivariate Logistic Regression Analysis for 48-Hour In-Hospital Mortality

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-Value
Heart Rate > 120 bpm	3.45	1.68 - 7.09	0.002*
Systolic Blood Pressure < 90 mmHg	4.12	1.95 - 8.72	0.001*
Diastolic Blood Pressure < 60 mmHg	2.89	1.35 - 6.17	0.007*
Shock Index ≥ 1	6.25	2.72 - 14.36	<0.001*
Modified Shock Index ≥ 1.3	5.88	2.57 - 13.43	<0.001*

Note: OR = Odds Ratio; CI = Confidence Interval. Variables with higher ORs indicate a stronger association with increased 48-hour in-hospital mortality.
(*)Statistically significant result (p-value < 0.05)

DISCUSSION

The purpose of this study was to correspond to the 48-hour mortality rate along SI and MSI among patients with bruises who were admitted to the emergency room. The findings of this study indicated that there were more male patients in the exposed and non-exposed groups than female patients. The patients in the medication-exposed group were 48.32 ± 10.89 years old on average, whereas the patients in the non-medication-exposed group were 38.44 ± 13.61 years old on average. For both the exposed and unexposed groups, traffic accidents were the most frequent trauma mechanism. The exposed and unexposed groups had in-hospital mortality rates of 72% and 12%, respectively [12]. Numerous approaches to assessing fatality, predicting mortality in humans, and predicting trauma-related injuries have been studied. Additionally, because these conditions were so complex and advanced for specific information about clinics and laboratories, most calculation tools were challenging when first applied at the ED [13, 14]. The study showed that within 48 hours, patients with a Shock Index ≥ 1 or a Modified Shock Index ≥ 1.3 had significantly higher mortality rates (73.1%) in the exposed group compared to the unexposed group (26.9%). In contrast, those with lower indices had a mortality rate of only 8.3% which showed similar results. However, Liu YC *et al.*, contended that modified SI which was determined by

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dividing heart rate by mean arterial pressure was considered a more reliable indicator of shock state and mortality because diastolic blood pressure declines before systolic blood pressure [5]. A few investigations have shown that modified-SI was a better predictor of mortality than SI [15, 16]. A study by Carsetti A *et al.*, suggested that the Shock Index (SI) has limited effectiveness in detecting the risk of Massive Transfusion (MT) in adult trauma patients. However, when it comes to mortality, SI may be more effective in identifying patients at low risk of death due to its low sensitivity but high specificity [17]. According to different retrospective studies, various medical measurements, including age, SI, BP, HR, PR, and MSI, were found to be useful in predicting the severity of serious patients admitted to an emergency ward [12, 18]. SI made use of the hypovolemic shock severity prediction from previous research. SI values greater than 0.9 have been linked to a higher death rate in trauma patients, according to studies [19, 20]. Liu YC *et al.*, claim that because emergency room patients were often complex, it was essential to predict their severity using SBP and DBP [5]. Our results showed a significantly higher mortality rate (SI of ≥1.0), which was consistent with other studies [21]. The non-significant correlation between mortality and SI in emergency patients, with a range of 0.5-0.9.80, was also reported by the researcher [10]. According to another study by Kim MJ *et al.*, with 628 patients, SI was a reliable indicator of death in patients with polytrauma [6]. The study's results cannot be extrapolated to larger populations because it was based on a single hospital's research with the smallest sample size, conducted in an urban area.

CONCLUSIONS

The study concluded a significant association between medical mortality in older adults and bruises at emergency departments, and that SI and Modified SI were viable markers to assess severity. The current study's results also showed that these indices can be used as a stronger scale for fatality detection because they significantly outperform HR, SBP, and DBP taken separately. The Shock Index (SI) and Modified Shock Index (MSI) were crucial in emergency care for early detection of shock, guiding resuscitation, and risk stratification. They enable rapid assessment of the patient, improving outcomes by facilitating timely interventions. The study was based on single hospital research having smallest sampling size, conducted in urban region, however, the findings cannot be generalizable for the larger populations.

Authors Contribution

Conceptualization: AZ
Methodology: FA
Formal analysis: UK
Writing, review and editing: YFZ, RR, SM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Comprehensive Analysis of Empathy by Using Jefferson Scale of Empathy – Student Version Among Undergraduate Medical and Dental Students

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ABSTRACT

Empathy is essential in medicine, but many healthcare professionals struggle to integrate empathetic communication in practice. This study aims to assess empathy levels among medical and dental students and their association with age. **Objectives:** To evaluate empathy levels among medical and dental students using the Jefferson Scale of Physician Empathy-Student Version and examine the correlation with age. **Methods:** Conducted at a private medical college in Lahore, this study involved 324 medical and dental students. Empathy levels were measured using the Jefferson Scale of Physician Empathy and the data were analyzed with SPSS version 24.0. Non-parametric tests were employed to assess differences in the Jefferson Scale of Physician Empathy and subscale scores among participants, with statistical significance set at $p<0.05$. **Results:** The average Jefferson Scale of Physician Empathy score was 66.67 ± 9.5. Among the subscales, "standing in the patient's shoes" had the lowest average score. Bachelor of Dental Surgery students scored slightly higher in perspective-taking and compassionate care, while MBBS students scored higher in standing in the patient's shoes. An inverse relationship between age and empathy scores was observed, with older students exhibiting lower empathy levels. **Conclusions:** It was concluded that Empathy levels among medical students in Pakistan were lower compared to international studies. Emphasizing empathy in medical education should be a priority to enhance compassionate care and professional development among future healthcare professionals.

INTRODUCTION

Developing a healthcare professional with the necessary technical skills and an understanding of how to relate to their patients is essential in medical and dental education. While specialized knowledge can be gained through a carefully crafted curriculum, fostering qualities like professionalism and compassion proves more difficult [1]. The patient-provider relationship relies significantly on empathy, which is defined in medical practice as the capacity of the physicians to comprehend the perspective, emotions, and concerns of patients; communicate this comprehension effectively and confirm its correctness. Positive interpersonal relationships are crucial and contribute to encouraging behaviours that benefit others [2]. In contrast, healthcare literature defines sympathy as an emotional response of pity towards the adversity of others, particularly those perceived to be suffering unjustly. Empathy plays a crucial role in the clinical relationship and offers advantages for both the patient and the healthcare provider. Studies have demonstrated that physicians who demonstrate empathy tend to have more cooperative patients, resulting in improved health outcomes, higher satisfaction levels [3], enhanced quality of life, and reduced stress [4]. Empathy in physicians has been associated with improved communication and

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patient relationships, enhanced clinical abilities, better inter-professional collaboration, increased satisfaction and well-being, reduced professional burnout, lower levels of substance abuse or attempted suicide, heightened ethical consciousness, and a decrease in official complaints. Similarly, medical students who exhibit greater empathy and experience less burnout tend to derive more pleasure from their lives [5]. Empathy comprises three fundamental elements: Compassionate concern, which involves the capacity to empathize with the patient and is influenced by behavioural, cultural, physiological, and religious factors. Empathy requires the ability to see things from the point of view of the patient and relates to a physician's skill in separating their feelings from those of the patient and avoiding having an emotional impact. Lastly, putting oneself in a patient's shoes encompasses understanding others, actively observing them, and comprehending their thought processes [6, 7]. Numerous research efforts have been dedicated to examining the trend of empathy in medical students, with varying and inconclusive findings. Some studies have indicated a steady decrease in empathy [8]. while others have found no significant change over time [9], and yet some have even observed an overall increase in empathetic response. Research has shown that distress significantly impacts the self-reported empathy of medical students, trainees, and residents. Initially, these individuals exhibit high levels of idealism, enthusiasm, and compassion at the start of their medical education. However, as they are exposed to harsh clinical realities such as patient illness, disease severity, and human suffering and mortality, there is a noticeable decrease in these qualities. Consequently, their focus shifts toward technological and objective aspects of medicine rather than maintaining a human-centred approach [10]. This is to say that in Pakistan, while higher credence is always given to the underlying cognitive skills and technical expertise in medical education, humanistic qualities such as empathy play second fiddle. Moreover, these unintended variations in the sets of cultural norms and hierarchical pressures within the healthcare system work to perpetuate this dichotomy, which sends patients down the order regarding the importance of communication. This runs quite contrary to the general trend worldwide, with increased focus given in Western medical education to emotional intelligence and empathetic modes of care by integrating these into the curriculum. The high level of academic pressure and limited exposure to patient care during the initial years of medical training in Pakistan can also be a contributory factor toward low levels of empathy among students compared to their counterparts in international studies. This is where addressing these shortcomings by culturally adapted reforms in education, integrating global best practices, becomes relevant for nurturing empathy along with technical skills among future healthcare professionals. This research seeks to gauge the levels of empathy in a private medical college, among medical students and pinpoint contributing factors. The findings will be valuable for shaping future studies and strategies aimed at bolstering empathy among medical students.

This study aimed to assess the empathy levels among medical and dental students and to analyze the relationship between empathy levels and age among medical and dental students, specifically assessing how advancing age affects different subscales of empathy, including compassionate care, perspective-taking, and standing in the patient's shoes.

METHODS

This descriptive cross-sectional study was conducted at a private medical and dental college in Lahore, Pakistan, from January to April 2024. Approval for the study was obtained from the Institutional Review Board (IRB) and the Ethical Review Committee of the college (IRB Approval No: IRB-48/01/24/AVC). All participants provided informed consent before data collection, and confidentiality was maintained throughout the study. The sample size was determined using the Open Epi Statistical Calculator, known for its reliability and validity. The sample size was calculated by the maintenance of a 5 percent margin of error & a 95 percent confidence interval, resulting in a total of 324 students. In this study, a convenient sampling technique was used to select the participants. The data were collected through a validated JSPE-S [11], which consists of 20 items measuring empathy. Participants responded on a Likert-Scale which consisted of 5 points, with 10 negatively worded items reverse coded. The three components of empathy, as measured by the Jefferson Scale of Physician Empathy-Student Version (JSPE-S), are (1) Compassionate Care (8 questions): This component assesses the healthcare professional's emotional concern and care for patients. Compassionate care is influenced by cultural, behavioural, and psychological factors and represents the emotional aspect of empathy in the physician-patient relationship. (2) Perspective Taking (10 questions): Perspective taking refers to the cognitive ability to realize the patient's point of view. This skill is essential in helping healthcare professionals make informed, empathetic decisions and foster meaningful, trust-based relationships with their patients. (3) Walking in Patient's Shoes (2 questions): This component evaluates the physician's ability to truly comprehend the patient's condition by imagining oneself in the patient's circumstances. The total score ranged from 20-100, where greater levels of empathy are indicated by higher scores. Additionally, the age and gender of the students were also part of the questionnaire. The online platform was used for the distribution of Google Forms. Data were analyzed using SPSS version 24.0. The Kolmogorov-Smirnov test was

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employed to assess the normality of the data, which revealed a non-normal distribution. As a result, non-parametric tests were chosen for further analysis. The Mann-Whitney U test was used to compare empathy scores between groups, such as gender and degree programs (MBBS vs. Bachelor of Dental Surgery (BDS) students), while the Kruskal-Wallis test was employed for analyzing differences in empathy across age groups. Spearman's correlation was used to examine the relationship between age and the various subscales of empathy, as measured by the Jefferson Scale of Physician Empathy-Student Version (JSPE-S). A p-value of <0.05 was examined as statistically significant throughout the analysis.

RESULTS

The data were collected from 324 medical and dental students. About 135 (41.7%) of the students were male and the remaining 189 (58.3%) were females. The mean age of the students was 23.1 + 0.53 (in years). About three-fourths of the students were enrolled in MBBS and remaining enrolled in BDS. The average empathy score of all the students was 66.67 + 9.5 SD (range: 20-100). A high overall empathy score indicates greater empathy. The average score of standing in the patient's shoe was the lowest among all subscales. A p-value less than 0.05 shows statistical significance, meaning the relationship is unlikely to be due to chance. In this study, the significant p-value for 'walking in the patient's shoes' (p=0.05) suggests a meaningful association between age and this specific empathy subscale. In contrast, the non-significant p-values (p>0.05) for overall empathy, perspective-taking, and compassionate care suggest that any observed correlations may not be statistically reliable. The average score of the three subscales is shown in table 1.

Table 1: Scores for Empathy and Its Subscales Among Participants (SD=Standard Deviation)

Subscales of Empathy	Questions	Mean ± SD
Compassionate Care	1, 7, 8, 11, 12, 14, 18, 19	26.28 + 4.06
Perspective Taking	2, 4, 5, 9, 10, 13,15,16, 17, 20	32.89 + 5.19
Walking In Patient's Shoes	3, 6	7.50 + 1.68
Total Empathy Scores	All Questions	66.67 + 9.5

Responses to various questions of JSPE-S are given in table 2.

Table 2: Frequency of Various Responses of JSPE-S

Factors			Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
C.C	1	My understanding of how my patients and their families feel does not affect medical or surgical treatment	40 (12.3%)	113 (34.9%)	75 (23.1%)	71 (21.9%)	25 (7.7%)
C.C	14	I believe in the treatment of medical ailments there is no place for emotions	39 (12.0%)	149 (46.0%)	60 (18.5%)	57 (17.6%)	19 (5.9%)
P.T	10	My patients value my understanding of their feelings which is therapeutic in its own right	13 (4.0%)	31 (9.6%)	62 (19.1%)	170 (52.5%)	48 (14.8%)
P.T	20	In my opinion, a key therapeutic component of medical and surgical care is empathy	18 (5.6%)	26 (8.0%)	57 (17.6%)	146 (45.1%)	77 (23.8%)
P.T	15	The success of treatment is limited without the usage of empathy, as empathy is a therapeutic skill	16 (4.9%)	28 (8.6%)	58 (17.9%)	156 (48.1%)	66 (20.8%)
P.T	2	My patients feel better, when I understand their feelings	12 (3.7%)	25 (7.7%)	50 (15.4%)	149 (46.0%)	88 (27.2%)
P.T	16	My comprehension of my patients' emotional states as well as their families' is a vital part of our interaction	09 (2.8%)	24 (7.4%)	59 (18.2%)	174 (53.7%)	58 (17.9%)
C.C	11	Emotional ties to my patients do not significantly affect the results of medical or surgical procedures because the ailments of my patients can only be healed by medical and surgical treatment	32 (9.9%)	91 (28.1%)	62 (19.1%)	115 (35.5%)	24 (7.4%)
C.C	18	I don't let the close relationships that exist between my patients and their families affect me	12 (3.7%)	35 (10.8%)	73 (22.5%)	167 (51.5%)	37 (11.4%)
C.C	8	Attentiveness towards the personal experiences of my patients, does not influence treatment outcome	33 (10.2%)	110 (34.0%)	75 (23.1%)	84 (25.9%)	22 (6.8%)
P.T	17	In order to provide better care, I attempt to think like my patients	18 (5.6%)	38 (11.7%)	78 (24.1%)	159 (46.0%)	41 (12.7%)
P.T	4	In caregiver-patient relationships, I believe that reading my patients' body language is just as crucial as speaking with them verbally	13 (4.0%)	19 (5.9%)	68 (21.0%)	174 (53.7%)	50 (15.4%)
P.T	13	I make an effort to decipher my patients' mental states by observing their body language and nonverbal clues	10 (3.1%)	27 (8.3%)	65 (20.1%)	163 (50.3%)	59 (18.2%)
P.T	9	I try to imagine myself in the shoes of my patients when providing care to them	10 (3.1%)	50 (15.4%)	62 (19.1%)	162 (50.0%)	40 (12.3%)
C.C	7	During history taking, I try not to pay attention towards the emotions of my patients, and ask about their physical health	27 (8.3%)	80 (24.7%)	70 (21.6%)	119 (36.7%)	28 (8.6%)
P.S	3	It is a bit difficult for me to see things from my patients' Perspectives	23 (7.1%)	87 (26.9%)	85 (26.2%)	112 (34.6%)	17 (5.2%)

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P.T	5	I believe that having a strong sense of humour improves healthcare outcomes	17 (5.2%)	31 (9.6%)	70 (21.6%)	156 (48.1%)	50 (15.4%)
P.S	6	It is challenging for me to perceive things from the view points of patients because people are not the same	20 (6.2%)	54 (16.7%)	86 (26.5%)	135 (41.7%)	29 (9.0%)
C.C	12	It is useless to enquire about a patient's personal life to comprehend their physical complaints	42 (13.0%)	130 (40.1%)	63 (19.4%)	66 (20.4%)	23 (7.1%)
C.C	19	I don't enjoy reading arts and non-medical writings	43 (13.3%)	80 (24.7%)	77 (23.8%)	93 (28.7%)	31 (9.6%)

CC = Compassionate Care
PT = Perspective Taking
P.S = Walking in Patient's Shoes

The average score of JSPE-S, perspective taking and compassionate care of BDS students was slightly higher as compared to MBBS students. While the scores of standing inpatient shoes were higher in MBBS students as shown in figure 1.

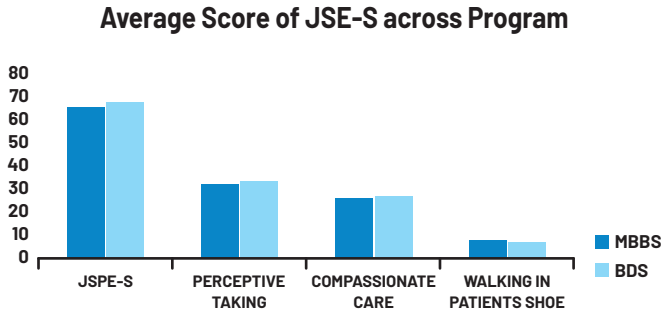

Figure 1: Average Score of JSPE-S Scale and Subscales Among MBBS and BDS Students

Spearman's correlation test was used to analyze the relationship between age and the empathy subscales. The test was chosen because it is appropriate for non-parametric data. The p-value of 0.05 indicated a statistically significant inverse correlation between age and the 'walking in the patient's shoes' subscale. No significant correlation was observed for the overall JSPE-S score or other subscales such as perspective-taking and compassionate care in table 3.

Table 3: Correlational Analysis of Age with JSPE-S and Subscales

Factor	Correlation	p-value
JSE-S Score	-0.11	0.06
Perspective Taking	-0.05	0.42
Compassionate Care	-0.09	0.12
Walking in Patient's Shoes	-0.11	0.05

Accordingly, minor differences in the scores of empathy were present among BDS and MBBS students. The overall mean scores for BDS students were relatively higher in the subscales of perspective-taking and compassionate care, with means of 33.12 ± 5.2 and 26.40 ± 4.1, respectively. In contrast, for the 'walking in the patient's shoes' subscale, the score for MBBS students was higher, 7.65 ± 1.7, compared with BDS students, who scored 7.40 ± 1.6. Though these differences are not significant, p-value>0.05, it would thus appear that medical and dental students differ in their perception regarding empathy-which MBBS students are better at cognitively empathizing with their patients by putting themselves in the place of the patients.

DISCUSSION

Empathy is the capacity for individuals to comprehend, engage with, and acknowledge the internal emotional experiences of others. It plays a significant role in helping people achieve their emotional, social, and professional aspirations as an essential component of socio-emotional wellness [12]. The study objective was to evaluate the empathy levels in a private medical college, among medical and dental students and it involved 324 students with a predominance of female cohort. The student's mean empathy score was 66.67 + 9.5, which is notably lower compared to studies carried out in other parts of Pakistan like Karachi & Sukkur, where they described average scores of empathy as 98.11 ± 12.31 [10] and 101.9 ±16.3 [13] correspondingly. The study in India found that the total average score of empathy was 99.87 ± 14.71 [14] in Bihar among medical college students. Similarly, at the University of Tabuk, a cross-sectional study showed average total empathy scores of 99.05 + 13.75 among medical undergraduates in Saudi Arabia. Several research findings have indicated elevated average empathy scores among medical students, including Australia at 109.07 ± 14.937 [10], South Korea at 105.48 ± 14.67 [16] and Brazil at 119.7 ± 9.9 [17]. This type of variation might be attributed towards the unique educational environment in each country, variances in sampling techniques, and the distinct cultural interpretations of empathy. Medical schools in different countries have varying admission criteria and follow diverse curriculums aligned with their cultural and traditional norms. These factors can influence the levels of empathy displayed by students from various nationalities and backgrounds [1]. This study involved the application of the Jefferson Scale of Empathy and offered additional perspectives on the particular attitudes held by medical students. Within the three subscales, it was observed that the lowest score pertained to walking in the patient's shoes. This discovery indicates a lack of ability among students to empathize emotionally with their patients' perspectives. It highlights the necessity for educational initiatives aimed at cultivating empathy and comprehension of patients' emotional journeys. However, Mirani et al., found contrasting results in a study conducted in Sukkur, Pakistan [10]. They discovered that the average score for walking in a patient's shoes was higher across all empathy subscales among fifth-year female medical

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students. The dental students had slightly higher average scores in perspective-taking and compassionate care on the JSPE-S compared to MBBS students. A study conducted during the Syrian crisis among health professionals found similar results, with medical students scoring lower in empathy (95.55 + 22.99) compared to dental students, although this difference was not statistically significant (99.17 + 15.83; p=0.259). Male dental students in Finland demonstrated less empathy compared to their peers in medical studies [18]. This contrast is thought to stem from the belief held by male applicants to dental programs that patient care in dentistry emphasizes technical proficiency over interpersonal abilities. Our research results revealed a connection between age and JSPE-S score, suggesting that older students are likely to show reduced levels of empathy. Likewise, there was an indirect correlation found between age and perspective-taking, compassionate care, and walking in the shoes of the patients. Similar conclusions have been made regarding the decrease in empathy as age or years of education increase [19]. Various studies have associated several factors with this consistent finding. Factors such as stress related to academic performance, long working hours, insufficient sleep quality, and increased responsibilities with advancing age [20] contribute to declining empathy among older individuals [10]. Separate research from Pakistan carried out by Bangash et al., [9], found no association between empathy and age or years of medical education. The variations in results concerning the relationship between years of education and empathy may be due to diverse educational environments in different nations and societies. From these international comparisons, cultural backgrounds seem to bear considerable importance in the light of how empathy is viewed and expressed. For example, studies conducted in Western countries, Australia and Brazil, reveal notably higher scores for medical students in terms of empathy; such a tendency may express certain cultural traits that attach substantial importance to the nurturing of patient-oriented approaches and effective communication during clinical practice [15, 17]. Most of the studies from South Asian contexts, Pakistan and India, tend to report relatively low scores of empathy, and this may relate to the cultural influence of hierarchical relationships between patients and providers or a greater emphasis on technical competence at the expense of emotional engagement [10, 14]. Understanding such differences is of important while interpreting the levels of empathy globally, and this would suggest that medical education has to be tailored in a way to consider these cultural variations for better patient-provider communication across diverse contexts.

CONCLUSIONS

This study highlights that medical students in Pakistan exhibit lower levels of empathy compared to students in other countries. Dental students demonstrated slightly higher empathy scores than medical students, particularly in perspective-taking and compassionate care. The results also showed a decrease in empathy as students aged, suggesting that as professional experience increases, empathy may diminish under the pressures of academic and clinical environments. These findings emphasize the importance of incorporating empathy training into medical curricula, ensuring that humanistic values are nurtured alongside technical skills. Fostering empathy should be a core focus of medical education to prevent burnout and improve patient care outcomes. Continuous professional development in empathy and emotional intelligence is essential for future healthcare professionals to effectively meet the emotional and psychological needs of their patients.

Authors Contribution

Conceptualization: SN
Methodology: SN, AR, AI, IS
Formal analysis: SN, ANA
Writing-review and editing: ANA, FA, AR

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Diagnostic Accuracy of Beta-D-Glucan and Galactomannan as Fungal Markers in the Detection of Positive Fungal Cultures among Immunocompromised Patients

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ABSTRACT

As fungal infections pose a significant threat to immunocompromised patients, necessitating timely and accurate diagnostic approaches for effective management, non-invasive diagnostic markers are direly needed to detect the presence of fungi during the early stage of the infection. **Objectives:** To determine the diagnostic accuracy of Beta-D-Glucan and Galactomannan as fungal markers in the detection of positive fungal cultures among immunocompromised patients. **Methods:** This cross-sectional study was conducted at the Intensive Care Units of Shifa International Hospital, Islamabad, from April 2024 to July 2024. 57 immunocompromised patients of both genders with an age range of 12 to 80 years, who had positive fungal cultures were included in the study via Non-probability, consecutive sampling while patients who were taking any antifungal medications were excluded. Diagnostic accuracy, sensitivity and specificity of Beta-D-Glucan and Galactomannan were calculated by comparing these assay results against the gold standard of CSF analysis of fungal culture. **Results:** The Beta-D-Glucan and Galactomannan assays showed a specificity of a moderate nature for both assays, slightly higher for Beta-D-Glucan (77.78%) than Galactomannan (72.73%), with a high sensitivity of 92.31% for Beta-D-Glucan and 90.20% for Galactomannan. Overall, the diagnostic accuracy was high for both assays, with Beta-D-Glucan at 96.49% and Galactomannan at 94.74%. **Conclusions:** It was concluded that while the Beta-D-Glucan assay is more sensitive, the Galactomannan assay appears to be more specific. Thus the combined use of both tests enhances diagnostic accuracy for detecting fungal infections in immunocompromised patients.

INTRODUCTION

Over the last two decades, there has been a notable surge in fungal infections (FI), especially among immunocompromised patients, such as those with hematological malignancies, organ transplants, or undergoing prolonged immunosuppressive therapy. These infections significantly contribute to increased morbidity and mortality, with rates reported as high as 60% to 90% in these vulnerable populations [1, 2]. The growing burden of FI in healthcare settings highlights the critical need for improved prevention, early detection, and effective treatment strategies. In particular, the prevalence of FI among patients with hematological malignancies has been found to range from 24% to 31%, emphasizing the importance of prompt diagnosis and intervention in this high-risk group [3]. One of the primary challenges in managing FI is the timely identification of the causative fungal species, as delayed or inadequate treatment can lead to fatal outcomes. This challenge is compounded by the often non-specific clinical presentation of fungal infections, which can resemble bacterial or viral infections. As a result, many cases are diagnosed late, leading to poor outcomes. Hence, there is an increasing demand for the development of more reliable and rapid diagnostic methods that can detect fungal pathogens at an earlier

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stage, potentially improving patient outcomes [4]. This is particularly crucial in immunocompromised patients, who are more susceptible to invasive fungal infections (IFIs), where early detection can significantly impact the course of the disease. In recent years, the detection of fungal biomarkers in clinical samples has emerged as a promising diagnostic approach for IFIs. The identification of fungal cell walls components, such as fungal DNA, galactomannan (GM), and 1,3-β-D-glucan (BG), has shown potential in improving diagnostic accuracy. GM, a polysaccharide component of the fungal cell wall, is shed into the bloodstream during fungal growth, making it a valuable marker for invasive aspergillosis. Similarly, BG is a major component of the fungal cell wall that is released during active fungal infection, particularly in deeper fungal layers [5, 6]. These biomarkers can be detected in serum or Broncho alveolar lavage fluid, providing a non-invasive means of diagnosing fungal infections. However, the sensitivity and specificity of these assays can vary widely, depending on the fungal species and the clinical context. The GM assay, for instance, has shown a sensitivity range of 30% to 100% and a specificity of 38% to 98%, depending on the type of patient population and the timing of the test [7]. In contrast, the BG assay has a reported sensitivity and specificity of 70% to 90%, making it a useful tool for the detection of a broader range of fungal infections, including candidiasis and aspergillosis [8]. However, both assays have their limitations, including false positives due to factors such as concurrent use of antibiotics or the presence of other non-fungal conditions that may interfere with the results. Over the past several decades, fungal infection (FI) has been increasing following the growing number of immunosuppressed or immunocompromised patients with its high associated morbidity and mortality up 60–90%. The major obstacle is to recognize which fungus causes the infection and prescribe appropriate therapy. Thus, there is a need for newer diagnostic modalities for FI. Early detection of FI markers as cell wall components and fungal DNA is important for prompt diagnosis. The most extensively evaluated diagnostic marker is the cell wall surface antigen galactomannan (GM), followed by β-d-glucan, present in deeper layers of the cell wall [9, 10]. The increasing incidence of FI, particularly among immunocompromised individuals, underscores the need for novel diagnostic approaches that can improve early detection and guide timely therapeutic interventions.

This study aimed to determine the diagnostic accuracy of Beta-D-Glucan and Galactomannan as fungal markers in the detection of positive fungal cultures among immunocompromised patients. By enhancing the detection of fungal biomarkers, this research hoped to contribute to the growing body of evidence supporting the use of non-invasive diagnostic methods in the management of fungal infections, ultimately aiming to reduce the high morbidity and mortality associated with these infections.

METHODS

This cross-sectional study was conducted at the Intensive Care Units of Shifa International Hospital, Islamabad, from April 2024 to July 2024. The sample size calculated was 57 immunocompromised patients of both gender with age range of 12 to 80 years, who had positive fungal cultures, chosen via non-probability, consecutive sampling. The sample size was calculated via taking expected sensitivity of B- galactomannan as 70% [10]. The confidence level was taken as 90% with 10%, desired precision. Patients who (at the time of taking samples) were taking any antifungal medications were excluded from the study. The IRB approval was obtained prior to the study (070-24). Informed written consent was taken from every participant. Positive fungal cultures were identified by growing fungal organisms in culture media under laboratory conditions, confirming the presence of viable fungi in collected samples. The β-d-Glucan levels were measured using the fungi tell assay, based on the Limulus gametocyte lysate (LAL) method, with a positive result defined by levels exceeding 80 pg/mL. Additionally, the Platelia Aspergillus enzyme immunoassay was employed to detect Aspergillus Galactomannan, with an optical density index greater than 0.5 indicating a positive result. Diagnostic accuracy, sensitivity and specificity were calculated by comparing these assay results against the gold standard of CSF analysis of fungal culture. The Receiver Operating Characteristic (ROC) curve was plotted to evaluate and compare the diagnostic performance of the Beta-D-Glucan (BG) and Galactomannan (GM) assays. The Area Under the Curve (AUC) provided a summary measure of diagnostic accuracy, with higher AUC values indicating better discriminatory ability of the assays. Data were analyzed using SPSS version 25.0. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated.

RESULTS

The mean age was 45 + 18.5 years, the majority being male (61.4%). Most participants belonged to the middle or lower socioeconomic classes (82.5%). The primary underlying conditions were malignancy (43.9%) and organ transplantation (31.6%), with hematologic malignancies being more common than solid tumors. Kidney transplants were the most frequent among organ transplant recipients. A significant portion of patients were on steroids (73.7%) and antibiotics (87.7%), with 52.6% experiencing neutropenia. The average duration of the disease was 12.5 ± 7.8 months, and blood samples were collected after an average of 18 days of hospitalization (Table 1).

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Table 1: Demographic and Clinical Characteristics

Variables	Results
Age	45 ± 18.5 years
Gender	
Male	35 (61.4%)
Female	22 (38.6%)
Socioeconomic Status	
Upper	10 (17.5%)
Middle	25 (43.9%)
Lower	22 (38.6%)
Underlying Disease	
Malignancy	25 (43.9%)
Organ Transplantation	18 (31.6%)
Other	14 (24.5%)
Type of Malignancy	
Hematologic	15 (60%)
Solid Tumor	10 (40%)
Type of Organ Transplantation	
Kidney	12 (66.7%)
Liver	4 (22.2%)
Heart	2 (11.1%)
Use of Steroids	
Yes	42 (73.7%)
No	15 (26.3%)
Use of Antibiotics	
Yes	50 (87.7%)
No	7 (12.3%)
Neutropenia Present	
Yes	30 (52.6%)
No	27 (47.4%)
Duration of Disease/Condition	12.5 ± 7.8 months
Duration of Hospitalization till Collection of Blood Sample	18 ± 10 days

The Beta-D-Glucan (BG) and Galactomannan (GM) assays both demonstrated high sensitivity, indicating their effectiveness in detecting positive fungal cultures among immunocompromised patients. Both assays also showed strong positive predictive values (PPV), with BG at 96.00% and GM at 93.88%, suggesting that a positive result is highly indicative of a true fungal infection. Specificity was moderate for both assays, slightly higher for BG (77.78%) than GM (72.73%). Overall, the diagnostic accuracy was high for both assays, with BG at 96.49% and GM at 94.74%, reinforcing their utility as reliable markers in this patient population (Table 2).

Table 2: Diagnostic Parameters of Beta-D-Glucan (BG) and Galactomannan (GM) Assays

Diagnostic Parameter	BG	GM
Positive	48 (84.2%)	46 (80.7%)
Negative	9 (15.8%)	11 (19.3%)
Positive Predictive Value	96.00%	93.88%
Negative Predictive Value	63.64%	61.54%
Sensitivity	92.31%	90.20%
Specificity	77.78%	72.73%
Diagnostic Accuracy	96.49%	94.74%

The study displays the ROC curves for Beta-D-Glucan (BG) and Galactomannan (GM) assays, comparing their diagnostic performance in detecting fungal infections in immunocompromised patients. The Area Under the Curve (AUC) for BG was 0.94, indicating high diagnostic accuracy, while GM showed a slightly lower AUC of 0.92. Both assays demonstrated strong sensitivity and specificity, but BG outperformed GM in terms of positive predictive value (96.00% vs. 93.88%) and overall diagnostic accuracy (96.49% vs. 94.74%). The ROC analysis confirms BG as a slightly more reliable marker for fungal infections in our study (Figure 1).

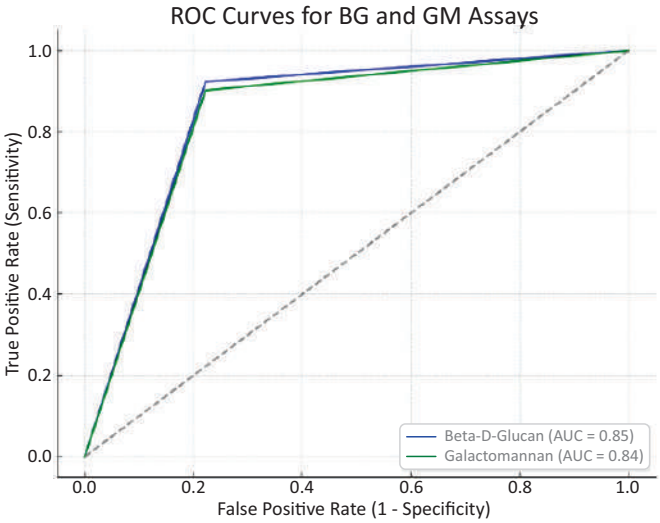

Figure 1: ROC Curve for Beta-D-Glucan (BG) And Galactomannan (GM) Assays

DISCUSSION

Fungal infections (FIs) remain a diagnostic challenge for clinicians and microbiologists due to the imperfections of current diagnostic tools. While fungal culture is considered a superior method, it often takes longer to yield detailed information about the various fungi involved in infections [11]. This technique is regarded as the gold standard for diagnosis through histopathological examination of tissue biopsy specimens [12]. However, in immunocompromised patients, its invasive nature can lead to increased morbidity. As a result, there has been a growing emphasis on less invasive serological assays, such as Beta-D-Glucan (BG) and Galactomannan (GM), for diagnosing fungal infections. In this study, the BG assay returned positive results in 48 of the 57 cases, yielding a sensitivity of 90% and a specificity of 65.56%, with a positive predictive value (PPV) of 96% and a negative predictive value (NPV) of 3% (%p≤0.001). These findings align with previous studies by Ostrosky *et al.*, [13], which reported a sensitivity of 70% and specificity of 87%, and Pazos *et al.*, [14], which found a sensitivity of 87.5% and specificity of 89.6%. The lower specificity observed in our study (65%) indicates that while

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BG is a valuable tool, it may not be suitable for all fungal species. The typical concentration of Beta-D-Glucan in human serum ranges from 10 to 40 pg/mL, with levels exceeding 80 pg/mL considered clinically relevant and indicative of fungal infections. However, this assay does not identify fungi at the genus or species level and serves primarily as a rapid presumptive screening technique. Additionally, false positives can occur due to external factors, such as contamination during specimen collection, particularly when cotton gauze is used. Furthermore, the BG assay's accuracy is highly dependent on procedural conditions that may not be achievable by non-laboratory personnel, impacting the reliability of results—an aspect that highlights significant limitations in this study. Although the assay can specifically identify fungi like Aspergillus, Candida, and Fusarium, it cannot accurately differentiate species lacking BG in their cell walls, such as Zygomycetes and Cryptococcus [15]. In our study, the GM assay demonstrated a sensitivity of 90.2% and a specificity of 72.73%, with 46 positive tests out of 57 cases. In comparison, PCR testing is more sensitive (100%) for diagnosing both fungemia and non-fungemia infections without the interference of masking agents like Voriconazole, serving as a specific backup to culture methods. This aligns with findings from Sims et al., [16] and Cornillet *et al.*, [17], particularly regarding the diagnosis of Aspergillus infections. However, caution is necessary when interpreting GM assay results in patients receiving beta-lactam antibiotics, as these can cross-react with GM and produce false positives [17]. Additionally, the sensitivity of the GM assay may decline in patients who have undergone prior antifungal treatment, particularly with azole medications, as noted by Foy *et al.*, [18]. This underscores the importance of collecting serum samples before initiating antifungal therapy. Dietary factors should also be considered, particularly in young children, as humanized milk can serve as a minor source of Galactomannan and lead to misleading test results. Notably, all patients who tested positive for GM in our study were also positive for BG, indicating that while BG demonstrates greater sensitivity, this specificity necessitates dual assessment. Combining these assays could enhance diagnostic accuracy among high-risk patients, including those receiving antifungal therapy [19, 20].

CONCLUSIONS

It was concluded that our study demonstrates that both Beta-D-Glucan (BG) and Galactomannan (GM) assays are effective for detecting fungal infections in immunocompromised patients. BG exhibited superior diagnostic accuracy at 96.49% and a positive predictive value (PPV) of 96.00%, while GM achieved an accuracy of 94.74% and a PPV of 93.88%. These findings highlight BG as a more reliable biomarker, suggesting its potential to enhance timely treatment and improve patient outcomes. Future studies should focus on optimizing these assays across diverse immunocompromised populations and exploring their combined use to increase diagnostic accuracy.

Authors Contribution

Conceptualization: SA,
Methodology: SA, ZS, MMS, MAA, SR, AA
Formal analysis: SR
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Original Article

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Postoperative Immunosuppression Following Breast-Conserving Surgery vs. Mastectomy: The Role of Surgical Injuries and Intraoperative Sympathetic Activation

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ABSTRACT

Breast cancer is the second most prevalent cancer among all types of cancers. **Objectives:** To evaluate the role of surgical tissue injury and intraoperative sympathetic activation in postoperative immunosuppression after breast-conservative surgery and mastectomy. **Methods:** This prospective/observational study investigated 36 breast cancer patients in the Department of Surgery Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat from June 2022 to May 2023. Patients who were on schedule to undergo either mastectomy or breast-conserving surgery enrolled. Patients were categorized into two groups; Group I (breast-conserving surgery group n=18) and Group II (mastectomy group n=18). The intraoperative sympathetic activation, plasma Damage-associated molecular patterns, and postoperative immune function were compared in both groups. Descriptive statistics were done using SPSS version 28.0. **Results:** The overall mean age and body mass index of Group I and Group II were 62.8 ± 8.9 vs. 60.6 ± 10.6 years and 26.9 ± 3.8 vs. 25.8 ± 3.7 kg/m2, respectively. The overall duration of surgery (minutes) was 56 ± 18 and 85 ± 22, respectively. The prominent indication for surgery in Group I and Group II was Invasive carcinoma 17(94.4%) and 11(61.1%), respectively. The concentration of plasma alarmins and IL-6 was significantly higher in patients who underwent mastectomy as compared to breast-conserving surgery. **Conclusions:** It was concluded that differences in Damage-associated molecular patterns release and intraoperative sympathetic activation between mastectomy and breast-conserving surgery may influence, and potentially contribute to, postoperative immune homeostasis to improve survival seen after breast-conserving surgery.

INTRODUCTION

Breast cancer is the second most prevalent cause of malignancy-associated mortality among all types of cancers [1]. Delays in the treatment of breast cancer can lead to worse outcomes and survival. Remarkably, the survival rates of breast cancer significantly vary from developing countries like Brazil 58%, India 52.1% to developed world 83.2% [2, 3]. The majority of cases in Pakistan delay their treatment due to various factors such as lack of ignorance and adequate facilities. Other contributing factors include fear of surgery and chemotherapy delays in seeking treatment. As a result, breast conservation is often not possible for many patients with breast cancer [4]. Surgery for breast cancer depends on many factors, including timing, availability of resources, and patient preference. Numerous studies compared the survival rates of mastectomy with breast-conserving

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surgery (BCS) and reported that BCS showed a higher survival rate as compared to mastectomy [5]. A potential contributor to this diagnosis is radiotherapy, as most patients with BCS receive radiotherapy, whereas few patients receive radiotherapy after mastectomy [6]. An earlier study reported an increased prevalence of surgical trauma associated with higher susceptibility to post-operative complications [7]. However, patients who underwent conservative breast cancer showed lower complication rates. In contrast, another study revealed that a higher incidence of postoperative complications was reported in mastectomy as compared to BCS [8]. Damage-associated molecular patterns (DAMPs) act as a ligand for receptors inducing inflammation followed by an immunosuppressive state. In addition, activation of sympathetic pain nerves is known to stimulate the immune system. Greater surgical trauma can cause greater pain and greater visceral sympathetic activation. Several DAMPs have been associated with postoperative immunosuppression and infectious complications. Individual DAMPs generally reflect tissue damage or surgical injury. Elevated DAMP levels contribute to the higher rate of mortality and morbidity [9]. This study should be regarded as hypothesis-generating rather than definitive since it is not clear why minimally invasive surgery for early-stage breast cancer might improve survival rates compared to mastectomy. Since radiation is administered to most patients undergoing BCS, as opposed to fewer people after mastectomy, it is reasonable to assume that it plays a role in this finding. On top of that, mastectomy involves more severe surgical trauma, which raises the risk of complications after the procedure. After breast cancer surgery, the risk of complications is minimal. Despite this, a new study found that compared to BCS, the risks of medical and surgical complications following a mastectomy were greater [10]. Following major surgeries like cholecystectomy and oesophagectomy, the risk of postoperative complications and death is greater in older individuals [11]. Nevertheless, there is no correlation between age and the risk of complications following breast surgery, even when undergoing extensive reconstruction [7–10]. Significantly, the main complication rates are 2.1% lower with therapeutic mammaplasty or even more intensive oncoplastic breast-conserving surgeries compared to mastectomy without (5.0%) or with breast reconstruction (14.4%). Other cancer types, including colorectal, gastric, lung, and head and neck cancers, have demonstrated that POCs have a deleterious effect on survival rates. Findings in breast cancer have been inconclusive. New research from Sweden's National Quality Register for Breast Cancer confirms a strong correlation [12].

This study aims to assess the impact of intraoperative sympathetic activation and surgical tissue damage on postoperative immunosuppression following mastectomy and breast conservatoire procedures.

METHODS

This prospective/observational study investigated 36 breast cancer patients in the Department of Surgery Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat from June 2022 to May 2023 with study approval Ref No. IRB/22/18. Non-consecutive sampling technique was used. The calculation of the sample size was based on the prevalence of 18%, the margin of error was 10%, and the confidence interval was 95%. This was done since the required sample size was 36 patients [1]. Patients who were on schedule to undergo either mastectomy or breast-conserving surgery (BCS) enrolled. Patients were categorized into two groups; Group I (BCS group n=18) and Group II (mastectomy group n=18). Each individual provided a consent form. Before surgery, blood samples were taken from each individual. Other specimens were taken after 1 and 3 hours of surgery. Plasma DAMP levels were measured using anti-coagulation blood prepared after the withdrawal of the blood. Baseline, tumor and treatment type, and postoperative data were recorded. Patient details including age, body mass index, tumor characteristics, ASA grades, anesthesia, and pain-related parameters were compared in both groups. The intraoperative sympathetic activation, plasma Damage-associated molecular patterns (DAMPs) [1]. and postoperative immune function were compared in both groups. Postoperative immune function was measured by ANOVA and ELISA tests. Qualitative variables were presented as mean with standard deviation (SD) and quantitative variables were presented as frequencies and percentages. Independent samples T-tests and chi-squared tests were used to determine differences between the groups (BCS versus mastectomy) for each of the time points. Descriptive statistics were done using SPSS version 28.0. $p<0.005$ was considered significant.

RESULTS

The overall mean age and body mass index of Group I and Group II were 62.8 ± 8.9 vs. 60.6 ± 10.6 years and 26.9 ± 3.8 vs. 25.8 ± 3.7 kg/m2, respectively. The overall duration of surgery (minutes) was 56 ± 18 and 85 ± 22, respectively. Baseline parameters such as age, body mass index, and ASA grade in both groups were similar and comparable. Demographic details are shown in table 1.

Table 1: Demographic Details of the Presented Cases

Variables	Group I (BCS)	Group II (Mastectomy)	p-value
Age (Years)	62.8 ± 8.9	60.6 ± 10.6	0.189
BMI (Kg/m^2)	26.9 ± 3.82	5.8 ± 3.7	0.318
Duration of Surgery (Minutes)	56 ± 18	85 ± 22	<0.001

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ASA n (%)			
I	5 (27.8%)	4 (22.2%)	0.669
II	12 (66.7%)	13 (72.2%)	
III	1 (5.6%)	1 (5.6%)	

The prominent indication for surgery in Group I and Group II was Invasive carcinoma found in 17 (94.4%) and 11 (61.1%), respectively. The concentration of plasma alarmins and IL-6 was significantly higher in patients who underwent mastectomy as compared to BCS. Clinical characteristics are shown in table 2.

Table 2: Comparison of Outcomes among Both Groups

Variables	Group I (BCS)	Group II (Mastectomy)	p-value
Invasive Carcinoma	17 (94.4%)	11 (61.1%)	0.018
Carcinoma in Situ	1 (5.6%)	3 (16.7%)	
Invasive Lobular Carcinoma	0	4 (22.2%)	
Sentinel Node Excision			
Yes	14 (77.8%)	15 (83.3%)	0.672
No	4 (22.2%)	3 (16.7%)	
Type of Tumor			
Unilateral	17 (94.4%)	17 (94.4%)	0.699
Bilateral	1 (5.6%)	1 (5.6%)	
Oestrogen Receptor			
Positive	16 (88.9%)	15 (83.3%)	0.699
Negative	2 (11.1%)	2 (11.1%)	
Unknown	0	1 (5.6%)	
Progesterone Receptor			
Positive	14 (77.8%)	13 (72.2%)	0.918
Negative	4 (22.2%)	4 (22.2%)	
Unknown	0	1 (5.6%)	
Postoperative Pain	2.5 ± 4.10	3.9 ± 2.27	0.004

Neither the pre- nor the post-operative DAMP plasma concentrations varied significantly across the groups. Nevertheless, individuals who had undergone a mastectomy had noticeably elevated amounts of S100A8/A9 and S100A12 on postoperative day 3, as shown in table 3.

Table 3: Concentrations of DAMPs in Plasma Before and After Surgery

DAMPs (pg/ml)	Group I (BCS)	Group II (Mastectomy)
Before Surgery	4023.7 ± 5.784	4317.44 ± 12.367
1h After Surgery	4000.7 ± 5.784	4327.13 ± 11.228
3 Days After Surgery	10000.1 ± 2.235	20000.78 ± 16.478

DISCUSSION

The present study mainly focused on the comparison of conservative breast surgery versus mastectomy and investigating the role of surgical tissue injury and intraoperative sympathetic activation. Significant variances were reported between mastectomy and breast-conservative surgery. Several previous studies have reported increases in these DAMPs after surgical procedures [13-15]. There is the possibility of no increase in DAMPs or growth occurring after the time of measurement. Breast cancer surgery is a critical milestone in a female's life. Its treatment improved dramatically over the past decades, with an increasing number of patients opting for breast conservation combined with various therapies [16-18]. Many of these patients follow treatment regimens affecting chemotherapy and radiotherapy together. Although strict adherence to such procedures may improve surgical outcomes, any delay in treatment due to comorbidities may adversely affect overall survival [19]. In Pakistan, most women are reluctant to seek medical advice on breast-related issues, mainly due to unemployment living standards. This highlights the need to address the unmet psychosocial aspects of breast cancer patients in Pakistan, from medical counselling to social support and referral to appropriate healthcare plants. Although surgeons strive to perform operations with excellent postoperative outcomes, achieving optimal cancer-related outcomes often requires a multifaceted approach, including patient education. The increased surgical trauma experienced during mastectomy may increase sympathetic and adrenergic prostaglandin responses. It is widely accepted that primarily autoimmune is the initial postoperative immune response. Propofol was found to impair the function of several monocytes and neutrophils, while remifentanil also exhibited potent immunosuppressive effects. Generally, severe depression occurs in cytokine production immediately after surgery in cancer patients, which often with comorbidities requires reassessment management of anesthesia. Previous studies have reported no difference or serious adverse events, but a reasonable difference may occur during the analgesic phase of triple anesthesia [20].

CONCLUSIONS

It was concluded that differences in DAMP release and intraoperative sympathetic activation between mastectomy and breast-conserving surgery may influence, and potentially contribute to, postoperative immune homeostasis to improve survival seen after BCS.

Authors Contribution

Conceptualization: HR
Methodology: HR, MAQ, NY
Formal analysis: AI, NF,
Writing review and editing: S

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Feto-Maternal Complications of Anticoagulant Use Before and After Childbirth

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ABSTRACT

Anticoagulants prevent blood clotting, but their use in pregnancy poses challenges due to bleeding risks, particularly during delivery and postpartum. **Objectives:** To evaluate the maternal and fetal complications associated with anticoagulant use before and after childbirth, considering the safety and effectiveness of low molecular weight heparin and Warfarin. **Methods:** A cohort study was conducted at the Tertiary Care Hospital of Sindh, from August 2022 to July 2023. 266 pregnant women were chosen via consecutive sampling. Pregnant women with a gestational age of > 12 weeks, aged 18-35 years probably taking anti-coagulation therapy during pregnancy and puerperium were included in the study. While women suffering from any major systemic illness and women taking any other potential teratogenic drugs were excluded. **Results:** Maternal complications occurred in 53% of participants, with postpartum hemorrhage being the most frequent (19.9%), significantly higher in the low molecular weight heparin group ($p<0.05$). Pre-eclampsia affected 10.5% of participants, predominantly in low molecular weight heparin users ($p=0.028$). Fetal complications were reported in 59.3% of cases, with intrauterine growth restriction (13.5%) and premature birth (18.0%) being the most common. Stillbirths were more frequent among Warfarin users. Neonatal intensive care admission was required for 11.3% of infants, with low molecular weight heparin exposure showing the highest incidence. **Conclusions:** It was concluded that low molecular weight heparin was with poor maternal outcomes such as postpartum hemorrhage, wound hematoma, deep vein thrombosis, and pre-eclampsia, while fetal complications included intrauterine growth restriction, stillbirth, premature birth and low birth weight.

INTRODUCTION

Pregnancy is a hypercoagulable state due to significant alterations in maternal hemostatic mechanisms driven by hormonal changes. This hypercoagulability persists up to eight weeks postpartum, increasing the risk of thrombotic events by three to five times compared to non-pregnant women [1, 2]. Consequently, anticoagulant therapy is often administered during pregnancy and the puerperium to mitigate this risk. However, concerns remain regarding the potential risks to both the mother and fetus, and there is limited robust evidence guiding the safe and effective use of anticoagulants in pregnancy [3-5]. Warfarin, although effective and well understood, crosses the placental barrier and is associated with fetal risks, including warfarin embryopathy if used during critical periods of gestation [6]. Low Molecular Weight Heparin (LMWH) is considered a safer alternative. However, its dosing regimens during pregnancy are still not well defined, and maternal side effects such as osteoporosis and thrombocytopenia have been reported [7-9]. Despite the widespread use of anticoagulants, there is a lack of comprehensive research that defines their safety profiles during pregnancy and postpartum. This study aims to address this gap by investigating the maternal and fetal complications associated with anticoagulant therapy during these critical periods. By focusing on the clinical significance of anticoagulants, this study seeks to evaluate the maternal

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and fetal complications associated with anticoagulant use before and after childbirth, considering the safety and effectiveness of low molecular weight heparin (LMWH) and Warfarin.

METHODS

A cohort study was conducted at the Department of Gynaecology & Obstetrics with the collaboration of the Department of General Medicine & Pathology of Liaquat University of Medical & Health Sciences, from August 2022 to July 2023. The study protocol was approved by ERC of LUMHS-wide letter no. LUMHS/REC/-354. The study population consisted of 266 pregnant women, chosen via consecutive sampling who received anticoagulant therapy during the perinatal period. The sample size was calculated by taking the expected miscarriage rate of 22.2% due to the use of direct oral anticoagulants in pregnancy [10]. The margin of error was 5% with 95% of Confidence Interval. Pregnant women with a gestational age of >12 weeks, aged 18-35 years probably taking anti-coagulation therapy during pregnancy and puerperium were included in the study. Women suffering from any major systemic illness and women taking any other potential teratogenic drugs were excluded from the sample. Informed written consent was taken from each participant after debriefing her about the details of the research. All women were followed up till the end of puerperium (6 weeks' post-partum). Information regarding demographics, anticoagulant type and dosage, gestational age, mode of delivery, and maternal and fetal outcomes were gathered on pre-defined proforma. Data were analyzed using SPSS version 26.0. The Chi-square test was used to assess the association of categorical variables. p-value<0.05 was declared as statically significant.

RESULTS

The study involved 266 participants who received anticoagulant therapy during the perinatal period. The majority of participants were aged 18-25 years (41.4%), with 34.6% aged 26-30 years and 24.0% aged 31-35 years. In terms of gestational age, 48.1% were in the second trimester (13-28 weeks), while 51.9% were in the third trimester (29-40 weeks). The predominant type of anticoagulant therapy used was Low Molecular Weight Heparin (LMWH), administered to 54.1% of the participants, followed by Warfarin (27.1%) and Aspirin (18.8%). Regarding the mode of delivery, 60.9% of deliveries were vaginal, and 39.1% were cesarean sections (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Population (n=266)

Characteristic	Frequency (%)
Age (Years)	
18-25	110 (41.4%)
26-30	92 (34.6%)
31-35	64 (24.0%)
Gestational Age (weeks)	
13-28 (Second Trimester)	128 (48.1%)
29-40 (Third Trimester)	138 (51.9%)
Type of Anticoagulant Therapy	
Low Molecular Weight Heparin	144 (54.1%)
Warfarin	72 (27.1%)
Aspirin	50 (18.8%)
Mode of Delivery	
Vaginal Delivery	162 (60.9%)
Cesarean Section	104 (39.1%)

The frequency of feto-maternal complications among participants using anticoagulant therapy with 53% of mothers developed complications in the perinatal period while 59.3% of babies developed complications (Figure 1).

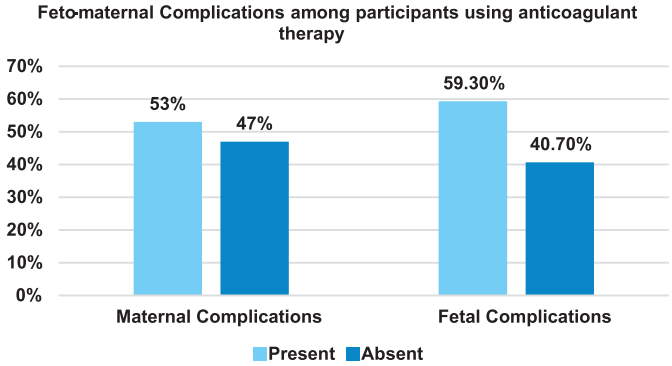

Figure 1: Frequency of Feto-Maternal Complications among Participants Using Anticoagulant Therapy

Among the maternal complications, postpartum hemorrhage was the most frequent, affecting 53 women (19.9%), with the majority (49.1%) in the LMWH group. Deep vein thrombosis and pulmonary embolism were less common, occurring in 12 (4.5%) and 4 (1.5%) participants, respectively, with LMWH users experiencing the highest rates. Wound hematoma and thromboembolic events were observed more frequently in those receiving LMWH. Pre-eclampsia was reported in 28 cases (10.5%), predominantly among LMWH users (Table 2).

Table 2: Feto-Maternal Complications Based on Anticoagulant Therapy (n=266)

Complication	LMWH (n=144)	Warfarin (n=72)	Aspirin (n=50)	Total (n=266)
Maternal Complications n=141 (53%)				
Postpartum Hemorrhage (PPH) (n=53)	26 (49.1%)	22 (41.5%)	5 (9.4%)	53 (100%)
Deep Vein Thrombosis (DVT) (n=12)	6 (50.0%)	4 (33.3%)	2 (16.7%)	12 (100%)
Pulmonary Embolism (PE) (n=4)	2 (50.0%)	1 (25.0%)	1 (25.0%)	4 (100%)
Wound Hematoma (n=24)	12 (50.0%)	10 (41.7%)	2 (8.3%)	24 (100%)
Thromboembolic Event (n=8)	4 (50.0%)	3 (37.5%)	1 (12.5%)	8 (100%)
Pre-eclampsia (N = 28)	16 (57.1%)	10 (35.7%)	2 (7.1%)	28 (100%)

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Fetal Complications n=158 (59.3%)				
Intrauterine Growth Restriction (IUGR) (n=36)	18 (50.0%)	12 (33.3%)	6 (16.7%)	36 (100%)
Premature Birth (<37 weeks) (n=48)	22 (45.8%)	20 (41.7%)	6 (12.5%)	48 (100%)
Low Birth Weight (<2.5 kg) (n=39)	18 (46.2%)	16 (41.0%)	5 (12.8%)	39 (100%)
Stillbirth (n=5)	2 (40.0%)	3 (60.0%)	0 (0.0%)	5 (100%)
Neonatal Intensive Care Admission (n=30)	14 (46.7%)	12 (40.0%)	4 (13.3%)	30 (100%)

Fetal complications included intrauterine growth restriction (IUGR) in 36 infants (13.5%), premature birth in 48 cases (18.0%), and low birth weight in 39 infants (14.7%). IUGR and low birth weight were most common among LMWH users, while premature birth also affected a significant portion of the LMWH group. Stillbirths were rare, with a higher rate observed in Warfarin users. Neonatal intensive care admission was required for 30 infants (11.3%), with the highest frequency in those exposed to LMWH (Table 3).

Table 3: Maternal and Fetal Complications Before and After Childbirth (n=266)

Complication	Before Childbirth	After Childbirth	p-value
Maternal Complications n=141 (53%)			
Postpartum Hemorrhage (PPH)	N/A	53 (37.6%)	N/A
Deep Vein Thrombosis (DVT)	8 (5.7%)	4 (2.8%)	0.182
Pulmonary Embolism (PE)	3 (2.1%)	1 (0.7%)	0.403
Wound Hematoma	N/A	24 (17.0%)	N/A
Thromboembolic Event	6 (4.3%)	2 (1.4%)	0.157
Pre-eclampsia	28 (19.9%)	N/A	N/A
Fetal Complications n=158 (59.3%)			
Intrauterine Growth Restriction (IUGR)	36 (22.8%)	N/A	N/A
Premature Birth (<37 weeks)	N/A	48 (30.4%)	N/A
Low Birth Weight (<2.5 kg)	N/A	39 (24.7%)	N/A
Stillbirth	5 (3.2%)	N/A	N/A
Neonatal Intensive Care Admission	N/A	30 (19.0%)	N/A

(Chi-square test was applied) but none of the values was of statistical significance)

DISCUSSION

Globally, LMWH is regarded as the first-line anticoagulant for pregnant women due to its safety profile, especially its minimal placental transfer and reduced risk of teratogenicity compared to Warfarin. Feto-maternal complications were a significant area of investigation in this study, with postpartum hemorrhage (19.9%) being the most common complication. This aligns with the global concern about hemorrhagic complications in anticoagulated pregnancies, particularly those using LMWH, which is known to pose a risk for bleeding complications, especially during delivery. Bannow et al., highlighted that while LMWH is effective in reducing thromboembolic events, it increases the likelihood of hemorrhagic events, including postpartum hemorrhage [4]. In contrast, our study did not find Warfarin or Aspirin to be associated with as high a frequency of hemorrhagic complications, although these agents are also known to increase bleeding risks in general. The incidence of deep vein thrombosis (DVT) (4.5%) and pulmonary embolism (PE) (1.5%) in our cohort mirrors the lower rates of thromboembolism seen in LMWH users in other international studies, such as that by Rodger et al., who demonstrated that LMWH effectively reduces DVT and PE risks during pregnancy [11]. However, our study's slightly higher rates of thromboembolic events in LMWH users (compared to Warfarin or Aspirin) may reflect a population with higher baseline thrombotic risk, necessitating LMWH use. Pre-eclampsia was reported in 10.5% of participants, predominantly in the LMWH group. This is consistent with other international studies showing an increased incidence of hypertensive disorders in pregnancies requiring anticoagulation. The use of LMWH in such cases is often multifactorial, aimed at preventing not just thromboembolic events but also placenta-mediated complications, as suggested by the work of McLintock C et al., [12]. One key contrast between our findings and those from international literature is the lower overall incidence of cesarean sections (39.1%). In studies from higher-income countries, cesarean delivery rates tend to be higher in anticoagulated pregnancies, likely due to concerns about the risk of hemorrhage during vaginal delivery. This may be reflective of differences in local clinical practices, with a preference for vaginal delivery in our cohort, even among women on anticoagulants [2]. Additionally, while postpartum hemorrhage was the most common complication in our cohort, the overall rate of feto-maternal complications appears somewhat lower than in some international studies. This could be due to variations in healthcare systems, anticoagulation protocols, and the baseline health status of the study populations [13, 14]. The analysis of maternal and fetal complications among women receiving anticoagulant therapy during the perinatal period revealed significant findings. Postpartum hemorrhage (PPH) was the most common maternal complication, affecting 37.6% of women, with the highest occurrence among Low Molecular Weight Heparin (LMWH) users (49.1%). This aligns with international studies of McLintock C & Riley LE highlighting PPH as a frequent complication in anticoagulated pregnancies, although our overall rate appears lower compared to some reports from higher-income settings, where PPH rates can exceed 30% in similar cohorts [12, 13].

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) were less frequent, with 5.7% of DVT cases occurring before childbirth and 2.8% afterwards, predominantly in the LMWH group. These rates are consistent with findings that LMWH effectively reduces the risk of thromboembolic events, though these complications still occur at a notable rate [14]. Fetal complications were also prevalent, with intrauterine growth restriction (IUGR) reported in 13.5% of pregnancies and premature births in 18.0%. Premature birth was most frequent among LMWH users (45.8%), aligning with a study by Abd et al., identifying anticoagulation therapy as a risk factor for preterm labour due to its association with placental insufficiency [15]. However, the rates of low birth weight (14.7%) and neonatal intensive care admission (11.3%) were comparable to international reports of Meng et al., underscoring the risks of fetal complications associated with anticoagulant use during pregnancy [16]. Interestingly, stillbirths were rare but more common in Warfarin users (60.0%), highlighting the increased risk of fetal demise linked to this specific anticoagulant as expressed by Lo [17]. In comparison to global data, the relatively low incidence of severe maternal thromboembolic events and fetal complications in our cohort may reflect differences in healthcare settings, anticoagulation protocols, and maternal characteristics. Studies by Lafalla and Kearsley from high-income countries often report higher rates of cesarean sections and maternal complications due to concerns over bleeding risks during vaginal delivery [18, 19]. However, in our population, the preference for vaginal delivery (60.9%) among anticoagulated women suggests more conservative management strategies, possibly contributing to the lower rates of severe maternal and fetal outcomes [20]. This study was limited by its single-center design, which may reduce the generalizability of the findings. The use of consecutive sampling could introduce selection bias too. Additionally, the study did not account for potential confounding factors such as socioeconomic status or access to healthcare, which may influence maternal and fetal outcomes.

CONCLUSIONS

It was concluded that anticoagulant therapy, particularly LMWH, significantly influences both maternal and fetal outcomes. Before childbirth, LMWH use is linked with higher rates of deep vein thrombosis and pre-eclampsia, alongside a notable prevalence of intrauterine growth restriction and stillbirth. After delivery, LMWH is associated with increased risks of postpartum hemorrhage, wound hematoma, and adverse fetal outcomes such as premature birth, low birth weight, and the need for neonatal intensive care.

Authors Contribution

Conceptualization: SK
Methodology: SK, RP, SF, MAM, PK
Formal analysis: FL, UJK
Writing review and editing: RP, SF, MAM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Association between Metabolic Syndrome and the Severity of Ischemic Heart Disease

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ABSTRACT

Ischemic Heart Disease (IHD) was a leading cause of mortality worldwide, often complicated by metabolic syndrome, which includes hypertension, hyperglycemia, and dyslipidemia. **Objective:** To investigate the association between metabolic syndrome and the severity of ischemic heart disease. **Methods:** Data were collected from the cohort's existing records, including clinical assessments, laboratory tests, and self-reported questionnaires. Metabolic syndrome components were evaluated using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. Participants were classified as having metabolic syndrome if they met three or more of the following criteria: abdominal obesity, elevated blood pressure, elevated fasting glucose, high triglycerides, and low HDL cholesterol. IHD incidence was determined through medical records, hospital admissions, and mortality data, defined as non-fatal myocardial infarction, unstable angina, or coronary revascularization. Statistical analysis included calculating the incidence rate of IHD for participants with and without metabolic syndrome, expressed as IHD cases per 1,000 person-years. Cox proportional hazards regression models were used to assess the association between metabolic syndrome and IHD incidence, adjusting for confounders such as age, sex, smoking status, physical activity, and family history of cardiovascular disease. Hazard Ratios (HRs) with 95% Confidence Intervals (CIs) were reported. **Results:** The incidence of IHD was significantly higher in participants with metabolic syndrome. Cox regression showed metabolic syndrome was associated with increased IHD incidence (HR: 2.70, 95% CI: 1.50–4.80, $p < 0.001$). **Conclusion:** Metabolic syndrome was significantly associated with IHD incidence. Early identification and management were essential to reduce IHD risk.

INTRODUCTION

Ischemic Heart Disease (IHD) is one of the most frequent causes of morbidity and death globally. The World Health Organization (WHO) estimates that cardiovascular illnesses, including IHD, cause 17.9 million deaths worldwide each year, or 32% of all fatalities [1]. In Pakistan, IHD has emerged as the leading cause of death, surpassing conditions such as diabetes and cancers. The prevalence of IHD is increasing, driven by urbanization, sedentary lifestyles, and poor dietary habits, contributing significantly to the national healthcare burden [2]. IHD is typified by atherosclerosis-induced coronary artery constriction, which lowers blood flow to the heart muscle and causes symptoms including angina, myocardial infarction, and heart failure. The progression of Ischemic Heart Disease (IHD) is influenced by both non-modifiable risk factors, including age, sex, and family history, as well as modifiable factors such as hypertension, dyslipidemia, smoking, and obesity. Understanding the underlying risk factors is critical for reducing disease incidence and improving clinical outcomes [3]. A collection of metabolic

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disorders known as metabolic syndrome includes low levels of High-Density Lipoprotein (HDL) cholesterol, high triglycerides, raised blood pressure, elevated fasting glucose, and central obesity. These factors raise the chance of cardiovascular illnesses, such as IHD, occurring. The presence of three or more of these disorders is defined as metabolic syndrome by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). Globally, the prevalence of metabolic syndrome ranges between 20% and 30% in adult populations [4, 5]. In Pakistan, the incidence is alarmingly high, with recent studies estimating that approximately 34% of the adult population suffers from metabolic syndrome, driven by increasing rates of obesity and sedentary lifestyles [6, 7]. Several studies have established the association between metabolic syndrome and IHD. The components of metabolic syndrome, particularly abdominal obesity, hypertension, and dyslipidemia, were known to accelerate atherosclerosis and contribute to the progression of IHD [8, 9]. However, there is a lack of comprehensive data specifically addressing how the individual components of metabolic syndrome affect the incidence of IHD in specific populations, such as those in Pakistan. Most existing research has focused on the severity of established IHD rather than the onset or incidence of the disease itself [10, 11].

This study aimed to address this gap by investigating the association between metabolic syndrome and the incidence of IHD in a cohort from Lahore, Pakistan. The objective is to determine how the presence of metabolic syndrome components influences the likelihood of developing IHD, while adjusting for confounding factors such as age, sex, smoking, and family history. By identifying specific metabolic risk factors that drive the incidence of IHD, this study seeks to provide valuable insights that can guide early intervention strategies in high-risk populations.

METHODS

This observational cross-sectional study was conducted at Ghurki Trust and Teaching Hospital, Lahore, from June 2023 to May 2024. All ethical considerations were strictly adhered to, and the study followed the principles outlined in the Declaration of Helsinki. The confidentiality of patient information was maintained, and an ethical approval certificate (Ref No. 2023/59C) was obtained from the Ethical Review Committee of the University of Biological and Applied Sciences (UBAS), a project of Lahore Medical and Dental College (LMDC). To be eligible for participation in this study, patients were required to have an established diagnosis of ischemic heart disease, which was verified through angiographic evidence or comprehensive medical records. Only patients who agreed to participate and provided their complete medical history were included in the study. The sample size was set at 100 participants, determined using a G*Power formula. This calculation was based on the expected prevalence of metabolic syndrome and ischemic heart disease in the local population, using an effect size of 0.30, a significance level (alpha) of 0.05, and a power of 80%. Although the sample size was relatively small, which may limit the generalizability of the findings, it was considered adequate for the study objectives. Participants ranged in age from 35 to 65 years and had a confirmed diagnosis of ischemic heart disease based on angiographic findings or detailed medical records. They were divided into two groups: Group A, consisting of participants without metabolic syndrome, and Group B, consisting of participants diagnosed with metabolic syndrome. A stratified random sampling technique was used to select the participants, ensuring that the groups were appropriately representative. Data collection focused on several key variables, including age, sex, body mass index (BMI), smoking status, and family history of cardiovascular disease. For Group A (those without metabolic syndrome), the inclusion criteria required participants to be aged 35 to 65 years, have a confirmed diagnosis of ischemic heart disease, and show no signs of metabolic syndrome. This was determined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, which specify the following: a waist circumference of less than 102 cm for men and less than 88 cm for women, triglyceride levels below 150 mg/dL, HDL cholesterol levels greater than 40 mg/dL for men and greater than 50 mg/dL for women, blood pressure lower than 130/85 mmHg, and fasting glucose levels below 100 mg/dL. For Group B (those with metabolic syndrome), participants were also aged between 35 and 65 years and had a confirmed diagnosis of ischemic heart disease. In addition, they met at least three of the following NCEP ATP III criteria for metabolic syndrome: a waist circumference of 102 cm or greater for men and 88 cm or greater for women, triglyceride levels of 150 mg/dL or higher, HDL cholesterol levels below 40 mg/dL for men and below 50 mg/dL for women, blood pressure of 130/85 mmHg or higher, and fasting glucose levels of 100 mg/dL or higher. The study excluded individuals in Group A who met three or more of the metabolic syndrome criteria, as well as those with significant comorbidities such as advanced liver disease, renal failure, or malignancies. Similarly, participants from both groups were excluded if they had experienced acute cardiovascular events, such as myocardial infarction or stroke, within the last six months. Clinical measurements were performed using standardized methods. Blood pressure was measured after participants had been seated for at least five minutes, using a standard sphygmomanometer. The average of two measurements, taken at least one minute apart, was used for analysis. Diastolic blood pressure was determined by

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the fifth Korotkoff sound. Abdominal obesity was measured by determining waist circumference at the narrowest point between the umbilicus and the lower rib cage using a measuring tape. Blood serum lipid profile and fasting glucose levels were assessed using a colorimetric method with commercial kits. Ischemic heart disease was diagnosed based on clinical presentations, including acute coronary syndrome, stable angina pectoris, and a history of chest pain accompanied by electrocardiographic changes suggestive of myocardial infarction. Coronary artery disease severity was assessed using angiographic reports, including the number of affected vessels, degree of stenosis, and presence of significant lesions. The severity was quantified using the Gensini score. Data analysis involved comparing the two groups using t-tests to examine differences in means, and logistic regression was applied to explore associations between the components of metabolic syndrome and the severity of ischemic heart disease. Multivariate logistic regression models were used to account for potential confounding factors, such as age, sex, BMI, and smoking status. The risk of severe ischemic events was evaluated using COX proportional hazards models, with Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) reported. Statistical significance was set at a p-value of ≤ 0.05.

RESULTS

Group A (without metabolic syndrome) and Group B (with metabolic syndrome) were compared, and specify whether these groups were matched for any baseline characteristics such as age, sex, or BMI. The study sample comprised 100 participants, out of which 52 were male and 48 were female. Participants were divided into two groups: Group A (without metabolic syndrome) and Group B (with metabolic syndrome). There were 30 male and 29 female participants in group B, compared to 22 male and 19 female individuals in group A. The individuals underwent screening with respect to their lifestyle and genetic susceptibility to cardiac problems, as indicated in Table 1. 5 males and 14 females in Group A (those without metabolic syndrome) and 18 males and 16 females in Group B (those with metabolic syndrome) showed positive genetic histories. When the group data were compared, it was evident that there were statistically significant differences ($p < 0.05$). Lifestyle considerations revealed that Group B had a higher proportion of participants leading sedentary lives than Group A. There were 35 individuals who had an inactive lifestyle; 18 of them were men and 17 of them were women in Group B, while 16 of them were men and 12 of them were women in Group A ($p \leq 0.05$).

Table 1: Distribution of Independent Variables among study participants

Independent Variables	Group A (Mean ± SD)	Group B (Mean ± SD)
Gender		
Male	22.12 ± 2.01	30.10 ± 5.02
Female	19.11 ± 4.03	29.14 ± 5.04
Age (Years)		
Male	49.14 ± 1.05	48.15 ± 1.02
Female	39.11 ± 1.03	47.13 ± 4.01
Body Mass Index (BMI)		
Male	20.07 ± 2.01	37.15 ± 4.02
Female	19.11 ± 4.01	39.10 ± 1.02
Genetics (Positive)		
Male	5.06 ± 1.01	18.10 ± 3.01
Female	14.06 ± 1.01	16.10 ± 2.01
Lifestyle (Inactive)		
Male	18.01 ± 1.01	12.10 ± 3.01
Female	4.06 ± 1.01	17.10 ± 2.01
Socioeconomic Status		
Rich	5.06 ± 1.01	18.10 ± 3.01
Poor	18.01 ± 1.01	12.10 ± 3.01

Significant at $p \leq 0.05$

The study evaluated the following metabolic syndrome components: blood pressure, blood glucose, cholesterol, triglycerides, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL). Comparison of Group A and Group B was done using t- tests and logistic regression to test for significant differences between them as shown in table-2. There were notable variations in the metabolic syndrome components, with Group B showing considerably higher values than Group A for triglycerides, fasting glucose, systolic and diastolic blood pressure, and waist circumference. In addition, there was a higher likelihood of sedentary lifestyle and a positive family history of cardiovascular disease among participants in Group B. These differences consistently had p-values below ($p \leq 0.05$), indicating that they were statistically significant. In table 2, the comprehensive breakdown was displayed. It was evident that the highest correlations with higher severity of IHD in Group B were seen in systolic blood pressure and fasting glucose, with the latter exhibiting the most significant link.

Table 2: Regularity of Metabolic Syndrome Components among study participants

Dependent Variables	Units	Group A (Mean ± SD)	Group B (Mean ± SD)	p-Value (t-test)	Odds Ratio (95% CI)
Systolic Blood Pressure	mmHg	122.10 ± 3.02	150.20 ± 2.04	0.01	2.45 (1.33–4.50)
Diastolic Blood Pressure	mmHg	78.01 ± 1.01	102.10 ± 3.01	0.01	2.30 (1.26–4.18)
Fasting Blood Glucose	mg/dL	123.14 ± 1.01	178.12 ± 1.02	0.01	2.70 (1.45–5.02)
Total Cholesterol	mg/dL	189.11 ± 1.01	238.12 ± 1.02	0.02	1.90 (1.10–3.25)
Triglycerides	mg/dL	149.24 ± 1.01	198.11 ± 1.05	0.03	1.75 (1.01–3.10)

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LDL Levels	mg/dL	99.34 ± 1.03	148.10 ± 1.02	0.02	1.80 (1.06–3.07)
HDL Levels	mg/dL	38.04 ± 1.01	48.10 ± 1.01	0.03	2.05 (1.12–3.75)

Significant at $p \leq 0.05$

The study employed the Cox proportional hazard model to assess the effect of metabolic syndrome components on the development of ischemic heart disorders. According to the results, those with metabolic syndrome were shown to have a greater risk than those without metabolic syndrome of experiencing serious ischemic heart disease events, such as myocardial infarction or hospitalization for angina. This was showed in table 3. The findings showed a strong correlation between the severity of ischemic heart disease and metabolic syndrome. In comparison to Group A participants with ischemic heart disease alone, the results of Group B participants with metabolic syndrome were higher in all components as per the previously mentioned parameters, including blood pressure, fasting blood glucose, cholesterol, triglycerides, LDL, and HDL levels. This directly contributes to the study's goals, which were to demonstrate that metabolic syndrome exacerbates the symptoms of ischemic heart disease. All of these findings were further verified using Cox proportional hazards models and logistic regression.

Table 3: Cox Proportional Hazards Model for Metabolic Syndrome Components

Variables	Hazard Ratio (95% CI)
Systolic Blood Pressure	1.45 (1.12–1.88)
Diastolic Blood Pressure	1.38 (1.10–1.73)
Fasting Blood Glucose	1.65 (1.28–2.13)
Total Cholesterol	1.22 (0.99–1.50)
Triglycerides	1.30 (1.04–1.63)
Waist Circumference	1.55 (1.17–2.04)

Significant at $p \leq 0.05$

DISCUSSION

This study aimed to investigate the association between the severities of ischemic heart disease. The significant hazard ratio of 1.65 for fasting blood glucose indicates a substantial increase in risk for severe ischemic events in patients with elevated glucose levels, highlighting the importance of glycemic control in preventing adverse cardiovascular outcomes. The study showed the relationship between the severity of ischemic heart disease and the components of the metabolic syndrome in a population from Lahore, Pakistan. The current study's findings demonstrate a relationship between the severity of ischemic heart disease and several components of the metabolic syndrome, including triglycerides, fasting blood glucose, systolic and diastolic blood pressure, and waist circumference [12, 13]. For instance, the hazard ratio for fasting blood glucose was 1.65, suggesting that patients with higher glucose levels were at a notably increased risk of severe ischemic events. Likewise, the hazard ratio of 1.55 for waist circumference raises awareness of the presence of central obesity in clinical practice [14]. The cross-sectional design limits the ability to infer causality between metabolic syndrome components and ischemic heart disease severity. Additionally, the relatively small sample size may limit the generalizability of the findings to broader populations. Future prospective studies with larger and more diverse samples were necessary to confirm these associations and to determine the temporal relationships between metabolic syndrome components and the progression of ischemic heart disease. While these findings underscore the critical role of metabolic syndrome components, it was essential to view them within the broader context of cardiovascular risk, which includes genetic predisposition, lifestyle factors, and environmental influences. The findings of this study support previous findings that reveal a close relation between metabolic syndrome and the adverse effects on cardiovascular health [15]. Ge H et al., in 2020 suggested that High blood pressure, high blood sugar level, high cholesterol level were all established risk factors for cardiovascular disease, and metabolic syndrome was characterized by the worsening of cardiovascular diseases when these factors were all present [16]. Hutcheson R et al., in 2012 stated that the moderate effect sizes imply that these metabolic syndrome components were just one of the factors affecting the severity of ischemic heart disease. Thus, although these factors influence the disease, they need not be viewed as exclusive factors driving the process [17]. Marott JL et al., in 2023 stated that more attention should not be paid to the components of the metabolic syndrome since the study proved its relevance. They should be seen as additive factors that, along with other variables such as hereditary factors, habits, and surroundings, determine the degree of the ischemic heart disease. This was because cardiovascular disease risk factors were multiple, and risk practices that have to involve the control of metabolic syndrome components alongside other health practices [18]. There were few limitations of this study that need to be discussed. However, due to cross-sectional design it was difficult to establish the causal relationships, although the associations were found. Prospective studies were required to determine the time-dependent associations between metabolic syndrome factors and severity of ischemic heart disease. The sample size was not large enough to demonstrate the significance of the associations which may restrict the generalization of the results . However, the larger and more diverse sample size in the future research will give more accurate results of the effect sizes and replicate these findings. In order to get a better understanding of the various linkages, it was also necessary to emphasize that confounding factors including nutrition, degree of physical activity, and socioeconomic position should be taken into account in future studies [20]. Therefore, the present study reveals the extent to which the components of metabolic

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syndrome influence the severity of ischemic heart disease [21]. The findings underscore the importance of addressing these factors in clinical practice. However, the results of the study should be judged within the context of the limitations of the study and in connection with the existing risk factors for cardiovascular diseases [22]. Therefore, the management of metabolic syndrome and cardiovascular risk factors should continue to be a multifactorial process, which includes the other important intervention strategies.

CONCLUSIONS

This study identified a significant link between metabolic syndrome components i.e. severity of ischemic heart disease. However, the study's cross-sectional design and small sample size limit the ability to establish causality and generalize the results. Future research should explore these associations in larger, more diverse populations to strengthen the evidence. A comprehensive approach to cardiovascular risk management remains essential.

Authors Contribution

Conceptualization: SJ, MS
Methodology: SJ, AA, IAS, QS, FAK, MHI
Formal analysis: MHI, MS
Writing, review and editing: FAK, MS

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

Conflicts of Interest

The authors declare no conflict of interest.

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Biomarker Profiles in Serum and CSF for Early Diagnosis of Selected Neuro-degenerative Diseases

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ABSTRACT

Biomarker research and justification for neurodegenerative illnesses have seen enormous efforts over the last ten years. Bio-fluid-based biomarkers have been believed to provide a better and easier approach to detecting biomarkers for diagnosing nervous system pathologies. **Objectives:** To evaluate the diagnostic potential of certain biomarkers in serum and cerebrospinal fluid to diagnose Alzheimer's disease, Parkinson's disease, and Huntington's disease at an initial stage. **Methods:** 280 participants were taken and distributed into four groups, comprising, 70 patients with early-stage Alzheimer's disease, 70 with early-stage Parkinson's disease, 70 with early-stage Huntington's disease, and 70 age-matched healthy controls. Blood and cerebrospinal fluid samples were drawn and medical history was taken from the patients. Serum and cerebrospinal fluid levels of amyloid-beta (Aβ42), total tau (t-tau), phosphorylated tau (p-tau), alpha-synuclein, huntingtin protein, and neuro-filament light chain were evaluated using enzyme-linked immunosorbent assays. **Results:** Alzheimer's disease patients showed reduced serum Aβ42 (80.4 ± 15.6 pg/mL) and elevated t-tau (140.5 ± 18.2 pg/mL). Parkinson's disease patients had raised serum alpha-synuclein (12.5 ± 2.3 ng/mL) and neuro-filament light chain. Huntington's disease patients showed significant increases in serum huntingtin protein (8.2 ± 2.0 ng/mL). These profiles indicate efficacy in early diagnosis. **Conclusions:** It was concluded that Aβ42 and tau effectively detect Alzheimer's disease, while Parkinson's disease patients can be effectively diagnosed with Serum and cerebrospinal fluid levels of the neuro-filament light chain. Similarly, huntingtin protein and neuro-filament light chain are sensitive enough to detect Huntington's disease at its early stages.

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are among the major public health concerns due to their progressive nature. These neurodegenerative diseases are known to destroy the cognitive and motor functions of our body. Alzheimer's disease is one of the most common and persuasive causes of dementia in older age individuals, affecting over 50,000,000 individuals globally [1]. Alzheimer's disease is recognized by the intracellular formation of neurofibrillary masses and the extracellular accumulation of amyloid-β (Aβ) peptide fibrils. Its complex pathophysiology and multiple aetiology remain unclear [2]. Since there is currently no treatment for Alzheimer's disease, the high failure rate in clinical trials may stem from inclusion criteria, research design, or attempts to treat the disease after it has progressed [3]. Parkinson's disease is a complicated neurological condition that is mainly caused by the decrease of dopamine-releasing neurons present in the brain area (substantia nigra), ultimately resulting in the progressive loss of motor function [4]. As of right now, the sole clinical criteria used for Parkinson's disease diagnosis are the presence of neuro-motor symptoms, which have limited accuracy in the initial phases of the disease [5]. It is

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thought that neurodegeneration is neither severe nor widespread during this early stage, providing an ideal opportunity for new medicines and treatments that modify the disease. However, more factors would be needed in addition to the clinical criteria for the diagnosis of early Parkinson's disease [6]. Huntington's disease is an autosomal dominant condition resulting from a Cytosine, Adenine, and Guanine (CAG) tri-nucleotide replication extension in the gene named Huntington's disease (HTT). This genetic mutation ultimately causes the creation of a non-functional protein, known as huntingtin-protein, which gathers within the nerve cells, causing neurodegeneration primarily in the striatum but also affecting other brain parts. Huntington's disease is established through a combination of motor, cognitive, and psychiatric symptoms, with a premanifest stage that offers a critical prospect for early therapeutic intervention. There are no treatments available at the moment that can cure Huntington's disease but its progression can be slowed down [7]. However, the identification of novel biomarkers linked to the early stages of the disease is crucial since molecular changes occur well in advance of the emergence of neurodegenerative symptoms [8]. Although biomarkers for neurodegenerative disease diagnosis have been thoroughly studied, more research is still necessary to determine their clinical applicability [9]. Several imaging techniques have been created to offer detailed insights into the anatomy and operation of the brain [10]. However, because of their high costs and infrastructure requirements, these approaches are difficult to deploy in a clinical context and have limited application in routine early diagnosis cases. Detectable molecular biomarkers in bodily fluids are thought to be the best way to support clinical diagnosis. Because CSF is thought to act as the brain's surrogate, it is the recommended bio-fluid for biomarker research about neurodegenerative illnesses. Even though CSF is widely used in Parkinson's disease biomarker research, there are still few validated biomarkers that can be used in a clinical context [11]. Serum, plasma, and cerebrospinal fluid (CSF) are considered the most authentic and easily available body fluids to detect various metabolites or toxins to detect a disease at an early stage. While CSF biomarkers such as Aβ1-42, total tau, and phosphorylated tau have shown utility in Alzheimer's disease, and α-synuclein and neuro-filament light chain (NfL) are being explored for Parkinson's disease and Huntington's disease, the invasiveness of CSF collection limits its widespread clinical application. Therefore, identifying non-invasive, cost-effective blood-based biomarkers is a critical research priority.

This study aims to establish some diagnostic parameters that use blood to detect these factors for the detection of Alzheimer's disease, Parkinson's disease, and Huntington's disease at an early stage. By leveraging the differential expression of specific biomarkers linked with these disorders, we propose that these parameters will significantly improve diagnostic precision and feasibility in clinical settings.

METHODS

This comparative cross-sectional study included 280 participants: 70 with early-stage Alzheimer's disease, 70 with early-stage Parkinson's disease, 70 with early-stage Huntington's disease, and 70 age-matched healthy controls. Participants were recruited from Bhitai Medical and Dental College, Mirpurkhas, Sindh, from April 2023 to September 2023. The duration of the study was six months and a convenience sampling technique was used. Written consent was taken from all the patients before the study, and it was started after approval from the institutional ethics committee of Bhitai Medical and Dental College, Mirpurkhas, Sindh (Ref. No. BDMC/R&D/ERC/2023-15). The sample size was calculated on the basis of 80% statistical power and a significance level of ≤0.05. The following formula for sample size calculation in diagnostic studies was used:

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

Where Z is the Z-value (1.96 for 95% confidence), P is the expected prevalence 2.21%, and d is the desired precision (5%). The inclusion criteria for this study involved participants aged 40-75 years who were clinically suspected for the diagnosis of initial-stage Alzheimer's disease, Parkinson's disease, and Huntington's disease based on established clinical criteria, as well as similar age group healthy controls without any history of neurodegenerative disorders. Participants were required to provide informed consent and have the capacity to undergo blood sampling and, where applicable, lumbar puncture for CSF collection. The patients were excluded from the study with a history of any known psychiatric condition, any cardiovascular or systemic ailment, active infections, or those on medications known to affect the central nervous system. Blood samples were drawn from all selected patients and centrifuged at 2000 RPM for 10 minutes, to obtain serum. CSF was drawn by a lumbar puncture. All the samples taken in this way were preserved at -80°C until further analysis. Serum and CSF levels of amyloid-beta (Aβ42), total tau (t-tau), phosphorylated tau (p-tau), alpha-synuclein, huntingtin protein, and NfL were measured using enzyme-linked immunosorbent assays (ELISAs). The samples were sent to the lab with the tag numbers without mentioning the names of the patients to ensure blinding. Statistical analyses were carried out using SPSS-27. Differences among the groups were assessed by one-way analysis of variance (ANOVA) followed by Turkeys' post-hoc test to find significant differences among the groups.

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RESULTS

Serum levels of Aβ42 were significantly decreased in Alzheimer's disease patients, while t-tau and p-tau levels were significantly raised compared to the controls. In Parkinson's disease patients, serum levels of alpha-synuclein and NfL were significantly raised. NfL levels were also raised in Huntington's disease Huntington's disease. In Huntington's disease patients, serum huntingtin protein levels were significantly higher, compared to all the other groups (Table 1).

Table 1: Serum and Plasma Biomarker Levels in Study Groups

Biomarker	Healthy Controls (n=70)	Alzheimer's Disease (n=70)	Parkinson's Disease (n=70)	Huntington's Disease (n=70)	p-value
Serum Aβ42 (pg/mL)	150.5 ± 20.3	80.4 ± 15.6**	145.8 ± 18.4	148.7 ± 17.3	<0.001
Serum t-tau (pg/mL)	75.2 ± 10.4	140.5 ± 18.2**	80.2 ± 12.1	78.6 ± 11.9	<0.001
Serum p-tau (pg/mL)	32.4 ± 5.8	90.7 ± 14.3**	33.2 ± 6.2	35.0 ± 6.0	<0.001
Plasma α-synuclein (ng/mL)	4.6 ± 1.0	4.8 ± 1.1	12.5 ± 2.3**	5.0 ± 1.2	<0.001
Plasma NfL (pg/mL)	22.7 ± 5.5	30.5 ± 6.4**	35.8 ± 7.2**	60.2 ± 10.5**	<0.001
Serum huntingtin protien (ng/mL)	1.5 ± 0.5	1.6 ± 0.6	1.4 ± 0.4	8.2 ± 2.0**	<0.001

Values are shown as mean ± standard deviation (SD). ** shows a statistically significant difference compared to healthy controls (p<0.001) in the post-hoc analysis.

Similarly, the analysis of cerebrospinal fluid (CSF) biomarkers provided further differentiation between the groups. In Alzheimer's disease patients, CSF levels of Aβ42 were significantly reduced, while t-tau and p-tau levels were significantly elevated. These biomarkers are strongly associated with Alzheimer's disease pathology, with lower Aβ42 and higher tau proteins reflecting the presence of amyloid plaques and neurofibrillary masses in the brain. In Parkinson's disease patients, CSF alpha-synuclein levels were significantly higher, consistent with the accumulation of this protein in the brain, supporting its use as a biomarker for early Parkinson's disease detection. NfL levels in CSF were moderately increased, indicating ongoing neurodegenerative processes in Parkinson's disease. In Huntington's disease patients, CSF levels of huntingtin protein were significantly elevated, providing a clear distinction between Alzheimer's disease, Parkinson's disease, and healthy controls. This specific increase in huntingtin protein, along with elevated NfL levels, underscores its utility as a diagnostic biomarker for Huntington's disease (Table 2).

Table 2: Cerebrospinal Fluid Biomarker Levels in Study Groups

Biomarker	Healthy Controls (n=70)	Alzheimer's Disease (n=70)	Parkinson's Disease (n=70)	Huntington's Disease (n=70)	p-value
CSF Aβ42 (pg/mL)	800.2 ± 95.5	350.4 ± 60.8**	780.1 ± 92.3	790.2 ± 88.7	<0.001
CSF t-tau (pg/mL)	70.2 ± 12.6	150.3 ± 20.2**	75.5 ± 10.8	72.3 ± 11.1	<0.001
CSF p-tau (pg/mL)	20.5 ± 4.0	60.7 ± 9.3**	21.0 ± 4.3	22.4 ± 4.2	<0.001
CSF α-synuclein (ng/mL)	3.0 ± 0.8	3.2 ± 0.9	15.0 ± 2.7**	3.3 ± 0.8	<0.001
CSF NfL (pg/mL)	30.2 ± 7.5	40.4 ± 8.2**	45.8 ± 9.0 **	75.2 ± 13.5**	<0.001
CSF huntingtin protein (ng/mL)	0.8 ± 0.3	0.9 ± 0.4	0.7 ± 0.2	4.2 ± 1.5**	<0.001

Values are shown as mean ± SD. ** presents a statistical significance level compared to healthy controls (p<0.001) in the post-hoc analysis.

DISCUSSION

The results of the current study highlight the potential of specific serum and CSF biomarkers in the early detection of Alzheimer's disease, Parkinson's disease, and Huntington's disease. These results are consistent with existing literature, which highlights the importance of biomarkers in identifying neurodegenerative diseases at an early stage, potentially before significant clinical symptoms emerge [12, 13]. In Alzheimer's disease, the observed decrease in serum and CSF levels of Aβ42 and the increase in tau proteins (both total and phosphorylated) align with the well-documented pathological processes underlying the condition [14, 15]. Hampel *et al.*, [2], Michno *et al.*, [16], and Xu *et al.*, [17] have shown that Aβ42 aggregates into amyloid plaques in the brain, a hallmark of Alzheimer's disease, leading to a reduction in its levels in the CSF. Similarly, Moore *et al.*, described the accumulation of hyper-phosphorylated tau, which forms neuro-fibrillary tangles, another key feature of Alzheimer's disease pathology [18]. The correlation between decreased CSF Aβ42 and elevated tau levels has been extensively validated in previous studies by Campbell *et al.*, [19], Grangeon *et al.*, [20] supporting their use as reliable biomarkers for early Alzheimer's disease diagnosis. For Parkinson's disease, the significant increase in alpha-synuclein levels in both serum and CSF is consistent with its role in the development of Lowy bodies. Ganguly *et al.*, [21] have demonstrated that alpha-synuclein accumulates in the brain, with its ultimate build-up in the CSF, making it a critical biomarker for Parkinson's disease. Furthermore, the observed rise in NfL levels in Parkinson's disease patients suggests axonal degeneration, a hallmark of the disease's neurodegenerative nature. These findings are in line with the existing research, as noted by Chen *et al.*, [6] which reports elevated alpha-synuclein and NfL levels in the CSF in most Parkinson's disease cases. The results of our study indicate that huntingtin protein levels are significantly elevated in the serum and CSF of patients in the Huntington's disease group. The results of a study by Caron *et al.*, [22] support these findings, having reported increased huntingtin protein levels in the CSF of advanced-stage Huntington's disease patients. Similarly, the

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significant elevation of NfL levels in Huntington's disease patients in our study confirms the initiation of neuronal damage, a typical feature of the disease. The observed differences in biomarker levels across Alzheimer's disease, Parkinson's disease, and Huntington's disease patients underscore the importance of these biomarkers in serum and CSF for diagnosing these neurodegenerative diseases at an early stage. it is recommended that routine screening of these biomarkers in both serum and CSF be considered for individuals at risk of neurodegenerative diseases to facilitate early diagnosis and intervention. Further large-scale studies should be conducted to validate the use of these biomarkers in clinical practice, potentially leading to the development of more standardized diagnostic protocols.

CONCLUSIONS

It was concluded that the study establishes the potential of specific serum and CSF biomarkers for the initial detection of Alzheimer's disease, Parkinson's disease, and Huntington's disease. Aβ42, NfL, t-tau and p-tau are useful biomarkers for early diagnosis of Alzheimer's disease, α-synuclein and NfL for Parkinson's disease whereas NfL and huntingtin protein can be assessed for early detection of Huntington's disease.

Authors Contribution

Conceptualization: MA
Methodology: MA, MT, AI
Formal analysis: IA, AZ, NA
Writing review and editing: MA

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

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Suicidal Deaths by Poisoning in Muzaffargarh: Observational Study Comprising of Regional Toxicity Patterns of Acute Poisoning in Cases of Suicidal Deaths in Muzaffargarh

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ABSTRACT

Cases of suicidal deaths are increasing day by day and one of the main reasons is acute poisoning, which is the preferred method of suicide in many areas. The increasing number of deaths led us to conduct a study on this particular aspect. **Objectives:** To determine the frequency of toxic agents used for poisoning, regional trends of availability, modes and methods of use and reasons for self-poisoning. **Methods:** In this retrospective study, dead bodies of both genders and all age groups were studied with their respective data and history, for the years of 2019 to 2023. Unidentified, burnt, putrefied and bodies of chronic narcotic abuse were excluded. All the variables were analyzed through SPSS version 27.0. **Results:** Out of 387 cases of suicidal deaths due to poisoning, 67% were females with the predominant age group of 21 to 40 years. The majority were married and belonged to rural areas of Muzaffargarh with illiteracy levels up to 75%. The widely used poisonous agents were Kala Pathar, Wheat pills and Organophosphorus. Almost 61.7% of families did not allow postmortem of the deceased. **Conclusions:** It was concluded that suicidal deaths due to poisoning are soaring day by day due to the lack of proper legislation, suicide prevention strategies and provision of health facilities for the people of district Muzaffargarh.

INTRODUCTION

The Silent Suicide problem is happening every second of day globally and it affects mostly underdeveloped countries like Pakistan. Suicide is a phenomenon, it's not just a time act, it has a series of psychological, emotional, and physical milestones that a person encounters and surpasses to finish his /her life. In terms of Forensic Medicine, Suicide is an act of taking one's own life voluntarily and intentionally. The term Attempted Suicide is used when a person attempts to take his/her life or has the tendency to take his/her life. Partial Suicide is another form of suicide in which a person is involved in self-mutilation. Chronic Suicide is used for habitual behaviour patterns that are injurious to life and can ultimately lead to the death of the person. There are various methods used for suicide, like hanging, intoxication, cutting of radial artery, drowning in water, and firearms, but the most common form of suicide

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prevailing in Pakistan is done by self-poisoning. Poison is a substance that can be a solid, liquid or gas, that when introduced into the body via ingestion, inhalation or dermal contact can produce harmful effects and can lead to death. Acute Poisoning is the major route of suicidal deaths in Pakistan. It is the reason for frequent emergency visits of victims and the leading cause of death across the country. World Health Organization (WHO) estimated in 2021 almost 703,000 suicidal deaths per year globally, of which 77 percent were recorded in underdeveloped countries [1]. In Pakistan, 8.9 suicides occurred per 100,000 people in 2019 [2]. It is estimated that around 20 percent of global suicides are due to pesticide self-poisoning, most of which occur in rural agricultural areas of underdeveloped countries like Pakistan. According to a study in Pakistan, from 2000 to 2021, the rate of suicide increased by 36 percent and it accounts for 48,183 deaths which is equivalent to almost 1 death every 11 minutes [3]. Suicide due to poisoning is very common all over the world and it used to be a common practice for ages. Unnatural deaths caused by poisoning ranks 2nd after Road Traffic Accidents all over the world [4]. There are a variety of chemical substances used for poisoning. An ideal suicidal poison has many qualities that make it feasible for people to go for, like; its availability, cost, tastelessness, no aroma, high toxicity, less time to act, easily mixed in food or drinks, and capability to produce painless death. It can be derived that there are many factors involved in cases of suicidal poisons. Keeping in view the fact that Pakistan is an agricultural country, the common suicidal poisons, that fulfil all criteria for being ideal suicidal poisons, are organophosphorus, black stone and wheat pill. Organophosphorus is most common in south Punjab and interior Sindh. In north Punjab, the common agent is Aluminum Sulfide, also known as a wheat pill. Another agent is Para Phenylene diamine also called Kala Pathar, which is also commonly used in south Punjab. Other agents like rat poison, kerosene oil, benzodiazepines and other household products are also used. Variation in clinical presentation in self-poisoning cases depends upon factors like; age group, gender, reason for suicide, geography and economy. The majority of cases of suicide involve the age group of 20 to 39 years. Females are affected more than males. Domestic issues like marital conflicts and depression due to economic reasons are the main factors. Rural areas have the predominance of such cases where pesticides are easily accessible [5]. In this 5 years observational study for the years 2019 to 2023, rising cases of suicide by poisoning came into the spotlight, as the district of Muzaffargarh still lacks basic health facilities, psychosocial education and rehabilitation and a lack of proper legislation about suicide. In the 2023 census, the total population of Muzaffargarh is 5,015,325 [6]. The district comprises agricultural and industrial areas with a majority of rural areas and a low literacy rate. This neglected region of the country is the major source of wheat and cotton production, still lacks advanced health facilities and is deprived of psychosocial awareness. The rationale of this study is to converge attention towards the formulation of Regional Suicide Prevention Strategy Programs and proper Suicide Legislation.

This study aims to determine the frequency of toxic agents used for poisoning, regional trends of availability, modes and methods of use and reasons for self-poisoning at the district level.

METHODS

After receiving ethical approval from the concerned authority (ref no: 437/24) study was conducted at District Headquarters Hospital (DHQ) Muzaffargarh for the years 2019 to 2023. Dead bodies of suspected acute poisoning cases for autopsy of both genders and all age groups were studied. Bodies with a chronic history of narcotic abuse, putrefied bodies or burned bodies and unidentified bodies without any hospital record were excluded. Retrospective data records were taken from the hospital and studied according to the variables required. Those variables were collected and analyzed through the latest version of SPSS 27.0. The statistical analysis of data was carried out using tables, graphs and percentages.

RESULTS

According to this study, out of 387 suicidal cases due to poisoning, a large number of the female population is involved, almost 67% and the most affected group is from the ages of 21 to 30 years, that is 41.6%. The second most happening age group is 31 to 40 years which is 28.16%. The majority of the cases are of people who were married which is 48.3%. But there are also a considerable number of divorced people who committed suicide, which is about 12.14%. The majority of the cases are from rural areas of Muzaffargarh, almost 61.5% which includes the highest number of people that belong to the combined family system which is 74.6%. Almost 33.3% are housewives and 24.03% are domestic workers of both genders. Labourers comprise 19.89% and 19.6% are unemployed. The illiteracy level reaches the highest degree by covering about 75.2% of the population in various areas of Muzaffargarh. Out of a total of 387 cases, only 20.15% of people have education under matric. 52.97% of people committed suicide at their homes. When inquired a little further, the majority of the reasons fall under 4 major categories that have almost equal prevalence; 31.26% and 30.74% go for financial and marital issues respectively, 22.4% and 15.5% for family and relationship issues respectively. In the majority of the cases, 61.7% of families didn't allow for autopsy of dead bodies to be done (Table 1).

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Table 1: Frequency and Percentage of Different Variables

Parameters	Subcategory of Parameters	Frequency (%)
Gender	Male	130 (33)
	Female	257 (67)
Age (Years)	10-20	67 (17.3)
	21-30	161 (41.6)
	31-40	109 (28.16)
	41-50	48 (12.4)
	51-60	2 (0.51)
Marital Status	Married	187 (48.3)
	Unmarried	153 (39.5)
	Divorced	47 (12.41)
Locality	Urban	149 (38.5)
	Rural	238 (61.5)
Family Setup	Single Unit	98 (25.32)
	Joint System	289 (74.6)
Occupation	Unemployed	76 (19.6)
	Housewife Domestic	129 (33.34)
	Worker Laborer	93 (24.03)
	Employed	77 (19.89)
Literacy Level	Under Matric	291 (75.2)
	Undergraduate	78 (20.15)
	Graduate	11 (2.84)
	Postgraduate	5 (1.3)
Location of Consumption of Poison	Home	205 (52.97)
	Workplace	149 (38.5)
	Others	33 (8.5)
Reason of Suicide	Family Issues	87 (22.4)
	Marital Problems	119 (30.74)
	Financial Issues	121 (31.26)
	Relationship Failures	60 (15.5)
Poison Used for Suicide	Organophosphorus Wheat Pill	77 (19.8)
	Kala Pathar	89 (22.9)
	Bleach/Detergent	149 (38.5)
	Rat Poison Insect	24 (6.2)
	Killing	29 (7.5)
	Powder/Spray	19 (4.9)
Autopsy Done	Yes	148 (38.2)
	No	239 (61.7)

The most prevalent poison found was Kala Pathar, almost 38.5%. Other common poisons are also widely used among citizens like rat poison, bleach and insecticides, having 7.5%, 6.2% and 4.9% respectively. The second most common was Wheat Pill with a percentage of 22.9. Organophosphorus was marked to be in third place securing almost 19.8% (Figure 1).

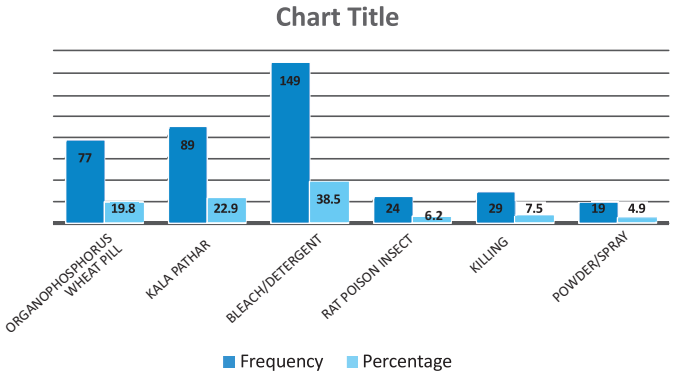

Figure 1: Poisons Used by the Suicide Victims

DISCUSSION

In this five-year study, a total of 387 suicide cases of self-poisoning are encountered. This is not a normal number, it's huge, and it's a huge proportion of the population of a single district that is harmed. All over Pakistan, such an issue is already under constructive work, for the benefit of the general population. Many significant studies demonstrate factual data of prime importance all over Pakistan, which supplement this particular study as a whole, like; in Bahawalpur, the most common poison is organophosphorus (20%) [7]. Another study from Sindh shows that organophosphorus is the main agent of choice for suicide and married people take the lead in that particular area [8]. According to a study conducted in Karachi, young female victims outnumbered males regarding suicide through self-poisoning [9]. Another research study concluded that wheat pills are widely used poisoning agents, especially in the agricultural lands of Pakistan [10]. Complementing the results of this research piece, another study implied that young females are mostly affected and the choice of agent was mostly kala pathar for the south Punjab areas [11]. Moving to another study, it demonstrate that suicidal deaths are rising day by day in Pakistan and the method of choice is self-poisoning for the majority of people [12, 13]. In compliance with one research study in Hyderabad reflected that kala pathar, organophosphorus and rat poison are the chief suicidal agents used by victims of suicidal deaths in cases of self-poisoning [14]. A similar study conducted in Sindh shows that uneducated and jobless people have a greater number of cases of suicide through self-poisoning. [15]. According to research conducted in Khyber Pakhtunkhwa, the suicide death scale is on the rise and one of the main reasons is domestic violence and marital abuse [16]. Suicide is a social dilemma, it has become a sensitive and imperative anthropological, psychological and public health issue, which needs to be tackled as soon as possible [17]. Middle and Lower-Income countries like Pakistan lack a proper systematized National Suicide Prevention Program and it has to be introduced in our society to benefit the local population [18]. In conformity with another study, pesticide self-poisoning has become the second most common suicidal method in underdeveloped countries like Pakistan

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[19]. Under the fact that Pakistan is the fifth most populated country globally and the second most populous country in Southeast East Asia, the most prevalent suicidal deaths are due to self-poisoning in married women, because they suffer psychological and emotional traumas in their married life [20, 21] data collected in Chitral, low socioeconomic background and burden of responsibilities for extended family setup on women leads to their death every month in last 5 years in Chitral [22]. Another common factor regarding suicidal deaths, the majority of the young women in extended family systems with high illiteracy rates, never discuss their intent to suicide, which leads to never never-ending vicious circle of mortality passed onto generations [23]. But melancholy is the fact that there are no official suicide reporting guidelines available, which leads to ignorance on the part of health care and the government [24]. The need of the hour is not only to visualize the problem but also to implement solutions in the form of generating suicide prevention strategies so that many precious lives can be saved [25].

CONCLUSIONS

It was concluded that suicidal deaths due to poisoning are expanding day by day in many prime areas of Pakistan and Muzaffargarh is one of them, which is highly neglected in terms of proper legislation, psychosocial education programs, suicide prevention strategies, literacy level, awareness programs for the general population and advanced treatment facilities. It is highly recommended to properly plan out the structural and systematized method of suicide prevention for the benefit of the long-neglected population of Muzaffargarh.

Authors Contribution

Conceptualization: SGS
Methodology: SGS, SHN
Formal analysis: HH, TM, RM
Writing review and editing: SGS, MAS

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

Conflicts of Interest

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Original Article

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Comparison of Bracket Failure with Resin Modified Glass Ionomer Cement and Resin-Based Adhesive

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ABSTRACT

A high strength of bonding materials is needed for orthodontic attachments to sustain therapeutic forces and patients' masticatory habits. **Objectives:** To compare the bond strength of the resin modified glass ionomer cement (RMGIC) and resign based adhesive system which leads to bracket failure in orthodontic treatment (failure to bracket attachment) for the duration of 6 months at the a tertiary care hospital at Hyderabad, Sindh Pakistan. **Methods:** This comparative cross-sectional study involved 30 patients, each with 20 brackets, using non-probability sampling. Participants were between the ages of 13 and 30 with fully erupted permanent teeth and mild skeletal discrepancies. Quadrants were randomized, and 120 attachments were placed in total, split evenly between the two types of materials. The study involved bonding orthodontic brackets using either composite resin or RMGIC. The teeth were prepared and cleansed, and the brackets were bonded following standard procedures. Patients were monitored each month for six months (six visits) to check for any debonded or missing brackets. Chi-Square test was run to compare bracket failure between two groups. **Results:** There were significant differences in bracket failure rates between the composite and RMGIC sides. Composite had a lower failure rate, with 90% of brackets remaining intact compared to 63.3% with RMGIC (p=0.04). Gender comparisons showed both male and female participants experienced more failures with RMGIC than with composite, with p-values of 0.039 and 0.038, respectively. **Conclusions:** RMGIC could not withstand the forces experienced during fixed appliance treatment as effectively as composite resin, resulting in a higher debonding rate.

INTRODUCTION

Orthoodntic brackets are used to achieve tooth movement for correction of malocclusion [1, 2]. Various materials are used for bonding brackets to the enamel surface, with composite being the most commonly used [3]. Although its bonding strength is acceptable for clinical practice, it does not have a fluoride-releasing effect. Orthodontic brackets, along with archwires, create a network that results in plaque retention and white spot lesions. Glass ionomer cement (GIC) was introduced for its fluoride-releasing properties, but it has low strength for orthodontic bonding purposes [4]. This GIC was modified by adding composite to form a hybrid material called resin-modified GIC (RMGIC) [5, 6]. Ideally, the material should provide a constant, low concentration of fluoride in the mouth for continuous protection, reducing reliance on patient compliance [7]. White spot lesions and enamel surface loss due to etching and adhesive removal have become more common after bracket debonding with composite. Glass ionomer cements (GIC) release fluoride, resulting in fewer white spot lesions and easier debonding due to their weak bond strength [8]. Fluoride is known for its anti-cariogenic effect. Resin-modified glass ionomer cements (RMGIC) combine the benefits of conventional GIC and resin properties, offering less moisture sensitivity and higher strength [9]. RMGIC can be a good alternative to composite for orthodontic bonding, as they do not require

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etching or conditioning [10-12]. One study showed that the failure rate with RMGIC and NaOCl as 15%, while with Trans bond XT was 4% [13].

The study aimed to evaluate the failure rate of orthodontic brackets bonded with resin-modified glass ionomer cement (RMGIC) using sodium hypochlorite (NaOCl) enamel conditioning in comparison to brackets bonded with conventional composite resin. The rationale is that while in-vitro comparisons between RMGIC and composite resin exist in the literature, only one study has examined their failure rates in vivo. RMGIC's fluoride release can prevent enamel demineralization and cariogenic activity, especially significant for orthodontic patients who are at risk of food stagnation. The study seeks to provide insight into the clinical performance of RMGIC in preventing demineralization and its impact on bracket failure rates, filling a gap in existing research specific to the study's population. To compare the bond strength of the resin modified glass ionomer cement t(RMGIC) and resign based adhesive system which leads to bracket failure in a orthodontic treatment (failure to bracket attachment) for the duration of 6 months at the a tertiary care hospital at Hyderabad, Sindh Pakistan.

METHODS

This comparative study was conducted in the Orthodontic Department at Liaquat University of Medical & Health Sciences Jamshoro/Hyderabad from November 2020 to October 2021 using a non-probability sampling technique. A total sample size of 120 attachments (with each of the 6 patients having 20 brackets) was calculated using the WHO calculator, based on a failure rate of 15% for RMGIC (P1) and 4% for composite resin (P2). The calculation maintained a 5% level of significance and 80% test power. However, to meet normality assumptions, the study included 30 patients [12]. Ethical approval was obtained from the Ethical Review Committee at LUMHSJamshoro/Hyderabad (LUMHS/ REC 914). Written informed consent was obtained from participants and their parents (for those under 16 years old). The inclusion criteria were both male and female subjects with fully erupted permanent teeth, enamel free from buccal enamel defects, restorations, veneers, or crowns, and normal to mild skeletal discrepancies. The eligible participants must be between the ages of 13 and 30. In contrast, the exclusion criteria disqualify individuals with systemic diseases, trauma, mild to severe skeletal issues, and mental disabilities. Participants with severe periodontal disease, facial and skull abnormalities, or para-functional behaviors are also excluded. Additionally, those requiring surgical correction or growth augmentation are not eligible for the study. Quadrants were randomized using lottery method in each patient and total 120 attachments were placed (60 bonded with each type of materials). Both cements were used to bond the orthodontic brackets to the teeth. Initially, the teeth were cleansed with abrasive slurry for 5 seconds and then etched with 37% phosphoric acid for thirty seconds. After rinsing and air drying the teeth until a frosty enamel surface was visible, the teeth were prepared for composite resin by curing the surface with a curing light. Stainless steel brackets were held with tweezers and a thin layer of composite resin was evenly applied to the mesh surface of the bracket base. The bracket was then placed on the tooth surface in an occluso-gingival, mesio-distal order with proper angulation. The brackets were compressed onto the enamel surface, excess adhesive was removed, and the surface was cured for 20 seconds using a blue spectrum dental curing light on both the distal and mesial sides of the brackets. For bonding RMGIC, the adhesive was hand-mixed. The tooth was etched, washed, and dried using a cotton roll, similar to the composite bonding procedure. A cotton roll was also used to moisten the tooth surfaces after they had dried. Moisture was essential for optimal binding strength. Since the setting period was short, the adhesive was prepared for two brackets at a time. The brackets bonded with RMGIC were allowed to set for 10 minutes. RMGIC brackets were bonded first, followed by composite bonding, to save time and ensure adequate strength. Bracket retention was measured by tallying the number of brackets that had come loose in each group. Patients were monitored for six months, with monthly follow-up visits every 30 days to check for any brackets that had deboned or were missing. The data were analyzed using the computer software "Statistical Package for Social Sciences Version 23.0. Qualitative variables such as gender, occupation, and ethnicity were summarized using frequency and percentage. The mean and standard deviation were computed for quantitative variables like age. Effect modifiers such as gender were controlled through stratification. After stratification, a Chi-Square test ($\chi 2$) was applied with a significance level of <0.05.

RESULTS

The mean age was 19.95 years, with a standard deviation of 4.11 years. The age ranged from a minimum of 13 years to a maximum of 30 years. The frequency of gender and age group in a sample of 30 participants is displayed. The gender distribution was 12 male (40.0%) and 18 female (60.0%). Regarding age groups, 15 participants (51.7%) were aged 13-18 years, 10 participants (33.3%) were aged 18-23 years, and 5 participants (13.7%) were aged 24-30 years (Table 1).

Table 1: Frequency of Gender and Age Group *n(%)

Variables	Characteristic	n= 30
Gender	Male	12 (40.00)
	Female	18 (60.00)
Age group (years)	13-18	15 (51.67)
	18-23	10 (33.33)
	24-30	5 (13.67)

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Table 2 presents the comparison of bracket failure rates for composite and RMGIC sides over a six-month period. Bracket failure was absent in 27 (90%) composite cases and 19 (63.3%) RMGIC cases, with a p-value of 0.04. Bracket failure was present in 3 (10%) composite cases and 11 (36.7%) RMGIC cases. The p-value of 0.04, calculated using Fisher's exact test, indicates a statistically significant difference in bracket failure rates between the two materials.

Table 2: Comparison of Bracket Failure of Composite and RMGIC Side during Six Months

Bracket Failure	Composite, n = 30	RMGIC, n = 30	p-value*
Absent	27 (90%)	19 (63.33%)	0.04
Present	3 (10%)	11 (36.7%)	

*n(%), *Fisher exact test

Table 3 shows the comparison of bracket failure rates for composite and RMGIC sides during a six-month period, categorized by gender. In male participants (n = 12), bracket failure was absent in 11 (91.7%) composite cases and 8 (66.7%) RMGIC cases, with a p-value of 0.039. Failure was present in 2 (9.4%) composite cases and 4 (33.4%) RMGIC cases. In female participants (n = 18), bracket failure was absent in 17 (94.4%) composite cases and 11 (61.1%) RMGIC cases, with a p-value of 0.038. Failure was present in 1 (5.6%) composite case and 7 (38.9%) RMGIC cases. Both male and female groups showed a significant difference in bracket failure rates between the composite and RMGIC sides.

Table 3: Comparison of Bracket Failure of Composite and RMGIC Side during Six Months by Genders

Gender	Bracket Failure	Composite	RMGIC	p-value*
Male (n=12)	Absent	11 (91.6%)	8 (66.66%)	0.039
	Present	2 (9.4%)	4 (33.44%)	
Female (n=18)	Absent	17 (94.44%)	11 (61.11%)	0.038
	Present	1 (5.55%)	7 (38.88%)	

*n(%), *Fisher exact test

DISCUSSION

Our results show a statistically significant difference in bracket failure rates between the composite and RMGIC sides over a six-month period. Bracket failure was more common with RMGIC than composite (p=0.04). When comparing bracket failure rates by gender, the failure rate was higher with RMGIC than with composite in male (p=0.039). Similar results were found in female (p=0.038). This indicates that composite is superior to GIC in both genders over a six-month period. The literature shows that conventional GIC is not suitable for regular orthodontic bonding due to its weak strength and durability. However, RMGIC has higher bonding strength due to the addition of resin, making it a more promising option in orthodontics [14]. Though RMGIC may still have lower bonding strength than resin composite systems, in vitro studies show that current RMGICs perform well for bonding brackets in orthodontics. Studies report that satisfactory adhesion and mechanical stability can be achieved with RMGIC in orthodontic treatments [15-17]. Justus *et al.*, explored whether treating human dental enamel surfaces with 5.25% sodium hypochlorite (NaOCl) before etching would improve orthodontic bracket shear bond strength (SBS) using either a composite resin or a resin-modified glass ionomer cement (RMGIC) [18]. Their in vitro study concluded that NaOCl use resulted in similar bracket bond strength between Fuji Ortho LC and Transbond XT, suggesting that fluoride-releasing RMGICs might be viable for bonding brackets to minimize white spot lesions. In contrast, the present study, which is conducted in vivo, found that conventional composite resin outperformed RMGIC in terms of success rate, particularly in the upper arch. Clinical bond strength values may be influenced by various forces acting on brackets, such as occlusal interferences and masticatory forces. It is important to recognize that the methodology in these studies compares two adhesive systems and may not apply universally to all patients. Therefore, the findings should be approached cautiously and tailored to each patient's individual needs and aesthetic preferences [19, 20].

CONCLUSIONS

Resin-modified glass ionomer cement cannot withstand the typical forces experienced during fixed appliance treatment and has a higher debonding rate compared to composite resin.

Authors Contribution

Conceptualization: AJ, MA
Methodology: SRS
Formal analysis: MSK, JT
Writing, review and editing: AHS

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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The Functional Outcome of Patients Treated with Proximal Femoral Nail (Pfn) for Sub Trochanteric Femur Fracture in Ayyub Teaching Hospital, Abbottabad

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ABSTRACT

Sub-trochanteric femur fractures are challenging for orthopedic surgeons to fix owing to their location and associated consequences. Different intramedullary and extra-medullary implant stabilization techniques have been explored with varying degrees of effectiveness. **Objective:** To assess the functional outcomes of proximal femoral nail in patients treated for sub-trochanteric femur fracture. **Methods:** This cross-sectional study investigated 28 patients of sub trochanteric femur fracture treated with proximal femoral nail in Orthopedic Unit of Ayub Teaching Hospital, Abbottabad from January 2021 to March 2024. Patients aged≥20 years who suffered from sub-trochanteric femur fracture and fit for surgery were included. All the patients were immobilized before surgery. Skin traction was applied and prepared for surgery. Postoperative outcome was assessed using the Harris hip score. **Results:** The overall mean age was 56 ± 10.8 years. Out of 28 cases, there were 18 (64.3%) male and 12 (35.7%) female. The overall mean of hospital duration was 14 ± 4.6 days. The majority of patients were 41-60 years old. Postoperative independence of ambulation was assessed in each patient after three, five, and six months. After 5 months, only two patients were unable to move around unassisted. Based on the Harris Hip Score, the incidence of exceptional, good, and fair outcomes was 6 (21.4%), 5 (17.9%), and 17 (60.7%) respectively. **Conclusions:** It was concluded that sub-trochanteric femur fractures can be treated with a proximal femoral implant, which offers advantages in terms of increased stability, quick disposition and minimal exposure.

INTRODUCTION

Sub-trochanteric (ST) fractures manifest in a region extending 5 cm distally to the lesser trochanter region just at the junction of the diaphysis of the shaft. These fractures account for 10-30% of all hip fractures [1, 2]. The closed proximal femoral fractures need firm fixation because it is difficult to treat due to strong deforming forces at the fracture site, tenuous blood supply and immense load-bearing forces exerted through the per-trochanteric region. Hip fractures rank in the top ten injuries worldwide for individuals 50 years of age and older, resulting in significant disability [3]. The effects of hip fracture are profound, with mortality and negative effects on patient function and quality of life [4]. Sub-trochanteric fractures represent approximately 10-30% of all hip fractures. They occur more frequently in older individuals experiencing low-speed impacts and in younger individuals exposed to high-speed impacts. Implant systems have been developed to reduce the incidence of complications during its function [7].The lesser trochanter of the femur has particularly strong cortical bone, making it less susceptible to fracture compared with other areas and occurring more frequently at a younger age. Approximately 5-10% occur in the sub trochanteric (ST) [9]. Sub-trochanteric femur fractures are more common in females, with a reported prevalence of 33% compared with men [10, 11]. Older age and sex are recognized as important risk

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factors, in addition to low total bone mineral density, diabetes mellitus, and the use of bisphosphonates for the management of osteoporosis [12]. Non-surgical methods of managing these fractures were previously associated with a higher risk of stroke, shortening, and even death due to delayed fixation. Unlike other proximal femoral fractures, sub-trochanteric fractures present additional clinical challenges. Recently, effective treatments for sub-trochanteric fractures have begun, with advances in fracture biology, reduction techniques, and biomechanically refined implants.

This study aims to assess the functional outcomes of proximal femoral nail (PFN) in patients treated for sub-trochanteric femur fracture.

METHODS

This cross-sectional study investigated 28 patients of sub-trochanteric femur fracture treated with proximal femoral nail (PFN) in the Orthopedic Unit of Ayub Teaching Hospital, Abbottabad from Feb 2022 to March 2024 after getting ethical committee approval (RC-EA-2024/090). Non-probability consecutive technique was used. A total number of 28 patients (n=28) sample size was calculated using WHO software for sample determination in health studies having a confidence level of 95%, an anticipated population of 82.2%, and an absolute precision required was 8%. After getting informed written consent detailed demographics of enrolled cases were recorded [13]. Patients aged≥20 years who suffered from sub-trochanteric femur fracture and fit for surgery and provided written consent were included. Open fractures along with pathological sub trochanteric (ST) femur fractures were excluded. All procedures were performed under spinal or epidural anesthesia. Every single patient who had a sub-trochanteric femur fracture was scheduled for an elective procedure. A typical lateral skin incision just above the tip of the greater trochanter was used throughout the surgical operation, which was performed and the patient was supine on a regular traction table. A guide wire was inserted using a drill sleeve through the tip of the greater trochanter until it reached the subtler-trochanteric area crossing the fracture site while the ante version of the femoral head and neck was maintained. Proximal reaming was done and then distally from the fracture site. The proximal femoral nail was passed. Drilling on the lateral trochanteric region was done for the lag screw crossing the lateral cortex to the neck and head and tapped and a spiral screw of the correct size was placed over the wire. The distal locking screw was passed. Assembly was removed, the wound was closed and the dressing was applied. Patients received intravenous antibiotics and analgesics and were monitored for two days after surgery in the postoperative ward. Patients were put on crutches and photographed thereafter. Patients were given intravenous antibiotics, analgesics, and calcium supplements on the second day following surgery. Over the first six weeks, they were permitted to touch down and mobilize with a walker on the operated leg, and then they were allowed to fully bear weight. At two weeks, four weeks, monthly, and then every three months for two years after surgery, all patients were evaluated. Patients were examined, x-rays were taken, and fracture assessments were performed at each subsequent appointment. High-risk individuals received subcutaneous low-molecular-weight heparin during their hospital stay. Length of stay, blood transfusion requirements, and any in-hospital complications were carefully recorded. At the end of the follow-up assessment of functional outcomes using the Harris Hip Score (HHS) was done. Post-operative complications were assessed. The HHS is to measure the functional deficit of the hip so the higher the score, the better the outcome for the patient. Results can be recorded and calculated online. The maximum possible score is 100. Open reduction and internal fixation were implemented. Harris Hip Score (HHS), Improvement Level Score, Excellent 90-100, Good 80-90, Fair 70-80, and Poor<70. The statistical analysis of data was carried out using SPSS version 26.0. The quantitative variables were assessed using the mean and standard deviation, while the qualitative variables were measured using frequencies and percentages. To compare the qualitative and quantitative variables, the chi-square test and the student t-test were employed, respectively. A statistical significance level of $p<0.05$ was maintained.

RESULTS

The overall mean age was 56 ± 10.8 years. Out of 28 cases, there were 18 (64.3%) male and 12 (35.7%) female. The overall mean of hospital duration was 14 ± 4.6 days. The age group of patients were as follows; 8 (28.6%) in 20-40 years, 18 (64.3%) in 41-60 years, and 2 (7.1%) in >60 years (Table 1).

Table 1: Baseline Characteristics of Patients (n=28)

Parameters	Value
Age (Years)	56 ± 10.8
Gender n (%)	
Male	18 (64.3%)
Female	12 (35.7%)
Length of Hospitalization (Days)	14 ± 4.6
Age Groups (Years)	
20-40	8 (28.6%)
41-60	18 (64.3%)
>60	2 (7.1%)

Type of sub-trochanteric femur fracture, mechanism of injury, and average duration of surgery (Table 2).

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Table 2: Preoperative Assessment of Patients (n=28)

Parameters	n (%)
Type of Sub-Trochanteric Femur Fracture	
Type-I	56 ± 10.8
Type-II	
Mechanism of Injury	
Road Traffic Accident	18 (64.3%)
Fall from Height	12 (35.7%)
Average Duration of Surgery (Hours)	
<1	8 (28.6%)
1-1.3	15 (53.6%)
1.3-2	5 (17.9%)

Post-operative complications are illustrated (Figure 1).

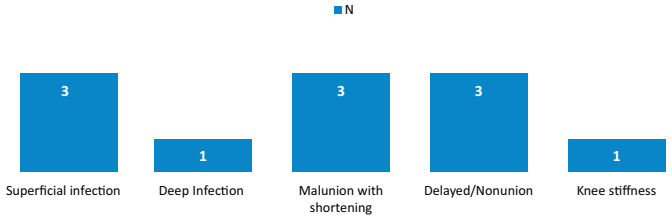

Figure 1: Post-Operative Complications (n=11)

Postoperative independence of ambulation was assessed in each patient after three and five months. After 5 months, only two patients were unable to move around unassisted. Based on the Harris Hip Score, the incidence of exceptional, good, and fair outcomes was 6 (21.4%), 5 (17.9%), and 17 (60.7%) respectively (Figure 2).

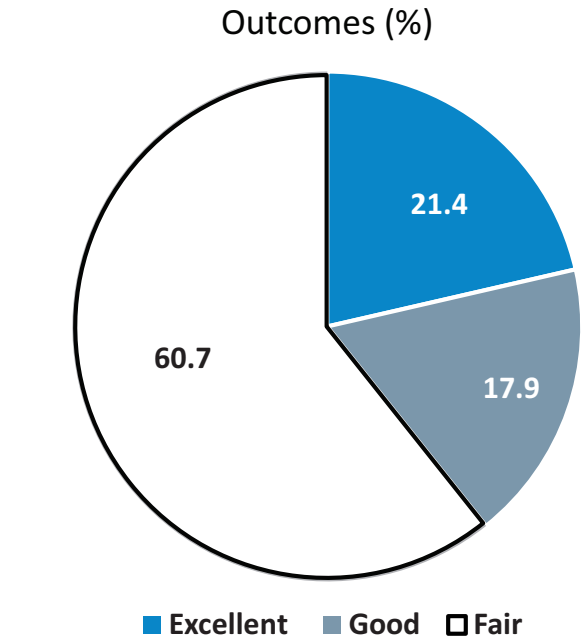

Figure 2: Harris Hip Score-Based Outcomes (n=20)

DISCUSSION

The present study mainly focused on the assessment of the functional outcome of patients treated for sub-trochanteric femur fracture with proximal femoral nail (PFN) and reported that Sub-trochanteric femur fractures can be treated with a proximal femoral implant, which offers advantages in terms of increased stability, quick disposition and minimal exposure. Because of its ability to produce early and sustained movements, PFN may be ideal for the prevention of ST fractures in older individuals. Studies have found the effectiveness of PFN in preventing ST fractures. In addition, based on the Harris hip score, all treated participants fell into excellent, good, and fair groups, which is consistent with the results of the previous study [11, 12]. Closed procedures focus on anatomic realignment, correction of length and rotation abnormalities to achieve optimal results [13]. Sub-trochanteric fractures generally result from high-energy trauma and are difficult to manage with traction. Radical approaches have been neglected due to treatment delays, contradictions, and frequent treatment failures [14]. Consequently, conservative treatments, as proposed by Gokul *et al.*, are considered obsolete in contemporary trauma care. Dynamic compression hip screws have emerged as the preferred method of fixation in sub-trochanteric femur fractures. Compressing the femoral neck improves stability in reduced fracture, allowing the bone and implant to distribute stress more effectively [15]. Sub-trochanteric fractures of the femur pose significant complications and are considered serious injuries by orthopedic surgeons. The primary goal in treating these fractures is to obtain a stable surgical fixation, for treatment has been facilitated, allowing earlier mobilization, and returning the patient to his or her pre-fracture functional status as quickly as possible. In the present study, the majority of patients were male, and road traffic accidents (RTAs) were the main cause of fractures. This observation can be attributed to factors such as increasing urbanization, increasing traffic, non-compliance with traffic rules, reckless driving, and preference for outdoor activities increases in men. Ibrahim *et al.*, reported that RTA accounted for the majority (86%) of proximal femur fractures in their series [16]. Similarly, Kachewar et al., reported that 77% of the patients were between 20 and 60 years of age, which resemble our study findings [17]. Sub-trochanteric fractures of the femur usually result from high-energy trauma. This is due to the complex stress distribution in this area and the geometry of its irregular skeletal structure. Consequently, a fracture is evident in a relatively simple approach through the proximal femur. The majority of sub-trochanteric fractures occurred in younger individuals because of road accidents; whereas low-energy trauma such as falls from standing heights or stairs is the cause of bone loss, interstitial fractures occur mainly in the elderly [18]. PFN represents a superior implant technique for the management of femoral sub-trochanteric (ST) fractures because, unlike DHS, it is a weight-shearing implant. However, it will be important to conduct comparative studies with other implants to confirm our findings [19]. Several cases describe clear

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recurrence of irreversible tumors supporting our findings. The findings in Pakistan are consistent with the results of our present study. In addition, this study showed that the Harris Hip Score favors a closed approach over an open approach to sub-trochanteric fracture repair. Notably, there was no statistically significant difference between the groups in fracture union rate and complication rate [20].

CONCLUSIONS

It was concluded that sub-trochanteric femur fractures can be treated with a proximal femoral implant, which offers advantages in terms of increased stability, quick disposition and minimal exposure. It has the ability to produce early and sustained movements, so PFN may be ideal for the prevention of ST fractures in older individuals.

Authors Contribution

Conceptualization: MY
Methodology: MY, SUS
Formal analysis: AR, AGSK, SA, RK
Writing review and editing: SUS, MSZ

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Correlation of Serum Lactate and Shock Index as Mortality Predictor in Polytrauma Patients

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ABSTRACT

In polytrauma patients, serum lactate and hypovolemic shock are critical biomarkers for prognosis and treatment guidance. Elevated lactate levels indicate tissue hypoperfusion and anaerobic metabolism, often correlating with increased mortality. **Objective:** To analyze the correlation between serum lactate levels and shock index as predictors of in-hospital mortality in polytrauma patients. **Methods:** A Cohort study was conducted from August 2022 to July 2023 at a single tertiary care hospital in Karachi. Patients were chosen via consecutive sampling techniques and included adult patients with polytrauma injuries (ISS ≥ 15) who survived at least 24 hours. Patients with a history of diabetes were excluded. The serum lactate levels and shock index at the time of admission and over the first 24 hours were the exposures while in-hospital mortality, was the primary outcome. Statistical analyses were conducted using Stata 16.0. Categorical variables were analyzed using the chi-square test. Multivariable logistic regression evaluated mortality risk, adjusting for age, ISS, and shock index. **Results:** The in-hospital mortality rate in the study was 6.4% with significant predictors of mortality included increasing age (47.05 vs. 27.62 years, p<0.001), higher Injury Severity Scores (ISS) (24 vs. 19, p= 0.02), and elevated shock index at admission (0.84 vs. 0.71, p<0.001). Lactate metrics were strongly associated with mortality, showing significant correlations. **Conclusions:** Higher serum lactate levels and shock index are strong predictors of mortality in polytrauma patients. Greater age and injury severity also contribute to poorer outcomes.

INTRODUCTION

Trauma is a leading global health issue, responsible for approximately 5 million deaths annually and a significant cause of disability-adjusted life years, particularly in low- and middle-income countries such as Colombia [1-3]. Young, economically active men are disproportionately affected, which highlights the socioeconomic burden of trauma [3]. The metabolic response to trauma often results in hypoxia and anaerobic metabolism, with lactate production as a key consequence. Lactate, produced from pyruvate via lactate dehydrogenase, is elevated in patients experiencing shock and serves as a critical marker of oxygen supply-demand imbalance [4, 5]. Elevated serum lactate levels are well-established predictors of mortality in trauma patients and have been shown to correlate with injury severity and the need for resuscitative interventions such as blood product administration [6, 7]. When considered alongside vital signs like blood pressure, lactate levels provide valuable prognostic information about injury severity and patient outcomes [7-9]. Research has shown that patients with lactate levels exceeding 4 mmol/L face significantly higher mortality risks, emphasizing the importance of early lactate measurement in trauma settings [7-11]. Additionally, lactate clearance is a useful parameter for evaluating the effectiveness of resuscitation efforts and predicting early mortality in trauma patients [8]. Similarly, the shock index

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(SI)—calculated as the ratio of heart rate to systolic blood pressure serves as an important predictor of trauma-related mortality. The SI is a rapid, non-invasive tool that aids in assessing trauma severity and detecting early hemorrhagic shock, providing critical guidance in prehospital and emergency care settings [12, 13]. Despite early recognition and treatment efforts, morbidity and mortality associated with shock remain high, often due to delayed diagnosis and treatment. Rapid identification of mortality predictors like serum lactate and SI can facilitate early intervention, improving patient outcomes and reducing irreversible damage caused by hypoperfusion [14-16]. However, the comparative effectiveness of these predictors remains unclear, highlighting a gap in the current literature.

This study aimed to fill this gap by analyzing the correlation between serum arterial lactate levels at admission, 12-hour lactate clearance, and polytrauma mortality, in conjunction with the shock index.

METHODS

A cohort study was conducted at one Tertiary Care Hospital from August 2022 to July 2023. Approval for the project was obtained from the institutional review board (IRB)(F.2-81/2022-GENL/205/JPMC). Informed written consent was taken from each participant/guardian. The study included 500 adult patients, chosen via consecutive sampling, aged 18 to 85 years who had sustained a blunt injury, had an injury severity score (ISS) of 15 or higher, were hospitalized, and survived for at least 24 hours. Sample size were computed via open-epi sample size calculator with 4% margin of error and 95% confidence interval with expected frequency of poly trauma as 29.57% having hypovolemic shock [17]. Baseline characteristics, including patient demographics (age, ethnicity, gender, smoking status, presence of hypertension), trauma mechanism, and vital signs, were recorded. The shock index was computed by dividing the patient's heart rate by systolic blood pressure (mmHg)[14]. Serum lactate (mmol/L) levels were measured using blood gas analysis (BGA) from arterial blood samples collected upon at admission and 24 hours post-admission.

The following lactate metrics were calculated:

- Lac_{adm}: First lactate at admission
- $Lac_{24hMean}$: Mean lactate over the first 24 hours
- Lac_{24hTW}: Time-weighted lactate over 24 hours

Time-weighted measurements reduce surveillance bias by accounting for irregular sampling intervals. The steps included measuring the time between data points, averaging the values, multiplying the average by the time interval, summing these products, and dividing by the total elapsed time. The main endpoint was death during the hospital stay. Patients who were released within 24 hours were not included in the analysis. Descriptive statistics characterized the study population, presenting categorical variables as frequencies and percentages, which were analyzed using the χ^2 test. Continuous variables were examined for normal distribution. Symmetric data were analyzed using the Student's t-test and reported as mean with standard deviation (SD). Whereas, the non-symmetric data were assessed using the Kruskal-Wallis test and presented as median with interquartile range (IQR). Univariate analysis tested the association between patient demographics, injury severity, glucose, lactate metrics, and mortality. Spearman correlation assessed relationships between glucose and lactate metrics. Chi-square goodness of fit was used for model fitting. Multivariable logistic regression models evaluated the association between these metrics and adjusted mortality risk, considering confounders like age, ISS, and admission shock index. Lactate metrics were scaled and tested in separate models with confounders. All statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX). P value <0.05 was considered as statistically significant while P value < 0.001 was regarded as highly statistically significant.

RESULTS

The cohort consisted of 500 patients. The study population was predominantly male (367, 73.40%) with a median age of 34 years (IQR: 18-60). The largest ethnic group belonged to the Muhajir community (219, 43.80%) and 34 patients (6.4%) died in the course of treatment. In-hospital mortality was observed at an average of 8.23 days (SD: 7.62)

Table 1: Overview of the Study Population

Parameters (n=500)	Values n (%) / Mean ± SD
Age (Years)(IQR)	34 (18-60)
Male (Sex)	367 (73.40)
Muhajir Ethnicity	219 (43.80)
ISS (IQR)	20 (16-30)
Smoking	291 (58-20)
Hypertension	211 (42.20)
BMI, kg/m^2 (IQR)	23.9 (18.2-31.1)
SBP, mmHg	104.25 ± 25.81
HR, bpm	129.48 ± 28.13

Mortality was associated with increasing age (47.05, SD: 18.18 vs 27.62, SD: 13.03, p<0.001), increasing severity score of the injury (24, IQR 20-30 vs 19, IQR 16-24, p=0.02), and admission shock index (0.71, SD: 0.24 vs 0.84, SD 0.39) among other parameters (Table 2).

Table 2: Analysis of the Study Population by Mortality Status: Deceased vs. Survived

Variable n (%) / Mean ± SD	Alive (n=466)	Dead (n=34)	p-Value
Age (Years)	27.62 ± 13.03	47.05 ± 18.18	<0.001
ISS (IQR)	19 (16-24)	24 (20-30)	0.02
Muhajir Ethnicity	204 (43.77)	15 (44.11)	0.12
Male (Sex)	332 (71.24)	5 (14.70)	<0.001

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Admission SI	0.71 ± 0.24	0.84 ± 0.39	<0.001
Smoking	269 (57.72)	22 (64.70)	<0.001
Hypertension	188 (40.34)	23 (67.64)	<0.001
Lac_{adm}, mmol/L	3.25 ± 1.22	5.65 ± 2.21	<0.001
$Lac_{24h-mean}$, mmol/L	2.67 ± 1.18	4.15 ± 2.03	<0.001
Lac_{24hTW}, mmol/L	2.59 ± 1. 06	4.02 ± 1.89	<0.001

Multivariate logistic regression analysis was used for the analysis of multiple independent variables on mortality

DISCUSSION

This study highlights the importance of early serum lactate measurement in trauma patients, demonstrating its strong association with increased mortality. Elevated lactate levels are a critical biomarker for assessing trauma severity and guiding resuscitation. While Shock Index is also related to mortality, its significance diminishes after adjusting for lactate levels, highlighting lactate as a more reliable indicator of trauma severity. Tracking lactate over time offers valuable insights into the effectiveness of resuscitation and patient prognosis. Evidence from prior studies indicates that elevated lactate levels are linked to greater injury severity, increased rates of multiple organ failure (MOF) [18], and higher mortality rates [19]. Our findings are consistent with this literature, reinforcing the role of lactate as a key prognostic tool in trauma care. Furthermore, trauma is a leading cause of mortality and disability globally, particularly in individuals under 50 years old. Lactate, which reflects anaerobic metabolism and tissue hypoperfusion, emerges as a critical marker even in vitally stable trauma patients [20], aiding in early risk stratification and resuscitation guidance. Clinically, these findings suggest that lactate should be routinely measured and monitored in trauma settings, as its levels can guide interventions aimed at improving tissue perfusion and oxygenation. The dynamic monitoring of lactate over time, rather than relying on a single measurement, provides more comprehensive insights into resuscitation progress and patient outcomes. Our data indicate that mean 24-hour lactate may be a better predictor of mortality than the admission lactate level alone, underscoring the importance of ongoing lactate tracking in clinical decision-making. In addition to lactate, there is evidence that trauma patients with elevated glucose levels also tend to have higher morbidity and mortality [21]. This association between hyperglycemia and worse outcomes mirrors that of lactate, further emphasizing the need to monitor metabolic derangements in trauma patients. The strengths of this study include its prospective longitudinal design, which allows for real-time data collection, a relatively large sample size, and the use of time-weighted measurements to minimize bias. However, several limitations should be considered. The single-center design restricts the generalizability of the findings to broader populations of critically ill patients. Furthermore, the exclusion of diabetic patients limits the application of the results to nondiabetic trauma populations. We also focused on the first 24 hours of admission, potentially missing delayed complications. Additionally, we could not assess the impact of resuscitation techniques, such as intravenous fluids or blood products, on patient outcomes.

CONCLUSIONS

Higher serum lactate levels and shock index are strong predictors of mortality in polytrauma patients. Greater age and injury severity also contribute to poorer outcomes. Obtaining early serum lactate levels in trauma patients offers a valuable tool for early risk stratification, guiding prehospital care, and improving clinical outcomes. As more evidence emerges, integrating this biomarker into standard prehospital protocols could revolutionize trauma care, providing vital information to make informed decisions and enhance patient survival rates.

Authors Contribution

Conceptualization: NUSS
Methodology: NUSS, MA, SS[1], SS[2], SZM, MMK
Formal analysis: MA, SS[1], SS[2], SZM, MMK
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Original Article

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Evaluation of Iron Deficiency Anemia in Pregnancy

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ABSTRACT

Anemia in pregnancy was the common nutritional deficiency and a frequent medical concern that leads to numerous known complications, impacting both maternal and fetal health. **Objective:** To evaluate the biochemical parameters such as serum Iron, Ferritin TIBS and TfS in anemic and non-anemic pregnant women. **Methods:** In this cross-sectional study, pregnant women age 18-45 years attending the gynecological department of Niazi welfare foundation teaching hospital, Sargodha from April 2023 to January 2024 were included. Serum iron, ferritin, total iron-binding capacity, and transferrin saturation were assessed from blood samples. Independent sample t-test in SPSS version 26.0 was applied to see significant difference in biochemical parameters at value of <0.05. **Results:** Findings revealed mean hemoglobin level of 10.26 ± 1.52 g/dl in all participants. Anemic results were found in majority, accounting for 268 (70.9%) cases. Among these anemic patients, 149 (55.5%) had mild anemia, 107 (40%) had moderate anemia, and 12 (4.5%) had severe anemia. Anemic patients had significantly lower serum ferritin level ($p = 0.02$), serum iron ($p < 0.001$), and transferrin saturation ($p < 0.002$) than non-anemic patients. Additionally, total iron-binding capacity, ($p < 0.001$) indicated the anemic status of the pregnant women. **Conclusions:** Biochemical parameters of pregnant women with anemia were reduced compared to those without anemia. Healthcare providers should closely monitor pregnant women with reduced biochemical levels to prevent complications for both the mother and the fetus.

INTRODUCTION

It is a frequent medical concern during pregnancy, as the need for iron increases from 2.5 mg/day in the first few weeks to 6.6 mg/day in the later trimesters [1]. Typically, 30-50% of pregnant women are iron deficient during pregnancy. Anemia is a significant public health issue with prevalence rate reported to be 56% during pregnancy in underdeveloped countries [2]. Iron deficiency anemia is frequently used interchangeably with the term anemia during pregnancy [3]. The definition of pregnancy anemia according to World Health Organization (WHO) criteria comprises Hemoglobin (Hb) concentration of less than11 g/dl [4]. During pregnancy, various changes occur, particularly in hematological serum levels, which require monitoring and intervention. Many of these changes result in plasma expansion and hemodilution throughout the pregnancy [5]. Various biochemical markers are utilized to evaluate iron levels for diagnosing anemia during pregnancy. These parameters include serum iron, ferritin, transferrin, total iron-binding capacity (TIBC) and transferrin saturation [6] It is clear that measuring hemoglobin, iron, ferritin, and TIBC provides valuable criteria for assessing iron deficiency during pregnancy [7]. Total iron-binding capacity (TIBC) gradually increases throughout pregnancy [8]. Low blood iron levels and elevated TIBC in pregnant women are attributed to dietary iron deficiency [9]. Consequently, iron supplementation

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during pregnancy is beneficial for maintaining serum iron and TIBC levels closer to those of non-pregnant women [10]. There is a strong correlation between the decrease in serum iron and the increase in iron-binding capacity [11]. Moreover, various biochemical changes related to anemia (i.e. Hb, RBC, WBC) in pregnant women have been documented in the literature. Anemia during pregnancy is associated with several known complications for mother and fetus, such as preterm delivery, intrauterine growth restriction, and infant death [12]. During pregnancy, maternal iron stores are diminished to support the fetus in producing fetal hemoglobin [13]. Throughout pregnancy, various assays are performed at regular intervals to monitor all parameters and ensure the well-being of both the mother and the fetus. Although anemia is a treatable pregnancy complaint, but lack of ample knowledge regarding biochemical differences in pregnancy hinder the cure. Iron, ferritin, TIBC, and TfS are crucial indicators for assessing anemia, particularly iron deficiency anemia in pregnancy. Ferritin reflects the body's iron reserves, and low levels result in reduced Hemoglobin (Hb) production, leading to anemia. Serum iron levels represent the circulating iron necessary for Hb synthesis, and when these levels are low, anemia develops. TIBC indicates the capacity of the blood to bind iron, with elevated levels suggesting a deficiency of circulating iron as the body attempts to transport more iron for Hb synthesis. TfS measures the percentage of transferrin saturated with iron, and low TfS levels indicate decreased iron availability, confirming iron deficiency anemia. These parameters are vital for diagnosing anemia in pregnancy to ensure effective and timely management. Therefore this study is undertaken to see the correlation of biochemical parameters like serum ferritin level, Iron level, TIBS and transferrin saturation with maternal anemia during pregnancy for timely diagnosis and management to avoid unwanted consequences. Anemia is a preventable disorder and linked to various biochemical factors. In countries like Pakistan, it is a common pregnancy complaint linked to iron deficiency.

This study aimed to identify the biochemical parameters in anemic pregnant women in their first trimester to intervene effectively. Early detection is a key to successfully manage and follow treatment protocols along with best clinical practices. Dietary counseling and supplementation will aid further to reduce feto-maternal complications resulting from these biochemical factors.

METHODS

A cross-sectional study was performed at Niazi welfare foundation teaching hospital, Sargodha from April 2023 to January 2024, following approval from the Institutional Review Board (NM and DC-IRB-65) on 1st April 2023 with Ref#: IRB/NMDC/187. Sample size was calculated on Open Epi software, considering 95% confidence limits, 5% margin of error, and a reported anemia prevalence of 56% among pregnant women [2]. The calculated sample size was 378. Pregnant women aged 18-45 years visiting first time the gynecological department of NWFTH were included in this study after obtaining informed consent. Excluded cases were women requiring urgent care or having risk of gestational diabetes, preeclampsia, eclampsia and/ or HIV. The study population was categorized into four groups based on WHO criteria: non-anemic (Hb >11 g/dl), mildly anemic (Hb between 10–10.9 g/dl), moderately anemic (Hb between 7–9.9 g/dl), and severely anemic (Hb <7 g/dl) [4]. In data collection phase, demographic variable of pregnant women like age, Hb levels were noted. Under aseptic measures, 5 ml blood samples from all pregnant women were collected and stored in vials (ATLASLABOVAC Italiano) with EDTA (AK3EDTA) as an anticoagulant. Serum iron levels and TIBC were measured using the ferrozine calorimetric method. Serum ferritin levels were measured using electro-chemiluminescence immunoassay on Cobas c311 analyzer (Roche, Germany). Mean and SD was calculated for values of serum Hb, serum ferritin, serum iron, TIBC, and TfS. Frequencies and percentages were determined for variables such as the types and severity of anemia. Independent sample t-test in SPSS version 26.0 was applied to see significant difference in biochemical parameters at value of <0.05. Pearson correlation coefficient was applied to reveal relationship of association between pregnancy anemia and biochemical parameter at significance value of $p<0.05$.

RESULTS

Among the 378 patients, the average age was 27.20 ± 2.54 years. Mean hemoglobin level was 10.26 ± 1.52 g/dl. Of these patients, 268 (70.9%) were anemic and 110 (29.1%) were non-anemic. Within the anemic group, 149 patients (55.5%) had mild anemia, 107 patients (40%) had moderate anemia, and 12 patients (4.5%) had severe anemia depicted in table 1.

Table 1: Demographic Characteristics of Participants

Variables	Mean ± SD / N (%)
Mean Age (Years)	27.20 ± 2.54
Mean Hb Level (g/dL)	10.26 ± 1.52
Anemia Status	
Anemic Patients	268 (70.9%)
Non-Anemic Patients	110 (29.1%)
Anemia Severity	
Mild Anemia	149 (55.5%)
Moderate Anemia	107 (40%)
Severe Anemia	12 (4.5%)

The biochemical analysis in table 2 showed a mean serum ferritin level of 33.24 ± 24.82 ng/ml, serum iron level of 99.01 ± 29.27 µg/dl, TIBC of 587.6 ± 73.93 µg/dl, and TfS of 18.96 ±

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6.8 in pregnant anemic women. Anemic patients had significantly lower serum ferritin level ($p = 0.02$), serum iron ($p < 0.001$), and transferrin saturation ($p < 0.002$) than non-anemic patients. TIBC (p-value <0.001) was indicative of anemia in pregnant women.

Table 2: Mean differences of Biochemical Parameters in Anemic and Non-Anemic Patients

Variables	Anemic Pregnant Women Mean ± SD	Non-Anemic Pregnant Women Mean ± SD	p-Value
Hemoglobin (g/dL)	9.04 ± 0.63	11.84 ± 0.59	<0.001
Serum Ferritin (ng/mL)	33.24 ± 24.82	42.43 ± 26.20	0.02
Serum Iron (µg/dL)	99.01 ± 29.27	156.06 ± 20.24	<0.001
TIBC (µg/dL)	587.6 ± 73.93	405.2 ± 26.48	<0.001
TfS (%)	18.96 ± 6.84	21.32 ± 6.44	<0.002

The Pearson correlation results demonstrated a negative relationship between anemia and biochemical markers such as serum ferritin, iron, and transferrin saturation (TfS) percentage. These negative associations indicate that lower values of these parameters were observed in cases of anemia during pregnancy. A p-value of <0.05 confirmed the significance of these associations given in table 3. Additionally, a positive correlation was found between anemia and total iron-binding capacity (TIBC), with the statistically significant result.

Table 3: Association between Pregnancy Anemia and Biochemical Parameters

Biochemical Parameters	Pearson Correlation Coefficient	p-Value
Serum Ferritin (ng/mL)	-0.465	<0.001
Serum Iron (µg/dL)	-0.523	<0.001
TIBC (µg/dL)	0.475	<0.001
TfS (%)	-0.380	<0.003

DISCUSSION

This study found that ratio of pregnant women with anemia was high. A more detailed analysis revealed mild and moderate anemia was mostly common among the pregnant women; overall anemia was evident in 70.9% cases. This is consistent with recent research from Lahore, Pakistan, which also reported a high anemia prevalence of 57.7% among pregnant women. Similar to this findings, their study found that mild anemia was the most common, followed by moderate anemia, with severe anemia being the least prevalent [14]. This study observed significantly lower hemoglobin levels in pregnant anemic women compared to non-anemic. These results align with existing literature. Studies, including those conducted on pregnancy anemia, such as those by Ray JG *et al.*, Okoroiwu IL *et al.*, and Agarwal AM *et al.*, similarly report reduced hemoglobin levels [15-17]. This study found that pregnant women with anemia had significantly lower levels of biochemical parameters (serum iron, ferritin levels and transferrin saturation) compared to non-anemic women. Also, the results of Pearson correlation coefficient revealed statistically significant association between biochemical parameters and anemic pregnant women. Lower serum iron, ferritin levels and transferrin saturation in anemic pregnant women were evident in other studies reveling the significant impact of these parameters with anemia [16, 17]. In anemic pregnant women, the observed low levels of serum iron, ferritin, and transferrin saturation align with outcomes from current studies of Aloy-Amadi O *et al.*, and Anwar Z *et al.*, Lower serum iron levels, ferritin levels, and transferrin in blood tests suggest iron deficiency anemia [18, 19]. This study's higher incidence of low iron among pregnant anemic women supports the presence of iron deficiency anemia. This was further reinforced by this finding of higher mean TIBC levels in pregnant anemic women than non-anemic, as elevated TIBC also indicates iron deficiency. These findings correlate with other studies revealing elevated TIBC and low iron levels [20]. The notably lower levels of serum iron, ferritin, and transferrin saturation observed among anemic pregnant women in this study were consistent with the findings of Raza N *et al.*, indicating iron deficiency anemia [21]. Reduced concentrations of iron, ferritin, and transferrin saturation strongly suggest iron deficiency anemia. Additionally, it observed a significantly elevated TIBC in the anemic group, which aligns with Bleyere MN *et al.*, study in pregnant women [22]. The elevated TIBC can be attributed to reduced iron levels and transferrin saturation, common features of iron deficiency anemia. Anemia was a linked to various biochemical factors. In countries like Pakistan, it was a common pregnancy complaint linked to iron deficiency. Anemic status of pregnant women should be assessed early to monitor these parameters in routine clinical practice, So that it can prevent devastating consequences. The findings of the current study should be considered in light of several limitations, including the lack of reported biochemical profiles for each trimester of pregnancy. There is a need to conduct a comprehensive research on pregnancy anemia in relation to each trimester.

CONCLUSIONS

Maternal health, along with its associated morbidity and mortality, was a significant concern in Pakistan. Anemia in pregnancy was linked to low levels of biochemical parameters. It was advisable for healthcare providers to closely monitor pregnant women with low biochemical levels to prevent complications for both the mother and the fetus.

Authors Contribution

Conceptualization: SA[1]
Methodology: SA[1], MA
Formal analysis: SA[2]
Writing, review and editing: SR, MFJ, RM, MA

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Original Article

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Prevalence of Early Seizures in Acute Stroke Patients

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ABSTRACT

A stroke is defined as a sudden neurological deficit of cerebrovascular cause that persists beyond 24 hours. Stroke is associated with a whole spectrum of complications, especially post-stroke seizures. These seizures may adversely affect the outcome of stroke in terms of mortality and morbidity. This study was designed to find out the frequency of early post-stroke seizures. **Objective:** To determine the frequency of early-onset seizures after stroke among patients presenting to tertiary care hospitals. **Methods:** Two hundred and forty patients, presenting on the Medical floor of Jinnah Hospital Lahore with acute stroke and fulfilling the selection criteria, were approached after informed consent. The patients were followed for 14 days for the development of early seizures after the stroke. **Results:** Among 240 stroke patients, there were 123 (51.3%) male patients and 117 (48.8%) female patients. The minimum age observed was 30 years and the maximum was noted as 77 years. In 45% of patients, hemorrhagic stroke was detected and 55% of patients had ischemic stroke. From 108 cases of hemorrhagic stroke, there were 10.4% cases in which an episode of seizure occurred within 14 days of stroke. On the other hand, in 132 patients with ischemic stroke, 15.9% of patients developed seizure episodes. **Conclusions:** It was concluded that ischemic stroke was more common in frequency than hemorrhagic stroke in our population and the occurrence of episode early seizure within 14 days of stroke was more prevalent in ischemic stroke patients.

INTRODUCTION

A stroke is a neurological emergency characterized by a sudden onset neurological deficit of cerebrovascular cause that persists beyond 24 hours [1]. Establishing an accurate diagnosis is critical in the management of stroke because sometimes neurologic symptoms cannot reliably predict the occurrence of an infarct. Noncontract computed tomography (CT) is carried out first of all as an investigation of choice in patients with suspected stroke as it has a high sensitivity for the diagnosis of acute hemorrhage. The annual incidence of stroke is about 89.13 million patients; with one-third succumbing to death and another one-third suffering from disability [2]. Age, sex, and race are important demographic variables known to affect the prevalence of stroke worldwide with men having four times more chances of developing stroke as compared to their counterparts [3]. Stroke incidence in developing countries like Pakistan and India is much higher as compared to the developed world [4]. It is believed that this higher prevalence is secondary to higher values of stroke risk factors like hypertension, diabetes, dyslipidemias and poor socioeconomic circumstances. A recent community-based survey conducted in Pakistan suggested an estimated 1.2% prevalence of stroke [5]. Stroke-specific fatality has been reported between 11% and 30% in various studies from Pakistan with up to 63% of all stroke patients developing complications and up to 89% dependent on activities of daily living thus making it a highly debilitating disease [6, 7]. Early onset seizure frequency was reported as 8% in a local study [8]. Development of post-stroke seizure is a serious sequel of stroke and carries a high risk (>60%) of subsequent development of epilepsy especially in the first year [9]. Large areas of stroke and cortical involvement are reported to be particularly associated with post-stroke seizures [10]. Post-stroke seizures hurt stroke

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outcomes in terms of mortality, morbidity and hospital stay [11]. These seizures can worsen already existing dementia [12].

This study aims to look into the frequency of early-onset seizures in various types of stroke patients in a teaching hospital and their statistical significance concerning age, gender and type of stroke.

METHODS

It was a descriptive cross-sectional study conducted on the Medical Floor, Jinnah Hospital Lahore from 7th February 2024 till 31st May 2024 after taking hospital ethical review board (ERB) approval vide number ERB159/9/06-02-2024/S1. A total of 240 patients were included in the study by taking a 95% confidence level, 3.5% margin of error and expected percentage of early seizure among patients of ischemic stroke as 8% (least among all factors) [8]. Non-probability consecutive sampling was done. It included patients of both sexes, between 30 to 80 years of acute stroke determined by clinical features and confirmatory CT scan (as per operational definition). Patients with a previous history of ischemic or hemorrhagic stroke, seizure and epilepsy, metabolic disturbance (determined by abnormalities in serum electrolytes, blood sugar level, renal function test and acid-base disorders) or brain tumor (determined by CT Scan) were excluded from the study. Similarly, patients with subarachnoid hemorrhage, arteriovenous malformations or subdural hematoma evident on CT scan were not enrolled in the study. An informed consent was taken from their family and patients' baseline data were taken. Data confidentiality was maintained. The patients were followed for 14 days for development of early seizure after stroke and all the information was recorded in the questionnaire. Data were entered and analyzed using SPSS version 23.0. Quantitative variable i.e. age was summarized as mean and standard deviation. Nominal variables like sex, type of stroke and development of early onset seizure following stroke (outcome variable) were presented as frequency tables and percentages. Data were stratified for age, gender and type of stroke (ischemic and hemorrhagic). Post-stratification chi-square test was applied to determine the significant difference. A p-value of <0.05 was taken as statistically significant.

RESULTS

In our study, from the sample of 240 stroke patients, there were 123 (51.3%) male and 117 (48.8%) female. The age range was 30 to 77 years with the mean and standard deviation being 55.17 ± 12.02 years. The stratification of age was also done in which three groups were defined such as 30-45 years, 46-60 years and above 60 years. There were 22.9% of patients in the first age group, 37.9% in the second age group and 39.2% patients in the third age group. It was observed that from 240 patients with stroke, there were 108 (45%) patients in which hemorrhagic stroke was detected and the rest of the 132 (55%) patients had an ischemic stroke. From one hundred and eight cases of hemorrhagic stroke, there were 10.4% cases in which an episode of seizure occurred within 14 days of stroke. On the other hand, from 132 patients with ischemic stroke, 15.9% of patients developed episodes of seizure within 14 days of stroke (Table 1).

Table 1: Cross-tabulation of Type of Stroke and Early Seizure Following Stroke

Type of Stroke	The episode of Early Seizure Following Stroke Within 14 Days		Total
	Yes	No	
Hemorrhagic	13	95	108
Ischemic	21	111	132
Total	34	206	240

χ^2=0.732, DF=1, p-value=0.392

There was no significant difference was found for stratified age, gender and type of stroke on early episodes of seizure (p=0.45, 0.83 and 0.39 respectively) (Table 2).

Table 2: Cross-tabulation of Age and Early Seizure Following Stroke

Age Group	The episode of Early Seizure Following Stroke Within 14 Days		Total
	Yes	No	
30-45 years	5	50	55
46-60 years	15	76	91
Above 60 years	14	80	94
Total	34	206	240

χ^2=1.61, DF=2, p-value=0.448

The chi-square test was also applied to find significant differences for stratified age, gender and type of stroke for early episodes of seizure (Table 3).

Table 3: Cross-tabulation of Gender and Early Seizure Following Stroke

Gender	An Episode of Early Seizure Following Stroke Within 14 Days		Total
	Yes	No	
Male	18	105	123
Female	16	101	117
Total	34	206	240

χ^2=0.045, DF=1, p-value=0.831

DISCUSSION

This study revealed that ischemic stroke was more frequent in occurrence than hemorrhagic stroke in our local setup (55% vs. 45%). It was comparable to a study conducted by Khealani *et al.*, in which 72% of the patients had ischemic stroke and one hundred seventeen (8%) cases were having episodes of early seizures after stroke [8]. Stroke frequency was slightly higher (51.3%) in male patients in our study than in female patients (48.8%) and stroke occurrence was highest (39.2%) in patients with age > 60 years. In our study, episode of early seizure within 14 days of stroke was greater than reported in Khealani *et al.*,

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study, especially in ischemic lesions (15.9% vs. 10.4%). The frequency of post-stroke seizures was described as around 2.8% in another study including 138 patients of stroke whereas patients with seizures had increased mortality at one month (36.2% vs. 16.8%, p<0.0001) and 1-year post-stroke (48.6% vs. 27.7%, p<0.001), prolonged hospital stay and marked dependency (p<0.001) later on [13]. Our study findings were of even higher post-stroke seizure frequency, however, it was not designed to explore further post-seizure sequel.De *et al.*, reported that late-onset seizures after stroke were more commonly associated with future epilepsy [14]. In contrary to our findings, DeHerdtV *et al.*, stated that the occurrence of seizures was more closely related (14%) to intracerebral haemorrhages [15]. Nevertheless, it was equivocally witnessed that early-onset seizures had a guarded prognosis with a high in-hospital mortality rate, especially in hemorrhagic strokes. Incidence of status epilepticus was also reported by Wang *et al.*, (6.9 per 1000 stroke) in stroke patients [16]. Our study didn't find any significant impact of age, gender and type of stroke on the occurrence of early episodes of seizure. (p=0.45, 0.83 and 0.39 respectively). A study was conducted by Chen *et al.*, in which at the molecular level, early onset epileptic seizure was described to be associated with dysfunction of the sodium-potassium pump and marked glutamate release secondary to ischemic and hypoxic insult [17]. A study conducted by Kilpatrick *et al.*, concluded that early-onset seizures after stroke carried a significant risk of subsequent recurrence in later life regardless of the type or location of stroke [18]. However, in a study Lin *et al.*, severe neurological deficit at the onset of stroke was reported to be more strongly associated with post-stroke epilepsy [19]. Short-term therapy with anti-epileptic drugs, for secondary prophylaxis of seizures after stroke, was found associated with improved quality of life according to Freiman *et al.*, [20]. Our research highlighted important statistics about the stroke burden in the Pakistani population and stroke-associated seizures. Ischemic stroke accounts for a major portion of stroke patients in our population and post-stroke seizures have a worse effect on stroke outcomes. There were a few limitations of this study as well like it was a single-center study and it assessed only seizure frequency in stroke patients. Multicenter and prospective studies are needed to truly find out the incidence of post-stroke seizures and their impact on stroke outcomes.

CONCLUSIONS

It was concluded that ischemic stroke was more common in frequency than hemorrhagic stroke in our population and the occurrence of episode early seizure within 14 days of stroke was more prevalent in ischemic stroke patients. Ischemic stroke accounted for a major portion of stroke patients in our population and post-stroke seizures have a worse effect on stroke outcomes.

Authors Contribution

Conceptualization: ZAW
Methodology: HF, MA, UR,
Formal analysis: ZJ
Writing review and editing: NA, ZJ

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

Conflicts of Interest

The authors declare no conflict of interest.

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Percutaneous Transhepatic Biliary Drainage as a Viable Alternative to Failed Endoscopic Retrograde Cholangiopancreatography in Hepatobiliary Disorders: A Retrospective Analysis

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ABSTRACT

The conventional second-line treatment for failed ERCP was Percutaneous Transhepatic Biliary Drainage (PTBD). Because of its high level of success and accessibility, PTBD has evolved into a well-established rescue therapy. **Objective:** To assess the procedural outcomes of PTBD following a failed ERCP in patients with hepatobiliary disorders. Additionally, it was focused on finding the significant factors that impact PTBD outcomes. **Methods:** A retrospective descriptive analysis was performed on 128 individuals at Dow Hospital Ojha Campus Karachi, who received PTBD following a failed ERCP. Between January 2023 and March 2024, we evaluated the clinical success rate, post-PTBD complications, and mortality. **Results:** The mean age of the patients was 65.9+/-11.7 years, and 76 (59.4%) patients were female. The clinical success rate was 77.3%, and complications after PTBD were 20(15.6%). A prolonged hospital stay was reported in 29 (22.7%) patients, and 13 (10.2%) patients died within 30 days. Younger age, etiology, and type of PTBD had a significant association with clinical success (P<0.05). Older age, female patients, and malignant etiology had a higher complication rate and mortality (P<0.05). **Conclusions:** PTBD provides a safe, effective, and viable alternative approach for patients with hepatobiliary disorders. It has a low rate of complications, a high rate of procedural success, and a low risk of mortality after a failed ERCP. Adverse events were more common in patients with a malignant etiology, older age, and female gender.

INTRODUCTION

Biliary obstruction is commonly defined as the blockage of the extrahepatic biliary obstruction. It might occur anywhere along this path and lead to serious complications [1]. Furthermore, the biliary obstruction may get colonized by germs, leading to infections. Pancreatic cancer, cholelithiasis, choledocholithiasis, cholangitis, and cholangiocarcinoma are only a few of the malignant and benign hepatobiliary illnesses that frequently result in biliary blockage [2]. These obstructions have an effect on a significant proportion of the global population, leading to low life expectancy and elevated rates of morbidity and mortality. For every 1,000 individuals, there are around five cases of biliary obstruction [3]. The fluoroscopic or combined fluoroscopic and ultrasound guidance can be used to perform image-guided PTBD functions. There are several signs and symptoms associated with it, ranging

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from obstructive to non-obstructive etiologies. The indications of PTBD for palliation in obstructive jaundice include cholangiocarcinoma, reduced serum bilirubin before beginning chemotherapy, cholangitis, pain relief, pruritus, and accessing the biliary system for additional palliative procedures like stent implantation [4]. Because of its high degree of technical success and accessibility, PTBD has evolved into the standard rescue therapy. However, there are a number of significant drawbacks to PTBD, such as a generally high incidence of adverse events (20-30%), a need for repeated reinterventions, and a decline in the quality of life for patients [5, 6]. In order to treat such hepatobiliary disorders, ERCP serves as the gold standard for obtaining biliary access. Over 90% of ERCP cases are successful [2]. Despite being the most often used treatment to palliate patients with biliary blockage, ERCP with biliary drainage is unsuccessful in 3–10% of cases. Inadequate drainage, anatomical variance, tumor expansion, previous surgery, and/or operator inexperience all contribute to failure [7]. There are typically three more approaches to accessing the biliary tree in the event that an ERCP fails. With a success rate of 63–78%, the initial procedure is a repeat ERCP. In 63–86% of cases, biliary access is obtained using the PTBD method for biliary tree drainage [2, 8]. According to guidelines, biliary cannulation of dilated ducts should be performed in 95% of cases, with serious complications in 10% of cases [9]. Because it requires immediate diagnosis and treatment, advanced malignant biliary obstruction continues to be a difficult clinical scenario [10]. In situations of malignant or benign blockage, PTBD is used to decompress the intra and extrahepatic biliary channels in order to relieve symptoms, lower bilirubin levels, and make biliary placement of stents easier [3, 11]. However, the in-hospital death rate estimated almost 20% for patients undergoing PTBD. Higher mortality is correlated with older age, male gender, and those with co-morbidities, for unresectable biliary tract blockage, and, specifically, to inexperienced clinicians [12]. Based on the location of the blockage and the cause of the disease, multidisciplinary teams should choose the appropriate kind of intervention. Though it is currently the standard of therapy and readily available, endoscopic ultrasound's ongoing advancements may eventually result in a declining indication of percutaneous drainage. A significant benefit of percutaneous intervention is its high technical success rate, which can reach 94–100% when compared to the less successful outcomes of ERCP [13, 14]. This study seeks to assess the therapeutic efficacy and safety profile of PTBD as a minimally invasive alternative to failed ERCP for the management of biliary symptoms, with the potential to inform evidence-based practice and optimize patient outcomes. Advancing patient care and outcomes through innovative research and evidence-based practice. This groundbreaking study on PTBD addresses a critical knowledge gap in hepatobiliary management, improving patient safety, reducing morbidity, and enhancing quality of life.

By investigating the efficacy and safety of PTBD, we will generate crucial data to inform institutional guidelines, refine treatment protocols, and contribute meaningfully to the global scientific community.

METHODS

This retrospective descriptive study was conducted at the Department of Vascular Interventional Radiology, Dow Hospital Ojha Campus Karachi, after receiving ethical approval (Ref: IRB-3470/DUHS/EXEMPTION/2024/138) from the Institutional Review Board. The IRB waived the prerequisite for written informed consent because the study was retrospective in nature. Sample size was calculated 128 using PTBD success rate 77% (3) at margin of error 7.5% and confidence interval 95%. All 128 patients aged over 18 years with hepatobiliary obstruction who underwent PTBD after failed ERCP from January 2023 to March 2024 were included in the study following non-probability consecutive sampling technique. Patients with deranged LFTs (liver function tests) and optimal intrahepatic ductal dilatation were included. The exclusion criteria comprised missing clinical data but the data was well maintained and properly reported and all the required information's were extractable during data collection of data. Patient's demographic details, laboratory tests, imaging results, and outcomes of PTBD, such as hospital stay, mortality, complications (such as infection, fever, post-procedural bleeding, had drain dislocation, and sepsis etc.), and clinical success were obtained from electronic health records and the photo archiving and communication system. Technical success of PTBD was deemed as the procedural completion with the placement of biliary catheter and clinical success considered as the normal WBC count, with no fever or organ failure within one month. Procedural complications were reported as per society of interventional radiology guidelines [8]. The Experienced interventional radiologists utilizing conventional tools and standardized methods carried out the PTBD procedures. In the current study, all PTBD procedures were conducted with the placement of an around 8 Fr small pigtail drainage catheter and were performed by interventional radiologists with more than ten years of experience in biliary intervention. All statistical analyses were performed using IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, New York, USA). Continuous variables were measured as the mean± SD, and categorical variables were presented as frequency and percentage. Study outcomes (clinical failure, complications, and mortality) were compared using the logistic regression analysis. A univariate and multivariate analyses were performed to identify risk factors associated with clinical outcomes for PTBD. A P-

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value<0.05 was considered statistically significant.

RESULTS

Demographic and procedural outcomes data of 128 patients with hepatobiliary disorder who underwent PTBD after failed ERCP were shown in Table 1. The mean age of the patients was 65.9+/-11.7 years, and 76 (59.4%) patients were female. Most of the 99 patients (77.3%) who underwent PTBD procedures had malignant conditions. Clinical failure was reported in 29 (22.7%) patients, and complications after PTBD were 20 (15.6%). A prolonged hospital stay was reported in 29 (22.7%) patients, while 99 (77.3%) patients were discharged the next day of the procedure, and 13 (10.2%) patients died within 30-days (Table 1).

Table 1: Demographic Characteristics and Procedural Outcomes of Patients

Study Variables		Mean ± SD / N (%)
Age (Years)		65.9 ± 11.7
Serum Bilirubin (umol/l)		364.6 ± 192.6
Age Groups	65 or Less	57 (44.5%)
	More Than 65	71 (55.5%)
Gender	Female	76 (59.4%)
	Male	52 (40.6%)
Etiology (BO)	Benign	29 (22.7%)
	Malignant	99 (77.3%)
Diagnosis	Benign Biliary Stricture	25 (19.5%)
	Carcinoma Gallbladder	22 (17.2%)
	Cholangiocarcinoma	59 (46.1%)
	Pancreatic Head Carcinoma	22 (17.2%)
Indication for PTBD	Contra Indicated ERCP	5 (3.9%)
	Failed ERCP	123(96.1%)
Clinical Failure	No	99 (77.3%)
	Yes	29 (22.7%)
Complications	Yes	20 (15.6%)
	No	108 (84.4%)
Prolonged Hospital Stay	Discharged Next Day	99 (77.3%)
	Prolonged	29 (22.7%)
Mortality	Yes	13 (10.2%)
	No	115 (89.8%)
Total		128 (100%)

Mean+/-SD; n (%);BO :Biliary Obstruction ; PTBD: percutaneous transhepatic biliary drainage

Clinical failure was compared with the associated factors to identify the risk factors. Univariate analysis identified older age, female gender, diagnosis and type of PTBD as the significant factor for clinical failure (P<0.20). Multivariate analysis found older age of patients as a highly associated factors for clinical failure. (OR: 3.39, 95% CI: 1.22-9.40; P=0.019)(Table 2).

Table 2: : Association of PTBD Outcomes(Clinical Failure)with Associated Factors

Study Variables		Clinical Failure N (%)		Unadjusted OR (95% CI; Sig)	Adjusted OR (95% CI; Sig)
		Yes	No		
Age Groups	65 or Less	6 (10.5%)	51 (89.5%)	Ref	Ref
	More Than 65	23 (32.4%)	48 (67.6%)	4.07 (1.53-10.86; 0.005)	3.39 (1.22-9.40; 0.019)
Gender	Male	7 (13.5%)	45 (86.5%)	Ref	Ref
	Female	22 (28.9%)	54 (71.1%)	2.62 (1.02-6.69; 0.044)	1.95 (0.72-5.27; 0.190)
Etiology (BO)	Benign	4 (13.8%)	25 (86.2%)	Ref	-
	Malignant	25 (25.3%)	74 (74.7%)	2.11 (0.67-6.66; 0.202)	-
Diagnosis	Benign Biliary Stricture	3 (12%)	22 (88%)	Ref	Ref
	Carcinoma Gallbladder	4 (18.2%)	18 (81.8%)	1.63 (0.32-8.25; 0.555)	0.87 (0.14-5.43; 0.879)
	Cholangiocarcinoma	16 (27.1%)	43 (72.9%)	2.73 (0.72-10.38; 0.141)	1.18 (0.26-5.49; 0.141)
	Pancreatic Head Carcinoma	6 (27.3%)	16 (72.7%)	2.75 (0.59-12.68; 0.194)	1.08 (0.18-6.89; 0.936)
Indication for PTBD	Contra Indicated ERCP	1 (20%)	4 (80%)	Ref	-
	Failed ERCP	28 (22.8%)	95 (77.2%)	1.18 (0.13-10.98; 0.885)	-
Type of PTBD	Internal/External	10 (14.7%)	58 (85.3%)	Ref	Ref
	External	19 (31.7%)	41 (68.3%)	2.69 (1.13-6.38; 0.025)	2.10 (0.74-5.98; 0.164)

For Univariate logistic regression significance level set at 0.20.
For Multiivariate logistic regression significance level set at 0. 05.

Post PTBD complication status was compared with the factors. Univariate analysis identified older age, female gender, malignant etiology, diagnosis and type of PTBD as the significant factor for post-operative complications (P<0.20). Multivariate analysis found older age of patients as a highly associated factors of post PTBD complication similar to the clinical failure. (OR: 7.48, 95% CI: 1.58-35.5; P=0.011) while other factors remained insignificant (P>0.05)(Table 3).

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Table 3: : Association of PTBD Outcomes (Post-Operative Complications) with Associated Factors

Study Variables		Post-Operative Complications N (%)		Unadjusted OR (95% CI; Sig)	Adjusted OR (95% CI; Sig)
		No	Yes		
Age Groups	65 or Less	55 (96.5%)	2 (3.5%)	Ref	Ref
	More Than 65	53 (74.6%)	18 (25.4%)	9.34 (2.07-42.23; 0.004)	7.48 (1.58-35.49; 0.011)
Gender	Male	49 (94.2%)	3 (5.8%)	Ref	Ref
	Female	59 (77.69%)	17 (22.4%)	4.71 (1.30-17; 0.018)	3.86 (0.96-15.57; 0.058)
Etiology (BO)	Benign	27 (93.1%)	225 (6.9%)	Ref	Ref
	Malignant	81 (81.8%)	18 (18.2%)	3(0.65-13.78; 0.158)	0.41(0.03-5.75; 0.508)
Diagnosis	Benign Biliary Stricture	24 (96%)	1 (4%)	Ref	Ref
	Carcinoma Gallbladder	18 (81.8%)	4 (18.2%)	5.33 (0.55-51.9; 0.149)	8.44 (0.26-272.8; 0.229)
	Cholangiocarcinoma	48 (81.4%)	11 (18.6%)	5.50 (0.67-45.14; 0.112)	5.40 (0.23-128.8; 0.297)
	Pancreatic Head Carcinoma	18 (81.8%)	4 (18.2%)	5.33 (0.55-51.88; 0.49)	5.66 (0.17-182.9; 0.329)
Indication for PTBD	Contra Indicated ERCP	5 (100%)	0 (0%)	Ref	Ref
	Failed ERCP	103 (83.7%)	20 (16.3%)	-	-
Type of PTBD	Internal/External	61 (89.7%)	7 (10.3%)	Ref	Ref
	External	47 (78.3%)	13 (21.7%)	2.41 (0.89-6.52; 0.083)	1.32 (0.38-4.64; 0.662)

For Univariate logistic regression significance level set at 0.20.
For Multivariate logistic regression significance level set at 0.05.

Older age was indicated as the significant factor for mortality (P=0.024), and as compared to male patients, mortality was found to be higher in female patients (P = 0.032). The type of PTBD also had a significant association with mortality. Mortality status was compared with the associated. Univariate analysis identified older age, female gender, malignant etiology, diagnosis and type of PTBD as the significant factor for mortality (P<0.20) (Table 4).

Table 4 : Association of PTBD Outcomes (Mortality) with Associated Factors

Study Variables		Mortality N (%)		Unadjusted OR (95% CI; Sig)	Adjusted OR (95% CI; Sig)
		No	Yes		
Age Groups	65 or Less	57 (100%)	0 (0%)	Ref	-
	More Than 65	58 (81.7%)	13 (18.3%)	26.5 (1.54-457; 0.024)	N/A
Gender	Male	51 (98.1%)	1 (1.9%)	Ref	Ref
	Female	64 (84.2%)	12 (15.8%)	9.56 (1.20-76; 0.032)	3.57 (0.91-14.02; 0.068)
Etiology (BO)	Benign	29 (100%)	0 (0%)	Ref	-
	Malignant	86 (86.9%)	13 (13.1%)	9.21 (0.53-159.7; 0.127)	N/A
Diagnosis	Benign Biliary Stricture	25 (100%)	0 (0%)	Ref	-
	Carcinoma Gallbladder	18 (81.8%)	4 (18.2%)	12.4 (0.63-244.8; 0.098)	N/A
	Cholangiocarcinoma	52 (88.1%)	7 (11.9%)	7.28 (0.40-132; 0.179)	N/A
	Pancreatic Head Carcinoma	20 (90.9%)	2 (79.1%)	6.22 (0.28-136.9; 0.25	N/A
Indication for PTBD	Contra Indicated ERCP	5 (100%)	0 (0%)	Ref	-
	Failed ERCP	110 (89.4%)	13 (10.6%)	1.34 (0.07-25.7; 0.844)	N/A
Type of PTBD	Internal/External	65 (95.6%)	3 (4.4%)	Ref	Ref
	External	50 (83.3%)	10 (16.7%)	4.33 (1.13-16.58; 0.032)	8.09 (1.0-65.3; 0.05)

For Univariate logistic regression significance level set at 0.20.
For Multiivariate logistic regression significance level set at 0.05.
N/A: Not Applicable (0 frequency)

DISCUSSION

ERCP and PTBD have been the mainstays of treatment choices for many years. As with biliary drainage, initial ERCP was the gold standard of treatment; PTBD was often done following an unsuccessful ERCP surgery. If the biliary tree was endoscopically inaccessible, PTBD was the recommended course of action for treating either benign or malignant hepatobiliary disorders. Anatomical landmarks have been used to guide biliary punctures under fluoroscopic guidance in the past; however, the current procedural approach differs depending on operator expertise and preference [15]. Recent advanced procedural approaches have resulted in a notable decline in overall morbidity and mortality rates for malignant hepatobiliary diseases. In the current situation, patient-centered death with improved quality of life and clear immediate survival advantages makes palliative care with

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PTBD the recommended norm for instances of hepatobiliary illnesses. It was now abundantly clear that the operator's expertise plays a major role in both technological success and unfavorable incidents [10]. In current study, PTBD's documented technical success rate was 100%, which was a reflection of previous studies as well, where the clinical success rate was reported to be over 90% with a smaller number of complications observed. By using adequate antibiotic coverage and limiting biliary manipulation, these problems can be further decreased [4, 16]. In this cohort results suggested that younger age, benign etiology, and the type of PTBD optimize success rate and minimize complications. Out of 128 patients enrolled in the current study, 59.4% were female. The patients' mean age was 65.9 ± 11.7 years. The most common cause of hepatobiliary disorder was cholangiocarcinoma 46.1%. For patients with malignant hepatobiliary disorders, PTBD, or minimally invasive surgery, was a crucial part of their management. It was most frequently performed as a palliative procedure with the goal of reducing morbidity related to the disease and improving quality of life while relieving symptoms (such as cholangitis, pruritus, etc.). However, it will not change the underlying prognosis of the disease. It was an affordable and safe way to clear obstructions in the biliary obstruction [17]. This study investigated the PTBD clinical success rate of 77.3% (benign 86.2% and malignant 74.7%) in patients with hepatobiliary disorders. Similar to this study finding, Hsu YC *et al.*, demonstrated the clinical success rate of PTBD at 77% in malignant biliary obstruction patients, which was comparable to this study clinical success rate, and also other studies reported similar rates of 76% and 76% and 76% [3, 18, 19]. Furthermore, we found that the type of PTBD affected its clinical success. According to this study findings, internal/external PTBD clinical success rates were substantially higher than external ($P<0.05$). Koutlas NJ *et al.*, reported in a review of PTBD following an unsuccessful ERCP [5]. High technical success rates of 98% for PTBD were demonstrated by the analysis's findings. In this investigation, PTBD achieved 100% technical success. Lesmana CR et al., did another trial that revealed 75% clinical success and 58% reported adverse effects for PTBD[10]. A total of 90 patients with failed ERCP subsequently PTBD. Although technical success was higher in the PTBD group 78%, clinical success was 63%. PTBD was associated with adverse event rate 28% [20]. In a recent local study 100% technical success and over 9% clinical success was achieved with 5% procedural complications [21]. In this study post-procedural complications rate was 15.6%, which was relatively low as compared to previous studies. In another retrospective study complications were reported in 5.9% and 20% in 3-months. Infection was the most common complication, with 2.4% of patients experiencing this within a week and 9% within a month. In addition, this study showed that morbidity and death were related to provider PTBD expertise, age, gender, co-morbidities, deprivation, type of malignancy and pre-existing renal failure [12]. In the current study, 20(15.6%)patients suffered from post-PTBD complications (19/20; 95% of patients had post-PTBD infection and fever, 5/20; 50% had post-procedural bleeding, 2/20; 10% had abdominal bleeding, 2/20; 10% had drain dislocation, 2/10; 10% had sepsis), prolonged hospital stays were reported in 22.7% of cases, and 10.2% died within 30-days. Associated factors such as older age, female gender, malignant etiology, cholangiocarcinoma, carcinoma gallbladder, and pancreatic head carcinoma were identified as significant contributors to post-PTBD complications and mortality. We recognized the limitations of the study; the sample size might not be large enough. The retrospective design because participants in the current research were not randomized and data collection relied on the availability and quality of registration and follow-up information, the design of the study was more prone to bias. The study's retrospective design restricts the amount of data that can be analyzed, including data on long-term outcomes and quality of life post-PTBD. Moreover, the study's strength was its focus of patients underwent PTBD after failed ERCP, regardless of the cause. The expert clinicians have utilized the strict standard protocols, potentially improvising outcomes.

CONCLUSIONS

In Patients with Hepatobiliary Disorders, PTBD offers a safe, efficient, and viable alternative approach with a high rate of clinical and technical success, a low rate of complications, and a low risk of death following failed ERCP. The findings further showed that PTBD was associated with complications, in particular infection, bleeding, prolonged hospital stay, and mortality. Moreover, mortality within 30 days in patients undergoing PTBD for relief of biliary obstruction was high at 10.2%. Older age, female gender, and malignant etiology have a poorer prognosis. It was determined that PTBD, which relieves hepatobiliary disorders and provides symptomatic relief, should only be carried out at experienced facilities in order to attain low rates of death and morbidity and high success rates. Additionally, palliative care for these terminally ill patients should also be provided. Aside from being economical, the process doesn't require plenty of expensive equipment to be installed.

Authors Contribution

Conceptualization: MA
Methodology: AS
Formal analysis: NAQ
Writing, review and editing: MA, NN, PA, ZA

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Prevalence of Hypokalemia in Diabetic Ketoacidosis Patients Presenting to the Emergency Department

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ABSTRACT

Diabetic Ketoacidosis (DKA) is a potentially life-threatening hyperglycemic emergency that leads to severe metabolic derangements which may cause low potassium concentrations, resulting from insulin and hence a poorer outcome among patients admitted in emergency departments. **Objective:** To determine the prevalence and severity of hypokalemia in patients with Diabetic Ketoacidosis (DKA) presenting to the emergency department. **Methods:** A cross-sectional study was conducted at the Department of Emergency Medicine of Jinnah Postgraduate Medical Centre, Karachi from November 2022 to April 2023. 97 patients with a blood glucose level of 250 mg/dL or higher at the time of arrival and aged between 18 and 65 years were included in the study, using consecutive sampling, meeting the diagnostic criteria for DKA. **Results:** The prevalence of hypokalemia was 53.61% (n=52). Within this group, 39.18% had mild hypokalemia, 11.34% had moderate hypokalemia, and 3.09% had severe hypokalemia. Conversely, 45.36% of patients maintained normal potassium levels, while only 1.03% presented with hyperkalemia. Furthermore, among those with hypokalemia, 53.16% were using insulin, with a p-value of 0.082 indicating no significant association with insulin use. In terms of gender, 30 males (53.57%) and 22 females (42.31%) experienced hypokalemia, but this was also found to be statistically insignificant (p=0.42). **Conclusions:** This research revealed that significant prevalence of hypokalemia in diabetic ketoacidosis (DKA), with 53.61% of participants affected (3.1% of cases exhibited severe hypokalemia), highlighting the importance of adhering to the American Diabetes Association's recommendation to assess serum potassium levels before initiating DKA treatment.

INTRODUCTION

Diabetic Ketoacidosis (DKA) is a potentially life-threatening hyperglycemic emergency that leads to severe metabolic derangements, including ketone production, metabolic acidosis, and electrolyte disturbances [1]. Approximately thirty-three percent of children who are newly diagnosed with type 1 diabetes exhibit Diabetic Ketoacidosis (DKA) at the time of diagnosis [2]. Abnormally low potassium concentrations have been observed in DKA patients admitted to the ED [3]. Usually, the patients are predicted to exhibit a significant decrease in total body potassium levels, ranging from 300 to 600 mEq. This reduction is attributed to several factors, including kaliuresis resulting from osmotic diuresis, limited oral intake, and gastrointestinal losses due to diarrhea and vomiting [4]. Insulin, part of the DKA treatment regimen, shifts potassium back into the intracellular space, which can result in profound hypokalemia, even with aggressive replacement. Consequently, monitoring potassium levels closely during the initial hours of treatment is essential. Continuous cardiac monitoring is strongly recommended

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because of the potential for a rapid shift in potassium levels and the associated risk of cardiac arrhythmia [5]. While potassium replacement is a key component of DKA management, its depletion and subsequent treatment are not fully explained. Potassium is often depleted before the patient's potassium levels are even documented, and treatment with fluids and insulin can exacerbate this imbalance. Proper correction of hypokalemia before initiating insulin therapy is critical, as untreated hypokalemia can result in life-threatening complications such as paralysis or severe cardiac arrhythmias the recognition of the significance of potassium replacement in the management of Diabetic Ketoacidosis (DKA) has substantially reduced the mortality rate [6]. Previously, the mortality rate was as high as 30 to 50%, even after the introduction of specific management strategies [7]. Hypokalemia has historically been reported in 4% of patients, with associated complications such as paralysis and abnormal heart rhythms. However, it is noteworthy that these findings are based on studies with varied sample sizes and certain limitations, indicating a need for further conclusive evidence [8]. At the national level, there is a lack of published data on the prevalence and severity of hypokalemia among patients with Diabetic Ketoacidosis (DKA) at the time of their initial presentation to the emergency department. This research gap highlights the need for a focused investigation into the potassium levels of DKA patients before fluid resuscitation and insulin therapy.

Therefore, it conducted an observational study to address this gap and determine the prevalence and severity of hypokalemia in adult patients with DKA presenting to the emergency department.

METHODS

A cross-sectional study was conducted at the Department of Emergency Medicine of Jinnah Postgraduate Medical Centre, Karachi from November 2022 to April 2023. Approval for the study was obtained from the institutional review board (No. F.2-81/2022-GENL/206/JPMC). Informed written consent was taken from participants/their attendants. A sample size of 97 patients was calculated via WHO open epi sample size calculator keeping incidence of DKA in newly diagnosed patients as 6.7% with 5% margin of error and 95% confidence interval [9]. Patients diagnosed with DKA having a blood glucose level of 250 mg/dL or higher at the time of arrival and aged between 18 and 65 years were included in the study, using consecutive sampling. Exclusion criteria included patients aged 65 and above, those on potassium-sparing diuretics, individuals who had taken insulin within 12 hours before arriving at the emergency department, patients with pre-existing heart conditions, those diagnosed with septic shock, and pregnant individuals. Prevalence and severity of hypokalemia was the main outcomes of the study. Patients who fulfilled the inclusion criteria underwent an assessment that included a Venous Blood Gas (VBG) and a serum chemistry panel to diagnose DKA. The diagnosis of DKA was confirmed if patients met all the criteria established by the American Diabetes Association (ADA), which included a serum glucose level of 250 mg/dL or higher, a serum anion gap greater than 10 mmol/L, carbon dioxide levels of 18 mmol/L or greater, and a pH of 7.30 or lower. The VBG was used solely to determine the serum pH, acknowledging that there may be some potential inaccuracies in pH measurement compared to Arterial Blood Gas (ABG) analysis; however, VBG was a practical choice for rapid assessment in the emergency department setting. The serum chemistry panel provided the electrolyte levels. Additionally, to verify insulin use within the 12 hours prior to presentation, patient interviews were conducted, and medical records were reviewed to ensure accuracy. Hypokalemia was classified based on the following ranges: mild hypokalemia was defined as a potassium level between 3.1 and 3.5 mmol/L, moderate hypokalemia as 2.5 to 3.0 mmol/L, and severe hypokalemia as less than 2.5 mmol/L [10]. The data analysis was conducted using IBM SPSS version 21.0 and Microsoft Excel 365. Descriptive statistics, including mean ± standard deviation, were used for continuous variables such as age, duration of diabetes, glucose levels, and potassium levels. Frequency and percentages were employed to calculate the categorical variables such as gender, prevalence and severity of hypokalemia, history of diabetes, insulin usage, and type of treatment. Chi-square was used to determine the association between severity of presence of hypokalemia with gender and insulin usage.

RESULTS

The mean age was 40.6 years (SD, 13.6 years; range, 18-65 years). The cohort was 57.27% male and 42.31% female. Among them, 79 (81.40%) patients, were using insulin, and 18 (81.60%) were on oral hypoglycemic agents, as detailed in table 1.

Table 1: Description of the Study Parameters (n=97)

Variables	N (%) / Mean ± SD
Age (Year)	40.6 (13.6%)
Male	56 (57.7%)
Female	41 (42.3%)
Insulin Use	79 (81.4%)
Oral Hypoglycemic Agents	18 (18.6%)
Mean Serum Potassium (mmol/L)	5.2 ± 1.4 (2.2-6.9)

The prevalence of hypokalemia was observed in 52 patients (53.61%). Among these, 38 patients (39.18%) had mild hypokalemia, 11 patients (11.34%) had moderate hypokalemia, and 3 patients (3.09%) had severe hypokalemia. Additionally, 44 patients (45.36%) had normal potassium levels, while only 1 patient (1.03%) exhibited hyperkalemia.

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Table 2: Potassium Profile of Dka Patients

Potassium Level	Range (mmol/L)	N (%)
Hyperkalemia	>5.5 mmol/L	1 (1.03%)
Normokalemia	3.6 - 5.5 mmol/L	44 (45.36%)
Prevalence of Hypokalemia	<3.5 mmol/L	52 (53.61%)
Mild Hypokalemia	3.1 - 3.5 mmol/L	38 (39.18%)
Moderate Hypokalemia	2.5 - 3.0 mmol/L	11 (11.34%)
Severe Hypokalemia	<2.5 mmol/L	3 (3.09%)

Table 3 shows that 53.61% of patients had hypokalemia, while 46.39% did not. Among those with hypokalemia, 42 patients were using insulin, with a p-value of 0.082, indicating no significant association. For gender, 30 males (53.57%) and 22 females (42.31%) had hypokalemia, with a p-value of 0.42, suggesting no significant relationship.

Table 3 : Presence of Hypokalemia Vs Insulin Use and Gender

Variables	N (%)		p-Value
	Present	Absent	
Hyperkalemia	52 (53.61%)	45 (46.39%)	-
Insulin Use Present	42 (53.16%)	37 (46.84%)	0.082
Insulin Use Absent	10 (55.56%)	8 (44.44%)	
Male	30 (53.57%)	26 (57.78%)	0.42
Female	22 (42.31%)	19 (42.22%)	

DISCUSSION

This research analyzed serum potassium levels in a cohort of 97 patients with DKA and found that 3.1% had severe hypokalemia, 39.18% had mild hypokalemia, and 1.03% presented with hyperkalemia. These findings were consistent with other studies. For instance, Makinouchi R, *et al.*, reported a 5.6% prevalence of hypokalemia among 54 DKA patients, where severe cases correlated with higher mortality [11]. Qassabi SS *et al.*, found hypokalemia in 9% of their sample [12]. In contrast, a 2024 study involving 537 DKA patients reported only 1.3% with mild hypokalemia and no cases below 3.3 mmol/L [13]. Collectively, these studies indicate that while hypokalemia is relatively rare in DKA, it can lead to severe complications if not promptly addressed. Recent research has indicated that routine potassium replacement in patients with mild hypokalemia may not always be warranted and could potentially result in adverse events, particularly hyperkalemia, especially in patients with coexisting medical conditions [14, 15]. This suggests that potassium management should be tailored based on individual patient profiles and the severity of their hypokalemia. Moreover, studies recommend conducting serum potassium measurements 2 hours after initiating insulin therapy and then at 4-hour intervals until DKA resolution for most DKA patients, administering 20–30 mmol of potassium per liter of intravenous fluid is generally sufficient to maintain serum potassium within the target range [16-18]. The 3.1% prevalence of severe hypokalemia in this study highlights the importance of proactive potassium monitoring and replacement to prevent potentially fatal outcomes. This aligns with the recommendations from Coregliano-Ring L *et al.*, and Lee MH *et al.*, who advocate for initiating potassium replacement when levels drop below 5.0 mmol/L and delaying insulin therapy until potassium exceeds 3.5 mmol/L to prevent life-threatening complications [19, 20]. This study benefits from a well-defined inclusion and exclusion criteria and clear diagnostic criteria for DKA, ensuring the accuracy of these findings. Additionally, using both venous blood gas and serum chemistry panels for measurements enhances the reliability of the data. However, limitations include the small sample size and single-center setting, which may limit the generalizability of these findings.

CONCLUSIONS

This study reveals a significant prevalence of hypokalemia among patients with Diabetic Ketoacidosis (DKA), with 53.61% of participants exhibiting varying degrees of potassium deficiency. Notably, the majority of hypokalemic patients presented with mild hypokalemia, highlighting the need for vigilant potassium monitoring in this population. Despite the observed prevalence, no significant associations were found between hypokalemia and insulin use or gender, suggesting that other factors may contribute to potassium imbalances in DKA.

Authors Contribution

Conceptualization: NUSS
Methodology: NUSS, FF, AA
Formal analysis: NUSS
Writing, review and editing: MA, SS1, SS2, SZM, FF, AA

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

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Original Article

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Comparison of Hospital Duration and Analysis of Harmonic Scalpel Surgery with Conventional Protocols in Patients Undergoing Thyroid Surgery

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ABSTRACT

A thyroidectomy is a common surgical procedure, and while traditional methods including electrocautery pose a danger of tissue damage, harmonic scalpels have recently seen a rise in their use for this purpose. **Objective:** To determine whether or not the Harmonic Scalpel is beneficial in dealing with patients who are undergoing thyroidectomy. **Methods:** This qusai-experimental study was performed at Department of Surgery, Ghulam Muhammad Mahar Medical College Sukkur from 1st October 2022 to 31st March 2023 and 60 patients were enrolled and divided into 2 equal groups for conventional and harmonic thyroidectomy. Patients with Basedow' illness or thyroid cancer were included regardless of lymph node dissection. For 5mm blood vessel division, 55kHz ultrasound pulses were employed for coagulation. Cutting and coagulation were done using active blade. A well-structured questionnaire recorded operation length, 24-hour drainage volume, hospital stay, post-operative hypocalcaemia, drain placement, RLN paralysis, and blood loss for each patient. **Results:** There were 78.3% females as compared to the males 21.6%. Less operation time was taken in surgery performed by harmonic scalpel as compared to conventional surgery. Significant difference was observed in intra-operative blood loss in study group. Harmonic scalpel lost 40ml blood whereas traditional surgery lost 124ml. Both research groups had similar post-operative problems. **Conclusions:** Harmonic scalpel thyroidectomy appeared to be the most reliable and feasible method as compared to conventional surgery protocol in relevance to intra-operative blood loss, surgery duration, total volume drainage.

INTRODUCTION

Thyroid surgery is considered as the most common endocrine surgery. In spite of the routine surgical procedure, various complications are associated with it including damage to superior laryngeal nerve/recurrent laryngeal nerve, bleeding, hypothyroidism. Another major complication which observed commonly is intra-operative bleeding which occurred due to presence of several blood vessels and narrow visual field. Bleeding leads to numerous post-operative complications and cause air passageway blockage. For that reason, haemostasis in dry field and dissection of blood vessel is imperative to minimize the adverse effects of post-operative bleeding [1-4]. Advance surgical methods have been developed to combat the negative outcomes of routine surgical procedures. Harmonic surgery is the latest surgical instrument that can cauterize and cut tissue simultaneously. Ultrasonic waves are mainly used in harmonic scalpel and this energy is converted into mechanical energy for blade activation. Activated blade performs the main function and delivers high-grade frictional force. On the other hand, inactivated upper arm helps in the maintaining the tissue position [5-8]. It helps in minimizing the procedure time, blood loss,

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volume of drainage in thoracic surgery, abdominal laparoscopic surgery and parotid surgery [7, 8]. Recent studies have also highlighted the role of harmonic scalpel surgery in reduction of surgical time and postoperative blood loss in thyroidectomy as well. Nowadays, harmonic scalpel surgery is actively used in thyroidectomy [9, 10].
Present study was designed for the comparison of hospital duration and analysis of harmonic scalpel surgery with conventional protocols in patients undergoing thyroid surgery.

METHODS

This qusai-experimental study was performed at Department of Surgery, Ghulam Muhammad Mahar Medical College Sukkur from 1st October 2022 to 31st March 2023 with IRB approval letter No. Gen. Surgery/SMBBMU/98. Patients with Basedow' disease or thyroid malignancy were included irrespective of the presence or absence of lymph nodes dissection. The sample size was calculated by using the WHO sample size calculator with psower of test (1-β)=80%, level of significance (α)=5%. The difference in the mean hospital stays in groups ligate and group Harmonic Scalpel was 2.18+0.72 and compared to 3.41+1.12 [11]. The sample size was calculated to be 30+30=60 patients. To adapt it to the circumstances, the non-probability purposive sampling method was tweaked. Those patients who were undergoing lobectomy or total thyroidectomy were included in this study. Those patients having complicated comorbidity or autoimmune disease, patient with Hepatitis B and C positive along with the patient with alcoholic abuse and pregnant ladies were excluded from the study. Patients in group A underwent conventional thyroidectomy performed (inferior middle and superior were tied using silk sutures3/0, and all other vessels were sutured by 4/0 or electro cauterized) and patients in group B were underwent thyroidectomy with harmonic scalpel ligated all thyroid vessels. A generator, a hand piece, and a blade make up the harmonic scalpel arrangement. A piezoelectric crystal stack, compressed between two metal cylinders, serves as the ultrasonic transducer in the hand piece. Mounting the transducer to the blade allows it to be securely fastened. A microprocessor controls the 110-volt generator, which is a high-frequency switching power source, and pulses AC current to the transducer in the hand piece. The transducer may vibrate at 55.5 kHz, its natural harmonic frequency, thanks to this current. The blade that is most commonly utilized in otolaryngological operations resembles a curved paddle. It has a rough outside radius for captive coagulating and a sharp inner beveled edge for cutting. A well-structured questionnaire was used for recording between 6.1-18%g surgery duration, volume of drainage in 24 hours of surgery, hospital stay duration, drain placement duration, post-operative hypocalcaemia RLN paralysis, and blood loss of individual patient. Post-operative hypocalcaemia was only noted in those patients who were receiving total thyroidectomy. Statistical analysis was performed by using SPSS version 26.0. Chi-square was applied to compare the following variables: time of operation, intraoperative blood loss in milliliters, volume of fluid drainage in milliliters, and number of days spent in the hospital. Student's t-test and the $\chi 2$-test were used to analyzes the results. Difference was considered as significant by considering p-value <0.05.

RESULTS

There were 78.3% females as compared to the males 21.6%. Forty cases of malignant and 20 benign cases were enrolled and divided equally in harmonic scalpel (HS) and conventional surgery (CS) group. Similarly, 30% of the participants in HS group underwent total thyroidectomy whereas 43% of the patients in CS group underwent total thyroidectomy (Table 1).

Table 1: Demographic Variables in the HS and CS Groups (n=60)

Variables	HS N (%) / Mean ± SD	CS N (%) / Mean ± SD
Gender		
Female	24 (80%)	23 (76.7%)
Male	6 (20%)	7 (23.3%)
Age (Years)	51.2 ± 10.79	56.9 ± 12.79
BMI (Kg/m^2)	22.9 ± 3.38	24.1 ± 3.89
Disease Nature		
Malignancy	20 (66.7%)	20 (66.7%)
Benign	10 (33.3%)	10 (33.3%)
Surgery Extent		
Partial Thyroidectomy	21 (70%)	17 (56.7%)
Total Thyroidectomy	9 (30%)	13 (43.3%)

Less operation time was taken in surgery performed by harmonic scalpel as compared to conventional surgery. Significant difference was observed in intra-operative blood loss in study group. Only 40ml blood was lost during HS whereas 124ml blood was lost during CS group. Overall blood drainage volume was also very less in HS group as compared to CS. No difference in hospital stay duration was observed in both study groups (Table 2).

Table 2: Post-Operative Surgical Complications in Study Groups

Variables	Harmonic Scalpel Mean ± SD	Conventional Surgery Mean ± SD	p-Value
Operation Time in Minutes	95.3 ± 18.4	112.2 ± 21.0	0.045
Intraoperative Blood Loss (mL)	40.1 ± 32.7	124.8 ± 39.6	0.055
Gender			
First 24 Hours Post-Surgery	54.4 ± 24.5	51 ± 22.7	0.041
Overall volume	119 ± 87.8	178 ± 91.6	0.049
Duration of drain placement (Days)	3 ± 1.5	4 ± 1.2	0.82
Hospital duration (Days)	3 ± 1.7	3 ± 1.4	0.61

Post-operative surgical complications were also assessed in present study. No significant variation was observed in terms of post-operative complications in either of the study group (Table 3).

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Table 3: Postoperative Surgical Complications Between the HS and CS Groups

Variables	HC N (%)	CS N (%)	p-Value
Complications	3 (10%)	4 (13.3%)	0.751
RLN Paralysis			
Temporary	2 (6.6%)	2 (6.6%)	0.652
Permanent	-	-	-
Hypocalcemia			
Temporary	2 (6.6%)	2 (6.6%)	0.652
Permanent	-	-	-
Hemorrhage Requiring Surgery	-	-	-
Surgical-Site Infection	-	-	-

DISCUSSION

Thyroidectomy is a routine surgical procedure which can be done through various ways. Conventional clamp/tie techniques are still being employed, however technological advancement is now shifting the trend towards harmonic scalpel surgery. Various adverse effects are associated with conventional procedure such as drainage volume, long procedure time and post-operative bleeding is appeared to be the major concern [12-14]. In the present study, harmonic scalpel surgery showed better outcome in shortening the procedure duration during thyroidectomy in contrast to conventional protocols. This might be attributable to the reason that harmonic scalpel helps in coagulation, detachment and dissection of tissue in a continuous-operation without need of changing instruments. Another important parameter that should be considered is recurrent laryngeal paralysis. It has been proven that lesser chances of RLN paralysis was associated with harmonic scalpel surgery [15-18]. However, in present study, RLN paralysis was not observed in both study groups. Shorter surgical duration minimizes the risk and chances of infections associated with surgeries. It helps in early hospital discharge and accelerates patient recovery process. Shorter surgical duration also linked with cost effectiveness of the procedure [19, 20]. Present study also highlights that shorter duration was observed in harmonic scalpel group as compared to the other group. Few limitations are also associated with this study. Small sample size and inclusion of both benign and malignant diseases might influence the study outcomes.

CONCLUSIONS

Harmonic scalpel thyroidectomy appeared to be the most reliable and feasible method as compared to conventional surgery protocol in relevance to intra-operative blood loss, surgery duration, total volume drainage. Post-operative complication rate of harmonic scalpel was similar to conventional method.

Authors Contribution

Conceptualization: DA
Methodology: DA
Formal analysis: MAK
Writing, review and editing: MN, AN, AHK, KM, RHU

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Acute Biliary Stone-Induced Pancreatitis: The Outcomes of Early vs. Delayed Laparoscopic Cholecystectomy

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ABSTRACT

Gallstones often lead to biliary pancreatitis. While the majority of individuals may only have minor symptoms, a small percentage (around 20%) will develop severe pancreatitis, which can lead to catastrophic problems if it occurs again. **Objective:** To determine patients who have acute pancreatitis caused by biliary stones and evaluate the results of laparoscopic cholecystectomy performed early versus delayed. **Methods:** Total 390 patients with acute biliary stone-induced pancreatitis were presented in this study. After getting informed written consent detailed demographics of enrolled cases were recorded. In the group I, laparoscopic cholecystectomy was done within 72 hours; in the group II, it was done later after 72hours. Post-operative outcomes were compared by using t-test and chi square test among both groups. **Results:** Among all, 216 (55.4%) were males and 174 (44.6%) were females. Majority of the cases 140 (35.9%) had age 41-50 years. Most common complication was abdomen pain in 340 (87.2%) cases. Compared to delayed surgery, early laparoscopic cholecystectomy had a lesser complication rate ($p<0.04$), a shorter inpatient stay ($p<0.003$), and a faster recovery time. The mortality rates of the two groups were comparable ($p=0.001$). Less recurrence rate was experienced with early laparoscopic cholecystectomy ($p<0.002$). **Conclusions:** Compared to a late cholecystectomy, an early one greatly reduces the likelihood of postoperative complications, recurrent biliary events, the length of operation, and the length of time the patient must remain in the hospital for treatment of acute biliary pancreatitis.

INTRODUCTION

One of the most prevalent gastrointestinal disorders requiring hospitalization globally is acute pancreatitis. One common cause of acute pancreatitis is alcohol consumption or gallstones. The prevalence of gallstones ranges from 10% to 20% of the population. The risk of biliary pancreatitis is 14–35 times greater in males and 12–25 times higher in women [1-3]. After reviewing the causes, symptoms, and outcomes of acute pancreatitis, researchers have concluded that biliary pancreatitis is far worse than alcoholic acute pancreatitis. The condition is modest in 80% of people presenting with biliary pancreatitis, nevertheless. In order to reduce the risk of gallstone-related complications, same-admission cholecystectomy is performed after hydration and pain management are administered as the first lines of treatment for biliary pancreatitis [4]. A major worry with post-discharge cholecystectomy is the possibility of recurrence, which has been documented in as many as 63% of patients in the scientific literature. There is currently no substitute for laparoscopic cholecystectomy when it comes to treating gallstone pancreatitis. Reports indicate that the likelihood of recurrence without cholecystectomy

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might reach 30%, and there is an accompanying rise in healthcare expenses [5]. The best time to have a cholecystectomy is still up for dispute, however some organizations recommend doing it early to reduce the likelihood of recurrence. On the other hand, there are those who believe that, because of the acute inflammatory condition that is characteristic of early pancreatitis, the risks of complications from surgery are higher if performed too soon [6]. Late cholecystectomy is no longer recommended by the majority of worldwide organizations. "Early" might mean different things to different people. It is recommended by the International Society of Pancreatology to do a cholecystectomy with index admission. Along with index admission, the American Gastroenterology Society suggests cholecystectomy [6]. The incidence of cholecystectomy at index admission is still quite low, with only around 10% of patients reporting obtaining definitive therapy within the first two weeks, even though these recommendations have been made [7]. Early cholecystectomy is more common in Latin America than any other location in the world. Almost 60% of patients admitted with biliary pancreatitis in Latin America had the procedure done during their first visit [8]. Almost half of all patients in North America and Europe had cholecystectomy procedures performed during initial hospitalization, while just a fifth of all patients in India had this procedure done [8]. The removal of the gallbladder is recommended by many recent nonrandomized trials that were released at the same time as the index admission for ABP. According to [9, 10], the reasoning behind doing the cholecystectomy during the same hospitalization rather than at intervals is that it reduces the occurrence of biliary events like biliary colic, symptomatic choledocholithiasis, acute cholecystitis, recurrent biliary pancreatitis, and cholecystitis. According to Ito et al., recurrence is more likely to occur between two and four weeks following discharge. Recurrent acute pancreatitis occurred in 13.4% of patients who did not get cholecystectomy on their first hospitalization. Half of the recurrences were within four weeks of discharge, 12.5% within one week, and 31.3% within two weeks. The eleventh The severity and potential mortality of biliary pancreatitis episodes make this discovery all the more important. However, cholecystectomy performed simultaneously with admission is still uncommon, despite the existence of such recommendations and literature [11]. One research found that just 14.7% of the more than 25,000 patients treated to English hospitals for acute gallstone-related illness actually had a cholecystectomy performed during their stay. Half of the individuals treated for ABP in another US research also had cholecystectomy performed during admission. Initial cholecystectomy for ABP was less common among patients referred to facilities with lower cholecystectomy volumes or greater acute pancreatitis admission volumes per year. [12, 13] The median time between hospital release and cholecystectomy was six weeks, according to a Dutch countrywide research that found 75% of patients treated with moderate biliary pancreatitis had the procedure done [12]. Fearing for their patients' safety and the effectiveness of an early cholecystectomy, most experts opt for interval cholecystectomy instead. Maybe it's because there isn't enough data from randomized controlled studies that look at the long-term effects. Potential barriers to early cholecystectomy compliance include shortages of surgeons, operating room time, and postoperative critical care unit beds, all of which are resources that hospitals struggle to meet. It should be noted that a considerable number of patients in this group have postoperative nausea and vomiting. [13, 14]. Whether a laparoscopic cholecystectomy performed late would be more beneficial for certain individuals than an early procedure is still up for debate. The local community also does not provide enough information on the procedure's outcomes and their effects on patients.

Patients undergoing laparoscopic cholecystectomy for acute pancreatitis were the focus of the current study, which aimed to evaluate the clinical impact.

METHODS

This comparative analytical study was conducted at Lahore General Hospital, Lahore after getting approval from the ethical review board with reference number 340/23. The sample size was calculated by using the recurrence of biliary pancreatitis in early and delayed Laparoscopic Cholecystectomy was 0% Vs 50% with a power of 80% and a 95% confidence interval, with a 10% expected drop-out rate, was 195 in each group [15]. This included all patients over the age of 16 who had confirmed lithiasis AP and had a SIRS < 1 either at admission or at the 48th hour, a CTSI (CT severity score) ≤ 3, and a CRP. Exclusion criteria included cholangitis linked to AP, severe AP, and significant comorbidities (ASA 4 and 5). After getting informed written consent detailed demographics of enrolled cases were recorded. The diagnosis of gallstone pancreatitis was made possible by the technique employed by our institution. Bile duct stones were detected using an abdominal ultrasound examination. Researchers included patients with epigastric discomfort and cholelithiasis on ultrasound imaging after doing clinical evaluations. This comprised cases with and without common bile duct (CBD) stones. Individuals who fulfilled the inclusion criteria and had mild to moderate biliary AP were then divided into two groups: In the group I, laparoscopic cholecystectomy was done within 72 hours; in the group II, it was done later after 72hours. Cholecystectomy with Intraoperative Cholecystokinin(IOC) was carried out in patients assigned to the early group during the index hospitalization when they were able to accept a regular oral diet, no longer needed narcotic analgesics, and their blood C-reactive protein

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concentration was less than 100 mg/L. Approximately six weeks following the pancreatitis episode, patients in the delayed group had interval cholecystectomy with intraocular pressure (IOC) as an elective procedure following hospital release from the original stay. In most cases, a laparoscopic cholecystectomy was carried out. However, if there were any contraindications, an open cholecystectomy would be conducted instead. Just one consultant hepatobiliary surgeon was involved in every procedure. Proper antibiotic prophylaxis was administered to all patients prior to surgery. The severity of AP (CRP) was determined using the Systemic Inflammatory Response Syndrome Score (SISS), computed tomography images (CTSI), and the strength of the inflammatory reaction. Mortality and recurrence rate were crucial outcomes. Recovery, hospitalization, and postoperative discomfort were secondary outcomes. SPSS version 22.0 was used for statistical analysis; chi-square and t-tests were applied to analyzed data. Continuous variables were presented as Mean ± SD (standard deviation), while categorical variables were conveyed as frequencies and percentages. To compare categorical variables, the Chi-square test was employed. For continuous variables, the independent t-test was conducted, with statistical significance set at $p < 0.05$.

RESULTS

Among all, 216 (55.4%) were males and 174 (44.6%) were females. Majority of the cases 140 (35.9%) had age 41-50 years. Most common complication was abdomen pain in 340 (87.2%) cases. Majority of the cases had ASA1 score. CTSI score was lower in group I as compared to group II (table 1).

Table 1: Demographics of the Included Cases (n=195)

Variables	Group I N (%)	Group II N (%)
Gender		
Male	121 (31.03%)	95 (24.4%)
Female	74 (18.97%)	100 (25.6%)
Age (Years)		
17-30	45 (11.5%)	30 (15.4%)
31-40	40 (10.3%)	50 (12.85)
41-50	80 (20.5%)	70 (17.9%)
>50	30 (15.4%)	45 (11.5%)
Complications		
Abdomen Pain	160 (41.03%)	180 (46.2%)
Fever	5 (1.3%)	4 (1.03%)
Other	30 (7.7%)	11 (2.8%)
ASA Score		
I	130 (33.3%)	140 (35.9%)
II	65 (16.7%)	55 (14.1%)
CTSI		
1	160 (41.03%)	100 (24.4%)
2	35 (8.97%)	95 (25.6%)

Mean operative time in group I was 35.3 minutes and in group II mean time was 43.8 minutes. Compared to delayed surgery, early laparoscopic cholecystectomy had a lesser complication rate ($p<0.004$), a shorter inpatient stay ($p<0.003$), and a faster recovery time (table 2).

Table 2: Operative Time and Post-Surgery Outcomes (n=195)

Variables	Group I N (%)	Group II N (%)	p-Value
Mean Surgery Time (Minutes)	35.3	13.8	0.002
Complication			
Yes	2 (1.03%)	8 (4.1%)	<0.004
No	193 (98.97%)	187 (95.9%)	
Hospital Stay			
<5 Days	170 (87.2%)	35 (17.9%)	<0.03
>5 Days	25 (12.8%)	160 (82.1%)	
Fast Recovery Time			
Yes	186 (95.4%)	120 (61.5%)	<0.005
No	9 (4.6%)	75 (38.5%)	

The mortality rates of the two groups were comparable ($p=0.001$). Less recurrence rate was experienced with early laparoscopic cholecystectomy ($p<0.002$) (table 3).

Table 3: Post-Operative Recurrence and Mortality among Both Groups (n=195)

Variables	Group I N (%)	Group II N (%)	p-Value
Mortality			
Yes	1 (0.5%)	4 (2.04%)	0.001
No	194 (99.5%)	191 (93.96%)	
Recurrence Rate			
Yes	6 (3.1%)	23 (11.8%)	<0.002
No	189 (96.9%)	172 (88.2%)	

DISCUSSION

Biliary pancreatitis is often not severe, and the first line of defense is supportive care. To avoid recurrent pancreatitis and lower readmission rates, cholecystectomy should be performed thereafter [15]. Patients without a cholecystectomy are three to six times more likely to require readmission, and patients with recurring episodes have a greater risk of death and longer hospital stays [16]. For mild biliary pancreatitis, cholecystectomy should be performed during the index hospitalization, according to international standards [17]. While some sources recommend cholecystectomy as soon as possible (within 48 to 72 hours of admission), others recommend waiting a week or until pancreatitis symptoms go away before the procedure [18]. The optimal time to have a cholecystectomy following mild to severe biliary AP has long been debated. The inflammatory effects of the PA are known to the surgeon to be a source of operational problems. From 13% to 44% of patients experience a

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gallstone-related problem while waiting for treatment (cholecystectomy) [19, 20]. A much longer hospital stay (p-value<0.03) is seen in DC. There was no correlation between early cholecystectomy and an increase in the 0.8% morbidity rate that we saw in these patients. None of the patients who had laparoscopic procedures had any sort of conversion. We still consider laparoscopic cholecystectomy as the best option for patients with acute pancreatitis. There is no correlation between an early cholecystectomy and a higher conversion rate. There seems to be an increase in operational complications in patients who have delayed cholecystectomy [17-20]. In this study, biliary events were avoided in patients who had an early cholecystectomy at 72nd hour. There is no rise in the time required for the operation or the frequency of laparotomy conversions. In all of the documented cases, the only cause of death was a hemorrhagic stroke (DC). Findings from prior research were consistent with the. [21, 22]. There is a larger risk of biliary problems after late cholecystectomy, according to all of the published research. Despite being compelled to quit, Da Costa et al [19]. discovered the highest percentage in the literature at 44%. A 33.3% (p=0.02) increase in the incidence of biliary recurrence was seen in a large prospective and randomized multicenter trial (Da Costa) that showed delaying cholecystectomy. Even though the sample size was limited, a randomized prospective trial in Sweden reached the same result [20, 21]. Early laparoscopic cholecystectomy was associated with a longer operation time and a shorter hospital stay, according to an analysis of four clinical trials by Siddiqui et al. [22]. However, there was no statistically significant difference in conversion rates between the two groups. A best-evidence topic reviewed 92 articles, including systematic reviews, randomized control trials, prospective controlled studies, and retrospective cohort studies, and found that early laparoscopic cholecystectomy over acute cholecystitis is beneficial in terms of hospital stay length without increases in morbidity or mortality [23]. The mortality rates of the two groups were comparable (p=0.001). Less recurrence rate was experienced with early laparoscopic cholecystectomy (p<0.002). These results were in line with the previous researches [24, 25]. It took the time to insert the first port and close the skin incision in order to determine how long the procedure took. Significantly lengthier operation times were seen in the late group when contrasted with the early group. Possible explanations for this variation include the existence of thick adhesions in the latter group, gallbladder-related problems, and repeated biliary events, all of which significantly complicated the biliary architecture. Attack frequency increased and presentation times were longer for patients in this group because treatment was postponed. Consistent with previous research, this study found that the late group had a longer duration than the early group [26, 27]. These results are consistent with those of the previous research, which found that the late group had more postoperative problems. For mild to severe pancreatitis, this suggests that early LC considerably lessens postoperative complications when contrasted with late LC [26-28].

CONCLUSIONS

Compared to a late cholecystectomy, an early one greatly reduces the likelihood of postoperative complications, recurrent biliary events, the length of operation, and the length of time the patient must remain in the hospital for treatment of acute biliary pancreatitis.

Authors Contribution

Conceptualization: MSA, SM, MK
Methodology: MR
Formal analysis: BH
Writing, review and editing: HMI, MK, RHU

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Assessment of Invitro Antibacterial Activity of *Moringa oléifera* and *Murraya koenigii* Leaf Extracts Against Clinically Important Bacteria

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ABSTRACT

Resistant gram-negative bacteria are increasing in prevalence, causing health concerns, particularly in hospitals and intensive care units, leading to increased healthcare expenses due to sickness, and death. One frequent bacterial infection that affects many people is Urinary Tract Infection (UTI), both men and women, with women. **Objective:** This study was conducted to assess the anti-microbial activity of leaf extracts from *Murraya Koenigii* (Mk) and *Moringa oleifera* (Mo) against multidrug-resistant Klebsiella pneumoniae (MDR-Kp) in vitro. **Methods:** It was a Preclinical in-vitro study, carried out at Ziauddin University from December 2022 to May 2023. Using a rotary evaporator, MO and MK leaves were extracted. Utilizing the Agar well diffusion assay and the broth dilution assay, the antibacterial activity of both plants were assessed. **Results:** For both extracts, concentrations ranging from 7.812 mg/ml to 500 mg/ml were prepared in 10% Dimethyl Sulfoxide (DMSO). Minimum Inhibitory Concentration (MIC) of *Murraya Koenigii* leaf extract was found to be 15mg/ml against MDR-Kp. *Moringa oleifera* leaf extract did not exhibit any discernible antibacterial action against MDR-Kp at any of the tested concentrations. **Conclusions:** While MOLE did not impede the growth of MDR-Kp strains at the tested doses, MKLE hindered the growth of MDR-Kp strains at 15 mg/ml(MIC).

INTRODUCTION

Resistant gram-negative bacteria are increasing in prevalence, causing health concerns, particularly in hospitals and intensive care units, leading to increased healthcare expenses due to sickness, and death. One frequent bacterial infection that affects many people is Urinary Tract Infection (UTI), both men and women, with women being more likely to develop it due to the easier penetration of microorganisms through the shorter female urethra [1]. The traditional warning signs and symptoms of UTI include discomfort at the cost vertebral angle, dysuria, and frequent or urgent urination [2]. It has been documented that there have been 15 billion cases of UTIs reported worldwide [3]. *Escherichia coli* and *Klebsiella pneumoniae* are the notable pathogens causing resistant UTIs globally, leading to kidney damage, scarring, and failure if untreated [4]. With a percentage of 73.7%, *Escherichia coli* is by far the most dominant organism that causes UTIs, followed by *Klebsiella pneumoniae* (30%), *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [5]. UTI often occurs due to the reverse movement of bacteria into the bladder, with *Escherichia coli* and *Klebsiella pneumoniae* being more infectious and resistant to complement due to its production of cytotoxin. Unique physical features of the gram negative organisms include type 1 fimbriae, which stick to urothelial cells and travel upstream with the help of

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their flagella [6]. The management of UTI includes treatment with broad-spectrum antibiotics including nitrofurantoin, fosfomycin, trimethoprim-sulfamethoxazole, and quinolones [7, 8]. However, the misuse of antibiotics leads to development of Antibiotic Resistance Worldwide (ABR), causing the strains that are resistant to several medications to arise (MDR strains) [8]. MDR bacteria show resistance to penicillin and cephalosporin as well as to non-β-lactam antibiotics such as fluoroquinolones, trimethoprim-Sulfamethoxazole or aminoglycosides. The frequency of strains of MDR-Ec and MDR-Kp has increased; however, their patterns of their antimicrobial susceptibility vary from country to country [9]. Additionally, research indicates that MDR-Ec and Kp is becoming alarmingly more common worldwide, especially in South Asia [10]. The application of broad spectrum antibiotics has been limited due to resistance mechanisms produced by MDR-Ec and MDR-Kp [11]. Since the organisms have developed resistance to the different antibiotics, it is important to identify new treatment choices that are less expensive, more effective, tolerable, and less likely to cause side effects. Numerous beneficial properties, including antibacterial, antifungal, antipyretic, anti-inflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol-lowering, antioxidant, anti-diabetic, hepatoprotective, anticancer, cardiac and circulatory stimulants, have been discovered in *Moringa oleifera* (Mo) leaves [12]. A 2024 study revealed that employing curry leaf extract inhibited *carbapenem-resistant streptococcus pnemoniae*, which provides compelling evidence for further research into the antibacterial activities of curry leaves against MDR-Kp [13]. According to reports, *Murraya koenigii* (Mk) leaves have similar benefits, including the ability to heal wounds, prevent cancer, reduce inflammation, act as an antioxidant, fight infection, fight fungal growth, lower blood pressure, hepatoprotective against hypercholesterolemia, and fight diabetes [14, 15]. This investigation was carried out to assess the antibacterial activity of two consumable leaves over MDR-Kp, taking into consideration their previously reported antibacterial activities against a number of pathogens, in light of their known antibacterial characteristics against a variety of organisms.

METHODS

At Ziauddin University, an in-vitro pre-clinical experimental investigation was conducted between December 2022 and May 2023.The urine used in the experiment was taken from the Microbiology Laboratory at Ziauddin Hospital. In order to separate the bacteria MDR-*Kp* from the urine, these samples underwent further processing. A rotary evaporator was used to extract plants. The broth dilution assay and Agar well diffusion methods were employed in estimating the minimum inhibitory concentration. Included were UTI samples that demonstrated MDR-*Kp* growth. Agar plates on which other species were growing were excluded. The Ziauddin University Ethics Review Committee granted Waiver for the research and issued study approval, Reference Code: 5510622HAPHA [16]. Assortment and verification of plant: Fresh MK and MO leaves were purchased from Karachi's retail market. The plants were washed and then left in a shaded spot for two weeks to air dry. Plant authentication was performed by a botanist from the University of Karachi, department of Herbarium. Voucher number 96826 and 96827, were assigned to MK and MO specimens respectively. MO Leaf and MK Leaf Extract Preparation: Both plant leaves, weighing 500 g, were finely pulverized by machine. By immersing the 50g of powder residue in 500 mL of 80% ethanol in a stoppered flask, the residue was extracted. After that, the mixture was passed through Whatman® filter paper, Grade 1, the solvent was removed with a rotary evaporator (at 40°C to 50°C for 5 to 20 minutes duration), and the suspension was kept in airtight bottles. The extraction process was carried out for 48 hours with intermittent pulsating. To create a stock solution, plant extracts (MOLE and MKLE) were dissolved in 10% Dimethyl Sulfoxide (DMSO). Isolation of Bacteria from Clinical Specimens: Gram stain, Microbiological examination, and biochemical tests were used to identify the isolates. Identification of MDR *K-Pneumoniae* (*Kp*) By Modified Kirby-Bauer Disk Diffusion Test: Using antibiotic discs that contained 10 µg of ampicillin, 5 µg of ciprofloxacin, 300 µg of nitrofurantoin, 30 µg of cefuroxime, and 10 µg of gentamicin, isolates were found to be multidrug resistant if they demonstrated resistance to at least one antibiotic in at least three distinct antibiotic groups. Furthermore, Mueller Hinton agar plates were swabbed with the bacterial colonies, and they were cultured at 37ºC for 24 hours [17, 18]. Broth Dilution Assay: The test organisms' MIC values for MOLE and MKLE were determined (2018 CLSI). In order to reconstitute the MOLE and MKLE standard solutions (200 mg/ml), 12.5 ml of distilled water and 2.5 g of leaf extract were mixed [19]. To achieve different concentrations of the stock, the obtained extract (MOLE and MKLE separately) remained serially dilute in MH broth (Mueller Hinton). Using stock solutions in three separate test tubes, three strengths of extracts were prepared, resulting in a 2.5 ml broth with extract concentrations of 500 mg/ml, 250 mg/ml, and 125 mg/ml. The vial held 0.1 mL of the inoculum for each organism used in the operation. The negative control was the MH broth. After being correctly labeled and cultured for 24 hours at 37°C, the bottles were examined for any obvious change in color. The lowest concentration at which the test organisms were unable to grow was determined to be the MIC [20]. The experiment was run in triplicates. The information was

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given as to whether turbidity was present in the falcon tubes or not. Agar Well Diffusion Method: This test was used to check MOLE and MKLE antibacterial activity against MDR-*Kp*. On the surface of MHA plates, the fresh inoculums of MDR bacterial isolates were evenly distributed in comparison with 0.5 McFarland standard. Wells with a diameter of 7 mm were punched into the inoculation plates using a sterile cork borer. A micropipette was used to transfer 50µl of various MOLE and MKLE concentrations (500, 250, 125, 62.5, 31.25, 15.625, 7.81 mg/ml) into the labeled wells. The negative control used in the experiment was 10% DMSO. The plates were incubated at 37°C for 2 days after the extract was allowed to diffuse for 15 minutes. Afterwards, the zone of inhibition, presence or absence was assessed after two days. Using a diameter scale, the zones of inhibition for MKLE and MOLE were determined [21]. Using SPSS version 22.0, data analysis was carried out. ZOI's mean and standard deviation were computed. ZOIs between several groups were compared using the ANOVA test. At the 95% confidence level, a P-value of less than 0.05 was regarded as significant.

RESULTS

A) Broth dilution test: Findings for the broth dilution test for MOLE and MKLE for MDR-Kp were shown in Figs. 1 and 2. The experiment was run in triplicate. For every plant extract, three different concentrations (500 mg/ml, 250 mg/ml, and 125 mg/ml) were assessed. MOLE: The concentration of MOLE in the falcon tubes H1, H2, and H3 was 500 mg/ml; the concentration in tubes I1 I2, and I3 was 250 mg/ml; and the concentration in tubes J1, J2, and J3 was 125 mg/ml. MKLE: The concentrations of MKLE in Falcon tubes C1, C2, and C3 were 500 mg/ml, D1, D2, and D3 were 250 mg/ml, and E1, E2, and E3 were 125 mg/ml. The three tubes for MOLE (H, I, and J) and MKLE (C, D, and E) have been shown to have a murky color, demonstrating unfavorable outcomes. Moreover, the negative control group displayed no effect. B) Agar Well Diffusion Method: The results of the Agar well diffusion assay were shown in Fig. 3 and 4. The MDR-Kp strains were tested at seven different concentrations: 7.81, 15.62, 31.25, 62.5, 125, 250, and 500 mg/ml for both extracts in seven labeled wells; DMSO was used as a negative control in the eighth well. MKLE inhibit the growth of MDR-Kp at almost all tested concentrations. The MIC was found to be 15.625mg/ml. Antibacterial activity was absent in the negative control. The Experiment was run in triplicates. In figure 4 it was depicted that MOLE did not inhibit the growth of MDR-Kp at any tested concentration. Label Tubes H, I and J: All Tubes Were Turbid Showing No Inhibitory Activity.

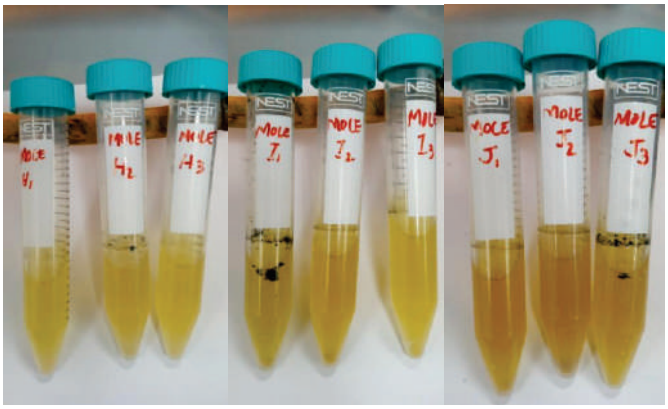

Figure 1: Result of Antibacterial Activity of Mole against MDR-Kp

Label Tubes C, D and E: All Tubes Were Turbid Showing No Inhibitory Activity

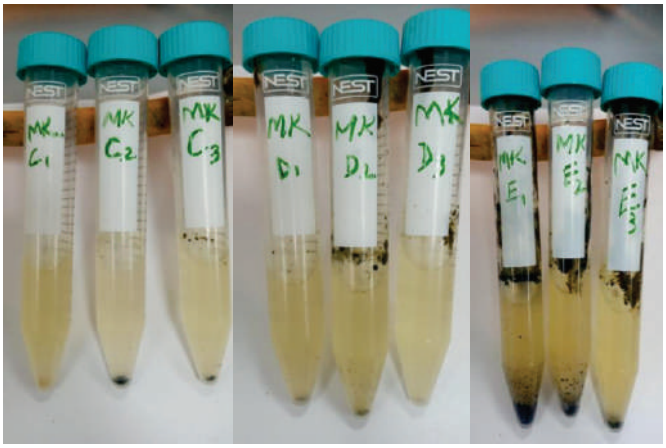

Figure 2: Result of Antibacterial Activity of Mkle against MDR-Kp

Various ZOIs were calculated using a diameter scale as per CLSI standards as follows:

Label 1 (500 mg/ml): Zone of inhibition of 18.3mm
Label 2 (250 mg/ml): Zone of inhibition of 17.3mm.
Label 3 (125 mg/ml): Zone of inhibition of 17.6mm.
Label 4 (62.5 mg/ml): Zone of inhibition of 15.3mm.
Label 5 (15.625 mg/ml): Zone of inhibition of 11.6mm.
Label 6 (lower concentrations): No inhibitory effects.
Label C (control group): No inhibitory effects.

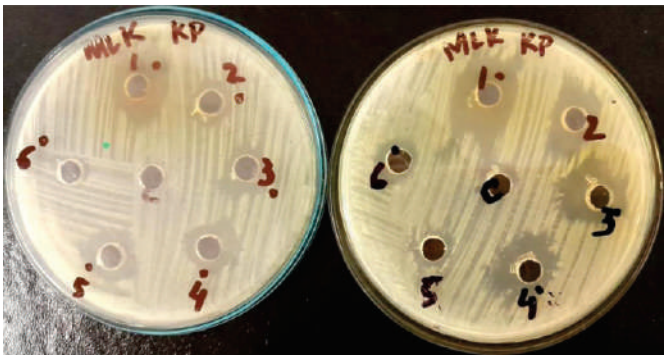

Figure 3: ZOI of Murraya Koenigii Leaf Extract (Mkle) For Mdr K.Pneumoniae –Agar Well Diffusion Using Mh Agar Plate

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ZOIs were calculated using a diameter scale as per CLSI standards as follows:
Label 1(500 mg/ml): No inhibitory effects.
Label 2(250 mg/ml): No inhibitory effects.
Label 3(125 mg/ml): No inhibitory effects..
Label 4(62.5 mg/ml): No inhibitory effects.
Label 5(15.625 mg/ml): No inhibitory effects.
Label 6(lower concentrations): No inhibitory effects.
Label C(control group): No inhibitory effects.

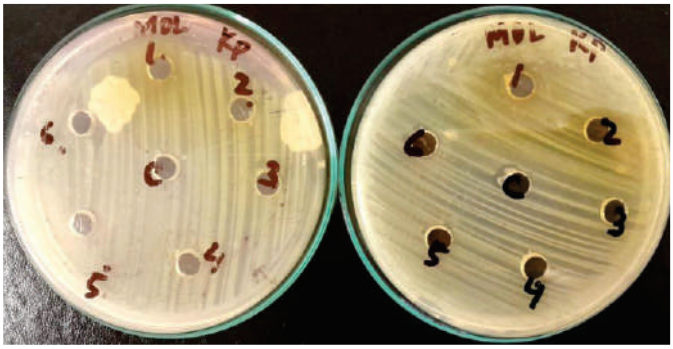

Figure 4: ZOI of Moringa Oleifera Leaf Extract (Mole) For MDR K.Pneumoniae –Agar Well Diffusion Using Mh Agar Plate

Table 1 illustrated the dose-dependent bactericidal activity of MKLE against MDR-Kp. This study's maximum dose, 500 mg/ml, resulted in an incredibly outstanding mean zone of inhibition of 18.3 mm. The mean ZOI dropped to 17.3 mm at 250 mg/ml. This drop further suggests that MKLE's potency may be reduced when the concentration was lowered from 125 to 15 mg/ml, even though it still shows antibacterial action. At doses below 15 mg/ml, no inhibitory potential was seen, indicating the absence of ZOIs. Because MKLE's antibacterial efficacy was concentration-dependent, employing larger doses has remained crucial for achieving the optimum outcomes.

Table 1: ZOI of MKLE for MDR-Klebsiella pneumoniae –Agar Well Diffusion

S. No.	Concentration of Herb (mg/mL)	ZOI (mm) (Mean ± SD)	p-value*
1	500	18.3 ± 0.57	*0.001
2	250	17.3 ± 0.57	
3	125	17.6 ± 0.57	
4	62.5	15.3 ± 0.57	
5	31.25	12.6 ± 2.08	
6	15.625 (MIC)	11.6 ± 0.57	
7	7.8125	-	
8	Control	-	

*Comparison of ZOIs of MKLE against MDR-*Klebsiella pneumoniae* at various concentrations by ANOVA

DISCUSSION

The field of medicine has confirmed that plants could serve as the basis for drugs that prevent and cure illnesses in people. Antimicrobial resistance has been identified by the WHO as a global fitness safety problem for which politicians and the general public must take comprehensive action. Surprisingly, because of their numerous issues, especially in developing nations like Pakistan, MDR pathogens were currently regarded as a general warning signal [22]. Considering the information above, it was necessary to investigate novel antimicrobial compounds obtained from healing flora in order to combat the growing threat posed by these harmful bacteria. In this study, two edible plants, MO and MK, were used to test it against MDR-Kp [23]. Ethanolic plant extracts were tested in vitro for their antibacterial efficacy against MDR Kp, which was known to cause UTI and other infections in humans. Out of the two extracts examined for this experiment, only MKLE exhibited antimicrobial action against MDR-Kp, while MOLE failed to demonstrate antibacterial activity against MDR-Kp. In line with this research, another investigation discovered that Moringa has negligible or nonexistent antimicrobial properties for MDR-Kp [24]. In this study MOLE was unresponsive to sensitivity for Kp, which was in accordance with the other studies who also reported no sensitivity of MOLE for Kp using broth dilution assay [24]. A study carried out in Saudi Arabia reported positive ZOIs ranging between 2 and 3 mm by MOLE using concentrations between (45 to 200 mg/ml) for MDR-Kp, which was in contrasts with this results. This study highlights that MDR-Kp strains that it tested may have developed resistance for the MOLE [25]. Another study Soulaimani B *et al.*, in 2020 negates this finding and supports the exceptional antibacterial activity of MOLE against MDR-Kp. According to literature many reasons may have been responsible for the inactivity of the MOLE, including the nature of solvent used and bacterial resistance. It has been discovered that bacteria that were resistant to many drugs do so by means of various changes and modifications in their structure [22, 26]. Since well-evolved resistance genes were present, it becomes more challenging to eradicate the expanding bacterial population using herbal extracts [27, 28]. Gram-negative bacteria have a double lipid layer, which increases resistance. Changes to this membrane, such as modifications to its hydrophobic characteristics or changes in its porins, can also increase resistance [25]. Furthermore, the majority of resistant infections, including UTIs, were linked to the formation of biofilm. By acting as a barrier, biofilm shields microorganisms from the effects of antimicrobials. Target genes linked to virulence in gram-negative bacteria another possible explanation for the plant extract potential lack of effectiveness against MDR-Kp could be related to the biofilm-forming Kp (fimH gene and papC gene) found in Kp isolates suffering from urosepsis [26]. Therefore, it was essential to look for possible biofilm impeders with a unique or multimodal mode of action. The establishment of a robust resistant bacteria biofilm may be a contributing factor to the inefficiency of the MOLE against MDR-Kps, in addition to the resistance mechanisms previously highlighted,

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particularly the efflux pumps. Furthermore, microbes have the ability to alter the chemical properties of the active substances in plant extracts, which further lessens their antimicrobial efficacy [23]. A significant amount of ethno medical research would be necessary to compare plant extracts with antimicrobial qualities since regional variables like environment influence the genomic and bodily alterations that occur in plants around the globe. Consequently, as this study also showed, a herb that works for a microbe in a particular area of the biosphere might be in-effective in different area. It was strongly advised to combine these plant extracts with additional plants and antibiotics to create a new ecological medication in order to combat such a resistant bacterium. MKLE was shown to be efficacious against MDR-Kp in this research at all tested concentrations (15 to 500 mg/ml), demonstrating the wide ZOIs between 11mm to 18mm. This investigation yielded a MIC of 15.625 mg/ml for MKLE against MDR Kp, which was consistent with previous investigations on the MDR-Kp employing other plant extracts. The ethyl acetate extract of MK leaves gave MIC value between 15.63-1000 µg/mL against *S. aureus, E. coli* and other bacteria [25]. MK Leaves contain a pharmacologically significant amount of alkaloids (such as mahanine, girinimbine, and koenimbine), flavonoids (such as quercetin, rutin, catechin, and myricetin), triterpenoid (mahanimbine), and phenolic compounds (such as caffeic acid, ferulic acid, and pcoumaric acid). The most common mechanism of antimicrobial action reported by these phytochemicals was the disruption of the plasma membranes of the tested bacteria (*Escherichia coli, Staphylococcus aureus*) that it assumes might have been responsible for the activity of MKLE against MDR-Kp. Since MDR pathogenic microorganisms because UTIs, this research has demonstrated that novel MKLE was effective against MDR-Kp and has provided a preview of upcoming future therapeutic improvements. Therefore, further studies investigating the mechanism of action behind its activity should be carried out to endorse its antibacterial potential.

CONCLUSIONS

MKLE showed antibacterial potential against MDR-Kp and inhibited its growth at 15 mg/ml concentration however, at all tested concentrations, MOLE failed to demonstrate the ability to impede the growth of MDR-Kp strains.

Authors Contribution

Conceptualization: HA, ZI, MOI

Methodology: HA, ZI, AA, MOI

Formal analysis: HUR, SM

Writing, review and editing: HA, ZI, AA, MOI, HUR, SM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Detection of In-Vitro Antibacterial Activity of *Tinospora cordifolia* Leaf Extracts against Multidrug Resistant- *Staphylococcus aureus* Isolated from Diabetic Foot Infections

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ABSTRACT

The manifestations of diabetes are always a great challenge to the medical practitioners and one of its challenging ones are the Diabetic Foot Infection (DFI). There are multiple ways of managing this condition such as using antibiotics to eliminate bacteria and boosting the patient's intrinsic factors, for example, through blood glucose optimization. DFIs are difficult to treat nowadays because of antibiotic resistance; as a result, scientists have turned to medicinal plants for finding drugs against Multi-Drug Resistant(MDR) bacterial strains. *Tinospora cordifolia* is a promising plant with untapped wealth of chemical compounds with high therapeutic potential. These biologically active metabolites work together through different mechanisms causing antibacterial action against the MDR strains. **Objective:** To assess the antibacterial potential of Tinospora cordifolia Leaf Extract (*Tc*LE) against MDR-*Staphylococcus aureus* isolated from pus samples of patients with DFIs. **Methods:** In-vitro experimental study conducted in Ziauddin University from December 2022 to September 2023. Extraction of *Tc*LE was done using a rotary evaporator. The antibacterial activity of *Tc*LE was evaluated by the Agar well diffusion assay. **Results:** Eight different doses were prepared in 10% DMSO using TC's ethanolic leaf extracts. Growth of MDR-*Staphylococcus aureus* strain was inhibited by *Tc*LE at the tested concentration of 250 mg/ml, which was the MIC (the lowest concentration of *Tc*LE which suppressed the growth of MDR-*Staphylococcus aureus* strains). **Conclusions:** *Tc*LE showed antibacterial activity against MDR-*Staphylococcus aureus*, thus establishing it as a potential lead compound source of anti-staphylococci drugs.

INTRODUCTION

Antibiotic resistance is an evolving health problem aggravated by reckless and indiscriminate use of antibiotics. It has resulted in endless struggle between bacteria and new drugs. The microorganisms are now resistant to many drugs. The adverse effects which are the result of this widespread antibiotic resistance are terrifying [1]. The majority of antibiotic resistance mechanisms include enzymatic breakdown or modification, restriction of antibiotic entry into cells to prevent antibiotic accumulation, changes to metabolic pathways, modification of drug-binding sites such as ribosomes to decrease drug efficacy and increased antibiotic efflux from cells. Moreover, bacteria form surface-bound communities called biofilms that make the antibiotics difficult to get inside the bacterial cells. An increasing number of previously treatable diseases have

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become challenging to treat due to multi drug resistance, leading to major clinical challenges. Antibiotics may have more severe adverse effects. This attracts the attention to search for new natural sources of antibacterial agents [2]. The resistant bacterial strains have made the treatment of complications linked with diabetes very difficult. It is estimated that by 2045, about one person in ten shall have diabetes worldwide. As a result of the increased cases of diabetes mellitus in the world, cases of diabetic foot infections are also on the rise. Any infection in the tissue beneath the malleolus in a diabetic person is referred to as a Diabetes Foot Infection, or DFI [3]. 15% of the world's population is suffering from diabetes mellitus, a chronic metabolic disorder, while 19–34% of those who have some form of diabetes, have diabetic foot ulcers. It is estimated that every year, between 9.1 and 26.1 million people will develop DFIs worldwide, putting a heavy burden on any healthcare system because of the recurrent nature of hospitalization and poor healing [4]. *Tinospora cordifolia*, or *TC*, has its place under ayurvedic medicine traditionally. On classification, *TC* falls under the subclass of the larger Angiosperm genus and the family Menispermaceae. Geographically, they are located in the tropical and subtropical regions of Australia, Asia, and Africa. However, the use of *TC* in modern medicine is common for treating rheumatoid arthritis, nausea, headache discomfort, throat infections, flu, diarrhea, stomach ulcers, asthma etc. Anti-stress, antiulcer, anticancer and antitumor actions are a few examples of ethnomedical qualities of *TC*. Various in-vitro studies on agar well diffusion and broth microdilution assays were conducted where *Tc*LE extracted in various solvents was tested against a collection of multidrug-resistant bacteria isolates, such as *Acinetobacter baumannii*, MRSA and *Pseudomonas aeruginosa* [5].

The purpose of this study was to evaluate the antibacterial activity of *Tinospora cordifolia* leaves against MDR-Staphylococcus aureus strains isolated from DFIs by Agar well diffusion method, in light of their well-known antibacterial properties. MIC of *Tc*LE against MDR-*Staphylococcus aureus* using varied concentrations of *Tc*LE was also determined by this method.

METHODS

An in-vitro pre-clinical experimental investigation was conducted at Ziauddin University. The MDR-*Staphylococcus aureus* experimental samples were gathered from Ziauddin Hospital's Microbiology Laboratory. A rotary evaporator was used to extract *TC* leaves. The minimum inhibitory concentration, or MIC, was determined using the Agar well diffusion method. DFI pus samples demonstrating MDR-*Staphylococcus aureus* were included. Agar plates containing additional species growing on them were excluded. The approval for the study was obtained by the Ethical Review Committee, Ziauddin University (Reference code # 60710SMPHA). Fresh leaves of *TC* were obtained from a market in Karachi. The plants were first washed and then kept in the shade for around 15 days to get dry. Plant authentication was performed by a botanist at the Herbarium department; University of Karachi. The specimen of *TC* leaves was given voucher number 97677 respectively. 500 g of air-dried *TC* leaves were mechanically ground into fine powder. The 50g of leaf powder was soaked in 80% ethanol (500 mL). The mixture was then filtered and rotary evaporator was used to remove the solvent and the suspension was stored in airtight bottles. The extraction process was carried out for 48 hours with intermittent pulsating. To create a stock solution, *Tc*LE was dissolved in 10% Dimethyl Sulfoxide (DMSO) [6, 7]. Gram staining, microbiological examination on MacConkey, blood agar and biochemical tests (Catalase test, coagulase test) were performed to identify the isolates of MDR- *Staphylococcus aureus* strains [8]. The identities of MDR- *Staphylococcus aureus* strains were established using a Kirby-Bauer disc diffusion test. MH agar was used to plate antibiotic discs and incubation was done at 37 degrees Celsius for 24 hours. The isolates were characterized as multidrug resistant based on the development of resistance to at least 1 antibiotic in 3 or more different antibiotic groups. For *Staphylococcus aureus*, the following antimicrobial discs were used: Penicillin-10 units, Cefoxitin-30 µg, ciprofloxacin-5 µg, and erythromycin-15 µg discs [9].

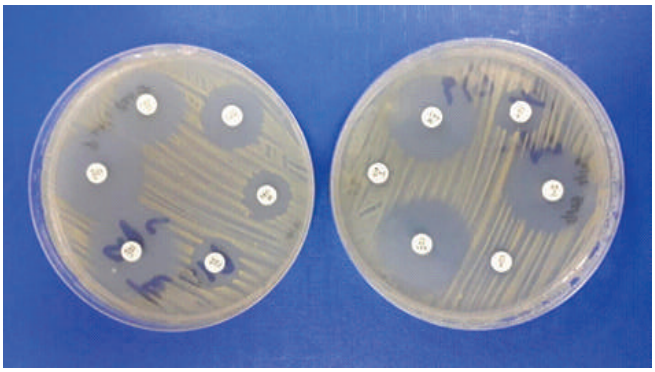

Figure 1: MDR-*Staphylococcus aureus* Identification

After a 24-hour incubation period, it was obtained by selecting the lowest concentration of plant extract that suppressed bacterial growth and was recognized without the need of special equipment [12]. Utilizing the Agar well diffusion method, *TcLE*'s antibacterial effectiveness against MDR-*Staphylococcus aureus* was examined. Generally, colored extracts were preferably assayed using the agar well diffusion method for a number of reasons. Colored extracts will not fully dissolve in the broth medium. This may result in precipitation or aggregation which leads to inconsistent concentrations of active ingredients, which may subsequently affect the reliability and validity of the outcome. The agar medium was particularly useful for studying the diffusion rates of leaf extracts since it was

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stable and uniform; when the latter was placed in an agar, it maintains its structure and supports predictable diffusion patterns [13]. On the surface of MHA plates, the fresh inoculums of MDR bacterial isolates were evenly distributed in comparison to the 0.5 McFarland standards. 50µl of different concentrations of TcLE (3.9 to 500mg/ml) were poured to the wells (6-7mm diameter). The negative control used in the experiment was 10% DMSO. The negative control (DMSO) allowed to distinguish between the solvent's effects and the extract's antimicrobial activity. It was also used as a vehicle control to ensure any observed effects were due to the active ingredient, not the vehicle and to confirm the absence of inherent antimicrobial activity in the medium [14]. Incubation was done at 37°C for 24 to 48 hours after the extract was allowed to diffuse for 15 minutes. The zone of inhibition's presence or absence was assessed after 48 hours. The *TcLE*'s zones of inhibition were assessed and contrasted utilizing a diameter scale [15]. Data analysis was carried out utilizing SPSS version 22.0. Mean and standard deviation were calculated for ZOI. T-test was used in statistical analysis to compare the means of two groups such as experimental(s) versus a control to find if there was a difference in ZOI at varied plant extract concentrations. $P < 0.05$ was considered significant at 95% confidence level.

RESULTS

The growth of MDR-*Staphylococcus aureus* strains was evaluated at 8 concentrations from 3.9, 7.81, 15.62, 31.25, 62.5, 125, 250 and 500 mg/ml made for *Tc*LE, while DMSO was used as negative control. *Tc*LE inhibited the growth of MDR-*Staphylococcus aureus* at two tested concentrations. The MIC was found to be 250mg/ml. The experiment was conducted three times for verification of results.

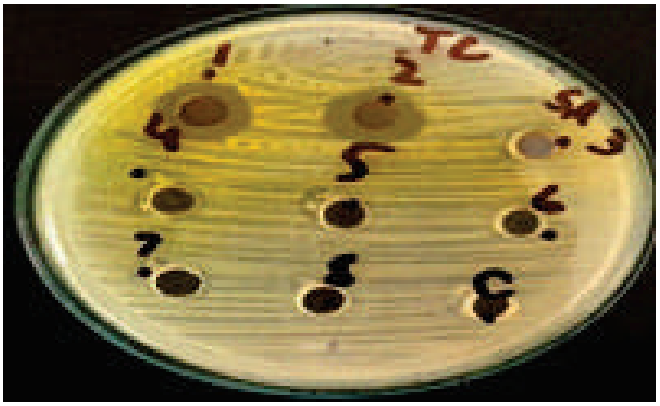

Figure 2: ZOI of *Tinospora cordifolia* Leaf Extract (*Tc*LE) for MDR-*Staphylococcus aureus*. Results of Agar Well Diffusion using MH Agar Plate

Label 1 (500 mg/mL): Zone of Inhibition of 9.6 mm
Label 2 (250 mg/mL): Zone of Inhibition of 7.3 mm.
Label 3-8 (Lower Concentrations): No Inhibitory Effects.
Label C (Control Group): No Inhibitory Effects.

Table 1 depicted that the antibacterial activity of *Tc*LE against MDR-*Staphylococcus aureus* was dose-dependent. The highest concentration used in this study, that was, 500 mg/ml produced a mean zone of inhibition of 9.6 mm, which was genuinely impressive. With 250 mg/ml, the mean ZOI decreased to 7.3 mm. Although it still indicates antibacterial activity, this decrease further implies that the potency of *Tc*LE may be reduced when the concentration was lowered. No inhibitory potential was observed at concentrations lower than 250 mg/ml, the lack of ZOIs, especially for 125 mg/ml and lower concentrations, also establishes this. Thus, the use of higher concentrations has remained an essential aspect of using *Tc*LE for best results as it also signifies that *Tc*LE antibacterial effectiveness was concentration-related.

Table 1: ZOI of *Tinospora cordifolia* Leaf Extract *(TcLE)* for MDR-*Staphylococcus aureus*, Agar Well Diffusion

S. No.	Concentration of Plant Extract used (mg/ml)	ZOI (mm) (Mean ± SD)	p-Value
1.	500	9.6 ± 0.57	*0.045
2.	250 (MIC)	7.3 ± 0.46	
3.	125	-	-
4.	62.5	-	
5.	31.25	-	
6.	15.625	-	
7.	7.8125	-	
8.	3.90	-	
9.	Control	-	

*Comparison of mean ZOIs of *TcLE* against MDR-*Staphylococcus aureus* at various concentrations by T-test

DISCUSSION

The impact of multi-drug resistance microorganisms on worldwide public health has given rise to grave worries. They have inflicted global socioeconomic catastrophe. Antibiotic overuse is making MDR bacteria more common, and nosocomial illnesses brought on by MDR bacteria is on the rise. Wound infections caused by diabetes are the most common, dangerous, and costly infections. It is anticipated that the frequency of DFIs will rise in tandem with the global rise in the incidence of diabetes mellitus. Drug-resistant bacteria, such as MDR-*Staphylococcus aureus* are important contributors of Diabetic Foot Infections (DFIs) [14]. There is a substantial risk of morbidity associated with DFI, leading to lower limb amputation. Diagnosing DFIs can be difficult, which may lead to medication misuse. Because of the polymicrobial nature of DFI and the presence of MDR bacteria, creative antibacterial treatments are needed. Numerous factors, such as geographical features, the intensity of the illness, patient data, and antibiotic use, may influence the bacterial diversity in DFIs [15]. There is an

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infinite and unexplored reservoir of highly medicinal chemical compounds found in plants. A huge variety of these phytochemicals with different structures and functions are utilized to create novel antimicrobials. These phytochemicals have the potential to decrease bacterial resistance processes or act in concert with existing antibiotics to kill bacteria. As an alternative, they might function by obstructing particular molecular targets that are necessary for cell division and proliferation within the cell. Therefore, in order to battle the resistant bacterial diseases, it is essential to develop unique therapeutic medicines using a variety of herbal extracts [16]. Based on the results of Agar well diffusion method, it found that *Tc*LE inhibited the growth of MDR-*Staphylococcus aureus* strains at tested concentrations of 500 mg/ml with a mean ZOI of 9.6 mm and 250 mg/ml with a mean ZOI of 7.3 mm. The MIC of *Tc*LE against MDR- *Staphylococcus aureus* was determined to be 250 mg/ml in this investigation. *TC* is an herbaceous shrub renowned for its medicinal properties. Numerous studies have shown that *Tc*LE has antibacterial qualities against microorganisms, such as MDR-*Staphylococcus aureus*, that can cause potentially fatal infections in humans. Hussein MA *et al.*, evaluated the antibacterial potential of *Tc*LE using the disc diffusion technique. ZOI against Staphylococcus aureus in his study was found to be 25 mm, highlighting the possible antibacterial action of *TC* on sensitive strains and highlighting the need to investigate its activity against MDR strains [17]. The agar-well diffusion method was utilized in an in-vitro investigation to assess the antibacterial activity of *Tc*LE. *Tc*LE's ZOI measured against *Staphylococcus aureus* was 19 mm [18]. Significant amounts of quercetin have been detected in the ethanolic leaf extracts of *TC* [19]. This flavonoid is a remarkable and potent antibacterial agent against drug-resistant strains [20]. There was an isoquinoline alkaloid referred to as berberine which was found in *Tc*LE. It binds to biofilm amyloid proteins, thereby destabilizing its stability, thus *Tc*LE has been in use to combat antibacterial diseases. It was also a potent antibacterial synergist with antibiotics like erythromycin, cefoxitin, and linezolid. Recent studies indicate that berberine can enhance the antibiotics' ability to suppress clinical isolates of MRSA that were resistant to multiple drugs. Based on this kind of evidence, one can deduce from this finding that *Tc*LE might have the ability to be used as a more effective treatment for strains of bacteria that have now become resistant to antibiotics [21, 22]. In an in-vitro study, the phytochemical test of ethanolic extracts of *TC* demonstrated the presence of alkaloids, glycosides, polyphenol, saponins, and terpenoids which have antibacterial properties [23]. These phytoactive compounds present in *Tc*LE can play a very key role in combating MDR bacteria, as they can inhibit the efflux pumps. These compounds interfere with bacterial cell walls, thereby disrupting the integrity of the cell and also inhibiting vital enzymes that play an important role in bacterial life and consequently, their reproduction was inhibited. This makes bacteria prone to environmental stress factors as well as other antibacterial agents [24]. In a study, the anti-biofilm activities of *Tc*LE and the silver nanoparticles from this phytoextract were tested against the biofilm of *S. aureus*. It was observed that both phytoextract from the leaves of *TC* and the biogenic AgNPs from *Tc*LE were successful in reducing the biofilm of S. aureus. Biofilm-producing bacteria produce adhesion molecules that enable them to attach tightly to the extracellular matrix of the wound bed in DFIs, which includes collagen and soft tissues. Bacterial cells, embedded in biofilms, can even become genetically mutated or accumulate resistance genes, contributing to their antimicrobial resistance. This might culminate in the production of subpopulations of bacteria within the biofilm that were highly resistant to various antibiotics. Overall, all these factors contribute to improved tolerance of biofilm-associated bacteria to antibiotic treatment, making the eradication of DFIs more challenging when cases of MDR staphylococci were concerned. It was for such reasons that anti-biofilm activity by *Tc*LE could prove useful in the treatment of DFI by MDR-S. aureus strains [25]. This study also had few limitations. The bioactive compounds of *Tc*LE were not evaluated for the anti-staphylococcal action. The underlying mechanism of action of *Tc*LE against MDR-Staphylococcus aureus strains was not evaluated. Further studies might include experiments to explore whether *Tc*LE could be used in conjunction with other antimicrobial agents to achieve higher efficacy especially at lower concentrations.

CONCLUSIONS

*Tc*LE showed antibacterial potential against MDR resistant *Staphylococcus aureus* and inhibited its growth at 250 mg/ml concentration.

Authors Contribution

Conceptualization: SM[1], AA, MOI
Methodology: SM[1], AA, MOI
Formal analysis: SM[2], HA
Writing, review and editing: SM[1], MK, AA, MOI, SM[2], HA

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Types of Uropathogens and Pattern of Antimicrobial Resistance among Urinary Tract Infected Patients Presenting to Primary Care

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ABSTRACT

Urinary Tract Infections (UTIs) were prevalent bacterial infections with significant public health impacts, particularly affecting females due to anatomical predispositions. **Objective:** To assess the types of uropathogens and their antimicrobial resistance profiles among patients with UTIs presenting to a private clinic in districts Dir Lower and Upper, Pakistan. **Methods:** A prospective observational study was conducted, enrolling 109 patients with symptoms suggestive of UTIs. Urine samples were collected and subjected to culture and sensitivity testing. Data on patient demographics, uropathogen identification, and antibiotic susceptibility patterns were analyzed using SPSS version 21.0. **Results:** *Escherichia coli* was the predominant uropathogen, isolated in 51.90% of patients, followed by *Pseudomonas aeruginosa* (12.00%), *Enterococcus* (9.80%), *Staphylococcus aureus* (3.80%), and *Serratia odorifera* (1.50%). Among *Escherichia coli* isolates, Nitrofurantoin exhibited the highest sensitivity (91.30%), while Ampicillin, Cefixime, Amoxicillin, and Ceftriaxone showed substantial resistance rates (>85%). *Pseudomonas aeruginosa* demonstrated high resistance to all tested antibiotics. *Enterococcus* and *Staphylococcus aureus* exhibited variable sensitivity patterns, while *Serratia odorifera* displayed uniform sensitivity to the antibiotics tested. **Conclusions:** *Escherichia coli* was the predominant uropathogen isolated among patients with UTIs in districts Dir Lower and Upper, Pakistan, with varying susceptibility patterns to commonly prescribed antibiotics.

INTRODUCTION

Urinary Tract Infections (UTIs) are among the most prevalent bacterial infections globally, affecting individuals across diverse demographics and healthcare settings. These infections encompass a spectrum of clinical manifestations, ranging from asymptomatic bacteriuria to severe kidney infections culminating in sepsis [1]. UTI is characterized as urethritis (urethral infection), cystitis (bladder inflammation), or pyelonephritis (kidney infection), or it can progress to a bloodstream infection, resulting in urosepsis [2]. Uncomplicated UTIs (cystitis and pyelonephritis) affect healthy individuals in the absence of anatomical or neurological urinary tract problems. Complicated UTIs are associated with conditions that limit urinary tract or host defense, such as urinary obstruction, urine retention, immunosuppression, renal failure, pregnancy, and indwelling catheters or other drainage device [3]. The intestinal flora was the primary source of uropathogens that cause UTIs, which supports the reasoning for empirical treatment approaches for CA-UTIs (community-acquired UTIs) [4]. Uropathogenic Escherichia coli (UPECs), the primary etiological agent of UTIs, account for approximately 75% of all cases [5]. Although empirical treatments are useful, they pose limitations by impeding the monitoring of antibiotic responses and fostering antibiotic resistance among UTI-causing pathogens [4]. In recent years, the alarming rise in

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Antimicrobial Resistance (AMR) among uropathogens has emerged as a pressing global concern [6]. This phenomenon poses a grave threat to public health, with over 700,000 deaths attributed to AMR-related complications each year worldwide [7]. If left unchecked, projections indicate that by 2050, AMR could claim the lives of over 10 million individuals annually and impose substantial economic burdens [7]. Importantly, this crisis transcends national boundaries, impacting countries irrespective of income levels or developmental statuses. Of particular concern are regions such as Africa and South-East Asia, where the lack of established AMR surveillance systems exacerbates the challenge [8]. In 2014, the World Health Organization (WHO) highlighted the absence of such systems in these regions. Within Pakistan, studies have underscored the severity of AMR, revealing resistance rates of 83% to four antibiotics and 65.5% to more than eight antibiotics [9, 10]. Although UTI is treatable, multidrug-resistant strains lead to treatment failure and complications, resulting in significant morbidity and mortality in hospitals [11].

In light of these challenges, this study endeavors to elucidate the landscape of common uropathogens and their antimicrobial resistance profiles, aiming to establish a localized antibiogram. By shedding light on the prevailing resistance patterns, this research seeks to inform clinical decision-making, mitigate morbidity associated with UTIs, foster community awareness regarding culture and sensitivity testing, and guide the judicious prescription of antimicrobial agents, contributing to the global efforts to combat antimicrobial resistance.

METHODS

This prospective observational study investigated UTIs among patients presenting with symptoms such as frequency, urgency, painful urination, flank pain, and fever. Conducted during November 1st 2022 to October 31st 2023 at the medical outpatient department of DHQ Timergara Medical College Teaching Hospital, the study aimed to provide insights into patient demographics, urinary pathogens, and antibiotic resistance patterns.

A total of 109 patients were enrolled in the study. The sample size was determined based on convenience sampling of eligible patients presenting during the study period, rather than through prior power calculations. This approach was adopted due to practical constraints, including time and resource availability. All patients with white cells in urine at a count of ≥ 8-10 per high power field and who had not used antibiotics for at least 72 hours prior to presentation were included in the study. While those who had taken antibiotics within the last 72 hours were kept under the exclusion criteria.

Data collection involved clinical examinations and laboratory investigations, with patient samples cultured and tested for sensitivity using standard protocols. Urinary pathogens and their antibiotic susceptibility profiles were identified through established microbiological techniques. Standardized procedures for urine culture and sensitivity testing were employed to ensure accuracy and consistency of results. Quantitative variables assessed the number of white cells in urine per high-power field, bacterial colony counts on culture, and antibiotic susceptibility/resistance patterns of identified pathogens. Cultures were performed using media such as McConkey agar and cystine lactose electrolyte deficient medium. Data were analyzed using SPSS version 21.0, with descriptive statistics summarizing patient demographics and characteristics of urinary pathogens. Frequency distributions and percentages were calculated for qualitative variables, while means and standard deviations were used for quantitative variables. The study was conducted after receiving ethical approval from the institutional ethical review board, Ref# 1070/TMC.CE.2023-24. Written consent was obtained from patients who met the inclusion criteria and demonstrated bacterial growth on urinary culture and sensitivity testing, ensuring they were fully informed about the study.

RESULTS

A total of 109 patients were enrolled in this study, comprising 37.60% males and 44.40% females, with a median age of 50.15 ± 18.42 years. The most prevalent presenting symptoms among the patients were urinary frequency (67.70%) followed by fever (Table 1).

Table 1: Baseline Characteristics of the Patients with Urinary Tract Infection (n=109)

Variables	Mean ± SD/N (%)
Age (Years)	50.15 ± 18.42
Gender	
Male	50 (37.60%)
Female	59 (44.40%)
Urinary Tract Infection Manifestations	
Urgency	81 (60.90%)
Frequency	90 (67.70%)
Flanks pain	47 (35.30%)
Fever	89 (66.90%)
Pathogens	
E. coli	69 (51.90%)
Pseudomonas aeruginosa	16 (12.00%)
Enterococcus	13 (09.80%)
Klebsiela pneumonia	4 (03.00%)
Staphylococcus aureus	5 (03.80%)
Serration ordorifera	2 (01.50%)

The predominant pathogen isolated from the urine cultures was *Escherichia coli*, which was identified in 51.90% of patients. It was followed by *Pseudomonas aeruginosa* in 12.0%, *Enterococcus* in 9.80%, *Staphylococcus aureus* in 3.80%, and *Serratia odorifera* in 1.50% of patients. Among patients infected with *Escherichia coli*, the most sensitive drugs were

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Nitrofurantoin (91.30%), Fosfomycin (98.90%), Meropenem (89.90%), and Piperacillin (87.0%), while the most resistant drugs included Ampicillin (92.80%), Cefixime (88.40%), Amoxicillin (87.0%), and Ceftriaxone (87.0%). *Pseudomonas aeruginosa* exhibited high resistance to all tested drugs, as detailed in table 2. *Enterococcus* demonstrated equal sensitivity patterns, with 92.30% of patients exhibiting sensitivity to Fosfomycin, Nitrofurantoin, Piperacillin, and Meropenem. *Staphylococcus aureus* displayed 80% sensitivity to Nitrofurantoin and Meropenem, while *Serratia odorifera* exhibited 100% sensitivity to Nitrofurantoin, Fosfomycin, Meropenem, and Piperacillin, respectively. *Escherichia coli* was the most commonly isolated pathogen in patients presenting with urinary tract infection. It was highly sensitive to Nitrofurantoin, Fosfomycin, Meropenem, and Piperacillin. Conversely, *Pseudomonas aeruginosa* exhibited resistance to all tested antibiotics. *Enterococcus* and *Staphylococcus aureus* displayed varying sensitivity patterns, with *Serratia odorifera* demonstrating uniformly high sensitivity to the antibiotics tested.

Table 2: Uropathogens Pattern of Sensitivity and Resistance

		Isolates N (%)					
Antibiotics Used	Pattern	*Escherichia coli*	*Pseudomonas aeruginosa*	*Enterococcus*	*Klebsiela pneumonia*	*Staphylococcus aureus*	*Serration ordorifera*
Fosfomycin	S	62 (89.90%)	2 (12.50%)	12 (92.30%)	2 (50.00%)	3 (60.00%)	2 (100.00%)
	R	7 (10.10%)	14 (87.50%)	1 (7.70%)	2 (50.00%)	2 (40.00%)	-
Nitrofurontoin	S	63 (91.30%)	3 (18.80%)	12 (92.30%)	3 (75.00%)	4 (80.00%)	2 (100.00%)
	R	6 (8.70%)	13 (81.20%)	1 (7.70%)	1 (25.00%)	1 (20.00%)	-
Levofloxacin	S	28 (40.60%)	2 (12.5%)	5 (38.50%)	1 (25.00%)	1 (20.00%)	2 (100.00%)
	R	41 (59.40%)	14 (87.50%)	8 (61.50%)	3 (75.00%)	4 (80.00%)	-
Ciprofloxacin	S	26 (37.70%)	1 (6.20%)	4 (30.80%)	1 (25.00%)	1 (20.00%)	2 (100.00%)
	R	43 (62.30%)	15 (93.80%)	9 (69.20%)	3 (75.00%)	4 (80.00%)	-
Ofloxacin	S	28 (40.60%)	1 (6.20%)	5 (38.30%)	1 (25.00%)	1 (20.00%)	2 (100.00%)
	R	41 (59.40%)	15 (93.80%)	8 (61.50%)	3 (75.00%)	4 (80.00%)	-
Amoxicillin	S	9 (13.00%)	2 (12.50%)	8 (61.50%)	2 (50.00%)	2 (40.00%)	2 (100.00%)
	R	60 (87.00%)	14 (87.50%)	5(38.50%)	2 (50.00%)	3 (60.00%)	-
Ampicillin	S	5 (7.50%)	1 (6.20%)	7 (53.80%)	-	2 (40.00%)	2 (100.00%)
	R	65 (92.80%)	15 (93.80%)	6 (46.20%)	4 (100.00%)	3 (60.00%)	-
Cefixime	S	8 (11.60%)	2 (12.50%)	7 (53.80%)	1 (25.00%)	2 (40.00%)	2 (100.00%)
	R	61 (88.40%)	14 (87.50%)	6 (46.20%)	3 (75.00%)	3 (60.00%)	-
Ceftriaxone	S	9 (13.00%)	2 (12.50%)	6 (46.20%)	1 (25.00%)	2 (40.00%)	2 (100.00%)
	R	60 (87.00%)	14 (87.50%)	7 (53.80%)	3 (75.00%)	3 (60.00%)	-
Piperacillin	S	60 (87.00)	4 (25.00)	12 (92.30)	3 (75.00)	3 (60.00)	2 (100.005)
	R	9 (13.00%)	12 (75.00%)	1 (7.70%)	1 (25.00%)	2 (40.00%)	-
Meropenem	S	62 (89.90%)	4 (25.00)	12 (92.30%)	3 (75.00%)	4 (80.00%)	2 (100.00%)
	R	7 (10.10%)	12 (75.00%)	1 (7.70%)	1 (25.00%)	1 (20.00%)	-
Doxycycline	S	32 (46.40%)	3 (18.80%)	3 (23.10%)	1 (25.00%)	3 (60.00%)	-
	R	37 (53.60%)	13 (81.20%)	10 (76.90%)	3 (75.00%)	3 (60.00%)	-
Co-trimoxazole	S	20 (29.00%)	3 (18.80%)	3 (23.10%)	1 (25.00%)	3 (60.00%)	-
	R	49 (71.00%)	13 (81.20%)	10 (76.90%)	3 (75.00%)	2 (40.00%)	2 (100.00%)

S-Sensitive; R-Resistance

DISCUSSION

This study aimed to determine the prevailing uropathogens in the population of districts Dir Lower and Upper, Pakistan, along with their antimicrobial sensitivity and resistance patterns, with the ultimate objective of establishing a localized antibiogram. These findings underscore the common occurrence of UTIs and highlight concerning trends in resistance to commonly utilized antibiotics. *Escherichia coli* emerged as the predominant pathogen in this study. Consistency in the prevalence of *Escherichia coli* as the primary uropathogen was noted across various geographical locations. Studies conducted by Haindongo EH *et al.*, in Namibia, Abongomera G *et al.*, in Uganda, and Tanvir R *et al.*, in Lahore, Pakistan, reported similar findings, with prevalence rates ranging from 40.70% to 73.1% [12, 13, 10]. Furthermore, these findings align with those of Adugna B *et al.*, where *Escherichia coli* emerged as the most predominant bacterium isolated from urine, followed by *Enterobacter spp.*, *Enterococcus spp.*, and *Klebsiella spp.* Similar trends were observed in other studies as well, further supporting the consistency and

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reliability of this findings [6, 14-16]. Additionally, this study's observation of a predominance of Gram-negative organisms (80.9%) aligns closely with comparable research (81.3%) [17]. Firissa YB *et al.*, found that gram-negative bacteria accounted for 84% of the isolates, with gram-positive bacteria comprising the remaining 16% [18]. These results were consistent with findings reported by Tiruneh M *et al.*, and Kasew D *et al.*, from Gondar, Ethiopia, as well as other studies conducted elsewhere [15, 19]. Nitrofurantoin showed the highest sensitivity rate of 91.30% of the tested antibiotics against *Escherichia coli*, closely followed by Fosfomycin (89.90%) and Meropenem (89.90%). On the other hand, resistance rates to ampicillin, cefixime, amoxicillin, and ceftriaxone were much higher than 85%. The results of this investigation suggest high sensitivity of Nitrofurantoin (91.30%) against *Escherichia coli*, aligning with empirical treatment guidelines, which may warrant consideration as a first-line oral therapy. However, disparities were noted in the sensitivity rates of injectable antibiotics such as Meropenem and Piperacillin, which were lower than previously reported figures. Fosfomycin, particularly in single-dose preparations, demonstrated promising sensitivity rates (89.90%), consistent with previous study highlighting its efficacy against Gram-negative microorganisms [20]. Conversely, quinolones, including levofloxacin, ciprofloxacin, and ofloxacin, exhibited significant resistance rates exceeding 55%, reflecting trends observed in developing countries. In a study by Firissa YB *et al.*, *Enterococcus spp.*, *Enterobacter spp.*, and *Klebsiella spp*. were found to be resistant to Ceftriaxone, Ceftazidime, Ciprofloxacin, Cotrimoxazole, Gentamicin, and Nalidixic Acid but sensitive to Nitrofurantoin, Vancomycin, and Cefoxitin [18]. Of significant concern was the escalating resistance observed among cephalosporins, namely ceftriaxone, cefixime, amoxicillin, and ampicillin, with resistance rates surpassing 85%. This stark contrast with previously reported figures (33.9% and 22%) underscores the urgent need for interventions to curb the indiscriminate use of these antimicrobial agents, often exacerbated by self-medication practices within the local community [12, 21]. However, it was imperative to acknowledge the limitations inherent in this study. Although the data were primarily collected from a single private clinic in districts Dir Lower and Upper, Pakistan, expanding the data collection to multiple setups could have provided a more representative sample of the entire population. Additionally, extending the duration of the study could improve the sample size, thereby enhancing the reliability of the results. Moreover, the exclusion criteria of patients who had received antibiotics within 72 hours prior to urine sample collection might have led to the underrepresentation of certain patient groups, potentially affecting the generalizability of the findings. Furthermore, the study did not assess factors such as comorbidities or previous UTI episodes, which could influence both the prevalence of uropathogens and their antimicrobial resistance patterns.

CONCLUSIONS

The observation of Antimicrobial Resistance (AMR), particularly with cephalosporins, suggests a need for further investigations into initiatives aimed at curbing indiscriminate antimicrobial use. Against Escherichia coli, Nitrofurantoin, fosfomycin, meropenem, and piperacillin have shown significant sensitivity, suggesting their potential as empirical therapy alternatives pending confirmation in larger studies. The study highlighted the significance of current empirical management strategies and initiatives to combat AMR nationally and internationally.

Authors Contribution

Conceptualization: SB, FU
Methodology: AR[1]
Formal analysis: AG
Writing, review and editing: AR[2], HUR, AG

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Unveiling the Impact of Enhanced Recovery After Surgery Programs on Post-Operative Morbidity and Mortality

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ABSTRACT

Enhanced recovery after surgery is an evidence-based and holistic perioperative care approach and a real revolution in surgical settings. Initially, this concept referred to as "fast-track surgery" has evolved to enhanced recovery after surgery and acquired remarkable attention for its potential to improve patient recovery and surgical adverse outcomes, reduce the length of hospital stay, and yield beneficial impact on post-surgical mortality and morbidity. **Objective:** To evaluate the impact of enhanced recovery after surgery programs on Post-Operative Morbidity and Mortality. **Methods:** A comprehensive overview was provided based on several studies' data on the impact of enhanced recovery after surgery programs on postoperative mortality and morbidity. Nine years of epidemiological studies published between 2014-2023 were included based on the presence of qualitative and quantitative data. **Results:** Enhanced recovery after surgery significantly reduces the overall morbidity, surgical site infections, and complications associated with different surgeries, and shortens the length of stay at the hospital without escalating the readmission and mortality rate. However, only one study reported a significant difference in mortality rate between enhanced recovery after surgery and the control group. **Conclusions:** It was concluded that enhanced recovery after surgery protocols have increasingly been recognized as pivotal tools in reducing postsurgical mortality and morbidity, highlighting their efficacy in optimizing surgical consequences. By synthesizing core insights this review emphasizes the concrete advantage of enhanced recovery after surgery programs inpatient rehabilitation mobilization, encompassing faster recovery, and reducing surgical-related adverse effects.

INTRODUCTION

Post-operative complications including surgical morbidity and mortality are a significant public health concern [1-3]. It is estimated that 300 million patients undergo surgical intervention worldwide yearly [4]. The international Surgical outcomes study globally reported that 26.8% of patients who underwent major surgery exhibited postoperative complications [5]. 30-day post-surgical mortality is considered the third most common cause of death in the United States with 7.7% of deaths worldwide [6]. Post-surgical complications after major surgery increase the length of hospital stay, cost, infections, and mortality [7, 8]. Research shows that numerous endeavors have been directed toward reducing postoperative mortality and complications, which have been achieved in a few hospitals [2]. The enhanced recovery after surgery (ERAS) is a second revolution after laparoscopy experienced by the surgical community which marked a significant improvement in postoperative care [9]. Enhanced recovery after surgery ERAS programs have become the norm in surgical settings mostly for major surgery [10]. ERAS is a multimodal series of research-based healthcare approaches in the perioperative period that alleviates the physiological and physical reactions to traumatic stress, post-surgical complications, incidence

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of infections, readmission rate, hospital stay times, mortality, and hospital costs [11]. It was initially applied in colorectal surgery around the mid-1990s and extensive research data showed that the ERAS protocol may lead to a significant decrease in the Length of Stay (LOS) and overall morbidity of up to 50% in colorectal surgery compared with standard perioperative approaches. Subsequently, the application of the ERAS protocol has been implemented in other surgical areas including hepatectomy, gastrointestinal surgery, and orthopedic surgery [12]. ERAS programs aim to enhance patient outcomes and reduce postoperative morbidity and mortality by directing attention to intra-operative, and postoperative care management mainly [13, 14]. These phases encompass technical interventions that pertain to all surgical areas as well as measures that are specific to surgical specialities. The possible mechanism of surgical procedure involves surgical stress, pathophysiological dysfunction, anxiety, pain, hypoxia, long-term fasting, and changes in blood volume, which initiates the release of inflammatory mediators and hyperglycemia leads to the development of complications [15]. ERAS plays a role in the decrease of postoperative complications by reducing surgical assertiveness and its adverse effects [10].

This systematic review aims to evaluate the impact of ERAS on postoperative mortality and morbidity in surgical settings. This involves compiling multiple studies providing data on the influence of ERAS on post-surgical complications and mortality in several types of surgeries. Investigating the ERAS program's impact on postoperative mortality and morbidity would help surgical specialities tailor patient recovery. Research in this area could identify standard procedures within ERAS protocol leading to advancement and improvement in surgical settings.

METHODS

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed to write this systematic review. The nine years of published data (2014-2023) were collected using several databases (PubMed, Google Scholar, Sci-hub, and Science Direct) using Boolean logic "AND" and "OR", Medical Subject Headings (MeSH Terms) and keywords. Different terminologies were used to explore the literature "Enhanced recovery after surgery," combined with "Postoperative mortality", and "Postoperative morbidity". A total of 331 articles were retrieved from the included databases. Out of them, 170 studies were excluded as non-relevant after reading the titles and not written in English, 70 studies were excluded because of only the presence of qualitative data, 40 studies were excluded after considering them duplicates, and then finally out of the remaining 51 studies, 38 were excluded because they did not directly address the impact of ERAS on postsurgical outcomes. Eventually, 13 articles were considered eligible after applying inclusion/exclusion criteria and deleting the duplicates and irrelevant articles (Figure 1).

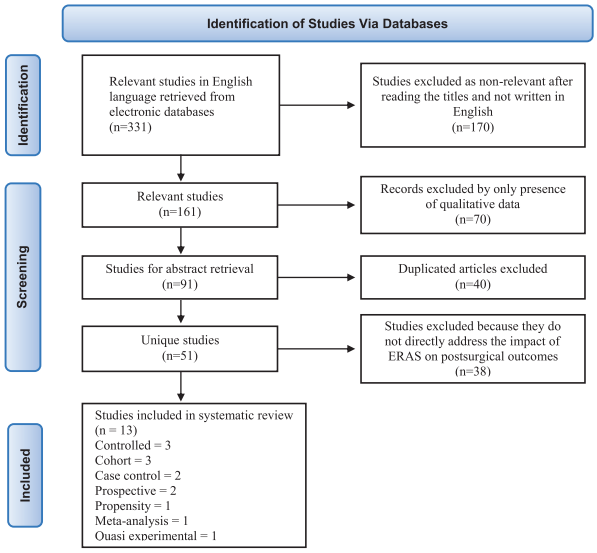

Figure 1: Depiction of the Study Selection Process

RESULTS

Enhanced recovery after surgery (ERAS) is a paradigm shift in surgical care composed of protocol designs related to the management of surgical facilities and guidelines applicable to various surgical subspecialties including Pancreatectomy, radial cystectomy, and arthroplasty bladder surgery [16]. By systematically categorizing the key components into pre-operative, intra-operative, and post-operative phases, the figure provides a clear and concise overview of the strategies employed to optimize patient outcomes. The figure plays a crucial role in enhancing the article's clarity, comprehensibility, and persuasive power. By providing a visual overview of ERAS protocols, the figure effectively conveys the key strategies that contribute to improved patient outcomes (Figure 2).

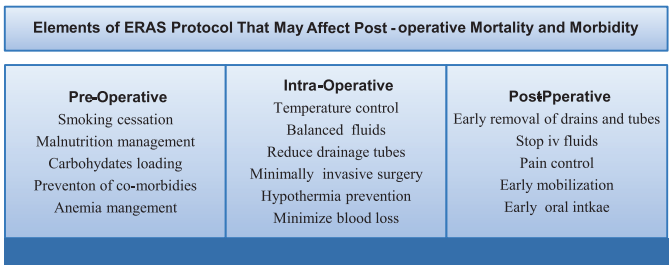

Figure 2: Elements of the ERAS Program

All of the identified studies assess the impact of ERAS on postoperative mortality/morbidity by comparing the ERAS group implemented with intervention against a control group subjected to the conventional approach [17-28]. Key endpoints of the study included feasibility, postoperative mortality/morbidity, complications, and LOS [29]. One study examined the ERAS impact on pancreatectomy [30]. Two studies included patients undergoing Pancreaticoduodenectomy (PD). Three studies evaluated

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the ERAS impact on colorectal surgery. Three studies included radial cystectomy whereas the other two included liver resection and one study was on ERAS impact on joint arthroplasty. Each study involved a different number of participants but a total of 23805 patients were evaluated in this analysis, out of which 10462 were provided with ERAS services and 13343 were included as control (Table 1).

Table 1: Summary of Extracted Data on the Impact of ERAS on Postoperative Mortality and Morbidity

S. No.	ERAS Group	Control	Surgery	Key Outcomes	Study Type	References
				Safe effective		
1	97	75	Pancreatectomy	Reduced LOS without Increasing Mortality and Morbidity	Controlled	[17]
2	2008	2139	Pancreaticoduo denectomy	Decrease Overall Morbidity Incidence of SSI Reduced LOS without Compromising Mortality	Controlled	[18]
3	97	87	Pancreaticoduo denectomy	Reduced LOS without Compromising Mortality	Case-Control	[19]
4	140	167	Lobectomy in lung cancer	Decrease LOS and Complication Rate	Propensity Score-Matched	[20]
5	100	100	Radial Cystectomy	Reduced LOS and Infectious Complications Reduced Time to Recovery and Cost	Cohort	[21]
6	110	NR	Radial Cystectomy	Shortens LOS without Compromising the Readmission Rate 82% had a Bowel Movement on day 2 /Reduced Complications	Prospective	[22]
7	79	121	Cystectomy	Reduction in LOS No increase in Complications and Readmissions	Quasi-Experimental	[23]
8	282	224	Colorectal Resections	Reduction in Morbidity and LOS/ Lesser Complications	Prospective	[24]
9	319	360	Colorectal	Reduction in LOS and Morbidity	Cohort	[25]
10	61	122	Colorectal	Reduction in LOS and Morbidity	Cohort	[26]
11	134	100	Liver Resection	Safe / Effective No Adverse Outcomes	Case-Control	[27]
12	91	93	Liver Resection	Safe / effective Reduced Postoperative Complications	Prospective Cohort	[28]
13	6944	9755	Joint Arthroplasty	Significantly Reduce Mortality Rate, LOS, and Complications	Meta-Analysis	[30]

LOS, Length of stay; PD Pancreaticoduodenectomy; SSI, Surgical site infections; NR, not reported Intra-operative management

To examine the influence of ERAS intra-operative protocol, brief data from two studies were included. According to the study, there was a decrease in intra-operative blood loss, red blood cell transfusion, and plasma transfusion in the ERAS group compared to the control group. Whereas the use of According to prophylaxis carbohydrate loading and hemodynamic monitoring increased in the ERAS group [31] (Table 2).

Table 2: Enhanced Recovery After Surgery Pathway Intraoperative Management Outcomes

S. No.	ERAS Pathway	Control Group	ERAS Group	Surgery	References
1	Perioperative Oral Carbohydrate Drink	No	Novel	Cystectomy	[21]
	Thrombosis Prophylaxis	Common	Increased		
	Hemodynamic Monitor Use	Lower	Higher		
	Postoperative use of Nasogastric Tube	Higher	Lower		
	Blood Loss	Higher	Lower		
	Red Blood Cell Transfusion	Increased	Decreased		
	Fresh Frozen Plasma Transfusion	Increased	Decreased		
	Crystalloid Use	Increased	Decreased		
2	Operation Time	Longer	Shorter	laparoscopic surgery / colorectal cancer	[18]
	Blood Loss	Higher	Lower		
	Length of Surgical Site	Longer	Shorter		
	Oral Fluid Intake Time	Longer	Shorter		
	Postoperative LOS	Longer	Shorter		

Data on postoperative outcomes were extracted from thirteen studies. Heterogeneity was observed in the data. Despite a thorough review of the study results showed a significant reduction in the length of stay (LOS), readmission rate, morbidity, and associated complications (details discussed later). In four studies compliance rate of

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the ERAS protocol was observed to be high. However, no significant difference was found in the mortality rate between the two groups. Out of 13 studies, only one conducted by Deng et al,. reported a significant reduction in mortality between the control and ERAS groups [30]. The reason for this can be explained by the fact that the reported incidence of mortalities in the studies was too low to identify any significance or it might be due to the small sample size which leads to the wrong conclusion that there is no difference [32] (Table 3).

Table 3: Postoperative Outcomes

LOS days		Morbidity %		Mortality%		Mortality Significance Level	Readmission Rate %		Compliance Rate%		References
ERAS	Control	ERAS	Control	ERAS	Control	ERAS / Controls	ERAS	Control	ERAS	Control	[17]
10	13	Decr	No diff	Decr	No diff	Not Significant	Incr	Incr	74	34	
Shorter	Longer	48.1	62.3	1.5	3.50	Not Significant	11	12.9	NR		[18]
14	20	NR	NR	4.7	6.20	Not Significant	12.8	14.4	NR		[19]
5	7	29.3	36.5	NR	NR	NR	3.6	5.4	81		[20]
7	10	NR	NR	2	2	Unchanged	20	38	95		[21]
4	NR	NR	NR	NR	NR	Unchanged	21	NR	NR		[22]
5	8	NR	NR	NR	NR	NR	NR	NR	NR		[23]
5	6	Lesser	NR	Lesser	NR	Not Significant	NR	NR	NR		[24]
11	13	NR	NR	4.7	2.5	Not Significant	4.3	6.3	88		[25]
6	9	14.8	33.6	0	1.6	Not Significant	1.6	3.3	NR		[26]
4	6	NR	NR	0	0	No difference	3	2	NR		[27]
6	6	NR	NR	1	1	No difference	12	9	NR		[28]
Shorter	Longer	Lesser	NR	Decr	NR	Significant	NR	NR	NR		[30]

LOS, Length of Stay; decr, decrease; incr, increase; NR, Not Reported

DISCUSSION

The present systematic review provides strong evidence for the efficacy of ERAS protocols in significantly reducing postoperative morbidity and length of stay. The consistent findings across diverse surgical specialities underscore the versatility and strength of the ERAS approach. The observed reductions in surgical site infections, complications, and readmission rates highlight the substantial benefits for patient outcomes. While the majority of studies demonstrated the effectiveness of ERAS in improving postoperative outcomes, the inconsistent findings regarding mortality are noteworthy. This inconsistency may be attributed to several factors, including variations in study populations, sample sizes, and the specific ERAS protocols implemented. Further research with larger sample sizes and standardized methodologies is warranted to elucidate the impact of ERAS on mortality rates. The integration of intraoperative management strategies within ERAS protocols appears to be a critical component in optimizing patient outcomes. The observed reductions in intraoperative blood loss and transfusion requirements suggest potential cost-effectiveness and improved patient safety. To determine the impact of the ERAS program on postoperative morbidity and mortality in an initial effort, a prospective controlled study was undertaken by Perinel *et al.*, [17] in Lyon France compared two teaching hospitals, intervention and control with the duration of 3 years, to evaluate the ERAS program intervention on postoperative outcomes after pancreatectomy (surgical removal of the pancreas). The study compared two groups one that implemented an ERAS program (n=97) and the other that followed traditional care (n=75). According to the findings, the ERAS program exhibited a high compliance rate of 95% and was associated with significantly reduced length of days at the hospital (LOS) based on hazard ratio (1.61; 95% CI), and postoperative morbidity, Furthermore, overall mortality and readmission rates were decreased in the ERAS group but the difference was not significant ($p<0.005$). These findings are similar to the retrospective cohort study carried out by Balzano *et al.*, at a tertiary referral university hospital with a duration of 3 years, which compared ERAS and control groups after PD for the outcomes LOS, readmission rate, and morbidity reported a significant decrease in (LOS 13 vs 15 days $p<0.001$) in the ERAS group [33]. A meta-analysis encompassing 22 studies published between 1990 to 2019 (multiple countries) was carried out by Wang *et al.*, in China [18]. Among them, 3 studies were randomized controlled trials and 19 were non-randomized, including a combined total number of 4147 patients to examine the impact of ERAS on postoperative outcomes after pancreaticoduodenectomy (PD) for the surgical outcomes, LOS morbidity, infection, readmission rate. The results of the study demonstrated that ERAS had significantly decreased overall morbidity (Relative risk; RR: 0.80, 95% CI, $p<0.001$) and incisional infections (RR: 0.75, 95% CI). A reduction in the duration at

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the hospital was noted in the ERAS group (WMD: -5.07, 95% CI) without compromising the mortality (RR: 0.70, 95% CI) and readmission rate (RR: 1.03, 95% CI). However, no substantial variance in mortality rate (p<0.005) was found between ERAS and the control group. These results were similar to the meta-analysis undertaken by Coolsen *et al.*, in the university hospital Maastricht in the Netherlands, which included 8 studies of multiple countries (data published between 1996 to 2012) in which two were retrospective, three were case-control, and one was prospective [34]. The study included a total no 1558 patients to evaluate the influence of ERAS on post-surgical outcomes (LOS, morbidity, complications, and readmission rate) after PD. Results indicated that implementation of ERAS significantly reduced the length of hospital stay by 2-6 days, complications and cost and increase in mortality and readmission rate were not found. An additional systematic review composed of six randomized control studies (RCTs) and 8 clinical controlled trials (CCTs) was conducted by Lei *et al.*, China [35]. The study aimed to assess the efficacy of ERAS including (control group n=1199 and ERAS group n=1366) composed of a total no of 2565 patients who underwent PD. Findings reported a decrease in postoperative complications (morbidity) (OR=0.73, 95% CI) and mortality rate (OR=0.63 95% CI: p<0.005) in the ERAS group compared with the control group. Another study executed by Coolsen *et al.*, took place in Maastricht University Medical Center between January 1995 and January 2012 in the Netherlands and included the ERAS group (n=97) and no ERAS group (n=87) underwent PD [19]. Findings suggested that implementation of the ERAS program aided in decreasing the duration of stay at the hospital from 20 days in the control group to 14 days in the ERAS group p<0.0001 and postoperative complications from 16 to 9 days without influencing other outcomes, whereas mortality and readmission rates were unchanged. A propensity score-matched study was conducted by Forster *et al.*, which evaluated the impact of ERAS protocol on postoperative outcomes in patients undergoing thoracoscopic lobectomy including 167 pre-ERAS/ 140 ERAS between January 2014 and October 2019 [20]. The outcomes of the measures were LOS, postoperative complications, and readmission rate. Findings reported a high compliance rate of 81% with a significant reduction in the length of days at the hospital (7 to 5 days, p=0004). Based on the propensity score, there was a 13% reduction in surgical complications. Readmission rates (5.4% vs 3.6% p=0.75) were the same between the two groups. As radial cystectomy is associated with postoperative morbidity, Dunkman *et al.*, carried out a cohort study to assess the impact of the ERAS program in an academic medical center in North Carolina with a duration of 3 years [21]. In this study cohort of 100 patients undergoing radial cystectomy with ERAS was compared with a cohort of radial cystectomy with traditional care. Results of the study indicated a significant reduction in postoperative complications, days to pass first stool (Control/ERAS: 5.83/3.88; p<0.001), days to first solid food (9.68 vs 3.2; p<0.001), and a reduction in infectious complications. Decreased hospital stay (ERAS/Control: median LOS 7 days IQR=6-11 vs 10 days IQR=8-18) and 26.6% reduction in costs were observed in the ERAS group, whereas the mortality rate was unchanged. The findings of implementing the ERAS program with radial cystectomy were in contrast with a prospective randomized controlled study carried out by Jensen *et al.*, in a hospital in Denmark among patients who underwent radial cystectomy with a duration of three years [36]. The study included an intervention group (n=50) and a standard group (n=57) that reported similar LOS and severity of complications in both groups. However, postsurgical mobilization was improved in the intervention group. A research study composed of data from 11 articles (multiple countries), conducted by Cerantola *et al.*, to systematically assess the impact of ERAS applied to cystectomy patients, demonstrated a reduction in morbidity, quick bowel recovery, and shortened LOS [37]. The results are similar to the prospective study carried out by Daneshmand *et al.*, in the department of urology in California encompassing a total of 110 patients who underwent radial cystectomy with ERAS implementation between May 2012 to July 2023, reported 82% bowel movement on day 2 after surgery, LOS 4 days, 64% complication rate, without an increase in readmission rate [22]. Dhruva *et al.*, undertook a prospective study to examine the impact of ERAS on laparoscopic colorectal surgery among pre-ERP/post-ERP groups (total: 580) between 2008 and 2012 in Charles Hospital in the United Kingdom [24]. The findings indicated a reduction in hospital stays (pre-ERP; 6 days: post-ERP; 5 days) and other complications. A decrease in morbidity and mortality rate was observed in the ERP group but did not reach a statistical significance level. Additionally, another study carried out by Ripollés *et al.*, in a teaching hospital in Spain between 2010 through 2015, examines the impact of the ERAS program encompassing perioperative measures on postoperative complications associated with colorectal surgery [25]. In this study pre-ERAS (360) and post-ERAS (319) groups were compared. Results of the study showed a decrease in the length of stay at the hospital in the post-ERAS (11 days) group as compared to the pre-ERAS (13 days), whereas the pre-ERAS group (15.5%; p<0.001) experienced more severe complications as compared to post-ERAS (5.3%; p<0.001). No significant difference was found between mortality rates (pre-ERAS/post-ERAS;

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4.7%/2.5%: p=0.154). Deng *et al.*, conducted out meta-analysis through 2 May 2018 encompassing 25 studies that included 16699 patients in the Tahie Hospital orthopedics department in China, to compare the impact of ERAS after Joint arthroplasty [30]. Results of the study showed a significant reduction in mortality rate (RR: 0.48, 95% CI), incidence of complications (RR: 0.74, 95% CI), and a 26% reduction in overall morbidity whereas no impact was shown on the readmission rate. It is noteworthy that in this systematic review majority of studies did not find a significant difference in mortality rate between the ERAS and control group except for the one study conducted with a large sample size. The lack of this significant difference might be due to several factors small sample size, variations in protocol, and limitations in the studies included. There is a need for multidisciplinary auditing of ERAS Programs to further evaluate its impact [38]. The implementation of Enhanced Recovery After Surgery (ERAS) protocols in Pakistan is still in its emerging stages, although demonstrating promising outcomes. A study conducted at Shifa International Hospital, Islamabad, revealed a significant reduction in the length of hospital stay and surgical site infections (SSIs) among patients undergoing colorectal surgeries when managed under ERAS compared to conventional care [39]. These findings align with the global evidence supporting the efficacy of ERAS in optimizing postoperative care. However, the successful and widespread adoption of ERAS in Pakistan faces several challenges, as highlighted by a qualitative study conducted in Lahore [40]. These challenges include inadequate resource allocation, limited patient education, and a lack of standardized protocols. Additionally, the study emphasized the importance of interdisciplinary collaboration and strong leadership for successful ERAS implementation. While these challenges are not unique to Pakistan, their impact on the adoption of ERAS in a resource-constrained setting is particularly pronounced. To fully realize the benefits of ERAS in Pakistan, concerted efforts are required to address these challenges through policy changes, educational initiatives, and capacity building. Moreover, further research is needed to evaluate the cost-effectiveness of ERAS in the local context and to identify strategies for sustainable implementation.

CONCLUSIONS

It was concluded that the present systematic review of the literature shows that implementation of ERAS programs significantly reduces the overall morbidity, incidence of infections, and complications, and shortens the LOS without intensifying the risks of re-hospitalization and mortality. However, more large-scale research is required to provide valuable insight into the impact of ERAS on postoperative mortality and morbidity.

Authors Contribution

Conceptualization: AS
Methodology: KR
Formal analysis: MUFK
Writing review and editing: ZA, DN, MUK

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

Conflicts of Interest

The authors declare no conflict of interest.

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Systematic Review

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Clinicopathological Insights to the Nerve Growth Factor NGF Associated Stress Response in Pregnancy and Therapeutic Potential in Fetal Neurodevelopment

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ABSTRACT

The nerve growth factor has a significant role in fetal neurogenesis and sustaining pregnancy. **Objectives:** To investigate the effects of nerve growth factor in stress response during pregnancy on developing fetus to bring clinicopathological correlation on the role of nerve growth factor in maternal stress markers (cortisol levels, glucocorticoids, depression, anxiety, and brain-derived neurotrophic factor levels) and fetal brain development. **Methods:** Following PRISMA guidelines, this study was extracted from PubMed, ScienceDirect, Nature, and Google Scholar articles from January 2014 to April 2024. The examination of pregnant women in published research gave a possibility to understand the application of nerve growth factor as a suitable biomarker for brain stress and fetal neuronal development. To exclude studies with lower ranks, each of the selected studies was assessed for adherence to evidence-based research methodology. The studies were taken from China, Europe, America and South Asia (including Pakistan). **Results:** Increased nerve growth factor levels were associated with maternal stress reactions which caused changes in cortisol levels and the amygdaloidal complex area. However, the increased nerve growth factor level was linked to changes in the fetal brain such as the weight of the fetal brain and stress biomarkers in the amniotic fluid sample inferring a critical role in the modulation of maternal stress on the fetal neurodevelopmental spheres. **Conclusions:** It was concluded that it is important to note how stress and nerve growth factors interact during pregnancy to create effective interventions to reduce stress dependence for the better health of both the mother and child.

INTRODUCTION

Nerve growth factor (NGF) has been found to have multifunctional tasks, including the contribution to the fetal neurodevelopment and stabilization of pregnancy processes [1]. Current studies reveal that hypoglycaemia is linked with preterm delivery, which affects the fetal organisms' growth, including the basic neurotrophin NGF present in maternal and umbilical cord plasma in lesser measure in our cases. On the other hand, increased levels of NGF have been associated with structural reorganisation of the fetal head, especially the amygdala and hippocampus thus causing developmental anomalies. Moreover, NGF plays a role in the modulation of physiological interactions between the nervous, endocrine, and immune systems and stress associated with the increase in NGF levels is able to cause negative pregnancy outcomes such as spontaneous abortion [2].

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There is an increased oxidative stress during pregnancy, coupled with variations in neurotrophin levels, which affect the growth of the fetal brain [3]. This can impose on preterm offspring cardiovascular, metabolic and neurodevelopmental risks throughout their lifetime [4]. Maternal stress levels also differ across the world with Asia having the highest (up to 31% of the surveyed mothers), Europe next and America, with up to 15% [5-7]. The situation is the same with maternal age; women above the age of 35 are more at risk of stress-related complications than younger women. These age differences may be attributable to age-related changes in stress buffering, as postpartum women reported higher levels of prenatal stress, increased cortisol, anxiety, and depressive symptoms [8]. For that, stress markers are significantly higher among Asians than Western people and give solid evidence of the impact of socioeconomic status on stress in mothers [9, 10]. Because of these internal and external factors combined, it is important to understand the role of maternal stress, NGF and fetal neurodevelopment [11].

This study aims to review and consolidate existing literature on NGF as a mediator of the stress response during pregnancy and its impact on the fetal brain. If NGF is proven to have a strong correlation with maternal stress and fetal neurodevelopment then by controlling its levels complications during pregnancies can be controlled. Thus, through making such linkages, this research aims to contribute to programmes that can reduce maternal stress with the view of enhancing the general welfare of pregnant and postnatal mothers and their unborn babies in different communities.

METHODS

According to the recommendations by PRISMA for reporting, the review was conducted from June 2024 to August 2024. Initially, it included 60 articles in English from 2014 to 2024. The articles were systematically sorted based on inclusion criteria searched and reported the details including author, year, region, title, design, analysis, method, variables, sample, outcome, and references. Several search engines were employed; Science Direct, Google Scholar, Springer and, PubMed. Google Scholar was used for 50% of the articles. Search phrases included China, Asia, and South Asia. It assisted in providing more relevant papers for scrutinizing research and its evaluation. Research conducted in peripheral regions was also represented in the pool of articles. Article searches were done using keywords: NGF, stress, pregnancy, fetal neurodevelopment, and stress response in pregnancy. Pregnancy, NGF, stress markers, fetus, neural development, young women, and maternal stress were significant words. The articles which did not fulfil our inclusion criterion were eliminated. The inclusion criteria were focused on NGF and its effects on neurodevelopment along with other stress markers and all papers taken were from the latest years, no paper older than the year 2015 was taken. Sixty articles in total were downloaded from databases. Eighteen duplicate articles were found and removed, leaving forty-two for analysis. A total of twenty articles from the systematic review were eliminated based on merely the qualitative data added to them. After elimination, twenty-two papers were picked and sorted which fulfilled inclusion criteria as shown in figure 1.

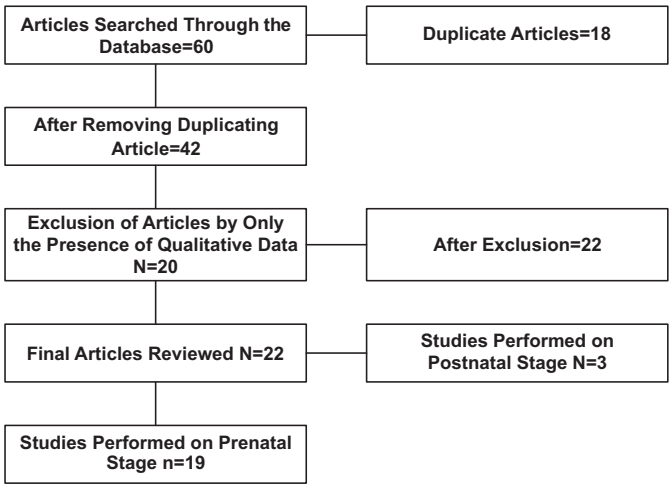

Figure 1: PRISMA Model Illustrating Selection of Studies for Review Process Showing Elimination of Studies That Were Not Lying Under the Inclusion Criteria.

RESULTS

The majority of the pregnant women in all the studies ranged from 18 to 45 years of age. The pregnant women taken as a sample had shown signs of stress. One of the studies took adolescent pregnant women between 14 to 19 years of age. 19/22 of studies were taken from the prenatal stage however 3/22 of studies were conducted on the postnatal stage. The studies were taken from all regions of the world including Asia, Europe and America. Research studies were taken from the last five years (70%) and from year 2014 to 2019 (30%). The study reviewed papers that were conducted in Europe (40%), Asia (30%) and America (30%) respectively. The studies were taken from Google Scholar (47%), Science Direct (30%), Nature (20%) and others (3%) from Research Gate and PubMed. The research used a cross-sectional study design (60%), longitudinal study design (30%) and perspective-based and observational studies (10%). Results of these studies [12-26] are shown in the Table 1.

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Table 1: Characteristics of The Studies Included in Systematic Review

Reference	Study Population (Mean Age in years ± SD)	Study Methodology, Statistical Tool, Software (Sample Size, N)	Study Variables	Key Findings
[12]	Normotensive women (27 ± 2.1) Women with preeclampsia (26 ± 3.6)	In a longitudinal study, Promega was used for measuring NGF levels in the plasma of the motherand cord, the analysis of data was done by SPSS/ PC+ package	Maternal: NGF levels, BP, BMI Fetal: Cord NGF levels, baby's birth weight, head and chest size	-Stable Maternal NGF levels-Higher Cord NGF levels in women with preeclampsia-NGF levels of cord affected by fetal parameters
[13]	Term infants at birth and at age 4 months	Longitudinal study, MILLIPLEX® MAP was used for determining NGF levels, IBM SPSS statistics 19.0 was used for statistical analyses	Fetal: Birth weight Z-score, NGF levels	-Higher NGF levels in SGA infants. -NGF levels remained elevated for 4 months -NGF levels correlated negatively with the index at birth.
[14]	Pregnant women with ≥20 years of age	Correlational study, Bayley 3 was used for the assessment of neurodevelopment, and ANOVA and chi-square tests were used for statistical analyses.	Maternal: Anxiety, Depression, Blood lead levels. Fetal: Umbilical cord blood lead levels	-Impaired neuro development in offspring due to lead and stress.-NGF downregulation is caused by hormonal stress during pregnancy. -Social-emotional skills, communication, and language development were affected.
[15]	Pregnant women of 18 to 43 years	Prospective study, NGF and NT-3 levels were determined using ELISA kits, statistical analyses were done by SPSS statistic package.	Fetal Variables: NT-3, NGF	-NT-3 levels rose as fetal growth velocity decreased.-NGF levels are affected by the nutritional status of the fetus.
[16]	Pregnant women from 20 to 40 years	Cross-sectional study, ELISA was used for the determination of FGF-2, and ANOVA was used for statistical analysis.	Maternal Variables: Depression, FGF-2	-Higher FGF-2 linked with maternal anxiety. - NGF regulates FGF-2 expression and signalling.
[17]	Pregnant women from 29 to 39	Cross-sectional prospective study, the Luminex 200 reader was used to measure BNDF levels,SPSS 20.0 package was used for statistical analysis.	Maternal Variables: BDNF levels. Fetal Variables: Umbilical cord blood BDNF levels	-Umbilical cord BDNF levels were generally lower than maternal serum BDNF levels.-NGF - NGF-induced BNDF expression enhances neuron survival and brain plasticity.
[18]	Pregnant women aged 23 to 40 years	Cross-sectional study, ELISA was used for the measurement of BNDF in amniotic fluid, Shapiro-Wilk test was used for statistics.	Fetal Variables: BDNF levels in amniotic fluid, glucocorticoids	-Higher glucocorticoids in amniotic fluid were linked with raised fetal BDNF levels.-Both BNDF and glucocorticoids are linked with the expression of NGF.
[19]	Pregnant women from 20 to 45 years	Longitudinal study, UPLC-MS/MS was used for measuring cortisol levels, LMR test was used for statistical analysis	Fetal Variables: FHR reactivity, salivary cortisol	-Fetuses in the PHSG showed slower central nervous system development. -Levels of cortisol and FHR are both factors that influence the levels of NGF,an important factor in neurodevelopment.

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[20]	Neonates at 30–40 days followed up to 2 years of age.	Observational prospective study,an ELISA kit was used for measuring biochemical parameters, and GraphPad Prism 6.01 was used for the statistical study.	Fetal Variables: Urinary levels of NGF	-NGF showed potential as an indicator of motor and cognitive impairment.
[21]	Pregnant women older than 18 years	Cross-sectional study, IA-LC-MS/MS was used for measuring NGF levels, and ANOVA was used for statistical analysis	Levels of total NGF (tNGF), proNGF	-tNGF levels rose significantly from the first to the third trimester
[22]	Pregnant women younger than 35 years	Prospective cohort study, an ELISA kit was used to measure BNDF levels, and Kruskal-Wallis and Kolmogorov -Smirnov tests were used for statistical analysis.	Fetal variables: BDNF levels in cord blood	-BDNF levels had a non-linear relationship with cognitive development.-During fetal neurodevelopment, the expression of BNDF is modulated by NGF.
[23]	Children aged 7-12 years, Specific Learning Disorder (SLD)	Correlational study, an ELISA kit was used for measuring neurotrophic levels in serum,IBM SPSS 20.0 statistics was used for statistical analysis	Neurotrophic factor (BDNF, NGF, GDNF) levels in serum	-BDNF and NGF serum levels were significantly higher in children with SLD.
[24]	Pregnant women less than 40 years of age	In longitudinal and cross-sectional studies, MRI was used, and Shapiro-Wilks and chi-square tests were used as statistical methods.	Maternal Variables: Psychological distress, anxiety Fetal Variables: Brain volume measurements, cortical features.	-Maternal depression scores were significantly higher in psychological distress. -Decreased volumes in fetal white matter, and cerebellar -Psychological stress plays an important factor in disrupting the expression of neurotrophic factors like NGF.
[25]	Pregnant young females 14 to 19 years	longitudinal study, maternal cortisol levels were assessed using 24-hour ambulatory cortisol collection, SPSS 23 and Spearman rank correlation was used as statistical analysis.	Maternal Variables: Depression scores, salivary cortisol Fetal Variables: Neonatal hippocampal connectivity, Infant memory	-Higher levels of perceived stress-Different dimensions of maternal distress on the neurodevelopment of fetus. -the change in maternal cortisol levels caused by stress can potentially affect neurodevelopmental changes influenced by NGF.
[26]	Infants 2 to 5 weeks	Cross-sectional study, MRI was used, and IBM SPSS Statistics 23 was used for statistical analysis	Maternal Variables: Psychological distress, anxiety	-Maternal psychological distress effects negatively on amygdala volumes. - NGF is crucial for the development of neurons in the amygdala.

DISCUSSION

This study aimed to address the NGF as a precursor to neurodevelopment in fetuses. By large studies showed that pregnancies related to stress and stress-related disorders faced complications in fetal neurodevelopment and NGF had been seen as an underlying cause of it. Stress, anxiety, and depression during pregnancy are associated with decreased fetal brain weight but the pathways are unclear [27]. Risk factors situated in maternal nutrition, exposure to toxins, and exercise behaviour can influence fetal brain development. Environmental stimuli such as polluted air and socioeconomic status may cause maternal inflammation and oxidative stress that may in turn have an impact on fetal brain morphogenesis through epigenetic regulation [28]. One of the proteins that are involved in

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stress responses and stress-induced disorders in the nervous system is NGF. Studies have demonstrated that levels of NGF rise with stress stimuli of psychological, aggression and other environmental pressures [29, 30]. As mentioned earlier, NGF is not only involved in stress responses but also takes part in communicating the external information to the physiological and pathological outcomes. Research has shown that NGF contributes to stress-induced mental disorders including schizophrenia and depression, as well as metabolic disorders [29]. The stress-induced skin disorders have been revealed to share the "brain-skin connection" system and the NGF-dependent pathways act within this system [31]. In addition, NGF has also been identified to rise in the plasma and central nervous system of both animals and humans during stress events, implying a role in vertebrate physiological regulation. Pregnancy-associated changes have been reported in the aspect of NGF with diverse trends. There are lower concentrations of NGF in maternal and cord plasma in preterm deliveries compared to term, which can influence fetal growth or neurodevelopment [32]. It has been established that NGF plays a vital role in normal pregnancy since both depletion and excessive amounts have been associated with adverse pregnancy outcomes [33]. Mature NGF -β reduces in rat uteri during pregnancy, while pro-NGF accumulates, which could aid pregnancy-associated uterine denervation [34]. In humans, serum total NGF levels exhibit a moderate upward trend in smokers. 7-fold increase through gestation, while pro-NGF levels were unchanged at 36 weeks. Neurotrophins (NTs) are a family of trophic factors that play a major role in controlling crucial traits of development, survival, and the function of neurons [35]. The complete form of NTs binds to high-affinity tropomyosin-related kinase (Trk) A, B, or C receptors or the low-affinity p75 pan-neurotrophin receptor (p75NTR). The TrkA receptor demonstrates the highest affinity for NGF. The major cytosolic/endosomal pathways stimulated by the TrkA are Ras-mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K)-Akt, and Phospholipase C (PLC)-γ [1]. The binding of NGF to p75NTR triggers additional signalling pathways that, in the absence of co-expressed TrkA, may lead to the apoptosis of the cell. NGF formed by hippocampal and cortical neurons is known to bind TrkA and p75NTR and create a trimeric complex with NGF, leading to neuronal survival pathways [36]. NGF is essential for the development and phenotypic maintenance of neurons in the peripheral nervous system (PNS) and its highest amount is produced in the cortex, the hippocampus, and the pituitary gland, although important amounts of this neurotrophin are also produced in other areas, including the basal ganglia, thalamus, spinal cord and in the retina. In pediatric neurology, NGF is progressively recognized as a key player in the pathophysiology of various brain disorders affecting children, such as autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and pediatric epilepsy. Dysregulation of NGF signalling pathways has been implicated in the abnormal neurodevelopmental trajectories detected in these conditions, suggesting potential insights into novel therapeutic strategies targeting NGF modulation [37]. NGF is important for neuron survival and there are several issues when regarding findings of studies that include NGF. Hypotheses involving social demographics and population-specific factors including pre-terms and IUGR further add variability that reduces the possibility of the results reflecting the actual normal population. Because NGF supports neuronal growth, survival, and regeneration, it is considered a promising candidate for multiple neurological disorders [38, 39]. Thus, during pregnancy, NGF and other neurotrophins regulate fetal brain development and activity of placenta; disturbance in these processes may result in such complication as preeclampsia and preterm births [40]. The application of diverse assessment measures across multiple studies makes the integration of the results a challenging process; this is accompanied by the development of the divergent picture of the effect of NGF dysregulation in ASD, ADHD and pediatric epilepsy. Neurogenesis does not only occur during development but also during an adult life as part of neuroprotection and repair and may, therefore, be therapeutic for neurodegenerative disorders such as Alzheimers and Parkinsons diseases. For example, the relation between synthesis and release of NGF in the brain and cognitive deteriorization in Alzheimer's disease have been revealed and therefore, it may be used for diagnostic and treatment purposes [41]. Novel treatments intended for increasing NGF availability are under development and include intranasal application and the use of nano-carriers to increase concentration and reduce off-target effects. Further, including NGF therapy with blood-brain barrier techniques such as focused ultrasound may enhance treatment outcomes of neurodegenerative disorders [42].

CONCLUSIONS

It was concluded that this review highlights the importance of Nerve Growth Factor (NGF) in fetal

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neurodevelopment and the related maternal factors involved during pregnancy. It has been inferred that stress indirectly or indirectly correlates with disruption in levels of NGF. BNDF and cortisol levels are also other important factors of stress induction and find their linkage with NGF expression. To reduce the threats arising from stress during pregnancy there is a need to employ stress-reducing measures, which could comprise psychological interventions, relaxation, and treatment for maternal mental health. It would therefore be advisable for every pregnant woman to improve her lifestyle by taking a balanced diet, exercising and avoiding substances such as tobacco and alcohol. The considerations for further research include the use of better diagnostic markers of stress-associated ND risks in early pregnancy, as well as potential therapeutic interventions promoting NGF delivery and fetal brain development. By targeting these factors, we can improve the conditions of the mother and fetus to decrease inconvenient neurodevelopmental consequences.

Authors Contribution

Conceptualization: TS, SB, NS
Methodology: TS, SB, NS, MAJ
Formal analysis: TS, SB, NS
Writing review and editing: AZ, ST, HK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Interlinking Human-Derived Leukemia Cells with Clinicopathological Therapeutics: Exploring Capsaicin's Anti-Cancer Mechanisms/potential for Leukemia Patients

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ABSTRACT

Capsaicin, a bioactive compound isolated from chilli peppers, comes out as a potential agent for its anti-proliferation role in leukemia patients' therapy. **Objectives:** This systematic review describes the Clinicopathological therapeutic potential of capsaicin against leukemia emphasizing the mechanism by which it inhibits growth through apoptosis, the cell cycle, and regulation of oncogenic signalling pathways in human-derived leukemia cell lines. **Methods:** According to PRISMA guidelines, the 75 studies were obtained from the various databases January 2013 and April 2024; Semantic Scholar, Google Scholar, PubMed as well as Frontiers and Link Springer. 50% (38) of the articles were taken from Semantic Scholar, 30% (22) from Google Scholar and 20% (15) from other search engines including PubMed and Link Springer. The papers included the inclusion criteria of PRISMA based on demographics, key outcomes and Anti-Cancer mechanisms majorly. **Results:** Capsaicin research published in America, Europe, Asia and Africa proves that it regulates vital processes at the cellular level including production of ROS, inhibition of NF-κB, STAT3, MAPK and cellular apoptosis. As human-derived cell lines are playing a pivotal role in cancer therapy, silicon methodologies along with in-vitro and in-vivo verification also shed more light on the improvement by capsaicin of the effectiveness of standard chemotherapeutic agents in combination with preferential killing of leukemic cells. **Conclusions:** Significantly, there were low levels of cytotoxicity of capsaicin to normal peripheral blood hematopoietic cells indicating that the compound is safe to use inhibiting the key oncogenic pathways and enhancing the efficacy of existing chemotherapeutic agents makes it a promising candidate for future therapeutic development.

INTRODUCTION

Leukemia is a hematological malignancy that starts in the marrow of the bones, leading to the uncontrolled spread of abnormal immunity-based blood cells which hinder the production of healthy blood cells. This condition is classified into different types, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [1, 2]. The global prevalence of leukemia varies, with higher values as seen in developed regions like North America and Europe, where the incidence can reach 8-10 cases per 100,000 individuals annually [3]. In contrast, Asia and Africa have lower incidence rates, although increasing industrialization and environmental changes have caused a slight rise in the number of cases [4]. The etiology of leukemia is multifactorial. Genetic problems such as mutations in tumour suppressor genes and oncogenes, chromosomal abnormalities like the Philadelphia chromosome t (9; 22) in CML, and defects in DNA repair mechanisms are well-established internal factors contributing to disease onset [5]. External factors, including exposure to ionizing radiation, chemicals like benzene, and infections caused by viruses such as the

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Epstein-Barr virus (EBV), also increase leukemia risk, particularly in individuals with pre-existing vulnerabilities [6, 7]. Region-specific causes vary across the world. In developed countries, leukemia is more frequently associated with environmental toxins and genetic factors, while in Asia, infections induced by viruses such as Human T-lymphotropic virus type 1 (HTLV-1) are more prevalent contributors [8]. In Europe, radiation exposure remains a significant risk factor, especially in regions affected by nuclear accidents like Chornobyl [9]. Unfortunately, the technology of these individualized treatments is not provided effectively to each patient, and patients in developing nations receiving initial-stage diagnosis and breakthrough treatment planning are excluded. Capsaicin has demonstrated anticancer properties by influencing pathways such as apoptosis, autophagy, and cell cycle arrest, making it a promising candidate for future therapies [10]. Knowledge of these risk factors is important for considering potential therapeutic strategies, for example, capsaicin – the substance responsible for the spiciness of chilli pepper. The present review has established that capsaicin has huge potential as an anticancer agent since it activates pathways that oppose the development of cancer such as apoptosis, autophagy as well as the cell cycle. It may reduce the risks linked with such risk factors through one or more processes. For instance, capsaicin can provoke apoptosis in leukemic cells due to oxidative stress and activation of pathways promoting pro-apoptosis and overcoming the benefits of genetic mutations and environmental carcinogens. Besides, inflammation is also considered a factor for cancer development, thus it could also work as an anti-inflammatory agent. The potential for capsaicin to enhance current chemotherapeutic regimens or act as a standalone treatment provides new hope for overcoming treatment resistance commonly observed in leukemia[11].

This study aims to establish how capsaicin targets and alters the activity of specific cancer-related genes, induces cell death and enhances the effectiveness of chemotherapeutic drugs in leukemia cells. The hypothesis is that the capsaicin through the transient receptor potential vanilloid 1 (TRPV1) receptor damages the mitochondria and triggers apoptosis in leukemia cells through the adenosine monophosphate-activated protein kinase and mechanistic target of rapamycin (AMPK/mTOR) pathway and other signaling pathways. The research will also assess its role in improving treatment outcomes and reducing chemotherapy-related toxicity. Knowing anti-cancer mechanisms is crucial when considering that substances like capsaicin can negatively influence cancer cell proliferation, promote cell death, and regulate pathways that are instrumental to cancer development. This work connects basic in vitro investigations of human-derived leukemia-derived cell lines (HL-60, K562, and Jurkat) to possible antineoplastic treatment strategies elucidated by the laboratory studies.

METHODS

The PRISMA guidelines for reporting were followed throughout the conduct of this study, which took place between January and August of 2024. It included 75 articles in English from the last 11 years (2013-2024). The papers included the following information, which was arranged systematically according to the inclusion criteria of PRISMA: author name followed by year, demographics, key outcomes, mechanisms, factors, study design, and references. The PRISMA guidelines were adopted to guide the systematic review of 75 articles used in the study. The inclusion criteria depended upon the essential features such as mechanism pathways, cell lines and outcomes peculiar to the investigations related to leukemia and capsaicin. To assess the potency of capsaicin in the various leukemia models, data analysis was directed to IC50 values together with cytotoxicity. Several search engines were used for the study; Semantic Scholar, PubMed and Google Scholar. 50% of the articles were taken from Semantic Scholar, 30% from Google Scholar and 20% from other search engines including PubMed. The search was conducted using phrases such as leukemia, capsaicin, cancer signalling pathways, cell lines anti-cancer activity etc. Article searches were done using keywords: Leukemia, capsaicin, NF-kb, STAT HL 60 etc. The articles which did not contain leukemia, and capsaicin as keywords and did not come under the range of years selected for study, did not meet the inclusion criteria and were eliminated in the filtering process. Inclusion criteria also focused on demographics and study design. 75 articles in total were downloaded from databases, 2 duplicates were removed and 73 were left for further study analysis. A total of 58 articles from the systematic review were eliminated out of 73 and 17 were left which were sorted and used (Figure 1).

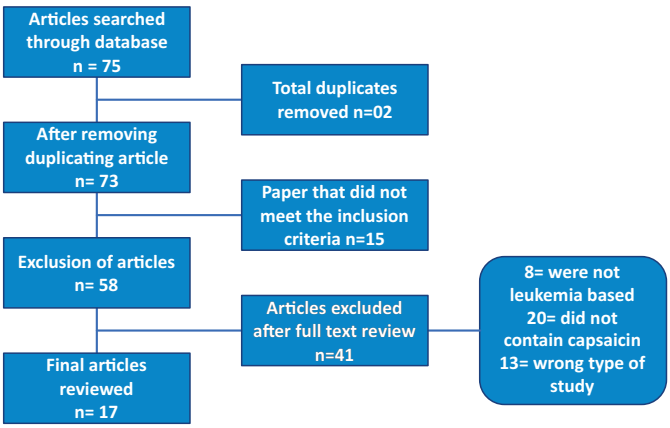

Figure 1: PRISMA Work Flow for Filtering Out Articles Focusing on Inclusion and Exclusion Method

RESULTS

The majority of papers were based on Acute Myeloid Leukemia and some were Chronic Myeloid Leukemia and

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Acute Lymphoblastic Leukemia. In this review, 47% of the articles belong to Asia, followed by Africa with 28%, and America and Europe both contribute 25% of the remaining. Out of 17 studies, 9 were taken from Semantic scholar, others were from various sources including Link Springer, Science Direct and Google Scholar [12]. 8 studies focused on Acute Myeloid Leukemia, 5 were focused on Chronic Myeloid Leukemia and 2 were focused on Acute Lymphoblastic Leukemia. Results of these studies [13-27, 28] are shown in the table 1.

Table 1: Systematic Review of Articles and Their Main Findings That Met the Inclusion Criteria of PRISMA

Reference (Location)	Study Design (Mechanism Pathway)	Cell line/ Human Model	Acute/ Chronic Leukemia	Results/ Findings	Conclusion
[13]	In silico and in-vitro (cell survival assay, microarray analysis)	K562 human cell line	Acute and chronic myeloid leukemia	14 out of 17 predicted pairs showing synergistic anticancer effects in cell survival assays.	The combination of capsaicin and mitoxantrone was highlighted for its significant anticancer synergy.
[14]	In vitro (lysosomal degradation)	Hsp 70	Chronic lymphocytic leukemia	Capsaicin promotes lysosomal degradation of Hsp70 and enhancing the anti-tumor effects.	Capsaicin can serve as a scaffold for developing novel Hsp90 and Hsp70 inhibitors. Acts as cancer co-therapeutic. This study demonstrates lysosomal degradation of Hsp70 by enhancing efficacy of chemotherapy.
[15]	In vitro (cell cytotoxicity)	CEM/CCRF, CEM/ADR5000	Acute myeloid leukemia	Capsaicin showed the highest cytotoxicity against p53 knockout HCT116 and CEM/CCRF leukemia cells. It showed reduced proliferation leukemia cells in a body.	Capsaicin is a potent anti-proliferative agent
[16]	In vitro (apoptosis, STAT3, NF-κB and cancer cell signalling pathway)	Jurkat cells	Jurkat cells	N-AVAM analogues induce apoptosis in leukemia cells, showing increased activity of caspase -8 and FADD, resulting in cancer cell death.	N-AVAM capsaicin analogues present promising potential for cancer therapy
[17]	In vitro (apoptosis)	K562 cells	Chronic Myeloid Leukemia	Capsaicin-loaded nanoliposomes showed significantly improved anticancer activity with lower IC50 values (17.88 μM) against leukemia cells	Capsaicin-loaded nanoliposomes enhance the anticancer effects of capsaicin by improving its bioavailability and selectivity for cancer cells
[18]	Invitro and Insilico (ROS generation)	CCRF-CEM, HL-60, K-562, MOLT-4, RPMI-8226, SR Cell lines	Acute and chronic myeloid leukemia	Capsaicin derivative 2a showed strong antiproliferative activity with 29.16% growth inhibition in MOLT-4 and 34.67% in CCRF -CEM leukemia cells.	The synthesized capsaicin analogues, particularly compound 20a, demonstrated significant anticancer activity.
[19]	In Vitro (JAK/STAT pathway)	K562 cells	Chronic myeloid leukemia	Capsaicin inhibited STAT3 expression. Downregulation of miR-520a-5p enhanced the inhibition of cell proliferation and increased apoptosis in K562 cells.	miR-520a-5p acts as an oncogene by targeting STAT3, and its inhibition, combined with cap saicin treatment, reduces leukemic cell viability and induces apoptosis.
[20]	Invitro (JAK-STAT signalling pathway, apoptosis)	HEL, THP1 cells	Acute myeloid leukemia and chronic myelogenous leukemia	Phytochemicals like capsaicin inhibited JAK-STAT pathway activation,reducing leukemia cell proliferation and inducing apoptosis	Phytochemicals, particularly those targeting STAT3, demonstrate potential in treating leukemia by disrupting the JAK-STAT pathway.

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[21]	In Vitro (MAPK signalling pathway)	JSC-1 cells	Acute lymphoblastic leukemia	Capsaicin-induced apoptosis via caspase -9 activation.	Capsaicin shows potential as a therapeutic agent for PEL by inhibiting ERK and p38 MAPK signaling pathways
[22]	In vitro (oxidative stress, and apoptosis)	K562, KU812, MOLM-6 cell lines	Chronic Myeloid Leukemia	Capsaicin worked synergistically when combined with imatinib to improve anticancer activity.	Capsaicin, in combination with imatinib, shows significant potential as a complementary treatment for chronic myeloid leukemia.
[23]	In Vitro (cell cycle progression , apoptosis)	Human KB cancer cells	General	Capsaicin inhibited the proliferation of KB cells,induced apoptosis, and led to cell cycle arrest at the G2/M phase.	Capsaicin modulates cell cycle progression and induces apoptosis through mitochondrial and caspase pathways in human cancer cells
[24]	In vitro (apoptosis and various cell signalling pathways)	HL-60 and HL-525 cell lines	Acute and chronic myeloid leukemia	Capsaicin induces apoptosis in leukemia cells through oxidative stress and activation of caspase pathways.	Capsaicin holds promise as an anticancer agent by targeting apoptosis pathways in leukemia cells, particularly through the generation of ROS and the activation of apoptotic signals.
[25]	In Vitro (apoptosis)	JSC-1 cell lines	Acute lymphoblastic leukemia	Capsaicin promotes apoptosis in leukemia cells by upregulating ATF4 protein levels	Capsaicin triggers the ATF4-CHOP-PUMA pathway to induce apoptosis in leukemia cells, suggesting its potential as a treatment option for leukemia
[26]	In Vitro (apoptosis induction, anti-inflammatory actions, and cell cycle regulation)	Human CML cell lines	Acute and chronic myeloid leukemia	Capsaicin can inhibit metastasis by modulating pathways such as VEGF,MMP9, AMPK-NF-kB, and p38 MAPK.	Capsaicin holds potential for preventing cancer metastasis by inhibiting critical pathways involved in angiogenesis, matrix degradation,and cell migration as in leukemia
[27]	In vitro (Apoptosis)	HL 60 cell line	Acute Myeloid Leukemia	Capsaicin effectively induces apoptosis in HL-60 cells by increasing Caspase-3 and Caspase-9. With an IC50 value of 16.7 µM.	Capsaicin demonstrated strong potential as a natural chemotherapeutic agent against leukemia, specifically through pro-apoptotic mechanisms.
[28]	In vivo and in vitro (tumour-induced Angiogenesis)	Human endothelial cells	N.A	Tumor-induced angiogenesis is directly related to blood cancer. Capsaicin inhibited VEGF-induced angiogenesis in cells in the chorioallantoic membrane of the chick model.	Capsaicin suppressed tumor -induced angiogenesis in the chick chorioallantoic membrane assay. Angiogenesis is linked with the spread of cancer through blood

DISCUSSION

Leukemia, as a systemic disease, is the result of multiple factors including genetics and environment in which malignant or cancerous cells with special-functional properties than normal cells proliferate and multiply out of control [29]. The reports also reveal that when a woman is pregnant, contracting the influenza virus through the use of antibiotics puts her and her fetus at a higher risk of acute lymphoid leukemia [30]. Infections are involved especially for acute lymphoblastic leukemia as shown in some mice models [31]. Epidemiological evidence indicates that smoking is the most substantial risk for leukemia mortality and morbidity, it has a more severe effect in males than in females, and body mass index also plays a pivotal role here [32]. Some of the relevant risk factors for developing AML include hepatitis C virus infection and a history of exposure to environmental factors that can be used as home

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decoration [33]. Leukemia is a malignancy of hematopoietic stem cells characterized by abnormal differentiation and proliferation [33]. Recent research has highlighted the complex interplay of various factors in leukemia pathogenesis. Natural killer (NK) cells, critical for cancer cell elimination, are being explored for immunotherapy, including adoptive transfer and CAR-NK approaches. Non-coding RNAs have emerged as potential diagnostic and prognostic biomarkers due to their involvement in oncogenic processes [34]. The transient receptor potential vanilloid 1 (TRPV1) receptors, which are essential for maintaining cellular homeostasis, are one of the primary mechanisms through which capsaicin performs its therapeutic job. When capsaicin binds to TRPV1, calcium enters the cell, causing mitochondrial malfunction, the production of reactive oxygen species (ROS), and the resulting activation of pro-apoptotic pathways [35]. This initiates the release of cytochrome c from the mitochondria, activating the caspase cascade, and leading to programmed cell death, which is essential for controlling malignant cell growth [36]. Furthermore, it has been demonstrated that capsaicin affects several important transcription factors, including NF-κB, STAT3, and p53, which frequently get abnormal in leukemia cells and are implicated in the development of leukemia. Capsaicin increases the effectiveness of traditional chemotherapy by inhibiting NF-κB activity, which makes leukemia cells more susceptible to apoptosis [37]. Moreover, capsaicin enhances the expression of p53, a well-known tumor suppressor, facilitating the repair of damaged DNA and inducing cell cycle arrest [38]. Capsaicin's ability to induce autophagy, a cellular breakdown process, demonstrates its therapeutic value. In cancer, autophagy serves as a trigger for some cancer-related cell death events as well as a survival strategy for cancer cells undergoing stress. It has been demonstrated that capsaicin causes apoptotic cell death in leukemia via altering the AMPK/mTOR signalling pathway, which controls autophagy and cellular metabolism. [39]. It is observed that capsaicin triggers autophagy in different types of human cancer cells such as oral squamous cell carcinoma and renal cell carcinoma. This autophagy induction occurs through several signaling pathways such as TFEB, AMPK/mTOR and ULK1. Capsaicin possesses anticancer effects in the following ways: anti-inflammatory, antioxidant, and anti-mutagenic. It is involved in the regulation of apoptosis, angiogenesis, and cell division; modulating signalling networks like PI3K/AKT and NF-κB. Capsaicin regulates TRPV1 receptors which leads to the release of calcium, disruption of mitochondrial membrane, and induce production of ROS that cause apoptosis. A study showed that capsaicin caused apoptosis through the AMPK/mTOR signalling pathway. Despite its promising anticancer effects, the therapeutic application of capsaicin in leukemia has certain limitations. The concentration of capsaicin required to induce apoptosis in cancer cells can sometimes cause cytotoxicity in normal cells, raising concerns about its safety and potential side effects in clinical settings [40]. Furthermore, the bioavailability of capsaicin is relatively low, as it is rapidly metabolized in the liver, which limits its effectiveness when administered orally [41]. These limitations necessitate further research into optimizing capsaicin formulations, such as using nanoparticles or liposomes to enhance its delivery and reduce off-target effects [42]. The experiments carried out on cultures and animals prove the hypothesis that capsaicin has a pro-apoptotic effect and increases the chemotherapy efficacy in leukemia therapy. Investigation revealed that capsaicin inhibits cell proliferation and causes apoptosis in various Human leukemia cell lines including HL-60 K, 562, and Jurkat cells through caspase 9 activation with downregulation of anti-apoptotic oncogenic signal transduction Pathways including AMPK/mTOR. The above cellular effects were substantiated in in-vivo models where treatment with capsaicin caused a massive decrease in tumour volume ranging from 20-40 % and this was due to the density of the pro-apoptotic and anti-proliferative effects of the compound. Further, the present study revealed that capsaicin can potentiate normal chemotherapeutic drugs including mitoxantrone and cause increased tumour regression in vivo. Combined cellular and organism-level findings suggest that capsaicin acts as an independent chemotherapeutic agent; it also boosts the effects of traditional chemotherapy drugs and may be useful for leukaemia types that are resistant to conventional treatments. These results have the potential to improve chemotherapy efficacy by increasing the biological effects of the usual chemotherapeutic drugs and decreasing the toxicity as well. For instance, there is evidence that capsaicin enhances the sensitivity of leukemia cells to such drugs as doxorubicin and vincristine thus making it possible to use small doses of these products for similar desired effects. This is attained by its capacity to bring about apoptosis and disarm significant revival circuits in the malignant growth cells hence making them vulnerable to chemo treatments. Also, the synergy between capsaicin and other agents like imatinib has been

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found to boost antitumor effects through multiple pathways as well as to overcome the resistance that is a particular issue in cancer therapies, in particular, leukemia. Although the systemic bioavailability of capsaicin is low because of first-pass metabolism, future endeavors require long-term studies for the enhancement of delivering capsaicin to maximize its pharmacological effects. Some of the concrete strategies may be liposome formulation, nanoparticles or solid lipid nanoparticles as the solubility and stabilization of capsaicin can be an issue [43]. Nonetheless, future works which involve observing the enhancement of the co-administration with absorption enhancers or the development of transdermal delivery systems will improve the bioavailability. Since these strategies are based on a synthesis of capsaicin and its delivery to the target therapeutic site, clinical trials testing these approaches will be necessary to identify the most effective ways of delivering it therapeutically [44].

CONCLUSIONS

It was concluded that capsaicin exhibits promising anticancer activity, yet the following gaps need to be filled. Future work should analyze the safety of capsaicin in the Leukemia patient profile and its bioavailability, and toxicity when administered at therapeutic concentrations. Specific experimental procedures should be in vitro and animal studies to assess capsaicin's interaction with the baseline chemotherapy protocols. Further, there is a need to conduct clinical trials to determine the effectiveness of advanced formulation of capsaicin in enhancing the clinical results in the leukemia management. Closely evaluating these gaps will be quintessential in the provision of further understanding of the role of capsaicin as adjuvant therapy in hematological malignancy.

Authors Contribution

Conceptualization: MM, FC, AK
Methodology: MM, FC, AK
Formal analysis: MM, FC, AK
Writing review and editing: ATN, JA, SK, DD

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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The Impact of School-Based Caries Prevention Programs on DMFT Scores and Oral Health Behaviors in School Children

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ABSTRACT

Oral health promotion is recognized as one of the fundamental components of health-promoting schools. However, few studies have demonstrated the efficacy of supportive school environments for school children's Oral health. This systematic review evaluates the impact of school-based caries prevention programs on DMFT scores and Oral health behaviours in school children. **Objective:** To evaluate the impact of school-based caries prevention programs on DMFT Scores and Oral Health Behaviors in school children. **Methods:** Databases like PubMed, Google Scholar, Cochrane Library, Springer, and Science Direct were searched from January 2009 to February 2024. Prisma guidelines were followed; 1, 950 studies were identified on the first search, titles, and abstracts of 500 papers were screened, 500 full-text papers were screened for eligibility, and 25 studies meeting the inclusion criteria were evaluated, relevant information was extracted, and a systematic review was conducted. Twenty-five studies were included in the systematic review. **Results:** These results indicate the significant role of SCPP among school-going children. Children with school-based caries prevention programs compared to those with no school-based caries prevention programs showed improved DMFT scores, reduced caries increment, healthy oral health behaviours, consistent Oral health hygienic habits, frequent use of flossing, fluoride toothpaste and mouth rinsing, and increased caries prevention knowledge. **Conclusions:** It was concluded that based on the pooled results, school-based caries prevention programs provide better, easily accessible, and sustainable caries prevention activities to school children to improve DMFT scores and Oral health behaviours.

INTRODUCTION

Oral diseases, also known as non-communicable diseases (NCDs), are preventable oral health conditions. It is a major public health problem affecting 60-90% of school-going children and adults in developing countries [1]. Dental caries is the major chronic disease affecting more than 600 million children globally and 135 million children in the Southeast Asian region. [2]. 35% of the world's population is affected by caries. Of which, 2.4 billion and 486 million populations are reported with caries of permanent and primary teeth, respectively [3]. Dental caries is caused by the bacterial fermentation of dietary carbohydrates in the susceptible host. Smooth surface caries in primary maxillary anterior teeth, and missed, or decayed surfaces are indicative of early childhood caries (ECC) in children <6 years [4]. Oral health (OH) conditions, if left untreated, may lead to gingivitis, oral submucous fibrosis, and oral cancer. It can cause pain, discomfort, poor ability of children to eat or drink, malnutrition, speaking and sleeping issues, impaired social and behavioural patterns, and low self-esteem [5]. Caries potentially contribute to reduced school

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attendance rates, lack of children's proper concentration, and poor participation in school activities. OH is recognized as equally important as general health conditions like cardiovascular disease (CVD), mental health conditions, diabetes mellitus (DM), and cancers. Due to increased cost and uneven distribution of OH services in developing countries; developed countries are now reported to be well below the WHO's goal of less than 3 decayed, missing, or filled teeth (DMFT) per 12-year-old child [6]. DMFT index is a valuable and simple tool used to determine, measure, and monitor the oral health status in a community. Preventive behaviours play a pivotal role in ensuring proper OH for children. The scale of the preventive behaviour may include aspects such as oral health hygiene, accessibility to OH services, appropriate oral care, use of clean objects and fluoridated toothpaste. These dimensions along with access to caries prevention programs should be conducted periodically from an early age to prevent the occurrence of poor OH conditions in school children. The limited OH education (OHE) includes caries preventive measures, inadequate access to OH services, increased sugar consumption, and reduced exposure to fluoride products compound ECC risk over time. Public health managers and stakeholders, especially in lower-middle-income countries (LMICs), should take evidence-based preventive steps to prevent ECC and concurrently promote OH. OHE is an important and effective public health prevention program tool as it provides not only caries education but also curative, preventive, and promotional dental health activities [7]. Promoting OH in children by using health-promoting schools (HPS) has been recommended by the World Health Organization (WHO). HPS is a comprehensive school-based concept focused on developing healthy lifestyles, and behaviour, and preventing diseases by engaging schoolchildren in healthy school activities using a multi-sectoral approach. WHO first launched the Global School Health Initiatives in 1995 [8]. This key intervention helps countries, especially LMICs, to develop caries prevention programs and build partnerships between health and educational organizations [9]. Globally, schools have been identified as an ideal environment and opportunity for caries prevention as children spend maximum time in their school. A school-based caries prevention program (SCPP) is a preventive strategy aimed at improving the OH status of school children during school years. It exclusively focuses on providing accessible and appropriate caries prevention guidance during school years that last a lifetime. They are considered supportive settings to promote OH in terms of implementing policies and caries prevention programs in schools to improve caries awareness, nutritional intake, school safety for dental injuries, caries screening and dental referral facilities [10]. According to Tahani et al., active involvement of school children and their caregivers in SCPPs are more likely to report improved caries knowledge and lower DMFT scores [11]. SCPPs may consist of a range of initiatives such as integrating OH services and caries prevention programs as part of the curriculum, implementing OH-enhancing social environments, supervised daily group dental brushing, and topical fluoride application programs [12]. The majority of these programs in school settings are delivered using either traditional approaches such as lectures, demonstrations, and models or the utilization of modern approaches such as flipcharts, videos, slide presentations, and other actionable tasks like daily brushing, fluoridated water, and toothpaste applications [13].

This study aims to evaluate the impact of school-based caries prevention programs on DMFT Scores and Oral Health Behaviors in school children.

METHODS

The final eligibility of papers was analyzed by using the inclusion and exclusion criteria (Table 1).

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Papers published between January 2009 to February 2024	Studies that have been previously included in the reviewor are duplicates of other included studies.
Directly linked to SBCPP, DMFT scores, and OH behaviours	Studies with inadequate methodological rigour, such as case reports or poorly designed observational studies.
Studies written in English language only	Studies with insufficient or unreliable data on SBCPP implementation, DMFT scores, or OH behaviours.
Studies conducted in school settings among school children (aged 5-14 years) as target population	Studies with a high risk of reporting bias, such as selective reporting of outcomes or lack of blinding.
Studies using SBCPP to address OH behaviors and improve DMFT scores	Studies with extreme or outlier results could significantly distort the overall findings.
Papers mentioning the impact of SBCPP on DMFT scores and OH behaviours in school children	Studies conducted in non-school settings that not accurately reflect the challenges and opportunities of school-based interventions.

PubMed and Google Scholar were systematically searched to detect all the relevant studies published during the last 15 years (January 2009 to February 2024) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement by using the following search key terms “caries”, “school children”, “decayed, missing, or filled teeth”, “impact”, “DMFT score”, “oral health”, “dental”, “caries prevention”, “oral health behaviours”, “school-based program.” Initially, a total of 1,950 studies were identified, a total of 2,000 potential studies were screened, and 1500 studies were excluded, followed by an in-depth reading of 500 remaining full-text articles led to the exclusion of 475 studies. 25 studies were included for qualitative synthesis (Figure 1).

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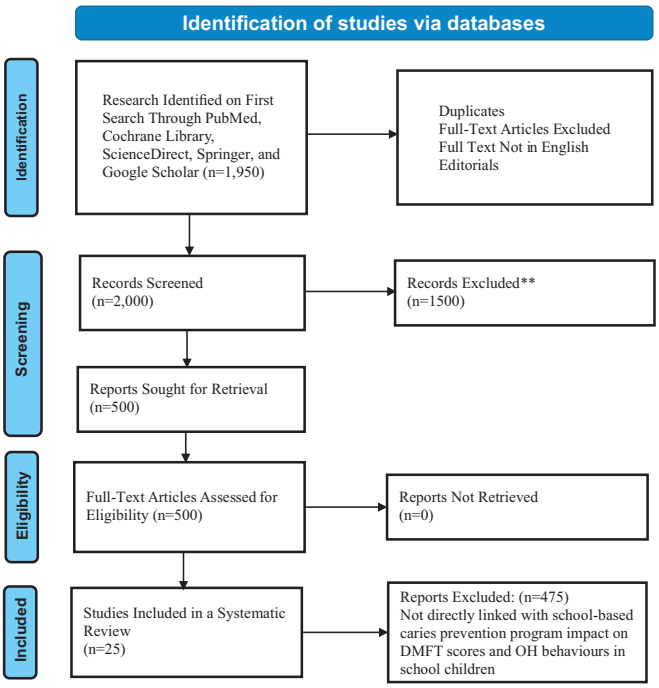

Figure 1: Screened Studies Included in the Systematic Review

The program components include 1): Program vision involving schoolchildren (aged 5-16 years) as the target population and school as the location for implementation of the prevention program 2) program activities imparted by schoolteachers or dentists using OHE methods such as OH demos, lectures, games, and dental counselling 3). The impact of SCPP on overall health statuses such as improved DMFT score, OH behaviors and hygiene, and reduced caries prevalence. The overview of the program design of the SCPP as per the systematic review was illustrated (Figure 2).

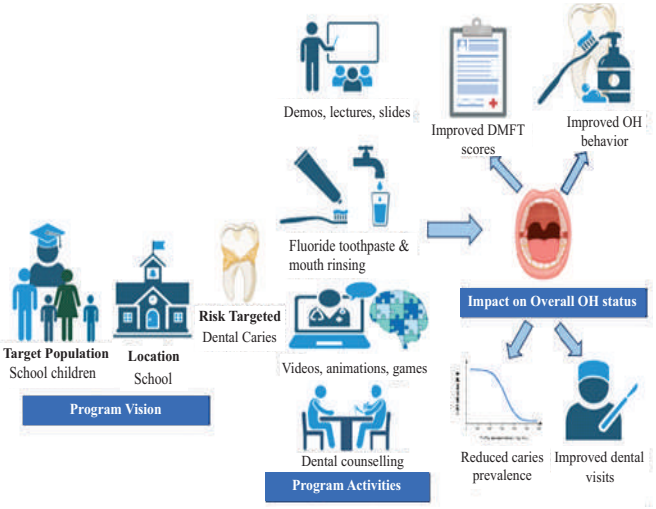

Figure 2: Program Design of the SCPP as Per the Systematic Review

RESULTS

This systematic review yielded a total of 23 studies, of which, 6 were RCT studies, 5 were cross-sectional studies, and 5 were cohort studies. The remaining studies were clinical trials, longitudinal studies, quasi-experimental studies, and follow-up studies. A combined total of 28,882 schoolchildren included in the studies have been evaluated in this systematic review. A comprehensive summary of the included study findings in 23 studies is presented (Table 2).

Table 2: Summary of Study Findings Evaluated

Sr. No.	Country	Total Participants / Studies	Intervention	Outcome	Evaluation Method	Reference
1	Japan	2573 Participants	After-Lunch Tooth-Brushing Program	Zero Excess DMFT	ZINB	[14]
2	Australia	34 Studies	SCPP	Improved DMFT Scores	DMFT Index	[15]
3	India	1,100 Participants	OHE	Improved Oral Hygiene Status	OHI-S	[16]
4	India	600 Participants	OHE	Improved OH Behaviors	KAP, DMFT Scores	[17]
5	Kuwait	440 Participants	OHE	Improved DMFT Scores	DMFT Indices	[18]
6	India	276 Participants	OHE	Improved Caries Status	DMFT Index	[19]
7	China	514 Participants	Monthly OHE Sessions	Improved OH Behaviours	DMFT Index	[20]
8	China	1,334 Participants	OHE	Reduced DMFT Increment	DMFT Index	[21]
9	Iran	12 Studies	OHE	Improved OH Behaviours	KAP Score	[22]
10	India	120 Participants	SCPP	Improved DMFT	Person Chi-Square	[23]
11	Taiwan	340 Participants	HPS Framework	Improved Hygienic Behaviours	Linear & Logistic Regression Model	[24]
12	Iran	470 Participants	OHE	Improved OH Behavior	SPSS	[25]
13	Iran	82 Participants	OHE	Improved Self-Care Behaviour	Mann-Whitney U-Test	[26]
14	Iran	200 Participants	OHE	Improved OH Behavior	SPSS	[27]
15	India	200 Participants	OHE	Improved OH Behavior	ALG	[28]
16	India	100 Participants	OHE	Improved Hygienic Behaviours	KAP Score	[29]
17	Sudan	423 Participants	OHE	Improved OH Behaviour	SPSS	[30]
18	USA	8,207 Participants	SCPSP	Improved DMFT Score	DMFT Index	[31]
19	Japan	173 Participants	OHE	Improved Hygienic Behaviours	OHI-S	[32]

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20	Pakistan	175 Participants	OHE	Higher Combined KBS Scores	GEE	[33]
21	Bangladesh	944 Participants	OHE	Reduced Caries Prevalence	Mcnemar's Chi-Square	[34]
22	USA	6,927 Participants	SCPP	Reduced Caries Prevalence	DMFT Index	[35]
23	Kuwait	300 Participants	SOHP	Better OHRQoL	X^2 Analysis	[36]

Zero-inflated negative binomial (ZINB); OHI-S, oral hygiene index simplified; OHE, oral health education; RCT, randomized controlled trial; HPS, health-promoting school; GEE, generalized estimating equations; FMR, fluoride mouth rinse; SOHP, school-based OH program; OHRQoL, oral health-related QoL; SPSS, statically package for the social science; ALG, absolute learning gain; SCPSP, school-based caries primary and secondary prevention program; SCPP, school-based caries prevention program; DMFT, decayed, missing, or filled teeth.

Seventeen studies used OHE interventions in the SCPP. Three strategy types were used in the studies evaluated (Figure 1). Among these, 11 studies used OHE interventions comprising OH lectures, practical demonstrations, caries prevention booklets, OH talks and counselling sessions. The remaining 6 studies used OHE based on OH-related animations, games, and videos. These interventions were delivered by either dentist, teacher, peer, or a combination of teacher and dentist. Eight studies included SCPP strategies consisting of the topic antibacterial therapy, after-lunch tooth-brushing, daily teacher-supervised group tooth-brushing, and fluoride mouth rinse (Figure 3).

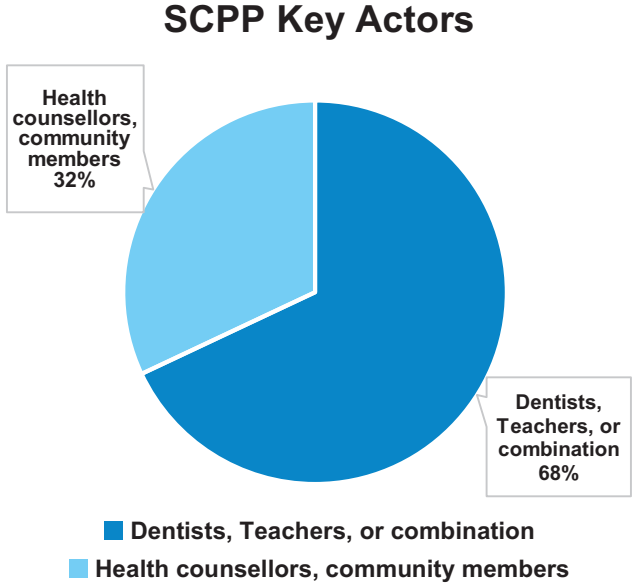

Figure 3: OHE Interventions Delivered by Key Actors As Per Systematic Review

SCPP strategies implemented in the included studies as per systematic review are studied. Traditional strategies include lectures, demonstrations, and OHE talk. Modern activities include caries animation, videos, and games. Others include fluoride mouth rinsing, daily supervised toothbrushing, and flossing practice (Figure 4).

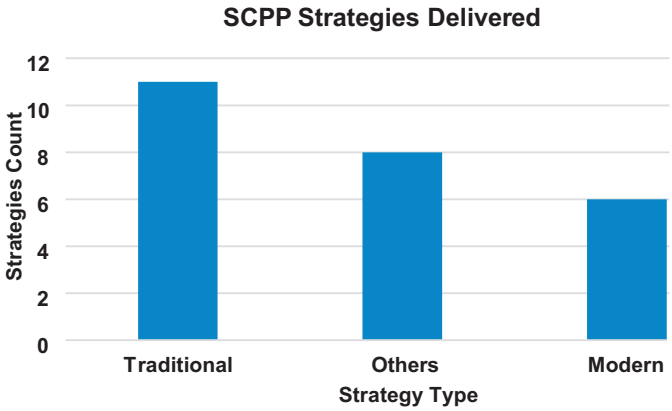

Figure 4: SCPP Strategies Implemented in the Included Studies

The WHO-modified DMFT index and KAP scores were used by the majority of the studies to measure the changes in DMFT scores and OH behaviours. Other studies used OHI-S, Person chi-square, linear & logistic regression model, SPSS, Mann-Whitney U-test, ALG, McNemar's chi-square, and X2 analysis to assess the improvements in levels of OH hygiene status, OHRQoL, and caries prevalence (Table 3).

Table 3: Table of Reference Used in Included Studies to Analyze DMFT Scores and OH Behaviors

Characteristics	Standard Reference Used In Studies
DMFT Scores and OH Status	WHO Modified DMFT* Index (Reference Values=0-12)
OH Behaviors	KAP** Score
Oral Hygiene Status	OHI-S (Reference Values =1-10, Ranging from Very Poor to Perfect Oral Hygiene)
Mean Plaque and Gingival Score	Silness And Loe Plaque Index, Low and Sillness Gingival Index
Combined OH Knowledge, Behavior, and Hygiene Status	KBS*** Score (Ranging From 0 To 36)
Caries Prevalence (Follow-Up Data Compared to Baseline)	Mcnemar's Chi-Square Analysis
Ohrqol	X^2 Analysis
Statistical Analysis	The Linear and Logistic Regression Model, Person Chi-Square, Quasi-Likelihood Poisson Regression

DMFT, Decayed, Missing and Filled Teeth; OH, oral health; KAP, Knowledge, attitude, and practice; OHI-S, Oral hygiene index simplified; KBS, knowledge, behaviour, and hygiene status; OHRQoL, OH-related quality of life *DMFT score is a useful index in determining OH status by taking the sum of several D (decayed), M(missing) due to caries, and F (filled) teeth in the permanent teeth. **KAP, also known as knowledge, attitude, behaviour, and practice surveys. It is a quantitative method that involves a predefined standardized questionnaire. It provides valuable

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insights into qualitative and quantitative information in health-related behavioural research. *** The KBS index is constructed by combining scores of OH knowledge, behaviour, and hygiene status.

DISCUSSION

Oral health (OH) is a fundamental part of general health. Several chronic illnesses such as asthma, diabetes, and oral cancer. Globally, the DMFT scale has been used as an important index for over 70 years to assess overall OH status and dental health. School-based caries prevention programs (SCPP) can positively impact the DMFT scores and OH behaviours in school children. A cross-sectional study consisting of 2573 children aged 10-11 years was conducted by Tashiro *et al.*, in Japan. The study found that children exposed to supervised after-lunch toothbrushing programs compared to children from schools without it showed higher odds ratio (OR) for zero excess DMFT (OR=1.47, 95% CI=1.00-2.15, p=0.049) as indicated by zero-inflated negative binominal (ZINB) [14]. A systematic review and meta-analysis of 34 studies published between 1996 and 2021 was conducted by Guray *et al.*, in Australia. Among them, 30 studies were experimental studies and 4 were observational studies conducted in LMICs. The study showed that SCPPs had a positive impact on dental caries as measured by DMFT index (standardized mean difference (SMD)=- 0.33; 95% CI – 0.56 – 0.10; p=0.005, DMFT and DMFT/ S (decayed, missing, and filled teeth/ surfaces) score >1 Risk ratio (RR)=0.70; 95% CI 0.53 to 0.94; p=0.02) and plaque scores (SMD=-0.32; 95% CI – 0.46 to -0.18; p<0.00001) [16]. A meta-analysis of 7 RCTs published between 2010 and 2019 (A combined total of 1,100 children aged 5-16 years) was undertaken by Karuveettil *et al.*, in India. The Intervention group (IG) received OHE methods such as demos, videos, posters, and oral hygiene instructions given by dental health professionals and the control group (CG) received traditional OHE methods such as OH talk or counselling. The study found that children exposed to IG compared to CG showed improved oral hygiene status and dental caries as indicated by oral hygiene index simplified (OHI-S), debris status, and DMFT index (cumulative mean difference (CMD); -0.37 (-0.74, 0.00), -0.20 (0.33, -0.07), and -0.17 (0.73, 0.38), respectively) [17]. A non-randomized controlled trial consisting of 600 school children (Group A; OHE imparted by a dental professional=300 school children, group B; OHE imparted by schoolteacher=300 children) was conducted by Alsumait *et al.*, in India. The results of the data analysis using knowledge, attitude, and practice (KAP) and DMFT scores indicated that curriculum-based educational OH intervention significantly improved OH behaviours and reduced caries experience among Indian school children (DMFT score; preintervention = 0.98 ± 1.69 and post intervention=0.75 ± 1.51, KAP score; Group A=10.74 ± 0.60 and group B=10.64 ± 0.60) [18]. A cross-sectional study comprising 440 primary school students (aged 11-12 years) was conducted by Bhardwaj *et al.*, in Kuwait. Study participants were classified into 2 groups; the school OH program (SOHP) group received at least 1 OHE session on the application of fluoride varnish and fissure sealants and the non-SOHP group without any OHE activity. The study found that SOHP children compared to non-SOHP children reported statistically significant differences in mean DMFTs as determined by DMFT indices (mean DMFTs for SOHP and non-SOHP children=1.41 (1.66) and 7.24 (7.78), respectively, (p<0.001) [19]. Gurav et al. conducted a cohort study consisting of 276 schoolchildren (aged 12-15 years old) in the Government Senior Secondary School, Sajauli India. The study found that the OHE program significantly improved mean plaque and gingival score, and caries status among participants irrespective of gender (p>0.05) as assessed by Silness and Loe plaque index, Low and Sillness gingival index, and WHO-modified DMFT index, respectively [16]. A clinical trial comprising 514 kindergarten children (aged 1-3 years) was conducted by Shan *et al.* The study reported that IG compared to CG showed a higher percentage of daily toothbrushing twice a day (87.6% vs. 69%, p<0.001), and reduced DMFS increment as determined by DMFT index (p=0.09) [20]. Similar findings were also reported in a RCT consisting of 1, 334 preschool children (aged 3 years) by Alsumait *et al.*, in China [18]. A cluster RCT comprising 2021 schoolchildren (aged 6-12 years) was conducted in Switzerland. IG participants (n=1107) received a 21-day brush day & night brush program and CG participants (n=915) did not receive it. The study revealed that IG compared to CG showed a 45% increased probability of no worsening in the DMFT score as indicated by the DMFT index [19-21]. OH behaviours and beliefs are built during childhood, therefore schools can provide an ideal environment to prevent caries increment [25]. SCPP aims to promote healthy OH behaviours and the adoption of healthy lifestyles such as daily toothbrushing, fluoride nutrition, and fissure sealant application [37]. A two-decade systematic review and meta-analysis of 12 studies (5 were individual RCTs, 4 cluster-RCTs, and 3 Quasi-experimental research work), including 2,838 students (aged 6-18 years) were performed by Dadipoor *et al.*, in Iran. IG received educational interventions such as lectures, albums, movies, and dental instructional models and the comparison group (CG) received any OHE intervention. The results of the RevMan 2014 analysis demonstrated that IG

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compared to CG showed improved OH behaviours and outcomes in terms of knowledge, attitude, behaviour, plaque and gingival index (SMD; knowledge=3.31, 95% CI 2.52 to 4.11, attitude=1.99, 95% CI 0.43 to 3.54, behaviour = 4.74, 95% CI 3.70 to 5.77, plaque index (PI)=-1.01, 95% CI -0.36 to 1.02, gingival index (GI)=0.33, 95% CI -0.36 to 1.02) [38]. A longitudinal study comprising 120 schoolchildren (aged 8 to 10 years) was conducted by You *et al.*, in India. The results of the study found that children with parental participation compared to children without parental participation in SCPP showed statistically significant changes, after the 36th week of program implementation, in mean DMFTS, lower caries increments, improved OHI, as assessed by person chi-square, quasi-likelihood Poisson regression (p<0.001) [39]. A quasi-experimental study comprising 340 schoolchildren (IG with HPS framework=166 children, CG without HPS framework=174) in rural high caries (>68%) elementary school was conducted by Wei *et al.*, in Taiwan. The study found that IG compared to CG reported increased participation in follow-up to OH-related knowledge (95% CI=0.27 to 3.28), improved hygienic behaviours (95% CI=0.76 to 2.15), self-efficacy regarding flossing and fluoride toothpaste (aOR=5.88, 95% CI=2.31 to 14.93) as determined by linear and logistic regression model [24]. Similar findings were also reported in a cluster RCT conducted by Salahshour *et al.*, among 470 elementary students in Iran [25]. An RCT consisting of 82 schoolchildren (aged 6-12 years) (IG; OHE games and animations=38 students, CG; routine school OHE=44 students) was conducted by Hashemi *et al.*, in Iran. The study revealed that IG compared to CG showed improved OH self-care education and behaviour, and self-efficacy, as indicated by data analysis, performed 5 months post-intervention using Mann-Whitney U-test (3.8 to 4.8, 36.8 to 48.9, and 17.07 to 18.29, respectively, p>0.05) [26]. These findings were similar to a quasi-experimental study comprising 200 schoolchildren conducted by Mohamad khan *et al.*, in Iran, a cross-sectional study undertaken by Sinha *et al.*, among 200 schoolchildren, RCT by Gauba *et al.*, in India among 100 children (10-12 years), cross-sectional study by Albani *et al.*, among 423 schoolchildren in Sudan [27-30]. A prospective cohort study comprising 8,207 schoolchildren (aged<12 years) was conducted by Ruff & Niederman., in the USA. Two caries prevention programs were designed: primary and secondary prevention program (6584 participants); glass ionomer sealant and interim therapeutic restoration activities, primary prevention program only (1623 participants); glass ionomer sealant. The study found that students in primary and secondary prevention programs compared to primary prevention programs only demonstrated a reduced risk of untreated decay on permanent dentition (OR=0.77, 95% CI=0.60, 0.98) [31]. A 6-month follow-up study comprising 173 schoolchildren (aged<12 years) was conducted by Nguyen *et al.*, in Japan. The WHO-modified debris index (DI) showed that OHE IG compared to CG (with no OHE intervention) reported improved OH knowledge (p<0.01), behaviour (p<0.05), and hygiene (p<0.001) [32]. A 2-year cluster RCT was conducted by Haleem *et al.*, among 175 schoolchildren in Pakistan. The generalized estimating equations showed that IG (OHE imparted by either a dentist or a teacher) compared to CG (did not receive any form of OHE) reported higher combined OH knowledge, behaviour, and hygiene status (KBS) scores (p<0.001) [33]. A cohort study conducted by Haque *et al.*, among 944 schoolchildren in Bangladesh compared baseline data regarding OH knowledge, attitude, and practice scores with 6 months of follow-up. The results of McNemar's chi-square analysis revealed that follow-up compared to baseline showed OHE intervention significantly reduced caries prevalence among study participants to 42.5% (p<0.01), higher healthy OH practices (AOR=1.64; 95% CI=1.12, 3.38), OH knowledge (95% CI=1.87, 3.45), and OH attitude (95% CI=1.44-2.87) [34] A clinical trial comprising 1, 363 children (grade 1-5) was conducted in the USA. The study found that the fluoride mouth rinse (FMR) program reduced caries prevalence and improved mouthwash practice in high-risk schools (≥1 untreated carious teeth) compared to low-risk schools (<1 untreated carious teeth)(55% vs. 10% caries reduction in 5-6 years of FMR participation compared to none). Starr *et al.* conducted a 6-year prospective open cohort study consisting of 6,927 children exposed to SCPP in 33 US public elementary schools. The study found that SCPP activities such as fluoride varnish, teacher-supervised daily toothbrushing, fluoride toothpaste, and oral hygiene instructions reduced untreated caries prevalence by >50% (95% CI) [35]. A cross-sectional study consisting of 300 schoolchildren (aged<13 years) was conducted by Alsumait *et al.*, in Kuwait. The X2 analysis showed that children attending SOHP compared to non-SOHP demonstrated better oral health-related QoL (OHRQoL) and overall OH status (OR=2.28, 95% CI=1.41 – 3.68, p<0.001, OR=2.85, 95% CI=1.31-6.18, p=0.008, respectively) [18].

CONCLUSIONS

It was concluded that this systematic review provides a detailed comprehensive review of the impact of SCPP on DMFT scores, OH behaviours in terms of daily toothbrushing, flossing, OH hygiene habits, use of dental care products, and a routine visit to the dentist in school children. The study found that SCPP demonstrated a

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positive correlation with the DMFT scores and OH behavioural patterns among school children.

Authors Contribution

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Conflicts of Interest

All the authors declare no conflict of interest.

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