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Period Poverty Beyond Hygiene: Intersectional and Feminist Public Health Research Perspectives

OPEN ACCESS

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Period poverty is often discussed as a matter of hygiene. Sometimes it is framed as a problem of access to sanitary products. Yet such descriptions are too narrow for what has become one of the clearest expressions of gendered public health inequality in low- and middle-income countries (LMICs) [1]. Period poverty is not simply about pads, cloths, medications, or menstrual cups. It reflects the unequal social organization of health, dignity, mobility, education, and power. It is a structural, social, political, and public health phenomenon, deeply relational [2]. Menstruation health remained hidden within policy and research spaces. Period health remained invisible in mainstream public health discourse for decades. Conditions that affect millions of menstruating individuals across schools, workplaces, prisons, refugee camps, and households were treated as private discomforts rather than collective policy failures [3]. This absence was never neutral, which reflected longstanding patriarchal assumptions about whose bodies matter in health systems and whose suffering remains socially acceptable. Research from LMICs consistently documents stigma, shame, taboos, and social isolation associated with menstruation. Girls miss school because they cannot afford sanitary materials or because schools lack WASH, including water, safe toilets and waste management facilities. Women improvise with unsafe materials, due to which some remain isolated during menstruation, whereas others continue to work in unsafe and unhygienic environments because missing a day's wage is also not a good option to choose for them [4]. These experiences are not isolated incidents, but they represent patterned inequalities that public health systems can measure, observe, and prevent. Manifestation of period poverty is relational and intersectional [5]. Menstruation itself may be biological, but menstrual disadvantage is socially produced. A girl studying in an urban private school with functioning toilets, disposal systems, water access, and family support experiences menstruation differently from a rural adolescent within the same country, supposed to be Pakistan, attending a school without support and sanitation facilities. A refugee adolescent faces different vulnerabilities than a university student. A menstruating person living with disability experiences barriers differently from others [2, 6]. These differences matter because period poverty is shaped through the interaction of gender with class, geography, disability, displacement, education, and social exclusion [7]. Period poverty is a measurable structural deprivation with identifiable biological, social, economic, institutional, and political determinants [8]. Research studies should map multidimensional indicators, including school and workplace absenteeism, menstrual stigma, psychosocial distress, WASH access, product affordability, disposal facilities, and mobility restrictions. Furthermore, participation barriers, reproductive infections, policy exclusion, gender norms, decision-making autonomy, safety concerns, productivity loss, and social isolation would also be considered to better understand its ontological and intersectional realities [9, 10]. This ongoing lack of visibility of period poverty is symptomatic of women's and marginalized communities' wider experience of structural inequality affecting them drastically. Thus, a critical and emancipatory public health strategy must go beyond the measurement of rates of prevalence. It requires interrogation of systems that normalize menstrual inequity. Menstrual taxation, as a treatment of essential products, rather

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than a luxury, underscores inequities in governance and economic policy. The understanding of menstrual inequity can only happen through an informed conversation [11]. Valid knowledge and facts in the field of public health must be backed up with quantitative evidence, as well as lived experiences. For the future of progress, political commitment and institutional recognition of the importance of menstrual health as not being a peripheral development issue will be required in LMICs. Instead, it is at the heart of education, gender equality, employment, social inclusion, and psychosocial well-being. Public health could not claim commitment to equity while menstrual needs remain neglected across societies, households, schools, workplaces, health systems, and humanitarian settings. Period poverty is not only a women's issue but a public health concern that has social and economic intergenerational implications. It requires more than awareness slogans to discuss this very important matter. It calls for structural action based on dignity, equity, empowerment, and justice. Addressing the menstrual situation in LMICs is no longer about 'better management' of menstruation, but about challenging unequal structures that persist in excluding, silencing, and disadvantaging millions of people from the function of menstruation. Women need to be supported inclusively so that they can be empowered socially, legally, morally, and economically.

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Original Article

OPEN ACCESS

Comparison of Efficiency of Intermaxillary Fixation Screws Versus Erich Arch Bars for Maxillomandibular Fixation in Maxillofacial Trauma

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ABSTRACT

Maxillomandibular fixation (MMF) is a popular intervention tool for maxillofacial fractures. Erich arch bars are used historically, but intermaxillary fixation screws provide some potential benefits, including less time in surgery and better oral health. **Objective:** To compare the Erich arch bar with intermaxillary fixation screws in maxillomandibular fixation in facial fractures. **Methods:** This prospective comparative trial was carried out in Sharif Medical and Dental College and involved 60 patients who needed maxillomandibular fixation after maxillofacial trauma. There were two groups of patients: intermaxillary fixation screws (n=30) and Erich arch bars (n=30). The assessment of the post-operative occlusal stability, duration of the surgery, and the assessment of oral hygiene based on the Oral Hygiene Index were performed with the help of SPSS version 23.0. **Results:** The intermaxillary fixation screw group showed a shorter surgical time, as well as superior oral hygiene ($p<0.05$). The groups did not show any significant difference in the postoperative occlusal stability ($p=0.389$). **Conclusion:** intermaxillary fixation screws offer similar occlusion potentialities at lower operative duration and with improved oral health as compared with Erich arch bar.

INTRODUCTION

Facial trauma is one of the most prevalent problems in maxillofacial surgery and can occur as a result of physical violence, injuries from sports, or a car accident. About 42% of face injuries affect the facial bones, with the maxilla accounting for about 30% of all instances and the mandible for nearly 70%. Restoring occlusion, functioning, and aesthetic appeal is the main objective of treatment for such fractures. Maxillomandibular fixation (MMF), whereby momentarily immobilizes shattered fragments to allow adequate healing to occur, is one of the most crucial components of this therapy [1, 2]. MMF has historically been obtained by using wire techniques and Erich arch bars. Although they have a number of drawbacks, including lengthy application times, soft tissue damage, the possibility of needlesticks to medical personnel, and challenges with maintaining oral hygiene, they offer firm fixing and repeatable outcomes [3, 4]. Gingival manifestation, mucosal damage, and patient discomfort during the fixation period are additional consequences of the extensive use of metal wiring and frames of metal [5]. Intermaxillary fixation (IMF) screws were created in 1989 as a more straightforward and efficient way to overcome

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these limitations. Since IMF screws are self-tapping and self-drilling implants that are inserted straight into the alveolar bone, they do not require tooth anchors. Their use has been shown to prevent periodontal damage, significantly shorten operating times, and improve post-operative dental hygiene [6, 7]. Additionally, since they tend to be more comfortable, they improve patient compliance and lower occupational risks such as wire-stick injuries [8]. Erich arch bars and IMF screws have been tested before with varying degrees of success. While some researches have shown similar occlusional results between the two methods, others have shown that IMF screws were better in terms of practicality and hygiene. Despite all of the research, there is still debate on the optimal method of fixation in various institutional and clinical settings, particularly in settings with limited resources [9–13].

There exists a discrepancy in comparative IMF screws and Erich arch bar application in maxillofacial fixation, which leaves a localized clinical guidance gap. It is discussed in this study through the direct comparative data of our setting, which is necessary to make an informed surgical choice. Therefore, the goal of this research is to assess how well intermaxillary fixation screws and Erich arch bars work for treating craniofacial fractures. This study aimed to evaluate surgery time, dental hygiene situation, and occlusal stabilization in order to determine whether the maxillomandibular fixation technique is more effective and comfortable for patients.

METHODS

This was a prospective comparative study done on 60 patients in order to assess and compare the effectiveness of IMF screws and Erich arch bars in maxillomandibular fixation (MMF) in facial trauma. The study was conducted between November 2023 and October 2024, in the Department of Oral and Maxillofacial Surgery, Sharif Medical and Dental Hospital, after ethical approval of the Sharif Medical Research Center, with the ethical number SMDC/SMRC/310-23. The sample size was determined with the use of the WHO sample size software, where the efficacy of an IMF screw was set at 94.1%. The confidence interval was 95% with precision = 0.06 [13]. The sample size was calculated using the following formula for comparison of two means: $n = 2 \times (Z\alpha/2 + Z\beta)^2 \times \sigma^2 / (\mu1 - \mu2)^2$. The patients aged 18 and above with fractures of the maxilla and mandible requiring maxillomandibular fixation were added to this study. Pathological fracture, polytrauma, neurosurgical patients, or panfacial trauma patients were excluded. All participants (or, in the case of children, their legal parents and guardians) gave written informed consent before being included in the study. While a technique referred to as non-probability convenience sampling was decided on, a number of steps were taken to lessen selection bias. Any prospective participants who satisfied the inclusion criteria and repeatedly visited the Department of Oral and Maxillofacial Surgery during the study period were invited to participate, regardless of age, gender, or socioeconomic background. For both groups, the lead researcher consistently used the same inclusion and exclusion criteria. Allocation into the IMF screw (Group A) versus the Erich arch bar (Group B) was based only on the type of fractures (whether there was a lack of dentoalveolar inclusion) rather than operator preference to ensure comparison between groups. Patients with no dentoalveolar fracture were added to group A and were treated with IMF screws, and patients with dentoalveolar fractures were added to group B and treated with Erich Arch bar. Group A included six self-drilling, self-threading screws (2.0x7 mm), which were positioned bilaterally at the maxilla and mandible. As per imaging, the insertion site was selected B/L between premolars and midline for screws insertion due to the absence of roots between them. Using flexible stainless-steel wires, IMF was attained. In Group B, MMF was done by attaching Erich arch bars to the labial surfaces of upper and lower teeth by using stainless steel wire, and then MMF was done by using elastics. The time of procedure was measured, from the start of the procedure till the MMF was done in minutes [6]. Efficiency was assessed using three measurable factors: operation time (in minutes), postoperative oral hygiene index ratings, and patient-reported comfort. Based on the patient's medical history and clinical examination, pre-trauma occlusion was identified. On the first postoperative day, the same operator conducted a clinical review of occlusion. The patient was instructed to achieve maximal intercuspation, and the outcomes were compared to the occlusal relations recorded before the trauma. Occlusion was categorized as adequate if the postoperative occlusion and midline alignments matched the pre-trauma condition, and as unacceptable if any early interactions, open bites, or midline deviations were noted. [14]. On the very first follow-up after seven days, the patients' hygiene was evaluated using the Oral Hygiene Index [6], which was graded as 0 (no evidence of soft plaque), 1 (1/3 of the surface of the tooth coated with soft plaque), 2 (one-third to two thirds of the tooth surface was coated with soft plaque), and 3 (over two thirds of the tooth surface was coated with soft plaque). To prevent bias, one surgical staff member was assigned to perform both procedures.

The data were analyzed using SPSS version 23.0. While continuous factors (surgical time, Oral Hygiene Index) are displayed as mean ± SD, categorical variables (occlusal outcomes) are displayed as frequency and %. The Shapiro-Wilk test was used to test the normality of continuous variables. The time of surgery was normally distributed and was compared by the independent samples t-test to

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determine the mean time of surgery between the two groups. The data scores on oral hygiene were not normally distributed and were tested through the Mann-Whitney U test to compare the median scores among the groups. The Chi-square test was used to determine postoperative occlusal stability, which is a categorical variable. The p-value below 0.050 was declared to be statistically significant.

RESULTS

The study incorporated 60 patients, 30 patients in the IMF screw and 30 patients in the Erich arch bar. An independent-samples t-test showed that there was a significant difference in the surgical time of the groups, t (58) = -23.07, p<0.001. The mean surgical time of the IMF screw group (39.60 ± 3.08 min), in comparison to the Erich arch bar group (66.03 ± 5.47 min), was much shorter. The Mann-Whitney U test was used to compare the scores of the Oral Hygiene Index (OHI). The results indicated a statistically significant difference, U = 47.00, Z = -6.16, p<0.001, and better oral hygiene in the IMF screw group (Mean Rank = 17.07) as compared to the Erich arch bar group (Mean Rank = 43.93) (Table 1).

Table 1: Surgical Time and Oral Hygiene Index (OHI) Outcomes by Group

Parameters	Group	n	Mean / Mean Rank	SD / Sum of Ranks	Test	Test Statistic	p-value
Surgical Time (min)	IMF Screws	30	39.60	08	Independent-Samples t-test	T (58) = -23.07	<0.001
	Erich Arch Bars	30	66.03	5.47			
Oral Hygiene Index (OHI)	IMF Screws	30	0.84 (Mean Rank)	512.00 (Sum of Ranks)	Mann-Whitney U test	U = 47.00, Z = -6.16	<0.001
	Erich Arch Bars	30	1.63 (Mean Rank)	1318.00 (Sum of Ranks)			

The Chi-square test was used to evaluate the results of postoperative occlusion. Satisfactory occlusion (IMF screws: 26/30, 86.7; Erich arch bars: 28/30, 93.3) was observed in most of the patients in each group, and the difference did not differ significantly, $\chi^2(1) = 0.74$, p=0.389 (Table 2).

Table 2: Postoperative Occlusion Outcomes by Group

Outcomes	IMF Screws	Erich Arch Bars	Total
Satisfactory	26	28	54
Unsatisfactory	4	2	6
Total (n, %)	30 (100%)	30 (100%)	60 (100%)

DISCUSSION

This research compared intermaxillary fixation (IMF) screws and Erich arch bars to achieve maxillomandibular fixation (MMF) in the case of facial trauma. Some of the variables that were measured included oral stability after surgery, dental cleaning, and the length of the surgery. The IMF screws exhibited significant gains in both reduced operating room time and better oral health after the surgeries, even when both techniques yielded exquisite outcomes of occlusion. The mean IMF screw group operating time (39.60 +3.08 minutes) was much lower in this research than the Erich arch bar group (66.03 ± 5.47 minutes). According to previous studies conducted by Thukral *et al.* [12], Jain *et al.* [2], Tükel and Benlidayı [15], and Ahmad *et al.* [16], the IMF screws were discovered to cause an immediate reduction in chair-side and operating time. The main causes of the fact that the time of the process is shorter are the simplified placement procedure and the absence of the long and wire ligation required to fix the arch bars. Also, IMF screws reduce the risk of needle stick injuries and intraoperative fatigue in operating surgeons [14, 17]. Following an improved oral hygiene treatment, an evaluation revealed that the IMF screw group was significantly lower in oral hygiene index scores than the Erich arch bar group. This finding correlates with the findings of earlier studies conducted by Tükel and Benlidayı [15], Jain *et al.* [2], and Salavadi *et al.* [18], which have also found that the IMF screws may be used to reduce the inflammation of the gums and facilitate the dental cleaning procedures. Nevertheless, its hard-to-insert wire and limitation to reach the mucosa cause the Erich arch bars to be associated with more accumulation of plaque, mucosal pain, and stress in the gums [9, 18]. It is suggested that maintenance of a high level of oral health following fixation prevents the occurrence of a surgical infection as well as eases the patient during his or her recovery period [19]. The comparison of occlusal stability of the two groups showed that no statistically significant difference was observed. Most of the participants in either category (Erich = 93.3%, IMF = 86.7%) had adequate occlusion. These results are in line with results found by Thukral *et al.* [12], Kumar *et al.* [14], and Qureshi *et al.* [11], who found no difference in the results of IMF screws and Erich arch bars when used correctly. The effects of occlusion in the long term were not, however, examined as the current study merely evaluated the effect of occlusion on the first postoperative day. Jain and Rai [6] and Rai *et al.* [9] also reported similar short-term outcomes. Further studies are needed on long-term follow-up to determine the stability of the occlusion throughout the long healing duration. In general findings of the study, the IMF screws prove to be a reliable, fast, and painless alternative to the traditional Erich arch bar. The IMF screws are extremely useful in the clinic since they reduce the operating time and enhance oral care after surgery. Moreover, the above advantages are achieved

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without compromising occlusion, and it implies that IMF screws could be used safely and effectively for both maxillary and mandibular fractures[20].

The short-term evaluation following surgery and the comparatively small sample size were two of the study's shortcomings. There was no measurement of the long-term effects of occlusion, as well as periodontal health. Additionally, the use of convenient sampling may have contributed to selection bias. However, all of the operations were carried out by operators with the same degree of expertise, which guaranteed consistency and reduced technique bias.

CONCLUSIONS

This study discovered that intermaxillary fixation (IMF) screws were better than Erich arch bars when used to treat mandibular fractures. The IMF screw group exhibited higher efficiency, evidenced by the reduction of treatment time, improvement of postoperative oral hygiene, and more patient comfort. Such findings suggest that IMF screws are a reliable, easy-to-use, and easy-to-swallow alternative to maxillomandibular fixation to treat fractures.

Authors' Contribution

Conceptualization: MK
Methodology: MK, MAK, MJ, IT
Formal analysis: MJ
Writing and Drafting: MK, UBA, KA, MAK, MJ
Review and Editing: MK, UBA, KA, MAK, MJ, IT

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Change in C-Reactive Protein Level with Anti-Tuberculosis Therapy in Patients with Pulmonary Tuberculosis

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ABSTRACT

Pulmonary tuberculosis is a widespread disease with high mortality and morbidity rates in developing countries, caused by Mycobacterium tuberculosis. However, there is limited information on how serum CRP levels relate to the severity of pulmonary tuberculosis. **Objective:** To determine the mean change in C-reactive protein with anti-tuberculosis therapy in patients with pulmonary tuberculosis. **Methods:** The quasi-experimental study was conducted at the Department of Pulmonology, Mayo Hospital, Lahore, from August 25, 2020, to February 25, 2021, enrolling 85 patients with pulmonary tuberculosis. A blood sample was obtained by using a 5cc disposable syringe under aseptic measures and stored in sterile vials for assessment of CRP level at baseline. Then all patients were given anti-tuberculosis therapy and followed up in OPD for 2 months. Change in CRP level was calculated. The data were analysed statistically by using SPSS version 25.0. A p-value ≤0.050 was taken as significant. **Results:** 60 (70.6%) were males, while 25 (29.4%) were females. Baseline levels of CPR were 60.15 mg/dl and 17.76mg/dl after 2 months; the mean change in CPR levels was 42.39mg/dl. The average change in CRP levels was 42.39 ± 21.52mg/dL (p-value<0.050). **Conclusions:** The results of the study showed a significant reduction in mean CRP levels before and after treatment with ATT. The patients with pulmonary tuberculosis had a high level of serum C-reactive protein (CRP), which implies that CRP can be used as an effective biomarker in the assessment of disease activity and treatment response.

INTRODUCTION

Tuberculosis (TB) remains a major global public health problem and is the second leading cause of death from infectious diseases worldwide after COVID-19. The World Health Organization (WHO) estimates that nearly two billion people have latent TB infection, and in 2021, TB caused approximately 1.6 million deaths globally, including 187,000 among people living with HIV [1, 2]. However, 22 countries with high burden carry more than 80% of the total number of cases, with Pakistan ranking 5th in the prevalence of TB and 4th in multi-drug-resistant TB (MDR-TB), and occurrence in the Eastern Mediterranean Region by the WHO [3]. A survey of the inventory of notified TB cases in Pakistan showed that out of all the diagnosed cases, only 32 percent were reported to the National Tuberculosis Control Program (NTP), and most of the cases were under-reported at 27 percent (Pakistan) [4]. National TB

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prevalence surveys are the most dependable way of estimating the disease burden and tracking epidemiological trends in most settings. Such surveys in Asia have shown that the prevalence of TB can be reduced significantly over a period of 10 years, with men being the most vulnerable and older age groups becoming the most affected in the disease burden [5]. Diagnostic biomarkers are a necessity in the treatment monitoring of TB. C-reactive protein (CRP), which is an acute-phase reactant and an element of innate immune response, has become a possible candidate [6]. It is crucial to measure treatment response among patients with pulmonary TB to determine the efficiency of therapy, detect resistance to the drug, and curb transmission of the disease. Traditional tests, namely sputum smear microscopy and culture, though informative, are time-consuming and time-lagging; therefore, there is a need to have dependable biomarkers that could offer rapid information on disease activity and treatment response [7]. A promising biomarker in the management of TB is C-reactive protein (CRP), an acute-phase reactant that is produced by the liver due to inflammation. The level of CRP has been very high in patients having active pulmonary TB and correlated with the severity of the disease and the degree of lung involvement [8]. Rapid CRP testing has also been found to be useful in the presumptive diagnosis of TB and the clinical progression of the disease in HIV-infected people during treatment [9]. Moreover, CRP concentrations are a measure of systemic immune reaction and have been utilized as a marker of airway inflammation in other respiratory diseases, including bronchial asthma [10]. Notably, research indicated that there is a marked decrease in the levels of CRP with the onset of anti-tuberculosis therapy, which is associated with clinical effect and the diminution of the total bacterial load [11]. This implies that serum CRP may be a simple, low-cost, and minimally invasive instrument to evaluate treatment response in pulmonary TB to be used in combination with microbiological and radiological tests. Nevertheless, the nature of CRP persists throughout the treatment, and its relationship with clinical and radiological patient outcomes is understudied in most groups, especially in high-burden, low-resource states [12].

C-reactive protein (CRP) is increasingly recognized as a useful biomarker for monitoring treatment response in pulmonary tuberculosis; however, evidence from Pakistan remains scarce. Given differences in disease burden, patient demographics, and healthcare infrastructure, locally generated data are essential to confirm its clinical utility. Establishing changes in CRP levels during anti-tuberculosis therapy may support timely disease monitoring, inform clinical decision-making, and improve patient outcomes. Therefore, this study aims to determine the mean change in serum CRP levels during anti-tuberculosis therapy in patients with pulmonary tuberculosis.

METHODS

This quasi-experimental research was performed at the Department of Pulmonology, Mayo Hospital, Lahore, from August 25, 2020, to February 25, 2021, after the ethical approval (Ref: CPSP/REU/PUL/-2019-062-522). A total of 85 patients were enrolled using non-probability consecutive sampling. The sample size was calculated with a 95% confidence level, absolute precision (d) of 1, and an expected mean change in CRP level of 38 ± 4.66 mg/dL, based on previous literature [13]. Patients aged 16 to 70 years of both genders presenting with pulmonary tuberculosis were included. C-reactive protein (CRP) was measured using a quantitative immunoturbidimetric assay on a Roche Cobas c311 automated chemistry analyzer (Roche Diagnostics, Mannheim, Germany) employing the CRP Latex reagent kit (Roche Diagnostics), according to the manufacturer's instructions. The normal reference range for CRP was <5 mg/L. Blood samples were obtained at two time points: at baseline before initiation of anti-tuberculosis therapy and after completion of the intensive phase of treatment (2 months). All patients received standard first-line anti-tuberculosis therapy, consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol during the intensive phase, in accordance with national TB treatment guidelines. Pulmonary tuberculosis was defined by compatible clinical symptoms (cough >14 days, chest pain, shortness of breath, and fever ≥100°F) with microbiological confirmation by positive acid-fast bacilli (AFB) smear and GeneXpert detection of Mycobacterium tuberculosis. Patients were excluded if they were pregnant, had a Karnofsky Performance Status score <40 [14], tuberculous meningitis on CT scan, other infectious or inflammatory conditions, prior anti-tuberculosis treatment for ≥1 week, or antiretroviral therapy for <3 months, or fluoroquinolone use within the preceding 8 weeks. After obtaining informed consent, demographic and clinical information, including age, gender, BMI, history of diabetes mellitus (random blood sugar >186 mg/dL), smoking status (>5 pack-years), hypertension (BP ≥140/90 mmHg), and duration of symptoms, was recorded. A baseline blood sample was collected under aseptic conditions using a 5cc disposable syringe and sent to the hospital laboratory for CRP level measurement. All patients were started on standard anti-tuberculosis therapy and followed up after two months. A second blood sample was obtained and analyzed for CRP levels. The change in CRP was calculated as the difference between the baseline value (T0) and the value after two months of treatment (T2), i.e., CRP (T0) – CRP (T2). All data were recorded using a structured proforma.

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The analysis of data was done in SPSS version 25.0. The quantitative variables (age, BMI, symptom duration, CRP levels), whereas the categorical variables (gender, diabetes, smoking, hypertension) were presented as the mean ± SD and as frequencies, and percentages, respectively. Normality of data was assessed by Shapiro Wilk test, and then the changes in the level of CRP at the time of treatment and before the treatment were evaluated using a paired t-test (p≤0.050). They were stratified on the basis of age, gender, BMI, duration of the symptoms, diabetes, smoking, and high blood pressure. The independent t-test and one-way ANOVA were used to test CRP changes by stratification.

RESULTS

The study involved 85 patients with pulmonary tuberculosis, including 60 males (70.6%) and 25 females (29.4%) of the study population. The mean age was 46.34 ± 17.03 years. Most patients (56.5%) were aged above 45 years of age, then 24.7 aged 18-30 years, and 18.8 aged 31-45 years. In terms of comorbidity, 10 patients (11.8%) were hypertensive, and 10 (11.8%) patients had diabetes mellitus. Twenty-five (29.4%) patients indicated a history of smoking. According to body mass index (BMI), 51 patients (60.0%) were of normal body mass index, 33 patients (38.8%) were overweight, and one (1.2%) patient was obese. In terms of the duration of the symptoms, 33 (38.8%) patients said they lasted below one month, and 52 (61.2%) patients said they lasted above one month (Table 1).

Table 1: The Baseline and Demographic Characteristics of the Study Patients (n=85)

Variables	Category	Frequency (%)
Gender	Male	60 (70.6%)
	Female	25 (29.4%)
Age Group	18–30 Years	21 (24.7%)
	31–45 Years	16 (18.8%)
	>45 Years	48 (56.5%)
Hypertension	Yes	10 (11.8%)
	No	75 (88.2%)
Diabetes Mellitus	Yes	10 (11.8%)
	No	75 (88.2%)
Smoking Status	Yes	25 (29.4%)
	No	60 (70.6%)
Body Mass Index (BMI)	Normal	51 (60.0%)
	Overweight	33 (38.8%)
	Obese	1 (1.2%)
Duration of Symptoms	<1 Month	33 (38.8%)
	>1 Month	52 (61.2%)

The baseline CRP level was 60.15 ± 21.97mg/dl, which decreased to 17.76 + 4.05mg/dl after two months of anti-tuberculosis treatment. The average change in CRP levels was 42.39 ± 21.52mg/dL, which means that there is a significant decrease in systemic inflammation as a result of treatment (p-value<0.050) (Table 2).

Table 2: A comparison of C Reactive Protein (CRP) Levels Before and After Anti-Tuberculosis Therapy (n=85)

CRP Measurement	Baseline (mg/dL)	After 2 Months (mg/dL)	Mean Change (mg/dL)	p-value*
Mean ± SD	60.15 ± 21.97	17.76 ± 4.05	42.39 ± 21.52	<0.001

*p-value obtained with paired sample t-test. A p-value of less than 0.050 was found to be statistically significant

A stratification of change in levels of C-reactive protein (CRP) was conducted on different baseline characteristics to determine whether these were significantly affecting response to the treatment. The difference in the change of CRP level between males (43.36 ± 22.78 mg/dL) and females (40.04 ± 18.36 mg/dL) was not significantly different (p=0.520). The mean decrease in CRP levels was highest in the patients of age group 18-30 years (48.32 ± 24.76 mg/dl), then 31-45 years (41.06 ± 17.32 mg/dl), and over 45 years (40.23 ± 21.21 mg/dl), and the difference between age groups was not significant (p=0.347). The mean change in CRP of patients with hypertension was 43.18 + 26.02mg/dl, with no hypertension being 42.28 + 21.05mg/dl (p=0.902). Similarly, the difference in CRP reduction between diabetic (38.35 ± 18.47 mg/dL) and non-diabetic patients (42.92 ± 21.94 mg/dL) was not statistically significant (p=0.531). Smokers experienced a mean change of 41.58 ± 20.90 mg/dL compared to 42.72 ± 21.93 mg/dL in non-smokers, again with no significant difference (p=0.825). With respect to BMI, normal-weight individuals had a mean CRP reduction of 43.27 ± 21.97 mg/dL, overweight individuals 41.64 ± 21.12 mg/dL, and the single obese patient showed a reduction of 21.73 mg/dL; the overall comparison was not statistically significant (p=0.598). Finally, patients with symptom duration <1 month had a mean CRP change of 42.97 ± 19.45 mg/dL, while those with symptoms for >1 month showed a change of 42.01 ± 22.91 mg/dL (p=0.843). Overall, none of the baseline variables, including gender, age, hypertension, diabetes, smoking status, BMI, or symptom duration, showed a statistically significant effect on the change in CRP levels, indicating that the reduction in CRP following anti-tuberculosis therapy was consistent across these subgroups (Table 3).

Table 3: Stratification of Change in CRP Levels with Respect to Baseline Variables (n=85)

Variables	Category	Mean Change (mg/dL)	p-value*
Gender	Male	43.36 ± 22.78	0.520
	Female	40.04 ± 18.36	
Age Group	18–30 Years	48.32 ± 24.76	0.347
	31–45 Years	41.06 ± 17.32	
	>45 Years	40.23 ± 21.21	
Hypertension	Yes	43.18 ± 26.02	0.902
	No	42.28 ± 21.05	

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Diabetes Mellitus	Yes	38.35 ± 18.47	0.531
	No	42.92 ± 21.94	
Smoking	Yes	41.58 ± 20.90	0.825
	No	42.72 ± 21.93	
BMI	Normal	43.27 ± 21.97	0.598
	Overweight	41.64 ± 21.12	
	Obese	21.73 ± 18.91	
Duration of Symptoms	<1 Month	42.97 ± 19.45	0.843
	>1 Month	42.01 ± 22.91	

*p-values were obtained by an independent sample t-test or ANOVA. A p-value of less than 0.050 was taken as significant

DISCUSSION

The growing burden of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) has drawn attention to tuberculosis, particularly in the context of antibiotic misuse [15-17]. These resistant forms significantly contribute to increased morbidity and mortality, highlighting the need for reliable, non-invasive biomarkers to monitor disease activity and treatment response. Moreover, TB-associated structural lung damage and reliance on invasive diagnostic and follow-up procedures increase the risk of secondary bacterial infections, further emphasizing the clinical value of C-reactive protein (CRP) as a simple inflammatory marker to assess treatment response and guide timely clinical decision-making [18]. Clinical symptoms of TB tend to be similar to those of other respiratory diseases, and hence, early diagnosis is not easy; thus, it usually takes too long to treat the disease before it becomes serious [19]. In the experiment, our results revealed that C-reactive protein (CRP) levels were significantly higher at the baseline among the patients with pulmonary tuberculosis (mean 60.15 ± 21.97 mg/dL). As an example, one study reported a significant reduction in CRP levels from a mean of 56.2 mg/dL to 8.6 mg/dL ($p<0.001$) [13], and another study showed a similar reduction of 60.71 ± 10.98 mg/dL to 22.71 ± 6.32mg/dL ($p<0.001$) [14]. This observation is in line with former studies reporting significantly elevated CRP levels in TB patients, particularly those who present with fever, dyspnea, tachypnea, hypotension, and respiratory distress [20]. Likewise, Kaminskaia et al. found that there is a close relationship between the extent of systemic intoxication and the CRP levels [21]. This study's data, however, did not find any significant correlation between CRP levels and the occurrence of hemoptysis, which agrees with the literature [22]. Notably, in current study, the study noted that there was a great improvement in CRP levels in two months of anti-tuberculosis therapy, whereby the baseline level of 60.15 ± 21.97mg/dL improved to 17.76 ± 4.05mg/dL after treatment. The statistical significance of the mean change in CRP was 42.39 ± 21.52mg/dl, which was significant ($p<0.001$). This trend of a progressive decline in CRP after treatment is similar to previous studies [23]. Furthermore, a study conducted by Githua *et al.* also indicated that CRP can be used as a reliable biomarker of treatment response in pulmonary tuberculosis [11].

No control, quasi-experimental design, small sample (n=85), short follow-up (2 months), no adjustment of confounding factors, two time points of CRP, no association with sputum conversion, non-probability sampling. Prospective cohorts with longer follow-ups, serial CRP measurements, and corruption of microbiological/radiological response, and validation of CRP as an inexpensive monitoring biomarker in Pakistani TB settings.

CONCLUSIONS

Our study revealed that patients with pulmonary tuberculosis have high serum CRP levels at baseline (mean 60.15 ± 21.97 mg/dL, p-value<0.001), which are likely to be normalized after successful treatment. This implies that CRP can be an effective biomarker to measure disease activity and treatment response.

Authors' Contribution

Conceptualization: SBK, HMFN, HKD, MZUA
Methodology: SBK, HMFN, MR, AH, MZUA
Formal analysis: SBK, HMFN, MR, HKD, AH, MZUA
Writing and Drafting: SBK, AH, MZUA
Review and Editing: SBK, HMFN, MR, HKD, AH, MZUA, SMF

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Diagnostic Value of Umbilical Artery Systolic/Diastolic Ratio and Amniotic Fluid Index for the Prediction of Respiratory Distress Syndrome among Term Pregnancies: A Cross-Sectional Validation Study

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ABSTRACT

The introduction of UA S/D ratio monitoring into the routine antenatal Doppler monitoring can improve the early detection of the at-risk baby and optimize the perinatal care. **Objectives:** To evaluate the diagnostic accuracy of umbilical artery (UA) systolic/diastolic (S/D) ratio, and amniotic fluid index (AFI) in term pregnancies for the prediction of RDS, keeping postnatal findings as the gold standard. **Methods:** This cross-sectional validation study was carried out at Department of Diagnostic Radiology, Pakistan Navy Ship Hafeez Hospital, Islamabad, from November 2024 to June 2025. There were 594 enrolled term pregnant women with term pregnancies. The obstetric ultrasound with color Doppler was performed to measure the umbilical artery S/D ratio and AFI. S/D ratio was declared positive when its >3, and AFI positive when it was < 8 cm. Neonates were followed 72 hours after birth, and the RDS diagnosis was confirmed by clinical and radiological means. Data were evaluated with SPSS version 25.0, and diagnostic indices were calculated. **Results:** The overall prevalence of RDS was 12.6%. For the umbilical artery S/D ratio, sensitivity and specificity were 77.3% and 88.1%, respectively. While for AFI, sensitivity and specificity were 64.0% and 75.7%, respectively. **Conclusions:** The Umbilical artery S/D ratio is a better and more reliable ultrasound parameter than AFI in predicting postnatal RDS in term pregnancies, as the AUC for the UA S/D ratio was found to be 0.840, which reflects its optimal performance, while the AUC for AFI was found to be 0.305, which shows its poor discriminative ability.

INTRODUCTION

Antenatal surveillance is a significant part of prenatal care. As, maternal and child health indicators are often found to be below the global average in Pakistan, and the rates of maternal and neonatal morbidity and mortality are very high [1, 2]. According to UNICEF, the feto-maternal mortality rate in Pakistan is one of the highest in South Asia, with an estimated neonatal death rate of over 42 for every 1000 live births [3]. Respiratory distress syndrome (RDS) has long been considered a pathology of preterm infants, but is now being recognized as a serious complication of term and late-term neonates. The disorder can be abrupt in onset, which triggers rapid clinical progression. Precise prognostication of RDS poses a diagnostic dilemma due to its clinical overlap with various other conditions of transitional neonatal diseases. [4, 5]. One of the main pillars of contemporary obstetric practice is ultrasound imaging, which is used to visualize the fetus in real-time and examine the fetal anatomy, development,

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and well-being in detail [6]. The UA (S/D) ratio and the AFI have become key instruments in the prediction and prevention of adverse perinatal outcomes. The UA S/D ratio measures the resistance in the placental circulation, whereas the AFI gives an estimate of the size of the amniotic fluid; both of these are important indicators of fetal health [7, 8]. Despite several local and global research studies conducted on this topic, the predictive usefulness of these ultrasonographic markers has yielded inconsistent results in forecasting unfavorable perinatal outcomes, and relevant findings for the local population remain elusive [9, 10].

The presence of these inconsistencies indicates that additional research is needed that can offer a fresh perspective and an improved approach to previous approaches. Current study will bridge this gap by the use of a robust methodology and a focus on unique outcome metrics that previous researchers have not extensively examined. This study aims to evaluate the diagnostic accuracy of umbilical artery (UA) systolic/diastolic (S/D) ratio, and amniotic fluid index (AFI) in term pregnancies for the prediction of RDS, keeping postnatal findings as the gold standard.

METHODS

The study was conducted in the Department of Diagnostic Radiology in collaboration with the Department of Gynecology and Obstetrics of Pakistan Navy Ship Hafeez Hospital, Islamabad. Patients were enrolled between November 2024 and May 2025 after obtaining the approval of the institutional ethics committee via approval letter no. 491/17. Participants were recruited using a non-probability consecutive sampling technique after getting informed written consent. Sample size was calculated by using the sensitivity and specificity sample size calculator by incorporating the sensitivity of AFI as 43.75%, specificity as 79.66%, and expected prevalence of RDS as 16% [11]. and keeping the 95% confidence interval and a 10% precision, the sample size was calculated as 594 pregnant women. Females with singleton term pregnancies (i.e., gestational age ≥36 weeks) with cephalic presentation and admitted for delivery, having a maternal age between 22 and 35 years, were included. While mother with preeclampsia or gestational diabetes, anemia, fetuses with a confirmed diagnosis of IUGR, sepsis, and those having congenital anomalies were excluded. A detailed clinical history, physical examination, and ultrasound with Aplio i600 color Doppler were performed for each participant at the time of enrollment. A consultant radiologist with a minimum of three years of teaching experience, who was blinded to the study participant conducted all the ultrasound examinations to ensure consistency and reliability of measurements. AFI and UA S/D were measured as per standard procedure, and AFI was labelled as positive if its value was <8cm, and UA S/D was positive if the ratio was>3. Every enrolled patient was given 72 hours of observation after delivery. RDS was labelled as positive if the patient had any two of the following conditions: 1) Tachypnea (respiratory rate > 60 breaths/ min) + nasal flaring, 2) Intercostal and subcostal recessions, 3) expiratory grunting, and 4) central cyanosis. RDS was confirmed through the radiologic workup, showing any of the following patterns: 1) reduced lung volume with a fine granular pattern of lung parenchyma and peripherally extending air bronchograms, 2) hypo-aerated lungs showing a prominent and uniformly distributed reticulogranular pattern than usual. Increased air bronchograms will be observed. 3) Reticulogranular opacities are present throughout both lungs, with prominent air bronchograms and total obscuration of the cardiac silhouette as per criteria defined in MSD manual and Sweet LR [12]. All the demographic, clinical, and ultrasound data were recorded on an organized proforma that was particularly designed by the combined consultation of radiologist and gynecologist and was tested and validated on the first ten patients to ensure the perfection of performa. Data entry was done by the principal investigator herself or under the strict supervision to maintain the reliability of the data.

SPSS version 25.0 was used to analyze the data. Diagnostic accuracy parameters of the ultrasound AFI and umbilical artery S/D ratio were evaluated by constructing 2×2 contingency tables. To reduce bias and compare consistency, stratified analysis was conducted on the potential confounding variables such as maternal age, gestational age, neonatal gender, mode of delivery, gravidity, and parity.

RESULTS

The mean maternal age and gestational age of the study participants were 28.3 ± 4.1 years and 38.5±1.4 weeks, respectively. Mean umbilical artery SD ratio and AFI were 2.79 ± 0.52 and 9.7 ± 5.63cm, respectively. Most of the study subjects (51.5%) belonged to the age group 22-28 years, while 64.1% of the subjects presented at≥38 weeks of gestational age. We further noticed that 67.2% deliveries were vaginal and neonates were male dominant (52.4%). Moreover, we analyzed that 20.2% of patients were positive for RDS on the U/A SD ratio, while 29.3% were positive on the AFI. However, as per gold standard criteria, only 12.6% of total neonates had postnatal RDS (Table 1).

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Table 1: Clinical and Demographic Profile of Study Subjects (n=594)

Variables		Frequency (%)
Maternal Age Group	22–28 Years	306 (51.5%)
	29–35 Years	288 (48.5%)
Gestational Age Group	≥38.0 Weeks	381 (64.1%)
	36.0–37.9 Weeks	213 (35.9%)
Neonatal Gender	Male	311 (52.4%)
	Female	283 (47.6%)
Mode of Delivery	Vaginal	399 (67.2%)
	C-section	195 (32.8%)
Gravida	Multigravida	343 (57.7%)
	Primigravida	251 (42.3%)
Parity	Multipara	357 (60.1%)
	Primipara	237 (39.9%)
RDS Predicted by UA S/D	Positive	120 (20.2%)
	Negative	474 (79.8%)
RDS Predicted by AFI	Positive	174 (29.3%)
	Negative	420 (70.7%)
Postnatal RDS (Gold Standard)	Positive	75 (12.6%)
	Negative	519 (87.4%)

The Umbilical artery S/D ratio was found to have high specificity (88.1%; 95%CI) and acceptable sensitivity (77.3%; 95%CI) in predicting postnatal RDS with a positive LR of 6.5 and a negative LR of 0.26 (Table 2).

Table 2: Diagnostic Accuracy Analysis of U/A SD Ratio for Predicting the Postnatal RDS

Umbilical Artery S/D Ratio	Postnatal RDS Positive	Postnatal RDS Negative	Total
Positive (Test +)	58 (48.3%) (True Positive)	62 (51.7%) (False Positive)	120 (20.2%)
Negative (Test –)	17 (3.6%) (False Negative)	457 (96.4%) (True Negative)	474 (79.8%)
Total	75 (12.6%)	519 (87.4%)	594 (100%)

Sensitivity = 77.3%, Specificity = 88.1%, Positive Predictive Value (PPV) = 48.3%, Negative Predictive Value (NPV) = 96.4%, Overall Diagnostic Accuracy = 86.6%, Positive Likelihood Ratio (LR+) = 6.50 and Negative Likelihood Ratio (LR–) = 0.26

On the other hand, AFI demonstrated a relatively lower sensitivity (64.0%; 95%CI) as well as specificity (75.7%; 95%CI) for predicting the postnatal RDS with a positive LR of 2.64 and a negative LR of 0.47. However, the overall accuracy of the AFI was in an acceptable range (74.3%;95%CI)(Table 3).

Table 3: Diagnostic Accuracy Analysis of AFI for Predicting the Postnatal RDS

Amniotic Fluid Index (AFI)	Postnatal RDS Positive	Postnatal RDS Negative	Total
Positive (Test +)	48 (27.6%) (True Positive)	126 (72.4%) (False Positive)	174 (29.3%)
Negative (Test –)	27 (6.4%) (False Negative)	393 (93.6%) (True Negative)	420 (70.7%)
Total	75 (12.6%)	519 (87.4%)	594 (100%)

Sensitivity = 64.0%, Specificity = 75.7%, Positive Predictive Value (PPV) = 27.6%, Negative Predictive Value (NPV) = 93.6%, Overall Diagnostic Accuracy = 74.3%, Positive Likelihood Ratio (LR+) = 2.64 and Negative Likelihood Ratio (LR–) = 0.47

ROC curves were generated for both parameters, and we found an AUC for the UA S/D ratio of 0.840, which reflects its optimal performance for the prediction of RDS (Figure 1).

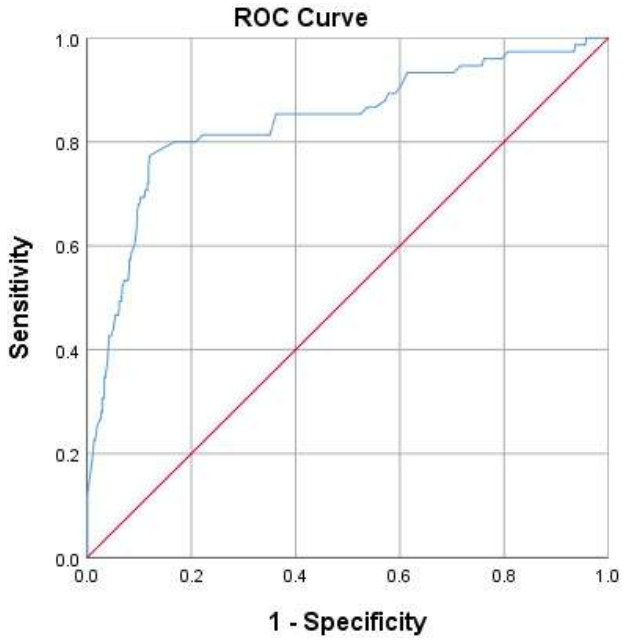

Figure 1: ROC Curve Analysis of Umbilical Artery SD Ratio for Predicting RDS

AUC for AFI was found to be 0.305, which shows its sub-optimal discriminative ability (Figure 2).

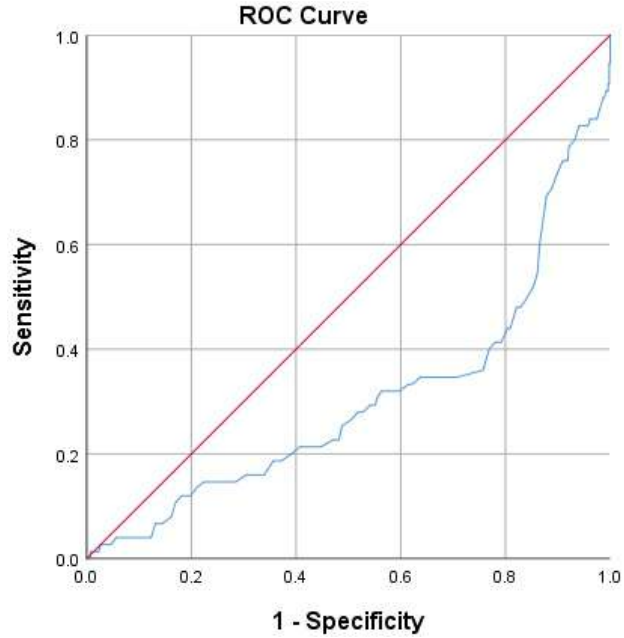

Figure 2: ROC Curve Analysis of AFI For Predicting RDS

Stratified analysis showed a high level of diagnostic performance in all maternal, fetal, and obstetric subgroups

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of the umbilical artery S/D ratio. The accuracy of diagnosis was high (85-88% across maternal age groups). Likewise, there was similarity in the accuracy of both gestational age groups. By mode of delivery, accuracy was nearly identical in vaginal and cesarean deliveries, i.e., 86.5% VS 86.2%. In case of gravidity and parity, diagnostic efficacy remained consistent (Table 4).

Table 4: Stratified Diagnostic Accuracy of Umbilical Artery S/D Ratio for Prediction of Postnatal RDS

Stratification Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall Accuracy (%)	LR+	Lr-
Maternal Age Group							
22–28 Years	71.9%	86.9%	39.0%	96.4%	85.3%	5.49	0.32
29–35 Years	81.4%	89.4%	57.4%	96.5%	88.2%	7.68	0.21
Gestational Age Group							
≥38 Weeks	77.1%	89.2%	50.7%	96.4%	87.1%	7.13	0.26
36.0–37.9 Weeks	77.8%	86.0%	44.7%	96.4%	85.0%	5.56	0.26
Neonatal Gender							
Female	75.8%	90.4%	51.0%	96.6%	89.0%	7.90	0.27
Male	78.6%	85.9%	46.5%	96.3%	86.5%	5.59	0.25
Delivery Mode							
Vaginal Delivery	80.0%	87.4%	47.6%	96.8%	86.5%	6.36	0.23
Cesarean Section	72.0%	89.4%	50.0%	95.6%	86.2%	6.78	0.31
Gravidity							
Primigravida	78.1%	87.7%	48.1%	96.5%	87.3%	6.34	0.25
Multigravida	76.7%	88.3%	48.5%	96.4%	87.2%	6.56	0.26
Parity							
Primipara	77.4%	86.9%	47.1%	96.2%	86.0%	5.91	0.26
Multipara	77.3%	88.8%	49.3%	96.5%	87.6%	6.90	0.26

On the other hand, AFI showed moderate sensitivity, which was 62-67%, and specificity as well, which was 69-80%, across all subgroups. Overall diagnostic accuracy was found to be highest in multipara and vaginal deliveries, that was 77.9% and 77.2%, respectively. Detailed stratification analysis for the diagnostic accuracy of AFI for predicting postnatal RDS is illustrated (Table 5).

Table 5: Stratified Diagnostic Accuracy of AFI for Predicting Postnatal RDS (n=594)

Stratification	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall Accuracy (%)	LR+	Lr-
Maternal Age							
22–28 Years	62.5%	76.3%	23.5%	94.6%	74.8%	2.64	0.49
29–35 Years	65.1%	75.1%	31.5%	92.5%	73.6%	2.62	0.46
Gestational Age							
≥38 Weeks	62.5%	78.1%	29.1%	93.5%	76.1%	2.85	0.48
36.0–37.9 Weeks	66.7%	71.5%	25.4%	93.7%	70.9%	2.34	0.47
Neonatal Gender							
Female	63.6%	78.0%	27.6%	94.2%	76.3%	2.89	0.47
Male	64.3%	73.6%	27.6%	93.0%	72.3%	2.44	0.49
Delivery Mode							
Vaginal Delivery	64.0%	79.1%	30.5%	93.9%	77.2%	3.06	0.46
C-Section	64.0%	68.8%	23.2%	92.9%	68.2%	2.05	0.52
Gravidity							
Primigravida	65.6%	73.5%	26.6%	93.6%	72.5%	2.48	0.47
Multigravida	62.8%	77.3%	28.4%	93.5%	75.5%	2.77	0.48
Parity							
Primipara	64.5%	69.4%	24.1%	92.9%	68.8%	2.11	0.51
Multipara	63.6%	79.9%	30.8%	94.0%	77.9%	3.17	0.46

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DISCUSSION

Although the Umbilical Artery S/D ratio is a direct hemodynamic indicator of the placental resistance and consequent fetal hypoxemia, AFI is a more general measure of fetal health and uteroplacental perfusion [13, 14]. The two parameters are therefore hypothetically involved in the pathways that result in dysfunctional pulmonary maturation and RDS [15, 16]. This research thus attempted to critically review and compare the diagnostic accuracy of these parameters of ultrasound on the specific prediction of RDS in term pregnancies with the view to providing evidence on their rational use in clinical practice. The study has shown that the umbilical artery S/D ratio is a better predictor of postnatal respiratory distress syndrome in term pregnancies, which has greater specificity, positive likelihood ratio, and overall diagnostic accuracy, and has a significantly higher area under the receiver operating characteristic curve. Both AFI and UA S/D ratio illuminated a high NPV that reflected that these tests have a strong capability to rule out postnatal RDS among our local population. However, the umbilical artery S/D ratio remains superior across all the diagnostic accuracy indices in comparison with AFI in predicting the neonatal RDS. The positive likelihood ratio (LR+) was 6.50, which means that the probability of a positive test result in neonates with RDS is 6.5 times higher than the probability of a positive test result in neonates without RDS, whereas the negative likelihood ratio (LR-) was 0.26, which implies that the likelihood of RDS given a negative outcome was low. Also, the area under the ROC curve (AUC) of the umbilical artery S/D ratio is 0.840, which indicates a good discriminatory power (table 2 and figure 1). The higher specificity and LR+ of the UA S/D ratio suggest greater competence to rule out the risk of RDS in case of an abnormal UA S/D ratio [17]. The NPV of the normal umbilical artery S/D ratio that will exclude postnatal RDS was 96.4%. This high NPV was justified by the low false-negative (3.6% of negative tests) and is similar in stratified subgroups (96.2-96.8%) (see table 2 and 4). The negative likelihood ratio (LR) was also 0.26, which once again highlights the validity of a normal finding in eliminating RDS. Our findings are sound in the pathophysiological basis. A high umbilical artery S/D ratio indicates a higher vascular resistance of the placenta, resulting in chronic fetal hypoxemia. This hypoxic condition has been known to alter the surfactant production and maturation in the fetal lungs, hence predisposing the neonate to RDS at birth [18]. AFI, being a volume measure of the amniotic fluid, is a more comprehensive measure of fetal health and placental competence. Oligohydramnios (AFI <8 cm) may be related to uteroplacental insufficiency, but it is also affected by a broader range of factors, including membrane integrity and fetal renal function, which can be used to understand why it is less specific and less predictive of RDS [19, 20]. The more modest LR+ of our study suggests that oligohydramnios alone is a weaker discriminator of imminent neonatal respiratory compromise at term, particularly when membranes are intact, and labor management is standardized [21]. Notably, the PPVs of the two tests were rather low, which is predictable in an environment with low disease prevalence (12.6%) and highlights a Bayesian concept that even special tests will provide poor PPV when the risk of the baseline is low. In contrast, the NPVs were outstanding, i.e., normal UA S/D and/or sufficient AFI have a significant impact on reducing the post-test risk of RDS and can be reassuring in the absence of other risk factors [22]. Current study findings are inconsistent with a few recent studies. In a recent study Sharma M and colleagues, while attempting to assess the value of umbilical artery S/D ratio and AFI for adverse fetal outcome, they reported that the prevalence of postnatal RDS as adverse outcome was 16% (n=16/100), while, the sensitivity and specificity of umbilical artery S/D ratio was 62.5% and 91.52% respectively, while the sensitivity and specificity of AFI was 43.75% and 79.66% respectively, where the RDS was confirmed through clinical and radiological neonatal findings within 72 hours of delivery among suspected neonates [11]. In contrast to Sharma *et al.* who evaluated the UA S/D ratio in a small sample population that represented a broad range of deleterious perinatal outcomes and a relatively lower sensitivity [11], this study included a bigger sample of term pregnancies and exhibited better and more predictive accuracy of postnatal respiratory distress syndrome (RDS). This difference is likely due to the increased consistency of the UA S/D ratio in low-risk term gestations. The main strengths of the study are the explicit juxtaposition of the UA S/D ratio and amniotic fluid index (AFI) with RDS as the main outcome and stratified analyses in the context of salient confounding variables in term pregnancies. The ensuing findings support the hypothesis that the UA S /D ratio is a better Doppler predictor of fetal surveillance in respiratory risk, but that the AFI should be applied as an adjunct rule-out measure rather than as a key predictive variable. Diagnostic performance of UA S/D ratio showed high consistency in all the study confounders as accuracy tended to cluster around 85 to 88 percent with LR- 0.25, indicating the strength of UA S/D as a term screening tool. In the case of AFI, accuracy was consistent but low in comparison with UA S/D. In multipara and vaginal delivery, accuracy was low but consistent (~ 77-78 percent and 68-69 percent). The positive LR values of AFI did not frequently exceed 3 altogether in any subgroup, which supports the argument that it is a better rule-out predictor, as opposed

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to a rule-in test. Combined, stratification implies that UA S/D is the main parameter of Doppler used to make decisions, and AFI provides some supplementary data, especially when ruling out the risk of RDS [23]. When the study discusses the clinical implications, these study findings can be beneficial for the triage and surveillance of pregnancy at term. It was established that the normal UA S/D meaningfully reduces the likelihood of neonatal respiratory disorders, so that these cases may be managed by routine obstetric care rather than being escalated just because of respiratory risk factors. Secondly, the normal UA S/D has a significant negative effect on the probability of early RDS, and these situations can be managed by routine obstetrics without increasing risks, only in the context of respiratory danger. Thirdly, Additional intrapartum care, preparedness of neonatal resuscitation, and prompt pediatric attention are warranted in subjects with an S/D ratio >3 and who's positive LR is meaningfully higher. Furthermore, the presence of low AFI (<8 cm) is not sufficient to declare high risk of RDS, but as AFI returns to normal, its high NPV should be used to support de-escalation in otherwise low-risk term pregnancies. Our study findings further implicated that when UA S/D is used hand-in-hand with clinical context (maternal comorbidities, intrapartum events, fetal heart rate patterns), it will be the most effective risk calibration than any given measure. Prediction can be further refined, where possible, with the addition of complementary Dopplers (e.g., middle cerebral artery or cerebroplacental ratio). Prioritization of UA S/D measurement in resource-constrained environments provides the highest payoff to detect the neonates who might need to receive early respiratory support/NICU preparedness, and the unnecessary escalations can be safely avoided by the normal studies.

Despite the various strengths and clinical implications, this study is not free from limitations. To begin with, single-center design and non-probability consecutive sampling can raise the question of generalizability outside similar tertiary settings. Second, cross-sectional validation has no causal inferences or longitudinal risk evaluation. Third, the study has not included other Doppler indices (e.g., MCA, CPR) or biophysical parameters; combining them is likely to perform better and predict better. Fifth, misclassification can be introduced through potential variability of measurement (e.g., fetal breathing, operator expertise) and lack of formal inter-observer reliability testing. At last, early RDS was the only available outcome; no longer-term respiratory follow-up and NICU course were examined. Combined Doppler parameters (UA S/D ratio, MCA, CPR) neonatal respiratory follow-up and cost-effectiveness analysis should be validated on the basis of long-term follow-up of multicenter prospective studies in the future in order to be regularly integrated into term pregnancy surveillance protocols.

CONCLUSIONS

This study's results demonstrated the diagnostic superiority of UA S/D ratio over AFI. An increased UA S/D ratio (>3) in clinical practice should be considered an opportunity to take proactive action, such as to activate the neonatal resuscitation team upon birth, prepare to provide immediate respiratory support, and expedited delivery planning should other alarming aspects be observed. On the other hand, an isolated low AFI (<8 cm) is a red flag that should be carefully monitored as a marker of fetal well-being but should not be used to cause high-risk interventions in otherwise normal term pregnancies. Instead, it must be used as additional information to help in decision-making in cases where UA S/D results are marginal or other clinical considerations are concerned. The regular introduction of the UA S/D ratio into routine third-trimester Doppler surveillance regimes in the context of term pregnancy may help to improve perinatal risk assessment, resource allocation, especially in resource-limited settings, and reduce the number of unnecessary interventions, and ensure that infants at high risk are ready to be born promptly.

Authors' Contribution

Conceptualization: AK
Methodology: AK, MS, NG
Formal analysis: AK
Writing and Drafting: AK, MS, NH, SS, FKM
Review and Editing: AK, MS, NH, SS, FKM, NG

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Recurrence of Seizures with Intravenous Versus Intramuscular Magnesium Sulphate in Women with Eclampsia

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ABSTRACT

Magnesium sulphate is increasingly being utilized in women with eclampsia. But there is still debate on the ideal route of administration. **Objectives:** To compare the recurrence of seizures between intravenous (IV) and intramuscular (IM) magnesium sulphate (MgSO4) in women with eclampsia. **Methods:** This open-label, parallel-group, randomized controlled trial was conducted at the Department of OBG, Nishtar Hospital, Multan, from 13th May to 12th November 2025. A total of 200 women aged 18–45 years, admitted with eclampsia, were enrolled after informed consent and demographic data were collected. Women with intracranial bleeding or prior use of anticonvulsants were excluded. Participants were randomly divided to receive either IV (4g IV bolus then 1g/hour infusion) or IM MgSO4 (4g IV+6g IM loading dose, followed by 2.5g IM, 4 hourly). $MgSO_4$ was continued for 24 hours post-seizure or delivery. The primary outcome was seizure recurrence within 48 hours. Data were analyzed using SPSS version 25.0 with the chi-square test. **Results:** The mean age was 24.5 ± 4.9 years, and the mean gestational age was 29.0 ± 3.1 weeks. Most participants were ≤25 years (67%), <30 weeks of gestation (60.5%), and obese (64%). Baseline characteristics were comparable across both groups. Seizure recurrence was higher in the IM group (70%) compared to the IV group (30%), with no statistically significant difference (p=0.059). No significant predictors of seizure recurrence were identified after stratification. **Conclusions:** Although seizure recurrence was high in the intramuscular $MgSO_4$ group, this was not statistically significant. The intramuscular route can be considered an alternative to the intravenous route.

INTRODUCTION

During childbirth and the puerperium, eclampsia is a significant source of morbidity and mortality. Every year, eclampsia alone causes almost 50,000 maternal fatalities globally [1]. In industrialized nations, eclampsia occurs in one out of every 2000 deliveries; in underdeveloped regions, it occurs in one out of every 50 to 500 deliveries [2]. Eclampsia is linked to a higher risk of placental abruption, cardiovascular and cerebrovascular problems, disseminated intravascular coagulation, and maternal death; it is only exceeded by hemorrhage [3]. The first and most important concept in eclampsia management is seizure control [4]. According to findings from a collaborative eclampsia trial, magnesium sulphate (MgSO4) is more effective than diazepam and phenytoin for routine anticonvulsant treatment of eclamptic women [5]. It was reported that toxicity-related issues might be avoided by administering MgSO4 intravenously [6]. It also has the advantage of being simple to administer, causing less pain to the patient, and allowing for easy control of the magnesium level [7]. However, because infusion sets are scarce, nursing personnel are inadequate, and frequent serum magnesium levels are expensive, most medical centers in low-resource countries prefer intramuscular (IM) delivery. Improper dosing, renal or underlying metabolic

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disorders (hypoglycemia or hypocalcemia), or refractory or severe eclampsia may cause recurrence of seizures despite treatment [6]. Bagariya et al. studied a total of 80 patients with eclampsia (40 in each intravenous or intramuscular group). They found that 3 out of 40 patients (7.5%) who received MgSO4 IM experienced recurrence of fits, while none of the patients who received an IV dose experienced either a recurrence or an onset of seizures. In the IM group, 25% cases, while in the IV group, 10% cases had loss of deep tendon reflexes (DTR) [7]. Saha et al. studied 41 women who presented with eclampsia, randomly splitting them into 2 groups: IV magnesium was used in group I, whereas IM MgSO4 was given in group II. Seizure recurrence and loss of DTR were observed in 10% and 65% of group I, while 4.8% and 14.3% of group II cases, respectively [8]. So, keeping in view the controversy regarding the better efficacy of various routes of administration of magnesium sulphate, we have planned this study in patients with eclampsia presenting to our local setting.

Although magnesium sulphate is the standard treatment of eclampsia, there still remains confusion about the best mode of administration, especially in a low-resource environment where data collection and human expertise might not be consistent. However, the prior investigations showed mixed results on the issue of seizure control by intravenous and intramuscular regimens, and it is necessary to directly compare them in a standardized clinical environment. The study aimed to compare the incidence of recurrence of seizures in IV and IM magnesium sulphate in women with eclampsia, with the hypothesis that there is a significant difference between the two routes to inform the practice and resource planning of evidence-based clinical practice.

METHODS

This open-label, parallel-group, randomized controlled trial (Reg. No. NCT06997575, https://clinicaltrials.gov/study/NCT06997575) was conducted at the Department of Obstetrics and Gynaecology, Nishtar Medical University and Hospital, Multan, over a period of six months from 13th May 2025 to 12th November 2025 after approval from the institutional ethics review committee (ERC # 8995/NMU). A total of 200 women, 18 – 45 years of age, admitted in labour room due to eclampsia were consecutively included in the study after informed consent. Women having intracranial bleeding (on CT-scan brain), already receiving MgSO4, phenytoin, or diazepam in the last 72 hours, were excluded from the study. Participants' age, gestational age, parity, and obesity (obtained on interview at enrollment) were documented. Through simple random sampling using the lottery method, the participants were assigned to intramuscular magnesium sulphate (intervention group) or intravenous magnesium sulphate (comparison group) groups in a 1:1 ratio. Allocation codes were placed in sequentially numbered, sealed opaque envelopes. At the time of enrollment, the recruiting surgeon opened the envelope in sequence to assign the participant in allocated group. Pregnant women, ≥ 20-weeks of gestation (using LMP), having blood pressure of ≥ 160/110 mm of Hg plus protein (+3 or +4) in spot urine examination, now presenting with new onset of grand mal seizure activity and/or unexplained coma were labelled as eclampsia positive cases. Seizure recurrence was labelled if the seizure episode (clinical tonic-clonic motor seizure activity) occurred within 48-hours of treatment. In the active comparator group, participants received a 20% solution bolus of 4 g of IV MgSO4 and a continuous IV infusion of 1 g per hour. A 10 g loading dose of MgSO4 (4 g IV as 20% solution, 6 g IM 50% solution, and 3 g in each buttock with 1% of 1 ml of lidocaine) was administered to the intervention group, whereas 2.5 g IM every 4 hours was administered as maintenance therapy. For 24 hours following the last seizure or 24 hours following birth, whichever came first, MgSO4 medication was maintained. A minimum sample size of 200 participants was calculated using OpenEpi online software through the formula for a randomized controlled trial (https://www.openepi.com/PDFDocs/SSCohortDoc.pdf. $n=(Z\alpha/2+Z1-\beta)2\,\bar{p}\bar{q}(r+1)/r(p1-p2)2$. Seizure recurrence of 10% in the intravenous magnesium sulphate group was used [8], seizure recurrence risk ratio of 2.5 in the intramuscular magnesium sulphate group, with a power of 80% and significance level of 5%. Normality of continuous data was assessed through the Shapiro-Wilk test at 5% significance level. Normally distributed numerical data were presented as mean ± SD, and categorical data as frequency and percentages. Data were analyzed using SPSS version 25.0. Seizure recurrence between the groups is compared through a chi-square test, and a p-value < 0.05 is taken as significant. The study followed Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting of randomized controlled trials [9].

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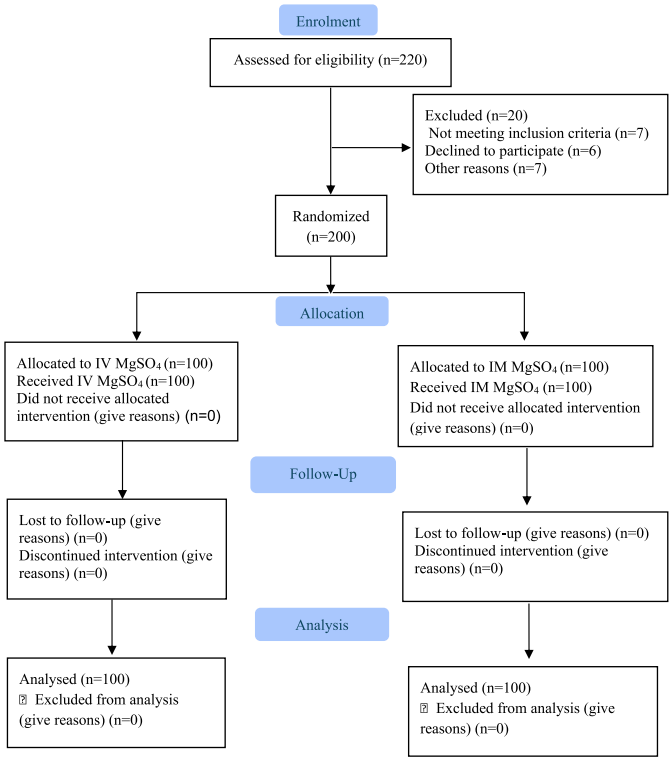

Figure 1: CONSORT 2010 Flow Diagram

RESULTS

The mean age of the women was 24.5 ± 4.9 years, with 134 (67%) ≤ 25-years of age. The mean gestational age was 29.0 ± 3.1 weeks, including 121 (60.5%) below 30-weeks. The median parity was one (IQR – 1) that included 125 (62.5%) para one women. Obesity was identified in 128 (64%) of the women. All the demographic characteristics were comparable between the intravenous and intramuscular magnesium sulphate treatment groups (Table 1).

Table 1: Characteristics of pregnant women presenting with eclampsia (n=200)

Characteristics	All (n=200)	Magnesium Sulphate		p-value*
		Intravenous	Intramuscular	
Age (Years)	24.5 ± 4.9	24.4 ± 4.2	24.6 ± 5.6	0.810
⩽ 25-Years	134 (67%)	66 (49.3%)	68 (50.7%)	0.881
> 25-Years	66 (33%)	34 (51.5%)	32 (48.5%)	
Gestational Age (Weeks)	29.0 ± 3.1	29.0 ± 3.1	29.0 ± 3.2	0.964
< 30 Weeks	121 (60.5%)	61 (50.4%)	60 (49.6%)	0.885
⩾ 30-Weeks	79 (39.5%)	39 (49.4%)	40 (50.6%)	
Parity	1 (1%)	1 (1%)	1 (1%)	1.000
Para 1	125 (62.5%)	63 (50.4%)	62 (49.6%)	0.884
Para ≥ 2	75 (37.5%)	37 (49.3%)	38 (50.7%)	
Obesity – Yes	128 (64%)	63 (49.2%)	65 (50.8%)	0.768

*chi-square test; categorical comparison, t-test for means comparison, and Mann-Whitney U test for median comparison

Seizure recurrence was high in the intramuscular compared to the intravenous magnesium sulphate group (70% vs. 30%), but this did not achieve statistical significance (Table 2).

Table 2: Seizure recurrence after treatment in pregnant women presenting with eclampsia (n=200)

Seizure Recurrence	All (n=200)	Magnesium Sulphate		p-value*
		Intravenous	Intramuscular	
Yes	20 (10)	6 (30)	14 (70)	0.059
No	180 (90)	94 (52.2)	86 (47.8)	

No significant determinant of seizure recurrence in the intramuscular compared to the intravenous magnesium sulphate group was identified after stratification of demographic characteristics (Table 3).

Table 3: Determinants of seizure recurrence in pregnant women presenting with eclampsia (n=200)

Characteristics		Magnesium Sulphate	Seizure Recurrence		p-value*
			Yes	No	
Age Groups	⩽ 25-Years	Intravenous	3 (4.5%)	63 (95.5%)	0.128
		Intramuscular	9 (13.2%)	59 (86.8%)	
	> 25-Years	Intravenous	3 (8.8%)	31 (91.2%)	0.469
		Intramuscular	5 (15.6%)	27 (84.4%)	
Gestational Age	< 30 Weeks	Intravenous	2 (3.3%)	59 (96.7%)	0.163
		Intramuscular	6 (10%)	54 (90%)	
	⩾ 30-Weeks	Intravenous	4 (10.3%)	35 (89.7%)	0.348
		Intramuscular	8 (20%)	32 (80%)	
Parity	Para 1	Intravenous	3 (4.8%)	60 (95.2%)	0.126
		Intramuscular	8 (12.9%)	54 (87.1%)	
	Para ≥ 2	Intravenous	3 (8.1%)	34 (91.9%)	0.480
		Intramuscular	6 (15.8%)	32 (84.2%)	
Obesity	Yes	Intravenous	3 (4.8%)	60 (95.2%)	0.206
		Intramuscular	8 (12.3%)	57 (87.7%)	
	No	Intravenous	3 (8.1%)	34 (91.9%)	0.301
		Intramuscular	6 (17.1%)	29 (82.9%)	

*Fischer's exact test

DISCUSSION

One of the main reasons for maternal morbidity and death is eclampsia. In industrialized countries, this disease affects 1 in 2,000 to 4,000 deliveries; in poorer countries, the rate is several times higher [10]. Eclampsia is a serious obstetric emergency that needs to be managed promptly and effectively to prevent disastrous results [11]. The preferred medication for preventing and treating eclamptic convulsions is magnesium sulphate [12]. The majority of the women in our study were under 25, and their mean age was 24.5 ± 4.9 years, highlighting the tendency of eclampsia in our population to affect younger mothers. This is consistent with research from Sukkur, Pakistan, which showed that women with pre-eclampsia/eclampsia were 23 ± 5 years old on average [13]. From Abbottabad, a cohort showed similar age patterns, with a mean age of 30 ± 10.9 years and 72% of eclamptic patients being between the ages of 18 and 27 [14]. A cross-sectional study conducted in Pakistan in 2022 found that 160 eclamptic primigravida had an average age of 26.4 ± 2.4 years,

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highlighting the continued vulnerability of younger mothers [15]. When taken as a whole, these recent studies demonstrate the necessity for focused prenatal surveillance in this age range and emphasize how susceptible younger mothers are to eclampsia. We found that the majority of pregnant women had gestational ages below 30 weeks, and the mean gestational age of eclamptic patients was 29.0 ± 3.1 weeks, indicating that eclampsia is common in the early third trimester. This result is in line with several previous studies that highlight early onset in comparable contexts. For instance, early-onset pre-eclampsia/eclampsia primarily occurs before 34 weeks and is linked to worse maternal outcomes and increased illness severity, according to a 2021 retrospective cohort study conducted in Ethiopia [16]. Furthermore, the median gestational age at intervention was approximately 29 weeks, which reflects the clinical threshold when eclampsia or severe symptoms appear, according to an expectant management study of severe pre-eclampsia among women at 24-34 weeks [17]. Another study emphasized the greater risks associated with early-onset hypertensive disorders of pregnancy, which often call for earlier intervention and closer monitoring if they appear before 32 weeks [18]. Together, these findings confirm our finding that eclampsia often appears before 30 weeks and emphasize the importance of prompt management and heightened prenatal care during this crucial gestational period. Although it was shown in our study that the intramuscular group experienced a higher rate of seizure recurrence than the intravenous magnesium sulphate group, this difference was not statistically significant. This pattern can be a result of the more stable serum magnesium levels attained by intravenous delivery, which enables a better titration of therapeutic levels and a quicker onset. The authors of a randomized controlled trial from Rawalpindi, in 2022, found that 92.5% of women treated with IM did not experience seizure recurrence compared to 97.5% of women getting IV medication (p=0.147) [19]. Despite not substantially impairing overall seizure control, recent pharmacokinetic analyses have shown that IM regimens (like the Pritchard protocol) produce more variable serum magnesium levels than IV protocols, possibly resulting in brief intervals of subtherapeutic concentrations that could predispose to breakthrough seizures [20]. Similar to our findings, a recent study published in 2024 found that two IV patients and four IM patients had recurrent convulsions, a non-significant difference, while the IM group showed more frequent symptoms of magnesium toxicity, including decreased deep tendon reflexes [21]. According to Kanti et al. 1/17 (5.88%) of eclamptic patients in the IV group and 1/17 (5.88%) in the IM group experienced a convulsion recurrence, which is statistically not significant (P=1) [22]. Fits were controlled in 62 (93.94%) of the women treated with the conventional Pritchard regimen, and only 4 (6.06%) experienced recurrences of convulsions, according to the research by Ali *et al.* Eight (12.12%) women in the loading (intravenous) dose group experienced another convulsion, while 58 (87.87%) women did not have another one. A single loading dose worked just as well as a typical Pritchard regimen [23]. Furthermore, because of its more predictable pharmacodynamics, revised clinical guidelines still support IV magnesium sulphate as a first-line seizure prophylactic; nevertheless, they also confirm that intramuscular administration is still a feasible option in cases where IV access or infusion pumps are not accessible [24]. When combined, these findings support the idea that, under strict monitoring and adherence to established protocols, IM delivery may show a tendency towards increased seizure recurrence, but this does not translate into a statistically or clinically significant difference when compared to IV administration. The benefits of intramuscular magnesium sulphate are; it can be used in circumstances when there is a lack of intravenous access, severe circulatory collapse, risk of rapid infusion toxicity, and limited monitoring facilities [24].

The current study's strengths were that it was a randomized controlled trial, which is the gold standard for comparing therapies, and lowering selection bias to increase the dependability of the results. Comparing seizure recurrence between two routes of magnesium sulphate delivery in eclamptic women was the study's specific and clinically relevant goal. For a single-center study, the sample size was comparatively big, which enhanced the study's power and generalizability to comparable contexts. The fact that this study was limited to a single institution may have limited its generalizability to different demographics or healthcare environments. Another limitation is that magnesium levels were not measured before and after magnesium sulphate treatment in study participants. Recurrence of seizures was only tracked for 48 hours. For a more thorough evaluation of therapy effectiveness, longer follow-up may be required. In particular, while evaluating results, a lack of blinding may increase observer and performance bias.

CONCLUSIONS

To summarize, though seizure recurrence was high in the intramuscular MgSO4 group, this was not statistically significant. The intramuscular route can be considered an alternative to the intravenous route, particularly in situations where IV access is restricted.

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Authors' Contribution

Conceptualization: LI
Methodology: LI, IA, MK, FK
Formal analysis: LI, IA, MK, FK
Writing and Drafting: LI, MK
Review and Editing: LI, IA, MK, FK

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

Conflicts of Interest

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Vitamin D Deficiency and Distal Radius Fractures: A Case-Control Study

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ABSTRACT

Deficiency of vitamin D is considered a significant risk factor for fragile fractures. It is highly prevalent in South Asia despite the fact that sunlight is abundant. In the literature, there is limited data available regarding any association between deficiency of vitamin D levels and distal radius fractures (DRFs) specifically for the Pakistani population. **Objectives:** To find out the prevalence and severity of deficiency of vitamin D in patients with DRFs and to determine the association of fracture type, severity, and mechanism of injury with vitamin D levels. **Methods:** It was a case-control study that was conducted at Naseer Memorial Hospital, Azad Kashmir, consisting of 216 cases and 100 controls. Vitamin D in serum was estimated using a chemiluminescent immunoassay (Abbott Architect i2000SR). DRFs were confirmed on radiography due to a standard PA and lateral view of the wrist using a GE Optima XR220amx digital X-ray system. The AO system was used to classify the fractures. Statistical analysis of the data was done in SPSS version 23.0, while $p<0.05$ was taken as significant. **Results:** Vitamin D deficiency was significantly higher among patient's vs controls ($p<0.001$). Lower vitamin D levels correlated inversely with fracture severity ($r = -0.47$, $p<0.01$). Extra-articular fractures and low-energy trauma predominated. Female and elderly patients exhibited greater deficiency and more complex fractures. **Conclusions:** The deficiency of vitamin D is an important and independent predictor of DRFs specially in elderly female patients, and routine screening of vitamin D levels should be integrated into the fracture prevention strategy.

INTRODUCTION

Distal radius fractures (DRFs) are recorded as among the common orthopedic injuries in the world, especially in the aged group. They account for around 15–20% of all fractures and are mainly prevalent among postmenopausal women owing to the combined effect of osteoporosis, hormonal decrease, and musculoskeletal degeneration due to aging [1]. The increasing incidence of DRFs is a rising public health alarm, driven mainly by aging demographics, a decrease in the density of bone minerals, and an increased hazard of falls among older adults [2]. In South Asian countries such as Pakistan, the load of DRFs is augmented by general vitamin D deficiency, a critical yet changeable factor that influences bone health and fracture resistance [3]. Despite rich sunlight in the country, more than 80% of the Pakistani population has sub-optimal vitamin D levels, probably due to less outdoor activity, traditional practices

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of clothing, and improper diet [4]. Vitamin D plays a crucial role in the absorption of calcium, mineralization of bones, and osteoblastic function; its deficiency leads to secondary hyperparathyroidism, demineralization of the bones, and fragility fractures [5]. Globally, several authors have investigated the association of a deficiency of vitamin D with hip and vertebral fractures. However, limited research has focused on distal radius fractures, which often serve as an early sign of systemic skeletal fragility [6]. Moreover, most of the data available in the literature is from Western populations, where environmental and nutritional factors are different from those in South Asia [7-9].

Furthermore, researchers have linked vitamin D deficiency with increased fracture risk and delayed healing, but regional Pakistani studies are limited, specifically from Azad Kashmir. This gap limits planning for prevention strategies and can serve as a guide for fracture management. The study aimed to find a deficiency of vitamin D among the patients having distal radius fractures in comparison to controls and to determine any association of fracture type, severity, and mechanism of injury with vitamin D deficiency.

METHODS

It was a case control study was conducted from 15 September 2021 to 15 March 2022 in Naseer Memorial Hospital, Dadyal, Azad Kashmir. Approval of the study was obtained from the hospital ethical review committee (ERC) before the initiation (REF: RA05/NMH/21/081) and was conducted following the Declaration of Helsinki. All participants gave consent to participate in the study, including patients and controls, after being informed about the objectives and aims of the study. The sample size was calculated as 196 based on the prevalence of vitamin D deficiency as the primary outcome variable. The study derived the sample size by using the formula: $n=Z2 \cdot p \cdot (1-p)/d2$; where: Z=1.96(confidence level set as 95%), p=0.85 based upon the previous regional data by Jamal AB [4], and d=0.05 (margin of error). The yielded sample size was increased by 10% (n=216) to account for expected non-responses or incomplete data. Patients were identified through the orthopedic outpatient clinic. Patients with confirmed distal radius fractures (DRFs) were selected using a consecutive sampling method. Age and gender-matched healthy 100 individuals were selected from the general population to be selected as controls. Controls were selected after confirming the absence of a history of fractures, chronic illnesses affecting bone health (e.g., osteoporosis, chronic renal disease), and no vitamin D supplements for the last 6 months. The data of the patients were recorded on a proforma from the Outpatient Department, like demographic details (age, sex, comorbidities) and fracture characteristics (type, location, mechanism, and severity) for further analysis. Blood for determining the vitamin D levels was drawn from both patients and the control group, and chemiluminescent immunoassay (CLIA) was performed using Abbott Architect i2000SR analyzer, two-point calibration, and internal quality controls. Levels of vitamin D were classified as deficient if <20 ng/mL, insufficient if 20–30 ng/mL, and sufficient if >30 ng/mL [4]. Fracture assessment was done by radiographs in standard posteroanterior (PA) and lateral wrist views using a GE Optima XR220amx digital X-ray system. Fractures were classified based on location (right or left limb), intra-articular or extra-articular, mechanism of injury (classified as trauma by low energy, such as a fall from altitude or trauma by high-energy, such as a road traffic accident), and fracture type A (extra-articular), moderate B (partial articular), or severe C (complete articular). Analysis of the fractures was done to find any association between fracture type, severity, and vitamin D deficiency. Subgroup analysis was also done to establish an association between vitamin D and any specific fracture characteristic.

Data were entered in SPSS version 23.0 for analysis. Continuous variables were presented as means with standard deviation (SD), whereas variables that were categorical were presented as frequencies and percentages. Normality of distribution was determined using the Shapiro- Wilk test. Independent t and Mann-Whitney U tests were used for continuous data comparison, while categorical variables analysis was done using Fisher's exact test and Chi-square test, whereas suitable. Multivariate logistic regression was conducted to look for vitamin D deficiency predictors among fracture patients after adjusting for age, sex, and comorbidities. Pearson's correlation analysis evaluated the association between levels of vitamin D and fracture severity, while taking a p-value <0.050 as significant.

RESULTS

Two hundred and sixteen patients having distal radius fractures and 100 age- and gender matched controls were included in the study. The Shapiro–Wilk test demonstrated a nonnormal statistical distribution for serum vitamin D levels; therefore, non-parametric tests were applied where appropriate. Patients with DRF were older than controls. The median age of the control group (58.3 years, IQR 52.0–66.0) was significantly more than that of the experimental group (56.1 years, IQR 49.0–63.0; Mann–Whitney U = 9824.0, p=0.04). Sex distribution was similar between groups (female 63.9 percent vs 58.0 percent; χ^2 = 1.79, p=0.18). Diabetes mellitus (χ^2 = 5.11, p=0.02) and osteoporosis (χ^2 = 14.02, p-value less than 0.001) were significantly more common among fracture patients, while hypertension showed no group difference

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(χ^2 = 0.54, p=0.46). Baseline characteristics of the participants are shown in table 1.

Table 1: Clinical Characteristics and Demography of the Participants

Variables	Patients (n= 216), n (%)	Controls (n= 100), n (%)	Test	p-value
Age, Median (IQR), Years	58.3 (52.0–66.0)	56.1 (49.0–63.0)	Mann–Whitney U = 9824.0	0.040
Female Sex	138 (63.9%)	58 (58.0)	χ^2 = 1.79	0.180
Diabetes mellitus	54 (25.0%)	13 (13.0%)	χ^2 = 5.11	0.020
Hypertension	91 (42.1%)	38 (38.0%)	χ^2 = 0.54	0.460
Osteoporosis	72 (33.3%)	11 (11.0%)	χ^2 = 14.02	—

Extra-articular fractures were found in 58% and intra-articular fractures in 42.0%. Low-energy trauma was the main mechanism, and high-energy trauma accounted for 30%. Right-sided fractures were found in 62% of patients. Based upon the AO Classification, 47.2 % of fractures were mild (Type A), 28.2 % moderate (Type B), and 24.5% were severe (Type C). Detailed characteristics of the fractures are shown in table 2.

Table 2: Characteristics of the Fractures among the Patients (n=216)

Variables	n (%)
Fracture Type	
Extra-Articular	125 (58.0%)
Intra-Articular	91 (42.0%)
Mechanism of Injury	
Low-Energy Trauma	151 (70.0%)
High-Energy Trauma	65 (30.0%)
Laterality	
Right Side	134 (62.0%)
Left Side	82 (38.0%)
AO Severity	
Type A (Mild)	102 (47.2%)
Type B (Moderate)	61 (28.2%)
Type C (Severe)	53 (24.5%)

Levels of vitamin D were significantly low in the patient group vs the control group (16.8 ng/mL, IQR 12.3–21.5 vs 31.4 ng/mL, IQR 26.0–36.8; Mann–Whitney U = 4121.5, p<0.001). Deficiency of vitamin D was found in 73.1% of patients vs 15.5% of controls; insufficiency and sufficiency distributions differed significantly (χ^2 = 112.6, p<0.001). Classification details are presented in table 3.

Table 3: Classification According to Levels of Vitamin D and Group Comparisons

Serum Levels of Vitamin D	Patients (n=216)	Controls (n=100)	χ^2	p-value
Deficient (<20 ng/mL)	158 (73.1%)	15 (15.5%)	112.6	<0.001
Insufficient (20–30 ng/mL)	43 (19.9%)	35 (35.0%)		
Sufficient (>30 ng/mL)	15 (7.0%)	50 (49.5%)		

Additional continuous comparison: Median vitamin D level in patients: 16.8 ng/mL (IQR 12.3–21.5)

Median vitamin D level in controls: 31.4 ng/mL (IQR 26.0–36.8). Mann–Whitney U = 4121.5, p<0.001

Vitamin D deficiency was found significantly more among intra-articular fractures compared with extra-articular fractures (χ^2 = 7.84, p=0.02). Fracture severity also exhibited a significant association with vitamin D status: severe fractures (Type C) had the maximum proportion of vitamin D-deficient patients, while mild fractures (Type A) had the lowest (χ^2 = 16.91, p<0.001). Low-energy trauma was strongly associated with vitamin D deficiency compared with high-energy trauma (χ^2 = 5.47, p=0.02). It was found that a significant negative correlation was present between serum vitamin D levels and AO severity grade (Pearson r = –0.32, p<0.001), indicating that lower vitamin D levels are associated with greater fracture complexity. Independent predictors of deficiency of vitamin D among fracture patients included age 60 years or older (AOR 1.78, 95 percent CI 1.20–2.64, p=0.005), female sex (AOR 1.92, 95 percent CI 1.23–2.99, p=0.004), osteoporosis (AOR 2.15, 95 percent CI 1.32–3.50, p=0.002), and low-energy trauma (AOR 1.63, 95 percent CI 1.05–2.56, p=0.03). Assessment of the model revealed acceptable calibration (Hosmer–Lemeshow p=0.42) and a moderate ability to explain the outcome (Nagelkerke R2 = 0.29), with full regression details listed in table 4.

Table 4: Multivariate Logistic Regression Detecting Predictors of Deficiency of Vitamin D

Predictor	Adjusted OR	95 percent CI	p-value
Age ≥ 60 Years	1.78	1.20–2.64	0.005
Female Sex	1.92	1.23–2.99	0.004
Osteoporosis	2.15	1.32–3.50	0.002
Low-Energy Trauma	1.63	1.05–2.56	0.030
Model fit			
Nagelkerke R^2	0.29	—	—
Hosmer–Lemeshow p	0.42	—	—

DISCUSSION

This study found that patients with DRF had vitamin D deficiency, which indicates a moderate link between serum levels of vitamin D and increased risk of fracture. This suggested its crucial role in bone integrity and making bones more prone to develop fractures. Our findings are consistent with the available regional data. Siddiqee et al. [11] and Dhibar et al. [3] found marked vitamin D deficiency in the South Asian population, with prevalence rates as high as 80%. The study findings are also in accordance with the research of Cianferotti et al. and Manoj, who found suboptimal vitamin D levels in patients having fragile fractures [9, 10]. These cross-population findings highlight a broader regional crisis. According to Siddiqee et al. and Jiang et al. Asian populations have a deficiency mainly due to behavioral and dress-related barriers to adequate

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sunlight [11, 12]. This study used AO classification to quantify the fracture severity and determine the correlation, and applied the regression analysis. The study found that extraarticular fractures and low-energy trauma were more prevalent in patients with a deficiency of vitamin D, which suggests that vitamin D deficiency deteriorates bone elasticity, and minor mechanical stress can damage bone integrity. These findings are in accordance with the research of Sahni et al. and Pilz et al. who also established that vitamin D deficiency leads to fragile fractures by weakening bone microarchitecture and mineralization [7, 13]. We also found a moderate inverse correlation of vitamin D and fracture severity, which also supports the biomechanical role of vitamin D in maintaining the strength of the bone. Our study indicated a gender difference in deficiency of vitamin D. Women, particularly those who had menopause, had a higher prevalence of deficiency of vitamin D and had complex fractures. Similar trends have been reported by Prietl and fellows, Lips et al. who have postulated that this difference is related to estrogen deficiency, lower muscle mass, and reduced calcium absorption in females [14, 2]. This necessitates targeted screening and supplementation programs in women over 50 years of age. In this study, age was found to be a critical predictor. The study observed a moderate negative correlation between vitamin D levels and age, which is similar to the recordings of LeBoff et al. who also documented limited outdoor exposure in adults with old age [15]. This study also confirmed that age ≥ 60, female gender, osteoporosis, and low-energy trauma are all independently related to deficiency of vitamin D, which is consistent with the findings of Fu et al. [16]. Comorbidities like hypertension and diabetes were prevalent among the patients in our study, but no statistically significant correlation with vitamin D levels was determined in our study. This suggested that deficiency of vitamin D acts as an independent risk factor and not as a mediator through systemic disease [17]. Similar findings were documented by Gatt et al. who also concluded that vitamin D influences bone repair and immune modulation independent of metabolic comorbidities [18]. The findings in this study have a very powerful public health impact. The finding of a high incidence of vitamin D deficiency despite plentiful sunlight suggests a cultural and behavioral etiology, mainly limited exposure to sunlight and low vitamin D intake in the diet among the Pakistani population. Similar deficiencies have been recognized across Europe, where vitamin D deficiency is a pandemic [19]. These findings are augmented by the recommendations of Rutigliano et al. and Holick, who emphasized region-specific supplementation and fortification of diet [8, 20].

Although this study is the first of its kind in the region but had many shortcomings. It was a single-center study, which does not represent the entire Pakistani population. Furthermore, diet and sunlight exposure time, which are the major reasons for vitamin D status, were not controlled. Physical activity, socioeconomic status, and genetic predisposition were also not evaluated. Blood samples were obtained after the injury, and acute inflammation could have influenced the serum levels of vitamin D. Nevertheless, the strength of the study is that detailed fracture classification was done, we included a control group, and biochemical assessment was done using CLIA. Therefore, it is recommended that routine vitamin D screening be incorporated in fracture prevention strategies, especially for elderly women and in patients presenting with low-energy trauma. Future longitudinal and interventional studies should be conducted to determine whether vitamin D supplements can reduce fracture incidence or improve healing results in DRF patients.

CONCLUSIONS

The study found that deficiency of vitamin D is an important and independent predictor of distal radius fractures specially in elderly female patients, and routine screening of vitamin D levels should be integrated in the fracture prevention strategy. Overall, this study has provided evidence that deficiency of vitamin D is a significant and modifiable predictor of fracture severity. Addressing this deficiency could play a key role in modifying the rising burden of osteoporosis-related fractures in Pakistan.

Authors' Contribution

Conceptualization: FN
Methodology: JJ, AM, A, FN
Formal analysis: AM, A, FN
Writing and Drafting: AM, FR, MR, FN
Review and Editing: JJ, AM, FR, MR, A, FN

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

Conflicts of Interest

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Original Article

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Comparison Of Operative Outcomes of Open Versus Percutaneous Pedicle Screw Fixation for the Treatment of Lumbar Spondylolisthesis

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ABSTRACT

Lumbar spondylolisthesis often requires surgical correction, with options like open or percutaneous pedicle screw fixation. **Objectives:** To compare their outcomes, focusing on reduced trauma, blood loss, and postoperative pain with the percutaneous approach. **Methods:** A quasi-experimental trial at Sir Ganga Ram Hospital, Lahore, included 44 patients with lumbar spondylolisthesis. Exclusion criteria were metabolic bone diseases, prior spine surgery, pregnancy, and spinal malignancy. Patients were divided into Group A (percutaneous fixation) and Group B (open Pedicle screw fixation). Intraoperative time, blood loss, and VAS pain scores were recorded. The outcome variables were postoperative hospital stay, blood loss, and surgery duration. Data was analyzed by using SPSS 25.0. **Results:** Among 44 participants, 20 were male, and 24 were female. Group A had 6 males (27.3%) and 16 females (72.7%), while Group B had 14 males (63.6%) and 8 females (36.4%). Mean intraoperative time was 44.45 ± 6.87 minutes in Group A vs. 51.27 ± 3.45 in Group B. Blood loss was significantly lower in Group A (52.82 ± 3.45 mL) compared to Group B (349.23 ± 92 mL, $p<0.05$). Postoperative pain at 6 weeks (Group A: 3.09 ± 1.41 vs. Group B: 3.36 ± 1.59) and 3 months (Group A: 2.18 ± 1.09 vs. Group B: 2.0 ± 1.02), indicating no statistical difference. **Conclusions:** Compared with traditional posterior muscle stripping treatments, percutaneous pedicle screw fixation proves an effective treatment in terms of less postoperative blood loss and operative time. This highlights the technique's potential advantages in improving patient recovery without compromising long-term pain outcomes.

INTRODUCTION

Spondylolisthesis is caused by vertebral migration or slip, mainly in the lumbar spine, and has spondylolytic and degenerative aetiologies [1]. Lumbar spondylolisthesis is a common spine condition causing pain and requiring surgery [2]. Children often experience it, but adults are more symptomatic [3]. Spondylolytic spondylolisthesis is a common youth or early adult fracture of the pars interarticularis [4]. Degenerative spondylolisthesis is the most frequent type of adult disease that causes vertebral body slip [5]. Spondylolisthesis prevalence in symptomatic and asymptomatic subjects varies, with most studies focusing on anatomical features [6]. Taiwan and Denmark have a 6% women's prevalence, while the USA has a 4-31% men's prevalence [7, 8]. Spondylolisthesis is a condition that affects women three times more often than men, typically causing back pain due to vertebral locking

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dysfunction. Diagnosis is confirmed through imaging techniques such as X-rays, MRI, or CT scans [9]. Surgical procedures for spondylolisthesis correction include neuronal decompression, interbody fusion, and fixation, available alone or in combination for effective treatment [10]. Conservative management is typically used for spondylolisthesis patients without neurological deficits. Surgery is recommended for significant deficits, advancement in spondylolisthesis grade, and daily life activities affecting daily activities [11]. Previous studies have shown the advantages of surgical procedures, but recent advances show the widespread popularity of minimally invasive procedures like PPF for lumbar interbody fusions. Pedicle screw fixation is crucial for degenerative lumbar spondylolisthesis, ensuring adequate spinal correction [12]. Screw invasion in upper facet joints can cause stress distribution changes, leading to spontaneous fusion, spondylolisthesis, and increased likelihood of revision surgery. Percutaneous fixation technique reduces paravertebral muscle mass stripping and iatrogenic injury in lumbar and back muscles [13]. Percutaneous pedicle screw fixation is gaining popularity among neurosurgeons due to its minimal invasiveness and minimal spondylolisthesis. However, the technique's degree of compression and spondylolisthesis remains controversial. Percutaneous pedicle screw fixation with posterior immobilization is gaining popularity due to its minimal spinal tissue trauma, shorter surgery time, blood loss reduction, and posterior arch preservation. However, long-term follow-up studies on clinical and radiological outcomes remain scarce for adults with grade 1 and grade 2 spondylolisthesis [14].

The rationale of the study is the choice of surgery for correction of spondylolisthesis, whether open or percutaneous. Although these procedures have been compared previously and have a very scarce literature review, prioritizing percutaneous screw fixation. The Percutaneous Pedicle Screw Fixation (PPSF) has been introduced as a less invasive procedure to replace an open pedicle screw Fixation (OPSF) in treating the Lumbar Spondylolisthesis, with the possible benefits being a lower surgical morbidity. Nonetheless, there is not much comparative data on early postoperative outcomes. The study aimed to compare the postoperative pain, intraoperative blood loss, and operative time between PPSF and OPSF.

METHODS

A quasi-experimental trial was conducted in the Department of Neurosurgery at Sir Ganga Ram Hospital, Lahore. The study duration was from June 2023 to June 2024. Ethical approval was obtained from the Institutional Review Board (Ref: 23-MD-Neurosurgery/IRB) before commencement of the study. All patients meeting the inclusion criteria were enrolled after obtaining written informed consent following an explanation of the risks and benefits. Basic demographic data were recorded for all participants. Each patient underwent a detailed pre-operative clinical and neurological examination as part of routine spine assessment. A total of 44 patients (aged 30–60 years) with lumbar spondylolisthesis were included. The calculated sample size using the mean difference of hospital stay in open Vs. Percutaneous pedicle screw fixation was (3.98 ± 1.17 vs 3.06 ± 0.89) was 44 (22 in each group), by taking 80% power of the test and 95% confidence interval [15]. Patients were allocated to Group A or Group B using non-random consecutive sampling based on surgeon preference and clinical indications. The prone position of patients was applied with the assistance of a C-arm under fluoroscopic guidance. In Group A (open pedicle screw fixation), an average midline posterior incision was used, and then the paraspinal musculature was dissected subperiosteally to reveal the posterior components of the spine. The pedicle screws were placed under the influence of fluoroscopes by using the traditional freehand method, and rods were fixed and fastened with set screws. In Group B (percutaneous fixation), AP-Ferguson views were used, and a Jamshidi needle was placed at right angles to the vertebra and moved in a bullseye direction to preserve the integrity of pedicles. A guide wire was inserted and then, successively, dilators and a working sleeve. A reamed pedicle was made, and a cannulated screw of suitable size was inserted. The screw tulips were passed with rods that were then fixed with set screws, and the result was confirmed on AP and lateral fluoroscopic images. Both groups underwent no interbody fusion or bone grafting; only pedicle screw fixation and stabilization were done. Fixation of wounds was followed by a layered wound closure. All surgeries were performed by consultant spine surgeons with more than 5 years of experience in spine surgery and pedicle screw fixation. After general anesthesia, a midline incision exposed the affected vertebrae. Pedicle entry points were identified, and screw trajectories were confirmed with a C-arm. Screws were inserted bilaterally, and rods were positioned to reduce spondylolisthesis via ligamentotaxis. Spinal decompression was performed, and hemostasis was achieved. The fascia was closed watertight, followed by subcutaneous and skin closure with aseptic dressing. The intraoperative time was noted from the time of incision to the closure of the wound and documented in the required proforma. After the surgery, intraoperative blood loss was calculated and documented. The pain relief was assessed at the 1st week, 6th week, and at 3 months postoperatively via VAS.

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All the data were noted and analyzed using SPSS version 25.0. Numerical variables, i.e., age, intraoperative blood loss, duration of surgery, post-operative pain, and postoperative hospital stay was presented by mean ± SD. All the qualitative variables, such as gender was presented by frequency and percentages. An independent sample t-test was applied for the comparison of mean postoperative hospital stay, blood loss, and duration of surgery between the two groups. The p-value of <0.050 was statistically significant.

RESULTS

Group A had a mean age of 45.18+3.02 years, and Group B had a mean age of 44.05 ± 2.34 years. The mean BMI in Group A was 28.2 ± 2.35, while in Group B, it was 28.18 ± 3.33. Of the total participants, 20 were male, and 24 were female. In Group A, there were 6 males (27.3%) and 16 females (72.7%), whereas Group B had 14 males (63.6%) and 8 females (36.4%) (Table 1).

Table 1: Age and Gender Distribution of Patients

Variables	Group A (n=22)	Group B (n=22)	Total (n=44)
Mean Age (Years)	45.18 ± 3.02	44.05 ± 2.34	–
Mean BMI (kg/m^2)	28.2 ± 2.35	28.18 ± 3.33	–
Male, n (%)	6 (27.3%)	14 (63.6%)	20
Female, n (%)	16 (72.7%)	8 (36.4%)	24

The average intraoperative time was 44.45 ± 6.87 minutes in Group A, compared to 51.27 ± 3.45 minutes in Group B. The difference between the two groups regarding operative time was statistically significant, with a p-value of 0.029. The mean blood loss in Group A was 52.82 ± 3.45 mL, whereas in Group B, it was significantly higher at 349.23 ± 92 mL. The comparison yielded a p-value of 0.001. The mean duration of hospitalization was 4.2 ± 0.32 days for Group A and 7.12 ± 0.45 days for Group B. The difference in hospital stay was statistically significant, with a p-value of 0.001 (Table 2).

Table 2: Comparison of Intraoperative Outcomes Among Both Groups

Variables	Group A	Group B	p-value
Operative Time	44.45 ± 6.87	51.27 ± 3.45	0.029*
Intraoperative blood loss	52.82 ± 3.45	349.23 ± 92.6	0.001*
Hospital stays	4.2 ± 0.32	7.12 ± 0.45	0.001*

VAS score- a gradual decrease in the duration of the post-operative symptomatic pain in Group A and Group B. The two groups had similar pain scores immediately after surgery. Nonetheless, the percentage decrease in the level of pain is observed in Group A at 1 week after the operation than in Group B (mean VAS: 4.18 vs 5.45). This continues up to the 6th week, where Group A still scores lower on the pain scale than Group B (mean VAS: 3.09 vs 3.36). The comparison of post-operative pain between the two groups is not significant (p>0.050), which means that the surgical method applied in Group A is related to better early and short-term pain results than in the case of Group B (Figure 1).

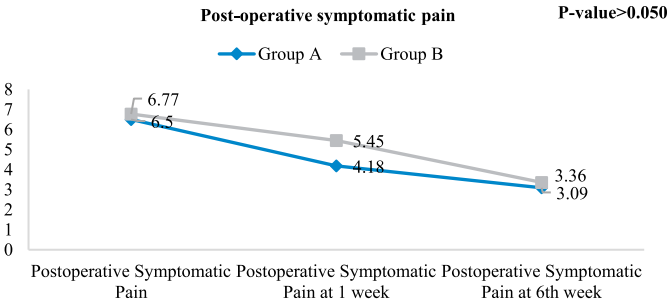

Figure 1: Postoperative Pain Comparison Between Study Groups

DISCUSSION

The aging population has led to a rise in low back pain from lumbar degenerative disease, often linked to spinal alignment and pelvic sagittal balance. Adjustments to spino-pelvic parameters are crucial for managing sagittal imbalance and associated symptoms. The demand for a better quality of life has driven advancements in surgical approaches for spondylolisthesis [16]. Therefore, this study was conducted to compare the outcomes of open and percutaneous pedicle screw fixation in the treatment of lumbar spondylolisthesis. In this study, we compared intraoperative outcomes between two groups. Group A had a significantly shorter average intraoperative time of 44.45 ± 6.87 minutes versus 51.27 ± 3.45 minutes for Group B (p=0.029). Blood loss was also notably lower in Group A at 52.82 ± 3.45 mL compared to 349.23 ± 92 mL in Group B (p=0.001). Additionally, the average pain score one-week post-operation was lower in Group A at 4.18 ± 1.53 compared to 5.45 ± 1.96 in Group B, reinforcing the significant advantages of Group A's outcomes. A randomized controlled study also reported that percutaneous pedicle screw fixation (PPSF) and open pedicle screw fixation (OPSF) lead to similar clinical outcomes in patients with thoracolumbar spine fractures without any neurological impairment. The research showed that PPSF was not linked with a lower intra-operative blood loss, whereas the scores of post-operative pain and operative time were comparable between the 2 methods [17]. However, literature reports that advanced percutaneous spinal fixation techniques have been developed to overcome the limitations of open screw-rod instrumentation, including higher infection rates, increased blood loss, and prolonged hospital stays, to enhance patient safety and clinical outcomes [18]. A major benefit of percutaneous spinal fixation over traditional open techniques that has been reported with high consistency is the large cutdown in intraoperative blood loss. It has been shown that percutaneous pedicle screw fixation (PPSF) is related to

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significantly reduced blood loss when compared to open posterior instrumented fusion (OPIF) [19]. This benefit is credited to a great extent to the least soft-tissue dissection, less paraspinal muscle stripping, and minimal surgical exposure in minimally invasive methods. A meta-analysis and systematic review of percutaneous and open surgical methods of thoracolumbar fracture in patients showed statistically significantly less intraoperative blood loss in patients who have undergone percutaneous fixation [20]. The same has been reported in patients with thoracolumbar spinal metastases, where PPSF had led to reduced blood loss in a significant margin over OPIF [21]. However, another investigation found that patients who underwent conventional open surgery experienced average intraoperative and postoperative blood losses of 380 and 441.1 mL, respectively [22]. Reduced postoperative pain may lead to faster mobilization, faster recovery, a shorter stay in the hospital, and lower hospital expenses. The recent study also reported the lesser postoperative pain and faster recovery. To compare the results, a systematic review and meta-analysis were done. 279 individuals getting percutaneous fixation were compared to 340 patients undergoing open fixation using data from 12 pertinent studies. The percutaneous group's surgical time was much shorter. A shorter hospital stay was also linked to the percutaneous method. Although there was no difference in screw mispositioning, the percutaneous technique had better clinical outcomes on the visual analogue scale and a lower incidence of infection [23].

Although the advantages of the percutaneous pedicle screw fixation (PPSF) have been well-documented, there are still significant factors to consider: first, the learning curve related to minimally invasive approaches, the required specific equipment, and the inability to reach the best result with complicated fractures. Effective practice of PPSF needs specific training and a comprehensive knowledge of the anatomy of the spine, the possibility of guidance of imaging, and operative biomechanics. This research has some limitations, such as it was carried out in one center, and this might not apply to the rest of the population. The quasi-experimental design did not have the possibility of blinding because it did not allow it, which could have affected subjective outcome measures. Also, the six-week follow-up was not sufficient to evaluate the long-term results, including the success of fusion and long-term clinical effectiveness.

CONCLUSIONS

It was concluded that, compared with traditional posterior muscle stripping treatments, percutaneous pedicle screw fixation proves an effective treatment in terms of less postoperative blood loss, pain, and operative time. The percutaneous pedicle screw technique offers reduced blood loss, less pain, and shorter hospital stays. Despite a steeper learning curve, its benefits, such as minimal muscle damage and comparable accuracy, make it a strong alternative to the traditional open approach. This paper has noted that percutaneous fixation with minimal invasion can be incorporated as a possible alternative to traditional open fixation in that it can provide better early post-surgical recovery and does not negatively affect the outcome of short-term stabilization.

Authors' Contribution

Conceptualization: SS, SF, TA, AH
Methodology: TA, AH
Formal analysis: SS, SF, DS, MA
Writing and Drafting: SS, AH
Review and Editing: SS, SF, DS, TA, MA, AH, FAKL

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Impact of Early and Delayed Stoma Closure on Patients and Their Family Life

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ABSTRACT

Temporary intestinal stomas are to preserve the distal anastomosis following colorectal surgery. Although stoma reversal is necessary to provide bowel continuity, the time of closure is debatable. Early closure might be more beneficial by minimizing stoma complications, hospitalization, and adverse psychosocial effects. **Objectives:** To compare clinical outcomes and psychosocial effects of early versus delayed stoma closure in patients with temporary stomas. **Methods:** This retrospective cohort study was done in the Surgical Wards of Jinnah Postgraduate Medical Centre (JPMC), Karachi, and involved 81 patients whose intestinal stoma was reversed. Patients were sorted into two groups: early closure (less than 6 weeks; n=40) and delayed closure (more than 6 weeks; n=41). The analysis of data was performed with the help of SPSS version 26. The p-value of 0.05 was taken to be statistically significant. **Results:** A total of 81 patients were included, with 40 undergoing early and 41 delayed stoma closure. Baseline characteristics were comparable between groups. Early closure was associated with shorter hospital stay (4.3 ± 1.9 vs 7.1 ± 2.4 days) and earlier resumption of oral intake (2.8 ± 1.2 vs 4.9 ± 1.8 days). Overall, postoperative complications were lower after early closure (17.5% vs 36.5%), particularly wound infection (10.0% vs 22.0%). Delayed closure showed higher psychological stress and greater socioeconomic burden. **Conclusions:** An earlier stoma closure had better clinical and psychosocial outcomes than a late stoma closure, which were characterized by quicker recovery.

INTRODUCTION

Temporary intestinal stomas, in particular loop ileostomies, are often established after surgery on the rectum and the rest of the colon to shield distal anastomoses and minimize the effects of anastomotic leakage [1]. However, as important as stomas are as protection, their presence has a physical impact on the patient, psychologically, socially, and on the family life of a patient, and thus, timely reversal is a critical part of the overall postoperative management [2]. Stoma reversal, however, is not morbidity-free because patients are at risk of getting wound infections, postoperative pains, delayed recoveries, and bowel functional disturbances that can interfere with their normal lives and family duties [3]. Various patient-specific and operative causes have been suggested to play a role in causing postoperative complications after ileostomy reversal, and this explains why they should be carefully chosen in terms of timing and patient selection [4]. The recommendation has been given to initiate early stoma closure to reduce complications associated with the stoma, enhance the quality of life, and be able to reintegrate easily into normal life and family roles [5]. On the other hand, there are situations in clinical practice where delayed closure could be required, and they have been linked with higher postoperative morbidity and extended recovery times [6]. Comparative research comparing early and late stoma closure reported inconsistent complication rates, implying that the best time to close the stoma is still disputable, and it might also

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be influenced by the institutional measures and patient-specific characteristics [7]. Stomas have also been described to cause emotional and dependency stress, caregiving effects on the family, on top of surgical outcomes, highlighting the overall psychosocial implications of delayed closure [8]. The socioeconomic and family-related consequences have also been increased by prolonged delays in stoma reversal that are associated with longer hospitalization and increased postoperative morbidity [9]. Such new strategies as early same-admission closure have proven to be promising in recent times, but they must be well evaluated in terms of safety, feasibility, and availability of resources [10].

Although the use of temporary intestinal stomas has increased, there is no consensus on the time to close them, and the available literature presents mixed results and relies primarily on the effects of surgery and not on the overall psychosocial and family consequences. Long duration of stoma can give a lot of physical, emotional, social, and caregiving burden to patients and their families, and its premature closure can also have some risks. These uncertainties in the clinical decision-making process on the timing of the most suitable reversal. Thus, the study aims to compare early and late stoma closure, considering its postoperative outcomes and their impact on the quality of life of patients and their families, to determine the most appropriate time to close them.

METHODS

A retrospective cohort study was conducted in the surgical wards of Jinnah Postgraduate Medical Centre, Karachi, from January 2025 to April 2025. The study protocol was approved by the Institutional Review Board of JPMC (IRB NO. F.2-81/2025-GENL/416/JPMC). Because of the study's retrospective design, informed consent was waived. All patient data were handled confidentially, and only de-identified records were used to ensure participants' privacy and compliance with ethical guidelines. The calculation of a sample size was conducted to provide sufficient statistical power to identify differences in the most important postoperative outcomes in the two groups of stoma closures: early and delayed. According to the existing literature, a 20% difference in absolute outcomes of overall post-operative complications was regarded as significant. When the alpha was assumed to be 2-sided and 0.05, and the power was assumed to be 80%, at least 36 patients in each group were needed. A total of 81 patients were enrolled to cover the possible exclusion and incomplete records (in the early closure, n=40, and delayed closure, n=41), which was considered adequate to identify any important variations in the clinical and psychological outcomes [5]. Selection bias was minimized by using consecutive sampling. Eligible subjects were aged 18 years and above, had a temporarily constructed loop ileostomy or colostomy due to benign or malignant colorectal disease, and were fit to medically undergo stoma reversal. Patients who had anastomotic leak, intra-abdominal sepsis, severe comorbidities, recurrent/metastatic disease, or incomplete records were eliminated. Demographic (age, gender) and clinical (type of stoma, indication, comorbidities, and time between stoma formation and closure) data were collected. Most of the postoperative outcomes were complications, length of stay, and oral intake time. The psychosocial burden was determined by a short interviewer-administered questionnaire of financial strain, emotional stress, returning to work, marital/relationship problems, and family planning effects. Before the actual use, the questionnaire was pilot tested on 10 local patients to test its clarity and cultural relevance.

SPSS version 26 was used to analyze data. The continuous variables were presented in the form of mean and standard deviation. Normality of hospital stay and time to oral intake were evaluated with the Shapiro-Wilk test; those with non-normal distribution were compared with the Mann-Whitney U test, whereas normally-distributed variables were compared with the independent t-test. Chi-square test was used in the comparison of categorical variables. To increase the statistical power, ordinal psychosocial responses were categorized as no-mild and moderate-severe stress. The stratified analysis was adjusted for potential confounders such as comorbidities, the type of stoma, and underlying pathology. A p-value below 0.05 was taken to be statistically significant.

RESULTS

Early and delayed stoma closure groups were comparable at baseline, with no significant differences in age, sex distribution, type of stoma, or indication for stoma formation, supporting baseline homogeneity and minimizing selection bias. By study definition, the interval between stoma creation and reversal was significantly shorter in the early closure group. Early stoma closure was associated with significantly faster postoperative recovery, demonstrated by shorter hospital stay and earlier resumption of normal oral intake. Overall postoperative morbidity—particularly wound infection—was significantly lower in the early closure group, while postoperative ileus and re-intervention rates did not differ significantly between groups (Table 1).

Table 1: Clinical Characteristics and Postoperative Outcomes of Early Versus Delayed Stoma Closure

Variables	Early Closure (n=40)	Delayed Closure (n=41)	Effect Size (95% CI)	p-value
Loop Ileostomy	29 (72.5%)	29 (70.7%)	OR 1.11 (0.43-2.86)	0.820
Loop Colostomy	11 (27.5%)	12 (29.3%)	OR 0.90 (0.35-2.33)	0.820

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Duration Between Creation and Closure (Weeks)	4.2 ± 0.9	13.6 ± 3.1	MD -9.4 (-10.5 to -8.3)	<0.001
Hospital Stays (Days)	4.3 ± 1.9	7.1 ± 2.4	MD -2.8 (-3.7 to -1.9)	<0.001
Return to Normal Oral Diet (Days)	2.8 ± 1.2	4.9 ± 1.8	MD -2.1 (-2.8 to -1.4)	<0.001
Total Postoperative Complications	7 (17.5%)	15 (36.5%)	OR 0.37 (0.14–0.97)	0.040
Wound Infection	4 (10.0%)	9 (22.0%)	OR 0.39 (0.10–0.98)	0.040
Postoperative Ileus	2 (5.0%)	5 (12.2%)	OR 0.38 (0.07–1.87)	0.180
Re-Intervention Required	1 (2.5%)	3 (7.3%)	OR 0.32 (0.03–3.04)	0.310

OR=Odds Ratio; MD=Mean Difference
Continuous variables: mean ± SD, MD calculated as Early – Delayed

Patients undergoing delayed stoma closure experienced a substantially higher psychosocial burden, characterized by greater levels of psychological stress, increased utilization of psychiatric consultation and treatment, and more pronounced socioeconomic and family-related difficulties. Delayed closure was significantly associated with financial strain, difficulty returning to work, marital disruption, and negative impact on family planning, underscoring the broader non-clinical consequences of prolonged stoma duration (Table 2).

Table 2: Psychosocial and Quality-of-Life Outcomes in Early Versus Delayed Stoma Closure

Variables	Early Closure (n=40)	Delayed Closure (n=41)	Effect Size (95% CI)	p-value
No stress	18 (45.0%)	8 (19.5%)	OR 3.38 (1.24–9.21)	<0.001
Mild stress	16 (40.0%)	15 (36.6%)	OR 1.16 (0.50–2.70)	0.010
Moderate stress	5 (12.5%)	12 (29.3%)	OR 0.35 (0.11–1.07)	0.030
Severe stress	1 (2.5%)	6 (14.6%)	OR 0.15 (0.02–1.10)	0.040
Psychiatric consultation required	5 (12.5%)	14 (34.1%)	OR 0.28 (0.09–0.81)	0.010
Psychiatric treatment received	3 (7.5%)	8 (19.5%)	OR 0.34 (0.08–1.40)	0.040
Severe financial burden	5 (12.5%)	16 (39.0%)	OR 0.23 (0.08–0.63)	0.010
Job loss/difficulty returning to work	4 (10.0%)	13 (31.7%)	OR 0.24 (0.07–0.78)	0.030
Marital separation/ divorce	3 (7.5%)	8 (19.5%)	OR 0.34 (0.08–1.40)	0.040
Negative impact on family planning	6 (15.0%)	11 (26.8%)	OR 0.49 (0.17–1.37)	0.040

DISCUSSION

This current research proves that early stoma closure correlates with significantly better postoperative recovery and lower morbidity as compared to the delayed closure without undermining patient safety. Such results are not isolated, as present-day evidence shows that early ileostomy reversal is a viable and useful intervention in selected patients after colorectal surgery [11]. Among the major discoveries that were made in this research was the fact that the overall rate of postoperative complications was much lower among the early closure group, especially in wound infection. The same results are also reported in the study by Li *et al.* who found a long stoma period as one of the independent risk factors of an incisional surgical site infection following stoma reversal [12]. Randomized and prospective cohort studies also demonstrated that early closure helps to decrease stoma-related skin contamination and chronic inflammation exposure and thus minimize infection risks [13]. The present cohort also related early stoma closure to accelerated gastrointestinal recovery as measured by the earlier oral intake and reduction in hospitalization. These results are consistent with recent prospective statistics that show that bowel continuity restoration at an early age can help in the earlier initiation of enteral nutrition and improved recovery following surgery [14]. Decreased hospitalization has a significant impact on patient outcomes as well as on healthcare resources. The more prevalent rates of postoperative ileus and re-intervention in the delayed closure group, even though not statistically significant, do carry clinical relevance and correlate with general findings that a longer duration of stoma results in a higher burden of complications. A systematic analysis by Solitano *et al.* emphasized the point that delayed closure was related to cumulative stoma-related complications, such as dehydration, electrolyte imbalance, and infectious morbidity [15]. In addition, it has been reported that delayed ileostomy closure is associated with higher chances of developing Clostridium difficile infection, which further supports the issue of prolonged fecal diversion [16]. This study, in addition to the outcome of the surgical procedures, highlights the huge psychosocial and socioeconomic effects of delayed stoma closure. The patients of the delayed group had a much greater level of psychological stress and demanded psychiatric consultation and treatment. These results indicate the increased awareness of the fact that stomas influence body image, emotional state, and social functioning, especially in the case of delay in reversal [15, 17]. The poor socioeconomic outcomes that were found in this research, such as the financial burden, the inability to resume work, marital instability, and the impact of the stoma care on family planning, reflect a rarely reported aspect of stoma care. Past clinical trials have also reported the same observation that an extended stoma period is detrimental to the employment rate and family life, especially in younger and economically active individuals [18]. The linkage of delayed closure to augmented wound complications has also been supported by meta-analysis data, which is likely to prolong recovery, resulting in worsened social and financial pressures indirectly [19]. Recent large-scale observational research still indicates that early ileostomy closure, when clinically warranted, does not elevate the risk after the operation and can greatly

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decrease physical and psychosocial morbidity [20]. Combined, the present study results contribute to the emerging recommendations of personalized yet prompt stoma reversal plans.

The limitations of this study include its retrospective design, which may be subject to residual confounding despite baseline comparability, and its single-center setting, which may limit generalizability. Future multicenter prospective studies with larger sample sizes are warranted to validate these findings and establish robust clinical guidelines regarding the optimal timing of stoma closure. Whenever feasible, early stoma closure should be considered, as it appears to be associated with fewer postoperative complications, shorter recovery, and improved psychological, social, and economic outcomes. Incorporating routine psychosocial assessment into postoperative decision-making may further enhance patient-centered care and support better reintegration into normal family life.

CONCLUSIONS

A timely closure of the stoma is linked to superior clinical and psychosocial results as compared with late closure. Patients who receive early reversal have a greater rate of bowel recovery, reduced post-operative complications, shorter hospital stay, and better quality of life with a lower financial and emotional cost. On the other hand, delayed closure predisposes to wound infection, ileus, stoma-related and social restrictions. Nevertheless, timing should be personalized according to the stability of the patient, his/her nutrition, and the integrity of the anastomosis. All in all, in case of the favorable clinical conditions, early stoma closure is the treatment of choice as it improves patient recovery and reduces long-term physical, psychological, and economic consequences.

Authors' Contribution

Conceptualization: TK
Methodology: TK, AI, NA
Formal analysis: DK, MI, NA
Writing and Drafting: DK, MI, NA
Review and Editing: TK, DK, AI, MI, NA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Fetomaternal Outcomes Among Pregnant Women Presenting with Thrombocytopenia

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ABSTRACT

Thrombocytopenia is a prevalent hematological disease during pregnancy that may cause fetomaternal adverse outcomes. It is imperative to know its prevalence and the complications associated with it so that it can be identified and dealt with at a very early stage. **Objective:** To determine the frequency of fetomaternal outcomes among pregnant women with thrombocytopenia. **Methods:** A descriptive cross-sectional study was done in the Department of Obstetrics and Gynecology, Mohtarma Benazir Bhutto Shaheed Medical College, Mirpur, AJ and K, among 151 pregnant women diagnosed with thrombocytopenia. Patients were also classified according to the severity. The outcomes of the mothers were measured in terms of preeclampsia, HELLP syndrome, placental abruption, and preterm birth. The low birth weight and preterm birth were among the fetal outcomes. Analysis of data was done through SPSS version 25.0. **Results:** The 151 participants presented the highest number of mild thrombocytopenia, 83(54.9%), moderate 40(26.4%), and severe thrombocytopenia 28(18.5%). Preeclampsia occurred in 54 (35.8%) of cases, HELLP syndrome in 15 (9.9%), and placental abruption in 3(2.0%). Preterm birth was observed in 15(9.9%) and low birth weight in 6(4.0%) of neonates. Maternal and fetal outcomes showed no statistically significant differences across thrombocytopenia severity groups (P-value >0.050). **Conclusions:** Thrombocytopenia in pregnancy was predominantly mild to moderate in severity, with generally favorable maternal and fetal outcomes. No statistically significant differences were observed across severity groups. Early identification and careful monitoring may help optimize maternal and neonatal care.

INTRODUCTION

The most common hematological disorder in pregnant women during the gestational period is known as thrombocytopenia, which is experienced by 6-10 per cent of pregnant women all over the world. It impacts approximately one out of every ten pregnant women worldwide. Pregnant women who have severe cases of thrombocytopenia would be at a greater risk of excessive bleeding throughout and after delivery, which may be associated with an augmented risk of maternal and fetal complications [1]. Approximately 10 per cent of the pregnancies lead to thrombocytopenia or a platelet count below 150×109/L. It may be linked with pathological diseases or physiological changes, some of which are unique to pregnancy and may put the mother and child at risk of severe danger [2]. Thrombocytopenia is the 2nd most prevalent hematological complication in pregnancy, following anemia, and is observed in around 7-10% of pregnancies. Normal pregnancy also results in a

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physiological reduction in platelet count because of hemodilution, further utilization in peripheral tissue, and increased aggregation [3]. Thrombocytopenia may also be frequent in pregnant women, with onset in the first trimester and slowly subsiding during gestation, reaching its highest point on delivery. It is a physiologic hemodilution brought about by the presence of large plasma volume, heightened platelet activation, and clearance [4, 5]. Severe thrombocytopenia develops in pregnancy when the idiopathic thrombocytopenic purpura (ITP) is diagnosed, rather than in a situation when the pregnant lady already has a prior history of chronic ITP [6]. This is most probably due to the delay in diagnosis. Severely thrombocytopenic patients (20, 000 platelets/mm) are vulnerable to placental abruption and postpartum hemorrhage. Pregnant women with ITP are prone compared to other women to develop gestational diabetes (GD), and postpartum hemorrhage is usually a constant source of concern with them [7]. Rare causes of thrombocytopenia include thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulopathy (DIC), and all of them might have dangerous clinical outcomes. In other conditions, thrombocytopenia may be associated with serious clinical conditions such as PE, HELLP syndrome, and ITP. It can be associated with severe, even fatal, clinical outcomes in expectant mothers and fetuses as a whole, such as preeclampsia in 22% of women with thrombocytopenia, placental abruption in 21.8%, and HELLP syndrome in 11%, and the neonatal outcome of women with thrombocytopenia disclosed low birth weight in 42.2% and preterm birth in 27.3% [8]. Previous literature indicates that thrombocytopenia is a relatively common hematological complication during pregnancy. It has a heterogeneous pathophysiology that can extend from benign conditions that may only require observation to severe microangiopathic disorders. In the latter, maternal and fetal outcomes can be reliant on timely intervention, such as emergency delivery or provision of specific therapy [9, 10].

On this basis, the current research assumes that etiology and severity of thrombocytopenia in pregnancy are largely linked to maternal and fetal outcomes, and that early diagnosis and proper treatment can positively influence these outcomes. Although clinically significant, data on fetomaternal outcome in thrombocytopenic pregnancy are scarce, especially in populations where possible confounding issues of bleeding disorders, diabetes mellitus, or infectious diseases are likely to confound results, highlighting a clear study gap. Lack of enough region-specific evidence necessitates the generation of descriptive data that can be used to define the trend of maternal and fetal outcomes in women who present with thrombocytopenia, emphasizing the underlying problem. Knowledge of such outcomes could help clinicians put laboratory results into the context of day-to-day antenatal care and enhance clinical awareness. Therefore, the study aimed to outline the fetomaternal outcomes in pregnant women with thrombocytopenia in our population.

METHODS

A descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Mohtarma Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur, AJ and K, after taking the ethical approval (REF. NO 10/Academic Block Trauma centre/Surgery/2025) from February 2025 to August 2025. The sample size was 151, keeping the frequency of HELLP syndrome in thrombocytopenia patients as 11% based on a previous study, confidence level being 95%, and margin of error 5% under the WHO sample size calculation formula [8]. All the patients were enrolled by using a consecutive sampling technique, all women having age of 18-40 years with singleton pregnancy and women with thrombocytopenia were included in this study and the bleeding disorder other than thrombocytopenia on medical records and history, already taking antihypertensive medication on history, diabetes mellitus, HIV on history and medical records and multiple pregnancies on ultrasound were excluded. All the pregnant women who met the inclusion criteria were invited to take part in the study and were admitted to the ward following OPD inclusion. All the patients were informed about the purpose and benefits of the study and assured that the study is conducted with the sole purpose of research and publication of data, and given a written informed consent in case they agreed. After taking a complete history and baseline investigation, a 5ml blood sample was obtained and sent to the laboratory to confirm thrombocytopenia. The level of thrombocytopenia was defined based on the number of platelets in the body as mild (100150 ×10 09/L), moderate (5099 ×10 09/L), and severe (50 09/L) [11]. After confirmation, women and neonates were followed till delivery to detect preeclampsia, HELLP syndrome, placental abruption, preterm birth, and low birth weight. Preeclampsia had been categorized as new-onset hypertension (140/90mmHg or higher on two occasions after 20 weeks of pregnancy) with proteinuria (300 mg/24h or above) or end-organ dysfunction. The HELLP syndrome was diagnosed on the grounds of hemolysis, increased liver enzymes, and reduced platelet count. Preterm birth entailed a birth that was less than 37 weeks of gestational age. Low birth weight was considered as a birth weight of the neonate that was less than 2500 g, irrespective of gestational age [12]. All the above-mentioned information was recorded on a pre-designed proforma.

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Data analysis was done with the help of SPSS software (version 25.0). All continuous variables like age, BMI, platelet count, and gestational age were shown as mean ± standard deviation (SD), and categorical variables like preeclampsia, placental abruption, HELLP syndrome, preterm birth, and low birth weight were presented as frequency and percentage. Fetomaternal outcome was stratified according to the severity of thrombocytopenia. After stratification, the chi-square test/Fisher Exact test was considered a P value ≤ 0.05 as significant.

RESULTS

The study included 151 pregnant women with a mean age of 28.46 ± 6.59 years. The mean body mass index (BMI) was 26.74 ± 3.54 kg/m^2, indicating that, on average, the participants were in the overweight category. The mean gestational age at presentation was 34.09 ± 3.88 weeks. Regarding thrombocytopenia, mild thrombocytopenia was observed in 54.9% of participants, moderate thrombocytopenia in 26.4%, and severe thrombocytopenia in 18.5%, suggesting that the majority of the study population experienced moderate to severe reductions in platelet count (Table 1).

Table 1: Participant Characteristics and Thrombocytopenia Severity (n=151)

Variables	Mean ± SD/n (%)
Age (Years)	28.46 ± 6.59
BMI (kg/m^2)	26.74 ± 3.54
Gestational Age (Weeks)	34.09 ± 3.88
Thrombocytopenia Severity	
Mild	83 (54.9%)
Moderate	40 (26.4%)
Severe	28 (18.5%)
Total	151 (100.0%)

Regarding maternal outcomes, preeclampsia was observed in 39.8%, 42.5%, and 14.3% of women with mild, moderate, and severe thrombocytopenia, respectively, while HELLP syndrome occurred in 7.2%, 15.0%, and 10.7% of the respective groups. Placental abruption was rare and was noted only in 3.6% of women with mild thrombocytopenia. Similarly, parity, gravidity, and a history of previous miscarriage, preterm birth, or low birth weight did not show statistically significant differences across thrombocytopenia severity groups ($p > 0.05$ for all comparisons) (Table 2).

Table 2: Maternal Outcomes by Thrombocytopenia Severity

Maternal Outcomes	Mild (n=83)	Moderate (n=40)	Severe (n=28)	Total (n=151)	p-value
Preeclampsia	33 (39.8%)	17 (42.5%)	4 (14.3%)	54 (35.8%)	0.474
HELLP Syndrome	6 (7.2%)	6 (15.0%)	3 (10.7%)	15 (9.9%)	0.397
Placental Abruption	3 (3.6%)	0 (0.0%)	0 (0.0%)	3 (2.0%)	0.285
Parity	15 (18.1%)	5 (12.5%)	6 (21.4%)	26 (17.2%)	0.422
Gravidity	6 (7.2%)	3 (7.5%)	4 (14.3%)	13 (8.6%)	0.229
Previous Miscarriage	11 (13.3%)	4 (10.0%)	4 (14.3%)	19 (12.6%)	0.695
Previous Preterm	6 (7.2%)	4 (10.0%)	5 (17.9%)	15 (9.9%)	0.615
Previous LBW	3 (3.6%)	1 (2.5%)	2 (7.1%)	6 (4.0%)	0.665

In case of fetal results, preterm birth was found in 9.6%, 10.0%, and 10.7% of infants born to mothers with mild, moderate, and severe thrombocytopenia, respectively, and low birth weight was found in 3.6%, 5.0%, 3.6% of the corresponding groups, respectively. However, these differences were not statistically significant ($p > 0.05$). Overall, these findings suggest that while thrombocytopenia is common in pregnancy, its severity alone may not predict the occurrence of maternal or fetal complications in this cohort (Table 3).

Table 3: Fetal Outcomes by Thrombocytopenia Severity

Fetal Outcomes	Mild	Moderate	Severe	Total	p-value
Preterm Birth	8 (9.6%)	4 (10.0%)	3 (10.7%)	15 (9.9%)	0.990
Low Birth Weight	3 (3.6%)	2 (5.0%)	1 (3.6%)	6 (4.0%)	0.940

DISCUSSION

In the current research, thrombocytopenia during pregnancy was more likely to remain mild to moderate in severity, whereas severe thrombocytopenia was not as common. Examining overall maternal and fetal outcomes showed that the overall results were quite positive, and no statistically significant differences were found (depending on the severity of thrombocytopenia) in any case. These results were in line with the previous research that has found that gestational thrombocytopenia is usually mild and it may not correlate with significant adverse pregnancy outcomes in the majority of cases [13, 14]. Even though the maternal complication that was most prevalent in this group was preeclampsia, there was no statistically significant association with the level of severity. This is why the current findings are to be viewed with some caution and do not support the existence of a causal or predictive relationship between the severity of platelet count and the hypertensive disorders of pregnancy. Other previous literature sources have stated similar observations, in which thrombocytopenia was detailed as a clinical observation in relation to some conditions occurring in obstetrics as opposed to a determining factor of risk [15, 16]. HELLP syndrome and placental abruption were quite rare, which is consistent with the previous findings that report severe maternal complications are actually uncommon, especially in groups with mild thrombocytopenia as the prevalent type [17]. In terms of fetal outcomes, preterm delivery and low birth weight were seen in a small percentage, and there was no statistically significant difference between the severity groups.

These results indicate that it is not possible that the severity of thrombocytopenia alone can reliably distinguish

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between fetal and maternal risk among this descriptive cohort, which is comparable to the findings of other observational studies that report heterogeneous or non-significant associations [18]. Also, obstetric history factors such as parity, gravidity, and previous adverse pregnancy outcomes did not differ in terms of severity. This can be used to point out that the baseline demographic or obstetric variables were more or less the same among the participants and can be taken as descriptive and not predictive observations [19, 20]. In general, the outcomes point to the fact that thrombocytopenia in pregnancy was frequent in this cohort, but severe complications were rather rare. As the results are descriptive in nature and the associations are not statistically significant, these findings should be interpreted with caution and should primarily serve to characterize fetomaternal outcomes in thrombocytopenic pregnancy rather than to establish any risk associations. Future studies with larger sample sizes, analytical study designs, and statistically powered analyses are recommended to explore causal relationships and validate these findings across diverse populations.

CONCLUSIONS

In conclusion, there were no statistically significant differences when the severity of thrombocytopenia was compared. Even though the most common maternal problem was preeclampsia, there were no major negative outcomes like HELLP syndrome and placental abruption. Low birth weight was more frequently observed than preterm birth as outcomes of fetuses, but these results did not prove significant relationships with the severity of thrombocytopenia.

Authors' Contribution

Conceptualization: FN
Methodology: FS, AA, SP
Formal analysis: FS, MK
Writing and Drafting: FN, AA, SP, M
Review and Editing: FN, FS, AA, SP, MK, M

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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A Quantitative Cross-Sectional Study Assessing the Prevalence and Distribution of Renal Amyloidosis Subtypes (AA and non-AA) in Biopsy-Proven Adult Cases

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ABSTRACT

Renal amyloidosis is a multisystem disease characterized by the deposition of misfolded proteins in various organs, leading to organ dysfunction. Renal amyloidosis subtypes vary across populations, depending on underlying conditions such as inflammatory diseases and plasma cell disorders. **Objectives:** To evaluate the prevalence and distribution of the different subtypes of renal amyloidosis. **Methods:** The sample for this quantitative, observational, cross-sectional study comprised 94 patients with biopsy-proven renal amyloidosis, aged 18 years or older, diagnosed during the period between January and December 2025. Renal biopsies were analyzed with the help of Congo red stain to confirm the amyloid deposition, and subtyping was done with the help of amyloid A (AA) immunostain. Cases with negative AA staining were classified as non-AA amyloidosis. **Results:** The most common subtype was AA amyloidosis (80%), followed by non-AA amyloidosis (20%). Males were 54.3 percent of the participants, while females were 45.7%. Mean age was 51.19 ± 20.45 years. There were no statistically significant gender differences in the distribution of amyloid subtypes or in biochemical parameters ($p>0.05$). **Conclusions:** The most common type of renal amyloidosis was AA amyloidosis, in which there were no significant gender-based differences in demographic or biochemical factors. The results are valuable to aid clinical planning and disease management.

INTRODUCTION

Renal amyloidosis is a constellation of aggressive protein-misfolding diseases characterized by extracellular insoluble amyloid fibrils in the kidney, leading to structural damage, progressive proteinuria, nephrotic syndrome, and eventual renal failure [1]. Systemic amyloidosis can be clinically heterogeneous, and the most prevalent forms of renal amyloidosis are AA amyloidosis and AL amyloidosis. More and more subtypes of amyloidosis are becoming familiar, including ALECT2 (leukocyte chemotactic factor 2) amyloidosis and ATTR (transthyretin) amyloidosis [2]. Amyloidosis is not a common disease, and therefore, the prevalence of amyloidosis worldwide has conventionally been low. Systemic amyloidosis, overall, is estimated to be approximately 30 cases per 100,000 people, with a median age of diagnosis in the mid-60s [3]. The most frequent systemic form, which in most cases involves the kidneys, is AL amyloidosis, whose incidence is estimated at 16.7 cases per million person-years, and prevalence is 69.0 per million

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adults in 2021 in the United States- one of the highest rates ever documented, probably due to improved detection and survival [4]. Traditionally, previous reports estimated the prevalence of AL at 30,000–45,000 cases in the United States and the European Union. Still, recent statistics indicate an escalating recognition and survival rate, so prevalence is on the rise [5]. Secondary to chronic inflammation, AA amyloidosis is also a well-known cause of renal amyloid deposition but is less common, with a historical incidence rate of about 12 cases per 1 million per year [6]. Modern data indicate that the incidence might be decreasing in developed countries, driven by advances in the treatment of chronic inflammatory diseases [7]. Nevertheless, in a cohort design based on renal biopsy, AA was found in most (61) cases of amyloidosis, with AL accounting for 19.5%, with a primary focus on regional variation and underlying disease burden on prevalence [8]. Besides the AL and AA types, other amyloid etiologies have surfaced, including leukocyte chemotactic factor 2 (ALECT2). ALECT2 is detected to be about 3 percent of all cases of amyloidosis worldwide, in large series (>4,000 cases), specifically more often in certain ethnic groups (e.g. Mexicans, South Asians, Punjabis, Native Americans and Egyptians). It is a major cause of renal amyloidosis in these groups [9]. There are significant socio-demographic trends of Amyloid diseases. In developed areas, AL amyloidosis is the most common form, which increases in prevalence with age, with an average age of diagnosis of the sixth and seventh decades of life, and with a small bias towards males [10]. Recent national death data in the United States indicate 8734 deaths related to renal amyloidosis annually, aged 22 and above with a decline in death rates up to 2016, after which the trend is reversing, and incurring a disproportionate burden on males, older adults, and Black/African Americans [11], in addition to highlighting expanding health disparities across geography and population. Geographic differences also indicate the presence of disease risk factors and the availability of diagnostics. In developing nations, AA amyloidosis is still important because of the chronic infection and inflammatory disorders, which lead to the increased biopsy prevalence in the given setting, as opposed to AL amyloidosis in developed countries [12]. Renal amyloidosis is associated with chronic inflammatory diseases (e.g., rheumatoid arthritis, infections) in the AA type, and with plasma cell dyscrasias (e.g., multiple myeloma and monoclonal gammopathy) in the AL type. Ethnic differences and genetic conditions contribute to the prevalence of certain subtypes, such as ALECT2, within particular groups. Renal amyloidosis is usually associated with heavy proteinuria, hypoalbuminemia, progressive renal dysfunction, and nephrotic syndrome clinically, negatively affecting prognosis in the case of no timely diagnosis and treatment [13].

Recent studies on renal amyloidosis subtypes with the use of immunohistochemistry have not been performed among the Pakistani population based on biopsy. The patterns of prevalence at the regional level are not known, and thus preventing proper diagnosis and specific treatment. The present research bridges that gap since it presents local information about the distribution. This study aims to determine the prevalence and distribution of renal amyloidosis subtypes (AA and non-AA) in biopsy-proven adult cases and to assess associated demographic and biochemical characteristics.

METHODS

The study was a quantitative, observational, cross-sectional study conducted at the Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Center, a tertiary-care referral center with specialized expertise in histopathology and renal pathology. The research was conducted from 1 January 2025 to 31 December 2025. It involved recruiting patients, collecting data, conducting laboratory testing, and analyzing results. An Institutional Review Board (IRB) of the Shaukat Khanum Memorial Cancer Hospital and Research Center reviewed and approved the study protocol before it started (Approval No: EX-26-08-23-01). A non-probability consecutive sampling method was utilized, in which all patients who met the eligibility criteria were included until the intended sample size was reached. The sample size was calculated using the formula: $n = Z2 \times p \times (1-p)/d2$. where Z = 1.96 (95% confidence interval), p = 10% (expected prevalence of renal amyloidosis based on prior biopsy-based studies), and d = 5% (margin of error). The minimum calculated sample size was 94 patients. Written informed consent was taken. The study included patients aged 18 years and above who had undergone renal biopsy and who had histopathological evidence of renal amyloidosis. The exclusion criteria included renal biopsies that did not contain glomeruli, tissue samples that were not well fixed, individuals who were known or treated cases of amyloidosis, along with those individuals who were recipients of renal transplantation. Retrospective data were collected from medical records, biopsy request forms, and clinical, laboratory, and epidemiological data. The variables collected were patient demographics (age, gender, residence), clinical history (chronic inflammatory or infectious diseases), and laboratory variables (serum creatinine, serum albumin, 24-hour urinary protein excretion). An automated biopsy gun (Bard MaxCore C, Bard Inc., Tempe, USA) was used to collect renal biopsy samples under real-time ultrasound guidance (Philips HD11 XE, Philips Healthcare, Amsterdam, Netherlands).

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Hematoxylin and eosin-stained slides of 4-5 microns thickness were prepared from formalin-fixed paraffin-embedded (FFPE) renal biopsy specimens. Congo red stain was done on all the biopsies for the confirmation of diagnosis, and amyloid A stain was done for typing and categorized as AA (Amyloid A-positive) and non-AA (Amyloid A-negative) amyloidosis. Immunofluorescence (IF) staining for κ (kappa) and λ (lambda) light chains or mass spectrometry-based proteomics, which could help in further subclassification, were not performed, as these methods were not available at the time of the study.

Data analysis was conducted using IBM SPSS Statistics version 26.0. Frequencies and percentages were used to describe the categorical variables, and the mean and standard deviation were used to describe the continuous variables. The histograms, skewness, and kurtosis values, and Kolmogorov Smirnov-test were employed to determine whether numeric variables were normal or not. The chi-square test was used to evaluate the association between categorical variables, and the independent-samples t-test was used to compare continuous variables when necessary. The p-value was taken to be statistically significant if less than 0.05.

RESULTS

The study sample comprised 94 participants, with a slightly larger number of males (54.3%) compared with females (45.7%). Most of the participants belonged to the rural population (54.3%). Cases of AA amyloidosis were 80.0%, and non-AA amyloidosis were 20.0%, Table 1.

Table 1: Socio-Demographic Characteristics and Renal Amyloidosis Types of Study Participants

Variables	Category	Frequency (%)
Gender	Male	51 (54.3%)
	Female	43 (45.7%)
Residence	Urban	43 (45.7%)
	Rural	51 (54.3%)
Amyloidosis Type	AA Amyloidosis	75 (80.0%)
	Non-AA Amyloidosis	19 (20.0%)

Respondents had an average age of 51.19 years, and the standard deviation of 20.45 years, which shows a wide age range. The laboratory findings demonstrated elevated mean serum creatinine and proteinuria, indicating significant renal involvement among the study participants, Table 2.

Table 2: Descriptive Statistics of Numeric Variables

Variables	Mean ± SD	95% CI Lower	95% CI Upper
Age (years)	51.19 ± 20.45	47.06	55.33
Serum Creatinine (mg/dL)	4.29 ± 1.89	3.91	4.67
Serum Albumin (g/dL)	3.21 ± 0.73	3.06	3.36
Proteinuria (g/day)	5.57 ± 2.78	5.01	6.14

Nearly half of the patients with AA amyloidosis 46 (49.33%) had no identifiable underlying disease at the time of diagnosis. Among known etiologies, tuberculosis was the most common association, followed by chronic inflammatory and rheumatologic disorders, Table 3.

Table 3: Underlying Diseases in Patients with AA Amyloidosis

Underlying Disease	Number of Patients (%)
Rheumatoid Arthritis	8 (8.00%)
Dermatopolymyositis	1 (1.33%)
Juvenile Idiopathic Arthritis	1 (1.33%)
Psoriatic Arthritis	1 (1.33%)
Tuberculosis	18 (18.67%)
Hodgkin Lymphoma	3 (2.67%)
Hepatitis	1 (1.33%)
Cystic Fibrosis	1 (1.33%)
Colitis	1 (1.33%)
Other Chronic Inflammatory Diseases	13 (13.33%)
Unknown Etiology	46 (49.33%)
Total	94 (100%)

The study compares the demographic and clinical characteristics of patients with AA amyloidosis (n=75) and non-AA amyloidosis (n=19). The mean age was slightly higher in patients with AA amyloidosis (52.36 ± 19.98 years) compared to those with non-AA amyloidosis (46.58 ± 22.15 years); however, this difference was not statistically significant (p=0.273). Similarly, no significant differences were observed between the two groups in terms of mean serum creatinine levels (4.05 ± 1.79 vs. 4.36 ± 2.19; p=0.525), serum albumin levels (3.23 ± 0.72 vs. 3.29 ± 0.68; p=0.765), or proteinuria levels (5.55 ± 2.64 vs. 6.07 ± 2.80; p=0.447). About gender distribution, males constituted a higher proportion of the AA amyloidosis group (49.3%) compared to the non-AA group (31.6%), while females were more frequent in the non-AA group (68.4% vs. 50.7%). However, this difference was also not statistically significant (p=0.203), Table 4.

Table 4: Comparison of Demographic and Clinical Variables between AA and non-AA amyloidosis

Variables	Non-AA, (n=19)	AA, (n=75)	p-value
	Mean ± SD, Frequency (%)		
Age (Years)	46.58 ± 22.15	52.36 ± 19.98	0.273
Serum Creatinine Level	4.36 ± 2.19	4.05 ± 1.79	0.525
Serum Albumin Level	3.29 ± 0.68	3.23 ± 0.722	0.765
Proteinuria Level	6.07 ± 2.80	5.55 ± 2.64	0.447
Male	6 (31.6%)	37 (49.3%)	0.203
Female	13 (68.4%)	38 (50.7%)	

DISCUSSION

The current study measured the socio-demographic distribution, prevalence of renal amyloidosis subtypes, selected biochemical parameters, and gender differences among patients with biopsy-proven renal amyloidosis. The

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subtype AA amyloidosis was more prevalent than non-AA amyloidosis in the current study population. This trend aligns with evidence from regional hospital studies in South Asia, where AA amyloidosis remains dominant because the prevalence of chronic inflammatory and infectious diseases remains high. For example, AA amyloidosis was found in 48% of cases of renal amyloidosis in a study (n=312), which is also very close to the figure in the current study alone [14]. On the national level, a renal biopsy registry study conducted in India (n=1250) reported a 52 percent prevalence of AA amyloidosis, a 28 percent prevalence of AL, and other types at 20 percent, with a slightly higher AA prevalence than in the present study [15]. Locally, evidence from the Middle East shows that AA prevalence ranges from 40 to 60 percent, depending on the burden of inflammatory diseases, corroborating the results of the present study [16]. Conversely, high-income populations, which are more globally connected, exhibit significantly higher rates of AL amyloidosis. A national study (n=30,000 cases) conducted in the United States estimated that AL amyloidosis accounted for 65.7% of systemic amyloidosis, and AA accounted for less than 10% of the latter, demonstrating improved management of chronic inflammatory diseases [17]. Therefore, the reduced percentage of non-AA amyloidosis in the current study indicates regional epidemiological variations rather than methodological discrepancies. The gender distribution of the study population was 54.3% males, and no statistically significant difference in the distribution of amyloidosis subtypes between genders was observed $\chi^2 = 0.214$, p=0.898). The same gender neutrality has been reported in a population-based cohort in France (n=1,006), where the distribution of amyloidosis subtypes did not differ significantly between females and males (p>0.05) [18]. On the other hand, elevated male dominance has been observed in most North American populations with AL amyloidosis, where 60-65% of cases were female [19]. The mean serum creatinine (4.29 ± 1.89 mg/dL), serum albumin (3.21 ± 0.73 g/dL), and proteinuria (5.57 ± 2.78 g/day) indicate significant renal impairment with severe protein loss and associated metabolic derangements in the study population. Nevertheless, Chi-square tests showed no significant association between gender and the categorized serum creatinine, albumin, or proteinuria (all p>0.05). Similar results were reported in a retrospective cohort study conducted in Egypt (n=210), which found no significant gender-based differences in the biochemical severity of renal amyloidosis [20].

The limitation of this study includes the unavailability of immunofluorescence (IF) staining for κ (kappa) and λ (lambda) light chains, as well as mass spectrometry, which prevented definitive subtyping of amyloid. Consequently, the non-AA cases could not be further classified into AL or other specific amyloid subtypes. Future research should incorporate IF and mass spectrometry–based proteomic analysis to enable accurate amyloid typing, improve diagnostic precision, guide targeted therapy, and enhance clinicopathological correlation through multicenter collaboration and improved resource availability.

CONCLUSIONS

This study highlights that AA amyloidosis is the predominant subtype of renal amyloidosis among adult patients in our population, reflecting the high prevalence of chronic inflammatory and infectious diseases in the region. The cases presented with severe renal involvement, with significant proteinuria and renal failure. There were no significant differences between male and female patients. The results offer valuable local epidemiological evidence and indicate the need for improved diagnostic facilities to perform further amyloid subtyping.

Authors' Contribution

Conceptualization: MH[1]
Methodology: MN
Formal analysis: MN
Writing and Drafting: MN, MH[1], UH, MH[2]
Review and Editing: MN, MH[1], UH, MH[2]

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Comparison of the Video Laryngoscopes with the Macintosh Laryngoscope for Nasotracheal Intubation in Patients Undergoing Oral and Maxillofacial Surgeries

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ABSTRACT

Nasotracheal intubation is more desirable, whereas Macintosh may be challenging to perform in certain patients. The video laryngoscopes offer an indirect, magnified image of the glottis, which may enhance the effectiveness of intubation and shorten the length of the procedure. **Objectives:** To assess the video laryngoscopes and the Macintosh laryngoscopes in nasotracheal intubation of patients undergoing oral and maxillofacial surgeries. **Methods:** This prospective observational comparative study was done at Jinnah Postgraduate Medical Centre, Karachi, between March and August of 2023. The time of intubation, the success of the first attempt, and complications were noted. A statistical test was conducted for data analysis, and $p \leq 0.05$ was regarded as significant. **Results:** Group A (98%) scored higher than Group B (76%) in terms of first-attempt intubation success (p=0.001). Video laryngoscopy lowered the mean intubation time (31.7 ± 3.97s) compared to Macintosh (54.7 ± 6.93s) (p=0.001). The stratified analysis showed a consistently better performance of video laryngoscopes in terms of age, gender, ASA status, BMI, and Mallampati class. **Conclusions:** Video laryngoscopes significantly improve first-attempt success and reduce intubation time for nasotracheal intubation in oral and maxillofacial surgery patients. Their use can enhance airway safety and procedural efficiency.

INTRODUCTION

In oral and maxillofacial surgery patients, airway management is a unique issue as the anesthesiologist and surgeon share airway access. Nasotracheal intubation would be best utilized in these procedures since it offers an unobstructed surgical field, enables intraoperative occlusal evaluation, and enables maxillomandibular fixation. Recent clinical audits and surgical series state that over 60% of elective oral and maxillofacial surgeries involve nasotracheal intubation, which is one of the most used airway methods in this group [1, 2]. The Macintosh direct laryngoscope has long been regarded as the conventional tool in nasotracheal intubation due to its simplicity, ubiquitous nature, and familiarity of clinicians with the tool. Challenging laryngoscopy and challenging airway intubation have been reported in up to 10%-15% of surgical patients, and more frequently with maxillofacial surgeries. Repeated attempts at intubation enhance the chances of airway trauma, hypoxia, epistaxis, and postoperative complications [3, 4]. The adoption of video laryngoscopes as a means of airway management has been

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growing over the last 10 years, since it offers an indirect, clear picture of the glottis without requiring ideal positioning of the oral, pharyngeal, and laryngeal axes [5]. Several video laryngoscope designs have been presented, such as hyper-angulated and channeled blades, which can come in especially handy with nasotracheal intubation [6, 7]. A recent study has shown that video laryngoscopes are linked to better visualization of the glottis, increased success in the first attempt, and decreased use of the Magill forceps over Macintosh laryngoscopy during nasotracheal intubation. Nevertheless, the results with respect to intubation time and overall success are inconsistent between the various devices and clinical conditions [8-10]. Even though various randomized and prospective trials have compared video laryngoscopes and Macintosh laryngoscopes when using nasotracheal intubation, due to differences in patient characteristics, outcome metrics, operator experience, and device type, there have been a variety of outcomes [11, 12].

There is disagreement over whether video laryngoscopes are better than Macintosh laryngoscopes for nasotracheal intubation in patients having oral and maxillofacial surgery, despite the fact that they are becoming more widely available. Past research has indicated mixed findings on first attempt success, intubation duration, and complication rates, typically because of differences in patient characteristics, operator experience, type of device, and study design. Additionally, there is no literature on literature dealing with specific populations of oral and maxillofacial surgery, where a smaller mouth aperture, facial injuries, and anatomic differences may make airway management more complex. There is also limited evidence in resource-limited settings where Macintosh laryngoscopy is still in widespread use. There is a need, therefore, to conduct a standardized, prospective study to compare video laryngoscopes and Macintosh laryngoscopes, since nasotracheal intubation is a standard procedure in maxillofacial procedures, and airway control can directly impact patient-safety and surgical productivity. The study aimed to compare the performance of video laryngoscopy and Macintosh laryngoscopy during nasotracheal intubation of patients undergoing oral and maxillofacial surgeries.

METHODS

This was a prospective observational comparative study conducted at the Department of Anesthesia in Jinnah Postgraduate Medical Centre, Karachi, for six months from 1st March 2023 to 31st August 2023. The ethical approval was obtained from the Institutional Review Board of Jinnah Postgraduate Medical Centre with approval number F.2.-81/2023-GENL/16/JPMC. The World Health Organization sample size calculator was used to calculate the sample size. The level of significance of 5% and the power of 80% was used. According to the recorded mean intubation times, the mean intubation time with the video laryngoscope was 32.9 seconds with a standard deviation of 10.5 seconds, and the mean intubation time with the Macintosh laryngoscope was 42.7 seconds with a standard deviation of 19.2 seconds. Based on these parameters, the derived sample size was 100 patients, with 50 patients in each group [13]. Participants were recruited using the non-probability consecutive sampling technique. The eligibility of patients scheduled for elective oral and maxillofacial surgery under general anesthesia was assessed. The inclusion criteria included both male and female patients aged twenty to sixty-five years, American Society of Anesthesiologists physical status I or II, and Mallampati class I or II airway. Consecutive enrolment of patients was carried out within the period of the study based on the inclusion criteria. Patients who had a history of difficult tracheal intubation, cervical spine instability, limited mouth opening (less than three millimeters as determined clinically), or recurrent suppurative sinusitis were excluded. All the participants provided informed consent following a discussion on the study purpose, procedures, and potential risks in the native language of the patient. The nasotracheal intubations were done by a senior anesthesiologist with at least two years of experience in post-fellowship. At the arrival in the operating room, standard monitoring, such as noninvasive blood pressure, electrocardiography (lead II), and heart rate, was used. The nasal anesthesia was done locally using an intranasal mucosal atomization device that administered xylocaine antiflatirinol 4% solution. Nalbuphine (0.1 mg/kg), propofol (1-2mg/kg), and cis-atracurium (0.2 mg/kg) were used to induce general anesthesia. This was done by manually ventilating the patients with 100% oxygen over three minutes after the loss of eyelash reflex. To inhibit hemodynamic responses, 1.5mg/kg of lidocaine was given, and the anesthesia continued with inhaled isoflurane (1.0-2.0), and the carbon dioxide end-tidal level was kept at 35-40 mmHg. Intubation was done as per the normal clinical practice, utilizing the laryngoscope chosen by the anesthesiologist. The time of intubation was recorded during the period when the laryngoscope was inserted into the mouth till proper placement of the nasotracheal tube was identified through the capnography. This proforma was formulated on the prior published research on nasotracheal intubation and airway evaluation, so that all the variables of interest were systematically represented in this group of patients [10]. The study was pre-tested with a pilot sample of 10 patients in order to ascertain its clarity, completeness, and ease of use. The main outcome was the mean intubation time, which was recorded in seconds on a stopwatch by the time the nasotracheal tube was inserted

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into the relevant nostril until the laryngoscope was removed from the mouth. Successful nasotracheal intubation on the first attempt under direct view, supported by the bilateral lungs' air entry directly seen and confirmed by the equal air entry within the lungs, was defined as success in the intubation. Body mass index was calculated by computing the following formula: BMI = weight in kilograms divided by height in meters squared. The weighing machine was used to measure weight, and the height was measured using a wall-mounted scale. Obese patients were identified as patients with a BMI above 25 kg/m2, and non-obese patients as patients with a BMI below 25 kg/m2. The assessment of airways consisted of the Mallampati classification [14].

Statistical Package for the Social Sciences (SPSS) version 24.0 was used to perform a statistical analysis. The continuous variables were represented by mean and standard deviation, whereas the categorical variables were reported in terms of frequencies and percentages. The Shapiro-Wilk test was used to test the normality of continuous data. The independent sample t-test was also used to stratify the analysis of mean intubation time with respect to age, gender, ASA status, Mallampati class, and body mass index. The chi-square test was used to compare the two categories of variables between the two groups. Stratification was done to manage the possible effect modifiers, such as age, gender, ASA status, Mallampati class, and body mass index, in the estimation of intubation success. A p-value ≤0.050 was taken as statistically significant.

RESULTS

The two groups were comparable with respect to baseline demographic and clinical characteristics. Age (p=0.680), gender (p=0.670), ASA physical status (p=0.810), body mass index (p=0.220), and Mallampati classification (p=0.700) did not differ significantly between Group A and Group B. These results confirm that both groups were well-matched at baseline (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Patients in Both Groups (n=100)

Variables	Group A (n=50), n (%) / Mean ± SD	Group B (n=50), n (%) / Mean ± SD	p-value
Age (Years)			
20–40	27 (54.0%)	24 (48.0%)	0.680
41–65	23 (46.0%)	26 (52.0%)	
Mean ± SD	39.12 ± 8.99	38.82 ± 8.47	
Gender			
Male	29 (58.0%)	31 (62.0%)	0.670
Female	21 (42.0%)	19 (38.0%)	
ASA Status			
I	27 (54.0%)	25 (50.0%)	0.810
II	23 (46.0%)	25 (50.0%)	
BMI (kg/m²)			
≤25	23 (46.0%)	28 (56.0%)	0.220
>25	27 (54.0%)	22 (44.0%)	
Mean ± SD	26.68 ± 4.04	25.68 ± 3.87	
Mallampati Class			
I	21 (42.0%)	23 (46.0%)	0.700
II	29 (58.0%)	27 (54.0%)	

The P-values were calculated using the chi-square test for categorical variables and the t-test for continuous variables. All baseline characteristics were statistically comparable (p>0.050)

When the two groups' nasotracheal intubation success rates were compared, 76% of patients in the Macintosh laryngoscope group (Group B) and 98% of patients in the video laryngoscope group (Group A) were successfully intubated on the initial attempt. This was statistically significant (p=0.001)(Table 2).

Table 2: Comparison of Success Rate Between Video Laryngoscope (Group A) and Macintosh Laryngoscope (Group B) for Nasotracheal Intubation (n=100)

Groups	Success (Yes), n (%)	Success (No), n (%)	p-value
Group A (Video Laryngoscope)	49 (98.0%)	1 (2.0%)	0.001
Group B (Macintosh Laryngoscope)	38 (76.0%)	12 (24.0%)	

In intubation time, the mean intubation time was much lower in Group A, 31.7 ± 3.97 seconds, than in Group B, 54.7 ± 6.93 seconds (p=0.001). These results indicate that video laryngoscopy increases first-attempt success and shortens the time required to perform nasotracheal intubation compared with Macintosh laryngoscopy (Table 3).

Table 3: Comparison of Mean Intubation Time Between the Two Groups (n=100)

Parameters	Group A (n=50), Mean ± SD	Group B (n=50), Mean ± SD	p-value
Intubation Time (Seconds)	31.70 ± 3.97	54.72 ± 6.93	0.001

Successful nasotracheal intubation was consistently higher in Group A across most patient subgroups. Statistically significant differences favoring Group A were observed among younger patients, males, females, ASA I patients, non-obese individuals, and those with Mallampati class I and II airways. Although success rates remained higher in Group A among older patients, ASA II patients, and obese individuals, these differences did not reach statistical significance (Table 4).

Table 4: Stratification of Intubation Success Rate with Respect to Demographic and Clinical Variables

Variables	Group A Successful, n (%)	Group B Successful, n (%)	p-value
Age (Years)			
20–40	27 (100.0%)	18 (75.0%)	0.006
41–65	22 (95.65%)	20 (76.92%)	0.079

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Gender			
Male	29 (100.0%)	25 (80.65%)	0.013
Female	20 (95.24%)	13 (68.42%)	0.026
ASA Status			
I	27 (100.0%)	19 (76.0%)	0.007
II	22 (95.65%)	19 (76.0%)	0.054
BMI (kg/m^2)			
≤25	23 (100.0%)	20 (71.43%)	0.005
>25	26 (96.30%)	18 (81.82%)	0.096
Mallampati Class			
I	20 (95.24%)	16 (69.57%)	0.027
II	29 (100.0%)	22 (81.48%)	0.015

Mean intubation time was significantly shorter in Group A compared with Group B across all analyzed subgroups. This difference remained consistent irrespective of age category, gender, ASA physical status, body mass index, or Mallampati class, with all comparisons demonstrating strong statistical significance. These findings indicate a uniform advantage of Group A in reducing intubation duration across both low- and higher-risk patient profiles (Table 5).

Table 5: Stratification of Mean Intubation Time with Respect to Demographic and Clinical Variables

Variables	Group A Mean ± SD (sec)	Group B Mean ± SD (sec)	p-value
Age (Years)			
20–40	33.33 ± 3.71	53.46 ± 6.21	0.001
41–65	29.78 ± 3.41	55.88 ± 7.46	0.001
Gender			
Male	31.62 ± 3.72	53.61 ± 6.78	0.001
Female	31.81 ± 4.38	56.53 ± 6.96	0.001
ASA Status			
I	31.11 ± 4.37	54.92 ± 7.70	0.001
II	32.39 ± 3.39	54.52 ± 6.21	0.001
BMI (kg/m^2)			
≤25	31.57 ± 3.36	52.18 ± 5.39	0.001
>25	31.81 ± 4.48	57.95 ± 7.42	0.001
Mallampati Class			
I	31.29 ± 4.26	55.61 ± 7.52	0.001
II	32.00 ± 3.79	53.96 ± 6.42	0.001

DISCUSSION

The present study found in this prospective observational comparative study that nasotracheal intubation with video laryngoscopes (VL) had a higher first-attempt success (p=0.001) and was linked with a significantly shorter average time to intubation (p=0.001) than the Macintosh laryngoscope. Several randomized clinical trials and observational studies have demonstrated increased success with intubation and shortened intubation periods when using VLs. A study by Erdivanli B *et al.* 2018 discovered that the King Vision video laryngoscopy also led to less time to mean intubation and greater first-attempt success than the Macintosh laryngoscopy used in nasotracheal intubation and fewer complications, including sore throat and mucosal injury [15]. The present study demonstrated shorter intubation time, improved glottic visualization, and fewer optimization maneuvers with video laryngoscopy compared to Macintosh laryngoscopy during nasotracheal intubation. Equally, the study by Ketata *et al.* in patients undergoing maxillofacial surgery showed that the Medcaptain® video laryngoscope had a significantly shorter total intubation time, glottic visualization, and decreased usage of Macintosh laryngoscopy as compared to the Medcaptain® video laryngoscope [16]. The stratified findings of our study revealed that VL had consistent benefits in terms of age, gender, ASA status, and Mallampati class, with a larger benefit in younger patients, men, ASA I, lower BMI, and Mallampati I/II groups. These subgroup trends are consistent with meta-analytic data presented by Ho *et al.* that revealed the improvement of glottic views and possibly increased success rates of video laryngoscopy-assisted nasotracheal intubation, although not all studies showed statistically significant differences [17]. Video laryngoscopy in the current study was linked to a shorter intubation time that was consistently shorter than the Macintosh laryngoscopy, hence it depicts a strong procedural value compared to Macintosh laryngoscopy. Nevertheless, although many published studies indicate a preference to use video laryngoscopes, the literature available shows. A study by Hansel *et al.* demonstrated that in immobilized-neck patients, video laryngoscopy facilitated a decreased number of airway manoeuvres during intubation compared to using the Macintosh laryngoscopy, although it did not necessarily result in the reduction of the absolute intubation time, depending on airway anatomy [18]. Also, Gangishetty *et al.* discovered that a non-channeled McGrath device did not have a significant effect on reducing intubation time in comparison to Macintosh and that the design of the devices and operator experience could be additional factors [19]. Consistent with our findings demonstrating quicker and more reliable nasotracheal intubation using video laryngoscopy. A study by Yadav *et al.* found that the use of cuff inflation and video laryngoscopy had a positive effect on intubation conditions, which validates our results of a quicker and more dependable intubation with VL [20].

There are certain limitations of this study. It was only performed in one center, a fact that can undermine the extension of the results to other organizations or patient groups. Second, experienced anesthesiologists executed the intubations; outcomes may be different in the case of inexperienced operators. Third, the patients who had severe airway problems or were unable to open their mouths were excluded, and hence, the results cannot be generalized to the worst-case airway situations. Also, the only type of video laryngoscope was applied, and the

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results can be different when using other instruments or a different blade. Lastly, as an observational study, bias concerns associated with the selection of patients, selection related to operator preference, cannot be completely dismissed. The number of centers, different levels of experience of the operators, and the types of video laryngoscopes should be covered in future research. These studies will be used to confirm these results and enhance their applicability to a wider patient population.

CONCLUSIONS

The video laryngoscopes have definite benefits over the Macintosh laryngoscopes in nasotracheal intubation in patients undergoing oral and maxillofacial surgery. They offer greater first-attempt success rates, fewer intubation times, and are reliable in demographic and clinical subgroups. Video laryngoscopes have the potential to promote airway safety, decrease complications, and increase efficiency in the surgical practice.

Authors' Contribution

Conceptualization: RZ
Methodology: AK
Formal analysis: FA, KZ
Writing and Drafting: FA, KZ
Review and Editing: RZ, AK, FA, KZ

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

Conflicts of Interest

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Comparison of the Effect of Induction of General Anesthesia with Propofol Vs Ketamine + Midazolam on Perfusion Index in Cardiac Patients Undergoing Non-Cardiac Surgery

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ABSTRACT

Hemodynamic stability is a critical concern in cardiac patients. The choice of induction agent significantly influences cardiac output and tissue perfusion. **Objectives:** To compare the effect of induction with ketamine and midazolam vs. propofol on perfusion index in cardiac patients under general anesthesia. **Methods:** This quasi-experimental study was done from January 2024 to June 2024 at the Department of Anesthesia, Mayo Hospital, Lahore. Total 146 patients undergoing non-cardiac surgery were included after taking written consent. Patients were assigned to two equal Groups: M (midazolam and ketamine) or Group P (propofol). Outcome parameters, including SBP, MAP, and perfusion index, were recorded pre- and post-induction. Data were collected using a proforma and analyzed with SPSS-26. **Results:** Post-induction, mean SBP in Group M was higher, 126.02 ± 12.58 mmHg, vs Group P, 120.61 ± 13.09 mmHg, p-value=0.01. Post-induction mean MAP in Group M and P calculated was 74.17 ± 10.06 mmHg, and 71.02 ± 9.82 mmHg, p-value=0.050. Post-induction PI in Group M was also higher, 1.88 ± 0.40, vs Group P, 1.69 ± 0.28, p-value=0.001. **Conclusions:** Findings of the current study suggest that induction with ketamine and midazolam may lead to increased post-induction mean perfusion index as compared to propofol in cardiac patients. Therefore, assists in maintaining peripheral perfusion in cardiac patients, which could be beneficial for postoperative recovery and minimizing complications.

INTRODUCTION

Modern surgery requires general anesthesia to perform intricate procedures while maintaining patient comfort and safety [1]. Because it establishes the foundation for steady hemodynamics and adequate tissue perfusion throughout the procedure, the induction phase is very crucial. Selecting the right induction agent is crucial for cardiac patients, since excellent outcomes depend on maintaining optimum perfusion [2]. Due to their underlying cardiovascular problems, cardiac patients might become more complex during the perioperative phase and pose particular challenges [3]. Cardiovascular stability and tissue oxygenation, two important factors, are greatly influenced by the induction agent. The perfusion index serves as an indicator of peripheral perfusion and tissue

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oxygenation [4]. An increase in PI suggests enhanced peripheral blood flow and oxygenation, while a decrease may indicate compromised perfusion [5]. A prior review examined how different induction agents affect hemodynamics in patients with IHD. Overall, all agents caused significant drops in blood pressure, heart rate, and cardiac index. However, the midazolam group uniquely avoided increases in blood pressure during induction [6]. Propofol, a lipid-soluble, non-opioid, non-barbiturate sedative-hypnotic with a quick onset and brief duration of action, is commonly used for induction. Propofol can have a substantial influence on the cardiovascular system despite its advantages. Patients with congenital heart disease may be more susceptible to arrhythmias. Propofol's suppression of the sympathetic nervous system and disruption of baroreflex-regulating systems, which are critical for preserving cardiovascular stability, are blamed for these cardiovascular consequences [7]. Ketamine is an anesthetic that has hypnotic, amnestic, and analgesic effects. It has a powerful analgesic impact with no cardiovascular or respiratory depression. However, because it tends to enhance myocardial oxygen demand and its arrhythmogenic effects, utilizing ketamine alone for induction in cardiac patients raises concerns [8]. A benzodiazepine with a quick onset and short half-life, midazolam has hypnotic, amnestic, anticonvulsant, and anxiolytic effects [9]. Propofol can be used effectively at lower doses when combined with ketamine to reduce its negative effects. According to a prior study, midazolam and ketamine together produced more hemodynamic stability compared to midazolam and propofol, although both combinations had comparable results in terms of post-anesthesia recovery and patient comfort [10].

Although previous studies have compared the hemodynamic effects of various induction agents in cardiac populations, most have focused on systemic parameters rather than direct measures of peripheral tissue perfusion. Therefore, this study aims to address the knowledge gap by investigating the effect of induction with ketamine and midazolam compared to propofol on perfusion index in cardiac patients undergoing general anesthesia.

METHODS

This quasi-experimental study was conducted after obtaining ethical approval from the IRB (367/RC/KEMU) of King Edward Medical University. Sample size of 146 (73 in each group) was estimated at 5% significance level and 95% power, based on the expected mean perfusion index of 1.5 ± 1.3 in the ketamine and midazolam group and 2.4 ± 2.4 in the propofol group [11]. This study was done from January 2024 to June 2024, and for patient enrollment, a non-probability consecutive sampling method was used. Written informed consent was obtained from patients before enrollment. Patients aged 40 to 65 years of both genders, belonging to ASA I or II, and diagnosed as cardiac patients undergoing elective non-cardiac surgery under general anesthesia were included. Cardiac patients were defined as having a history/medical record suggestive of CAD, ECG showing ischemic changes (ST segment depression/T wave inversions/LBBB/RBBB/Q waves), or Echocardiography with EF < 45% / segmental wall motion abnormalities. Patients with congenital or valvular heart disease, Raynaud's disease, uncontrolled diabetes mellitus or hypertension, known allergies to study drugs, those on vasoactive drugs such as calcium channel blockers or ARBs, individuals with substance abuse, and those suffering from severe systemic non-cardiac disease were excluded. Each patient's demographic data was recorded. A detailed medical history and thorough clinical examination were performed, and all relevant baseline investigations were done to ensure compliance with inclusion and exclusion criteria. Patients were assigned to two equal groups according to assigned drug: Group M (ketamine and midazolam) or Group P (propofol). All patients were kept NPO for at least eight hours before induction. Upon arrival in OT, the IV line was secured, and standard monitoring was established. A pulse oximeter sensor was attached to the forefinger of one hand, while noninvasive BP monitoring was applied to the opposite arm. A core body temperature probe was also attached to prevent hypothermia-induced vasoconstriction. Perfusion index, HR, BP, and MAP were recorded during the pre-induction phase. ECG and SpO_2 monitoring were initiated, and baseline vital signs were documented. Patients were preoxygenated with 100% oxygen at 6 L/min and premedicated with IV nalbuphine 0.1 mg/kg and dexamethasone 0.1 mg/kg. Induction in Group M was performed using intravenous ketamine 0.5 mg/kg combined with midazolam 0.4 mg/kg, whereas Group P received propofol 2 mg/kg administered slowly until loss of verbal response. After confirming adequate bag-mask ventilation, muscle relaxation was achieved with atracurium IV 0.5 mg/kg. Patients were ventilated with 100% oxygen and isoflurane at 1.2 MAC for five minutes, during which data were recorded for all parameters at five minutes post-induction, similar to pre-induction measurements. PI was recorded using a pulse oximeter before and 5 minutes after induction. It was measured after 5 minutes of induction. Endotracheal intubation was performed by an experienced anesthetist using an appropriately sized tube, and proper placement was confirmed by auscultation and end-tidal CO_2 monitoring. Mechanical ventilation was maintained with VT 6–8 mL/kg, RR 12 breaths/minute, I: E 1:2, and oxygen 2 L/min, while anesthesia was maintained with oxygen and isoflurane.

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MAP below 60 mmHg or systolic BP below 90 mmHg was considered severe hypotension and managed with intravenous fluids and adrenaline as required. Bradycardia, defined as a decrease in heart rate by 20% below baseline, was treated with atropine. Intraoperative management continued as necessary throughout the procedure. At the end of surgery, anesthesia was reversed with IV neostigmine (0.03mg/kg) and atropine (0.01mg/kg). After satisfactory recovery, patients were extubated and shifted to PACU, where they were observed for two hours. All data were recorded on a predesigned proforma.

Data were investigated in SPSS version 26. Normality of continuous variables was assessed using the Shapiro–Wilk test before analysis. Quantitative variables were presented as mean + standard deviation. Qualitative variables as frequency and percentage. The data were stratified by age, gender, BMI, and ASA classification. After stratification, comparisons of PI between groups were conducted using an independent samples t-test; a p-value of <0.050 was considered statistically significant.

RESULTS

Both groups were compared in terms of demographic characteristics. The mean age in Groups M and P was calculated to be 54.68 ± 7.00 years and 54.34 ± 7.32 years (p>0.05). Gender distribution found 49.3% males and 50.7% females in Group M and 50.7% males and 49.3% females in Group P (p>0.050). Mean BMI was similar between groups (25.76 ± 2.74 kg/m^2 vs. 25.28 ± 3.17 kg/m^2; p>0.050). Distribution of ASA physical status was also comparable, with 54.8% of patients classified as ASA I and 45.2% as ASA II in Group M, compared to 58.9% and 41.1%, respectively, in Group P (p>0.050) (Table 1).

Table 1: Comparison of Baseline Characteristics among Study Groups

Variables	Group M (Midazolam + Ketamine), n=73, Mean ± SD/n (%)	Group P (Propofol), n=73, Mean ± SD/ n (%)	p-value
Age (Years)	54.68 ± 7.00	54.34 ± 7.32	0.775
Male	36 (49.3%)	37 (50.7%)	<0.001
Female	37 (50.7%)	36 (49.3%)	
BMI (kg/m^2)	25.76 ± 2.74	25.28 ± 3.17	0.329
ASA Status I	40 (54.8%)	43 (58.9%)	0.738
ASA Status II	33 (45.2%)	30 (41.1%)	

Comparison of hemodynamic parameters revealed no significant difference in pre-induction systolic BP (p=0.94), MAP (p=0.45), and perfusion index (p=0.57). However, post-induction SBP was significantly higher in Group M (126.02 ± 12.58 mmHg) compared to Group P (120.61 ± 13.09 mmHg; p=0.01). MAP was also significantly higher in the Midazolam + Ketamine group (74.17 ± 10.06 mmHg) vs the Propofol group (71.02 ± 9.82 mmHg; p=0.05). Post induction, a significant increase in PI was observed in Group M (1.88 ± 0.40) compared to Group P (1.69 ± 0.28; p=0.001) (Table 2).

Table 2: Comparison of Hemodynamic Parameters among Groups

Variables	Phase	Group M (Midazolam + Ketamine) n=73 (Mean ± SD)	Group P (Propofol) n=73 (Mean ± SD)	Mean Difference (95% CI)	p-value
Systolic Blood Pressure (mmHg)	Pre-Induction	128.35 ± 12.24	128.49 ± 12.09	−0.14 (−4.03 to 3.75)	0.940
	Post-Induction	126.02 ± 12.58	120.61 ± 13.09	5.41 (1.18 to 9.64)	0.001*
Mean Arterial Pressure (mmHg)	Pre-Induction	75.82 ± 10.34	77.12 ± 10.73	−1.30 (−4.70 to 2.10)	0.450
	Post-Induction	74.17 ± 10.06	71.02 ± 9.82	3.15 (−0.12 to 6.42)	0.050*
Perfusion Index (PI)	Pre-Induction	1.60 ± 0.25	1.57 ± 0.28	0.03 (−0.06 to 0.12)	0.570
	Post-Induction	1.88 ± 0.40	1.69 ± 0.28	0.19 (0.08 to 0.30)	0.001*

*Statistically significant at p<0.050

Stratified analysis of post-induction perfusion index demonstrated significant differences in specific subgroups. Among males, Group M showed significantly higher PI values compared to Group P (p=0.004), while in females the difference was not statistically significant (p=0.11). When stratified by ASA status, significant differences were observed in both ASA I (p=0.040) and ASA II (p=0.01) patients, favoring the Midazolam + Ketamine group. With respect to age, patients aged ≤50 years (p=0.050) and those aged >50–65 years (p=0.006) both demonstrated significantly higher PI values in Group M. Similarly, when analyzed by BMI, patients with BMI >25–30 kg/m^2 showed significant difference (p=0.004), whereas those with BMI between 20–<25 kg/m^2 did not (p=0.080) (Table 3).

Table 3: Stratified Comparison of Post-Induction Perfusion Index (PI) Between Study Groups

Stratification Variables	Category	Group M (Midazolam + Ketamine) Mean ± SD	Group P (Propofol) n=73 (Mean ± SD)	Mean Difference (95% CI)	p-value	Interaction p-value
Gender	Male	1.92 ± 0.41	1.68 ± 0.29	0.24 (0.08 to 0.40)	0.004*	0.030*
	Female	1.83 ± 0.38	1.72 ± 0.27	0.11 (−0.03 to 0.25)	0.110	
ASA Status	I	1.90 ± 0.39	1.70 ± 0.26	0.20 (0.01 to 0.39)	0.040*	0.020*
	II	1.86 ± 0.42	1.65 ± 0.30	0.21 (0.06 to 0.36)	0.010*	

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Age (years)	≤50	1.84 ± 0.37	1.70 ± 0.25	0.14 (0.00 to 0.28)	0.050*	0.010*
	>50–65	1.91 ± 0.43	1.66 ± 0.30	0.25 (0.08 to 0.42)	0.006*	
BMI (kg/m^2)	20–<25	1.82 ± 0.36	1.73 ± 0.27	0.09 (–0.02 to 0.20)	0.080	0.040*
	≥25–30	1.94 ± 0.44	1.65 ± 0.29	0.29 (0.10 to 0.48)	0.004*	

DISCUSSION

Poor peripheral perfusion has been associated with poor surgical outcomes according to recent studies [12]. Improved peripheral perfusion enhances tissue oxygenation, which is essential for better wound healing, reduced infection rates, and decreased in-hospital mortality [13]. In the present study, post-induction mean perfusion index was significantly higher in Group M (ketamine + midazolam) at 1.88 ± 0.40 compared to Group P (propofol) at 1.69 ± 0.28 (p=0.001), indicating better peripheral perfusion with the ketamine–midazolam combination. These findings are consistent with Zhou *et al.* who reported that PI values remained consistently higher in patients receiving ketamine than those receiving propofol at several time points—during induction (mean difference = 1.01, p=0.007), pre-intubation (mean difference = 1.46, p=0.001), and post-intubation (mean difference = 1.28, p=0.010) [11]. Similarly, Mohamed *et al.* also observed an overall increase in PI with both dexmedetomidine and midazolam, though the difference was not significant (p=0.610), suggesting that sedative agents can improve PI to varying extents [14]. In contrast, Nakasuji and colleagues found that PI measurements after intravenous propofol induction remained comparable between high- and low-risk groups during the initial three minutes, with increases becoming evident only at four and five minutes post-induction (4.5 ± 1.7 vs. 6.1 ± 2.4 and 4.3 ± 1.8 vs. 6.5 ± 2.5, respectively). This finding reflects propofol's transient and delayed vasodilatory effect, which may explain the comparatively lower PI observed in our propofol group [15]. Ketamine's ability to maintain blood pressure and heart rate can counteract the depressant effects of midazolam, potentially leading to more stable hemodynamic parameters during anesthesia induction and maintenance [16, 17]. In the current study, both SBP and MAP were significantly higher in Group M (p=0.010 and p=0.050, respectively) as compared to Group P. Afghaniyan *et al.* also reported that propofol significantly decreases systolic and mean arterial blood pressure (p<0.001), particularly in patients undergoing CABG, as compared to midazolam [18]. Atchley *et al.* conducted a study on high-risk patients in the ICU and found similar results, showing that propofol was associated with significantly higher rates of hypotension (p<0.001) and bradycardia (p<0.001) compared with ketamine combined with dexmedetomidine [19]. Baysal *et al.* conducted a study on children who underwent cardiac catheterization and found that propofol use led to significant decreases in mean arterial pressure (p=0.001) and oxygen saturation, whereas ketamine/midazolam maintained more stable hemodynamic parameters with non-significant changes in mean arterial pressure (p=0.544) and a moderate reduction in heart rate [20].

Limitations of the current study include the relatively small sample size, which may limit the generalizability of the findings to a broader cardiac patient population. Additionally, variations in individual responses to anesthetic agents due to co-morbidities and baseline hemodynamic status may also have influenced the results. Finally, the use of non-invasive monitoring for perfusion index may not capture all hemodynamic changes compared to invasive measurements.

CONCLUSIONS

Findings of the current study suggest that induction with ketamine and midazolam may lead to increased post-induction mean perfusion index as compared to propofol in cardiac patients. These findings highlight the potential of using ketamine and midazolam for improving or maintaining peripheral perfusion in cardiac patients, which could be beneficial for postoperative recovery and minimizing complications.

Authors' Contribution

Conceptualization: MAK, FA
Methodology: FA, SY, SB
Formal analysis: SA
Writing and Drafting: SA, MF
Review and Editing: MAK, FA, SY, SB, SA, MF, HMUM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Effect of Tamsulosin in Prevention of Postoperative Urinary Retention

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ABSTRACT

Tamsulosin has shown effectiveness in the treatment of lower urinary tract symptoms, especially post-operative urinary retention (POUR). **Objectives:** To assess the efficacy of tamsulosin in the prevention of POUR and to determine the relationship between POUR incidence and urinary parameters such as urine pH, specific gravity, and color. **Methods:** This cohort (longitudinal) research was carried out at the Department of Urology, Liaquat University of Health Sciences, Jamshoro, for 6 months (from January 2025 to June 2025) after approval from the IRB. Data collection included baseline demographics, comorbidities, and pre-operative information. At 6, 12, and 24 hours post-operative post-void residual (PVR) was assessed. Analysis of urine was done for measuring urinary pH, color, and specific gravity. SPSS was used for analyzing the data, keeping $p<0.05$ statistically significant. **Results:** From 150 post-operative cases, the mean age was 53.5 ± 11.3 years, with around 71 % male. Tamsolusin substantially decreased POUR with a reduction in PVR from 186 ml (6 hours) to 82 ml (24 hours). Incidence of POUR reduced from 24.7 % to 6 %. Cases having POUR showed lower pH of urine, high specific gravity, and dark colored urine. **Conclusions:** The present study demonstrated that tamsulosin was effective in preventing postoperative urinary retention (POUR) by significantly reducing post-void residual volumes and improving urinary flow within the first 24 hours after surgery.

INTRODUCTION

Post-Operative Urinary Retention (POUR) is defined as the inability to completely or spontaneously void post-operatively [1]. Around 69 % of operations are complicated by it, and so it has substantial consequences for the patients. POUR causes discomfort to patients in general, coupled with embarrassment [2]. Cambise et al. reported in their study that the incidence of POUR post-various surgeries ranged as low as 3 % to as high as 70 %. Due to bladder distention, hemodynamic shifts take place along with prolonged dysfunction of the detrusor muscle and the possibility of injuries to the kidneys [3]. Moreover, managing POUR requires using urinary catheters for emptying the bladder. This causes risk for catheter-associated infection of the urinary tract (CAUTI) [4]. Amongst the most commonly reported infections in hospital settings, urinary tract infections (UTI) top the list, in which 70 to 80 % are attributed to an indwelling urinary catheter (IUC) [5]. Duration of catheterization is one of the most important predictors of CAUTI. It is estimated that around 4-7 % risk of causing bacteriuria increases with each day of use of IUC [6]. One of the most important factors in the management of CAUTI is the removal of the catheter as early as possible. Nonetheless, if catheters are removed early in post-operative patients, it has been linked with higher POUR incidences and needing re-catheterization [7]. Therefore, for facilitating early removal of the catheter without risking reinsertion of the catheter, efforts must be targeted at preventing POUR. One of the factors leading to POUR is thought to be the use of anesthetics that cause suppression of micturition control

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and reflex. However, the etiology of POUR is hypothesized to be multifactorial, and sympathetic stimulations due to surgery and pain are thought to play a vital part [8]. A selective alpha-1a antagonist of adrenoceptors, known as Tamsulosin, has shown effectiveness in the treatment of lower urinary tract symptoms, especially in male having benign prostatic hyperplasia [9]. Moreover, it is regarded as a well-tolerated and safe medication with few adverse effects, especially cardiovascular ones, as compared to other less-selective alpha blocking agents. Tamsulosin tends to relax smooth muscles present in the urethral sphincter, neck of the bladder, and the prostate. This leads to relief from symptoms of the urinary tract [10]. Even though tamsulosin is approved for use in male having BPH by the FDA (Food and Drug Administration), its role is also being explored for relief of symptoms or lower urinary tract symptoms in female as well, with successful results. Off-label, it is used clinically for treating POUR in patients having voiding difficulties [11]. In recent times, researchers have studied the use of tamsulosin in the prevention of POUR in a limited number of surgical cases, demonstrating mixed results [12]. A study by Baysden *et al.* showed no positive effect of administering tamsulosin at 0.2 mg post-operatively for 7 days in the prevention of POUR post-surgery of rectal cancer patients [13]. On the contrary, a couple of randomized controlled trials that involved male patients undergoing elective repair of inguinal hernia and other benign urological surgeries showed a positive tamsulosin effect when administered pre-operatively [14, 15]. Therefore, even though the published literature suggests a beneficial role of tamsulosin therapeutically in preventing POUR, its efficacy on a broader number of surgical cases undergoing abdominal surgeries is still unclear. Therefore, this study was carried out to assess the effectiveness of tamsulosin in preventing post-operative urinary retention in patients undergoing ureteroenoscopy by evaluating urine pH, specific gravity, and color. For enhancing the statistical outcome of the research, urine pH, specific gravity, and color were assessed. The typical range of urine pH is from 4.5 to 8, having much fluctuation post-operatively due to medications, anesthesia, and changes in metabolic activity. Any acute kidney injury can lead to a more acidic pH of urine both pre- and post-operatively. In contrast, a urinary pH of over 8.0 might point towards urinary tract infection (UTI), whilst a pH below 4.5 denotes either dehydration or metabolic acidosis [16]. The specific gravity of urine normally is between 1.002 and 1.035, reflecting hydration status and functioning of the kidneys. Research has shown that around half of surgical patients receiving I/V fluid intra-operatively tend to have low specific gravities (<1.010), while in around 10 to 20 % of cases, due to kidney dysfunction or dehydration, higher specific gravities (>1.030) are observed post-operatively [17]. Normally, the post-operative color of urine varies from pale yellow to deep amber, with transient hematuria presenting in about 15 % of cases. This occurs especially after abdominal or urological procedures. Due to hydration, some post-operative patients experience dark colored urine, whilst excess administration of I/V fluids causes diluted urine, indicating impairment of the kidneys [18].

There is limited evidence for post-operative renal function parameters, hydration status, associated complications, and the use of tamsulosin for preventing POUR, especially in the local population, which is a significant area of research that has been overlooked. There is a lack of robust data to understand the outcomes of surgery and the impact of preventative interventions for POUR in surgical patients. This study aimed to measure post-operative renal function parameters and hydration status, identify associated complications, and determine the efficacy of tamsulosin in preventing postoperative urinary retention (POUR).

METHODS

This longitudinal cohort study using consecutive sampling was done at the Department of Urology of Liaquat University of Health Sciences, Jamshoro. The duration of study was six months post- IRB approval of the research proposal (from January 2025 to June 2025). For the calculation of sample size, open epi online software tool was used. Keeping the prevalence of POUR at 9.9 % as reported in a study on the risk factors for post-operative retention of urine in post-surgical cases. Keeping the confidence level at 95 %, the frequency of cases developing retention of urine at 9.9 %, the sample size came out to be 150 [19]. Therefore, a total of 150 cases were included. Surgical cases of the Department of Urology between the ages of 18 and 65 years, of both genders, and undergoing ureteroenoscopy, wherein POUR was a known risk factor, were included in the study. Moreover, patients having normal pre-operative function of bladder, as recorded in the history of patients (from medical records), like the color of urine, its pH, and specific gravity, were noted. A urine pH between 4.5 and 8.0, color within the normal range, and specific gravity between 1.005 and 1.030 were included. Breastfeeding or pregnant female were excluded, in addition to patients with any systemic disease of neurological, renal, cardiovascular, or hepatic variety, and those having known contraindications to tamsulosin, similar alpha-1 blockers, or allergy were also excluded. After ethical approval from IRB with ref: LUMS/REC/-558, a self-designed questionnaire was employed for recording the baseline demographic data of patients, for instance, gender, age, pre-existing disease/s, and other medical and surgical history. Data collection was carried out in a total of 3 phases, viz. pre-operative, pre-operative and post-

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operative. In the pre-operative phase, patients eligible for the study were screened on the basis of medical records and then enrolled according to inclusion and exclusion criteria after taking informed consent from each patient. Baseline demographics and pre-operative variables included pH of urine, its specific gravity, and color as well. For urine analysis, mid-stream clean catch urine sample/s were analyzed for pH using either test strips or a calibrated pH meter, specific gravity by dipstick urinalysis or refractometer, and color was assessed through visual aid using a standardized chart for urine color. Pre-operatively, all patients received 0.4 mg tamsulosin the night before the surgical procedure and were continued post-operatively for 7 days. Operative anesthesia and surgical procedure details were recorded. A urologist of at least five years of experience at the urology department of the hospital performed all surgeries. Post-operatively, the patients were monitored for POUR, urinary pH, color, and specific gravity. Other than these, post-operatively, patients were also monitored for any urinary tract infection, dysuria, hematuria, and any complication associated with the catheter, i.e., discomfort, infection, or trauma to the urethra. Samples of urine for analysis were collected on days 1st, 3rd, and 7th after the surgery. Such a systemic approach ensured accuracy in the collection of data for evaluation of tamsulosin's effectiveness in the prevention of POUR and its effect on parameters of urine, whilst addressing its potential regarding post-operative complications for optimum care of the patient. Belmont report for human guidelines for research was followed. Informed consent and the study's purpose were communicated to each patient before inclusion in the study, with the option of refusal to participate in the study at any given point in time. All data was kept confidential and anonymous.

SPSS version 27.0 was used to analyze the data. Descriptive statistics were used to find the baseline demographic and clinical characteristics; continuous variables, including age and duration of surgery, were described in mean along with standard deviation, whereas skewed variables, including intra-operative fluid volume, post-void residual (PVR), time to first void, and length of hospital stay, were summarized in median with inter-quartile range. Frequencies and percentages were used to show categorical variables such as gender, comorbidities, ASA class, postoperative urinary retention (POUR), urine color, need for catheterization, urinary tract infection, and readmission. The tests of quantitative variables were the Shapiro-Wilk test used to determine whether the variables were normal. An independent sample t-test was used to compare the normally distributed variables (urine pH and specific gravity) of patients with and without POUR. The chi-square test was used to test the association of categorical variables, especially the urine color and POUR status. All the statistical tests were two-tailed, and a p-value below 0.005 was deemed to be significant.

RESULTS

A total of 150 patients were included in the study. Overall, the mean age of included patients was 53.47 ± 11.3 years. A total of 107 (71.33%) male and 43 (28.67%) female were included in the research. 67 (44.67 %) patients were hypertensive, 71 (47.33%) were diabetic, 77 (51.33%) had Benign Prostatic Hyperplasia (BPH), while 31 (20.67%) had cardiac disease. Around 81 (54%) cases were ASA class III-IV. Mean duration of surgery was 64.75 ± 10.2 mins, while median intra-operative fluid was 1237 ± 282 ml (Table 1).

Table 1: Baseline Demographics of Included Patients (n=150)

Variables		n (%), Mean ± SD
Mean Age ± SD (years)		53.47 ± 11.3
Gender	Male	107 (71.33%)
	Female	43 (28.67%)
Co-morbidities	Hypertension	67 (44.67%)
	Diabetes Mellitus	71 (47.33%)
	Benign Prostatic Hyperplasia (BPH)	77 (51.33%)
	Cardiac Disease	31 (20.67%)
ASA class III-IV		81 (54%)
Mean Duration of Surgery (mins)		64.75 ± 10.2
Median Intra-operative Fluid (ml)		1237 ± 282

At 6, 12, and 24 hours post-operatively, the median PVR was 186 ml (111-265), 131 ml (83-210), and 82 ml (52-112), respectively. The rate of POUR at 6 hours, 12 hours, and 24 hours was 37 (24.67%), 26 (17.33%), and 09 (6%), respectively. Post-operatively, 59 (39.33%) required catheterization. The occurrence of UTI within 7 days occurred in 10 (6.67%) cases, while readmission within 30 days was observed in 03 (2%) of cases. The post-operative outcomes and measures of urinary retention are presented (Table 2).

Table 2: Post-Operative Outcomes and Measures of Urinary Retention (n=150)

Outcomes	Values
Median PVR 6 h (IQR) ml	186 (111–265)
Median PVR 12 h (IQR) ml	131 (83-210)
Median PVR 24 h (IQR) ml	82 (52-112)
POUR Rate 6 h (%)	37 (24.67%)
POUR Rate 12 h (%)	26 (17.33%)
POUR Rate 24 h (%)	9 (6%)
Catheterization Required, n (%)	59 (39.33%)
Time to First Void (hrs), Median (IQR)	5.4 (3.9-10.8)
Length of Stay (days), Median (IQR)	2.4 (1.6-3.8)
UTI within 7 Days, n (%)	10 (6.67%)
Readmission within 30 Days, n (%)	3 (2%)

In cases with POUR, the mean pH of urine was 5.9 ± 0.9, while in patients without POUR, the mean urine pH was 6.3 ±

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0.8, with a significant difference of p-0.020. The specific gravity of patients with POUR was 1.026 ± 0.005, while in patients without POUR, the mean specific gravity was 1.021 ± 0.002 with a significant difference of p-0.010. A highly significant difference of p<0.001 was reported in terms of the color of urine in patients with POUR and without POUR (Table 3).

Table 3: Comparison of Post-operative Urinary Retention (POUR) according to Urine Parameters (n=150)

Variables		POUR Present, n=72	POUR Absent, n=78	p-value
Urine pH (Mean ± SD)		5.9 ± 0.9	6.3 ± 0.8	0.020
Specific Gravity (Mean ± SD)		1.026 ± 0.005	1.021 ± 0.002	0.010
Urine Color	Light Yellow	31 (43.1%)	39 (50%)	<0.001
	Amber	28 (38.89%)	32 (41.03%)	
	Dark Yellow	13 (18.1%)	07 (8.97%)	

DISCUSSION

In this study of 150 postoperative patients, the mean age was 53.47 ± 11.3 years, with a predominance of male (71.3%) and common comorbidities including diabetes (47.3%), hypertension (44.7%), and benign prostatic hyperplasia (51.3%). The mean operative duration was 64.8 minutes, and most patients were in ASA class III–IV (54%). Postoperatively, a marked reduction in post-void residual (PVR) was observed from 186 ml at 6 hours to 82 ml at 24 hours, with a corresponding decline in POUR incidence from 24.7% to 6%, demonstrating the effectiveness of tamsulosin in preventing urinary retention. Catheterization was required in 39.3%, the median time to first void was 5.4 hours, and the median hospital stay was 2.4 days, with minimal complications. Patients with POUR exhibited lower urine pH (5.9 ± 0.9), higher specific gravity (1.026 ± 0.005), and darker urine color, compared to those without retention (p<0.005), suggesting that acidic and concentrated urine profiles may correlate with a higher risk of POUR. Similar to the findings of this research, a systematic review and meta-analysis aimed at estimating the efficacy of prophylactic Tamsulosin on post-operative urinary retention (POUR) amongst male patients. The pool of 11 studies, including 1046 patients administered tamsulosin, while 1,113 controls reported significantly lower rates of POUR in the tamsulosin group, i.e., in 123 (11.8%) versus in 238 (19%) of patients in the control group (p-0.006). However, the research observed that the use of tamsulosin resulted higher risk of adverse reaction. The research concluded that prophylactic use of Tamsolusin helps in the prevention of POUR, especially among younger patients. However, the advantages must outweigh the possible adverse effects associated with its use. In most cases, the adverse events are self-limited [18]. Although in our study, adverse effects were not generally reported, the use of Tamsolusin was, in most cases, observed with no or minimal side effects. In line with the findings of our study, research done to evaluate Tamsolusin's efficacy when administered pre-operatively for preventing POUR reported to be effective in the reduction of POUR's incidence in patients who underwent elective abdominal surgery. On the contrary, Papageorge *et al.* in their study on 158 participants observed that perioperative prophylaxis using Tamsolusin was not effective in decreasing the prevalence of POUR in elective abdominal surgery cases [19]. In another study by Gao *et al.* on comparison of prophylactic effects of tamsulosin with placebo on POUR observed that from 232 male patients included in the study, POUR was observed in 5.9 % given tamsulosin, while in 21.1 % of patients given placebo for urinary retention (p-0.001). The study observed no adverse effect with the use of tamsulosin or a placebo. The study concluded that short pre-operative treatment with tamsulosin can aid in reducing incidences of urinary retention and need for catheterization post- urological surgeries [20]. This study utilized a well-defined postoperative cohort with standardized timing of urine assessments at multiple intervals, allowing objective evaluation of tamsulosin's effectiveness. The inclusion of urine biochemical parameters (pH, specific gravity, and color) provided novel insights into physiological factors influencing postoperative urinary retention. Statistical rigor, including repeated measures and post-hoc analyses, strengthened the validity of findings.

This single-center study with a relatively small sample size and absence of a randomized control group may limit the generalizability and causal interpretation of the findings. Future multicenter randomized controlled trials with larger and more diverse populations are warranted to confirm these results, determine optimal timing and dosage of tamsulosin, and evaluate long-term safety, patient-reported outcomes, and the predictive role of urine biochemical parameters in postoperative urinary retention.

CONCLUSIONS

The present study demonstrated that tamsulosin was effective in preventing postoperative urinary retention (POUR) by significantly reducing post-void residual volumes and improving urinary flow within the first 24 hours after surgery. Its prophylactic use appears particularly beneficial in patients at higher risk, such as male and those with benign prostatic hyperplasia. Furthermore, urine characteristics- specifically lower pH, higher specific gravity, and darker coloration were associated with an increased likelihood of POUR, suggesting a link between hydration status and postoperative bladder function. These findings support the use of tamsulosin as a safe and effective pharmacologic strategy to minimize POUR and emphasize the importance of maintaining adequate hydration in the perioperative period.

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Authors' Contribution

Conceptualization: FB, JA
Methodology: FB, I, IA
Formal analysis: MA, JA, MA, MA
Writing and Drafting: FB, JA, MA
Review and Editing: FB, JA, I. IA, MA, MA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Hand-Made Extra-Corporeal Knotting Versus Clip for Stump Closure in Laparoscopic Appendectomy

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ABSTRACT

Acute appendicitis represents one of the most frequent surgical emergencies encountered in Pakistan. The delayed appendicitis and increased infection risks may impact postoperative outcomes and surgical decision-making. **Objectives:** To evaluate and compare hand-made extracorporeal knotting with polymeric clip closure in laparoscopic appendectomy, focusing on intraoperative performance measures and the incidence of early postoperative complications, including postoperative ileus, wound infection, and intra-abdominal infection within 15 days. **Methods:** A randomized controlled trial (NCT ID: 07281612) was carried out in the Department of Surgery, Abbas Institute of Medical Sciences, Muzaffarabad, over a period of twelve months. Using simple lottery-based random allocation, 190 patients diagnosed with uncomplicated acute appendicitis were recruited and assigned to either the hand-made extracorporeal knotting group (n=95) or the polymeric clip closure group (n=95). Relevant demographic, clinical, and intraoperative parameters were systematically documented. **Results:** The two groups demonstrated broadly comparable baseline profiles. However, the mean duration of surgery was modestly but significantly greater in the knotting group than in the clip group (45.8 ± 8.9 vs 42.8 ± 8.2 minutes; p=0.025). Intra-abdominal infection was observed in 1.1% of patients undergoing knotting compared with 6.3% of those receiving polymeric clips (p=0.049). On logistic regression, polymeric clip use was associated with increased odds of intra-abdominal infection (adjusted odds ratio 4.82; 95% confidence interval 1.01–22.73; p=0.048). **Conclusions:** Hand-made extracorporeal knotting results in a significantly lower rate of intra-abdominal infection compared to polymeric clip closure. Despite a modest increase in operative time, the knotting technique may offer a safer and more effective option for stump closure.

INTRODUCTION

Acute appendicitis is one of the most common causes of emergency abdominal surgery worldwide [1]. Laparoscopic appendectomy has become the preferred approach in many centers because it is associated with reduced postoperative pain, shorter hospital stays, and improved cosmetic outcomes compared with open appendectomy; however, secure closure of the appendiceal stump remains a critical step, and no single technique has been universally accepted as the standard of care [2]. Several techniques are used for appendiceal stump closure during laparoscopic appendectomy. These include endoloops, endostaplers, metallic clips, polymeric clips, and hand-timed intracorporeal or extracorporeal knots [3]. Most studies show low complication rates with all common methods in uncomplicated appendicitis. Differences are mainly seen in operative time, technical difficulty, and device use rather than major clinical outcomes [4]. A systematic review found that approximately 20% of laparoscopic appendectomies use polymeric clips for stump closure, while 30% rely on

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intracorporeal knotting, with significant variability in technique preference across different regions [5]. A study in India found that hand-made knotting resulted in lower postoperative infection rates (2%) compared to clips (5%) in laparoscopic appendectomy for uncomplicated appendicitis [6]. Polymeric clips have gained popularity due to their ease of application and potential to reduce operative time; however, concerns remain about their performance in cases with a wide or inflamed appendiceal base, where secure clip placement may be challenging. Hand-made extracorporeal knotting offers a low-cost and versatile alternative that can be adapted to varying stump diameters and tissue conditions, making it particularly attractive in resource-limited settings. Several randomized and observational studies comparing extracorporeal knotting and polymeric clip closure have reported broadly comparable safety outcomes, though results regarding operative time and postoperative infection have varied across populations [7]. Evidence from low- and middle-income countries remains limited, and findings from high-resource health systems may not be fully generalizable to surgical practice in Pakistan due to differences in case presentation, infection burden, and resource availability [8-10].

In Pakistan, the lack of locally generated randomized data means that the stump-closure technique is often determined by device availability and cost rather than comparative effectiveness or context-specific outcomes. Given these uncertainties, further randomized evaluation of stump-closure techniques is needed to clarify their relative safety and feasibility in settings with higher rates of delayed presentation and limited resources. Therefore, this randomized controlled trial was conducted to compare hand-made extracorporeal knotting and polymeric clip closure of the appendiceal stump in laparoscopic appendectomy for uncomplicated acute appendicitis, focusing on early postoperative outcomes relevant to clinical practice in Pakistan.

METHODS

This randomized controlled trial took place in the Department of Surgery, Abbas Institute of Medical Sciences, Muzaffarabad as a one-year-long trial (Reference No. AIMS/SGR/1980/2024) following the College of Physicians and Surgeons, Pakistan (CPSP) approval of the study synopsis and the ethical permission granted by the Institutional Review Board of the Abbas Institute of Medical Sciences, Muzaffarabad. The study duration was from August 2024 to August 2025. The research was retrospectively enrolled on the clinicaltrials.org site with ID NCT07281612, which was registered. Patients were enrolled consecutively as they presented and met the predefined inclusion criteria, until the required sample size was achieved. Consecutive enrollment was used only for participant recruitment and did not determine group assignment. After enrollment and confirmation of eligibility, participants were randomly allocated to one of the two intervention groups using the predefined lottery-based randomization method. Thus, consecutive sampling ensured complete recruitment, while random allocation ensured unbiased group assignment. This was a single-centre, hospital-based study. The required sample size was calculated using the World Health Organization (WHO) sample size calculator for comparing two independent proportions. The calculation used a 95% confidence level ($\alpha = 0.05$) and 80% power ($\beta = 0.20$). Expected intra-abdominal infection rates were taken as p1 = 0.0% in the hand-made extracorporeal knotting group and p2 = 6.3% in the polymeric clip group, based on prior published data [11]. The sample size per group was computed using the standard formula for two proportions: $n = [Z_{1-\alpha/2sqrt}(2P(1-P)) + Z_{1-\beta sqrt}(p_1(1-p_1) + p_2(1-p_2))]2 \backslash (p_1-p_2)^2$. This yielded a minimum of 95 participants per group (total n = 190). The study illustrates the CONSORT flow chart of patient selection and inclusion of patients in the RCT (Figure 1).

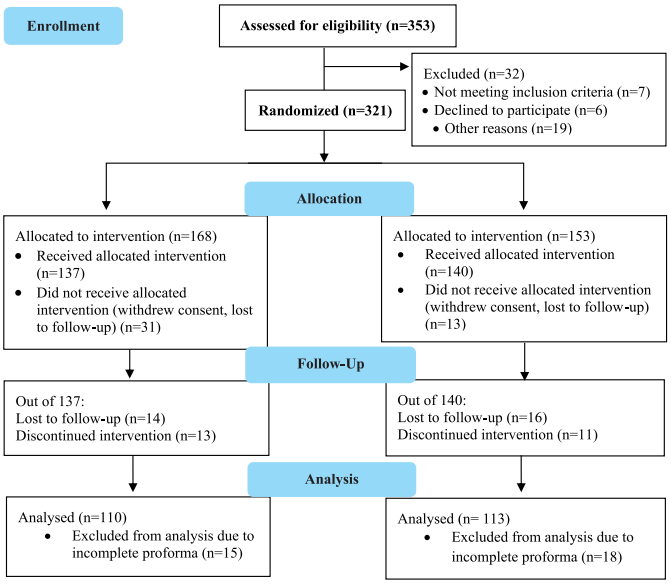

Figure 1: CONSORT 2010 Flow Diagram of the Included Participants

Only patients with uncomplicated acute appendicitis were included in the study. Patients with perforated appendix, appendicular abscess, appendicular mass, generalized or localized peritonitis, or friable appendiceal base were excluded. The subjects who chose to undergo an open appendectomy, or were found to have complicated appendicitis, before or during operative diagnosis, were left out. People with generalized or localized peritonitis, friable appendix base, or inflammatory disease of the pelvis were also not included. After taking informed written consent, demographic and clinical information were

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recorded in a structured proforma. Pre-operative laboratory investigations included hemoglobin, random blood sugar, and total leukocyte count. Diagnosis of acute appendicitis was made clinically and radiologically. Ultrasound findings considered diagnostic included a non-compressible, blind-ended tubular structure in the right lower quadrant with an outer diameter greater than 6 mm, associated peri-appendiceal inflammatory changes, or the presence of an appendicolith. All patients underwent laparoscopic appendectomy under general anesthesia performed by the same surgical team. Randomization into two groups was done by the lottery method. Participants were randomly assigned in a 1:1 ratio to hand-made extracorporeal knotting or polymeric clip closure. The allocation sequence was generated before the start of recruitment using a simple lottery method. Equal numbers of identical slips (95 for Group A and 95 for Group B) were prepared, folded to the same size, and placed in an opaque container. For each eligible patient, one slip was drawn by an operating-room staff member who was not involved in enrollment, surgery, or outcome assessment. The drawn slip determined the stump-closure technique. The slip was revealed only after diagnostic laparoscopy confirmed uncomplicated appendicitis and eligibility, to avoid allocating patients who were later excluded for complicated disease. The allocation record was stored separately and was not available to the postoperative assessor. The laparoscopic appendectomy was performed using a standardized three-port technique. A 10-mm camera port was placed at the umbilicus, and two 5-mm working ports were placed in the left lower abdomen and suprapubic region. The mesoappendix was divided using monopolar electrocautery, and the appendicular artery was secured with double ligation using non-absorbable suture material (polypropylene 3-0). No advanced energy devices were used, and conventional ligation was performed for securing vessels. Appendiceal stump closure was done using either hand-made extracorporeal knotting (modified Tayside technique) or a non-absorbable polymeric double clip (Hem-o-Lok), depending on the randomized group assignment. In Group A, appendiceal stump closure was achieved using hand-made extracorporeal knotting by the modified Tayside method with two knots using non-absorbable suture material. In Group B, the stump was secured using a non-absorbable polymeric double clip. Each procedure was performed according to standard surgical guidelines, and the choice of technique was determined by random allocation rather than operator preference. The study shows an inflamed appendix and stump closure using a handmade knot and a polymeric clip (Figure 2).

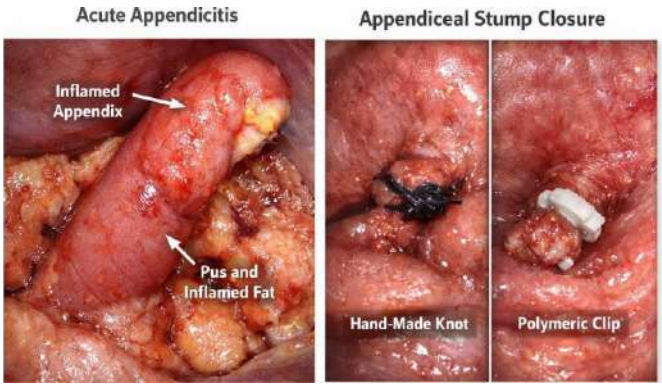

Figure 2: Appendiceal Stump Closure Techniques

The operative time was measured from initial skin incision to completion of skin closure. The failure of technique was defined as any insecure knotting or clip dislodgement identified intra-operatively requiring conversion or revision. Patients were followed for 15 days post-surgery and evaluated for postoperative ileus, wound infection, and intra-abdominal infection confirmed by clinical features and imaging. In this study, complications were defined as follows: postoperative ileus was characterized by delayed return of normal bowel function, including abdominal distension, nausea, vomiting, and an inability to tolerate oral intake, with no passage of flatus or stool beyond 48 hours. Wound infection was diagnosed based on clinical signs of redness, warmth, swelling, or purulent discharge at the incision site. Intra-abdominal infection was identified by clinical symptoms such as fever, abdominal pain, or distension, accompanied by imaging findings confirming infection, occurring within 15 days post-surgery. These complications were monitored during the 15-day follow-up period. Postoperative pain at the operative site was assessed using a visual analogue scale (VAS) at 24 hours after surgery. All patients received standardized analgesia according to hospital protocol, including intravenous paracetamol and non-steroidal anti-inflammatory drugs, with additional analgesics administered as needed. The analgesic regimen was uniform for both groups to avoid bias in pain assessment. Postoperatively, patients were kept nil by mouth (NPO) for 6-12 hours until they tolerated oral intake, starting with liquids and progressing to a soft diet. Pain management was provided with standard analgesics. Patients were monitored for 48 hours for any complications, including wound infection and ileus. All patients were discharged after 2 days if stable and without complications. A 15-day follow-up was conducted to assess early postoperative outcomes, including wound infection, intra-abdominal infection, and postoperative ileus. To reduce bias, all the operations were performed by one team, and all the postoperative evaluation has been made by one resident who was not supposed to know the participant assignment. Data were collected using a

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standardized proforma designed specifically for this study to ensure uniform and consistent documentation across both groups. The proforma was reviewed by senior faculty members for content validity before study initiation and was pilot-tested on a small number of cases to ensure clarity and completeness before final implementation. Possible confounding variables, such as comorbidities and duration of symptoms, were managed through stratified analysis when interpreting the data. All laboratory tests were in line with hospital requirements. The research procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, or from guardians when participants were minors. All study data were de-identified and handled with strict confidentiality. Baseline demographic and clinical characteristics, including age, sex, body mass index, and duration of symptoms, were comparable between the two groups.

The data were analyzed by SPSS version 25.0. Continuous variables were first assessed for normality using the Shapiro–Wilk test. Normally distributed variables were summarized as mean ± standard deviation and compared between groups using the independent samples t-test. Non-normally distributed continuous variables were expressed as median with interquartile range and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the chi-square test. Fisher's exact test was applied when expected cell counts were small. Binary logistic regression was performed as an exploratory analysis to evaluate factors associated with intra-abdominal infection, with results reported as odds ratios and 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant. Intraoperative appearance, including the presence of gangrenous changes without perforation, was recorded as a clinical variable and analyzed as a potential confounder in exploratory analyses.

RESULTS

A total of 190 patients with uncomplicated acute appendicitis were included in the study, with 95 patients allocated to the hand-made extracorporeal knotting group and 95 to the polymeric clip group. All patients completed a 15-day follow-up, and no data were missing for primary or secondary outcomes. Baseline demographic and clinical characteristics, including age, sex, body mass index, and duration of symptoms, were comparable between the two groups, confirming successful randomization. Operative outcomes showed that the mean operative time was significantly longer in the knotting group compared with the clip group. Early postoperative outcomes were evaluated according to predefined criteria. Postoperative ileus and wound infection rates were low and comparable between the two groups. Intra-abdominal infection within 15 days was observed more frequently in the polymeric clip group than in the knotting group, and this difference reached statistical significance. The mean operative time was longer in the hand-made knotting group compared with the polymeric clip group (45.8 ± 8.9 vs 42.8 ± 8.2 minutes). The mean difference was 3.0 minutes (95% confidence interval: 0.4 to 5.6 minutes), indicating a small but statistically significant increase in operative time with the knotting technique. The observed difference in intra-abdominal infection is clinically relevant, particularly in settings where patients often present late, and the inflammatory burden is higher. Although the adjusted odds ratio suggests higher odds of intra-abdominal infection with polymeric clips, the wide confidence interval (1.01–22.73) shows that the true effect size may be much smaller or much larger. The study shows the descriptive statistics of continuous variables, including age, operative time, and other time-related variables, in both study groups: hand-made extracorporeal knotting (n=95) and polymeric clip (n=95). Normality was assessed using the Shapiro–Wilk test. Variables following a normal distribution were expressed as mean ± SD, while non-normal data were presented as median (IQR). This table demonstrates that most variables, such as age, were normally distributed. Operative time was significantly longer in the hand-made knotting group (p=0.025). Other continuous variables showed no statistically significant differences between groups (Table 1).

Table 1: Descriptive Statistics of Continuous Variables (Mean ± SD / Median (IQR)) in Both Groups

Variables	Shapiro–Wilk (p)	Hand-Made ExtracorporealKnotting (n=95)	Polymeric Clip (n=95)	Test Statistic	p-value
Age (years)*	0.094	27.9 ± 10.8	29.3 ± 12.0	t = 0.82	0.414
Duration of Symptoms (hours)†	<0.001	24 (18–36)	24 (18–40)	U = 4408.5	0.521
Operative Time (minutes)*	0.107	45.8 ± 8.9	42.8 ± 8.2	t = 2.26	0.025
Pain Score at 24 hrs*	0.069	3.8 ± 1.1	4.0 ± 1.2	t = 1.13	0.261
Length of Stay (days)†	<0.001	2 (2–3)	2 (2–3)	U = 4489.5	0.611

Data represented as Mean ± SD (Independent t-test used for normally distributed data). †Data represented as Median (IQR) (Mann–Whitney U test used for non-normal data). Significance level = p<0.050

The results show categorical variables, including gender, and postoperative complications in both study groups. Data are expressed as frequency (n) and percentage (%). Chi-square and Fisher's exact tests were applied according to expected

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frequencies. This study demonstrates that both groups were similar in gender and comorbidity distribution (p>0.050). Intra-abdominal infection was significantly higher in the polymeric clip group (6.3%) compared with the knotting group (1.1%) (p=0.049). All other postoperative complications showed non-significant differences between groups (Table 2).

Table 2: Comparison of Categorical Variables Between Both Study Groups (n=190)

Variables	Hand-Made Knotting (n=95)	Polymeric Clip (n=95)	χ^2 / Fisher's	p-value
Gender (Male)	57 (60.0%)	57 (60.0%)	0.00	1.000
Post-op Ileus	7 (7.4%)	9 (9.5%)	0.28	0.598
Wound Infection	6 (6.3%)	9 (9.5%)	0.69	0.407
Intra-Abdominal Infection	1 (1.1%)	6 (6.3%)	–	0.049

Data are presented as n (%). Statistical significance determined using Chi-square or Fisher's Exact test as appropriate. Significance = p<0.050

The study shows the binary logistic regression analysis for predictors of intra-abdominal infection following laparoscopic appendectomy. Independent variables included closure method and symptom duration > 48 hours. Odds ratios (OR) with 95% confidence intervals (CI) and p-values were calculated. This table demonstrates that polymeric clip closure independently predicted intra-abdominal infection with a statistically significant OR = 4.82 (95% CI 1.01–22.73, p=0.048). The confidence interval for this estimate was wide (95% CI 1.01–22.73), indicating imprecision and uncertainty in the magnitude of the effect, likely due to the small number of infection events. Other variables showed non-significant associations after adjustment for confounders (Table 3).

Table 3: Binary Logistic Regression Analysis for Predictors of Intra-Abdominal Infection

Predictor Variables	β Coefficient	Adjusted OR (95% CI)	Wald χ^2	p-value
Polymeric Clip Closure	1.57	4.82 (1.01–22.73)	3.89	0.048
Symptom Duration > 48 hours	0.66	1.94 (0.61–6.18)	1.25	0.258

Significance = p<0.050 is considered statistically significant

DISCUSSION

A large multicenter observational study from Europe reported generally low abscess rates following laparoscopic appendectomy but highlighted that stump closure technique and local infection control practices may influence outcomes [12]. Similarly, data from Germany involving over 600 patients showed comparable safety between polymeric clips and staplers, but emphasized careful patient selection and stump assessment, especially in inflamed bases [13]. In comparison to previous studies, our findings are consistent with much of the existing literature, which shows that both hand-made extracorporeal knotting and polymeric clip closure are safe and effective techniques for appendiceal stump closure. Similar to an Asian study, which observed comparable complication rates between both methods, our study also demonstrated low complication rates, except for a statistically significant difference in intra-abdominal infection rates, favoring the knotting technique (1.1% vs. 6.3%, p=0.049) [14]. Overall, our results support the idea that, while polymeric clips may reduce operative time, the versatility and potentially lower infection rates of hand-made knotting make it a valuable alternative, particularly in resource-constrained environments where infection rates may be higher. Systematic reviews and meta-analyses from the United Kingdom and East Asia have generally concluded that both clips and ligatures are safe for uncomplicated appendicitis, with differences mainly related to operative time rather than complications [15]. In contrast, some randomized trials from Central Europe and the Middle East reported a trend toward higher infectious complications when clips were used in patients with thicker or more inflamed appendiceal bases, although statistical significance was not always reached [16]. These findings support the present results, suggesting that hand-made knotting may provide more secure closure in variable tissue conditions. Studies conducted in South Korea and China have shown that polymeric clips are easy to apply and reduce operative time, which is consistent with the shorter operative duration observed in the clip group in our study [17]. However, these studies were performed in settings with early presentation and lower rates of advanced inflammation, which may explain the lower reported infection rates compared with those seen in our population. International guidelines and large prospective studies from Europe and global cohorts emphasize that local disease patterns, surgeon experience, and resource availability should guide the choice of stump closure technique rather than a single universally preferred method [18-20]. In low- and middle-income countries such as Pakistan, where cost constraints and delayed presentation are common, hand-made extracorporeal knotting may offer an effective and economical alternative without compromising safety. Overall, the findings of this study align with contemporary evidence from diverse geographic regions while highlighting the importance of context-specific decision-making. The lower infection rate observed with extracorporeal knotting suggests that this technique may be particularly suitable for resource-limited settings, even if it requires slightly longer operative time. Large multicenter randomized trials with longer follow-up are still needed to confirm these findings and assess long-term outcomes.

This trial was registered retrospectively, which introduces a potential risk of reporting bias. Although the study protocol and outcomes were predefined before enrollment, retrospective registration may reduce transparency compared with prospective trial registration.

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Several secondary outcomes were tested without adjustment for multiple comparisons, which may increase the risk of type I error.

CONCLUSIONS

While both techniques resulted in similar postoperative outcomes, hand-made extracorporeal knotting was associated with a significantly lower rate of intra-abdominal infection compared to polymeric clip closure, despite a modest increase in operative time. The results suggest that, in settings with higher infection risks and resource limitations, hand-made knotting may provide a more secure and cost-effective option for stump closure. Further large-scale studies are needed to confirm these findings and evaluate long-term outcomes.

Authors' Contribution

Conceptualization: HUH
Methodology: MSR, FM
Formal analysis: SZHS
Writing and Drafting: HUH, ZAK, Z, FM
Review and Editing: HUH, ZAK, MSR, SZHS, Z, FM

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Association of Puerperal Sepsis with Income Level, Booking Status, and Mode of Delivery Among Patients at A Tertiary Care Setting

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ABSTRACT

According to the World Health Organization (WHO), puerperal sepsis is a contracted infection of the genital tract that occurs during labor or in a period of 42 days following the birth. It is the leading cause of preventable maternal disease and death in rich and poor countries. In Pakistan, it ranks third after hemorrhage and hypertensive diseases among women. **Objectives:** To determine the association of puerperal sepsis with booking status and mode of delivery among patients admitted at the Department of Obstetrics, Shaikh Zaid Women Hospital, Larkana. **Methods:** The study included 170 patients with puerperal sepsis in total. Demographic data were collected, including age, parity, socioeconomic position, and time since delivery. All the collected data were entered and analyzed using SPSS version 26.0. **Results:** According to the findings of this study, the mean age was 28.96 ± 6.41 years, the mean time since delivery was 22.11 ± 5.68 days, the mean parity was 1.58 ± 0.895, and the mean BMI was 24.51 ± 4.43. 103 (60.59%) patients were primigravida. 81 (47.65%) patients reported a monthly income of less than 50 thousand, and 81 (47.65%) patients reported a delay of more than 28 days. The income level (p-value=0.018) and mode of delivery (p-value=0.04) were found to have a significant association with puerperal sepsis. **Conclusions:** The puerperal sepsis is found to have a significant association with the caesarean section deliveries, income level, and case which remain un-booked during pregnancy.

INTRODUCTION

According to the WHO, puerperal sepsis is a genital tract infection that typically manifests itself within 6 weeks after birth [1]. It is also the second largest cause of maternal death in Pakistan and the cause of 11% maternal deaths in the world [2]. In Pakistan and other developing nations, possible risk factors that lead to the development of puerperal sepsis include the mode of delivery, Socioeconomic status, and chronic maternal disease [3]. Some of the common predisposing factors of puerperal sepsis include anemia, prolonged labour, vaginal check-ups in unsterilized conditions, and premature membrane rupture after long periods of time [4]. General sepsis is one of the leading 3 causes of pregnancy-related mortality in the world, with sepsis constituting about 10.7 per cent of pregnancy-related mortality in low and middle-income nations and 4.7 per cent of pregnancy-related mortality in

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high-income states [5]. Puerperal sepsis, a severe maternal infection often originating in the genital tract, is typically polymicrobial, involving both aerobic and anaerobic microorganisms. Escherichia coli is frequently identified as a major causative agent [6]. This serious public health issue is perpetuated in Pakistan by a combination of factors: deliveries by untrained traditional birth attendants (Dais), the insertion of foreign objects into the vagina as a traditional practice, and significant delays in accessing healthcare facilities due to transportation and resource limitations. When compounded by cultural factors that inhibit timely care-seeking, these elements pose a substantial challenge to the nation's overburdened healthcare system [7]. According to two separate studies, one from South Africa and one from Nigeria, caesarean sections are responsible for 12.5% and 25.6% of occurrences of puerperal sepsis, respectively, making them one of the most significant risk factors for the condition. Despite the use of preventative antibiotics, the prevalence of puerperal sepsis has increased. Puerperal sepsis rates are relatively low in different countries, with poorer countries recording higher rates. Puerperal sepsis is common in Asia, with a prevalence of 11.6%, in Africa, with a prevalence of 9.7%, in South America, with a prevalence of 7.7%, and in Caribbean countries with a prevalence of 7.7 [8]. Broad-spectrum parenteral antibiotics are often used as treatment until the patient is afebrile for 24 to 48 hours. Septicemia, endotoxin shock, peritonitis, abscess development, subfertility, and even death are possible maternal outcomes. Low Apgar scores, newborn septicemia, and pneumonia are examples of fetal effects. The use of antibiotics, aseptic measures, and improvements in investigative techniques have all contributed significantly to the decrease in puerperal infections [9].

There is no puerperal sepsis research conducted recently in Larkana, Sindh. There is no local information on the correlation with income, booking condition, and delivery mode that could be used to prevent it directly. Therefore, the objective of the study is to evaluate the association of income level, booking status, and mode of delivery with puerperal sepsis among patients admitted to Shaikh Zaid Women Hospital, Larkana.

METHODS

The analytical cross-sectional study was carried out at the Department of Gynaecology and Obstetrics, Shaikh Zaid Women Hospital, Larkana, during the period April 2024 to December 2024. The ethical approval was taken from Shaheed Mohtarma Benazir Bhutto Medical University with IRB ref no: SMBBMU/ORIC/2024. The 170 patients who were chosen in the study were using a nonprobability consecutive sampling technique and comprised those who had been hospitalized with puerperal sepsis. The sample size was calculated based on the WHO sample size calculator with 95% confidence level, a 12.5% expected population proportion, and a 5% absolute precision requirement. All patients aged between 20 years and 45 years, either multipara or primigravida, and fitting the definition of puerperal sepsis were included in the study. The diabetic and obese patients, immunosuppressed patients, patients with chronic illness, and patients presenting after 42 days of delivery were excluded from the study. One hundred and seventy individuals with puerperal sepsis were made part of this cross-sectional study after obtaining ethical approval from the hospital ethical review committee. Each patient gave their written informed consent after being briefed on the study's methodology. Demographic data were collected from patients' files and integrated for the patient or the attendant, including age, parity, socioeconomic position, and time since delivery, booking status, and mode of delivery. Ages were recorded in years, parity was recorded in numbers, weight was recorded in kilograms, and height was recorded in meters. BMI was calculated from height and weight; however, Age, time since delivery, and parity were further converted to categorical variables in SPSS. The status of the booking was inquired about from the patients while taking their history. Those patients who attended regular visits for assessment of fetal well-being at the antenatal clinic during pregnancy were labelled as booked cases; those cases who didn't attend regular assessment visits were labelled as un-booked cases. Mode of delivery was recorded from the patient's file as SVD (Spontaneous Vaginal Delivery) Instrumental delivery, and Cesarian Section. The Economic level was inquired from the patients and divided into two categories: less than 50000 per month and more than 50000 per month.

The data were entered and analyzed using SPSS version 26.0 for data analysis, while employing the Chi-Square test of association. For the quantitative variables like age, parity, and time since delivery, we used the mean and SD. For the variables like un-booked status and caesarean section patients, which are qualitative variables, the study reported the results in frequency and percentages. The study controlled the effect modifiers while determining the association tests, to evaluate the strength of the association, the Chi-square test was applied, taking p-value<0.050 as significant.

RESULTS

According to the findings of this study, the mean age was 28.96 ± 6.41 years, the mean time since delivery was 22.11 ± 5.68 days, the mean parity was 1.58 ± 0.895, and the mean BMI was 24.51 ± 4.43, as presented in table 1.

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Table 1: Descriptive Statistics of the Study Participants (n=170)

Variables	Min	Max	Mean ±SD	95% CI
Age (Y)	19	44	28.96 ± 6.41	27.99-29.94
Time Since Delivery (days)	4.5	28.5	22.11 ± 5.683	21.25-22.97
Parity	1	4	1.58 ± 0.895	1.45-1.72
Weight	45.5	93	58.34 ± 9.45	56.71-59.22
BMI	19.22	31.67	24.51 ± 4.43	22.87-25.91

In this study, most of the participants, 75 (44.12%), were aged below 25 years, followed by 53 (31.18%) patients aged between 31 years and 45 years. The remaining 42 (24.71%) patients were aged between 26 years and 30 years, as depicted in figure 1.

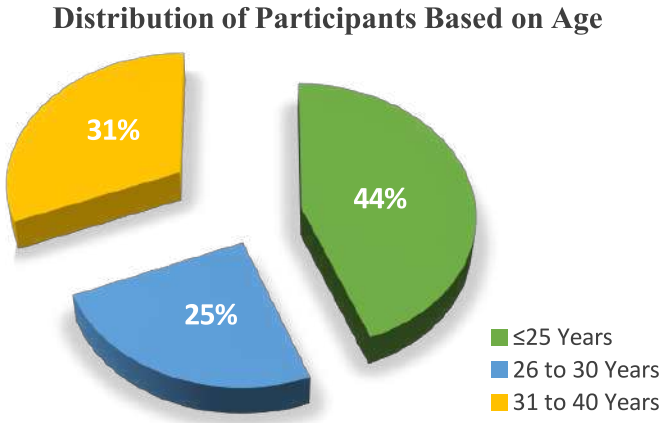

Figure 1: Distribution of Participants Based on Age

Most of the participants were aged below 25 years; 81 (47.65%) patients reported a delay of more than 24 days, followed by 37.06% patients reporting a delay of less than 20%. In this study, 103 (60.59%) patients were primigravida. 81 (47.65%) patients reported a monthly income of less than 30 thousand, as shown in table 2.

Table 2: Distribution of Study Participants Based on Sociodemographic Factors

Study Variables		Frequency (%)
Age Groups	≤25 Years	75 (44.12%)
	26 to 30 Years	42 (24.71%)
	31 to 45 Years	53 (31.18%)
Time Since Delivery (Days)	<15 Days	63 (37.06%)
	15 To 24 Days	26 (15.29%)
	>28 Days	81 (47.65%)
Parity	Primiparity	103 (60.59%)
	Multiparity	67 (39.41%)
Income Level Per (PKR Per Month)	Less than 50,000	81 (47.65%)
	More than 50,000	89 (52.35%)
Status of Booking	Booked	56 (32.9%)
	Un-booked	114 (67.1%)
Mode of Delivery	SVD	57 (33.5%)
	Instrumental Delivery	29 (17.1%)
	Caesarean Sections	84 (49.4%)

The chi-square test of association was employed to evaluate the association of various factors affecting the booking status in patients with puerperal Sepsis. Amongst several variables under the study, only income level showed a significant association (0.018) with booking status among patients reporting with puerperal Sepsis, as shown in Table 3.

Table 3: Chi-Square Association of Various Factors with Status of Booking During Antenatal Period

Factors		No	Booking Status		p-value
			Yes	No	
Age Groups	≤25 Years	75	51 (68%)	24 (32%)	0.380
	26 to 30 Years	42	25 (29.5%)	17 (40.5%)	
	31 to 45 Years	53	30 (56.6%)	23 (43.4%)	
Time Since Delivery (Days)	<15 Days	63	38 (60.3%)	25 (39.7%)	0.890
	15 To 24 Days	26	17 (65.4%)	9 (34.6%)	
	>28 Days	81	51 (63%)	30 (37%)	
Parity	Primiparity	103	64 (62.1%)	39 (37.9%)	0.940
	Multiparity	67	42 (62.7%)	25 (37.3%)	
Income Level Per (PKR Per Month)	Less than 50,000	81	58 (71.6%)	23 (28.4%)	0.018**
	More than 50,000	89	48 (53.9%)	41 (46.1%)	
Mode of Delivery	SVD	57	28 (49.1%)	29 (50.9%)	0.040**
	Instrumental Delivery	29	15 (51.7%)	14 (48.3%)	
	Caesarean Sections	84	25 (29.8%)	59 (70.2%)	

DISCUSSION

The world has 4.4 cases of puerperal sepsis per 100 live babies [10]. The statistics available to the WHO have put puerperal sepsis as the second cause of maternal death in developing countries. One of the studies showed that sepsis is nearly the cause of 15 percent of deaths among mothers in South Asia [11]. Recently WHO was able to designate maternal sepsis as a terrible illness resulting in organ dysfunction, which results in infection throughout pregnancy, intrapartum, post-abortion, and postpartum phases [12]. In case of critical sepsis, failure of the organs, insufficient perfusion of the cells, low blood pressure, and the syndrome of systemic inflammatory response may occur, which is supported by infections [13]. As of our findings in the very study, amongst the women aged between 20years to 40 years, the mean age was 28.96 ± 6.41 years. Most of the women (68%) were aged below 30 years. Nearly 2/5th (39.41%) was multipara, and the rest were primipara. In line with our findings, a study in the same country reported that 83.3% women experiencing puerperal sepsis were aged less than 30 years [11]. Due to a lack of knowledge about health care and financial challenges, instead of giving birth in a medical facility with adequate staff, the young and inexperienced mothers frequently end up in the hands of traditional birth attendants and give birth outside of a facility, increasing the risk for sepsis. According to our research, mothers from lower socioeconomic backgrounds had a much greater rate of puerperal sepsis. Low socioeconomic level

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was found to be a key un-booked factor contributing to puerperal sepsis in our study. The probability of developing sepsis is higher in women with low socioeconomic status, which is in line with recent research results [14]. A different study carried out in Ethiopia established that mothers who have lower family income are likely to develop puerperal sepsis [15]. According to this study, the primiparous mothers are more likely to endure protracted labor and trials in different hands. There is strong evidence of association of puerperal sepsis with prolonged labor among young women with lower parity. According to a study, the risk of developing puerperal sepsis is greater among mothers with fewer than five children, particularly primiparous women. This vulnerability is often attributed to their tendency to experience protracted labour and undergo numerous manual examinations before hospital admission [16]. The most significant contributing factor to puerperal sepsis exhibiting symptoms in 170 individuals was determined to be un-booked cases (62.35%). During the index pregnancy, most of the women in this research had no record of having prenatal care visits. In line with our study conducted in Hoima District, Uganda reported that puerperal sepsis was more frequent among un-booked mothers; the data showed that (64.7%) cases developed puerperal sepsis were un-booked [17]. The importance of early antenatal care (ANC) booking for positive maternal, fetal, and neonatal outcomes is well-established. In contrast, a lack of booking for antenatal care is a significant risk factor associated with elevated fetal and neonatal mortality and morbidity, as well as greater maternal morbidity [18]. Underscoring antenatal care with an equal importance similar to antepartum hemorrhage APH which established predictor of puerperal sepsis among post-natal mothers [19, 20].

Together with all the associated factors discussed in the study, the limited availability of local healthcare infrastructure in remote areas, poverty, poor literacy rate, and cultural practices in Larkana might explain differences from other regional studies. Introduce surveillance systems, focus on low-income/un-booked women, advocate aseptic institutional birth, formulate cesarean infection guidelines, and conduct multicenter studies.

CONCLUSIONS

The present study evaluated the association of multiple factors with puerperal sepsis; it was evident that mode of delivery, booking status, and income level were the most significant variables. Because the mothers from lower socioeconomic backgrounds had a much greater rate of puerperal sepsis, and it's unaffordable for socioeconomically challenged mothers to keep regularly visiting for fetal wellbeing assessment, therefore, provision of accessible antenatal care clinics for poor women is encouraged, which may further minimize the number of un-booked cases too. It will be highly effective to increase the number of experienced delivery attendants, ensure aseptic hospital delivery, and maintain good hygiene following birth, which may reduce the incidence of puerperal sepsis.

Authors' Contribution

Conceptualization: SK
Methodology: SK, SB, RS, SN
Formal analysis: RS, SN, MPS
Writing and Drafting: SK, SB, RS, SHA
Review and Editing: SK, SB, RS, SN, SHA, MPS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Sexual Dysfunction among Female Patients Presenting with Urinary Incontinence

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ABSTRACT

Urinary incontinence can negatively affect women's quality of life, often leading to reduced confidence and sexual dysfunction. Determining its frequency helps guide comprehensive clinical assessment and improve patient-centered management strategies. **Objective:** To determine the frequency of sexual dysfunction among female patients presenting with urinary incontinence. **Methods:** A cross-sectional study was conducted in the Department of Urology, The Indus Hospital, Karachi, Pakistan, from 1st April 2024 to 30th September 2024. This study included 180 sexually active women aged 16–80 years presenting with urinary incontinence. Participants were enrolled using non-probability consecutive sampling. Sexual function was assessed using the Female Sexual Function Index (FSFI), with a score ≤26.55 indicating dysfunction. Demographic data, comorbidities (diabetes, hypertension), and urinary incontinence characteristics (type and duration) were recorded. Data were analyzed using SPSS version 26. Chi-square and Fisher's exact tests were applied, and $p \leq 0.05$ was considered statistically significant. **Results:** Of the 180 participants, 44 (24.4%) had sexual dysfunction, and 136 (75.6%) had normal sexual function. Median age was 46 years, and mean BMI was 31.9 ± 5.8 kg/m^2. Sexual dysfunction showed no significant association with age, BMI, diabetes, hypertension, residence, or type and duration of urinary incontinence. However, FSFI domain scores—including desire, arousal, lubrication, orgasm, satisfaction, and pain were significantly lower among women with sexual dysfunction ($p<0.001$ for all). **Conclusions:** Nearly one-fourth of women with urinary incontinence experienced sexual dysfunction, independent of demographic or comorbid factors. Urinary incontinence adversely affected multiple aspects of sexual health.

INTRODUCTION

Urinary incontinence (UI) is one of the most frequently occurring and troublesome conditions in women all over the world. It plays a major role by affecting health and general well-being, making physical, psychological, and social performance worse [1]. It not only affects the urinary system but also has many other effects, including intimate ones, like sexual functioning, as stated by the International Continence Society (ICS) and the International Urogynecological Association (IUGA). UI is one of the subsets of female pelvic floor dysfunctions, also including fecal incontinence, pelvic organ prolapses, and sexual dysfunction [2]. UI affects different age groups, parity, and comorbid conditions differently, with estimates revealing that 25%-45% percent of adult women experience some type of UI, and higher rates of UI occur among older women or women with more than one child [3]. In Pakistan and other low- to middle-income countries, UI is underreported due to cultural taboos, lack of awareness, and access to medical care; additionally, many women are taught to accept UI as a natural aftermath of delivery or aging and do not seek help [4]. UI may hurt sexual functioning both physically, by causing weakness of the pelvic floor, changes in vaginal sensation, and fear of leakage, as well as psychologically, through embarrassment, low self-perception, anxiety, etc. [5]. Stressful women with UI frequently complain of coital incontinence, which results in

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the prevention of intimacy. Urge UI may result in unpredictability and increased anxiety; hence, urinary and bowel dysfunction are combined, which correlates with increased sexual disability [6, 7]. The new evidence highlights the importance of holistic management of UI, which focuses on sexual health. Pelvic floor muscle training (PFMT) is helpful as a conservative method, and pharmacological interventions, including mirabegron, have been shown to help with continence and sexual functioning [8]. Structured measures of sexual domains are available with validated assessment instruments like the Female Sexual Function Index (FSFI) and PISQ-12 [9, 10]. Although there is more and more global data, there is a relative dearth of research on the prevalence and trends of sexual dysfunction in women with UI in South Asia, where there is a lack of cultural competence and cultural stigma to report it. This study aims to implement culturally competent interventions to improve the quality of life and overall well-being of women with UI.

METHODS

A cross-sectional study in the Department of Urology, The Indus Hospital, Karachi, Pakistan, was carried out after the approvals of the Institutional Review Board and Ethics Review Committee of The Indus Hospital Research Centre (ERC No. IHHN_IRB_2024_02_015). A national research review body reviewed the research protocol and approved it regarding the Declaration of Helsinki. The research was conducted between 1st April 2024 and 30th September 2024 after receiving the consent of the College of Physicians and Surgeons Pakistan (CPSP). All the female patients aged 16 to 80 years who reported to the Outpatient Department of Urology with urinary incontinence were included. Non-probability consecutive sampling was used to recruit the participants. The sample size was estimated using the WHO sample size calculator with a 64.7% prevalence assessment of sexual dysfunction among women with urinary incontinence, which was determined in the literature [11], with a 95% confidence and a 7% margin of error, resulting in a required sample size of 180 participants. The participants had to be eligible to respond to the study questionnaire. Individuals who failed to give consent, had a history of prior pelvic or gynecological surgery, or who had neurogenic bladder, multiple sclerosis, or spinal cord injury affecting voiding were excluded. Pregnant mothers and those with active infections of the urinary tract were also excluded. The data were obtained with informed consent. The questionnaires were given privately in order to maintain confidentiality. A trained female research assistant helped the participant when it was necessary to clarify something, but this did not affect answers. Measures of sexual functioning were conducted by means of the Female Sexual Function Index (FSFI), a validated self-report questionnaire comprising 19 questions in the six domains: sexual desire (2 questions), arousal (4 questions), lubrication (4 questions), orgasm (3 questions), satisfaction (3 questions), and pain (3 questions). All of the domain scores were obtained by adding together the scores of individual items within the domain and multiplying by a domain-specific factor. There was a range of 2-36 in total FSFI score, with the higher the score, the better the sexual functioning. In accordance with the existing literature [12], the FSFI was applied to determine the presence of sexual dysfunction with a total FSFI score of 26.55 or below. Other variables that were gathered were the demographics, nature, and length of urinary incontinence, and comorbid conditions like diabetes mellitus and high blood pressure. Classification of urinary incontinence was made based on standard definitions, which included stress, urge, and mixed urinary incontinence. The principal investigator and trained research personnel were used to collect data. Each participant received an individual study code, and no personal identifiable data were entered.

SPSS version 26.0 was used to do statistical analysis. The Shapiro-Wilk test was used to test the normality of quantitative variables. Appropriate descriptive statistics were applied; frequencies and percentages were used to describe categorical variables, whereas mean and standard deviation were used to describe continuous variables. The stratification was done based on age, duration of symptoms, type of urinary incontinence, and comorbidities. Where necessary, chi-square or Fisher's exact tests were used. The independent sample t-tests are applied to compare the mean FSFI domain scores of women with sexual dysfunction and those without it. A value of $p \leq 0.005$ was regarded as statistically significant.

RESULTS

A total of 180 adult female participants were included. Among them, 44 (24.4%) had sexual dysfunction (FSFI ≤ 21) and 136 (75.6%) had normal sexual function (FSFI > 21). The median age was 46 years, and the mean BMI was 31.9 ± 5.8 kg/m^2. Baseline demographic and clinical characteristics such as age, BMI, diabetes mellitus, hypertension, and residence showed no significant association with sexual dysfunction, as shown in table 1.

Table 1: Baseline Demographic and Clinical Characteristics of Participants (n=180)

Variables	With SD (n=44), Mean ± SD/n (%)	Without SD (n=136), Mean ± SD/n (%)	p-value
Age (Years), median (IQR)	46 (39.3-52)	46.5 (42-52)	0.825
BMI (kg/m^2)	33.7 ± 6.6	32.3 ± 5.5	0.106
Diabetes Mellitus	11 (25.0%)	36 (26.4%)	0.847
Hypertension	11 (25.0%)	35 (25.7%)	0.923
Residence (Urban)	18 (40.9%)	68 (50.0%)	0.294

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Urinary incontinence characteristics, including duration and type, were also not significantly associated with sexual dysfunction. Most participants in both groups had symptoms for ≤1 year, and stress incontinence was the predominant type, as shown in table 2.

Table 2: Association between Type and Duration of Urinary Incontinence and Sexual Dysfunction (n=180)

Variables	With SD (n=44), n (%)	Without SD (n=136), n (%)	p-value
Duration of UI			
≤1 Year	25 (56.8%)	88 (64.7%)	0.190
2–4 Years	18 (40.9%)	38 (27.9%)	
5–7 Years	1 (2.3%)	10 (7.4%)	
Type of UI			
Stress UI	36 (81.8%)	111 (81.6%)	0.952
Mixed UI	8 (18.2%)	22 (16.2%)	
Urge UI	0 (0%)	3 (2.2%)	

Domain-wise comparison of FSFI scores revealed significant differences across all six domains—desire, arousal, lubrication, orgasm, satisfaction, and pain—with lower mean scores in women with sexual dysfunction. The total FSFI score was markedly lower in women with dysfunction, indicating a substantial reduction in overall sexual function, as shown in table 3.

Table 3: Comparison of FSFI Domain Scores between Women with and without Sexual Dysfunction (n=180)

FSFI Domain	With SD (Mean ± SD)	Without SD (Mean ± SD)	p-value
Desire	2.8 ± 0.9	4.6 ± 0.8	<0.001
Arousal	2.6 ± 0.8	4.3 ± 0.7	<0.001
Lubrication	2.4 ± 0.7	4.0 ± 0.6	<0.001
Orgasm	2.5 ± 0.8	4.0 ± 0.7	<0.001
Satisfaction	2.3 ± 0.9	3.8 ± 0.8	<0.001
Pain	2.1 ± 0.8	3.0 ± 0.9	<0.001
Total FSFI Score	16.8 ± 3.2	28.4 ± 4.1	<0.001

DISCUSSION

In the present study, the frequency of sexual dysfunction (SD) among females presenting with urinary incontinence (UI) and its association with various demographic and clinical variables were studied. Almost 1 out of 4 respondents experienced the SD, findings said. The UI and SD are interrelated entities of female pelvic floor disorders. The current study provides useful local data from Pakistan that may help in strengthening the case for a one-stop-shop approach to female urological disorders [13]. Our study findings corroborate these findings. Women suffering from UI scored significantly lower across all domains of sexual function than those without SD. The occurrence of SD in this study (24.4%) is similar to that which is reported in the literature across the world, which ranges from 20% to 70%, depending on the methodology and the study population [14]. In another study conducted at a tertiary hospital, a comparable frequency was observed among women with incontinence. A population-based study also noted that UI was an independent risk factor for female sexual dysfunction. Thus, there is a considerable burden of SD on women with UI, and it is important to routinely assess the sexual life of these women [15]. In the present study, SD was not significantly associated with demographic variables like age, BMI, diabetes, hypertension, or area of residence. A variety of studies done earlier have reported mixed findings. Some studies have shown an age-related decline of sexual function; however, others, including this one, have reported no such outcome. This difference can arise due to other popular demographics, views on sexuality, and openness to disclose sexual issues [16]. In the same way, although diabetes and hypertension harm blood vessels and nerves (and may cause some SD), they didn't matter so much in this group, presumably because they were well controlled [17]. There was also no significant association between UI type and duration with SD. Participants predominantly experienced stress incontinence but had similar sexual outcomes whether they experienced stress or mixed incontinence. This is consistent with recent findings from tertiary-care studies, reporting that SD occurs regardless of incontinence subtype [18]. The FSFI domains mainly impacted in our population were desire, arousal, lubrication, and orgasm, suggesting psychogenic and physiological mechanisms. The muscles that hold everything in your body are often weak if your libido and lubrication are reduced. Hormonal effects or the fear of wetting yourself may also make you not feel competent and smart. The marked drop in orgasm and satisfaction suggests emotional distress as well as physical discomfort in sensation. Compared with larger epidemiological datasets, women who wet themselves did not engage as frequently in sex and had less satisfaction than those who did not wet themselves [19]. The mechanisms linking UI and SD are multifactorial. Chronic pelvic floor muscle problems may affect blood flow and sensory feedback to the genitals and result in arousal and orgasm problems [13]. In addition, repeated infections, recurrent medication, or pelvic pain may promote sexual avoidance. Expressing problematic bladder symptoms, especially, has been connected to greater rates of dyspareunia and reduced sexual interest. But earlier data implies treatment of bladder symptoms can lead to a considerable improvement in sexual function [20]. Therapeutic methods like pelvic floor muscle training and behavioral therapy have shown benefits on continence and sexual outcomes. Pharmacologic agents similarly exert variable effects on sexual health. Cultural and social factors also play a crucial role in SD prevalence perception and reporting. In conservative societies like Pakistan, it is a

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taboo to talk about sexual issues because of stigma, shame, and a low level of sexual health literacy [21]. The strengths of the study were the use of FSFI questionnaires, which were validated, the average sample size, and systematic data collection.

However, some limitations should be noted. You cannot make a causal inference between UI and SD because of the cross-sectional design being a single-center study; the results cannot be generalized to all. Also, depression, anxiety, marital satisfaction, medication, and others were potential confounders that were not assessed. Even with these limitations, this research gives vital clinical evidence signaling that urological practice must think about sexual health.

CONCLUSIONS

This study demonstrates that sexual dysfunction is a common comorbidity among women presenting with urinary incontinence, significantly affecting multiple domains of sexual function. The absence of significant associations with age, BMI, comorbidities, and incontinence type indicates that the relationship is complex, multifactorial, and primarily driven by the physiological and psychological burden of UI. A multidisciplinary, patient-centered approach involving urologists, gynecologists, and psychosexual counselors is essential to improve both continence and sexual health outcomes. Integrating sexual health screening into UI management can enhance overall quality of life and promote comprehensive women's health.

Authors' Contribution

Conceptualization: MH[1]
Methodology: MH[1], SY, AJ, MH[2], ZK
Formal analysis: MH[1]
Writing and Drafting: MH[1], SY, AJ, MH[2], ZK
Review and Editing: MH[1], SY, AJ, MH[2], ZK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Association of TCF7L2 rs7903146 TT Genotype with Dyslipidemia in Type 2 Diabetes: A Case–Control Study in Pakistani Patients

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ABSTRACT

Type 2 diabetes is often accompanied by dyslipidemia, which markedly increases cardiovascular risk. Genetic factors, particularly the TCF7L2 rs7903146 variant, have been implicated in alterations in glucose and lipid metabolism in T2DM. **Objectives:** To assess the association between dyslipidemia and the TCF7L2 rs7903146 polymorphism in patients with T2DM as compared to healthy controls. **Methods:** In Karachi, Pakistan, 100 T2DM patients and 100 age- and sex-matched healthy controls participated in case-control research. Blood samples obtained during fasting were examined for cholesterol and glucose levels. PCR-RFLP was used to genotype TCF7L2 rs7903146, and sequencing was used to confirm the results. Associations ($p<0.050$) were assessed using logistic regression and ANOVA. **Results:** TT genotype and T allele frequencies were greater in T2DM patients than in controls ($p<0.010$). Hence, genotype carriers had significantly higher triglycerides, total cholesterol, and LDL-C levels, and lower HDL-C levels. Multivariate logistic regression demonstrated that the TT genotype independently predicted dyslipidemia. **Conclusions:** The TCF7L2 rs7903146 TT genotype is strongly associated with dyslipidemia in T2DM patients and may assist in risk stratification and personalized management planning.

INTRODUCTION

The prevalence of type 2 diabetes mellitus is rising at the fastest pace, making it a serious and quickly spreading global public health concern [1]. Chronic hyperglycemia is the most common feature of this metabolic disease [2]. Since dyslipidemia is nearly always present in glucose homeostasis, cardiovascular morbidity and mortality are markedly increased in this population [3]. Lipid abnormalities are linked to diabetes directly [4]. Increased release of fatty acids in adipose tissue, combined with decreased lipoprotein lipase activity and increased hepatic triglyceride production result in a dyslipidemia phenotype of T2DM because of insulin resistance [5, 6]. The gene TCF7L2 is one of the strongest and most effective genetic risk factors for type 2 diabetes in most of the ethnic groups belonging to various populations [6]. It helps in the metabolism of lipids along with the regulation of glucose [7]. The rs7903146 single-nucleotide polymorphism (C→T) has been associated with impaired insulin secretion and

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altered glucose homeostasis [7, 8]. According to a variety of studies, TCF7L2 variations may affect adipocyte differentiation, lipoprotein remodeling, and post-prandial triglyceride responses through the Wnt/β-catenin pathway. For example, in an Asian Indian cohort, T-allele carriers of rs7903146 exhibited significantly higher post-prandial glucose, higher HOMA-IR, and peak triglyceride response compared to non-carriers [6]. Hence, in South Asian people, type 2 diabetes was more common in earlier stages of life, and these people have more chances to develop dyslipidemia, which is again a greater risk factor for macrovascular disease [8]. In Pakistan and other neighboring nations, the early development and rapid progression of type 2 diabetes are frequently linked to the severe dyslipidemia phenotype and elevated cardiovascular risk [9]. Thus, from a clinical and public health perspective, it is extremely pertinent to look at genetic modifiers of lipid abnormalities, such as TCF7L2 polymorphisms, in the context of South Asian diabetes. Several investigations in populations with non-diabetes or mixed metabolic syndrome have discovered associations between TCF7L2 risk alleles and lipid variables, such as triglycerides or HDL-C, although the evidence is still limited and often conflicting [10]. Hence, individual polymorphism with dyslipidemia in Pakistani T2DM patients, controlling for the effects of age, sex, BMI, and duration of diabetes.

Pakistan does not have multi-ethnic genetic information on TCF7L2, and there are no mechanistic or intervention studies among the carriers of the TT genotype. The effects that are gender specific are not studied. Small single-centers restrict generalizability. Cross-sectional design prevents causality, results may be biased by unmeasured confounders, and functional validation of results is hampered by a lack of clinical translation. This study aims to assess the relationship of TCF7L2 rs7903146 individual polymorphism with dyslipidemia in Pakistani T2DM patients, controlling for the effects of age, sex, BMI, and duration of diabetes.

METHODS

The case-control study was done from January 2023 to December 2024 in the Department of Pharmacology and Molecular Biology Laboratory, Baqai Medical University and Hospital, Karachi, Pakistan. Informed Consent was taken from all the participants, and the institutional Review Board (BMU-EC/02-2020-04(OL)) approved the study protocol. The sample of this study consisted of 100 clinically diagnosed T2DM patients and 100 age- and sex-healthy matched controls without any history of diabetes or lipid disorders. The exclusion criteria included type 1 diabetes, liver or kidney disease, pregnancy, and other endocrine disorders. The 100 cases and 100 controls offered a power of more than 80 percent to discover genotype-associated variations in dyslipidemia at α = 0.05. Demographic data, family history, lifestyle, medication history, and diabetes duration were obtained using structured questionnaires. BMI was then calculated with the anthropometric measurements of height and weight used. Each participant was allowed to fast for 10-12 hours, and 5ml venous blood sample was gathered to undergo biochemical and molecular analyses. An automated clinical chemistry analyzer (Roche Cobas 311) was used to measure the fasting levels of glucose and lipids. Dyslipidemia was determined based on the criteria of the American Diabetes Association (ADA 2023): total cholesterol -200 mg/dL, triglycerides -150 mg/dL, LDL-C -100, and HDL-C <40 in men and women, respectively. The Qiagen QIAamp DNA Blood Mini Kit was used according to the instructions provided by the manufacturer to extract the genomic DNA from the EDTA blood samples. Genotyping The TCF7L2 (rs7903146 C> T) polymorphism was genotyped by polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP). The following primers were used in PCR in a Bio-Rad T100 Thermal Cycler: Forward: 5'-GGTGAAGTCTGTGAGAGTGC-3'. Reverse: 5'-AGTGCTGTTGAAGTTGAAGC-3'. PCR conditions: at 95°C for 30s for almost 35 cycles, 58°C for 30 s, 72°C for 30 s, and for 5 min at 72°C. PCR products were digested with Rsal restriction enzyme at 37C 2h and separated on 2% agarose gel stained with ethidium bromide. Genotypes (CC, CT, TT) were identified by the genotype patterns, and again, a 10 percent sample was re-genotyped, and the other 10 percent sequenced using Applied Biosystems 3500 Genetic Analyzer, with 100% concordance. Allele and genotype frequencies were determined by direct counting. Allele frequency was determined as the percentage of the number of times the allele appears within the total population of the study. Genotype frequency represents the percentage of those who have a given genotype. The chi-square (kh2) test was used to compare genotype frequencies in the control with the expected frequencies in the Hardy-Weinberg equilibrium (HWE) to determine the consistency of the population.

For analyzing the data, SPSS version 26.0 was used. An independent samples t-test (or nonparametric equivalents where applicable) was done to compare groups. To determine the homogeneity of variance of ANOVA, the Levene test was done. ANOVA was employed to determine the relationships between genotypes and lipid levels, and multivariate logistic regression was employed to correct the possible confounders. Hence, $p<0.005$ was considered a significant value.

RESULTS

The mean age of T2DM patients was 52.6, and that of controls was 51.9 ($p=0.540$). There was an equal number of

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males and females. T2DM patients had much higher BMI, systolic blood pressure, fasting glucose, and HbA1c levels as compared to the controls (Table 1).

Table 1: Clinical and Demographic Characteristics

Variables	T2DM (n=100)	Controls (n=100)	p-value
Age	52.6 ± 8.3	51.9 ± 7.9	0.540
Gender Ratio of Male: Female	1.2:1	1.1:1	0.720
BMI (kg/m^2)	28.4 ± 3.7	25.6 ± 3.2	0.001*
Systolic BP (mmHg)	134.2 ± 11.5	124.8 ± 9.3	0.003*
Fasting glucose (mg/dL)	158.6 ± 36.4	91.7 ± 12.8	<0.001*
HbA1c (%)	7.8 ± 1.1	5.4 ± 0.6	<0.001*

The diabetic group had significantly higher mean levels of LDL-C, triglycerides, and total cholesterol than the control group. On the other hand, individuals with diabetes had lower HDL-C levels (Table 2).

Table 2: Comparison of T2DM Patients and Controls Lipid Profiles

Parameters	T2DM Patients	Controls	p-value
Total Cholesterol (mg/dL)	213.5 ± 32.6	178.4 ± 28.3	<0.001*
Triglycerides (mg/dL)	192.8 ± 40.2	136.5 ± 31.9	<0.001*
HDL-C (mg/dL)	39.6 ± 6.5	48.1 ± 7.1	<0.001*
LDL-C (mg/dL)	131.7 ± 28.7	104.3 ± 24.1	<0.001*

HWE of the genotype distribution of the control of rs7903146 was also in Hardy Weinberg (2 = 0.46; p=0.500). Total genotype distribution was not the same between the two groups (cases and controls) (2 = 12.2; p=0.002). The TT genotype dominated in T2DM (28% vs 10%), and the T allele frequency of T2DM patients was higher (46% vs 27.5%; p=0.004) (Table 3).

Table 3: The arrangement of Genotype and Allele

Genotype/Allele	T2DM (n=100)	Controls (n=100)	χ^2	p-value
CC	36 (36%)	55 (55%)	12.2	0.002*
CT	36 (36%)	35 (35%)	–	–
TT	28 (28%)	10 (10%)	–	–
C allele	108 (54%)	145 (72.5%)	7.9	0.004*
T allele	92 (46%)	55 (27.5%)	–	–

Statistically significant at p<0.050

To understand whether the TCF7L2 polymorphism TCF7L2 rs7903146 would affect lipid levels in patients with diabetes, the latter were divided into various genotypes. Carriers of the TT genotype showed considerably higher LDL-C, triglyceride, and total cholesterol than carriers of the CC or CT genotype. The lowest levels of HDL-C were found in carriers of the TT genotype, and this could raise the possibility of a genetic component in lipid metabolism (Table 4).

Table 4: Lipid Levels by Genotype

Lipid Parameters	CC	CT	TT	p-value
Total Cholesterol	205.8 ± 29.1	216.2 ± 33.8	232.5 ± 31.4	0.018*
Triglycerides	181.6 ± 37.4	194.9 ± 39.2	211.8 ± 42.1	0.022*
HDL-C	41.2 ± 6.7	39.6 ± 5.9	36.9 ± 6.3	0.016*
LDL-C	122.6 ± 27.2	134.8 ± 28.5	145.7 ± 30.3	0.012*

In multivariate logistic regression analysis, age, sex, BMI, and diabetes duration were used to adjust the results, and TT genotype was found to be an important independent predictor of dyslipidemia (adjusted OR 2.93; 95% CI 1.36-6.29; p=0.005) and BMI was also found to be an important independent predictor (adjusted OR 1.15; 95% CI 1.05-127; p=0.002) (Table 5).

Table 5: Logistic Regression of Risk of Dyslipidemia

Variables	Adjusted OR	95% CI	p-value
CT vs CC	1.48	0.71–3.07	0.290
TT vs CC	2.93	1.36–6.29	0.005*
Age	1.02	0.98–1.06	0.210
BMI	1.15	1.05–1.27	0.002*
Duration of Diabetes	1.04	0.97–1.11	0.320

DISCUSSION

In Karachi, Pakistan, this case-control study indicated that this polymorphism contributes to both the dysregulation of lipid metabolism and the risk of diabetes; the TCF7L2 rs7903146 (C→T) variant was found to be significantly associated with abnormal lipid profiles [11]. Hence, the growing body of evidence shows that TCF7L2 is necessary to preserve lipid and glucose homeostasis [12]. In this study, diabetic patients with the TT genotype had lower HDL-cholesterol values and higher levels of total cholesterol, LDL-cholesterol, and triglycerides than those with the CC genotype [13, 14]. A crucial modulator of the Wnt signaling system that regulates the production of insulin, proliferation of pancreatic β-cells, and lipid metabolism of the hepatic system, transcription factor 7-like 2 is encoded by the gene [15]. Therefore, changes in this gene that affect the transcription of metabolic targets may result in resistance to insulin and subsequent dyslipidemia. The variant TCF7L2 rs7903146 is one of the most potent genetic predictors of type 2 diabetes in several populations worldwide [16]. The polymorphism TCF7L2 has a complex effect on lipid levels. Alterations in Wnt signaling have been proposed to promote fatty acid synthesis and inhibit hepatic lipid oxidation, which raises blood levels of triglycerides and LDL cholesterol [17]. Alterations in TCF7L2 can also lead to changes in insulin signaling, which can lower HDL cholesterol and lipoprotein lipase activity [18]. A study conducted in KSA revealed that for type 2 diabetes susceptibility polymorphism is a good indicator as it has less effect on lipid levels after adjusting

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for factors like body mass index and insulin resistance [19]. Further, the results of the study revealed that the T allele of females is strongly linked with dyslipidemia as compared to males [20]. The site of adipose tissue or the hormonal control of lipid metabolism may be the cause of this gender disparity [21]. Dyslipidemia may therefore be more common in female diabetic patients with the TCF7L2 risk mutation due to a combination of genetic predisposition and gender-specific metabolic responses. Therefore, it is crucial that genetic testing be used to treat type 2 diabetes from a public health perspective. Therefore, in addition to functional evaluations and demographic coverage, more multicentric research should be carried out.

A consistent sample and a thorough laboratory analysis were two drawbacks of the study. Although the sample size is sufficient to identify associations, it could not accurately reflect the heterogeneous Pakistani population. Future studies should examine the potential of TCF7L2-targeted therapies to reduce diabetic dyslipidemia and extend to larger, multiethnic groups.

CONCLUSIONS

TCF7L2 rs7903146 TT genotype is closely linked to dyslipidemia in Pakistani (T2DM) patients. Carriers of the TT genotype had 28% of T2DM patients and 10% of controls, and the T allele frequency was much more prevalent in the patients (46% vs 27.5; p=0.004). People who were carriers of the TT genotype carried much more triglycerides, total cholesterol, and LDL-C with low levels of HDL-C than people who carried the CC or CT genotype. Multivariate logistic regression established that the TT genotype was an independent predictor of dyslipidemia (adjusted OR 2.93; 95% CI 1.36-6.29; p=0.005) even after age, sex, BMI, and diabetes duration were controlled. These findings suggest that the TCF7L2 rs7903146 variant is also linked with impaired lipid metabolism in T2DM and could be used to determine patients at increased risk of cardiovascular complications, which has substantiated the application of personal metabolic risk evaluation and genetic screening in the management of diabetes.

Authors' Contribution

Conceptualization: SA
Methodology: SA, SMF, ZK, SAM
Formal analysis: SMF, FKT
Writing and Drafting: SA, MKS
Review and Editing: SA, SMF, ZK, FKT, SAM, MKS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Knowledge, Beliefs, and Perceptions among Alopecia Areata Patients: A Cross-Sectional Study in CMH Kharian

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ABSTRACT

Alopecia areata (AA) is an autoimmune condition, which is associated with hair loss that has a strong negative effect on the psychological and social well-being of patients. **Objective:** To determine the knowledge, beliefs, and perceptions of the patients with Alopecia Areata at CMH Kharian. **Methods:** This was a cross-sectional study that was carried out in 84 patients with alopecia areata. A structured questionnaire was used to collect demographic information, medical history, information on AA, beliefs, perceptions, coping strategies, and expectations of treatment. Associations between variables were determined using statistical procedures such as chi-square tests. **Results:** The mean age was 30.5 ± 11.4 years having females (59.5%) dominant. The main bulk, 45.2% of the patients, presented with symptoms of alopecia for less than one year. The majority of the patients (78.6%) were already aware of AA before being diagnosed. A large percentage of them considered that AA was hereditary (59.5%) and that stress was a contributing factor (73.8%). Chi-square tests showed significant relationships between educational level and the assumptions concerning the hereditary nature of AA ($p=0.037$) and perceived seriousness or effects on daily life ($p = 0.008$). Fifty-six (66.7%) patients agreed that the treatment had affected mental health, and half 42 (50.0%) of the patients had a view that with treatment, they would get complete hair regrowth. **Conclusions:** Comprehensive medical and psychosocial support techniques are essential in order to improve the quality of life for patients and address the psychosocial aspects related to alopecia areata.

INTRODUCTION

Alopecia areata (AA) is a long-term, immune-mediated condition that causes hair loss without scars. It affects people of all ages and genders, with varying degrees of severity. Although the exact pathology of the illness is yet unknown, it is thought to be polygenetic, polyetiological, autoimmune, and environmental. Alopecia areata is a disease that has enormous psychosocial implications since it manifests physically; many patients experience severe distress about the symptoms. Patients' perceptions and beliefs about the condition are important in managing the disease because numerous studies demonstrate that the body image changes caused by AA include social anxiety, low self-esteem, and a decreased quality of life [1, 2]. The start and progression of Alopecia areata are attributed to numerous environmental, immunological, psychological, and genetic risk factors, making it a complex disease. Additionally, it may be linked to other illnesses. The spectrum of clinical manifestations can include patchy hair loss from the head, various body regions, or total hair loss from the entire body, with each patient's course being inconsistent and random. Although it can happen at any age, the majority of research suggests

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that it happens between the ages of 20 and 30 [3]. Assessment of the knowledge, attitudes, and perceptions of people with alopecia areata enables both effective patient treatment and the development of educational programs customized to the patient's needs. It is well-established that people's perceptions of a particular disease can have an impact on their attitudes towards symptoms, treatment compliance, and how they use medical services. Alopecia areata may be perceived by some as a transient or persistent condition that impacts their mental well-being and compliance with treatment [4]. Secondly, cultural and social values, especially the perception of hair loss in relation to stigma, continue to influence patients' attitudes and greatly affect the management of alopecia areata [5]. Multiple studies have assessed the psychological implications of Alopecia areata, but just a few focused on patients' awareness and understanding of the disease; no comparable research has been carried out locally in Pakistan. Some of the studies have focused on how these individuals' beliefs about their disease and medical treatment are influenced by societal factors. The purpose of this study was to evaluate patients' perspectives of Alopecia areata, their perspectives on the disease's aetiology, treatment options, and outcomes, as well as their basic level of knowledge of the disease, all of which could be very helpful to healthcare professionals [6, 7]. The variable pattern of remission and relapses in alopecia areata is another reason that makes it conceptually difficult. Knowledge-related challenges include the stigmatization of the disease as well as worries about hair loss or the disease's relationship with other serious medical conditions, which lead to patient frustration and noncompliance with the recommended method of therapy [8, 9]. The exploration of knowledge, belief, and perception of the Alopecia Areata patients will be important for the healthcare providers, which should lead to dispelling myths and misconceptions, more effective information for patients, which will help in improving patients' quality of life [10].

Despite the several studies that have determined the psychological effects and clinical features of Alopecia areata, few studies have specifically investigated the knowledge, beliefs, and perceptions of patients, especially in the Pakistani context. The majority of existing evidence is based on the populations of the West or the Middle East, where the sociocultural factors and the health literacy rates are significantly different than those in South Asia. Furthermore, the connection between educational level and misconceptions concerning the disease, and what patients expect when receiving treatment are not sufficiently investigated in the local context. Without these context-specific data, the management strategies can be largely biomedical in nature, and they will not be effective in tackling psychosocial determinants that affect treatment compliance and coping behavior, and overall quality of life. Thus, the aim of this study is systematically assess the knowledge, beliefs, and perceptions of patients with alopecia areata at CMH Kharian to determine current misconceptions and gaps in education and to create evidence that can potentially inform more holistic, patient-centered management strategies.

METHODS

This cross-sectional study was conducted after taking approval from the Ethical Committee/Institutional Review Board, bearing no. A/24/07. Patients diagnosed with alopecia areata visiting the department of dermatology, Combined Military Hospital (CMH), Kharian, were selected for the study sample. All the research works were in line with the ethical standards of the institutional review board of CMH Kharian. The study was conducted over a period of eight months from March 2024 to October 2024. All the participants were briefly informed about the study, and informed written consent was taken before data were collected. The inclusion criteria were: patients over 18 years of age diagnosed with alopecia areata and willingness to give informed consent. Any other type of hair loss or any patient undergoing treatment for diseases that can predispose him/her to hair loss was not included. The sample size was estimated from the WHO sample size calculator with the help of 95% confidence level, a prevalence of alopecia areata (anticipated population proportion) of 2%, total absolute precision required 3%; the final number found to be 84 patients. Data were collected through a structured questionnaire designed for this study. The proforma was developed by the researcher based on previous studies and was verified by two specialty experts of consultant level. The researcher herself filled out the Performa forms for all patients. This proforma comprises information regarding socio-demographics, past medical history, psychosocial history: Alopecia areata knowledge and attitude, body image and perceived stigma, coping strategies, and treatment anticipation. The pilot test of the questionnaire was administered to 10 patients to check on the refinement and adequacy of the preparation of the final questionnaire to increase validity and reliability. The validity and reliability of the proforma were tested with Cronbach Alfa which showed a value of > 0.76.

All the data were entered and analyzed using Statistical Package for the Social Sciences (SPSS version 25.0). Descriptive statistics summarized the demographic and clinical characteristics of the participants, with mean ± SD for quantitative variables, and frequencies and percentages were calculated for categorical variables. Chi-square tests were used to measure relationships between

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different demographic variables and the knowledge, beliefs, and perceptions. A p<0.005 was taken as statistically significant.

RESULTS

A total of 84 patients diagnosed with Alopecia areata, having a mean age of 30.5 ± 11.4 years, were included in the study. The demographic breakdown revealed that 50 patients (59.5%) were females and 34 (40.5%) were males. In terms of educational level, 10 patients (11.9%), 22 (26.2%), 30 (35.7%), and 16 (19.0%) had obtained primary education, secondary education, higher secondary education, and graduates and postgraduate qualifications, respectively. In the study sample, 40 (47.6%) of the patients were single, 32 (38.1%) were married, and 8 (9.5%) were divorced (Table 1).

Table 1: Demographics of Alopecia Areata Patients

Characteristic	Frequency (%)
Gender	
Female	50 (59.5%)
Male	34 (40.5%)
Age of the patient	
Mean ± SD	30.5 ± 11.4
Educational Level	
Primary	10 (11.9%)
Secondary	22 (26.2%)
Higher Secondary	30 (35.7%)
Graduate	16 (19%)
Postgraduate	6 (7.1%)
Marital Status	
Single	40 (47.6%)
Married	32 (38.1%)
Divorced/Widowed	12 (14.3%)

The majority, 38 (45.2 %) of the patients had symptoms less than one year of duration, 26 (31.0 %) between 1 and 3 years, 10 (11.9 %) between 3 and 5 years, and 10 (11.9 %) more than 5 years. Family history of Alopecia areata, diabetes, hypertension, and thyroid disease was noted in 18 (21.4%), 10 (11.9%), 6 (7.1%), and 4 (4.8%) patients, respectively. Treatment history showed that 32 (38.1%) patients were still under medication, 28 (33.3%) were not currently using any treatment, and 24 (28.6%) had previously received treatment (Table 2).

Table 2: Duration of Alopecia Areata and Medical History

Characteristic	Frequency (%)
Duration of Alopecia Areata	
< 1 year	38 (45.2%)
1-3 years	26 (31%)
3-5 years	10 (11.9%)
> 5 years	10 (11.9%)
Family History of Alopecia Areata	
Yes	18 (21.4%)
No	66 (78.6%)
Other Medical Conditions	
Diabetes	10 (11.9%)
Hypertension	6 (7.1%)
Thyroid Disease	4 (4.8%)
None	64 (76.2%)
Total	84 (100%)

The majority of patients, 66 (78.6%), reported having heard of the condition before diagnosis. The primary sources of information were doctors for 40 (47.6%) patients, the internet for 22 (26.2%) patients, family or friends for 18 (21.4%) patients, and social media for 4 (4.8%) patients. Regarding beliefs about Alopecia areata, 50 (59.5%) patients considered it hereditary, while 6 (7.1%) thought it was contagious. Furthermore, 36 patients (42.9%) believed alopecia areata could be cured, while 28 (33.3%) thought it could not be cured, and 20 (23.8%) were unsure (Table 3).

Table 3: Knowledge and Beliefs about Alopecia Areata

Characteristic	Frequency (%)
Heard of Alopecia Areata	
Yes	66 (78.6%)
No	18 (21.4%)
Source of Information	
Doctor	40 (47.6%)
Internet	22 (26.2%)
Family/Friends	18 (21.4%)
Social Media	4 (4.8%)
Beliefs about Cause	
Hereditary	50 (59.5%)
Contagious	6 (7.1%)
Hormonal Disorder	0 (0%)
Unknown Cause	28 (33.3%)
Belief in Cure	
Yes	36 (42.9%)
No	28 (33.3%)
Don't Know	20 (23.8%)
Total	84 (100%)

When assessing beliefs and perceptions about the condition, 62 patients (73.8%) believed stress was a contributing factor to Alopecia areata, while 12 (14.3%) disagreed and 10 (11.9%) were unsure. Moreover, 54 patients (64.3%) considered alopecia areata as a severe disease. There was also a significant correlation between the level of education and the opinion that alopecia areata is a hereditary condition (p=0.037) (Table 4). A large number, 56 (66.7 %) of the patients noted that their mental health was affected by the condition, and 52 (61.9 %) patients said that their daily life activities were affected by the disease. A significant relationship was found between perceived seriousness of the condition and its impact on daily life activities (p=0.008). According to the results for coping mechanisms, it was observed that 40 patients

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(47.6%) reported using wigs, hairpieces, or other cosmetic measures to manage their appearance. In terms of treatment expectations, 42 patients (50%) hoped for complete hair regrowth, 30 (35.7%) thought partial improvement, and 12 (14.3%) had no expectations regarding treatment outcomes. Most of the patients (59.5%) believed that the condition was hereditary, and 64.3% of the respondents were of the opinion that the condition was severe. Chi-square analysis revealed a significant relationship between the educational level and the belief in the hereditary nature of AA (χ^2=10.24, p=0.037), and perceived seriousness and their effects on daily life (χ^2=9.67, p=0.008)(Table 4).

Table 4: Perceptions, Coping Mechanisms, and Chi-Square Test Results

Characteristic	Frequency (%)
Contributing Factor	
Stress	62 (73.8%)
Genetics	50 (59.5%)
Mental Health Impact	56 (66.7%)
Impact on Daily Life	52 (61.9%)
Hormonal Imbalance	30 (35.74%)
Coping Mechanisms Employed	
Use of Wigs/Hairpieces	40 (47.6%)
No use for Anything Practically	44 (52.4%)
Expectations from Treatment	
Complete Hair Regrowth	42 (50%)
Partial Improvement	30 (35.7%)
No Expectations	12 (14.3%)
Chi-Square Test Results	
Educational Level vs. Hereditary Belief	χ^2=10.24 (p=0.037)
Seriousness vs. Daily Life Impact	χ^2=9.67 (p=0.008)

DISCUSSION

Alopecia areata is an autoimmune condition characterized by hair loss that can have significant psychological impacts on affected individuals. In this present study, it was observed that alopecia areata was higher among the young adults, as the mean age was 30.5 ± 11.4 years. The female-to-male ratio was approximately 1.5:1, as described by prior researches like in a study by Lundin *et al.* which recorded a female-to-male ratio of 2.3:1 that indicated a higher rate in females as compared to males, Rasul *et al.* also had similar findings [11, 12]. The patients enrolled in the study sample were on a higher side with respect to educational status. More than half, i.e., 54.7% participants received at least higher secondary education; and a main bulk, 19% of them completed tertiary level education. This finding is consistent with the studies showing that health literacy and the ability to receive information about some diseases may be affected by education level [13]. The overwhelming majority, 78.6% of the patients, claimed that they knew about alopecia areata before the diagnosis, and in 47.6% patients' doctors were the main source of this knowledge. Similar findings were observed by Almulhim *et al.* who found that the majority of patients were aware of AA's seriousness, curability, and impact on quality of life, with healthcare providers serving as the primary source of knowledge (52.8%) [14]. This also supports the significant role of educating and supporting patients by healthcare professionals [15]. From this perspective, the reliance of patients on the internet as a source of information is also seen as a requirement of trustworthy information sources, which can help patients understand their circumstances [16]. Regarding the participants' knowledge about the causative factors of Alopecia areata, a substantial number, 59.5% of the participants, believed that the condition runs in the family, consistent with literature showing a genetic element to autoimmune diseases [17]. However, 11% of the respondents still believed that alopecia areata is an infectious disease, which underscores a general requirement of patient awareness on the accurate status of their diseases. Malik *et al.* observed an even higher rate of this perception, at 28% [18]. It was also perceived that there is a potential cure, which is again an important belief for patients to have regarding their treatment and is crucial for mental health stability [19]. The study also provides further evidence that stress is considered by many patients to be a causative factor of Alopecia areata, a view supported by other studies, which show that psychological stress is associated with the development or worsening of autoimmune responses [20]. The fact that a huge number of participants recognized the severity of the condition proves that hair loss can create serious psychological pressure because many patients with alopecia areata experience high levels of anxiety and depression. Patients who consider themselves to have a severe form of the disease are more likely to have bigger changes in the quality of life and mental health, which confirms the need for psychosocial interventions in the treatment plan [21]. Different coping mechanisms were used by the participants; although the majority sought professional assistance, some looked for social support. In order to better understand how alopecia areata influences patients and their lifestyles, the self-care practices of the patients were also monitored, with a focus on wigs and hairpieces. This finding is in concordance with previous literature, which has shown that patients with alopecia areata are inclined to seek esthetic outcomes in addressing the disease [22]. Moreover, the fact that nearly half of the participants were ready to consider the experimental treatment means that there is a continuous need for research and clinical trials to investigate new therapies and cure possibilities in detail [23].

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The study is a cross-sectional study with a relatively small sample size conducted in one center, which restricts the generalizability of the results. Self-reported questionnaires could have brought about response bias, and because of the study design, causal relationships cannot be drawn. It is suggested that future multicenter and longitudinal research with larger samples should prove these results and assess the effect of structured psychoeducational interventions on adherence to treatment and quality of life.

CONCLUSIONS

The majority of the patients in the study had prior knowledge of alopecia through doctors or through the internet, but common misconceptions about the disease's causes and treatment persisted. Stress and heredity remained major factors; over 50% of the patients claimed they had experienced a decline in their mental health. It was evident that most of the patients diagnosed with alopecia areata mentioned having mental health problems, burdens, or concerns, and the necessity of effective treatment approaches was identified. The results justify the necessity of a bio-psychoeducational model of alopecia areata treatment, which requires more than pharmacologic and dermatologic treatment of the disorder; it involves counseling and the creation of awareness in individuals with such a disease.

Authors' Contribution

Conceptualization: SS
Methodology: SS, AS
Formal analysis: AHM, FM, WN, MB
Writing and Drafting: SS, AHM, FM, MB
Review and Editing: SS, AHM, FM, AS, WN, MB

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Frequency of Iron Deficiency Anemia in Children Presenting with Febrile Seizures at Hayatabad Medical Complex, Peshawar: A Cross-Sectional Study

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ABSTRACT

Febrile seizures are the most common seizure disorder in early childhood. Iron deficiency anemia has been proposed as a potential risk factor due to iron's role in neuronal metabolism and neurotransmitter synthesis; however, evidence remains inconsistent, particularly in populations with a high burden of infection. **Objective:** To determine the frequency of iron deficiency anemia among children presenting with febrile seizures. **Methods:** This cross-sectional study was conducted in the Department of Pediatrics, Hayatabad Medical Complex, over six months. A total of 103 children aged 6–60 months presenting with simple febrile seizures were enrolled through consecutive sampling. Demographic and clinical data were recorded. Laboratory evaluation included complete blood count, serum ferritin, serum iron, total iron-binding capacity, transferrin saturation, and CRP. Anemia was defined as hemoglobin <11 g/dL, and iron deficiency anemia as anemia with serum ferritin <15 ng/mL. Data were analyzed using SPSS version 26.0. **Results:** The mean age was 35.47 ± 15.78 months. Anemia was present in 39 (37.9%) children, while iron deficiency anemia was identified in 6 (5.8%). Children with IDA had significantly lower hemoglobin and serum ferritin levels compared to non-IDA children (p=0.001). No significant associations were observed between IDA and demographic or clinical variables. **Conclusions:** Anemia was common among children with febrile seizures, whereas iron deficiency anemia was infrequent when defined strictly by low ferritin. Given the influence of inflammation on ferritin levels, reliance on ferritin alone may underestimate iron deficiency. Incorporating transferrin saturation and inflammatory markers may improve diagnostic accuracy.

INTRODUCTION

Febrile seizures are the most common seizure disorder of early childhood, affecting approximately 2–5% of children worldwide and typically occurring between 6 and 60 months of age [1]. They are associated with fever in the absence of central nervous system infection or underlying epilepsy [2]. Although generally benign, their recurrence and potential impact on neurodevelopment have prompted continued investigation into modifiable risk factors [3]. Iron deficiency anemia is the most prevalent nutritional deficiency globally, particularly in low- and middle-income countries [4]. Iron plays a critical role in neuronal energy metabolism, myelination, and neurotransmitter synthesis [3]. Deficiency may lower seizure threshold by altering dopaminergic and gamma-aminobutyric acid (GABA) pathways, providing a plausible biological link between iron deficiency and febrile seizures [5]. Several regional and international studies have reported higher frequencies of iron deficiency or iron deficiency anemia among children

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with febrile seizures compared to controls [6]. However, reported prevalence varies widely, largely due to differences in diagnostic criteria and laboratory thresholds [7]. Serum ferritin, the most commonly used marker of iron stores, is an acute-phase reactant and may be elevated during febrile or infectious illnesses, potentially masking underlying iron deficiency [8].

In Pakistan, data on iron deficiency anemia among children with febrile seizures are limited and inconsistent, despite a high burden of childhood anemia and infectious diseases. Local evidence incorporating inflammatory markers is therefore, essential to improve diagnostic accuracy and guide clinical screening. This study aimed to determine the frequency of iron deficiency anemia among children presenting with febrile seizures at a tertiary-care hospital in Peshawar.

METHODS

The study was a cross-sectional study carried out in the Department of Pediatrics, Hayatabad Medical Complex (HMC) in Peshawar, a teaching, a tertiary-care teaching hospital that serves a large pediatric population from both urban and peri-urban areas of Peshawar. A single-center design was adopted to ensure uniformity of clinical assessment, laboratory procedures, and data collection protocols [9], as well as feasibility within the defined study period. The study was conducted over six months, from 4 July 2024 to 4 January 2025. Consecutive enrollment of eligible children presenting to the Department of Pediatric Emergency or Pediatric Ward with febrile seizures was undertaken. Ethical approval for the study was obtained from the Research and Ethics Committee of the College of Physicians and Surgeons Pakistan (CPSP), Islamabad (Reference No. CPSP/REU/PED-2022-021-7261). The IRB ref no was 1823. Written informed consent was obtained from parents or legal guardians prior to enrollment. All study procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki [10]. The sample size was calculated using the World Health Organization (WHO) sample size calculator [11] for prevalence studies, based on the formula: $n = Z^2 \times p(1 - p) / d^2$, assuming an expected prevalence of iron deficiency anemia of 30% [12], a 95% confidence level ($Z = 1.96$), and an absolute precision of 9%. This yielded a minimum required sample size of 100 participants. To compensate for potential incomplete laboratory data, an additional 3% was added, resulting in a final target sample size of 103 children, which was successfully achieved. A non-probability consecutive sampling technique was employed, whereby all eligible children presenting during the study period were approached for inclusion. Children aged 6-60 months presenting with simple febrile seizures, defined as generalized tonic-clonic seizures associated with fever (≥38°C), lasting less than 15 minutes, and not recurring within 24 hours, were included. Children with a prior diagnosis of epilepsy or other neurological disorders were excluded. Exclusion criteria comprised complex febrile seizures, known epilepsy, neurodevelopmental delay, central nervous system infections, metabolic disorders, chronic systemic illnesses, hemoglobinopathies, iron supplementation within the preceding three months, recent blood transfusion, acute blood loss, or incomplete laboratory data. Data were collected using a structured proforma specifically developed for this study [7], which included demographic variables (age, gender, weight), clinical variables (duration of fever, seizure duration, first or recurrent episode, family history of febrile seizures, and source of infection), and laboratory parameters. The proforma was pretested on 10 children before formal data collection to assess clarity, completeness, and feasibility, and minor modifications were made accordingly. Anthropometric measurements were obtained using standardized techniques, and nutritional status was assessed using weight-for-age criteria. Venous blood samples were collected under aseptic conditions for complete blood count, serum ferritin, serum iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), and C-reactive protein (CRP). All laboratory analyses were performed using calibrated automated analyzers at the central pathology laboratory of Hayatabad Medical Complex, with internal quality control measures in place. Upon presentation, children were stabilized according to standard pediatric protocols. Demographic and clinical data were recorded following consent. Body temperature was measured using a digital thermometer, and seizure duration was documented based on caregiver history and clinical records. Blood samples were obtained within 24 hours of admission to minimize temporal variability in iron indices related to acute illness. Anemia was defined according to WHO criteria as hemoglobin <11 g/dL. Iron deficiency anemia was defined as the presence of anemia in combination with serum ferritin <15 ng/mL. Given that serum ferritin is an acute-phase reactant, transferrin saturation was additionally measured to aid interpretation of iron status in the presence of inflammation, and CRP was used to assess inflammatory activity [13]. Anemia severity was categorized as mild, moderate, or severe based on standard hemoglobin thresholds [14].

Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS), version 26.0. Normality of continuous variables was assessed using the Shapiro–Wilk test. Variables with normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were summarized using median and interquartile range. Categorical variables were presented as frequencies and percentages. Associations

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between iron deficiency anemia and categorical variables were analyzed using the Chi-square test, with Fisher's Exact Test applied when expected cell counts were less than five. Comparisons of hematological and iron parameters between iron deficiency anemia and non-iron deficiency anemia groups were performed using the Mann–Whitney U test due to non-normal data distribution. A p-value <0.005 was considered statistically significant.

RESULTS

A total of 103 children aged 6–60 months presenting with simple febrile seizures were included. The mean age was 35.47 ± 15.78 months, with a female predominance (53.4%), giving a male-to-female ratio of 0.87:1. Most children belonged to the 25–60 months age group (71.8%). The mean body weight was 12.54 ± 3.01 kg, and more than half of the participants (54.4%) were classified as underweight based on weight-for-age criteria. Additionally, the mean temperature at presentation was 39.26 ± 0.46°C. Fever duration of ≥24 hours before seizure onset was observed in 80.6% of children. Seizure duration most commonly ranged between 5–10 minutes (46.6%), followed by 10–15 minutes (34.0%). Recurrent febrile seizures were reported in 51.5% of children, and a positive family history of febrile seizures was present in 50.5%. Upper respiratory tract infection and otitis media were the most frequent sources of infection (Table 1).

Table 1: Demographic Characteristics and Fever and Seizure Profile of Children with Febrile Seizures (n=103)

Variables	Category / Summary	n (%) / Mean ± SD
Demographic Characteristics		
Age (Months)	Mean ± SD	35.47 ± 15.78
	6–12 Months	11 (10.7%)
	13–24 Months	18 (17.5%)
	25–60 Months	74 (71.8%)
Gender	Male	48 (46.6%)
	Female	55 (53.4%)
Weight (kg)	Mean ± SD	12.54 ± 3.01
Nutritional Status	Underweight	56 (54.4%)
	Normal	47 (45.6%)
Fever and Seizure Profile		
Temperature at Presentation (°C)	Mean ± SD	39.12 ± 0.68
Duration of Fever	<24 Hours	20 (19.4%)
	≥24 Hours	83 (80.6%)
Seizure Duration (Minutes)	<5	20 (19.4%)
	5–10	48 (46.6%)
	10–15	35 (34.0%)
First Episode	Yes	50 (48.5%)
	No (recurrent)	53 (51.5%)
Family History of Febrile Seizures	Yes	52 (50.5%)
	No	51 (49.5%)
Source of Infection	URTI	18 (17.5%)
	Gastroenteritis	14 (13.6%)
	Otitis media	18 (17.5%)
	Pneumonia	17 (16.5%)
	UTI	16 (15.5%)
	Others	20 (19.4%)

The mean hemoglobin concentration was 11.32 ± 1.36 g/dL. Mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were 73.50 ± 4.87 fL and 24.11 ± 2.37 pg, respectively, while red cell distribution width (RDW) was elevated (16.68 ± 2.03%). The mean serum ferritin level was 24.79 ± 11.28 ng/mL, the mean serum iron was 56.16 ± 16.90 µg/dL, and the mean transferrin saturation was 14.46 ± 4.84%. Raised C-reactive protein (CRP) levels were observed in 46.6% of children, indicating a high inflammatory burden in this febrile cohort. Given that serum ferritin is an acute-phase reactant, serum ferritin levels were compared between children with normal and raised CRP levels using the Mann–Whitney U test. Children with elevated CRP had slightly higher mean ranks for ferritin than those with normal CRP; however, this difference was not statistically significant (U = 1242.0, Z = −0.516, p=0.606), indicating that inflammation did not significantly influence ferritin levels in this cohort (Table 2).

Table 2: Hematological and Iron Parameters of Children with Febrile Seizures and Effect of Inflammation on Serum Ferritin Levels (n=103)

Parameters	Mean ± SD	Reference / Cut-off	n	Mean Rank	Mann–Whitney U	Z-value	p-value
Hematological and Iron Parameters							
Hemoglobin (g/dL)	11.32 ± 1.36	Anemia: <11	–	–	–	–	–
MCV (fL)	73.50 ± 4.87	Low if <75	–	–	–	–	–
MCH (pg)	24.11 ± 2.37	Low if <24	–	–	–	–	–
RDW (%)	16.68 ± 2.03	High if >14.5	–	–	–	–	–
Serum ferritin (ng/mL)	24.79 ± 11.28	Low if <15	–	–	–	–	–
Serum iron (µg/dL)	56.16 ± 16.90	Low if <50	–	–	–	–	–
TIBC (µg/dL)	395.40 ± 47.45	High if >360	–	–	–	–	–
Transferrin saturation (%)	14.46 ± 4.84	Low if <16	–	–	–	–	–
Effect of Inflammation on Serum Ferritin Levels							
CRP Status	Normal	55 (53.4%)	55	50.58	1242.0	−0.516	0.606
	Raised	48 (46.6%)	48	53.63			

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Anemia (hemoglobin <11 g/dL) was identified in 39 children (37.9%). Among these, 18 (17.5%) had mild anemia, and 21 (20.4%) had moderate anemia, while no cases of severe anemia were observed. Using the study's predefined criteria (anemia with serum ferritin <15 ng/mL), iron deficiency anemia was diagnosed in 6 children (5.8%) (Table 3).

Table 3: Frequency of Anemia and Iron Deficiency Anemia (n=103)

Variables	Category	n (%)
Anemia (WHO Cut-Off)	Yes	39 (37.9%)
	No	64 (62.1%)
Severity of Anemia	Mild	18 (17.5%)
	Moderate	21 (20.4%)
	Severe	0 (0.0%)
Iron Deficiency Anemia (IDA)	Yes	6 (5.8%)
	No	97 (94.2%)

The association between iron deficiency anemia and selected demographic and clinical variables was assessed. No statistically significant associations were found with age group, gender, nutritional status, seizure recurrence, family history of febrile seizures, or fever duration (all p>0.005). However, only six children fulfilled the criteria for iron deficiency anemia, resulting in very low statistical power for subgroup comparisons. Therefore, the absence of statistically significant associations should be interpreted cautiously and may reflect insufficient sample size rather than a true lack of relationship (Table 4).

Table 4: Association of Iron Deficiency Anemia with Selected Demographic and Clinical Factors (n=103)

Variables	Category	IDA Present, n (%)	IDA Absent, n (%)	χ^2 value	p-value
Age Group	6–12 months	1 (9.1%)	10 (90.9%)	1.444	0.486
	13–24 months	0 (0.0%)	18 (100.0%)		
	25–60 months	5 (6.8%)	69 (93.2%)		
Gender	Male	3 (6.3%)	45 (93.8%)	0.030	0.863
	Female	3 (5.5%)	52 (94.5%)		
Nutritional Status	Underweight	3 (5.4%)	53 (94.6%)	0.049	0.825
	Normal	3 (6.4%)	44 (93.6%)		
Seizure Episode	First episode	3 (6.0%)	47 (94.0%)	0.005	0.941
	Recurrent	3 (5.7%)	50 (94.3%)		
Family History	Yes	3 (5.8%)	49 (94.2%)	0.001	0.980
	No	3 (5.9%)	48 (94.1%)		
Fever Duration	<24 hours	2 (10.0%)	18 (90.0%)	0.789	0.375
	≥24 hours	4 (4.8%)	79 (95.2%)		

Chi-square test was applied; Fisher's Exact Test was used where expected cell counts were <5. Due to the small number of children with iron deficiency anemia (n = 6), subgroup comparisons are underpowered, and results should be interpreted cautiously. A p-value <0.005 was considered statistically significant

Normality testing using the Shapiro–Wilk test demonstrated that hemoglobin, MCV, MCH, RDW, serum ferritin, serum iron, TIBC, and transferrin saturation were not normally distributed (p<0.005); therefore, non-parametric tests were applied. Children with iron deficiency anemia had significantly lower hemoglobin and serum ferritin levels compared to non-IDA children (both p=0.001). No statistically significant differences were observed for MCV, MCH, RDW, serum iron, TIBC, or transferrin saturation (Table 5).

Table 5: Comparison of Hematological and Iron Parameters Between IDA and Non-IDA Groups (n=103)

Parameters	IDA Present (n=6) Median (IQR)	IDA Absent (n=97) Median (IQR)	Mann–Whitney U	p-value
Hemoglobin (g/dL)	9.40 (0.78)	11.60 (1.80)	58.5	0.001
MCV (fL)	76.25 (8.88)	73.20 (8.20)	214.5	0.281
MCH (pg)	24.15 (4.70)	24.00 (4.20)	279.0	0.866
RDW (%)	18.75 (3.25)	16.70 (3.85)	189.5	0.153
Serum Ferritin (ng/mL)	11.40 (5.95)	25.30 (18.80)	65.0	0.001
Serum Iron (µg/dL)	64.15 (31.63)	56.10 (28.80)	253.0	0.593
TIBC (µg/dL)	398.40 (90.95)	395.90 (84.70)	271.5	0.784
Transferrin Saturation (%)	16.90 (10.93)	14.10 (7.70)	263.5	0.699

Mann–Whitney U (non-parametric). Values are presented as Median (IQR); p<0.005 is considered significant

DISCUSSION

Febrile seizures remain the most common seizure disorder in early childhood, and the potential contribution of iron deficiency to seizure susceptibility continues to generate debate. In the present study, anemia was identified in 37.9% of children presenting with simple febrile seizures, whereas iron deficiency anemia (IDA), defined strictly as hemoglobin <11 g/dL with serum ferritin <15 ng/mL, was observed in only 5.8% of cases. These findings suggest that while anemia is common in febrile seizure patients, only a small proportion meet stringent biochemical criteria for IDA when ferritin-based definitions are applied during acute illness. Several recent international studies have reported higher frequencies of iron deficiency or IDA among children with febrile seizures than observed in our cohort. A systematic review and meta-analysis by Sulviani *et al.* concluded that iron deficiency and anemia were significantly associated with increased susceptibility to febrile seizures [15]. Similarly, Bakkannavar *et al.* reported consistent associations across multiple datasets, highlighting iron deficiency as a modifiable risk factor [14]. Case-control studies from India and Bangladesh have also demonstrated higher IDA prevalence among febrile seizure cases compared with controls [6, 16]. In contrast to these reports, our observed IDA frequency (5.8%) is substantially lower. Within Pakistan, Awais *et al.* and Nargis *et al.* documented higher proportions of iron deficiency anemia among children with febrile seizures [17, 18]. Hussain *et al.* [12]. Similarly, a stronger association between IDA and febrile seizures in a case-control design. The discrepancy between our findings and these regional reports may be

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explained by differences in study design and diagnostic criteria. Many prior studies relied primarily on hemoglobin levels or ferritin alone without incorporating inflammatory markers. In our study, CRP was measured to evaluate inflammatory burden, and ferritin interpretation was considered in this context. Given that 46.6% of children had elevated CRP, ferritin values may have been influenced by acute-phase responses, potentially masking iron deficiency at the individual level. Ferritin is a well-recognized acute-phase reactant, and its elevation during infection can obscure underlying iron deficiency, as described by Lee [5] and Weiss *et al.* [13]. Although ferritin levels did not differ significantly between CRP strata in our cohort (p=0.606), this does not exclude misclassification at the individual level. Acute inflammation may maintain ferritin within normal range despite depleted iron stores. Therefore, reliance on ferritin alone may underestimate the true prevalence of iron deficiency in febrile children. This study's finding of a mean transferrin saturation (TSAT) of 14.46%, below commonly accepted normal thresholds, further supports the possibility of functional or early iron deficiency not captured by strict ferritin criteria. The high prevalence of underweight children (54.4%) in our cohort also reflects underlying nutritional vulnerability. However, the coexistence of undernutrition and low ferritin-defined IDA suggests that anemia in this population may be multifactorial, including contributions from inflammation, recurrent infections, and other micronutrient deficiencies. Camaschella emphasizes that iron deficiency exists along a biological continuum, and early or functional deficiency may precede overt ferritin decline. This may partly explain why overall anemia was common (37.9%) while strict IDA frequency remained low [19]. Importantly, no statistically significant associations were observed between IDA and age, gender, nutritional status, seizure recurrence, or fever duration. However, only six children fulfilled IDA criteria, substantially limiting statistical power. The absence of association should therefore be interpreted cautiously. Studies with larger IDA subgroups, such as those by Mandal *et al.* and Jadhav *et al.* were able to detect stronger relationships, likely due to greater case numbers and comparative control groups [6, 8]. An important clinical implication arises from the study by Sharawat et al. which demonstrated reduced recurrence of febrile seizures with prophylactic iron supplementation [20]. Even if strict ferritin-defined IDA is infrequent, early identification and correction of iron deficiency may still influence seizure recurrence risk. Therefore, broader diagnostic strategies incorporating TSAT and inflammation-adjusted ferritin thresholds may provide a more clinically relevant assessment. Overall, our findings contribute to the ongoing debate by suggesting that strict ferritin-based definitions during acute febrile illness may underestimate iron deficiency prevalence. The variability across studies likely reflects differences in biomarker selection, timing of sampling, inflammatory burden, and regional nutritional patterns.

This study has several limitations. First, it was conducted at a single tertiary-care center, which may limit generalizability to other populations with different socioeconomic and nutritional profiles. Second, the cross-sectional design precludes causal inference between iron deficiency and febrile seizures. Third, the small number of IDA cases (n=6) reduced statistical power for subgroup analyses. Fourth, iron indices were measured during acute febrile illness, when inflammatory responses may influence ferritin interpretation despite CRP assessment. Finally, advanced biomarkers such as soluble transferrin receptor or post-recovery reassessment of iron status were not available. Future multicenter studies with larger sample sizes should employ composite definitions of iron deficiency incorporating ferritin, transferrin saturation, and inflammation-adjusted thresholds. Longitudinal designs evaluating iron status after recovery from acute illness would improve diagnostic accuracy. Randomized trials assessing whether iron supplementation reduces recurrence of febrile seizures in iron-deficient children are also warranted. Incorporating soluble transferrin receptor measurement may further refine differentiation between anemia of inflammation and true iron deficiency in febrile populations.

CONCLUSIONS

Anemia was common among children presenting with febrile seizures; however, iron deficiency anemia was infrequent when defined strictly by low ferritin in the presence of anemia. Despite the low prevalence of IDA, affected children demonstrated significantly lower hemoglobin and ferritin levels. Given that ferritin is an acute-phase reactant and may be elevated during infection, reliance on ferritin alone may underestimate true iron deficiency. Incorporating inflammation-adjusted diagnostic criteria and transferrin saturation into routine assessment may improve the detection of iron deficiency in febrile seizure patients. Further studies using standardized and composite definitions of iron deficiency are warranted to clarify its true prevalence and clinical relevance in this population.

Authors' Contribution

Conceptualization: MUS
Methodology: MUS, JK
Formal analysis: MS, WA
Writing and Drafting: MUS, MS, AH, AA, WA, JK
Review and Editing: MUS, MS, AH, AA, WA, JK

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Association of Blood Baseline Parameters with Alpha-Fetoprotein and Its Importance as a Prognostic Factor in Intrahepatic Ductal Carcinoma Patients: An Analytical Cross-Sectional Study

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ABSTRACT

Intrahepatic Ductal Carcinoma (IHDC), a subtype of cholangiocarcinoma, is an aggressive liver cancer with a poor prognosis and rising global incidence. Although Alpha-Fetoprotein (AFP) is a common tumor biomarker, its prognostic value in IHDC is limited when used alone. **Objectives:** To determine the association between AFP and blood baseline parameters to evaluate their combined prognostic significance in patients with IHDC. **Methods:** This analytical cross-sectional study was conducted at MINAR Cancer Hospital, Multan, Pakistan, from January 2019 to December 2020. A total of 107 histologically confirmed IHDC patients (61 males, 46 females; mean age = 56.8 ± 11.2 years) were included. CBC, LFTs, and serum creatinine were analyzed using standard automated methods, while AFP was measured via electro-chemiluminescence immunoassay (ECLIA). Data were analyzed using SPSS version 24.0. **Results:** Significant gender-based differences were found in eosinophil counts ($p = 0.041$) and serum creatinine ($p = 0.024$). Elderly patients (≥60 years) showed higher monocytes ($p=0.030$) and Mean Platelet Volume ($p=0.002$). Across tumor stages, neutrophils increased (66.8% → 78.2%, $p<0.001$), lymphocytes decreased (25.1% → 18.5%, $p < 0.001$), and ALP and bilirubin rose significantly ($p = 0.021$; $p=0.008$). AFP correlated positively with ALP ($r=0.85$), SGOT ($r=0.79$), bilirubin ($r=0.86$), serum creatinine ($r=0.99$), and blood urea ($r=0.98$), and negatively with lymphocytes ($r = -0.83$). **Conclusions:** AFP was associated with hepatic, renal, and inflammatory parameters in IHDC, suggesting its potential as a composite biomarker for staging and prognosis.

INTRODUCTION

Liver cancer is among the most common and deadliest malignancies occurring all over the world, as it is the third most common cause of cancer deaths globally. The GLOBOCAN 2022 estimates that liver cancer has more than 905,000 new cases and 830,000 deaths each year, making it a serious issue of global health concern [1]. Intrahepatic ductal carcinoma (IHDC), a subtype of cholangiocarcinoma, has gained growing clinical interest because of its

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aggressive pathophysiology, complicated diagnosis, and unfavorable prognosis [2]. IHDC is a complication of the epithelial cells of the intrahepatic biliary ducts that normally occurs at an advanced stage and thus limits the treatment modalities and survival rates [3]. The world has witnessed a significant increase in IHDC cases in the last thirty years, with 165 percent reported in the United States only. This has been observed to be similar in trends in Japan, the United Kingdom, and various areas in Europe, which demonstrates a shift in epidemiology across the globe [4]. The etiology of IHDC is multifactorial, and it includes chronic inflammation of the biliary tract, liver cirrhosis and fibrosis, viral hepatitis (especially hepatitis B and C), and exposure to environmental toxins [5]. Liver cancer is an emerging societal burden in Pakistan. The estimates presented by the Pakistan Medical Research Council and WHO show that liver cancer is among the five leading malignancies in the country [6]. The high rate of hepatitis B and C infections, extensive liver fibrosis, and inaccessibility to screening programs play a major role in the increased incidence of hepatocellular carcinoma (HCC) and IHDC [7]. Investigations conducted at tertiary care hospitals in Karachi, Lahore, and Islamabad have already shown that cholangiocarcinoma is occurring at an accelerating rate, and thus necessitating the implementation of superior prognostic and diagnostic methods [8, 9]. IHDC has no specific clinical manifestations but rather vague symptoms, including pain in the abdomen, jaundice, weight loss, and fatigue, thus making it difficult to diagnose. Alpha-Fetoprotein (AFP), Liver Function Tests (LFTs), and Serum Creatinine are also some of the extensively researched biochemical markers that could be used in the diagnosis and prognosis of the disease. High AFP concentrations are typically found in hepatobiliary tumors such as IHDC, and these levels indicate aggressiveness of the tumor, lack of differentiation, and high-stage disease [10]. But AFP is not sensitive and specific enough to be used as an independent marker. Thus, the integration of AFP with other biochemical and hematological data, including Complete Blood Count (CBC) indices, LFTs, and serum creatinine, can be a more accurate predictive model [11]. Recent studies in the world indicate that the deviations in the factors of the CBC, such as high red cell distribution width (RDW), changed platelet count, and high neutrophil-to-lymphocyte ratio (NLR), are linked to worse survival rates in IHDC [12]. Equally, high alkaline phosphatase (ALP), bilirubin, and AST/ALT ratios on LFTs are associated with obstruction of the bile ducts, hepatic dysfunction, and tumor load. Though serum creatinine is a classical indication of renal function, it can also signify systemic use and metabolic stress in liver malignancies [13]. Although there are limited studies that have evaluated the prognostic power of AFP, CBC, LFTs, and serum creatinine integrated in Pakistani IHDC patients, the predisposing conditions of the hepatic are highly prevalent [14].

Despite the recognized role of alpha-fetoprotein (AFP) in liver malignancies, limited data exist on its relationship with baseline hematological, hepatic, and renal parameters in intrahepatic ductal carcinoma (IHDC) patients. This gap hampers the understanding of AFP's prognostic potential when integrated with routine blood and biochemical markers. Therefore, the present study aimed to evaluate the association of serum AFP with CBC, liver function, and renal indices, and to explore its utility as a prognostic factor in relation to tumor stage and grade in IHDC patients.

METHODS

A descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Mohtarma Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur, AJ and K, after taking the ethical approval (REF. NO 10/Academic Block Trauma centre/Surgery/2025) from February 2025 to August 2025. The sample size was 151, keeping the frequency of HELLP syndrome in thrombocytopenia patients as 11% based on a previous study, confidence level being 95%, and margin of error 5% under the WHO sample size calculation formula [8]. All the patients were enrolled by using a consecutive sampling technique, all women having age of 18-40 years with singleton pregnancy and women with thrombocytopenia were included in this study and the bleeding disorder other than thrombocytopenia on medical records and history, already taking antihypertensive medication on history, diabetes mellitus, HIV on history and medical records and multiple pregnancies on ultrasound were excluded. All the pregnant women who met the inclusion criteria were invited to take part in the study and were admitted to the ward following OPD inclusion. All the patients were informed about the purpose and benefits of the study and assured that the study is conducted with the sole purpose of research and publication of data, and given a written informed consent in case they agreed. After taking a complete history and baseline investigation, a 5ml blood sample was obtained and sent to the laboratory to confirm thrombocytopenia. The level of thrombocytopenia was defined based on the number of platelets in the body as mild (100150 ×10 09/L), moderate (5099 ×10 09/L), and severe (50 09/L) [11]. After confirmation, women and neonates were followed till delivery to detect preeclampsia, HELLP syndrome, placental abruption, preterm birth, and low birth weight. Preeclampsia had been categorized as new-onset hypertension (140/90mmHg or higher on two occasions

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after 20 weeks of pregnancy) with proteinuria (300 mg/24h or above) or end-organ dysfunction. The HELLP syndrome was diagnosed on the grounds of hemolysis, increased liver enzymes, and reduced platelet count. Preterm birth entailed a birth that was less than 37 weeks of gestational age. Low birth weight was considered as a birth weight of the neonate that was less than 2500 g, irrespective of gestational age [12]. All the above-mentioned information was recorded on a pre-designed proforma.

Data analysis was done with the help of SPSS software (version 25.0). All continuous variables like age, BMI, platelet count, and gestational age were shown as mean ± standard deviation (SD), and categorical variables like preeclampsia, placental abruption, HELLP syndrome, preterm birth, and low birth weight were presented as frequency and percentage. Fetomaternal outcome was stratified according to the severity of thrombocytopenia. After stratification, the chi-square test/Fisher Exact test was considered a P value ≤ 0.005 as significant.

RESULTS

A total of 107 patients diagnosed with IHDC were analyzed. Participants' ages ranged from 39 to 76 years (mean ± SD=56.8 ± 11.2 years). Of these, 61 (57%) were male, and 46 (43%) were female (Table 1).

Table 1: Baseline Characteristics of IHDC Patients (n=107)

Variables	Categories	Frequency (%)	Mean ± SD
Age (Years)	–	–	56.8 ± 11.2
	< 60 years	64 (59.8%)	–
	≥ 60 years	43 (40.2%)	–
Gender	Male	61 (57.0%)	–
	Female	46 (43.0%)	–
Tumor Grade	II	38 (35.5%)	–
	III	45 (42.1%)	–
	IV	24 (22.4%)	–
Cancer Stage	II	29 (27.1%)	–
	III	48 (44.9%)	–
	IV	30 (28.0%)	–

Gender-based comparisons revealed significant differences in eosinophil counts (p=0.041) and serum creatinine levels (p=0.024), with males exhibiting slightly higher mean values. Among geriatric patients, Mean Platelet Volume (MPV) (p=0.002) and monocyte count (p=0.030) differed significantly from those of younger patients (Table 2).

Table 2: Comparison of Hematological and Biochemical Parameters by Gender and Age Group

Parameters	Male (Mean ± SD)	Female (Mean ± SD)	p-value[a]	<60 years (Mean ± SD)	≥60 years (Mean ± SD)	p-value[a]
Neutrophils (%)	72.1 ± 9.6	70.4 ± 8.8	0.281[a]	71.5 ± 8.9	72.9 ± 9.3	0.468[a]
Lymphocytes (%)	21.4 ± 7.5	22.2 ± 6.9	0.573[a]	22.8 ± 7.0	20.5 ± 7.6	0.152[a]
Monocytes (%)	5.1 ± 1.3	5.3 ± 1.4	0.417[a]	4.8 ± 1.2	5.7 ± 1.5	0.030*[a]
Eosinophils (%)	3.9 ± 1.5	2.8 ± 1.3	0.041*[a]	3.1 ± 1.4	3.6 ± 1.7	0.209[a]
Platelets ($\times 10^9$/L)	246.8 ± 75.5	258.2 ± 79.1	0.482[a]	250.6 ± 70.4	254.9 ± 83.7	0.714[a]
MPV (fL)	9.6 ± 1.1	9.8 ± 1.2	0.364[a]	9.2 ± 0.9	10.3 ± 1.0	0.002*[a]
ALP (U/L)	283.7 ± 95.2	275.1 ± 88.3	0.643[a]	278.6 ± 92.4	281.9 ± 94.7	0.827[a]
Serum Creatinine (mg/dL)	1.28 ± 0.34	1.09 ± 0.29	0.024*[a]	1.19 ± 0.33	1.22 ± 0.31	0.574[a]

[a]Independent sample Student's t-test
*Statistically significant at p<0.005

Significant changes in neutrophil, lymphocyte, and ALP levels were observed across cancer stages and grades. Patients with stage IV disease showed markedly elevated neutrophil counts (p<0.001) and ALP levels (p=0.021) compared to lower stages. Similarly, lymphopenia was more pronounced in advanced stages and higher grades (Table 3).

Table 3: Comparison of Hematological and Biochemical Markers Across Tumor Stage and Grade

Parameters	Stage II	Stage III	Stage IV	p-value[b]	Grade II	Grade III	Grade IV	p-value[b]
Neutrophils	66.8 ± 8.1	72.4 ± 7.5	78.2 ± 9.0	<0.001*[b]	68.7 ± 8.3	73.6 ± 8.0	77.9 ± 9.1	0.030*[b]
Lymphocytes (%)	25.1 ± 6.4	21.3 ± 6.7	18.5 ± 7.1	<0.001*[b]	24.2 ± 6.3	21.1 ± 6.9	18.7 ± 7.0	0.032*[b]
ALP (U/L)	255.6 ± 82.5	282.3 ± 90.7	315.8 ± 98.4	0.021*[b]	248.4 ± 77.2	286.6 ± 91.5	309.3 ± 94.1	0.063[b]
Bilirubin (mg/dL)	1.2 ± 0.4	1.5 ± 0.5	1.9 ± 0.7	0.008*[b]	1.3 ± 0.4	1.5 ± 0.5	1.8 ± 0.6	0.016*[b]

[b]One-way ANOVA
*Statistically significant at p<0.005

Correlation analyses using Pearson's and Spearman's coefficients showed distinct relationships between AFP and several laboratory markers. While no significant correlations were observed with CBC parameters in gender or age subgroups, several associations emerged when stratified by tumor grade and stage. Stage II: AFP correlated strongly with RDW-CV (r=0.91, p=0.03). Stage IV: AFP correlated significantly with platelet count (r=0.56, p=0.010) and plateletcrit (r=0.58, p=0.020).

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Grade II: Strong correlations were found with WBC (r=0.82, p=0.02) and neutrophils (r=0.88, p=0.010). Grade IV: AFP correlated negatively with lymphocytes (r = –0.83, p=0.030) and positively with ALP (r=0.85, p=0.020), (serum glutamic-oxaloacetic transaminase) SGOT (r=0.79, p=0.030), and bilirubin (r=0.86, p=0.020) (Table 4).

Table 4: Correlation of AFP with Hematological and Biochemical Parameters

Parameters	r-value	p-value[c]
WBC	0.82	0.020*[c]
RDW-CV	0.91	0.030*[c]
Platelets	0.56	0.010*[c]
PCT	0.58	0.020*[c]
Neutrophils	0.88	0.010*[c]
Lymphocytes	–0.83	0.030*[c]
ALP	0.85	0.020*[c]
SGOT	0.47	0.030*[c]
Bilirubin	0.52	<0.001*[c]
Blood Urea	0.98	<0.001*[c]
Serum Creatinine	0.99	<0.001*[c]

[c]Pearson correlation coefficient
*Statistically significant at p<0.005

ROC analysis demonstrated that AFP had an area under the curve (AUC) of 0.76 (95% CI: 0.67–0.84, p < 0.001) for predicting advanced-stage IHDC (Figure 1). At an optimal cutoff value of 220 ng/mL, AFP showed a sensitivity of 72% and specificity of 65% (Table 5).

Table 5: ROC Analysis of AFP for Predicting Advanced-Stage IHDC

Variable	AUC	95% CI	Cutoff	Sensitivity	Specificity	p-value
AFP	0.76	0.67–0.84	220 ng/mL	72%	65%	<0.001*

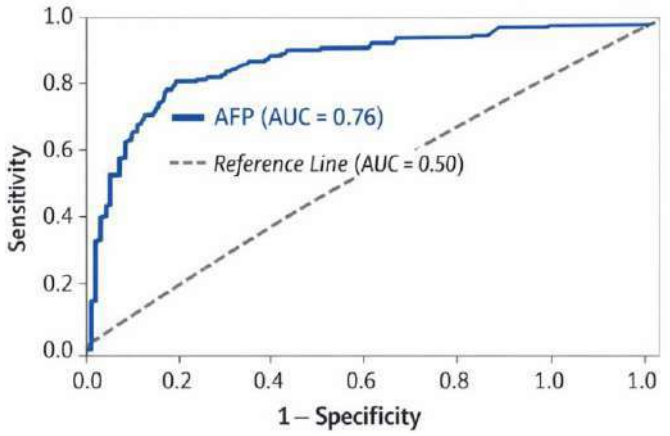

Figure 1: ROC Curve for AFP

DISCUSSION

This study investigated the correlation between AFP and baseline hematological, hepatic, and renal parameters in patients with IHDC to determine their prognostic value. These findings showed significant correlations between AFP and LFTs, especially ALP, SGOT, and bilirubin parameters, as well as hematological ones, including neutrophils and lymphocytes, and renal parameters, including urea and creatinine. These results support the role of AFP as a secondary prognostic biomarker in IHDC. Our mean age of patients was 56.8 and 11.2 years, which is similar to what Fu *et al.* stated, 57.4 and 10.6 years as the mean age of 132 patients with IHDC in China, and Hassan *et al.* found 58 and 9.4 years as the mean age of 50 patients with cholangiocarcinoma in Pakistan [15, 16]. Significantly higher serum creatinine levels in males (1.28 ± 0.34 mg/dL) compared to females (1.09 ± 0.29 mg/dL, p=0.024) are consistent with Chen *et al.* who found values of 1.32 ± 0.41 mg/dL in males versus 1.10 ± 0.33 mg/dL in females (p=0.03) [17]. These increases can indicate premature hepatorenal dysfunction as a result of chronic cholestasis or bile ductal blockage. The larger eosinophil percentage in males (3.9 ± 1.5) is consistent with Taylor *et al.* finding of 3.7 ± 1.4% in males and 2.9 ± 1.3 in females, indicating inflammatory cell activation is associated with cytokine activity of the tumor microenvironment [18]. Among elderly patients (≥60 years), we observed increased monocytes (5.7 ± 1.5%) and Mean Platelet Volume (MPV) (10.3 ± 1.0 fL) compared to younger individuals (4.8 ± 1.2% and 9.2 ± 0.9 fL, respectively, p=0.002). Beudeker *et al.* found the same results and reported MPV of 10.5 ± 1.1 fL and monocytes of 5.8 1.4% in older patients with IHDC [19]. High MPV and monocyte levels are the signs of chronic inflammation and tumor-related activation of macrophages, which are not associated with good prognoses. Upon stratification according to the cancer stage, our records indicated progressive neutrophilia and lymphopenia as the disease progressed. Neutrophils increased from 66.8 ± 8.1% in stage II to 78.2 ± 9.0% in stage IV (p<0.001), while lymphocytes declined from 25.1 ± 6.4% to 18.5 ± 7.1% (p<0.001). Ji *et al.* also provided the median neutrophil and lymphocyte percentages of 74.3 ± 10.2 and 19.7 ± 6.5, respectively, among biliary cancers in the advanced stage and found an NLR of over 4.0 as a predictor of poor survival [20]. As well, in current research, we identified higher ALP (255.6 ± 82.5 U/L vs. 315.8 ± 98.4 U/L, p = 0.021) and total bilirubin (1.2 ± 0.4 vs. 1.9 ± 0.7mg/dL, p=0.008) in the second and fourth stages. Similar biochemical changes were observed by Wang *et al.* reported that ALP 310 (202102) and bilirubin 1.8 (202102) in the end-stage IHDC, with a prominent emphasis on the cholestatic injury and hepatic dysfunction, were used as the prognostic factors [21]. One major result of this study is that AFP is closely positively correlated with ALP (r=0.85, p=0.020), SGOT (r=0.79, p=0.030), and total bilirubin (r=0.86, p=0.020). These results closely resemble those of Chicco *et al.* who observed AFP–ALP correlation (r=0.72, p = 0.010) and AFP–bilirubin correlation (r=0.69, p=0.020) among 92 IHDC

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patients [22]. In the same way, Ali *et al.* in Pakistan found that the AFP is associated with cholestatic injury and tumor burden because of correlations with AFP and ALP (r=0.80, p<0.01) and bilirubin (r=0.77, p<0.05) [23]. We further had a strong correlation between AFP and renal indices, serum creatinine (r=0.99, p<0.001), and blood urea (r=0.98, p<0.001), which is similar to Das *et al.* who showed the existence of AFP-creatinine correlation (r=0.94, p<0.001) in hepatic malignancies associated with hepatorenal syndrome [24]. Such results indicate that AFP could have an indirect relationship with renal failure that results from tumor progression or paraneoplastic nephropathy. The relationship between AFP and neutrophils (r=0.88, p=0.010) and WBC (r=0.82, p=0.020) was found to be positive, and it shows that AFP is produced because of inflammation. Similar results were obtained by Yap *et al.* who revealed that high AFP levels were coupled with neutrophil-induced cytokine release (IL-6, TNF-), which correlates with poor survival in cholangiocarcinoma [25]. In contrast, it is also negative and related to the lymphocytes (r = -0.83, p=0.03) in disease grade IV, which is appropriate since Blanco et al. (2025) reported a mean lymphocyte count of 17.9 ± 6.8 in advanced biliary tumors, highlighting immune exhaustion in advanced tumors [26]. The mean ALP (283.7 ± 95.2 U/L) and mean AFP (247.4 ± 110.6 ng/mL) in this study parallel Munir *et al.* who reported AFP of 236.8 ± 104.5 ng/mL and ALP of 295 ± 88 U/L in hepatobiliary malignancies at AFIP, Rawalpindi [27].

These uniform biochemical trends in the literature demonstrate the prognostic interaction of the AFP and hepatic enzymes. This study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. The lack of survival follow-up restricts causal and long-term prognostic interpretations. Larger multicenter prospective studies are needed to validate these results.

CONCLUSIONS

This study shows that AFP has high correlations with liver enzymes (ALP, SGOT, bilirubin), hematological indices (neutrophils, lymphocytes), and renal function indices (urea, creatinine) in patients with IHDC. The findings are that AFP in combination with CBC, LFT, and renal parameters can be used as a composite prognostic variable, which represents the tumor burden, hepatic damage, and systemic inflammation. Combining AFP and baseline laboratory profiles could thus improve the functioning of IHDC disease monitoring and prognostic accuracy.

Authors' Contribution

Conceptualization: BHR, RM
Methodology: RM
Formal analysis: KS, AK, AZ, AA
Writing and Drafting: KA, MM, TY, HA
Review and Editing: BHR, KA, MM, KS, AZ, RM, TY, HA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Prevalence of Depression in Patients with Spondyloarthritis and Its Impact on Disease Activity: A Cross-Sectional Study

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ABSTRACT

Spondyloarthritis refers to a chronic inflammatory rheumatic disorder that is characterized by pain, disability, and poor quality of life, potentially predisposing the affected patients to psychological comorbidity, including depression. Depression can hurt disease activity, treatment response, and clinical outcomes, but the burden has not been well acknowledged in clinical practice among patients with spondyloarthritis. **Objective:** To find the prevalence of depression in patients with spondyloarthritis (SpA) and to identify the association of depression with disease activity. **Methods:** A cross-sectional study was carried out in the Department of Rheumatology, Lady Reading Hospital, Peshawar, Pakistan. Adult patients who had verifiable cases of SpA were recruited in the study in six-month consecutive intervals between 1st February and 31st July 2025. Depression status was used to stratify the participants, and pertinent statistical tests were used to evaluate associations of normally and non-normally distributed variables. Independent t-test, Mann-Whitney U, and chi-square tests were used. Any p-value less than 0.050 was taken as statistically significant. **Results:** The prevalence of depressive symptoms in 323 spondyloarthritis patients was 51.1% with mild and moderate depression. Disease activity (BASDAI), inflammatory markers (ESR, CRP), and disease duration of depressed patients were considerably higher than those of non-depressed patients ($p<0.050$). **Conclusions:** Depression is very common among patients living with spondyloarthritis and is characterized by higher disease activity, systemic inflammation, and longer duration of disease, thereby supporting the importance of screening mental health during clinical care.

INTRODUCTION

Spondyloarthritis (SpA) is a collective of chronic inflammatory rheumatic diseases that mainly involve the spine, sacroiliac joints, and peripheral entheses and joints, provoking pain, stiffness, functional impairment, and reduced quality of life [1]. The social disability, inability to work, and progressive disability associated with chronic pain of SpA expose a patient to a higher risk of psychiatric comorbidity, which may affect the clinical outcome and treatment response [2]. Depression is one of the most prevalent and clinically significant comorbidities in chronic inflammatory rheumatic diseases, such as spondyloarthritis, and has a significant impact on the total disease burden [3]. A single center and registry-based reports of 20-35% of axSpA patients and less consistent but equally high rates in PsA, and a more accurately measured burden of depression of screening tools may be underestimated by formal diagnosis of depression on administrative databases [4-6]. The recent longitudinal and treatment-response research shows that baseline depression is linked with weaker response to biologic

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treatments and slower changes in composite disease activity scales, which, in turn, indicates that the presence of unidentified or untreated depressive symptoms may be a modifiable factor contributing to suboptimal effects [7-9]. It is necessary to understand the relative role of these factors in regular clinical populations in order to implement comprehensive care models that incorporate mental health screening and intervention into the practice of rheumatology [10]. A meta-analysis indicated that the overall pooled prevalence of depression in ankylosing spondylitis is approximately 35% (95% CI 28-43); however, with milder symptoms factored in, comorbid depressive symptoms are found in a substantially broader proportion of patients [11]. In Pakistan, the population and clinical research have identified that there is a significant burden of depressive symptoms, and meta-analyses of university student samples indicated a prevalence of about 51%, this depicts a high burden of mental health in the same socio-cultural backgrounds [12].

Although multiple studies are increasingly showing the fact that depression prevalence is quite common in spondyloarthritis and can have an impact on the outcome of the disease, there are several significant gaps in the existing literature. Numerous past investigations have employed heterogeneous screening instruments, inconsistent screening diagnostic limits, or administrative databases that do not reflect the true burden of depressive symptoms. Furthermore, there is less information on low- and middle-income nations, especially South Asia, where psychosocial determinants, disease burden, and availability of mental health services can be very different. Hence, locally generated evidence based on validated screening instruments is necessary to establish the prevalence of depression and its relationship to disease activity among patients with spondyloarthritis. The study aimed to identify the prevalence of depressive symptoms in patients with spondyloarthritis and its association with disease activity.

METHODS

The present study was based on a cross-sectional observational study and carried out in the Department of Rheumatology, Lady Reading Hospital (LRH), Medical Teaching Institute (MTI), Peshawar, for six months, 1st February 2025 to 31st July 2025. The ethical approval was taken with the Institutional Review Board (IRB) of Lady Reading Hospital, Medical Teaching Institute (MTI) (Approval number: 10/LRH/MTI). The present study used Open Epi version 3.01 to calculate a sample size according to the anticipated prevalence of depression of approximately 15% among patients with spondyloarthritis, confidence level of 95%, and margin of error (d) of 5% [13]. The resulting sample size was 323 participants. The final sample was found to be sufficiently precise with a post hoc precision analysis to estimate the prevalence. The study involved non-probability consecutive sampling. The sample was recruited consecutively to include all adult patients with a confirmed diagnosis of spondyloarthritis who visited the rheumatology outpatient department within the study period (18 years and above). Patients were not included in case they had a previously identified psychiatric condition besides depression, were under treatment with antidepressants or antipsychotics, had serious cognitive deficits or communication problems, or were severely ill and incapable of filling out the study questionnaires. Each patient who met the inclusion criteria was approached by trained investigators who explained the objective of the study, procedures, risks, and benefits in the local language and signed the written informed consent before enrollment. The confidentiality was highly ensured by assigning each participant a unique identification code, and all information was kept in secure places where only the research team could access it. The collection of data was done using face-to-face interviews and the reading of medical records. The medical files of the participants were reviewed to extract clinical and laboratory data, including disease duration, type of spondyloarthritis, past and current treatment regimens, laboratory investigations (CBC, ESR, CRP, ALT, creatinine), the presence of HLA-B27, and MRI results. The disease-specific features of spondyloarthritis, such as age of symptom onset, diagnosis time, disease duration, and disease activity measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [14]. The Patient Health Questionnaire-9 (PHQ-9) was used to measure depressive symptoms during the same visit [15]. It is a validated tool that scores nine symptoms over the past two weeks from 0 (not at all) to 3 (nearly every day), giving a total score of 0–27. Participants scoring ≥5 were classified as having depression, while scores <5 indicated no depression. Depression was defined according to DSM-5 and ICD-10 criteria as persistent low mood, loss of interest, or hopelessness affecting daily activities. Cronbach's alpha was used to determine the internal consistency of the PHQ-9 questionnaire to determine how reliable the instrument is for the study population. In this study population, the PHQ-9 had a good internal consistency, as indicated by a Cronbach's alpha of 0.82.

They were analyzed using the Statistical Package of Social Sciences (SPSS) version 26.0. The Shapiro-Wilk test was used to check the normality of the continuous variables, such as BASDAI scores. The test to determine the homogeneity of variance across groups was the Levene test. Mean ± standard deviation was used to express normally distributed data, and median with interquartile range was used to express non-normally distributed data.

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The frequencies and percentages were used to summarize categorical variables. The chi-square test was used to assess the associations between depression and disease activity (BASDAI) and other categorical variables, and the independent t-test and Mann-Whitney U test were used to compare continuous variables between the depressed and non-depressed groups. The duration of disease was classified into <10 years and ≥10 years to undertake post-stratification analyses. This age was chosen according to the previous literature and clinical importance because patients who have had the disease ≥ 10 years are more susceptible to physical disability, systemic inflammation, and psychological burden. Constant review of the duration of diseases was made as well in order to strengthen the results. To analyze binary, the PHQ-9 score was used to determine depression status. The respondents who scored ≥ 5 (mild, moderate, moderately severe, or severe depressive symptoms) on the PHQ-9 were considered to have depression, and participants who scored <5 were considered not depressed. A post-stratification chi-square test was conducted to take into account possible effect modifiers. The effect sizes were reported as odds ratios (ORs) and 95% confidence intervals (CIs) of variables that were significantly related to depression. Binary logistic regression and cross-tabulation were the methods by which ORs were computed. A p-value ≤0.050 was taken as statistically significant.

RESULTS

The average age of the study population was 38.6 ± 11.4 years. The majority of the patients were married (72%), and almost half were working (46%), with the percentage of nonworkers (28%), housewives (17%), and students (9%) being smaller. A slightly greater number of the participants lived in urban settings (56%), with the rest of the participants living in rural contexts (44%). Further, the symptoms of spondyloarthritis appeared in patients at an average age of 30.2 ± 9.8 years, and the duration of the disease was 8.4 ± 5.6 years on average. Most of the respondents had a diagnosis of axial SpA (68%), with peripheral SpA making up about a third of the cases. HLA-B27 positivity was detected in a bit higher percentage than half of the patients (52%). The MRI imaging revealed 63% had sacroiliitis. It was also reported that 37% of the cohort had comorbid conditions, indicating that these patients have other health burdens (Table 1).

Table 1: Sociodemographic Characteristics of Study Participants and Disease Characteristics of Patients with Spondyloarthritis (n=323)

Variables		n (%) / Mean ± SD
Sociodemographic Characteristics		
Age	Years	38.6 ± 11.4
Gender	Male	197 (61.0%)
	Female	126 (39.0%)
Marital Status	Married	231 (71.5%)
	Unmarried	92 (28.5%)
Occupation	Employed	148 (45.8%)
	Unemployed	89 (27.6%)
	Homemaker	56 (17.3%)
	Student	30 (9.3%)
Residence	Urban	182 (56.3%)
	Rural	141 (43.7%)
Disease Characteristics of Patients with Spondyloarthritis		
Age at Symptom Onset	Years	30.2 ± 9.8
Disease Duration	Years	8.4 ± 5.6
Type of SpA	Axial SpA	221 (68.4%)
	Peripheral SpA	102 (31.6%)
Family History of SpA	Yes	71 (22.0%)
	No	252 (78.0%)
HLA-B27 Status	Positive	168 (52.0%)
	Negative	155 (48.0%)
Others	BASDAI Score	4.9 ± 1.6
	MRI Sacroiliitis Present	204 (63.2%)
	Comorbidities Present	119 (36.8%)

Laboratory tests of the study group indicated that the mean hemoglobin was 12.6 ± 1.8 g/dL, and the mean MCV was 86.9± 6.4 fL with normal red cell indices. All the patients had normal total leukocyte count and platelet counts. Alanine aminotransferase (ALT) indicated slight increases in the liver enzymes in a few participants, with serum creatinine being in the normal range (Table 2).

Table 2: Laboratory Parameters of Study Participants (n=323)

Parameters	Mean ± SD / Median (IQR)
Hemoglobin (g/dL)	12.6 ± 1.8
MCV (fL)	86.9 ± 6.4
TLC ($\times 10^9$/L)	7.9 ± 2.1
Platelets ($\times 10^9$/L)	294 ± 78
ALT (IU/L)	34.2 ± 12.6
Serum Creatinine (mg/dL)	0.94 ± 0.21
ESR (mm/hr)	29.6 (18–42)
CRP (mg/L)	11.8 (6–18)

The PHQ-9 assessment of depression indicated that slightly less than 50% of the participants (48.9%) had no signs of depression, with the remaining 51% displaying some levels of depression. This prevalence was found to have a 95% level of confidence between 45.6% and 56.6%. Mild depression was the most prevalent, with 28.5% of the patients having mild depression, and moderate depression in about 14.9% of the cohort. The prevalence of moderately severe (5.9%) and severe (1.8%) depression was lower (Table 3).

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Table 3: Prevalence and Severity of Depression Based on PHQ-9 (n=323)

PHQ-9 Category	Score Range	n (%)
No Depression	0–4	158 (48.9%)
Mild Depression	5–9	92 (28.5%)
Moderate Depression	10–14	48 (14.9%)
Moderately Severe Depression	15–19	19 (5.9%)
Severe Depression	≥20	6 (1.8%)

The disease activity was found to be much higher among the depressed patients than the patients who were not depressed, as indicated by high BASDAI scores. There was also a significant increase in inflammatory markers, like ESR and CRP, in the depressed group, suggesting that there is a correlation between the state of the body and the psychological state and systemic inflammation. These were statistically significant and supported the association between depression and clinical and laboratory disease activity measures in spondyloarthritis (Table 4).

Table 4: Comparison of Disease Activity and Inflammatory Markers According to Depression Status

Variables	Depression Present, (n=165)	No Depression, (n=158)	p-value
BASDAI Score	5.6 ± 1.4	4.1 ± 1.3	<0.001
ESR (mm/hr)	34 (22–47)	25 (16–37)	0.002
CRP (mg/L)	14 (8–20)	9 (5–15)	<0.001
Disease Duration (Years)	9.2 ± 5.9	7.5 ± 5.1	0.013

Females were much more likely to be depressed than males. Depression was more likely to occur in patients whose disease lasted at least 10 years. Depression had a strong correlation with high disease activity (BASDAI >4). Comorbidities were also related to increased odds of depression. Depression was not significantly related to age group, type of spondyloarthritis, HLA-B27, or residence (Table 5).

Table 5: Post-Stratification Analysis of Depression with Selected Variables(n=323)

Variables	Depression Present, n (%)	Depression Absent, n (%)	χ^2	OR (95% CI)	p-value
Gender					
Male	91 (46.2%)	106 (53.8%)	4.55	1.63 (1.03–2.57)	0.032
Female	74 (58.7%)	52 (41.3%)			
Age Group (Years)					
18–30	38 (49.4%)	39 (50.6%)	4.27	—	0.123
31–45	72 (53.3%)	63 (46.7%)			
>45	55 (50.0%)	56 (50.0%)			
Disease Duration					
≥10 Years	63 (62.4%)	38 (37.6%)	6.31	2.05 (1.27–3.32)	0.012
High BASDAI					
>4	119 (65.0%)	64 (35.0%)	32.84	3.47 (2.20–5.49)	<0.001
Type of SpA					
Axial SpA	112 (50.7%)	109 (49.3%)	1.77	—	0.183
Peripheral SpA	53 (52.0%)	49 (48.0%)			
HLA-B27 Status					
Positive	88 (52.4%)	80 (47.6%)	0.87	1.13 (0.73–1.75)	0.352
Negative	77 (49.7%)	78 (50.3%)			
Comorbidities					
Present	74 (62.2%)	45 (37.8%)	9.86	2.23 (1.38–3.61)	0.002
No Comorbidities	91 (43.0%)	121 (57.0%)			
Residence					
Urban	94 (51.6%)	88 (48.4%)	0.57	1.07 (0.69–1.65)	0.451
Rural	71 (50.4%)	70 (49.6%)			

DISCUSSION

Overall, in this cross-sectional study of 323 patients with spondyloarthritis, over half (51.1%) displayed depressive symptoms by PHQ-9 criteria, with mild and moderate depression being the most common. This prevalence estimate is generally consistent with new literature that indicates that depressive symptoms are prevalent in SpA populations, but reported rates have been found to vary depending on screening tools and thresholds. Indicatively, a cross-sectional study that conducted PHQ-9 showed that depression was found in 46.7% of SpA patients, with moderate to severe symptoms in 25 percent of study participants, a significant burden of psychological distress in the group [16]. An extensive meta-analysis has found depression in between 11% and 64% of cohorts, with pooled estimates indicating mild depressive symptoms in around 38% and moderate to severe in 15% of axSpA patients [17]. These results are consistent with our observation that less severe mood disturbances are more common and can be used to put our overall prevalence into perspective, more so that PHQ-9 and a lower cut-off on any depression included a larger range of symptom severity. A different study conducted recently on cytokine associations in axSpA reported almost 49% prevalence of depressive symptoms, with higher levels of BASDAI and ASDAS being found in patients with depressive symptoms, but cytokine levels, including TNF-α and IL-1β, were not found to be positively related to depression [18]. This is consistent with the idea that psychological load in SpA is more directly related to clinical manifestations of diseases and patient experiences of the disease effect than to individual biochemical evidence of inflammation [19]. The results of the present study align with available literature since they showed a much more prominent rate of depressive symptoms in patients with ankylosing spondylitis as compared to healthy controls. The identified connection between chronicity of the disease and low levels of depression could be attributed to a process of adaptive coping with time, whereas gender disparity in the prevalence of the disease indicates that psychological

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evaluation should be gender-sensitive. In general, these findings highlight the need to conduct regular mental health screening as a part of AS management to enhance patient outcomes[20].

The cross-sectional nature would not allow the creation of a causal relationship between depression and disease activity. Second, only one tertiary care center was sampled, which can restrict the applicability of the results to other populations or regions. Third, the PHQ-9, or self-reported questionnaire, was used to measure depression as opposed to a complete clinical psychiatric assessment, which could also bring about reporting bias. Also, the research has not taken into consideration all possible confounders, including socioeconomic status, lifestyle issues, or access to mental health services. Longitudinal and interventional studies should be considered in future research to establish the causal association between depression and disease activity in spondyloarthritis. It is recommended that multicenter studies that comprise a larger and heterogeneous population increase the generalizability of the study findings to other regions and healthcare environments. Moreover, the conducted studies need to consider the full psychiatric assessment, socioeconomic and lifestyle measures, and treatment-specific variables to gain a more detailed insight into possible confounders. Research on the role of psychological interventions and combined multidisciplinary care strategies in shaping disease outcomes could also serve as a source of useful evidence to support clinical management and quality of life in patients with spondyloarthritis.

CONCLUSIONS

Depression among spondyloarthritis patients is very common and is associated with increased disease activity, duration, and comorbidity, especially in females. Regular mental health screening and early intervention are needed to enhance the outcomes and quality of life of patients.

Authors' Contribution

Conceptualization: TL, ZUD
Methodology: TL, ZUD, FR, SRAS
Formal analysis: TL, ZUD, MUK
Writing and Drafting: TL, ZUD, MUK, FR, SRAS, MF
Review and Editing: TL, ZUD, MUK, FR, SRAS, MF, SYMS

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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From Crash to Care: An Interdisciplinary Analysis of Road Traffic Accidents in Pakistan; Unifying Forensic Medicine and Public Health for Causes, Prevention and Emergency Response

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ABSTRACT

Road traffic accidents (RTAs) are an emerging public health concern in Pakistan and have become a major cause of death and disability worldwide. The escalation in traffic-related injuries and fatalities has been mostly caused by rapid urbanization, inadequate emergency services, bad infrastructure, and a lack of enforcement of traffic laws. **Objectives:** To determine the primary causes and contributing elements of traffic accidents in Pakistan. **Methods:** Secondary data from the District Emergency Service, Rescue 1122, for the years 2022–2023, were used in a descriptive retrospective study design. Data on 12,407 victims of 8,170 RTAs were analyzed. Major risk trends were identified using descriptive and inferential statistics. **Results:** Almost over 50% of crashes involved motorbikes, with the most impacted age group being those between the ages of 21 and 30. The most common cause of death and disability was head injuries. The most frequent causes were driving underage and speeding. During the study period, 177 fatalities were reported. **Conclusions:** The results highlight how important it is to improve emergency systems, enforce traffic laws, and raise public awareness in order to reduce RTAs.

INTRODUCTION

Even if science and technology are advancing day by day, public health and humanitarian issues are becoming more complicated. With advancements in every area, no person or society can totally prevent unanticipated crises. Any circumstance that is beyond human capacity to handle and requires coordinated, quick action to avoid deadly consequences is considered an emergency. Emergency management systems around the world are built on the capacity to successfully respond to such emergencies, whether they be mechanical, environmental, or medical [1].

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From an epidemiological standpoint, industrialization and population growth have resulted in an unparalleled increase in emergencies, especially RTAs. Rapid motorization, urbanization, and population growth have increased the exposure to traffic risks, but emergency management skills have not kept pace accordingly [2]. Despite accounting for less than half of all registered automobiles worldwide, the WHO reported that over 90% of RTAs worldwide occur in low- and middle-income nations [3]. Pakistan has an estimated 25.3 deaths per 100,000 people, which is still dangerously high by international standards, according to the WHO's 2009 study [4]. With increasing rates of traffic-related fatalities and injuries, the province of Punjab, and especially the Sahiwal Division, seriously takes these issues into account. People from low-income groups who rely on road transportation for their livelihoods and who are their families' only source of income suffer from life-altering and life-threatening conditions, including paralysis, fractures, or severe brain damage, which in turn force households into poverty traps, and there continues a never-ending vicious circle. Additionally, these injuries raise the socioeconomic load on communities and health systems as a whole, which results in long-term dependence on caretakers [5]. Pakistan, being one of the most populous countries in South Asia, nevertheless struggles with systemic inequality, resource shortages, violence, corruption, and illiteracy. Approximately 85 million men and 89 million women make up the nation's population of over 174 million, and more than 75% of them lack access to quality healthcare and education. [6]. The causes of traffic injuries and related problems are complicated and multifactorial, like rapid industrialization, urban overpopulation, terrorism, workplace dangers, unsuitable automobiles, inadequate law enforcement, and disregard for safety procedures [7, 8]. Due to traffic jams and overworked road systems, crash rates are typically greater in densely populated urban regions than in rural areas. According to a study by Dandona *et al.* in low-resource environments, underage, inexperienced, and unauthorized drivers considerably raise road traffic injuries [9]. Improved driver education, vehicle standards, and public awareness are essential components for lowering accident-related morbidity and mortality, according to the PLOS Medicine Editors [10]. Similar trends were found in Ghana by Keller *et al.* who emphasize three crucial aspects: behavioral irresponsibility, a lack of enforcement, and inadequate infrastructure. These all contribute to escalating cases of traffic injuries [11]. Furthermore, Ayuurebobi *et al.* demonstrated that the severity and results differ largely according to response systems, healthcare access, and road conditions [12]. According to Yousefifard *et al.* analysis of Iranian trends, the socioeconomic status always has a direct impact on the probability of death [13]. These results are relevant to Pakistan, where an enormous number of RTC victims have low-income families. Such socioeconomic differences influence the frequency and consequences of RTAs, according to a ten-year study conducted in Libya by Bodalal *et al.* [14]. The most common and avoidable causes of serious RTAs continue to be excessive speeding, careless driving, and negligence. Particularly in young individuals and daily wage earners, these activities lead to death or permanent impairments [15]. According to studies, accident rates can be significantly decreased by putting in place skill-based driver education, imposing severe penalties for violations, and performing routine vehicle fitness tests [16]. Risky driving practices are the primary cause of RTAs in low- and middle-income countries, according to Adams *et al.* and Hareru *et al.* [17, 18]. Moreover, the value of forensic medicine in this context cannot be overlooked, especially when it comes to identifying the exact cause of death, the kind of injuries, and contributing factors in traffic deaths; forensic specialists cannot be replaced. Their medico-legal investigations offer vital evidence for preventive policies, legal accountability, public health surveillance, and the formation of a proper service structure for catering to RTCs. Marri *et al.* analyzed 2,090 medico-legal autopsies in Karachi and discovered that 27.8% of cases were RTC victims, primarily males between the ages of 20 and 40, resulting in a male-to-female ratio of 7:1 [19]. In addition to improving the knowledge of patterns of fatal injuries, forensic documentation also greatly contributes to the modification of traffic safety regulations and driver education initiatives. Forensic medicine plays an important part in comprehending and handling traffic fatalities. To distinguish between main impact injuries and secondary traumas, such as ejection or post-impact falls, forensic specialists offer essential insights into the nature, mechanism, and causation of injuries [20]. Forensic specialists use post-mortem examinations to identify whether deaths were accidental, homicidal, or the result of negligence. This information is mandatory for both legal accountability and the development of road safety policies [21]. Integrating forensic data into traffic injury registries helps in terms of uncovering risk trends, enhancing legal enforcement, and informing public awareness efforts [22]. Thus, forensic medicine not only determines the cause of death but also acts as a cornerstone for justice, prevention, and systemic improvement in emergency and road safety management systems. Finally, research on traffic incidents in Sahiwal and throughout Pakistan shows that where forensic investigation and emergency preparedness need to work together, public education and awareness

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need to be done at an equal pace. To achieve a sustainable decrease in road traffic fatality, we need to bolster emergency response capabilities, uphold the law, encourage civic engagement, and incorporate forensic evidence into policies. Therefore, road safety is a multifaceted public health concern that requires cooperation from the government, the community, and individuals.

Road traffic accidents continue to be a major public health issue in Pakistan, but little research has been done to examine in detail the causes of the issue and the contribution of emergency response systems based on the local accident rates. This disparity restricts the formulation of effective measures to curb the number of traffic-related injuries and deaths. Thus, the study aims to examine the primary causes and risks of the RTAs in Pakistan and assess the role of the emergency response services in enhancing the survival rates and informing the evidence-based road safety measures.

METHODS

This study was a descriptive retrospective, conducted at the District Emergency Service, Rescue 1122, Sahiwal, Punjab, Pakistan. The study utilized one year of official emergency records covering the period from 2022 to 2023. Official approval for the study and access to the trauma register and emergency call records were granted by the District Emergency Officer, Rescue 1122, Sahiwal (ref. No.28/2022/REO (SWL-DIV)), along with the operational team. Ethical approval was obtained from the Ethical Review Board of Federal Medical College (Ref No. F.10/2025/Admin-FMC). Technical and ethical approval for the study protocol was provided to ensure compliance with ethical guidelines for the use of secondary data. The target population includes all victims of road traffic crashes reported in Sahiwal, Pakistan, during 2022-2023. These instances covered a broad spectrum of demographics, including age, gender, socioeconomic status, and place of residence (rural versus urban). The sample size included all instances (n=12,407) that were reported during the designated time frame. The practicality of examining all records and the comparatively manageable dataset size led to the adoption of this census-based method. A non-probability purposive sampling technique was adopted, as the study relied on existing official records from the emergency service database. The compiled data were presented through tables, charts, and graphs to visualize frequency distributions, relationships, and trends across variables. Data were cross-validated using the Trauma Registry Form from the District Headquarters Hospital, Sahiwal, to ensure accuracy between pre-hospital and hospital records.

Data were entered and analyzed using SPSS version 26.0. Descriptive statistics were applied to summarize frequency distributions, means, and percentages. Inclusion Criteria include: all victims of road traffic accidents recorded by Rescue 1122, both fatal and non-fatal injury cases, and cases involving motorbikes, cars, trucks, rickshaws, and other vehicles. Exclusion Criteria include: cases unrelated to road traffic incidents (e.g., burns, assaults, drowning) and incomplete or untraceable records with missing demographic or outcome data.

RESULTS

This study demonstrates various variables with respect to their data types and respective attributes with description, e.g., age groups, injury severity, gender, etc. (Table 1).

Table 1: Variables and Data Types

Types	Variables	Attributes / Description
Independent Variables	Driver's Age, Vehicle Type, and Cause of Accident	Age Groups (≤20, 21–30, 31–40, >40); Causes Include Over-Speeding, Negligence, and Mechanical Fault
Dependent Variables	Injury Severity, Mortality Rate	Minor, Moderate, Severe, Fatal
Confounding Variables	Response Time, Location, Time of Day	Continuous Data in Minutes/ Hours
Categorical Variables	Gender, Residence	Male/Female; Urban/Rural

The total number of Road Traffic crashes reported is 12407, amongst them, expiries are 177(1.43%), further broken up into 9757, 2650 males and females respectively (Table 2).

Table 2: Total number of RTCs with Victims Detail

Sr.#	Total No. of RTCs	Total No. of Victims	Male Victims	Female Victims	Expiries
1	8170	12407	9757	2650	177

If we further break up these road traffic crashes into annual, six-month, per month, per week, and per day, we have an average of 1992 emergencies annually, 996 emergencies biannually, 166 per month, 41 emergencies per week, and an average of 6 emergencies per day. If we look at the total experiences, we figure out that there are 44 experiences annually, and 3 per month. Out of the total 12407 victims, 9757 are males, and 2650 are female victims. If we further break it down, we find 3101 victims annually, 2439 of them are male, while 662 victims are female. Biannually, 1219 males and 331 victims are female. Monthly, 203 male and 55 female victims, while weekly, 50 male and 13 female victims, and daily, 7 male and 2 female victims suffer from road traffic accidents. As per the interpretation of the data which we have received about the vehicles involved so far is as follows (Figure 1).

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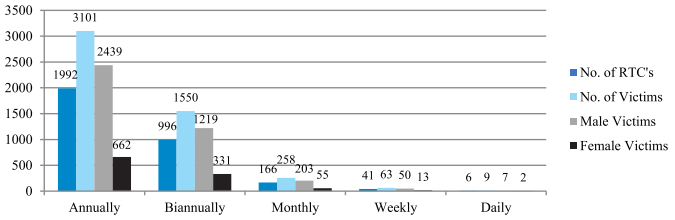

Figure 1: Bifurcation of Victims and Time Period

There is an alarming situation with respect to motorbike involvement (55.4%) and traumatic head injuries. Careless attitude and unskilled driving contribute up to 50.66% in overall cases. Fractures are the most common lower extremity injury and are diagnosed in 52% and 42% of riders with nonfatal and fatal injuries, respectively. Of the 12109 vehicles involved in road traffic accidents, 1080 are cars, accounting for 8.77% of the total. 489 of the totals are buses, which make 4.88% of total vehicles involved in the Sahiwal Division. 631 out of 12109 vehicles are trucks involved in RTAs, causing multiple injuries. Another major cause of road traffic crashes and traumatic head injuries is rickshaws and motorbike rickshaws. There are 1216 other vehicles, tractor trolleys, bull carts, donkey carts, bicycles, pedestrians, etc. This category-wise analysis helps to determine the most vulnerable age group with respect to mortality and morbidity on account of traumatic head injuries. The most vulnerable group is the third decade, 21-30 years of life, which has accounted for 4323 victims in this period, and the second most vulnerable age group is the second decade, from 11-20 years, which has accounted for 2646 victims. The third highest risk group is between 31 and 40 years, which accounts for 2283 victims during this study span. Amongst all the victims of road traffic crashes, the highest number is of victims of head injury, with the highest rate and ratio of death. The number reported so far is 1686. The next highest number is multiple injuries with multiple fractures in a single RTA, which is 1188. The lowest number is of the spinal injuries, which are 100, and the number of fractures of extremities, especially leg fractures, is 739. Minor injuries reported as 8694. In the number of incidents, any reason becomes the cause of so many fatal incidents, such as speeding, carelessness, wrong turns, and U-turns, etc (Table 3).

Table 3: Distribution of Vehicles Involved, Age Groups of Victims, Injuries Reported, and Causes of Road Traffic Crashes

Categories	Subcategory	No. of Accidents
Types of Vehicles	Bikes	6712
	Cars	1080
	Buses	489
	Trucks	631
	Vans	609
	Rickshaws	1372
	Others	1216
Age Group of the Victims	1Y-10Y	977
	11Y-20Y	2646
	21Y-30Y	4323
	31Y-40Y	2283
	41Y-50Y	1280
	51Y-60Y	593
	Above 60Y	305
Injuries Reported from Road Traffic Crashes	Spinal Injuries	100
	Head Injuries	1686
	Leg Fractures	739
	Multiple Fractures	1188
	Minor Injuries	8694
Causes of Road Traffic Crashes	Over Speeding	4578
	Carelessness	2583
	Wrong Turn	471
	U Turn	25
	Others	513

Among the causes of RTCs, the biggest reason is the speeding of vehicles (4578). It also indicates the lack of adherence to the traffic rules, as well as the poor monitoring of traffic black spots by the relevant department. During this span of study, it is determined that the death rate is on the higher side, that is, 65 per annum, only in road traffic crash emergencies, which was 35 at the start of this span of time, and reached the sad figure of 65. This clearly shows the proportion of deaths with an increasing number of risks and vulnerabilities on the roads (Figure 2).

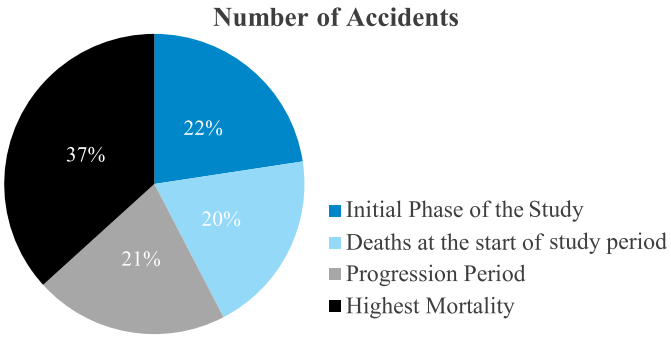

Figure 2: Pie Chart of the Proportion of Deaths

DISCUSSION

The present study focused on RTAs. The total number of crashes that took place is 8170, under which the victims are 12407, of whom 177 were mortalities. These affected 12407 people, out of which 9757 are males and 2650 are females, respectively. From a forensic medicine perspective, this distribution of injuries provides valuable insight into the mechanism, dynamics, and impact forces involved in road traffic collisions. Forensic experts play an essential role in differentiating between injuries caused by primary impact and secondary injuries resulting from falls, ejections, or subsequent hits. The predominance of head injuries and multiple fractures in this dataset is consistent with global

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forensic findings that identify the cranium and extremities as the most vulnerable anatomical regions in vehicular trauma [23]. Rapid deceleration and acceleration, coup and countercoup injuries, whiplash injuries, not wearing a helmet or seatbelt, and direct accidents with hard surfaces, dice injuries, and bird-foot injuries are common examples and can be confirmed during medico-legal autopsies and forensic biomechanical analysis [24]. The presence of many skeletal and spinal fractures is also consistent with forensic analysis that points to high-velocity collisions and inadequate vehicle restraint systems as the major causes of morbidity and mortality [25]. Despite being less common numerically, spinal trauma like railway-spine injury has serious medico-legal ramifications because it frequently results in permanent impairment. In addition to establishing the cause and manner of injury, forensic investigation of such cases helps determine driver accountability, usage of protective measures, and adherence to traffic safety regulations [26]. Injury patterns also assist investigators and forensic scientists in determining whether the injuries were self-inflicted, accidental, or homicidal in nature, a necessary distinction in medico-legal practice. While severe head and spinal injuries are symptomatic of high-velocity crashes and inadequate emergency care, the large number of minor injuries described in this study probably represents low-speed collisions and non-fatal impacts on people. Reconstructing the sequence of events, quantifying the kinetic energy transfer, and offering evidence-based suggestions for safety improvements are all made easier with the use of such forensic classifications [27].

This study includes victims who contacted rescue 1122 only, and the victims treated elsewhere are not reported here. Activating district-level road safety authorities, evolving driving schools to foster skill development, performing road safety audits of high or low-risk areas, and integrating road safety education into school curricula are some of the strategic ideas that can benefit the system as a whole.

CONCLUSIONS

This study emphasized how essential it is to raise public awareness, enhance road conditions, guarantee vehicle upkeep, and enforce strict traffic regulations. Additionally, forensic investigation helps discover patterns and avoidable causes of fatal injuries, which inform evidence-based safety actions. Ultimately, road safety is a communal obligation of the state, community, and individuals; that is why to lower risks, improve capacity, and save lives, a coordinated national response, incorporating medical, forensic, and preventive measures, is mandatory, since mortality from RTCs now surpasses that from major chronic diseases like HIV, TB, and cancer. With the help of this study, eventually we can be able to appreciate the presence of a life-saving emergency service that could respond in the golden time period to save precious lives, produce relief, and reduce grief.

Authors' Contribution

Conceptualization: SGS
Methodology: IUH, AZ
Formal analysis: AZ, SS, YK
Writing and Drafting: IUH, SGS, SS
Review and Editing: IUH, SGS, SS, AZ, SS, YK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Peripheral Neuropathy in Pregnant Women with Iron Deficiency Anemia: A Cross-Sectional Analytical Study

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ABSTRACT

Pakistan faces a high burden of nutritional anemias, with iron-deficiency anemia being the most prevalent. Imbalanced iron levels had a central role in neuropathies. **Objectives:** To assess the prevalence of peripheral neuropathy in pregnant women having Iron deficiency anemia through associated clinical and laboratory Parameters. **Method:** A cross-sectional analytical study was done at the Department of Obstetrics and Gynecology and the Clinical Neurophysiology Unit of Niazi Welfare Foundation Teaching Hospital, Sargodha, from July 1st, 2025 to November 30, 2025. A sample of 350 women was targeted using consecutive sampling. Both sensory and motor nerve conduction parameters of the lower limbs and upper limbs were evaluated. Data were analyzed using SPSS version 26. Chi-square tests assessed associations between anemia severity (mild: Hb 10–10.9 g/dL; moderate: 8–9.9 g/dL; severe: <8 g/dL) and peripheral neuropathy at significance level of p-value <0.050. **Results:** Out of 350 pregnant women, anemia was mild in 98 (28.0%), moderate in 164 (46.9%). Peripheral neuropathy was revealed in 102 women (29.1%,) Neuropathic symptoms involving numbness was revealed in 42.1%, tingling (paresthesia) in 38.7%, burning sensations in 35.5%, & reduced ankle reflexes in 27.4%. This study found a significant association between anemia severity and neuropathy frequency (χ^2 = 42.9, p<0.001), showing a marked increase in neuropathy prevalence with worsening anemia. **Conclusions:** Study reported that iron-deficiency anemia is associated with the onset and progression of peripheral neuropathy. These observations suggest that evaluation for iron deficiency should be routinely included when assessing patients presenting with peripheral neuropathy.

INTRODUCTION

Anemia represents a major contributor to the worldwide burden of disease [1]. World Health Organization estimates indicate that approximately 42% of children under five years of age and about 40% of pregnant women globally are affected by anemia [2]. Data show a high prevalence across different population groups in Pakistan, including 25% of men aged 15–49 years, 50% of women in the same age group, 31.1% of adolescent boys aged 15–19 years, 82% of adolescent girls, 70% of pregnant women aged 15–49 years, and 53.7% of children aged 6–59 months [3]. Anemia can be categorized into nutritional, hemorrhagic, aplastic, and hemolytic types according to its underlying cause [4]. As a developing country, Pakistan faces a high burden of nutritional anemias, with iron-deficiency anemia being the most prevalent [5]. Common causes of iron-deficiency anemia are inadequate iron intake, blood loss, malabsorption, and pregnancy [6]. Anemia affects children, women of reproductive age, and residents of lower socioeconomic status [7]. Iron is one of major element for neuronal and cognitive development of fetus.

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Inadequate iron delays cognitive, mental, and physical growth making prone to infections [8]. Iron is involved for brain metabolism, neurotransmitter functioning, and myelination [9]. Imbalanced iron levels had a central role in neuropathies, but clinically iron deficiency is not correlated with peripheral neuropathy in Pakistan. Peripheral neuropathy is a mechanism of nerve damage leading to weakness, numbness, pain etc. in hands and feet [10]. Nutritional deficiencies, diabetes mellitus, toxins exposure and injuries resulting from trauma contribute for damaging the nerves located outside brain and spinal cord leading to peripheral neuropathy [11]. In Pakistan, scarce data is available to reveal the relationship of IDA with peripheral neuropathy and stress the need of research studies to rule out the role of iron in neuronal development for fostering cognitive, physical, and mental development [12]. Neurologists perform nerve conduction studies (NCS) as parameter to measure the peripheral nerve dysfunction and find the extent of nerve fiber loss before appearance of clinical symptoms [13]. NCS serves a cost effective, non-invasive approach to investigate peripheral neuropathies for IDA patients [14].

Even though the earlier researches have addressed the diagnostic value of imaging and laboratory markers in obstructive jaundice, they have not been exhaustive in evaluating the combined validity and clinical value of both methods in distinguishing the underlying causes. Consequently, the research problem is to define the effective ways of diagnostic diagnosis, non-invasive, reliable methods of diagnosing the benign and malignant causes so that the patients may be managed in time and in a proper manner. This study was conducted to assess the prevalence of peripheral neuropathy in pregnant women with iron deficiency anemia through associated clinical and laboratory parameters. Finding will help policy makers to incorporate the evaluation of iron deficiency routinely when assessing patients presenting with peripheral neuropathy.

METHODS

A cross-sectional, analytical study was conducted at the Department of Obstetrics and Gynecology and the Clinical Neurophysiology Unit of Niazi Welfare Foundation Teaching Hospital (NWFTH), Sargodha, from July 1st, 2025 to November 30, 2025 after taking ethical approval letter (NM&DC-IRB-110) from the Institutional Review Board (IRB) committee having Ref No: IRB/NM&DC/758. NWFTH is a major tertiary care teaching hospital serving diverse urban and rural populations. Pregnant women aged 18–40 years with confirmed iron-deficiency anemia were eligible for inclusion. IDA was defined as hemoglobin <11 g/dL and serum ferritin <30 ng/mL [15]. Women were excluded if they had known diabetes mellitus, vitamin B12 deficiency (serum B12 <200 pg/mL), renal or liver disease, a history of alcohol misuse, neurological diseases unrelated to IDA, or if they declined consent. On the Open Epi software, using an expected frequency of peripheral neuropathy of 25% among anemic pregnant women (based on pilot observations), a confidence level of 95%, and a precision of 5%, the minimum sample size was calculated as 289. A sample of 350 women was targeted after considering dropouts using consecutive sampling and data collection was done after informed consent from patients. History pertaining to patients' demographics and symptoms of numbness, tingling, burning, AND Reduced ankle reflexes to verify peripheral neuropathy was documented in a predesigned performa. Neurological examination including sensory and motor function was conducted. Latest two weeks' lab investigation of CBC for Hb, Serum ferritin and B12 levels were reviewed. Both sensory and motor nerve conduction parameters of the lower limbs (sural nerve, peroneal nerve) and upper limbs (median nerve) were evaluated. Peripheral neuropathy was diagnosed if NCS indicated reduced conduction velocities and/or low amplitudes consistent with axonal or demyelinating patterns. Peripheral neuropathy was defined as presence of clinical symptoms or signs (sensory or motor) corroborated by abnormal NCS findings consistent with sensory, motor, or mixed neuropathy [11].

SPSS version 26.0 was used for data analysis. Mean, standard deviation, frequencies, and percentages were calculated for descriptive data. Chi-square tests assessed associations between anemia severity, mild: Hb 10–10.9 g/dL; moderate: 8–9.9 g/dL; severe: <8 g/dL [16], and peripheral neuropathy at p-value <0.005.

RESULTS

A total of 350 pregnant women with confirmed iron-deficiency anemia were enrolled. Mean age was 27.3 ± 5.4 years (range 18–40). The majority (72.6%) were in the second or third trimester of pregnancy. Mean hemoglobin was 8.9 ± 1.5 g/dL, and mean serum ferritin was 18.6 ± 7.2 ng/mL. Distribution of anemia severity was mild in 98 (28.0%), moderate in 164 (46.9%) & severe in 88(25.1%). The normality of data distribution was assessed using the Shapiro–Wilk test (Table 1).

Table 1: Demographics of Pregnant Women with Iron-Deficiency Anemia (n=350)

Characteristics	Mean ± SD / n (%)
Age (Years)	27.3 ± 5.4
Age Range (Years)	18–40
Hemoglobin (g/dL)	8.9 ± 1.5
Serum Ferritin (ng/mL)	18.6 ± 7.2
Gestational Age	
Second And Third Trimester	254 (72.6%)

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First Trimester	96 (27.4%)
Severity of Anemia	
Mild Anemia	98 (28.0%)
Moderate Anemia	164 (46.9%)
Severe Anemia	88 (25.1%)

Findings show that peripheral neuropathy was identified in 102 women, yielding a frequency of 29.1%. Among these sensory symptoms were present in 72 women (70.6%), motor symptoms in 12 women (11.8%), & both sensory and motor symptoms in 18 women (17.6%). The most frequently reported neuropathic symptoms were: numbness 43/102 (42.1%), tingling (paresthesia): 39/102 (38.7%), burning sensations: 36/102 (35.5%), and reduced ankle reflexes: 28/102 (27.4%). Symptoms were generally more pronounced in the lower limbs than the upper limbs (Table 2).

Table 2: Clinical Manifestation of Peripheral Neuropathy in Pregnant Women with Iron-Deficiency Anemia (n=350)

Clinical Manifestation	n (%)
Numbness	43 (42.1%)
Tingling (Paresthesia)	39 (38.7%)
Burning Sensations	36 (35.5%)
Reduced Ankle Reflexes	28 (27.4%)

Abnormal NCS results were categorized as sensory axonal neuropathy found in 82 women (80.4%) & mixed sensorimotor neuropathy in 20 women (19.6%). No cases of purely demyelinating neuropathy were observed. The sural nerve was affected in most cases, followed by peroneal nerve abnormalities. There was a significant association between anemia severity and neuropathy frequency (χ^2 = 42.9, p<0.001), showing a marked increase in neuropathy prevalence with worsening anemia (Table 3).

Table 3: Frequency of Peripheral Neuropathy by Anemia Severity (n=350)

Anemia Category	Total (n)	n (%)
Mild (Hb 10–10.9)	98	11 (11.2%)
Moderate (Hb 8–9.9)	164	42 (25.6%)
Severe (Hb <8)	88	49 (55.7%)

Cross-tabulation results showed observed counts with and without neuropathy across anemia categories (Table 4).

Table 4: Cross-tabulation of Peripheral Neuropathy by Anemia Severity

Anemia Category	Neuropathy Present, (n)	Neuropathy Absent, (n)	Total, (n)
Mild (Hb 10–10.9)	11	87	98
Moderate (Hb 8–9.9)	42	122	164
Severe (Hb <8)	49	39	88
Total	102	248	350

DISCUSSION

Iron plays a crucial role in nerve myelination, neuronal metabolism, and dopamine neurotransmission. Nerve conduction studies have the capacity to investigate cases of peripheral nervous system disorders, including peripheral nerves, nerve roots, muscles, and neuromuscular junction [17]. This study found that peripheral neuropathy was present in nearly one-third (29.1%) of pregnant women with iron-deficiency anemia attending a tertiary hospital. The frequency observed is higher than what is usually reported in general non-pregnant populations with IDA but aligns with the notion that pregnancy may amplify the neurological impact of iron deficiency [18]. Although direct comparisons are limited due to the scarcity of similar studies, available literature suggests a variable prevalence of neuropathic symptoms in IDA. Iron is associated with peripheral neuropathy in pregnancy. Similarly, a study examining the NC velocities of all the nerves revealed a decrease in amplitude and nerve conduction velocities in IDA patients compared to the controls, and these were reversed with iron replacement therapy [19]. The findings that iron is linked with peripheral neuropathy. Similarly, Paunikar *et al.* conducted a study on patients with iron-deficiency anemia. Motor nerve conduction studies (NCS) were performed bilaterally on the median, ulnar, and posterior tibial nerves. The neurophysiological parameters assessed included distal latency (DL), motor nerve conduction velocity (MNCV), and compound muscle action potential (CMAP) amplitudes under standardized conditions. The results showed that patients with iron-deficiency anemia had significantly prolonged distal motor latencies, slower MNCV, and reduced CMAP amplitude in all the nerves examined [20]. These findings support that iron deficiency affects nerve conduction and is associated with peripheral neuropathy, similar to the present study. Moreover, the study of Kulaszyńska *et al.* supports the idea that iron-deficiency anemia affects the peripheral nervous system. Results validate the notion that iron therapy in patients with polyneuropathy and carpal tunnel syndrome proved fruitful to combat neuropathies [21]. These results are similar to the current study findings and augment that imbalanced iron levels had a central role in neuropathies. Major strengths of this study are the reflection of valuable insights for promoting screening of anemic women in the early detection of subclinical peripheral neuropathy.

This study also has several limitations, such as the fact that multivariable logistic regression analysis could not be executed due to limited covariate data. Second, other potential contributing factors, such as gestational diabetes, thyroid disorders, folate deficiency, nutritional status, and socioeconomic factors, were not assessed. Third, the study lacks a non-anemic control group for comparison. Future research should include multicenter

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follow-up studies with larger sample sizes, non-anemic controls, and additional risk factors to evaluate the role of iron as an independent predictor of peripheral neuropathy and enhance the applicability of the results. Although the study offers valuable insights for improving peripheral neuropathies in IDA.

CONCLUSIONS

A study reported that iron-deficiency anemia is linked with the onset and progression of peripheral neuropathy. These findings can serve as a reference for clinicians and policymakers to consider including a complete blood count (CBC) as an initial screening measure when evaluating peripheral neuropathy in individuals with IDA.

Authors' Contribution

Conceptualization: JA
Methodology: MZ, TB, AZ
Formal analysis: MBAS
Writing and Drafting: MZ, TB, SA
Review and Editing: JA, MBAS, MZ, TB, AZ, SA, BJ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Comparison of Tranexamic Acid and Misoprostol in Reducing Blood Loss During Cesarean Section

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ABSTRACT

Excessive blood loss during cesarean section remains a major contributor to maternal morbidity and mortality. Various uterotonic and antifibrinolytic agents are used to reduce perioperative hemorrhage, with Tranexamic Acid and Misoprostol being commonly utilized options. However, evidence comparing their effectiveness in reducing intraoperative blood loss is limited. **Objectives:** To determine whether tranexamic acid or misoprostol is more effective in reducing blood loss during cesarean section. **Methods:** Between January 2025 and June 2025, this quasi-experimental study was conducted at the Department of Obstetrics and Gynecology, Shahida Islam Medical College, Lodhran. A total of 126 obstetric patients undergoing C-section were allocated into two groups, i.e. Tranexamic Acid group and the Misoprostol group, at the time of anesthesia. Baseline data regarding age, gravida, parity, and abortion history were recorded. Intraoperative mean blood loss was compared by using an independent samples t-test, and $p \leq 0.050$ was considered significant. **Results:** In the Tranexamic Acid group, mean intraoperative blood loss was lower as compared to the Misoprostol group (282.97 ± 82.80 mL vs. 366.68 ± 116.01 mL; $p<0.001$). Similar results were noted after stratification of gravida, parity, and abortion history. Postoperative hemoglobin and hematocrit decline were also less in the Tranexamic Acid group. **Conclusions:** Our results suggest that tranexamic acid provides superior control of blood loss during cesarean section when compared with misoprostol. Based on these outcomes, tranexamic acid may be a better choice for prophylactic use to limit intraoperative bleeding in cesarean deliveries.

INTRODUCTION

Cesarean section (C-section) has become one of the most commonly performed surgical procedures worldwide and is associated with a higher risk of postpartum hemorrhage (PPH) than vaginal delivery [1]. PPH is also a significant cause of postpartum morbidity, and uterine atony is the most common cause [2]. Consequently, intraoperative and postoperative blood loss during C-section is a clinical priority that needs to be optimized. An antifibrinolytic agent, tranexamic acid (TXA), has become prominent due to the ability to reduce the blood loss during obstetric procedures by preventing fibrinolysis [3]. Several meta-analyses and clinical trials have proved its safety and efficacy when used before skin incision in obstetric patients during C-section [4, 5]. Another agent that is used by many obstetricians because of its uterotonic effects is misoprostol, which is an analog of prostaglandin E1, especially in low-resource settings [6]. The two drugs possess different modes of action, and their administration as single or in combination has demonstrated potential in enhancing the outcomes of the mother. There have been mixed results on comparative studies of TXA and misoprostol. Other studies have

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documented that TXA is a much more effective agent in reducing the total blood loss as compared to misoprostol, with fewer side effects [7, 8]. Other trials, on the other hand, discovered that misoprostol was also just as effective or better in some environments, especially in the management of bleeding after operation [9]. Further, there are synergistic effects when both drugs are administered together to achieve the reduction of intraoperative bleeding and the unnecessary use of further uterotonics [10, 11].

Although both tranexamic acid (TXA) and misoprostol are widely used to reduce blood loss during cesarean section, existing studies show variable results due to differences in clinical protocols, patient populations, and routes of administration. This inconsistency creates uncertainty regarding the most effective, safe, and practical option, particularly in resource-limited settings. The study aimed to directly compare intraoperative blood loss between tranexamic acid and misoprostol during cesarean section to determine the more effective intervention for preventing obstetric hemorrhage and guiding evidence-based clinical practice.

METHODS

This quasi-experimental study was conducted in the Department of Obstetrics and Gynecology, Shahida Islam Medical College, Lodhran, from 03 May 2024 to 02 November 2024, after obtaining ethical approval from the institutional review committee (Approval No. SIMC/ET.C./0041/24). Given the quasi-experimental design, formal randomization and allocation concealment were not implemented. Eligible participants were allocated sequentially into two groups using an alternate allocation method at the time of enrollment. This allocation approach was applied uniformly throughout the study period to minimize selection bias, and baseline demographic and obstetric characteristics were assessed and found to be comparable between the two groups. The sample size was calculated using the WHO-recommended formula for comparison of two independent group means as described by Lwanga and Lemeshow [12]. The formula used was $n = 2(Z\alpha/2 + Z\beta)^2 \sigma^2 / (\mu_1 - \mu_2)^2$, where n represents the required sample size per group, $Z\alpha/2 = 1.96$ for a 95% confidence level, $Z\beta = 0.84$ corresponding to 80% study power, σ denotes the pooled standard deviation, and $(\mu_1 - \mu_2)$ represents the expected difference in mean blood loss. A previously published study by Bose and Beegum reported mean blood loss of 416.0 ± 135.77 mL in the tranexamic acid group and 505.83 ± 214.94 mL in the misoprostol group. Using these values, the pooled standard deviation was calculated as 179.17 mL and the expected mean difference as 89.83 mL. The calculated sample size was 63 participants per group, resulting in a total sample size of 126 patients [13]. A non-probability consecutive sampling technique was employed. Women aged 20–40 years with singleton pregnancies at or beyond 37 weeks of gestation undergoing elective lower segment cesarean section under spinal anesthesia were included after obtaining written informed consent. Patients with multiple pregnancies, placenta previa or placenta accreta spectrum, antepartum hemorrhage, known coagulopathy or thromboembolic disease, hypersensitivity to the study drugs, or preoperative hemoglobin levels below 10 g/dL were excluded. Baseline demographic and obstetric data, including age, gravida, parity, and history of abortion, were obtained from patients' medical records and obstetric charts at the time of admission. Participants were allocated into two treatment groups. In the tranexamic acid group, patients received 1 g of tranexamic acid administered intravenously over 10 minutes immediately after delivery of the neonate and clamping of the umbilical cord. This dose and route were selected based on previously published randomized controlled trials demonstrating efficacy in reducing blood loss during cesarean section. In the misoprostol group, patients received 800 µg of misoprostol administered rectally after delivery of the neonate. The rectal route was chosen due to its sustained uterotonic effect, improved bioavailability, and reduced gastrointestinal adverse effects. The selected dose is consistent with standardized obstetric protocols for hemorrhage prevention. All patients in both groups received 10 IU of oxytocin following placental delivery as part of routine uterotonic management. Due to the different routes of administration of tranexamic acid and misoprostol, blinding of surgeons and operating room staff was not feasible. To minimize observer bias, standardized methods for blood loss estimation were applied uniformly in all cases. Postoperative hemoglobin assessment and data recording were performed by personnel who were not involved in group allocation or intraoperative management. Intraoperative blood loss was estimated using a standardized method for all participants. Blood collected in suction bottles was measured directly at the end of surgery after exclusion of amniotic fluid. Blood loss from surgical mops was estimated using the gravimetric method, assuming that a 1 g increase in mop weight corresponded to 1 mL of blood. The same estimation technique was applied consistently across both study groups to ensure accuracy and uniformity of measurement. Hemoglobin and hematocrit levels were measured preoperatively and 24 hours postoperatively using automated hematology analyzers in the hospital laboratory following routine quality-controlled procedures. The estimated blood volume for each patient was calculated using the standard formula of 85 mL per kilogram of body weight. The primary outcome measure of

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the study was intraoperative blood loss during cesarean section. Secondary outcome measures included postoperative changes in hemoglobin levels and the requirement for additional uterotonic agents during the immediate postoperative period. Blood transfusion requirements were monitored; however, no patient in either group required transfusion during the study period, and therefore this outcome was not subjected to comparative analysis. Data on operative time, surgeon experience, and specific indications for cesarean section were not collected and were therefore not included in the analysis. All procedures were conducted at the same institution following standardized operative protocols to minimize procedural variability. Adverse effects or side effects related to tranexamic acid or misoprostol were not predefined outcome measures and were not systematically recorded. Patients were observed clinically during and after surgery as part of routine postoperative care; however, no structured documentation of adverse events was undertaken. Consequently, side-effect profiles such as nausea, vomiting, or shivering were not formally compared between the two groups. The collected data were entered and analyzed using SPSS version 26.0. Continuous variables, including age, intraoperative and postoperative blood loss, hemoglobin, hematocrit, and estimated blood volume, were assessed for normality using the Shapiro–Wilk test and visual inspection of histograms. As the data demonstrated approximate normal distribution, continuous variables were expressed as mean ± standard deviation. Categorical variables such as gravida, parity, and history of abortion were presented as frequencies and percentages. The mean intraoperative blood loss between the tranexamic acid and misoprostol groups was compared using the independent samples t-test. Stratified analyses were performed according to gravida, parity, and abortion history to assess their potential influence on outcomes. A p-value of 0.005 or less was considered statistically significant.

RESULTS

A total of 126 women were analyzed (63 received tranexamic acid and 63 received misoprostol). Intraoperative blood loss averaged 282.97 ± 82.80 mL with tranexamic acid and 366.68 ± 116.01 mL with misoprostol. Postoperative loss was 125.83 ± 55.99 mL and 176.29 ± 63.23 mL, respectively. Pre-operative hemoglobin was 11.67 ± 1.23 g/dL in the tranexamic acid group versus 11.50 ± 1.14 g/dL in the misoprostol group; 24-hour values were 10.92 ± 1.28 g/dL and 10.24 ± 1.07 g/dL. Pre-operative hematocrit measured 34.88 ± 3.76% and 34.37 ± 3.43%, falling to 32.49 ± 3.94% and 30.44 ± 3.49% at 24 hours. Estimated blood volume was 6132.62 ± 616.67 mL with tranexamic acid and 5974.33 ± 630.28 mL with misoprostol (Table 1).

Table 1: Descriptive Statistics of Blood Loss and Hematological Parameters in Both Study Groups

Variables	Tranexamic Acid Group	Misoprostol Group
Intraoperative blood loss (mL)	282.97 ± 82.80	366.68 ± 116.01
Postoperative blood loss (mL)	125.83 ± 55.99	176.29 ± 63.23
Hemoglobin (pre-op) (g/dL)	11.67 ± 1.23	11.50 ± 1.14
Hemoglobin (24 hr post-op) (g/dL)	10.92 ± 1.28	10.24 ± 1.07
Hematocrit (pre-op) (%)	34.88 ± 3.76	34.37 ± 3.43
Hematocrit (24 hr post-op) (%)	32.49 ± 3.94	30.44 ± 3.49
Estimated Blood Volume (mL)	6132.62 ± 616.67	5974.33 ± 630.28

For intraoperative blood loss, the between-group difference was −83.71 mL (tranexamic acid minus misoprostol), with a 95% CI of −119.29 to −48.14 mL and p<0.001, indicating lower blood loss with tranexamic acid during surgery (Table 2).

Table 2: Comparison of Intraoperative Blood Loss in the Two Study Groups

Group	n	Mean ± SD (mL)	Mean Difference (TXA–Miso)	95% Confidence Interval	p-value
Tranexamic Acid Group	63	282.97 ± 82.80	—	—	—
Misoprostol Group	63	366.68 ± 116.01	—	—	—
Independent t-Test	—	—	−83.71 mL	−119.29 to −48.14	<0.001*

(*) indicates a statistically significant difference at p≤0.005*

Among primigravida, intraoperative loss was 312.24 ± 91.55 mL (tranexamic acid) vs 394.25 ± 133.68 mL (misoprostol); mean difference −82.01 mL, 95% CI −151.92 to −12.11, p = 0.023. For multigravida, values were 268.88 ± 75.82 mL vs 342.50 ± 108.41 mL; difference −73.62 mL, 95% CI −119.40 to −27.84, p=0.002. In grand multipara, results were 266.00 ± 76.24 mL vs 382.71 ± 58.19 mL; difference −116.71 mL, 95% CI −193.31 to −40.12, p=0.006 (Table 3).

Table 3: Stratified Analysis of Intraoperative Blood Loss According to Gravida

Gravida Category	Group	n	Mean ± SD (mL)	Mean Difference (TXA–Miso)	95% CI	p-value
Primigravida	Tranexamic Acid	22	312.24 ± 91.55	−82.01	−151.92 to −12.11	0.023*
	Misoprostol	25	394.25 ± 133.68			
Multigravida	Tranexamic Acid	36	268.88 ± 75.82	−73.62	−119.40 to −27.84	0.002*
	Misoprostol	32	342.50 ± 108.41			
Grand Multipara	Tranexamic Acid	5	266.00 ± 76.24	−116.71	−193.31 to −40.12	0.006*
	Misoprostol	6	382.71 ± 58.19			

(*) indicates a statistically significant difference at p ≤ 0.005*

Among primipara, losses were 279.86±69.12 mL vs 351.72 ± 73.22 mL; difference −71.86 mL, 95% CI −113.86 to −29.86, p=0.001. For multipara, 289.00 ± 86.00 mL vs 380.28±137.57 mL; difference −91.28 mL, 95% CI −146.19 to −36.38, p=0.001. In grand multipara, 253.20±122.33 mL vs 356.50 ± 146.22 mL; difference −103.30 mL, 95% CI −289.76 to 83.16,

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p=0.242 (Table 4).

Table 4: Stratified Analysis of Intraoperative Blood Loss According to Parity

Parity Category	Group	n	Mean ± SD (mL)	Mean Difference (TXA–Miso)	95% CI	p-value
Primipara	Tranexamic Acid	22	279.86 ± 69.12	−71.86	−113.86 to −29.86	0.001*
	Misoprostol	25	351.72 ± 73.22			
Multipara	Tranexamic Acid	36	289.00 ± 86.00	−91.28	−146.19 to −36.38	0.001*
	Misoprostol	32	380.28 ± 137.57			
Grand Multipara	Tranexamic Acid	5	253.20 ± 122.33	−103.30	−289.76 to 83.16	0.242
	Misoprostol	6	356.50 ± 146.22			

Asterisk (*) indicates statistically significant difference at p≤0.005*

Among women without prior abortion, intraoperative loss was 287.22 ± 84.32 mL (tranexamic acid) vs 388.03 ± 122.70 mL (misoprostol); difference −100.80 mL, 95% CI −143.21 to −58.39, p<0.001. In those with prior abortion, values were 257.44 ± 71.89 mL vs 329.57 ± 94.70 mL; difference −72.12 mL, 95% CI −143.74 to −0.50, p=0.049 (Table 5).

Table 5: Stratified Analysis of Intraoperative Blood Loss According to Abortion History

Abortion History	Group	n	Mean ± SD (mL)	Mean Difference (TXA–Miso)	95% CI	p-value
No History of Abortion	Tranexamic Acid	54	287.22 ± 84.32	−100.80	−143.21 to −58.39	<0.001*
	Misoprostol	40	388.03 ± 122.70			
History of Abortion	Tranexamic Acid	9	257.44 ± 71.89	−72.12	−143.74 to −0.50	0.049*
	Misoprostol	23	329.57 ± 94.70			

Asterisk (*) indicates statistically significant difference at p ≤ 0.005*

DISCUSSION

The present quasi-experimental study demonstrates that tranexamic acid was more effective than misoprostol in reducing intraoperative blood loss during elective cesarean section. This finding is consistent with the randomized controlled study by Bose and Beegum, who reported that tranexamic acid significantly reduced intraoperative blood loss, perioperative hemoglobin decline, and the need for additional uterotonic agents compared with misoprostol, particularly in women without high baseline risk for hemorrhage [13]. The observed superiority of tranexamic acid in the current study may be attributed to its antifibrinolytic mechanism, whereby it inhibits plasminogen activation and stabilizes fibrin clot formation, thereby reducing surgical bleeding. In contrast, misoprostol primarily exerts its effect through uterine contraction, which may be less effective in controlling intraoperative blood loss where vascular disruption and tissue trauma coexist with uterine atony [14]. Contrasting findings have been reported in the literature. Hussein *et al.* observed that intrauterine misoprostol resulted in lower calculated blood loss compared with preoperative tranexamic acid in women undergoing cesarean section [14]. Similarly, Pakniat *et al.* reported reduced total blood loss, suction volume, and postoperative hemoglobin decline in patients receiving misoprostol compared with tranexamic acid [15]. These discrepancies may be explained by variations in drug dosage, route of administration, timing relative to skin incision or placental delivery, differences in baseline hemorrhage risk, and variability in surgical technique and blood loss estimation methods. Other studies have reported comparable efficacy between tranexamic acid and misoprostol. Dawoud *et al.* demonstrated that both agents were effective in reducing intraoperative and postoperative blood loss compared with oxytocin alone, with no statistically significant difference between the two interventions [16]. Similar findings were reported by Deeksha *et al.* who observed equivalent efficacy of tranexamic acid and misoprostol, with a slight advantage to tranexamic acid in terms of blood conservation and fewer side effects in low-risk cases [17]. Ogah *et al.* also reported no significant difference in mean intraoperative blood loss between tranexamic acid and misoprostol, although shivering was more frequently observed in the misoprostol group [18]. Evidence from recent meta-analyses further highlights this variability. Cheema *et al.* reported that tranexamic acid significantly reduced mean blood loss, hemoglobin decline, and transfusion requirements, particularly when administered before skin incision [19]. In contrast, Abu-Zaid *et al.* found no meaningful difference between tranexamic acid and misoprostol with respect to blood loss, hemoglobin change, uterotonic requirement, or transfusion rates, suggesting therapeutic equivalence [20]. Collectively, these findings indicate that both agents are effective in reducing blood loss during cesarean delivery, with relative efficacy influenced by study design and clinical context. Although tranexamic acid and misoprostol act through different pharmacological mechanisms, the present study evaluated these agents as individual interventions and did not assess their combined use. Therefore, no recommendation can be made regarding routine combination therapy based on the current findings. Given the complementary mechanisms of action, future well-designed randomized controlled trials may explore the efficacy and safety of combined tranexamic acid and misoprostol administration for improved hemostatic control during cesarean section.

This study has several limitations. Operative time, surgeon experience, and specific indications for cesarean section were not recorded and therefore could not be controlled for, which may have influenced intraoperative blood loss. Additionally, blinding of surgeons and operating room staff was not feasible due to the differing routes of drug

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administration, which may have introduced observer bias during intraoperative blood loss estimation. Adverse effects related to tranexamic acid and misoprostol were not systematically monitored or documented, and side-effect profiles such as nausea, vomiting, and shivering were not formally assessed, limiting comparison of safety outcomes between the two interventions. Furthermore, estimation of blood loss using gravimetric and visual assessment methods may be subject to inter-observer variability. Despite these limitations, the study provides clinically relevant comparative data using standardized operative protocols in a uniform institutional setting.

CONCLUSIONS

Results of this study showed that preoperative use of Tranexamic Acid is associated with significantly lower intraoperative blood loss as compared to Misoprostol in obstetric patients undergoing C-section. This effect remained consistent after stratification of gravida, parity groups, and history of abortion. These findings suggest that Tranexamic Acid is a more effective uterotonic adjunct for reducing intraoperative blood loss during C-section. Incorporating Tranexamic Acid into perioperative management protocols may help minimize maternal blood loss and reduce the need for blood transfusion, thereby improving postoperative outcomes

Authors' Contribution

Conceptualization: TP
Methodology: Q, S
Formal analysis: Q, TT, MKJ, SUN, S
Writing and Drafting: TT, MKJ
Review and Editing: TP, Q, TT, MKJ, SUN, S

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Career Decision Making, Stress, and Its Association with Emotional Intelligence among Medical Undergraduates at HITEC-IMS Taxila Cantt

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ABSTRACT

Medical students are exposed to a wide range of medical specialties during their medical school journey. The most crucial decision at that time is the choice of a career. **Objectives:** To assess the level of career decision-making stress and determine its association with emotional intelligence among medical undergraduates of HITEC-IMS, Taxila Cantt. **Methods:** A cross-sectional study was conducted among HITEC-IMS medical undergraduates from June to October 2025 via stratified random sampling. Data were collected through a structured questionnaire, covering sociodemographic variables, the Career Decision Difficulty Questionnaire (CDDQ), and the Brief Emotional Intelligence Scale 10 (BEIS-10). SPSS version 26.0 was used for analysis. For continuous variables, mean and standard deviation, and for categorical variables, frequency and percentages were calculated. Association between two variables was seen using Chi Square test and Spearman Correlation. **Results:** 48.6% individuals experienced moderate career decision stress, with most (62.8%) struggling with a lack of readiness. The majority (85.3%) had average EI, while 14.7% scored below average. Overall, CDDQ showed a significant association with study year (p=0.004), mother and father occupation (p=0.021 and p=0.010), lack of readiness to number of siblings (p=0.033), and year of study with lack of information(p-0.043). Career-decision stress showed a significant inverse correlation with emotional intelligence (p = –0.404, p<0.001). **Conclusions:** Almost half of the students face moderate stress in career decision-making, but those with higher Emotional Intelligence tend to experience less of it. Strengthening EI and implementing structured career counselling can be effective strategies to alleviate stress and support more informed, confident career choices.

INTRODUCTION

Medical students are exposed to a wide range of medical specialties during their medical school journey. The most important thought at that time in their minds is career choice, and it is among the most important decisions individuals make in their lifetime. Studies report that medical school applicants and entrants have already decided their medical specialties even before graduation. However, choosing a specialty can be confusing and complicated because many factors influence the career choices of undergraduate medical students [1]. These include a personal interest in the specialty, the reputation of the specialty, the desire for a stable and secure future, opportunities for career progression, availability of residency programs, advice from family or friends, working hours, high income potential, and the influence of role model [2, 3]. The Programme for International Student Assessment (PISA) 2022 reported that two in five 15-year-olds across Organization for Economic Co-operation and Development (OECD) countries lack clear career plans. Career uncertainty was found to be higher among boys (41%) than girls (36%), and affected both underachievers (44%) and high achievers (34%). Compared to 2018, career

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uncertainty has risen by over 50%. Research links this uncertainty among youth to lower well-being, future anxiety, and poses risks for academic motivation, decision-making, and workforce readiness, making it a key educational and public health concern [4]. Lately, the Emotional Intelligence (EI) role has gained attention in career development literature. Emotions and stress play a very crucial role and significantly affect the decisions of people. EI is defined as "the ability to perceive accurately, appraise, and express emotions; the ability to access and/or generate feelings when they facilitate thought; the ability to understand emotion and emotional knowledge; and the ability to regulate emotions to promote emotional and intellectual growth". This career decision process often exposes students to many uncertainties, which can result in stress and anxiety [5]. When individuals are stressed, their cognitive and emotional resources are low, and they may avoid making decisions. Studies support that students with low EI tend to avoid or delay making decisions. People with greater emotional intelligence (EI) are less likely avoid or procrastinate decisions. Students who demonstrate a higher EI exhibit strong career decision-making, confidence, and clarity for occupational exploration and career choice commitment [6, 7]. Career decision is relatively simple for some people, while for others, it can be quite a stressful decision due to the internal and external factors that influence one's decision, which often create dilemmas and conflicts [2]. Career indecision is complex, as people seek counselling for various reasons, such as lack of information, unclear identity, anxiety, parental influence, personal preferences, demographic status, and cultural barriers, which contribute to career decision-making difficulties. Lack of proper advice or counselling may lead to anxiety, stress, negative feelings, frustration, and difficulty in coping [8-10].

Researchers have explored career decision stress and emotional intelligence separately, but not much data is available about their interaction for medical undergraduates. This study aims to explore the role of emotional intelligence in career decision uncertainty and stress faced by medical undergraduates of HITEC-IMS. By understanding these influencing factors, we seek to provide insights and offer counseling services, aiding students in managing stress. Ultimately, this will help them make better career choices, improve their well-being, and enhance career satisfaction and performance.

METHODS

An analytical cross-sectional study was conducted on HITEC-IMS undergraduate medical students from June to October 2025 after approval (June 3, 2025) by the Institutional Review Board of HITEC-IMS (HITEC-IRB-53-2025). The Raosoft calculator (http://www.raosoft.com/samplesize.html), based on Cochran's formula (n=n0 / 1 + n0 – 1/N), was used for sample size calculation. An initial sample size of 384 was obtained assuming an infinite population. However, since our population is finite (N = 500), we applied the standard finite population correction (FPC), with a response distribution of 50%, a confidence level of 95%, and a margin of error of 5%; the resulting sample size was 218 [11]. Students from first to final year MBBS were selected through a stratified random sampling technique, with year of study used as the strata. All students from first to final year were included, and those diagnosed with psychiatric conditions and on medications were excluded from the study. Data were collected through a self-distributed structured questionnaire. Informed consent was taken from each participant before the collection of data. The questionnaire consisted of three parts, the first part consisted of socio-demographic variables like age, gender, year of study, number of siblings, parent's occupation. The second part contained the scale to assess the challenges in decision-making, it's a 34-item validated Career Decision Difficulty Questionnaire (CDDQ) (α=0.95) [12]. It had three subscales, first subscale is "Lack of Readiness" which measures general indecisiveness, dysfunctional beliefs and lack of motivation in making career choices, second one is Lack of Information which deals with lack of information in career decision making process, occupation, self and obtaining information, and third is Lack of Inconsistent information which measures lack of unreliable information, internal conflicts and external conflicts. These items were scored on a 9-point Likert scale, 9 being 'describes me well' and 1 being 'does not describe me' [12, 13]. The results were interpreted as Salient, Negligible, and Moderate difficulty levels for every three categories. A mean response of 6.34 and above was considered as "salient", mean scores between 3.33 and 6.34 were considered as "moderate", and mean scores lower than 3.33 were considered as "negligible" difficulty level. The third part consisted of the Emotional Intelligence Scale 10 (BEIS-10), used to assess the level of emotional intelligence. It's a validated 10-item scale (α=0.748), rated on a 5-point Likert scale anchored by 1 = "strongly agree" to 5 = "strongly disagree" [14, 15]. Emotional Intelligence was ranked by percentile: scores 95th and above indicated high EI, 76th–94th above average, 25th–75th average, 6th–24th below average, and 5th or lower reflected low EI.

SPSS version 26.0 was used for data analysis. For continuous variables (CDDQ and EI scores) Mean and standard deviation, and for categorical variables (sociodemographic), frequency and percentages were calculated. Chi-Square test and Spearman Correlation coefficient were used to see the association between two variables.

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RESULTS

The study enrolled first to final year students with an age range from 18 to 26 years. More than half of participants reported < 4 siblings, 122 (56.0%), while 56 (25.7%) had < 2 siblings. The study shows the sociodemographic characteristics of the participants (Table 1).

Table 1: Sociodemographic Characteristics of the Participants

Variables		Frequency (%)
Gender	Male	76 (34.9%)
	Female	142 (65.1%)
Year of Study	First Academic Year	29 (13.3%)
	Second Academic Year	45 (20.6%)
	Third Academic Year	50 (22.9%)
	Fourth Academic Year	75 (34.4%)
	Fifth Academic Year	19 (8.7%)
Occupation of Mother	Housewife	142 (65.1%)
	Skilled Professionals**	17 (7.8%)
	Teacher	50 (22.9%)
	Government Employee and Others	9 (4.1%)
Occupation of Father	Self-Employed*	52 (23.9%)
	Skilled Professionals**	42 (19.3%)
	Teacher	23 (10.6%)
	Army Officer	23 (10.6%)
	Government/Private Employees and Others	78 (35.8%)

*Self-employed: Businessman, Landlord. **Skilled professionals: Doctor, Lady Health Worker, Engineer, Lawyer

The majority of the students fell in the moderate difficulty level in the lack of readiness subscale 137 (62.8%), and evenly distributed responses were observed between negligible and moderate difficulty levels 91 (41.7%) in the Lack of Information subscale, whereas in the inconsistent information subscale, the majority fell in the negligible category 99 (45.4%). Detailed information on the difficulty level of three subscales of the CDDQ is displayed (Table 2).

Table 2: Distribution of Participant Responses among Subscales of CDDQ

CDDQ Subscale	Difficulty Level	Frequency (%)
Lack of Readiness	Negligible	48 (22%)
	Moderate	137 (62.8%)
	Salient	33 (15.1%)
Lack of Information	Negligible	91 (41.7%)
	Moderate	91 (41.7%)
	Salient	36 (16.5%)
Lack of Inconsistent Information	Negligible	99 (45.4%)
	Moderate	84 (38.5%)
	Salient	35 (16.1%)

The findings of the study revealed that almost half of the participants, 106 (48.6%), experienced a moderate level of stress in overall CDDQ, and about 27 (12.4%) fell into the salient difficulty level (Figure 1).

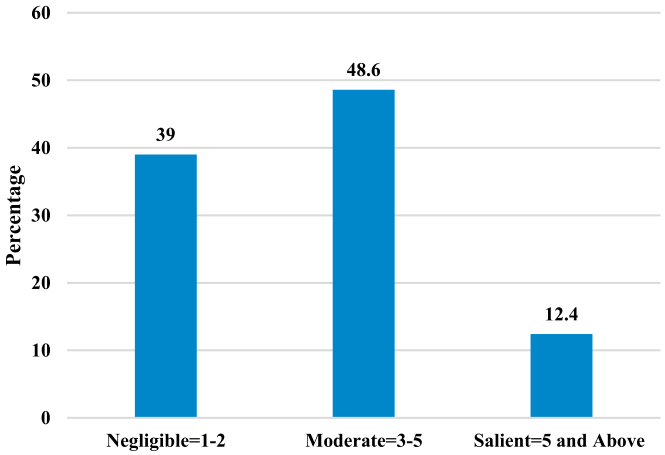

Figure 1: Distribution of Participants' Responses to the Overall CDDQ

The study showed that all the medical students lie in only two percentile groups of emotional intelligence, which are Average and Below Average. The majority of student 186 (85.3%) fell into the average EI percentile (Figure 2).

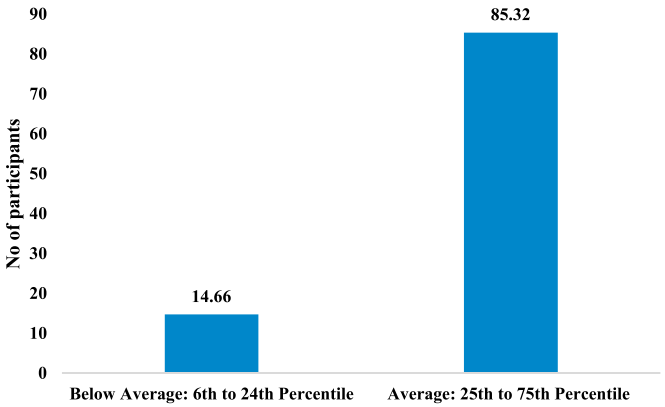

Figure 2: Emotional Intelligence Percentile of the Participants

The association between socio-demographic characteristics and the Career Decision Difficulty Questionnaire (CDDQ) and its subscales was examined. Statistically significant relationships were found between variables such as academic year of study, number of siblings, and parental occupation with both the overall CDDQ score and its subscales, suggesting that these factors influence career decision-related stress (Table 3).

Table 3: Association of Demographic Variables with Overall CDDQ and Its Subscales

Socio-Demographic Variable	Lack of Readiness	Lack of Information	Lack of Inconsistent Information	Overall CDDQ Level
	p-value			
Gender	0.517	0.258	0.151	0.538
Year of Study	0.390	0.043*	0.065	0.004**
Occupation of Mother	0.765	0.340	0.145	0.021*
Occupation of Father	0.159	0.188	0.172	0.010*
Number of Siblings	0.033*	0.146	0.916	0.698

*p<0.05 (statistically significant). ** p<0.01 (highly statistically significant)

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Emotional Intelligence (EI) and Career Decision-Making Stress (CDSS) were assessed using both Chi- square test and spearman correlation coefficient. A 95% confidence interval was applied for all inferential analyses. On applying chi square test, a statistically significant association was observed between these two variables (p<0.001). Spearman's correlation analysis showed a moderate but statistically significant negative correlation between EI and CDDQ scores (p = –0.404, p<0.001), indicating that students with higher emotional intelligence reported lower levels of Career Decision Stress (Table 4).

Table 4: Correlation and Association Between Emotional Intelligence and Career Decision-Making Difficulties

Analysis	Variable Groups	Negligible, (n=85)	Moderate, (n=106)	Salient, (n=27)	Correlation/p-value
Chi-Square Test[a]	EI Percentile Below Average (6th–24th)	4	13	15	0.001
	EI Percentile Average (25th–75th)	81	93	12	<0.001
Spearman Correlation[b]	Total EI vs. Sum CDDQ	—	—	—	ρ = –0.404, <0.001

Chi-square a test showed a significant association between EI percentile and group (p<0.001). Spearman's coefficient b indicates statistically significant correlation: ρ = –0.404, p<0.001

DISCUSSION

By exploring the relationship between career decision-making stress and emotional intelligence (EI) and sociodemographic factors, this study provides important insights into how emotional competence and sociodemographic variables influence the career decision-making process of medical students of HITEC-IMS Taxila. A moderate level of difficulty in career decision-making was experienced by nearly half 106 (48.6%) of the students. Chi-square test revealed a statistically significant association between CDDQ and EI; additionally, a moderate negative correlation was also found between these two variables through Pearson correlation. More than half of the students, 137 (62.8%), reported moderate difficulty in the "Lack of Readiness" subscale, indicating that a significant proportion of participants were uncertain and felt less motivated in their career decision. On the other hand, the Lack of Information subscale showed even distributed responses between negligible and moderate difficulty, 91 (41.7% each), signifying that less than half of the participants had enough information and were well aware of their career choice, while others still struggled to gain relevant career information. Studies conducted in India and China showed contrasting results, where the majority of students faced difficulty in the Lack of Readiness 60 (81.25%) and in the Lack of Information Scale 56 (70%) [16, 17]. The majority of students, 186 (85.3%) of HITEC-IMS Taxila Cantt, scored an average percentile for EI, while only 32 (14.7%) medical students feel below-average percentile, suggesting that most students had average emotional competence, which is necessary for decision-making power. Contradictory results were observed in another study where students had poor EI [18]. There could be several plausible reasons for our students' high EI percentile, such as we have a structured mentorship program and continuous feedback assessment, which can enhance EI development. Secondly, the difference in results could be due to different EI scales used in both studies [19]. Significant associations of sociodemographic variables such as year of study and parents' occupation with overall CDDQ scores were found. This indicates that both these variables had an influence on the career decision stress level. Students with a professional background may feel more supported and less stressed than those with less privileged backgrounds. Studies conducted in Multan, Saudi Arabia, and Vietnam also support our study results [20, 21]. Interestingly, the relationship between the number of siblings and lack of readiness was also seen, suggesting that larger families affect decision-making in career choices due to shared responsibilities or financial pressure. Other variables, gender, did not show any significant associations with the overall CDDQ score, indicating its limited role in career stress within medical students. In contrast to that, some studies have identified gender as a significant predictor of career decision-making difficulty [20, 22]. Another most important finding of this study is the moderately significant negative correlation between EI and CDDQ scores (r = –0.513, p < 0.001) that medical students with higher emotional intelligence experience less stress in making career choices than those with low emotional intelligence. Our findings are supported by studies conducted in China and the UK, which reported that individuals with high emotional intelligence have a better understanding of their abilities and preferences, which not only reduces stress but also increases self-confidence among university students [6, 9]. In contrast, a study conducted in Italy failed to find any significant association between these two variables, suggesting that one's ability to control one's emotions has no impact on the decision-making process [23].

There are a few limitations of our study. It was a single institution-based study, and students from only one academic discipline were included, which may limit the generalizability of the findings. The sample size was calculated using Cochran's formula through the Raosoft calculator, which assumes simple random sampling. In our

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study, stratified random sampling was applied, so the formula served as a guideline. Additionally, the cross-sectional design captures associations at one point in time and does not allow conclusions about causality. The study relied on self-reported questionnaires (CDQQ, EI scales), which may be influenced by social desirability or response bias. Teach students skills that help improve emotional intelligence. Provide career-guidance services so students can get help choosing a specialty. Support students who may not get enough guidance from home. Do more studies in other colleges and over longer periods to understand this issue better.

CONCLUSIONS

The findings show that most of the medical students had a moderate level of career decision stress and an average percentile for Emotional Intelligence. Students with higher Emotional Intelligence experience less stress in career decision-making. Sociodemographic factors such as parents' occupation and academic year highlight their influence on decision-making power. Overall, the study highlights that career decision-making difficulty stress is an issue among medical students, and emotional intelligence plays a protective role in coping with that stress.

Authors' Contribution

Conceptualization: AA
Methodology: AA, NR, RS, MZ
Formal analysis: AA, NR, RS, MR[1], MR[2],
Writing and Drafting: AA, MR[1], MR[2],
Review and Editing: AA, NR, RS, MR[1], MR[2], MZ

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Integration of Competency-Based Medical Education (CBME) in Undergraduate Curriculum: Opportunities and Challenges in Pakistani Medical Colleges

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ABSTRACT

Competency-Based Medical Education (CBME) is an outcome-oriented approach increasingly emphasized in undergraduate medical training. Its successful integration depends largely on faculty understanding and their perceptions of opportunities and barriers. **Objectives:** To assess the feasibility of integrating CBME into the undergraduate curriculum by examining faculty knowledge, perceived opportunities, and perceived challenges. **Methods:** This cross-sectional study was conducted at the Department of Medical Education, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan, from September 2024 to December 2024. Seventy-eight faculty members involved in undergraduate teaching were included through non-probability consecutive sampling. A structured self-administered questionnaire was used. The knowledge domain comprised five items scored 0-5; scores of 0-2 were categorized as inadequate knowledge and 3-5 as adequate knowledge. Opportunity and challenge domains were summarized as mean composite scores. Data were analyzed in SPSS version 26.0 using chi-square and independent-samples t-tests, with $p<0.05$ considered significant. **Results:** Mean age was 45.27 ± 9.17 years, and mean teaching experience was 12.17 ± 7.48 years. Mean CBME knowledge score was 2.50 ± 1.09. Knowledge level was significantly associated with gender ($p=0.007$). Faculty aware of PMDC guidelines had significantly higher Opportunity Scores ($p=0.020$). Challenge Scores did not differ significantly across subgroups. **Conclusions:** Faculty demonstrated modest knowledge of CBME, while perceptions of opportunities improved with greater policy awareness. Shared challenge scores suggest the need for broader institutional support, faculty development, and clearer dissemination of CBME guidance.

INTRODUCTION

Medical education is moving from time-based teaching models toward competency-based frameworks that define the knowledge, skills, attitudes, and professional behaviors expected from graduates. Competency-Based Medical Education (CBME) emphasizes observable outcomes, integration of learning, and accountability to patient and societal needs [1]. In Pakistan, curricular reform has increasingly focused on outcome-based undergraduate education. The Pakistan Medical and Dental Council (PMDC) has issued guidance that supports integration, skills development, and learner-centered approaches in undergraduate medical training [2]. These developments have made CBME an important topic for medical colleges attempting to align local curricula with contemporary standards. Despite its conceptual advantages, CBME implementation is not straightforward. Institutions in resource-constrained settings often face limited infrastructure, inadequate digital support, and insufficient assessment systems for workplace-based and competency-focused evaluation [3, 4]. Faculty development is therefore central to successful implementation, because teachers must move beyond

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traditional lecture-based delivery to facilitation, coaching, feedback, and competency-based assessment [5, 6]. CBME also creates opportunities. International experience shows that structured competency frameworks, better alignment of learning outcomes with assessment, and educational technology can improve the relevance and consistency of undergraduate training [7, 8]. In addition, contextual adaptation of global CBME principles may help medical schools respond more effectively to local healthcare priorities. At the same time, implementation depends heavily on how faculty understand CBME and how they perceive the opportunities and barriers associated with it. If faculty have limited understanding, inconsistent policy awareness, or concerns about feasibility, adoption may remain superficial despite curricular reform efforts [9, 10].

Even though the trend of competency-based medical education (CBME) is growing in the world, there is a gap in evidence concerning faculty knowledge, perceived opportunities, and challenges associated with the implementation of competency-based medical education in undergraduate medical education in Pakistan. The absence of local, institution-based information leaves a knowledge gap regarding the preparedness of faculty and the practicality of incorporating CBME into current programs, which could impede effective implementation plans. The present study aimed to assess the feasibility of integrating CBME into the undergraduate curriculum by examining faculty knowledge, perceived opportunities, and perceived challenges in a medical college in Lahore, Pakistan. The findings may help educators and policymakers design more realistic faculty development and implementation strategies.

METHODS

This cross-sectional study was conducted at the Department of Medical Education, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan, from September 2024 to December 2024. The study aimed to assess the feasibility of integrating Competency-Based Medical Education (CBME) into the undergraduate curriculum by examining faculty knowledge, perceived opportunities, and perceived challenges, and by exploring their association with selected demographic and institutional variables. Faculty members from both basic and clinical departments who were actively involved in undergraduate MBBS teaching were eligible for inclusion. Faculty on leave during the data-collection period or those not engaged in undergraduate teaching were excluded. Participants were enrolled through non-probability consecutive sampling, and the final analyzable sample comprised 78 faculty members. Data were collected using a structured self-administered questionnaire developed from published CBME faculty survey tools and reviewed by medical education experts for content relevance [11-13]. The questionnaire captured demographic variables (age, gender, designation, teaching experience, and department), prior CBME training, awareness of PMDC guidelines, perceived institutional support, and availability of CBME-related resources. The knowledge domain comprised five items scored as 1 for a correct response and 0 for an incorrect response, giving a total score from 0 to 5. For categorical analysis, scores of 0-2 were considered inadequate knowledge, and scores of 3-5 were considered adequate knowledge. Opportunity and challenge perceptions were measured using Likert-based items, and composite mean scores were calculated for each domain. Ethical approval was obtained from the Institutional Review Board of CMH Lahore Medical College and Institute of Dentistry, Lahore (IRB Ref. No. IERC No. IERC/OBS/2024/09). Administrative permission for data collection was obtained from the concerned department, and written informed consent was obtained from all participants. Confidentiality was maintained by anonymizing responses and storing the data in a password-protected database.

Data were entered and analyzed in IBM SPSS Statistics version 26.0. Quantitative variables, including age, teaching experience, knowledge score, Opportunity Score, and Challenge Score, were summarized as mean ± standard deviation. Categorical variables, including gender, designation, department, CBME training status, PMDC guideline awareness, institutional support, resource availability, and knowledge category, were summarized as frequencies and percentages. The chi-square test was used to examine associations between faculty characteristics and the categorized knowledge level. Independent-samples t-tests were used to compare mean Opportunity Scores and Challenge Scores across participant groups. A p-value of less than 0.005 was considered statistically significant.

RESULTS

A total of 78 faculty members participated in the study. Their mean age was 45.27 ± 9.17 years, and their mean teaching experience was 12.17 ± 7.48 years. The mean CBME knowledge score was 2.50 ± 1.09 out of 5, indicating a generally modest level of knowledge among participants. Knowledge was significantly associated with gender (p=0.007). No significant associations were observed with designation, department, previous CBME training, PMDC guideline awareness, institutional support, or the availability of CBME resources. Adequate knowledge in this analysis is defined as a score of 3-5, whereas inadequate knowledge is defined as a score of 0-2 (Table 1).

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Table 1: Association Between Faculty Characteristics and Knowledge Level

Variables	Subgroup	Inadequate Knowledge, n (%)	Adequate Knowledge, n (%)	p-value
Gender	Male	25 (69.4%)	11 (30.6%)	0.007
	Female	39 (92.9%)	3 (7.1%)	
Designation	Lecturer	18 (94.7%)	1 (5.3%)	0.268
	Assistant Professor	13 (86.7%)	2 (13.3%)	
	Associate Professor	19 (73.1%)	7 (26.9%)	
	Professor	14 (77.8%)	4 (22.2%)	
Department	Basic Sciences	32 (84.2%)	6 (15.8%)	0.628
	Clinical Sciences	32 (80.0%)	8 (20.0%)	
CBME Training	No	36 (87.8%)	5 (12.2%)	0.163
	Yes	28 (75.7%)	9 (24.3%)	
PMDC Awareness	No	34 (81.0%)	8 (19.0%)	0.785
	Yes	30 (83.3%)	6 (16.7%)	
Institutional Support	No	35 (83.3%)	7 (16.7%)	0.750
	Yes	29 (80.6%)	7 (19.4%)	
CBME Resources	No	37 (84.1%)	7 (15.9%)	0.593
	Yes	27 (79.4%)	7 (20.6%)	

Note: Adequate knowledge = score 3-5; inadequate knowledge = score 0-2

Faculty members who were aware of PMDC guidelines had significantly higher Opportunity Scores than those who were unaware (p=0.020). Differences according to gender, CBME training, department type, institutional support, and resource availability were not statistically significant, although some trends were observed (Table 2).

Table 2: Comparison of Opportunity Scores Across Participant Groups

Variables	Group	n	Mean ± SD	p-value
Gender	Male	36	2.93 ± 0.738	0.472
	Female	42	3.05 ± 0.690	
CBME Training	No	41	3.13 ± 0.740	0.066
	Yes	37	2.84 ± 0.651	
Department Type	Basic Sciences	38	3.11 ± 0.788	0.153
	Clinical Sciences	40	2.88 ± 0.618	
Institutional Support	No	42	2.96 ± 0.680	0.697
	Yes	36	3.03 ± 0.753	
PMDC Awareness	No	42	2.82 ± 0.699	0.020
	Yes	36	3.19 ± 0.679	
CBME Resources	No	44	3.07 ± 0.771	0.295
	Yes	34	2.90 ± 0.622	

Challenge Scores did not differ significantly by gender, CBME training, department, institutional support, PMDC guideline awareness, or resource availability. These findings suggest that perceived implementation barriers were broadly shared across faculty groups (Table 3).

Table 3: Comparison of Challenge Scores Across Demographic and Institutional Variables

Variables	Subgroup	n	Mean ± SD	p-value
Gender	Male	36	2.82 ± 0.78	0.431
	Female	42	2.95 ± 0.64	
CBME Training	No	41	2.90 ± 0.67	0.848
	Yes	37	2.87 ± 0.75	
Department	Basic Sciences	38	2.89 ± 0.72	0.997
	Clinical Sciences	40	2.89 ± 0.70	
Institutional Support	No	42	2.89 ± 0.63	0.946
	Yes	36	2.88 ± 0.79	
PMDC Awareness	No	42	2.82 ± 0.65	0.330
	Yes	36	2.97 ± 0.77	
CBME Resources	No	44	2.90 ± 0.72	0.826
	Yes	34	2.87 ± 0.70	

DISCUSSION

This study evaluated the feasibility of integrating CBME into the undergraduate curriculum through faculty knowledge and perceptions. Overall, faculty members demonstrated modest knowledge of CBME, while perceptions of opportunities were more favorable among those who were aware of PMDC guidance. In contrast, perceived challenges were similar across subgroups, suggesting that barriers to implementation are experienced at a broader institutional level rather than within a single faculty category. The finding of modest knowledge is consistent with previous studies showing that faculty often support the concept of CBME but remain uncertain about its operational details and implementation requirements [13, 14]. Studies from India have similarly reported that although faculty generally recognize the value of CBME, gaps remain in practical understanding, assessment planning, and curricular alignment [15-17]. The significant association between gender and knowledge level should be interpreted cautiously. Because this was a single-institution study with unequal subgroup sizes, the observed difference may reflect variation in prior exposure, teaching responsibilities, or access to faculty development rather than an intrinsic gender-related effect. Upadhyay et al. also reported variable faculty knowledge across subgroups, emphasizing the importance of institutional exposure and training opportunities rather than demographic labeling alone [11]. Faculty who had received CBME training showed higher knowledge levels numerically, but the association was not statistically significant. This may indicate that training exposure alone is insufficient unless it is recent, practical, and reinforced through mentorship and implementation support. Similar observations have been reported in studies showing that short or isolated training programs improve awareness but may not produce sustained readiness for CBME practice [12, 17]. Awareness of PMDC guidelines was associated with significantly higher Opportunity Scores. This likely reflects the role of

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policy familiarity in shaping faculty confidence about curriculum reform. However, self-selection is also possible, because more engaged or motivated faculty may be both more aware of guidelines and more optimistic about implementation. Earlier work has also shown that policy communication, administrative backing, and institutional readiness influence how faculty perceive the benefits of CBME [9, 18]. The lack of significant subgroup differences in Challenge Scores suggests that implementation barriers were widely recognized by participants regardless of background. Previous literature has similarly identified shared concerns related to infrastructure, workload, assessment methods, and administrative support [13-16]. At the same time, limited variation in challenge scores may also indicate that the scoring system had restricted sensitivity to detect smaller subgroup differences, which should be considered while interpreting the findings. Findings from qualitative and program-evaluation studies further support the need for faculty development that goes beyond orientation sessions. Effective CBME implementation requires continuous mentoring, assessment support, curricular coordination, and institutional commitment to resources and governance [19, 20].

The present findings therefore support a phased implementation strategy that combines faculty training with clearer policy dissemination and practical systems for assessment and feedback. This study is limited by its single-center design, modest sample size, and use of self-reported perceptions. Because the survey was conducted in one institution, the findings may not be generalizable to all Pakistani medical colleges. Nevertheless, the study provides useful local evidence on faculty readiness and perceived feasibility of CBME integration in the undergraduate setting.

CONCLUSIONS

Faculty demonstrated modest knowledge of CBME, and awareness of PMDC guidance was associated with more positive perceptions of implementation opportunities. Perceived challenges, however, were shared across groups, indicating the need for institution-wide solutions. Targeted faculty development, clearer policy dissemination, and stronger administrative and assessment support are likely to improve the successful integration of CBME into the undergraduate curriculum.

Authors' Contribution

Conceptualization: ZS
Methodology: ZS, SG
Formal analysis: SBN, SG, JSK
Writing and Drafting: ZS, FM, JSK
Review and Editing: ZS, SBN, SG, FM, JSK

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

Conflicts of Interest

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Original Article

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Frequency of Neonatal Morbidity and Mortality in Intrauterine Growth-Restricted Term Pregnancies in Karachi: A Hospital-Based Cross-Sectional Study

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ABSTRACT

Intrauterine growth restriction (IUGR) is a major cause of illness and death in neonates. Growth-restricted term neonates are susceptible to hypoglycemia, respiratory distress, and perinatal mortality. **Objective:** To determine the frequency of neonatal morbidity and mortality among intrauterine growth-restricted (IUGR) term pregnancies. **Methods:** A hospital-based cross-sectional study was performed at the Department of Obstetrics and Gynecology, Liaquat National Hospital, Karachi, from June to November 2024. A total of 143 women with singleton term pregnancies (≥ 37 weeks diagnosed with intrauterine growth restriction (IUGR) due to estimated fetal weight below the 10th percentile were enrolled through consecutive sampling. Neonatal outcomes were documented. Categorical variables were presented as frequency and percentage. A p-value of ≤ 0.005 was deemed statistically significant. **Results:** The median maternal age was 29 years, with a 30.8% having a history of IUGR and 37.8% experiencing intrauterine death; 53.1% delivered vaginally and 46.9% through a cesarean section. Meconium aspiration occurred on 31.5%, low birth weight in 9.1%, and NICU admission in 35.0%, with hypoglycemia (2.1%) and perinatal mortality (4.9%) being uncommon. Lower maternal age was associated with low birth weight and hypoglycemia, adverse Apgar scores with adverse neonatal outcomes, and increased NICU admission after cesarean delivery. **Conclusions:** Intrauterine growth-restricted term pregnancies are strongly associated with adverse perinatal outcomes, including respiratory compromise, metabolic instability, and increased risk of mortality.

INTRODUCTION

Intrauterine growth restriction (IUGR) is a condition in which the fetus fails to reach its genetically set growth potential. It is usually characterized as an estimated fetal weight less than the 10% for gestational age. It significantly contributes to poor perinatal outcomes, including increased risks of neonatal morbidity and mortality [1, 2]. IUGR can cause short- and long-term problems that increase mortality and morbidity in neonates. About 7%-9% of neonates have preterm IUGR, which is associated with 50% of unexplained stillbirths [3]. It affects 10-15% of births worldwide, with higher prevalence in low- and middle-income countries (LMICs) like Pakistan, where it can approach 25% [4, 5]. Although the substantial decline in perinatal morbidity and death over the past thirty years, IUGR remains the second most prevalent cause of perinatal mortality [6]. Birth weight under the 10th percentile for the gestational period affects 30 million neonates worldwide, primarily in LMICs [7, 8]. In Pakistan, IUGR accounts for around 20-24% of live births, acting as a major contributor to newborn problems and mortality [7]. Maternal factors such as pregnancy-induced hypertension (HTN) and thyroid dysfunction have been studied [9]. These risk

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factors increase the likelihood of intrauterine growth restriction and expose affected neonates to long-term health issues such as neurodevelopmental and metabolic issues [10]. Inácio *et al.* concluded that intrauterine growth restriction is associated with adverse perinatal outcomes. It increases the risk of respiratory distress and the need for neonatal resuscitation in neonates [11]. Pregnancies with undetected IUGR have an over eightfold heightened incidence of stillbirth relative to pregnancies without intrauterine growth restrictions (19.8 versus 2.4 per 1000 births)[12].

Previous studies have examined intrauterine growth restriction, but few have examined newborn outcomes in term pregnancies in local settings, underscoring the requirement for context-specific research. This study aimed to determine the frequency of neonatal morbidity and mortality among intrauterine growth-restricted (IUGR) term pregnancies.

METHODS

This hospital-based cross-sectional study was conducted in the Department of Obstetrics and Gynaecology, Liaquat National Hospital, from June 1, 2024, to November 1, 2024, after the approval of the synopsis by the institutional review board (IRB No. 1036-2024-LNH-ERC). A hospital-based cross-sectional study was conducted to assess morbidity and mortality in term IUGR pregnancies. The employed sampling technique was non-probability consecutive sampling. The sample size was determined using a single proportion formula based on a previously reported prevalence of neonatal hypoglycemia (24%) [13], with a 95% CI and a 7% margin of error. In the absence of comprehensive local data on composite neonatal morbidity in intrauterine growth restriction (IUGR) pregnancies, hypoglycemia was utilized as a representative indicator of neonatal morbidity to estimate sample size. The final computed sample size was 143. All patients fulfilling the inclusion criteria were enrolled after receiving informed consent. Study participants were enrolled in a study at delivery, and previous antenatal records from 20 weeks onward were reviewed to confirm the diagnosis. Patients were excluded if they had oligohydramnios or polyhydramnios, renal or hepatic dysfunction, premature rupture of membranes, or if neonates presented with congenital anomalies, chromosomal abnormalities, or syndromic conditions affecting growth. IUGR was considered positive as an estimated fetal weight below the 10th percentile for gestational age and sex, according to World Health Organization growth standards. Intrauterine growth restriction was considered positive as an estimated weight below the tenth percentile for gestational age and sex, based on WHO standards. Estimated fetal weight using ultrasound biometry (Hadlock formula), and diagnosis was supported by Doppler assessment, where available. Morbidity was assessed in terms of intrauterine death, meconium aspiration syndrome, Apgar score, hypoglycemia, low birth weight, and admission to the neonatal intensive care unit (NICU) within 24 hours of birth. Neonatal morbidity included meconium aspiration syndrome, low birth weight (<2500 g), hypoglycemia, poor Apgar score (<7 at 5 minutes), and neonatal intensive care unit stay. Neonatal mortality was defined as intrauterine fetal death (stillbirth) or premature neonatal death within 7 days of birth. Birth weight <2500 g after 37 weeks of gestation was considered low birth weight, which was measured using a calibrated digital weighing machine with appropriate adjustments for blankets or diapers. Apgar scores were recorded at 1 and 5 minutes post-delivery, based on standardized criteria. Meconium aspiration syndrome was diagnosed clinically in neonates with respiratory distress and meconium-stained amniotic fluid. Perinatal mortality was calculated as the number of stillbirths and neonatal deaths among births ≥37 weeks and ≥1500 g. Hypoglycemia was considered if blood glucose was <47 mg/dL within the first 24 hours of life, measured using a point-of-care glucometer.

Data were analyzed using IBM SPSS version 27.0. Data analysis was conducted to assess the association between maternal and clinical factors and neonatal outcomes within the intrauterine growth-restriction group. The Mann-Whitney U test was used for non-normally distributed continuous variables, such as birth weight and Apgar scores. Continuous variables were presented as median (IQR), whereas categorical variables were reported as frequency (%). The Mann-Whitney U test and the Chi-square test were used when applicable. A p-value of ≤ 0.005 was considered a significant value.

RESULTS

The median maternal age was 29 (IQR 22-34), and the median number of children was 2. Healthy neonates had median Apgar scores of 7 at 1 minute (IQR 4-7) and 9 at 5 minutes (IQR 5-9). The median birth weight was 2.1 kg (IQR 1.2-2.9) and blood sugar 130 mg/dL (Table 1).

Table 1: Baseline Clinical and Laboratory Characteristics of Study Participants

Variables	Median (IQR; min–max)
Mother's Age (years)	29.0 (6.0; 22.0–34.0)
Parity	2.0 (2.0; 1.0–5.0)
APGAR Score at 1 min	7.0 (3.0; 4.0–7.0)
APGAR Score at 5 min	9.0 (0.0; 5.0–9.0)
Birth Weight (kg)	2.1 (0.8; 1.2–2.9)
Blood Sugar Level	130.0 (31.0; 65.0–153.0)

The study shows the distribution of major clinical characteristics and neonatal outcomes across the study

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participants. 30.8% of patients had a history of IUGR, and 37.8% had intrauterine death (IUD). In terms of delivery mode, 53.1% of study participants had vaginal deliveries, while 46.9% underwent caesarean sections. Meconium aspiration occurred in 31.5% of neonates, as did low birth weight in 9.1%. Furthermore, 35.0% of neonates required NICU admission, although hypoglycemia and perinatal death were quite uncommon, occurring in 2.1% and 4.9% of cases, respectively (Table 2).

Table 2: Distribution of Clinical Characteristics and Outcomes

Variables	Category	n (%)
Previous History Of IUGR	Yes	44 (30.8%)
	No	99 (69.2%)
IUD	Yes	54 (37.8%)
	No	89 (62.2%)
Mode of Delivery	Vaginal	76 (53.1%)
	Caesarean	67 (46.9%)
Meconium Aspiration	Yes	45 (31.5%)
	No	98 (68.5%)
Low Birth Weight	Yes	13 (9.1%)
	No	130 (90.9%)
Admission to NICU	Yes	50 (35.0%)
	No	91 (63.6%)
Hypoglycemia	Yes	3 (2.1%)
	No	140 (97.9%)
Perinatal Death	Yes	7 (4.9%)
	No	136 (95.1%)

The results show strong associations between clinical parameters and adverse findings. Maternal age was lower in neonates with low birth weight (31 versus 28 years, p-value=0.005) and hypoglycemia (33.5 versus 28.5 years, with a p-value of 0.005). Parity was associated with meconium aspiration (2 vs 1, p=0.009), low birth weight (1 vs 2, p=0.046), and hypoglycemia (4 vs 2, p=0.047). Low birth weight, neonatal intensive care unit admission, and perinatal death were significantly associated with lower 1-minute and 5-minute Apgar scores (p<0.001). Low blood sugar levels were found in neonates with meconium aspiration, low birth weight, NICU hospitalization, and hypoglycemia (p<0.029) (Table 3).

Table 3: Comparison of Clinical Parameters by Neonatal Outcomes

Parameters	Meconium Aspiration (Yes/No)	Low Birth Weight (Yes/No)	NICU Admission (Yes/No)	Hypoglycemia (Yes/No)	Perinatal Death (Yes/No)
Mother's Age					
Median	27 / 29	31 / 28	29 / 29	33.5 / 28.5	30 / 28
p-value	0.426	0.005*	0.401	0.005*	0.055
Parity					
Median	2 / 1	1 / 2	2 / 2	4 / 2	2 / 2
p-value	0.009*	0.046*	0.733	0.047*	0.796
APGAR 1 min					
Median	7 / 7	5 / 7	6 / 7	7 / 7	6 / 7
p-value	0.071	<0.001*	<0.001*	0.353	<0.001*
APGAR 5 min					
Median	9 / 9	7 / 9	8 / 9	9 / 9	8 / 9
p-value	0.071	<0.001*	<0.001*	0.353	<0.001*
Birth Weight					
Median	2.225 / 2.125	1.5 / 2.15	2.04 / 2.55	1.525 / 2.15	1.98 / 2.15
p-value	0.178	<0.001*	<0.001*	0.051	<0.001*
Blood Sugar					
Median	121.5 / 130	104 / 130	128.5 / 139	101 / 130	127 / 130
p-value	0.023*	0.021*	0.029*	0.051*	0.690

A history of IUGR was not significantly associated with outcomes, although meconium aspiration (36/63 vs 9/35, p=0.003) and Neonatal Intensive Care Unit (NICU) admission (31/66 vs 19/25, p=0.013) were statistically significant, while low LBW (11/88 vs 2/42, p=0.221), hypoglycemia (2/97 vs 1/43, p-value<0.001), and perinatal death (5/94 vs 2/42, p<0.001) were not statistically significant. IUD was significantly associated with meconium aspiration (24/30 vs 21/68, p<0.001), but not with LBW (3/51 vs 10/79, p=0.209), neonatal intensive care unit admission (17/54 vs 33/87, p=0.436), or hypoglycemia (2/54 vs 1/87, p-value=0.558); however, it demonstrated a borderline significant association with perinatal death (0/54 vs 7/89, p-value=0.045). Mode of delivery (MOD) did not significantly influence meconium aspiration (26/50 vs 19/48, p-value=0.218), LBW (7/70 vs 6/61, p-value=0.975), hypoglycemia (2/74 vs 1/66, p-value = 1.000), or perinatal death (2/76 vs 5/62, p-value=0.243). However, neonatal intensive care unit (NICU) admission was significantly higher in cesarean sections compared to vaginal deliveries (22/64 vs 28/48, p-value=0.012) (Table 4).

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Table 4: Association of Maternal and Clinical Factors with Outcomes

Variables	Meconium Aspiration (Yes/No)	p-value	Low Birth Weight (Yes/No)	p-value	NICU Admission (Yes/No)	p-value	Hypoglycaemia (Yes/No)	p-value	Perinatal Death (Yes/No)	p-value
Previous History of IUGR										
Yes	9/35	0.003	2/42	0.221	19/25	0.013	1/43	<0.001	2/42	<0.001
No	36/63		11/88		31/66		2/97		5/94	
IUD										
Yes	24/30	<0.001	3/51	0.209	17/54	0.436	2/54	0.558	0/54	0.045
No	21/68		10/79		33/87		1/87		7/89	
Mode of Delivery										
Vaginal	26/50	–	7/70	–	28/48	–	2/74	–	2/76	–

DISCUSSION

Perinatal morbidity and death are associated with IUGR, which is a frequently observed situation in obstetrics [14]. Negative neonatal findings caused by intrauterine restrictive growth include hypoxia, poor neurodevelopment, and metabolic disorders in later life [15]. This study shows that intrauterine growth restriction in term pregnancies corresponds with a significant risk of negative neonatal outcomes. This study had a 4.9% perinatal mortality rate, and it's significant to consider that 37.8% of these deaths occurred within the uterus. These findings underscore the significant effects of affected fetal growth, even at term. The higher mortality observed in this study aligns with the findings of a study by Reibel *et al.* who found a substantially higher mortality rate among neonates with intrauterine growth restriction compared to appropriate-for-gestational-age extremely preterm infants (36.7% versus 7.1%, p<0.001) [16]. This study found that neonates with low birth weight showed markedly reduced Apgar scores, indicating the diminished physiological reserve typical of growth-restricted infants. A study conducted by Uniyal *et al.* found that neonates with IUGR had lower 5th-minute Apgar scores than controls [17]. The median birth weight difference of over 500g between neonates requiring admission to a neonatal intensive care unit (NICU) and those not requiring it underscores that even small reductions in birth weight have significant clinical implications. The NICU admission rate (35%) in the current study is higher than reported by Hubbard and Hay, suggesting higher disease severity in the current study participants [18]. The 31.5% prevalence of meconium aspiration in this study shows the significant fetal distress commonly associated with IUGR pregnancies. A study by Hubbard and Hay indicated that IUGR increases the risk of hypoglycemia due to reduced glycogen reserves and impaired glucose synthesis. The significant association between meconium aspiration and hypoglycemia shows that both arise from a common fetal problem [18]. Child hypoglycemia is a life-threatening disease with a complicated etiology and challenging diagnosis that requires early identification and comprehensive examination to prevent serious neurological complications [19]. In another study, most IUGR cases were found in women aged 21-25 years [20]. In a study, 22 of 120 IUGR cases (18.3%) died in the hospital, while 81.7% were discharged. Among the discharged infants, 66.3% were discharged in good condition, while 15.5% had abnormal neurological examinations. The morbidity and mortality patterns of complications indicated that hypoglycemia occurred in 63.3% of cases, while prenatal asphyxia was present in 45.0%, making them the most prevalent complications observed in the study [21]. The study confirms that IUGR infants are at significant risk of adverse outcomes. Our study revealed low hypoglycemia prevalence but high overall morbidity and mortality, suggesting population-specific variances or under-detection. Guidelines emphasize hypoglycemia as a serious concern. The use of a single diagnostic threshold and point-of-care testing shows the lack of universal criteria and practice variability, indicating the global need for standardized diagnostic and treatment protocols [22].

This study has some limitations. The findings may not generalize to other demographics or healthcare settings because this study was conducted at a single tertiary care hospital. The cross-sectional study design association, but not causal associations, between IUGR and neonatal outcomes. The outcomes may have been affected by maternal nutritional status, socioeconomic status, and prenatal care quality, which were not examined. Furthermore, the sample size was calculated based on a single neonatal measure finding (hypoglycemia) rather than a composite measure of morbidity and mortality, which may limit the generalizability of overall finding estimates.

CONCLUSIONS

This study illustrates that intrauterine growth restriction in term pregnancies is strongly linked to a high rate of neonatal morbidity and mortality, particularly neonatal intensive care unit admissions and respiratory issues. Early detection and optimized perinatal care are essential to improve outcomes.

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Authors' Contribution

Conceptualization: YA
Methodology: YA, ZN
Formal analysis: ZN, YQK
Writing and Drafting: ZN, YQK
Review and Editing: YA, ZN, YQK

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Effect of Collagen Cross-Linking on Corneal Thickness in Children with Progressive Keratoconus

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ABSTRACT

CXL tends to alter the collagen of the cornea via alteration of biochemical properties in Keratoconus using assisted riboflavin and UVA. This causes an increase in rigidity of the cornea and slows the progression of the disease. **Objectives:** To analyze the mean changes in corneal thickness after Corneal Collagen Cross-Linking (CXL) among children aged 8 to 15 years diagnosed with Keratoconus. **Methods:** This quasi-experimental study was conducted at the Department of Cornea, Al-Ibrahim Eye Hospital, Karachi, from March–September 2022. A sample size of 34 was calculated using G Power software with 80% power and a 95% confidence level. Non-probability consecutive sampling was used. Pediatric patients (8–15 years) with progressive keratoconus were included, while those with other ectatic disorders, active ocular disease, or prior anti-glaucoma medication were excluded. Ethical approval and informed consent were obtained. Clinical assessments were done before and after CXL, with follow-ups at weeks 4 and 12. Data were analyzed using SPSS version 23.0, applying appropriate statistical tests. **Results:** The study observed a mild reduction in keratometric values (K1, K2, Kmax) and central corneal thickness following collagen cross-linking in 34 children with progressive keratoconus over three months. Although Kmax decreased from 56.3 ± 10.3 to 53.4 ± 8.9 and corneal thickness from 487.88 ± 31.66 µm to 485.73 ± 31.90 µm, these changes were not statistically significant, indicating early stabilization without significant structural alteration. **Conclusions:** Collagen cross-linking in children with progressive keratoconus appears to stabilize corneal curvature with minimal impact on central corneal thickness over a short-term period, though changes are not statistically significant.

INTRODUCTION

Keratoconus is defined as a progressive, asymmetric, bilateral corneal ectasia of a non-inflammatory variety. Instability in the corneal collagen fibers causes thinning and a progressive increase in the curvature of the cornea [1]. This leads to loss of visual acuity with irregular astigmatism. Typically, Keratoconus presents during puberty, which tends to stabilize by the fourth decade of life [2]. In children <15 years of age, Keratoconus is seldom advanced at the time of diagnosis and might rapidly progress in children as compared to adults [3]. In treating Keratoconus, collagen cross-linking (CXL) causes strengthening of collagen bonds in the corneal stroma coupled with ultraviolet A (UVA) that is activated using riboflavin [4]. Initially, CXL was introduced by Wollensak and colleagues, while now it is regarded as the first line of treatment in patients having progressive Keratoconus [5]. Even the ability to halt progression of Keratoconus amongst adults has been established well in the published literature. Treating pediatric Keratoconus using CXL is an area of research that is limited [6, 7]. In the pediatric population with Keratoconus, progression has been reported in as high as 88 % of patients over a period of one year [8]. The requirement for penetrating keratoplasty among children is observed to be 7 times higher than in adults because of the disease's aggressive nature (especially in children below the age of 18 years) [9]. To

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avoid penetrating keratoplasty, it has become a necessity to halt or slow down Keratoconus progression using a more rapid and effective technique [10]. CXL tends to alter the collagen of the cornea via alteration of biochemical properties in Keratoconus using assisted riboflavin and UVA [11]. This causes an increase in rigidity of the cornea and slows the progression of the disease. In the procedure of standard epithelium-off CXL (SCXL) procedure, 5.4 J/cm2 of energy is delivered using 3 mW/cm2 intensity over the next 30 minutes (using the Dresden protocol) [12]. With the use of the standard protocol, visual stabilization coupled with decreasing keratometric values and reduced progression of KCN were observed in studies done on pediatric populations [13]. The etiology of KCN is unknown. Various associations are identified, including contact lens wear (rigid gas permeable, RGP), Down syndrome, Leber congenital amaurosis, chronic eye rubbing, and atopic disease/s [14]. A positive family history of KCN is found in around 6 to 8 % of patients, demonstrating possible familial transmission [15].

Even though CXL is a well-known treatment for halting Keratoconus progression, the majority of the researches have studies adult patients. With regards to corneal thickness specifically in the pediatric population, limited data persists, especially in patients exhibiting a more aggressive progression of disease. Moreover, local studies from developing populations also remain scarce. Progressive keratoconus amongst the pediatric age group causes rapid thinning of the cornea, resulting in deterioration of vision, substantially affecting quality of life. Whilst CXL is rising among children, its exact effect on the thickness of the cornea is not well established in the literature. This creates uncertainty in making clinical decisions and in devising management strategies in the long term. This study aimed to evaluate the effect (mean change) of corneal CXL on the thickness of the cornea in a pediatric population aged 8 to 15 years, diagnosed with Keratoconus.

METHODS

This was quasi-experimental research (pre and post-interventional study) carried out at the Department of Cornea, Al-Ibrahim Eye Hospital, Karachi, from March 2022 to September 2022. After ethical approval from the ERC (Ethical Review Committee) (Ref: ATMC/IERC/12(2021) dated 22 March 2021) of Al-Ibrahim Eye Hospital, data collection commenced. Using the freely available G*Power software for sample size calculation, the sample size was calculated as follows: with 80% power, 95% confidence level, a 5% margin of error, and mean pre-CXL of 486.9 ± 26.5 and post-CXL of 474.8 ± 28.6 [16]. The sample size came out to be 34. The sampling technique used for this research was a non-probability consecutive sampling technique. All eligible patients attending the department during the study period were selected to minimize selection bias. Pediatric population of either gender aged between 8 and 15 years, diagnosed with progressive Keratoconus with frequent changes in refractive error within the last three months, either before or after presenting in OPD, were included in the research. Patients with corneal progressive ectatic disorders apart from Keratoconus, such as pellucid marginal degeneration and Keratoglobus, were excluded from the study. In addition, patients having a history of active ocular disease such as allergy, inflammation, and infection, with severe corneal opacification or scarring on slip lamp examination, were also excluded. Patients with a history of anti-glaucoma drugs (Prostaglandin analogues) were also excluded from the research. All patients underwent standard epithelium-off collagen CXL (Dresden protocol), which was performed by an experienced ophthalmologist under aseptic measures. This ensured consistency of the procedure across all cases. Baseline ophthalmic examination was performed for all participants, including uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), slit lamp examination, fundoscopy, and refraction assessment. Patients attending the cornea clinic of the hospital were included as per the inclusion and exclusion criteria. A self-designed questionnaire was utilized for analysis of data. A thorough clinical examination was carried out along with history taking before and after CXL (which was carried out by an experienced Ophthalmologist). Informed consent was obtained from each patient before inclusion in the study. Baseline corneal thickness (central corneal thickness and thinnest corneal thickness) was measured before collagen cross-linking using pachymetry or Scheimpflug imaging. Progressive keratoconus was identified based on an increase in keratometric readings, reduction in corneal thickness, deterioration of visual acuity, or increase in refractive error over time.

Data analysis was carried out using SPSS version 23.0. Demographical information of patients included age, gender, and duration of KCN. Follow-up of patients was done at the 4th and 12th week post-CXL. The primary outcome measure was the change in thickness of the cornea. The secondary outcome measure was the change in keratometric parameters such as K1, K2, and Kmax, which were measured at baseline, 4 weeks, and at 12 weeks post-CXL. Continuous variables such as age, thinnest corneal thickness, K1, K2, Kmax, best corrected and uncorrected visual acuity were represented as mean and standard deviation (if normally distributed), while median and interquartile range (if data were skewed). Normality of data was tested using the Shapiro-Wilk test. Categorical data were recorded as frequency and percentage for

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gender. Stratification was done for confounders/effect modifiers such as gender, age, K1, K2, best and uncorrected visual acuity. Post-stratification, independent t-test was applied. From baseline, week four, and week twelve, comparison of mean differences of central corneal thickness was carried out using repeated measures ANOVA, keeping $p<0.05$ statistically significant.

RESULTS

The baseline demographics of patients included in the study are presented. The mean age of patients was 10.3 ± 3.15 years, with 19 (55.88 %) males and 15 (44.12 %) females. The mean duration of Keratoconus was 8.3 ± 2.9 months (Table 1).

Table 1: Baseline Demographics of Patients Included (n=34)

Variables	Frequency (%) / Mean ± SD
Age (years)	10.3 ± 3.15
Male	19 (55.88 %)
Female	15 (44.12 %)
Mean Duration of Keratoconus (months)	8.3 ± 2.9

The study illustrates the graphical comparison of keratometric values K1, K2, and Kmax before and after collagen cross-linking (CXL) in 34 children with progressive keratoconus. The mean K1 value decreased from 46.7 ± 4.5 diopters pre-operatively to 46.1 ± 4.4 at one month and 45.8 ± 3.9 at three months post-operatively. Similarly, the mean K2 value reduced from 50.2 ± 5.1 to 49.8 ± 4.8 at one month and further to 49.1 ± 4.6 at three months. The steepest keratometric value, Kmax, showed a decrease from 56.3 ± 10.3 pre-operatively to 55.7 ± 9.8 after one month and 53.4 ± 8.9 at the third month. All three keratometric indices demonstrated a consistent downward trend, indicative of corneal flattening following CXL (Table 2).

Table 2: Comparison of Mean K1, K2 And Kmax at Baseline, One Month Post-Op and Third Month Post-Op (n=34)

Variables	Mean ± SD	p-value
K1 Pre-Operative	46.7 ± 4.5	0.32
K1 Post-Operative 1 Month	46.1 ± 4.4	
K1 Post-Operative 3 Months	45.8 ± 3.9	
K2 Pre-Operative	50.2 ± 5.1	0.25
K2 Post-Operative 1 Month	49.8 ± 4.8	
K2 Post-Operative 3 Months	49.1 ± 4.6	
Kmax Pre-Operative	56.3 ± 10.3	0.25
Kmax Post-Operative 1 Month	55.7 ± 9.8	
Kmax Post-Operative 3 Months	53.4 ± 8.9	

The results provide a statistical comparison of mean central corneal thickness measured at baseline, one month, and three months after CXL. The mean corneal thickness at baseline was 487.88 ± 31.66 µm, followed by 486.73 ± 31.90 µm at one month and 485.73 ± 31.90 µm at three months. The ANOVA analysis yielded a mean square value of 39.35, an F statistic of 0.04, and a p-value of 0.96, indicating no statistically significant difference in corneal thickness over the study period. The 95% confidence intervals further support the consistency of the measurements: 476.83–498.92 at baseline, 475.60–497.86 at one month, and 474.60–496.86 at three months post-operatively (Table 3).

Table 3: Comparison of Mean Central Corneal Thickness Differences Between Baseline, One Month Post-Op and Third Month Post-Op (n=34)

Time Period of Measurement	Mean ± SD	Mean Square	F Statistics	95 % Confidence Interval	p-value
Baseline	487.88 ± 31.66	39.35	0.04	476.83- 498.92	0.96
Post-Op One Month	486.73 ± 31.90			475.60- 497.86	
Post-Op Third Month	485.73 ± 31.90			474.60-496.86	

DISCUSSION

In this study involving 34 children with progressive keratoconus, collagen cross-linking (CXL) resulted in a mild but consistent reduction in keratometric values and central corneal thickness over three months. The mean K1 decreased from 46.7 ± 4.5 to 45.8 ± 3.9 diopters, K2 from 50.2 ± 5.1 to 49.1 ± 4.6, and Kmax from 56.3 ± 10.3 to 53.4 ± 8.9, indicating a trend toward corneal flattening; however, these changes were not statistically significant ($p > 0.05$). Similarly, central corneal thickness showed a slight decrease from 487.88 ± 31.66 µm at baseline to 485.73 ± 31.90 µm at three months, with no significant difference over time ($p=0.96$). Similar results have been observed in other research as well [17]. Literature supports the use of CXL in pediatric Keratoconus [18]. The researchers reported CXL to be both safer and efficacious compared with other modalities for improving uncorrected distance visual acuity as well as corrected distance visual acuity among < 18-year-olds [19]. In current research, the mean age of the pediatric population was 11.3 ± 2.2 years. Similarly, another study also observed similar results, with a mean age of 12 ± 2.02 years in the study [16]. A study by Ng et al. observed the mean age of patients with Keratoconus to be 15.7 ± 2.1 years [20]. Likewise, the current study observed a reduction in mean corneal thickness from pre-operative to post-operative three months, even though insignificant, was also reported by a study from Egypt, where pre-operative mean corneal thickness was reduced from 486.9 ± 26.5 um to 474.8 ± 28.6 um and 470.2 ± 28.3 um at third and sixth month, respectively [16]. Ng *et al.* in their study found a reduction of mean corneal thickness from 469.6 ± 19.1 um to 467.7 ± 21.4 um post-operatively [20].

Although our study evaluated the mean change in corneal thickness pre-operatively and post-operatively at 1st and 3rd month, the study was not free from limitations. The sample size of the study was very limited since this was single-centered research. Even though the study made use

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of consecutive sampling, which is best suited for the study design used in the research. The findings of this study suggest that while CXL may help stabilize keratometric parameters in pediatric patients, its short-term effect on corneal thickness and curvature is not statistically significant. Larger long-term multicenter studies with larger paediatric populations and longer follow-up (>12 months) are required to confirm long-term stability of corneal thickness and keratometric parameters in children with progressive keratoconus after CXL.

CONCLUSIONS

Collagen cross-linking in children with progressive keratoconus appears to stabilize corneal curvature with minimal impact on central corneal thickness over a short-term period, though changes are not statistically significant.

Authors' Contribution

Conceptualization: NK
Methodology: NK, ST
Formal analysis: NK
Writing and Drafting: AF, AS, IA, MSF
Review and Editing: NK, AF, ST, AS, IA, MSF

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Diagnostic Accuracy and Surgical Outcomes of Deep Infiltrating Endometriosis Involving the Urinary Tract: A Systematic Review

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ABSTRACT

Deep infiltrating endometriosis (DIE) involving the urinary tract represents a severe phenotype of endometriosis that poses major diagnostic and surgical challenges. Accurate preoperative imaging and optimal surgical management are essential to prevent silent obstruction and long-term renal damage. **Objectives:** To evaluate the diagnostic accuracy of imaging modalities and to summarize surgical outcomes in patients with urinary tract deep infiltrating endometriosis. **Methods:** This systematic review was conducted in accordance with PRISMA 2020 guidelines. PubMed, Scopus, and the Cochrane Library were searched for studies published between January 2018 and March 2025. Diagnostic-accuracy studies and outcome-only surgical cohorts were synthesized as distinct evidence streams. Methodological quality was assessed using QUADAS-2 for diagnostic studies and the Newcastle–Ottawa Scale for surgical cohorts. **Results:** Twelve studies were included, comprising two formal diagnostic-accuracy studies and ten surgical outcome cohorts. Transvaginal ultrasonography using the IDEA protocol demonstrated high diagnostic performance (sensitivity 93.9%, specificity 99.4%, accuracy 98.7%), while magnetic resonance imaging showed good sensitivity (83.3%) and excellent negative predictive value (93.5%). Most surgical cohorts reported favorable postoperative outcomes with low urinary tract–specific recurrence when managed in specialized centers. However, none of the studies reported confidence intervals or complete diagnostic contingency matrices. **Conclusions:** Transvaginal ultrasonography and magnetic resonance imaging are complementary and highly specific modalities for diagnosing urinary tract DIE, and minimally invasive surgery yields favorable outcomes. Standardized diagnostic reporting and prospective multicenter diagnostic-accuracy studies are required to strengthen evidence-based clinical pathways.

INTRODUCTION

Endometriosis is a chronic estrogen-sensitive inflammatory disease characterized by the presence of functional endometrial glands and stroma outside the uterine cavity, affecting approximately 6–10% of women of reproductive age worldwide [1]. One of its most severe and clinically aggressive phenotypes is deep infiltrating endometriosis (DIE), defined by endometriotic tissue infiltrating more than 5 mm beneath the peritoneal surface. DIE is commonly associated with severe pelvic pain, infertility, and multisystem involvement, frequently affecting pelvic organs such as the bowel, bladder, and ureters [2, 3]. Urinary tract endometriosis (UTE) accounts for approximately 1–2% of all cases of endometriosis and up to 20–50% of DIE presentations, with the bladder and ureters being the most commonly involved sites [4]. Ureteric involvement is of particular clinical concern because it may remain asymptomatic until significant obstruction or hydronephrosis develops, leading to

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progressive renal impairment. Delayed diagnosis, therefore, represents a serious risk for irreversible renal damage, underscoring the critical importance of accurate preoperative identification [5, 6]. Urinary tract DIE is primarily managed by surgical excision, with minimally invasive laparoscopic approaches increasingly favored because of improved postoperative outcomes and organ preservation [7]. Recent advances, including the standardization of imaging protocols such as the International Deep Endometriosis Analysis (IDEA) consensus, have improved lesion mapping and surgical planning. Nevertheless, despite their widespread use, there remains substantial heterogeneity in diagnostic reporting, and only a limited number of studies provide complete parameters of diagnostic accuracy for urinary tract DIE. This lack of standardized diagnostic data hinders quantitative synthesis and the development of robust evidence-based guidelines [8]. Urinary-tract DIE, symptomatic management of which remains based on surgical excision, is becoming more popular using minimally invasive laparoscopic methods because of enhanced postoperative outcome and retention of organs [9].

However, reported recurrence rates, complication profiles, and long-term functional outcomes vary considerably across published series, reflecting differences in surgical techniques, patient selection, and outcome definitions. Given these diagnostic and therapeutic challenges, an updated systematic synthesis of contemporary evidence is required. Therefore, this systematic review was conducted to evaluate the diagnostic accuracy of imaging modalities and to summarize surgical outcomes of urinary tract deep infiltrating endometriosis, to inform standardized diagnostic pathways and optimize multidisciplinary surgical management. This study aims to assess the diagnostic performance of transvaginal ultrasonography and magnetic resonance imaging for the detection of deep infiltrating endometriosis of the urinary tract; to describe postoperative outcomes, recurrence rates, and complications following surgical management; and to identify gaps in standardized diagnostic reporting and priorities for future research.

METHODS

The systematic review was performed according to the Preferred Reporting Items on Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The aim of the review was to summarize the current evidence on the diagnostic quality of imaging modalities and the surgical outcome of deep infiltrating endometriosis of the urinary tract. Diagnostic-accuracy studies and outcome-only surgical cohorts were considered as two distinct evidence streams and were synthesized separately. A systematic literature review was conducted in PubMed, Scopus, and the Cochrane Library to find the relevant studies published between January 2018 and March 2025. The PubMed search strategy included the Medical Subject Headings (MeSH) and free-text keywords with the following syntax ("Endometriosis"[Mesh] OR "Deep Infiltrating Endometriosis" OR "Urinary Tract Endometriosis" OR "Bladder Endometriosis" OR "Ureteral Endometriosis") AND ("Ultrasonography"[Mesh] OR "Transvaginal Ultrasonography" OR "Magnetic Resonance Imaging"[Mesh] OR MRI) AND ("Diagnosis"[Mesh] OR "Diagnostic Imaging"[Mesh] OR "Sensitivity and Specificity"[Mesh]). Treatment- and surgery-related terms were used only to capture combined diagnostic–surgical studies and were not prioritized to define diagnostic accuracy evidence. Scopus and Cochrane were adjusted to equivalent keyword combinations and Boolean operators. Included studies reference lists were also screened manually to provide full coverage. Research articles that were original and provided diagnostic imaging results and/or surgical outcomes in patients with bladder or ureteric deep infiltrating endometriosis were eligible to be included in the research. These were prospective cohorts, retrospective cohorts, diagnostic accuracy studies, and retrospective case series of surgery. Articles written in English that are published after 2018 and before 2025 were only taken into account. The exclusion criteria were narrative reviews, systematic reviews, meta-analyses, animal studies, conference abstracts, case reports, and studies that did not have urinary tract involvement or quantitative clinical outcomes. Diagnostic-accuracy studies were required to use surgery and/or histopathology as the reference standard. Two reviewers independently screened titles and abstracts after duplicate removal. Potentially relevant articles underwent full-text assessment for eligibility, and disagreements were resolved by consensus. The PRISMA 2020 flow diagram summarizes the study selection process. Reasons for full-text exclusion were explicitly recorded and reported. Reasons for full-text exclusion were explicitly recorded and reported. Data were extracted through the use of standardized data collection form that constituted author details, year of publication, country, study design, size of the sample used, location of the urinary tract that was involved, type of imaging modality used, reference standard, type of surgical procedure, postoperative complications, recurrence rates, and duration of follow-up. Where applicable, diagnostic accuracy parameters such as sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and area under the curve were extracted; confidence intervals were recorded when

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reported. Diagnostic accuracy claims were restricted to formal diagnostic studies reporting numerical sensitivity and specificity and/or ROC-based analyses; outcome-only surgical cohorts were not used for diagnostic inference. Methodological quality was assessed using modality-appropriate tools. Formal diagnostic accuracy studies were evaluated using the QUADAS-2 tool, while observational surgical outcome cohorts were assessed using an adapted Newcastle–Ottawa Scale. This instrument assessed four areas, including selection of study groups, comparability of cohorts, outcome assessment, and sufficiency of follow-up. Each study was classified as having low, moderate, or high risk of bias. As a result of high heterogeneity in study design, imaging protocols, surgical procedure, outcome definitions, and lack of uniform reporting of diagnostic contingency matrices, statistical pooling of data was not possible. Very few studies provided full sensitivity and specificity, and the majority of cohorts were not created to determine the accuracy of diagnosing, but to determine surgical results. Thus, no meta-analysis was conducted, and the results were synthesized descriptively and presented in table form. A qualitative GRADE-based certainty assessment was performed, as formal domain-based GRADE profiling was not feasible due to the absence of meta-analysis, high heterogeneity, and predominance of observational study designs, indicating overall low-to-moderate certainty of evidence. A total of 330 records were identified through database searching (PubMed 148, Scopus 132, Cochrane 50). Before screening, 120 records were removed (94 duplicates and 26 removed for other reasons), leaving 210 records for title/abstract screening; 160 were excluded at this stage, and 50 reports were sought for retrieval. Six reports were not retrieved, 44 full-text articles were assessed for eligibility; 32 were excluded for predefined reasons (not quantitative/insufficient outcomes n=10, case reports/reviews n=14, and no urinary-tract involvement n=8), resulting in 12 studies included in the qualitative synthesis (Figure 1).

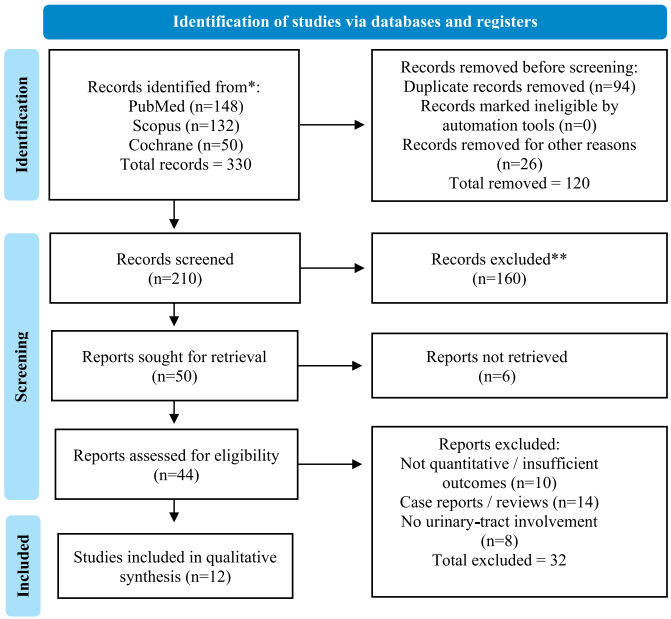

Figure 1: The Study Selection Process from Identification to Final Inclusion

RESULTS

Results summarize the characteristics of the included studies. The evidence base was predominantly composed of prospective and retrospective observational surgical cohorts conducted in tertiary referral centers, reflecting the complexity of urinary-tract deep infiltrating endometriosis (DIE). Only two studies were formal diagnostic-accuracy designs and were analyzed separately from outcome-only surgical series to avoid mixing evidence streams. Sample sizes varied widely, ranging from small case series to multicenter cohorts exceeding 200 participants, indicating heterogeneity in study power and population representativeness (Table 1).

Table 1: Characteristics of Included Studies on Urinary-Tract Deep Infiltration Endometriosis, Retrospective Cohort Studies, Diagnostic Accuracy Studies and Surgical Technique / Case Series (2018–2025)

Sr. No.	References	Country / Setting	Study Design, Modality Assessed	Sample Size	Urinary Tract Site	Reference Standard, Surgical Technique	Follow-up
Prospective / Multicenter Cohort Studies							
1	[10]	Italy, tertiary referral center	Prospective cohort	160	Ureter	Surgery + Histology	36 Months
2	[11]	France, multicenter	Prospective cohort	232	Bladder and ureter	Surgery	24 Months
Retrospective Cohort Studies							
3	[12]	Portugal	–	55	Bladder and ureter	Laparoscopic Excision; Recurrence and Complications	120 Months
4	[13]	Italy	–	105	Bladder and ureter	Predictors of Recurrence	48 Months
5	[14]	China	–	68	Ureter	Ureterolysis/Ureterectomy	36 Months
6	[15]	Germany	–	25	Bladder	Partial Cystectomy Outcomes	24 Months
Diagnostic Accuracy Studies							
7	[16]	–	TVUS (IDEA protocol)	74	Bladder and ureter DIE	Surgery	–
8	[17]	–	MRI	33 lesions	Intrinsic ureter DIE	Histology	–

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Surgical Technique / Case Series							
9	[18]	Japan	–	12	Bladder	"See-Through" Partial Cystectomy	–
10	[19]	Thailand	–	41	Bladder	Laparoscopic Partial Cystectomy	–
11	[20]	Italy	–	98	Bladder	Laparoscopic Bladder Wall Resection	–
12	[21]	USA	–	37	Ureter	Laparoscopic Ureterolysis	–

The study summarizes diagnostic accuracy reporting across included studies. Only two studies were formal diagnostic-accuracy investigations and reported numerical diagnostic performance metrics. The remaining cohorts primarily evaluated surgical outcomes and did not provide diagnostic contingency matrices, limiting comparative assessment of imaging performance. Therefore, diagnostic performance statements in this review are restricted to the two studies reporting numerical diagnostic accuracy metrics (Szabó 2022 and Rennan 2024), and outcome-only surgical cohorts were not used to infer diagnostic accuracy. In the two diagnostic studies, transvaginal ultrasonography (TVUS) using the IDEA protocol demonstrated sensitivity 93.9%, specificity 99.4%, PPV 95.8%, NPV 99.1%, and accuracy 98.7%, while MRI showed sensitivity 83.3%, specificity 77.8%, PPV 55.6%, NPV 93.5%, and AUC 0.806. No study reported 95% confidence intervals for sensitivity/specificity, and TP/FP/TN/FN numerical counts were not presented in the extracted results, despite both diagnostic studies indicating that diagnostic matrices were available. These reporting limitations precluded a pooled quantitative synthesis of diagnostic accuracy outcomes (Table 2).

Table 2: Diagnostic Accuracy Reporting in Included Studies

Sr. No.	References	Imaging modality	Did Study Report TP/FP/TN/FN?	Sensitivity	Specificity	PPV	NPV	Notes
1	[10]	MRI / US	No	NR	NR	NR	NR	Surgical outcome cohort; imaging used for preoperative assessment only; no diagnostic accuracy statistics reported
2	[20]	MRI / US / CT	No	NR	NR	NR	NR	Imaging used for surgical planning only; no contingency diagnostic analysis
3	[11]	MRI	No	NR	NR	NR	NR	Multicenter pilot outcome study; no diagnostic accuracy statistics reported
4	[12]	MRI/CT	No	NR	NR	NR	NR	Surgical outcome cohort
5	[13]	MRI	No	NR	NR	NR	NR	Recurrence-prediction cohort
6	[14]	CT / MRI	No	NR	NR	NR	NR	Surgical series
7	[15]	MRI	No	NR	NR	NR	NR	Bladder DIE surgical outcomes
8	[21]	MRI	No	NR	NR	NR	NR	Surgical recurrence cohort
9	[18]	MRI	No	NR	NR	NR	NR	Case series
10	[19]	TVUS	No	NR	NR	NR	NR	Descriptive verification only (no diagnostic matrix)
11	[16]	TVUS (IDEA protocol)	Yes (formal diagnostic accuracy study)	93.9%	99.4%	95.8%	99.1%	98.7% accuracy
12	[17]	MRI	Yes (ROC analysis)	83.3%	77.8%	55.6%	93.5%	AUC 0.806

95% confidence intervals and TP/FP/TN/FN counts were not reported in the extracted results for any included study; NR indicates not reported

The study summarizes postoperative outcomes and recurrence after surgical management of urinary-tract DIE. Across cohorts, minimally invasive approaches, particularly laparoscopic techniques, were the dominant surgical modality. Reported postoperative morbidity was generally low in specialized centers, and several studies documented low urinary-tract–specific recurrence during follow-up. However, outcome definitions, complication reporting, and follow-up duration varied across studies, limiting direct comparability and preventing pooled estimation of surgical outcomes (Table 3).

Table 3: Surgical Outcomes and Recurrence After Surgery for Urinary-Tract Deep Infiltrating Endometriosis (2018–2025)

Sr. No.	References	N	Urinary Tract Site	Key Surgical Approach (Reported)	Post-Op Complications	Recurrence / Relapse	Follow-up
1	[10]	160	Ureter (intrinsic/extrinsic)	Laparoscopic ureteroneocystostomy (many with extensive ureterolysis; psoas hitch described)	No major complications reported; bladder dysfunction/bladder dyskinesia 15% (reported as related to parametrial disease/parametrectomy)	1.2% recurrence + significant symptom regression ($p<0.001$)	–
2	[11]	232	Bladder + ureter	Surgical management patterns (laparoscopy/laparotomy/robot; ureterolysis/resection nephrectomy/cystectomy)	NR	NR	12 months

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3	[12]	55	Bladder/ureter / mixed	All managed laparoscopically (1 conversion mentioned)	10.9% overall complications (6/55); Clavien-Dindo: Grade I (2), Grade II (2), Grade IIIb needing surgery (2)	10.9% recurrence (overall); no urinary-tract recurrence observed	Long-term cohort (10-year frame stated; specific follow-up distribution not required if not explicit)
4	[13]	105	Ureter (50.5%) + bladder (49.5%)	Partial cystectomy 49.5%; ureteral reimplantation 23.8%; ureterolysis 15.3%; ureter end-to-end 6.7%; nephrectomy 4.7%	NR	28.6% overall relapse; 13.3% urinary-tract recurrences; median time to urologic recurrence 12 months d	Median 39 months (IQR 22–51)
5	[14]	68	Ureter	Ureterolysis/ureterectomy	NR	NR	NR
6	[15]	25	Bladder	Laparoscopic partial cystectomy / shaving discussed	NR	NR	NR
7	[20]	264	Bladder (some ureter obstruction)	Laparoscopic bladder resection; bowel resection in 53%; ureteroneocystostomy in 9.5%	Major complications <28 days: 7.2% (19/264)	2.3% recurrence	Follow-up visits at 1, 6, 12 months
8	[18]	12	Bladder	"See-through" laparoscopic partial cystectomy	NR	NR	NR
9	[19]	18	Bladder	Laparoscopic partial cystectomy (LPC)	NR	NR	NR
10	[16]	74	Bladder + ureter DIE	(Mainly imaging study; surgery mentioned as management)	NR	NR	NR
11	[17]	33 lesions	Intrinsic ureter DIE	Diagnostic paper (ROC)	NR	NR	NR
12	[21]	37	Ureter	Laparoscopic ureterolysis	NR	NR	NR

The results present the risk of bias assessment of included studies. Larger prospective and multicenter cohorts generally demonstrated low-to-moderate risk of bias, whereas small case series and early surgical technique reports tended to show higher risk, mainly due to limited comparability and incomplete follow-up reporting. Overall, the methodological quality was acceptable for qualitative synthesis, but the predominance of observational designs limits certainty of inference (Table 4).

Table 2: Risk of Bias Assessment of Included Studies

Sr. No.	References	Selection Bias	Comparability	Outcome Assessment	Follow-Up Adequacy	Overall Risk of Bias
1	[10]	Low	Moderate	Low	Low	Low
2	[11]	Low	Moderate	Moderate	Low	Moderate
3	[12]	Low	Moderate	Low	Low	Low
4	[13]	Low	Moderate	Low	Low	Low
5	[14]	Moderate	Moderate	Moderate	Moderate	Moderate
6	[15]	Moderate	Moderate	Moderate	Moderate	Moderate
7	[20]	Low	Moderate	Low	Low	Low
8	[18]	Moderate	High	Moderate	Moderate	High
9	[19]	Moderate	Moderate	Moderate	Low	Moderate
10	[16]	Low	Low	Low	Low	Low
11	[17]	Low	Low	Low	Low	Low
12	[21]	High	High	High	High	High

DISCUSSION

This systematic review indicates that deep infiltrating endometriosis (DIE) involving the urinary tract (bladder and ureters) remains a major challenge in both diagnostic pathways and surgical management because of its complex anatomy and often insidious clinical presentation. The present qualitative synthesis is supported and contextualized by international evidence from the past five years demonstrating substantial advances in diagnostic imaging, surgical outcomes, and multidisciplinary management strategies. Recent comparative imaging studies confirm that transvaginal ultrasonography (TVUS) and magnetic resonance imaging (MRI) are highly specific modalities for identifying urinary tract DIE, although each demonstrates differential performance depending on lesion location. In a 2025 systematic review, the combined use of these two modalities in preoperative planning was shown to improve lesion mapping and surgical decision-making, particularly within multidisciplinary care

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pathways. MRI was superior in delineating complex anatomy, whereas TVUS remained highly specific for selected anatomic compartments [22]. Similarly, high specificity for urinary tract DIE has been reported with structured imaging protocols, including the IDEA consensus, which enables surgeons to better anticipate intraoperative findings [22]. Current evidence supports the use of TVUS as a first-line imaging modality in DIE, particularly for selected ureteric lesions when performed by an experienced operator [23-25]. An innovation in MRI fusion 3D T1/T2 imaging in 2025 demonstrated non-inferior diagnostic accuracy and improved reproducibility compared with conventional MRI sequences, suggesting that imaging technology may continue to enhance preoperative assessment [26]. International imaging studies consistently emphasize that delayed or missed diagnosis may contribute to silent obstructive complications, particularly in ureteral disease, which can progress to hydronephrosis if not detected at an early stage [27]. Recent international cohorts and clinical reviews over the past five years support laparoscopic and minimally invasive approaches for urinary tract DIE, in agreement with the present findings of favorable surgical outcomes and acceptable complication rates when procedures are performed by specialized teams [28-30]. A large retrospective surgical series published in 2025 demonstrated that laparoscopic partial cystectomy or bladder shaving provided symptomatic relief in more than 90% of patients with bladder DIE, with low perioperative morbidity in the setting of interdisciplinary collaboration [31]. Narrative reviews and clinical analyses further support that complete excision of bladder DIE through shaving or partial cystectomy results in sustained symptom reduction and low recurrence rates when performed in high-volume centers [32]. Advanced minimally invasive techniques, including robotic-assisted laparoscopy, are increasingly reported in the literature as feasible alternatives with outcomes comparable to standard laparoscopy in complex DIE cases [33]. Contemporary case-based practice also highlights the role of multidisciplinary approaches, such as combined laparoscopic and ureteroscopic techniques for ureteral DIE with stricture formation, in restoring urinary tract function and preventing irreversible renal damage [34]. Recent studies focusing on patient-reported outcomes emphasize that urinary tract DIE significantly impairs quality of life through chronic pain, dysuria, and storage symptoms, and that surgical and multidisciplinary management leads to meaningful improvements in quality-of-life measures [27]. Symptom-guided diagnostic studies recommend maintaining a high index of suspicion for DIE in women with refractory pelvic or urinary symptoms, as delayed diagnosis is associated with prolonged morbidity [35].

The literature on standardized diagnostic accuracy reporting remains limited, although incremental improvements are evident. Only a small number of studies report complete diagnostic contingency matrices (TP, FP, TN, FN), which precludes quantitative pooling and robust meta-analysis. Structured reporting systems incorporating the Enzian classification or other standardized staging frameworks have therefore been repeatedly recommended for preoperative imaging reports. In addition, although emerging technologies such as 3D fusion MRI appear promising, their performance has so far been demonstrated only in early validation cohorts, and large multicenter studies are still required to establish reproducibility and generalizability across diverse clinical populations. Formal domain-based GRADE profiling was not feasible because of the absence of meta-analysis, high heterogeneity, and the predominance of observational study designs; therefore, only a qualitative assessment of evidence certainty was possible.

CONCLUSIONS

In summary, contemporary evidence indicates that transvaginal ultrasonography and magnetic resonance imaging are complementary imaging modalities with high specificity for the detection of urinary-tract deep infiltrating endometriosis, thereby enhancing preoperative mapping and multidisciplinary surgical planning. Organized imaging procedures, such as the IDEA criteria, and new methods, such as three-dimensional MRI fusion, have proven to show encouraging gains in diagnostic performance. Minimally invasive surgical management performed in specialized centers is associated with favorable postoperative outcomes, low recurrence rates, and significant symptomatic relief. Nevertheless, substantial heterogeneity in diagnostic reporting and surgical outcome definitions persists, limiting quantitative synthesis and comparability across studies. These findings highlight the need for standardized diagnostic-accuracy studies and prospective multicenter registries to strengthen evidence-based clinical pathways for this complex disease phenotype.

Authors' Contribution

Conceptualization: MAK, ZM[2]
Methodology: ZM[1]
Formal analysis: SU
Writing and Drafting: MAK, MUR, SU, ZM[1], ZM[2], SF
Review and Editing: MAK, MUR, SU ZM[1], ZM[2], SF

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

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Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Role of Cytochrome P450 Enzymes in Pediatric Drug Metabolism: Physiological and Biochemical Perspectives; Systematic Review

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ABSTRACT

Cytochrome P450 (CYP450) enzymes are central to pediatric drug metabolism. However, enzyme maturation (ontogeny) and pharmacogenetic variability produce substantial age-dependent differences in drug clearance, exposure, and toxicity risk across neonatal, infant, and childhood populations. Objectives: To synthesize contemporary evidence (2020–2025) on CYP450 ontogeny and pharmacogenetic variability in children and evaluate their clinical implications for drug clearance, dosing optimization, and safety. Methods: A systematic review was conducted according to PRISMA 2020 guidelines. PubMed, Scopus, Web of Science, and Google Scholar were searched for pediatric studies evaluating CYP450 ontogeny, pharmacokinetics, or pharmacogenetics. Eligible designs included observational studies, physiologically based pharmacokinetic (PBPK)/population PK modeling, real-world analyses, and systematic reviews. Risk of bias was assessed using the Newcastle–Ottawa Scale and AMSTAR. Due to heterogeneity, findings were synthesized narratively. Results: Sixteen studies from Asia, Europe, North America, and Australia were included. CYP2C19, CYP3A4, and CYP2D6 were the most frequently investigated isoforms. Ontogeny demonstrated enzyme-specific maturation patterns: CYP3A4 and CYP2C19 activity increased rapidly during infancy, whereas CYP2D6 and CYP1A2 matured more gradually, contributing to reduced neonatal clearance and prolonged half-life of several substrates. Clinically significant genotype–drug interactions were consistently reported for CYP2D6–codeine and CYP2C19–voriconazole/proton pump inhibitors, where poor or ultrarapid metabolizer phenotypes markedly altered exposure and toxicity risk. Evidence supports genotype-guided dosing and therapeutic drug monitoring for selected high-risk drugs. Conclusions: Pediatric drug clearance is governed by enzyme-specific maturation and functional polymorphisms. Integrating developmental dosing principles with targeted pharmacogenetic strategies may improve therapeutic precision and reduce avoidable toxicity in children.

INTRODUCTION

Cytochrome P450 (CYP450) enzymes play a central role in the metabolism of many medications prescribed in pediatric practice, including sedatives, opioids, antifungals, proton pump inhibitors, immunosuppressants, and antiseizure drugs. Pediatric pharmacotherapy presents unique challenges because drug exposure varies significantly across developmental stages, and the consequences of underdosing or overdosing may be more severe in neonates and infants [1, 2]. A major contributor to this variability is the dynamic change in hepatic metabolic capacity during growth and development, which limits the reliability of direct adult-to-child dose extrapolation [3]. A fundamental determinant of pediatric drug metabolism is ontogeny, defined as the age-

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dependent maturation of enzyme expression and catalytic activity. Importantly, CYP maturation is enzyme-specific and non-uniform, meaning that identical weight-based doses can result in markedly different drug exposures depending on the metabolic pathway involved [4, 5]. Among CYP isoforms, CYP3A4-mediated clearance is particularly sensitive to developmental changes and interacting clinical factors, increasing the likelihood of exposure variability and drug–drug interactions in early life [6, 7]. These observations underscore the need for developmentally tailored dosing strategies rather than simple proportional dose reductions from adult regimens. In addition to maturation, functional pharmacogenetic polymorphisms significantly influence drug exposure, therapeutic response, and toxicity risk, particularly when drug clearance or activation depends predominantly on a single CYP pathway [8, 9]. Clinically meaningful gene–drug interactions, such as CYP2D6 with certain opioids and CYP2C19 with antifungals and acid-suppressing agents, have demonstrated consistent clinical impact. Current evidence and practice guidelines support genotype-guided prescribing and early therapeutic drug monitoring (TDM) for selected high-risk medications to improve target attainment and reduce avoidable adverse effects [10, 11]. However, age and genotype alone do not fully explain variability in pediatric drug metabolism. CYP activity may also be influenced by inflammation, comorbid burden, organ dysfunction, and critical illness, further complicating exposure prediction in real-world clinical settings. Pharmacokinetic modeling studies have shown that dosing predictions are highly sensitive to assumptions regarding enzyme ontogeny functions, emphasizing the need for transparent and evidence-based translation of mechanistic data into clinical recommendations [12]. Additionally, neonatal pharmacokinetic investigations frequently demonstrate substantial inter-individual variability despite standardized dosing approaches, reinforcing the importance of individualized monitoring strategies in vulnerable populations [13]. From a regional perspective, implementation of pharmacogenetic strategies depends partly on allele prevalence and healthcare infrastructure capacity. Population-level pharmacogenomic data suggest clinically relevant frequencies of actionable CYP variants in South Asian populations, supporting the potential utility of targeted pharmacogenetic approaches for selected high-risk drug–gene pairs [14]. Furthermore, synergistic effects of age-dependent maturation and CYP genotype have been demonstrated in high-risk therapies such as transplantation, where dose requirements and target attainment are influenced by both developmental and genetic determinants [15].

Pediatric-specific CYP450 data are very limited, and the majority of the research done is on adults. The populations of South Asia, such as that of Pakistan, are not well represented, even though they have clinically significant genetic variants. There are no uniform age groups in the literature, and no implementation studies in the literature looking at the use of genotype-guided dosing in standard practice. The high degree of methodological heterogeneity does not allow meta-analysis and the synthesis of evidence. The dominance of retrospective and modeling research designs creates bias in selection and dependence on untested assumptions. Small sample sizes reduce statistical power and incomplete evaluation of confounding factors, such as inflammation and the interaction of drugs, which invalidate findings. This systematic review aims to synthesize contemporary evidence on CYP450 ontogeny and pharmacogenetic variability in pediatric populations and evaluate their clinical implications for pharmacokinetics, dosing optimization, drug–drug interactions, safety, and therapeutic outcomes across pediatric age groups.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [16]. The objective was to synthesize contemporary evidence (January 2020–March 2025) regarding cytochrome P450 (CYP450) enzyme ontogeny, pharmacokinetics, and pharmacogenetic variability in pediatric populations (neonates to adolescents). A structured literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar using combinations of Medical Subject Headings and free-text terms including "CYP450," "cytochrome P450," "pediatric," "neonate," "ontogeny," "pharmacokinetics," and "pharmacogenetics." Only peer-reviewed English-language studies involving pediatric participants and reporting clinically relevant pharmacokinetic, pharmacogenetic, or ontogeny-related outcomes were included. Eligible designs comprised original clinical studies, observational cohorts, population or physiologically based pharmacokinetic (popPK/PBPK) modeling studies, real-world analyses, and systematic reviews. Adult-only studies, animal experiments without clinical correlation, case reports, editorials, and studies lacking methodological clarity were excluded. Two reviewers independently screened titles, abstracts, and full texts, with disagreements resolved by consensus. Data extraction was performed using a standardized template that captured the study design, age group, CYP isoforms evaluated, genotyping/phenotyping methods, drug substrates, pharmacokinetic outcomes, and reported adverse events. Risk of bias was assessed using the

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Newcastle–Ottawa Scale for observational studies and AMSTAR for systematic reviews; modeling and database analyses were appraised narratively due to methodological heterogeneity. Given substantial clinical and methodological heterogeneity across studies, quantitative meta-analysis was not feasible; therefore, findings were synthesized descriptively with emphasis on developmental maturation patterns, genotype–exposure relationships, and clinical dosing implications. Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies for this systematic review. A total of 659 records were identified through database searching. After removal of 198 duplicate records, 461 records were screened by title and abstract, of which 402 were excluded. Fifty-nine full-text articles were sought for retrieval, 53 were assessed for eligibility, and 37 were excluded for predefined reasons. Finally, 16 studies were included in the qualitative synthesis (Figure 1).

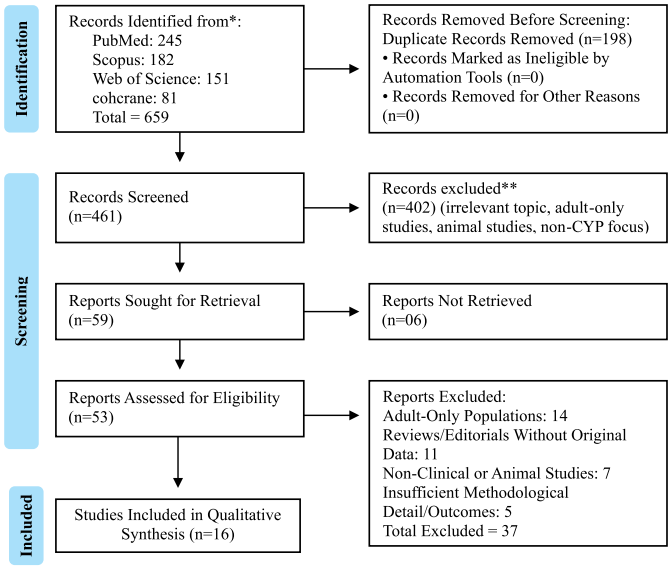

Figure 1: PRISMA 2020 for Study Selection

RESULTS

The included evidence (2020–2025) comprised 16 studies from Asia, Europe, North America, and Australia, with retrospective cohort/observational designs predominating, alongside PBPK/popPK modeling, real-world practice studies, and one systematic review. Across studies, the most frequently investigated isoforms were CYP2C19, CYP3A4, and CYP2D6, reflecting their common involvement in pediatric therapeutics and clinically actionable pharmacogenetic decisions (Table 1).

Table 1: Characteristics of Included Studies and Key Features

References	Region/Country	Design (Brief)	Pediatric Age Group	Main CYP(s)	Main Drug/Drug Class	Key Message
[17]	Europe (Poland)	Retrospective	2–17 y	CYP2C19	Voriconazole	CYP2C19 phenotype strongly affects exposure → TDM helpful
[18]	Asia (China)	Retrospective cohort	6–17 y (plus adults)	CYP2C19	Sertraline	Genotype + clinical factors influence concentrations
[19]	Asia (Japan)	Retrospective + PBPK	Neonates	CYP3A4	Fentanyl	Ontogeny is critical for neonatal exposure/AE prediction
[20]	Europe/Intl	popPK/PD/PGx model	Preterm neonates	CYP3A4	Fentanyl	Model-based dosing improves target attainment
[21]	Australia	Prospective feasibility	6–25 y	CYP3A4 /2C19/2D6	Probe drugs	Demonstrates phenoconversion impact in pediatrics
[22]	USA	Retrospective	Children/adolescents	CYP2C19/2D6	Oncology drugs	PGx testing informs exposure variability
[23]	USA	Ontogeny/tissue-based	Prenatal → adolescence	Multiple CYPs	Scaling factors	Provides pediatric physiology inputs for PBPK
[24]	Asia (China)	Retrospective	Preterm neonates	CYP1A2	Caffeine	Clearance low in preterm → prolonged half-life
[25]	Europe (Switzerland)	Real-world practice	Children	CYP2D6 /2C19/3A4	Mixed drugs	Practical PGx/phenotyping is feasible but heterogeneous
[26]	Europe (Netherlands)	Systematic review	Neonates/infants	CYP2D6 /2C9/2C18	Multiple	Pharmacogenetics clinically relevant early life
[27]	USA	Retrospective chart review	Children/adolescents	CYP2D6/2C19	Opioids/PPIs	PGx testing linked to prescribing decisions
[28]	Asia (Vietnam)	Clinical PGx study	Children	CYP2C19	PPIs (*H. pylori*)	CYP2C19 impacts response/ eradication outcomes
[29]	Europe (Netherlands)	Meeting report	All pediatric ages	Multiple CYPs	Mixed	Highlights PK prediction challenges
[30]	Europe (Switzerland)	Methodological review	Children	CYP1A2 /2D6/3A4	Probe drugs	Pediatric phenotyping approaches summarized

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[31]	USA	Database analysis	Neonate → adolescent	Multiple CYPs	Mixed	Ontogenic patterns reflected in ADE reports
[32]	Europe (Germany)	PopPK modeling	Pediatric extrapolation	CYP3A4	Midazolam	The model integrates induction /inhibition effects

Across pediatric age groups, CYP activity exhibits enzyme-specific maturation, leading to predictable shifts in drug clearance. CYP3A4 and CYP2C19 increase rapidly during infancy and early childhood, whereas CYP1A2 and CYP2D6 mature more slowly, contributing to prolonged half-life and reduced clearance in younger ages (Table 2).

Table 2: Ontogeny-Driven Change in Cytochrome P450 (CYP) Activity Across Pediatric Age Bands (Qualitative Synthesis of Included Studies)

CYP Isoform	Neonate (0–28d)	Infant (1–12mo)	Early Childhood (1–5y)	Late Childhood (6–11y)	Adolescence (12–18y)
CYP3A7	High (fetal)	Moderate (declining)	Low	Very low	Very low
CYP3A4	Low	Moderate	High	Adult-like	Adult-like
CYP2C19	Low	Moderate	High	Adult-like	Adult-like
CYP2D6	Low	Moderate	Moderate	High	Adult-like
CYP1A2	Very low	Low	Moderate	High	Adult-like
CYP3A5	Genotype-dependent	Genotype-dependent	Genotype-dependent	Genotype-dependent	Genotype-dependent

Legend: Very Low, Low, Moderate, High, Adult Like, Genotype Dependent

This heat-map matrix summarizes enzyme-specific developmental trajectories from neonatal to adolescent stages. CYP3A7 demonstrates high fetal/neonatal activity with rapid postnatal decline. CYP3A4 and CYP2C19 show rapid maturation during infancy and early childhood, approaching adult-like activity by early childhood. In contrast, CYP1A2 and CYP2D6 exhibit slower maturation, often reaching adult-like levels later in childhood or adolescence. CYP3A5 activity is primarily genotype-dependent rather than age-dependent. Categories (very low, low, moderate, high, adult-like) represent qualitative synthesis from included studies and are intended for visual comparison rather than exact quantitative enzyme activity. Drug exposure variability in children reflects the combined effect of enzyme maturation (age) and functional polymorphisms (genotype/phenotype). The most clinically significant genotype exposure differences were consistently observed for CYP2D6–opioid bioactivation and CYP2C19–PPI/voriconazole metabolism, supporting genotype-guided dosing and therapeutic drug monitoring (TDM) for selected high-risk therapies (Table 3).

Table 3: Clinically Actionable Drug–Gene Pairs in Children

Drugs	Key CYP	Pediatric Group	Key Polymorphism/ Phenotype	PK/Clinical Significance (Short)	Practical Implication	References
Codeine	CYP2D6	Children	PM vs UM	UM → ↑ morphine formation, toxicity risk; PM → poor analgesia	Avoid/contraindicate high- risk use; prefer alternatives	[25, 26]
Voriconazole	CYP2C19	Children/ Adolescents	PM/IM vs RM	PM/IM → higher troughs, hepatotoxicity/ neurotoxicity risk	Genotype-guided start + mandatory TDM	[16, 33]
PPIs (omeprazole/ esomeprazole)	CYP2C19	Children	LOF vs GOF Alleles	Large exposure differences affecting response/adverse effects	Dose adjustment by phenotype, where feasible	[27]
Tacrolimus	CYP3A5 (±3A4)	Pediatric Transplant	Expressers vs non-expressers	Expressers often need a higher dose to reach the target	Higher initial dose + TDM	[15]
Midazolam	CYP3A4	Neonates/Infants	Ontogeny-Dominant	Low clearance early life → prolonged sedation/resp. depression risk	Age-stratified dosing + interaction vigilance	[12, 31]
Caffeine	CYP1A2	Preterm Neonates	Ontogeny-Dominant	Very slow clearance → prolonged half-life	Monitor toxicity; dose spacing as needed	[13, 23]

Overall certainty of evidence was affected by the predominance of retrospective and modeling-based designs, which tend to increase susceptibility to selection bias, incomplete covariate capture, and assumption-dependent estimates. However, outcome measures were often objective (TDM levels, PK parameters, genotyping), reducing measurement bias. In general, most studies were rated moderate risk of bias, while structured clinical pharmacogenetic studies showed lower risk (Table 4).

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Table 4: Overall Risk of Bias Summary

References	Study Type	Main Bias Concern	Overall Risk	Tool
[17, 18]	Retrospective cohorts	Selection/covariates	Low–Moderate	NOS
[19, 20]	PBPK/popPK modeling	Assumption-dependent ontogeny + inputs	Moderate	NOS/Model appraisal
[21, 25]	Feasibility/real-world	Comparability + heterogeneity	Moderate	NOS
[23]	Tissue-based ontogeny	Generalizability	Low	NOS
[26]	Systematic review	Review process quality	Low	AMSTAR
[28]	Clinical PGx	Stronger design/standard methods	Low	NOS
[29, 31]	Report/database	Reporting + selection	Moderate	Narrative/NOS

DISCUSSION

Age-dependent ontogeny of CYP450 enzymes is a fundamental determinant of pediatric drug clearance. In early life, hepatic metabolic capacity is reduced due to immature enzyme expression, resulting in lower intrinsic clearance and prolonged half-life for many CYP substrates. As children grow, enzyme expression increases in an isoform-specific manner, producing predictable but non-uniform changes in systemic exposure. This maturation trajectory directly influences dosing requirements across neonatal, infant, and childhood populations and explains why simple weight-based extrapolation from adult dosing often leads to overexposure in neonates and underexposure in older children [4, 5]. CYP3A4, one of the most clinically relevant isoforms, demonstrates a rapid postnatal increase in activity. Neonatal clearance of CYP3A4 substrates such as midazolam and fentanyl is markedly reduced compared with later childhood, a finding consistently supported by physiologically based pharmacokinetic (PBPK) modeling and in vivo data [32, 33]. Modeling analyses confirm that predicted and observed midazolam clearance from birth to adolescence is highly sensitive to assumptions regarding CYP3A4 ontogeny curves [12]. These findings reinforce that neonatal and early infancy dosing must account for immature CYP3A4 activity to avoid respiratory depression and drug accumulation. Similar ontogeny-dependent variability has been demonstrated for fentanyl in preterm infants, where developmental physiology significantly alters exposure–response relationships [19, 20]. CYP2C19 maturation also has major clinical implications, particularly for antifungals and proton pump inhibitors. Pediatric voriconazole studies demonstrate that CYP2C19 poor metabolizers exhibit significantly higher trough concentrations and increased risk of hepatotoxicity and neurotoxicity, necessitating genotype-guided dosing and early therapeutic drug monitoring (TDM) [17, 34]. In contrast, rapid metabolizers may require higher starting doses to achieve target concentrations. These findings highlight how ontogeny and genotype interact: in younger children, incomplete maturation may amplify genotype effects, whereas in older children, genotype may become the dominant determinant of exposure variability. CYP2D6 presents a different pattern, characterized by gradual maturation through early childhood combined with strong genetic influence. For prodrugs such as codeine, ultrarapid metabolizers convert codeine to morphine more efficiently, increasing toxicity risk, while poor metabolizers experience inadequate analgesia. International pharmacogenetic guidelines, therefore, recommend avoiding codeine in high-risk phenotypes [35]. The clinical relevance of CYP2D6 polymorphisms becomes increasingly pronounced as metabolic capacity matures, demonstrating the shifting balance between developmental and genetic determinants of clearance across age groups. Slower-maturing enzymes such as CYP1A2 further illustrate ontogeny-dependent clearance. In preterm neonates, caffeine elimination half-life may extend to 80–100 hours due to immature CYP1A2 activity [13, 24]. Population pharmacokinetic studies confirm substantial inter-individual variability despite standardized dosing, supporting model-informed dose adjustments and close monitoring in vulnerable populations [13]. These examples collectively demonstrate that enzyme maturation is not uniform across isoforms and that clearance trajectories differ substantially by pathway. Beyond ontogeny and genotype, drug clearance in children is influenced by inflammation, comedication, organ dysfunction, and "phenoconversion," whereby environmental or disease-related factors temporarily alter CYP activity [21, 25]. Modeling studies suggest that assumptions regarding ontogeny functions significantly influence dose predictions, underscoring the need for transparent integration of mechanistic data into clinical dosing frameworks [12]. Real-world studies further show that drug–drug interactions are particularly impactful in early life, when metabolic reserve is limited. Regional considerations are also relevant. Pharmacogenomic data from South Asian populations demonstrate clinically meaningful frequencies of actionable CYP variants, suggesting that genotype-guided strategies may have practical relevance beyond Western cohorts [14]. In pediatric transplantation, for example, CYP3A5 genotype combined with age significantly influences tacrolimus dose requirements and time to target concentration [15].

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These findings support the concept that both developmental stage and population genetics must be considered in individualized dosing strategies. Taken together, the literature consistently supports a dual framework in which pediatric drug clearance is governed by enzyme-specific maturation and functional polymorphisms. In neonates and infants, ontogeny predominates; in older children, genotype becomes increasingly influential. This developmental transition explains much of the observed variability in exposure, efficacy, and toxicity across pediatric age groups.

This review is limited by substantial heterogeneity in study design, age stratification, endpoints, and reporting quality, which precluded quantitative meta-analysis. The predominance of retrospective and modeling-based studies introduces potential selection bias and reliance on ontogeny assumptions. In addition, inconsistent reporting of genotype frequencies and sample sizes limits cross-study comparability. Future research should prioritize prospective multicenter pediatric cohorts with standardized age bands, uniform genotype definitions, and clinically meaningful endpoints such as target attainment and toxicity. Implementation studies evaluating the cost-effectiveness and feasibility of integrating genotype-guided dosing with therapeutic drug monitoring in routine pediatric practice are also warranted.

CONCLUSIONS

Pediatric CYP450-mediated drug clearance is governed by enzyme-specific ontogeny combined with functional genetic polymorphisms. Age-dependent maturation strongly influences clearance in neonates and infants, whereas genotype becomes increasingly important in older children. Integrating developmental dosing principles, therapeutic drug monitoring, and targeted pharmacogenetic guidance, particularly for opioids, azole antifungals, calcineurin inhibitors, and antiseizure medications, has the potential to reduce preventable toxicity and improve therapeutic precision in pediatric populations.

Authors' Contribution

Conceptualization: RK
Methodology: MNK, FAS
Formal analysis: RK
Writing and Drafting: RK, ZS, MNK, FH, FAS, NF
Review and Editing: RK, ZS, MNK, FH, FAS, NF

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

Conflicts of Interest

All the authors declare no conflict of interest.

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