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## Artificial Intelligence in Internal Medicine: Opportunities and Challenges in Clinical Practice



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Artificial intelligence (AI) is the topic of choice in today's discussions. It is basically the replica of human intelligence by computers or robots, enabling them to observe, learn, reason, and resolve. Unlike usual software, AI uses data and algorithms to perform better with every passing day by learning from new information and experiences. Its key components are machine learning, deep learning, and cognitive functions. Its key types are artificial narrow intelligence, artificial general intelligence, and super intelligence [1].

Worldwide AI use has been superfast in early 2026, even more than the internet and smartphones. The countries leading the AI usage are India, 59 %, the United Arab Emirates, 58 %, Singapore 53 % and China, 50 % [2]. Pakistan has successfully launched its AI policy in 2025, with the potential to increase GDP growth from 7% to 15% by 2030. However, current usage is only confined to 15% in Pakistan. As far as health sector usage is concerned, it's at an emerging stage [3]. It can play a pivotal role in day-to-day clinical internal medicine practice and can revolutionize internal medicine physicians' hospitals and clinics, as well as outpatient and inpatient departments. Then it raises a question: will it replace internal medicine physicians [4]? In Pakistan, this opportunity is very useful in many ways. Our hospitals' overburdened outdoors are dealt with by limited human resources, and hence these AI-supported systems can diagnose and treat in less time, which will improve patient management and will handle patients' burden. In remote cities like Narowal, AI will definitely play a vital role in internal medicine physicians' quick diagnosis, timely management, and referrals where required [5]. It can give clues in history and examination, interpret investigations like computed tomography, magnetic resonance imaging, electrocardiograms, chest radiographs, and even routine ultrasounds. Similarly, state-of-the-art management is possible in emergencies where minute-to-minute management matters and hence increases physicians' efficiency and can change the patient's outcome. It can also be the clerical job of patient history notes and even tell us about the possible course of the disease and future admission rate [6].

AI can decrease internal medicine physicians' burnout by decreasing workload and repetitive administrative tasks. It promotes evidence-based medicine by setting standards of care. Hence, quality care can be assured in overburdened resource-limited settings. The WHO has also set a worldwide mechanism for the safe and ethical use of AI in healthcare. It ensures public interest by giving six core principles, including protecting autonomy, human well-being, transparency, responsibility, inclusiveness, and sustainability [7].

However, despite the advantages, there are significant challenges associated with AI usage. The lack of local data giving rise to algorithm bias is a critical limitation. Limited infrastructure and resources also hinder its effective deployment. Lack of regulatory frameworks is also challenging. Lack of internal medicine physicians trained with AI tools can also be a limitation. It may also hamper physicians' critical thinking skills, a risk of over-reliance. It could be difficult to define accountability if an incorrect clinical or medicolegal decision is made by AI, using Western data models [8].

There are possible solutions to best use AI systems in our country. It should be adapted to local data, disease patterns, and



population dynamics rather than relying purely on Western data. A systematic and cautious approach is important for integrating AI into internal medicine for accurate results. Physicians must be trained adequately before using AI tools critically rather than passively accepting them. Infrastructure and resources must be enhanced for effective functioning. Regulatory frameworks must be established to address ethical concerns, data protection, and accountability. AI should act as a decision support system, with the physicians being fully responsible for patient care [9].

AI can help evidence synthesis by analyzing large data and assist in applying guidelines at the point of care. It can increase adherence to best evidence-based medicine (EBM) and reduce variability in patient management. However, EBM is not totally about data. It incorporates clinical expertise, patient values, and the best clinical evidence. AI can assist the evidence component, but it cannot replace physicians' expertise. Therefore, AI should be taken as an extension of EBM rather than a substitute for it [10].

AI is revolutionizing internal medicine, but its role must be clearly defined. It is a good supportive tool that can enhance patient care, but it cannot replace internal medicine physicians. The future of medicine will not be determined by AI alone, but by how effectively physicians integrate it into their practice. Clinicians who embrace and thoughtfully adopt AI will thrive in this new era, while those who disregard it will become obsolete.

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## Original Article



## Comparative Efficacy of Low-Dose Alteplase versus Standard Dose among Acute Ischemic Stroke Patients: A Single-Centre Experience in Pakistan

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## ABSTRACT

Intravenous (IV) alteplase (tPA) at a dose of 0.9 mg/kg is the standard treatment of acute ischemic stroke (AIS), but it carries the risk of intracranial hemorrhage. **Objectives:** To assess the efficacy and safety of tPA low dose (LD; 0.6 mg/kg) as compared to standard-dose (SD; 0.9 mg/kg) in AIS patients in normal clinical practice. **Methods:** In this retrospective comparative cohort study, 320 AIS patients administered IV-tPA within 4.5 hours of stroke symptoms were selected in 2 groups (160 patients receiving LD; 0.6mg/kg), and 160 patients (SD; 0.9mg/kg) were developed in the Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, between January 2023 and December 2024. The measured outcomes were functional independence (mRS=02) at 90 days, incidence of symptomatic intracranial hemorrhage (sICH), and 90-day mortality. **Results:** Few individuals (32.5%) in the (LD; 0.6 mg/kg) group had positive functional outcomes compared to those in the (SD; 0.9 mg/kg) group (40.0%), but the difference was not significant ( $p=0.152$ ). The (LD; 0.6mg/kg) (1.9% vs. 5.6%) ( $p=0.038$ ) significantly reduced the risk of sICH. There were no differences in the 90-day mortality rates between the groups (11.3% vs. 13.8%,  $p=0.299$ ). Adjusted (LD; 0.6 mg/kg) was, however, associated with reduced risk of sICH (aOR 0.30; 95% CI 0.08–0.98;  $p=0.040$ ) but not functional outcome (aOR 0.82; 95% CI 0.54–1.25;  $p=0.361$ ). Functional outcomes were strongly predicted by age, baseline NIHSS, and treatment length. **Conclusions:** In routine clinical practice, (LD; 0.6 mg/kg) was selectively used in higher-risk patients and showed a promising safety profile with functional outcomes broadly comparable to (SD; 0.9 mg/kg) therapy.

## INTRODUCTION

The acute ischemic stroke (AIS) is a typical subtype, with almost 62 percent of all strokes that happen [1]. Although innovative treatment methods, including thrombolysis, have existed, the prognosis in a large proportion of patients is not clearly established by the risk and limitations posed by the existing treatment procedures [1, 2]. IV thrombolysis using recombinant tissue plasminogen activator (alteplase tPA) at 0.9mg/kg is the initial treatment of AIS [3]. This is a dose that is applicable in enhancing functional outcomes. It is, however, associated with a high risk of symptomatic intracranial hemorrhage (sICH), which casts doubts on its use in general [3, 4]. The Japan Alteplase Clinical Trial in

Japan resulted in a tPA of 0.6 mg/kg, which was approved and had similar efficacy with fewer bleeding issues [5]. Since its approval, the lower dose has gained support in other regions of Asia, driven by financial considerations and a desire to reduce treatment-associated hazards [5]. Despite its potential (LD; 0.6 mg/kg), tPA has not been widely adopted due to contradictory findings from observational studies and a lack of strong evidence of efficacy across diverse groups [5, 6]. Current evidence, including meta-analyses, suggests that (LD; 0.6 mg/kg) may be a safer alternative for specific categories, such as elderly individuals or those who are more likely to develop



problems [6]. However, inconsistent findings and inadequate data on patient-specific characteristics such as age and stroke severity underscore the need for future research [5, 6]. Notably, there is a paucity of data on tPA dose comparison from Pakistan, where patient demographics, comorbidity profiles, resource availability, and clinical practices may differ from those in previously studied populations.

Limited data are available in Pakistan and other comparable facilities where low-dose versus standard-dose alteplase is compared in a variety of patient groups, especially with long-term and multi-center data. The main question is to find out the best dose of alteplase that would provide a balance between the safety (less hemorrhage) and the effectiveness (functional recovery) of acute stroke patients with ischemia. This study aims to compare the effectiveness of doses of tPA (LD; 0.6 mg/kg) vs (SD; 0.9 mg/kg) in AIS patients from hospital records, to establish a balanced dosing strategy that improves treatment outcomes while minimizing adverse effects, thereby contributing to better stroke care.

## METHODS

This retrospective comparative cohort study was conducted at the Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, from January 2025 to April 2025. Patient data were retrospectively screened from the hospital management information system (HMIS) for the period spanning January 2023 to December 2024, during which patients received IV-tPA as part of routine stroke care. The hospital Institutional Review Board granted ethical permission for the access and analysis of retrospective data (Ref. No. A/28/ERC/02/2025). As this was a retrospective study using anonymized data, the IRB granted waiver of informed consent and permitted analysis of records generated before approval. The sample size was calculated by keeping the anticipated mRS  $\leq 2$  rates of 22.2% or the low and 34.8% for (SD; 0.9 mg/kg) patients [7], with a confidence level of 95%, and power of test as 80%, resulted in 392 sample size, by using the formula,  $n = (Z_{\alpha/2} + Z_{\beta})^2 (p_1(1-p_1) + (p_2(1-p_2))) / (p_1 + p_2)^2$  [8]. The inclusion criteria were individuals of either gender or ethnicity, aged  $\geq 18$  years, with AIS confirmed by CT/MRI within 4.5 hours of symptom start and an NIHSS score between 4 and 25. The exclusion criteria were patients having hemorrhagic stroke, bleeding disorders, a previous stroke within the last three months, or major surgery within the last two weeks. During the study period, 423 patients with AIS who received IV-tPA were screened for eligibility. As this was a retrospective study, only patients with complete baseline information and documented 90-day outcome data were eligible for inclusion. A total of 103 patients were excluded due to incomplete medical records or missing 90-day

outcome documentation, resulting in a final sample of 320 patients (160 per group). Due to the retrospective observational study design, patients were not randomly assigned to the (LD; 0.6 mg/kg) or (SD; 0.9 mg/kg) tPA groups. All dosing decisions were left to the treating neurologist based on routine clinical judgment at the time of presentation. Factors related to dose selection, as documented in clinical notes, included patient age, frailty, uncontrolled hypertension, elevated bleeding risk, delayed presentation, and physician preference, align with international evidence suggesting that low dose in selected patients is associated with lower risk of sICH. As the allocation was clinical-practice-based and derived from the hospital's electronic system, this introduces a potential risk of selection bias, which was acknowledged and addressed through comparison of baseline characteristics and stratified analysis. AIS diagnosis and haemorrhage detection were determined based on non-contrast CT imaging on admission and repeated at 24–36 hours. MRI was performed only in cases where further clarification was needed. Imaging was interpreted by the on-duty radiologists per institutional protocol; no blinded central imaging adjudication was available. AIS was defined as the sudden onset of focal neurological deficits consistent with cerebral ischemia, presenting within 4.5 hours of symptom onset, without evidence of intracranial hemorrhage on initial neuroimaging. The diagnosis was confirmed by a qualified neurologist using the National Institutes of Health Stroke Scale (NIHSS 0–42) and clinical presentation. Ischemia was verified by CT or MRI, and hemorrhage was ruled out. sICH was defined based on ECASS II criteria as a parenchymal hemorrhage involving more than 30% of the infarcted area (PH2), with mass effect or expansion beyond the infarct zone, and followed by a neurological impairment of at least four points on the NIHSS [9]. Treatment efficacy was evaluated using the mRS at 90 days, where a score of  $\leq 2$  denoted good functional recovery and independence in daily activities. Mortality referred to any death occurring between treatment initiation and the 90-day outcome assessment as documented in hospital records. Only those patients were included in the analysis whose routine clinical outcome data at 90 days were available in the hospital's electronic medical record system. All outcomes were assessed retrospectively through review of existing hospital electronic medical records; no patients were prospectively followed or contacted for outcome assessment. The NIHSS, a 15-item clinical stroke scale with a range of 0 to 42, was used to measure the severity of the stroke; higher scores indicate a more severe neurological loss. The total NIHSS is traditionally categorized as follows: 0 = no stroke symptoms; 1–4 = minor; 5–15 = moderate; 16–20 = moderate-severe; and 21–42 = severe [10]. With an

inter-rater reliability of 0.95, the NIHSS has been extensively validated and demonstrated to predict both short and long-term outcomes following AIS [11]. Demographic variables like age, gender, comorbidities, and baseline NIHSS scores were retrieved from the hospital's electronic medical records in order to identify eligible individuals. The treatment was tPA, with 10% given as a bolus and the rest infused over an hour. Patients were treated in the ICU or stroke units according to institutional guidelines. Outcome data recorded within 90 days in the hospital electronic records included NIHSS evaluations at 24 hours, functional outcomes using the mRS, and mortality. Although the final analyzed sample was smaller than the initially calculated sample size, it represents all eligible patients with complete outcome data available during the study period. The data were analysed using SPSS-27. Continuous variables (age, mRS score, and NIHSS scores) were tested by the Shapiro-Wilk test to ascertain that they are normal and reported as the mean + SD or median (IQR) accordingly. This was compared using an independent t-test or Mann-Whitney U test. Gender, comorbidities, functional outcomes, sICH, and mortality are all quantitative variables reported in frequencies and percentages and compared with one another based on the Chi-square test or Fisher's exact test, where a p-value of 0.050 or less was considered statistically significant.

## RESULTS

Among all 423 patients screened, only 320 (75.7%) patients had complete clinical and 90-day outcome data, while 103 (24.3%) individuals were excluded due to missing outcome documentation. The patients were split into two groups, with group A receiving (LD; 0.6 mg/kg) of tPA and group B receiving (SD; 0.9 mg/kg). The baseline features of both groups did not show any statistically significant differences. Group A's average age was  $64.2 \pm 11.5$  years, while group B's average was  $62.8 \pm 10.9$  years ( $p=0.251$ ). Males constituted 60.0% of group B and 57.5% of Group A, indicating a comparable gender distribution ( $p=0.683$ ). Group A's baseline NIHSS score was 14 (IQR 10–18), while Group B was 13 (IQR 9–17) ( $p=0.635$ ). The average time to treatment was  $205 \pm 39$  minutes and  $198 \pm 42$  minutes, respectively ( $p=0.127$ ). Comorbidities, including hypertension (68.8% vs. 65.6%,  $p=0.543$ ), diabetes (46.9% vs. 43.8%,  $p=0.572$ ), and atrial fibrillation (17.5% vs. 15.6%,  $p=0.642$ ), were also comparable between groups (Table 1).

**Table 1:** Baseline Characteristics

Characteristic		Group A (n=160)	Group B (n=160)	p-value
Age (Year)	Mean $\pm$ SD	64.2 $\pm$ 11.5	62.8 $\pm$ 10.9	0.251 <sup>a</sup>
Gender, n (%)	Male	92 (57.5%)	96 (60.0%)	0.683 <sup>b</sup>
	Female	68 (42.5%)	64 (40.0%)	
Baseline NIHSS	Median (IQR)	14 (10–18)	13 (9–17)	0.635 <sup>c</sup>

Time to Treatment (min)	Mean $\pm$ SD	198 $\pm$ 42	205 $\pm$ 39	0.127 <sup>a</sup>
Comorbidities, n (%)	Hypertension	110 (68.8%)	105 (65.6%)	0.543 <sup>b</sup>
	Diabetes Mellitus	75 (46.9%)	70 (43.8%)	0.572 <sup>b</sup>
	Atrial Fibrillation	28 (17.5%)	25 (15.6%)	0.642 <sup>b</sup>

Note: For comparison <sup>a</sup>Independent t test, <sup>b</sup>Chi-square test, <sup>c</sup>Mann-Whitney U test was used. \*Statistically significant at  $p<0.05$ .

Favourable outcomes (mRS  $\leq 2$ ) at 90 days were observed in 32.5 and 40.0% of patients in group A and group B, respectively, and the difference between the two groups was not found (RR 0.81, 95% CI 0.61108;  $p=0.152$ ). Group A had a lower rate of symptomatic intracranial haemorrhage (sICH) as compared to group B (1.9% vs. 5.6; RR 0.33, 95% CI 0.091.20;  $p=0.038$ ). The two groups did not differ in terms of mortality rates (11.3 vs. 13.8; RR 0.82, 95% CI 0.461.46;  $p=0.299$ ) (Table 2).

**Table 2:** Outcome on 90 Days

Outcomes	Group A (n=160), n (%)	Group B (n=160), n (%)	Risk Ratio, (95% CI)	p-value
Favorable Outcome (mRS $\leq 2$ )	52 (32.5%)	64 (40.0%)	0.81 (0.61 - 1.08)	0.152 <sup>a</sup>
Symptomatic ICH	3 (1.9%)	9 (5.6%)	0.33 (0.09 - 1.20)	0.038 <sup>b</sup>
Mortality (90-Day)	18 (11.3%)	22 (13.8%)	0.82 (0.46 - 1.46)	0.299 <sup>a</sup>

Note: Group B (SD; 0.9 mg/kg) was used as the reference category for risk ratio calculation. <sup>a</sup>Chi-square test or <sup>b</sup>Fisher's Exact test was used for comparison between groups. \*Statistically significant at  $p<0.05$

At 90 days, based on hospital record review, the distribution of mRS scores was broadly comparable between groups. mRS 0–2 was observed in 32.6% of group A and 40.1% in group B, while moderate to severe disability (mRS 3–5) occurred in 56.2% and 46.3%, respectively. Mortality rates were similar (11.3% vs. 13.8%) (Table 3).

**Table 3:** Modified Rankin Scale (mRS) Scores at 90 Days

mRS Score	Description	Group B (n=160), n (%)	Group A (n=160), n (%)
0	No Symptoms	15 (9.4%)	20 (12.5%)
1	No Significant Disability	18 (11.3%)	22 (13.8%)
2	Slight Disability	19 (11.9%)	22 (13.8%)
3	Moderate Disability	45 (28.1%)	38 (23.8%)
4	Moderately Severe Disability	32 (20.0%)	27 (16.9%)
5	Severe Disability	13 (8.1%)	9 (5.6%)
6	Death	18 (11.3%)	22 (13.8%)

After adjusting for confounders, (LD; 0.6 mg/kg) showed similar 90-day functional outcomes as (SD; 0.9 mg/kg), but was associated with a lower risk of symptomatic intracranial hemorrhage. Older age, higher baseline NIHSS, and delayed treatment predicted poorer outcomes, while only baseline NIHSS predicted sICH (Table 4).

**Table 4:** Multivariate Logistic Regression Analysis for 90-Day Outcomes

Dependent Variables	Independent Variables	Adjusted Odds Ratio (aOR)	95% CI	p-value
mRS ≤2	(LD; 0.6 mg/kg)	0.82	0.54 – 1.25	0.361
	Age	0.70	0.52 – 0.95	0.021*
	Baseline NIHSS	0.86	0.81 – 0.92	<0.001*
	Time to Treatment (Minutes)	0.98	0.97 – 0.99	0.045*
	Hypertension	0.88	0.62 – 1.25	0.482
	Diabetes Mellitus	0.75	0.50 – 1.12	0.155
	Atrial Fibrillation	0.68	0.41 – 1.13	0.138
sICH	(LD; 0.6 mg/kg)	0.30	0.08 – 0.98	0.040*
	Age	1.22	0.95 – 1.58	0.118
	Baseline NIHSS	1.10	1.03 – 1.18	0.006*
	Time to Treatment (Minutes)	1.01	0.99 – 1.03	0.334
	Hypertension	1.45	0.88 – 2.39	0.145
	Diabetes Mellitus	1.32	0.75 – 2.31	0.334
Atrial Fibrillation	1.25	0.65 – 2.41	0.501	

\*p-value<0.050 was significant

## DISCUSSION

This study's findings show that (LD; 0.6 mg/kg) is associated with a decreased incidence of sICH, albeit with a potentially minimal reduction in functional efficacy. This safety profile may justify its use as a practical option, particularly in patients at increased bleeding risk or in resource-constrained settings where close monitoring is difficult. Dose selection should therefore balance safety and efficacy concerns. Our findings are comparable with those of Rahimi *et al.* who found a higher proportion of positive outcomes with (SD; 0.9 mg/kg) tPA and a lower incidence of sICH in the (LD; 0.6 mg/kg) group. Their propensity score analysis revealed sICH rates of 2.3% in the (LD; 0.6 mg/kg) group versus 11.4% in the (SD; 0.9 mg/kg) group [12]. Although (LD; 0.6 mg/kg) tPA exhibited a trend toward lower sICH (1.9% vs 5.6%), the limited number of events reduces statistical confidence; these data should be regarded with caution. Larger, well-powered research is needed to corroborate this observation. Similarly, Wang *et al.* reported an insignificant difference in functional results between low- and standard-dose tPA, despite lower sICH with the lower dose [13]. Additionally, meta-analyses demonstrate that the two doses are equally effective in terms of 90-day functional independence and recanalization, with no discernible variations in sICH or mortality [14]. Karedath *et al.* showed comparable death and sICH rates, but (SD; 0.9 mg/kg) treatment was linked with a slightly larger proportion of good functional outcomes [1]. However, these study findings only partially align with broader literature. The (LD; 0.6 mg/kg) group had a functional independence rate (mRS ≤2) of 32.5%, which was lower than previous studies' reported rates of 48-76.9% [13-15]. Xu *et al.* reported poorer functional outcomes with (LD; 0.6 mg/kg) tPA in Asian

patients, suggesting that ethnicity and regional treatment patterns may influence results [16]. Additionally, Chen *et al.* found improved outcomes with (SD; 0.9 mg/kg) tPA in patients receiving combined thrombolysis and thrombectomy [7]. Overall, our data did not demonstrate a meaningful functional advantage for (LD; 0.6 mg/kg) tPA, supporting the idea that dose reduction may compromise efficacy in certain populations [17-19]. Regarding safety outcomes, our findings align with existing evidence. The rate of sICH in the (LD; 0.6 mg/kg) group was 1.9% compared to 5.6% in the (SD; 0.9 mg/kg) group, which is similar to Rahimi *et al.* [12]. Although the mortality differences were not statistically significant, the numerically decreased mortality in the (LD; 0.6 mg/kg) group corresponds to a safer profile described in other studies [20, 21]. However, due to the small number of incidents, these safety data should be taken as exploratory tendencies rather than definite evidence. It is important to emphasize that the current study is based on real-world clinical practice rather than a controlled comparison. In our center, physicians utilized (LD; 0.6 mg/kg) tPA on patients who were thought to be at increased risk of bleeding. This method was linked with a low incidence of sICH and functional outcomes that were roughly equivalent to those receiving (SD; 0.9 mg/kg).

Limitations of the study include that it is a retrospective study with a single center, possible selection bias and the lack of full data of all patients; therefore, the study may not be generalized. Further studies ought to involve large, multicenter randomized trials and extended follow-up to confirm the results and inform standard treatment procedures.

## CONCLUSIONS

In this retrospective analysis, (LD; 0.6 mg/kg) was used selectively in high-risk patients and had less sICH incidence than (SD; 0.9 mg/kg). The general outcomes of the functional outcomes at 90 days were similar, but with lower numbers in the (LD; 0.6 mg/kg) group. As the study is observational, these findings should be interpreted as descriptive observations rather than evidence of non-inferiority. Treatment decisions should be individualized, particularly when considering bleeding risk or resource-limited settings. While (LD; 0.6 mg/kg) tPA may be a safer option for selected patients, further experimental studies are required to determine its comparative effectiveness.

## Authors' Contribution

Conceptualization: JL

Methodology: TK<sup>1</sup>, JL

Formal analysis: JL, TK<sup>2</sup>

Writing and Drafting: JL, AH, IA, HUR

Review and Editing: TK<sup>1</sup>, JL, AH, IA, HUR

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



## Incidence of Urethrocutaneous Fistula Formation in Patients Undergoing Urethroplasty with and without Stent for Hypospadias

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## ABSTRACT

Hypospadias is a common congenital anomaly in boys, and urethrocutaneous fistula (UCF) remains a frequent complication after urethroplasty. The routine use of urethral stents is still debated, especially in low-resource settings such as Pakistan. **Objectives:** To compare UCF incidence between stented and stentless urethroplasty and to identify factors associated with fistula formation. **Methods:** A randomized controlled trial was carried out in the Department of Pediatric Surgery, Children's Hospital Multan, from 10 May to 10 November 2025. A total of 110 boys aged 1-12 years with distal or mid-penile hypospadias were randomized to stent urethroplasty (Group A, n=55) or stentless urethroplasty (Group B, n=55). Data were analyzed using t-test, Mann-Whitney U test, chi-square test, and binary logistic regression with p<0.05 as significant. **Results:** Mean age was 6.1±2.6 years in Group A and 5.7±2.9 years in Group B. Overall UCF incidence was 10% (11/110), higher in Group A than Group B (14.5% vs 5.5%; p=0.046). At 12 weeks, UCF occurred in 14.5% of stented repairs and 5.5% of stentless repairs (p=0.046). Postoperative infection and longer operative duration were independently associated with UCF. Hospital stays, a secondary outcome, were longer in the stented group. **Conclusions:** In this cohort, stentless urethroplasty demonstrated a lower 12-week UCF incidence compared with stented repair.

## INTRODUCTION

Hypospadias is a severe malformation in boys that still leaves a huge surgical and psychosocial burden in places like Pakistan. Incidence of hypospadias is reported worldwide as 1 in 200-1 in 300 live male births, and it may be increasing [1]. There are scant strong population-based data in Pakistan, but single-center series suggest that hypospadias repair is one of the most popular pediatric urology procedures, and complications like urethrocutaneous fistula (UCF) are common [2, 3]. Hypospadias refers to the abnormal location of the urethral

meatus on the ventral surface of a penis that is usually accompanied by ventral curvature (chordee) and underdevelopment of the corpus spongiosum and ventral prepuce. Recently, in Asia, an Indian study reported a mean UCF incidence of approximately 4% in children undergoing distal hypospadias surgery using tabularized incised plate (TIP) urethroplasty [4]. A different prospective cohort of children receiving TIP repair is also found to have a UCF rate of approximately 9.6 per cent in total, with a higher rate aged above three years old (25.9%) [5]. Several systematic



reviews and meta-analyses in the world literature have demonstrated that UCF rates following hypospadias repair range (less than 5 percent to over 30 percent) with severity of the hypospadias, surgical style, use of protective flaps, stent control, and other factors [6, 7]. To illustrate, a recent meta-analysis of double versus single dartos flap coverage in TIP urethroplasty discovered a considerably lower fistula rate when compared to the double dartos flap (odds ratio approximately 9.6) [8]. Nevertheless, such studies are frequently based on rich countries with well-equipped units and repairs at a young age; it is unclear whether they can be applied in resource-constrained environments [9]. In spite of these data, there are some important gaps in knowledge. To begin with, Pakistan (or other low-resource) based high-quality randomized information on a stented vs. stentless urethroplasty in hypospadias repair and its associated influence on UCF formation are rare. Second, numerous local series fail to stratify by stent use, length of stent, or end-follow-up at a standard point in time (e.g., 12 weeks) to be able to make meaningful comparisons. Third, the results of these studies conducted internationally using adequately resourced centers might not apply to the Pakistani setting, where patients are more likely to be older at the time they have surgery, the resources used in operating theatres are more limited, and the post-surgery follow-up is weaker [10]. The clinical burden is very high in the Pakistani setting. Repeat surgery may frequently be required, recovery time may be extensive, use of hospital resources and psychological impact on the child and family may be more significant in low-resource areas.

There is a lack of high-quality randomized controlled trial data that has compared stented versus stentless urethroplasty to hypospadias, and most of the local evidence is found in small observational studies or series with unequal follow-up times. Children's Hospital Multan's single-center design limits the generalizability to other regions in Pakistan with varying surgical facilities and patient populations. There is the possibility of detection bias, with the stented group being revealed in follow-up, because of the inability to blind outcome assessment at 12 weeks at UCF. This study aimed to compare UCF incidence between stented and stentless urethroplasty and to identify factors associated with fistula formation.

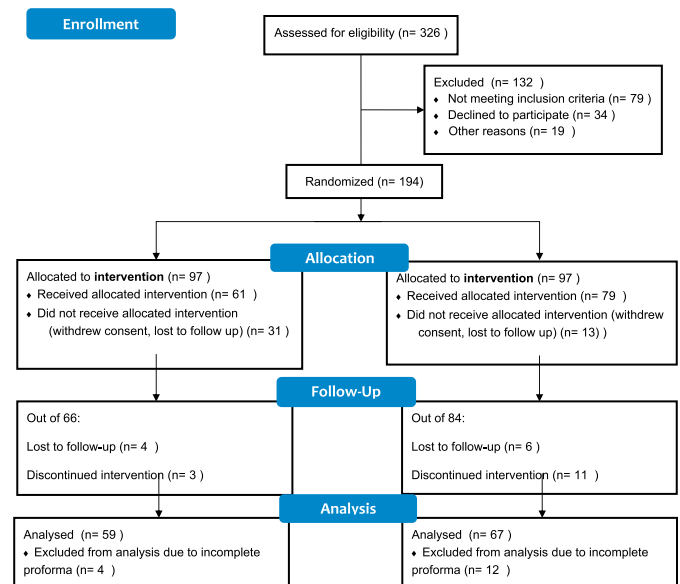
## METHODS

All the eligible patients were enrolled after the approval of the synopsis by the College of Physicians and Surgeons, Pakistan, and ethical clearance by the Institutional Review Board of Children's Hospital and Institute of Child Health (approval number 898/IRB/CHICH). The research was carried out at the Department of Pediatric Surgery, Children's Hospital, Multan, from 10th May 2025 to 10th November 2025. This was a randomized controlled trial

registered at ClinicalTrials.gov. The trial was registered at ClinicalTrials.gov (ID: NCT07243457) after recruitment had begun. Therefore, the registration was retrospective. It was a single-centered, hospital-based study. Urethrocutaneous fistula (UCF) was the primary outcome. All repairs were performed using a tubularized incised plate (TIP) technique. Children who met the inclusion criteria were enrolled consecutively. After enrolment, they were randomly allocated to the stent or stentless group using sealed, opaque envelopes. The purpose of the study and the possible risks were explained in simple language. Participation was voluntary, and families were free to withdraw at any time without affecting the child's care. All patient information was kept confidential, and the study was carried out in accordance with the Declaration of Helsinki (2013 revision). Randomization was done in a 1:1 ratio. A computer-generated random sequence was prepared by a statistician who was not involved in recruitment or surgery. The group assignments (stent or stentless) were printed on cards and placed in thick, opaque envelopes. Each envelope was sealed and numbered in sequence from 1 to 110. The envelopes were stored in a locked drawer. After a child met the inclusion criteria and written consent was obtained, the ward nurse took the next envelope in numerical order and opened it. The surgeon only learned the group assignment after the envelope was opened. This method kept allocation concealed until the moment of assignment. The sample size has been computed through the WHO sample size calculator according to the formula for comparing two independent proportions. The sample size was calculated using the WHO sample size calculator for two independent proportions. A two-sided alpha of 0.05 and a power of 80% were applied. The expected fistula rates (13.3% with stent and 33.3% without stent) were derived from a South Asian comparative study, as this study was considered the closest match to our population. Based on these parameters, a required sample of 55 patients per group (110 in total) was produced by the calculator. No adjustment for loss to follow-up was made, as the follow-up period was short (12 weeks) and early postoperative visits in our setting are usually completed. These were dependent on already published comparative studies on the hypospadias repair in South Asia [11]. All boys (children aged 1 to 12 years old) who had been planned to undergo urethroplasty to correct isolated cases of distal or mid-penile hypospadias and whose parents had provided informed written consent were included. The patients who had a history of failed urethroplasty, proximal hypospadias that needed a staged repair, or related disorders of sexual differentiation were excluded. This was randomly done through a lottery approach of assigning participants to two equal groups (A and B) using sealed opaque envelopes. Group A had

urethroplasty and a stent, and Group B had no stent urethroplasty. The whole process of deciding who to categorize the patient under was influenced by blind selection and not by preference of the operator to eliminate selection bias. The data collector and the statistician were blinded to group allocation. Outcome assessment for UCF at 12 weeks could not be blinded, because the stent group could be identified during follow-up examinations, and the saline test required direct inspection of the repair site. For this reason, blinding of the outcome assessor was not feasible. All the procedures were done under general anesthesia by a consultant pediatric surgeon who had a history of over 5 years in hypospadias repair. The clinical confirmation of the diagnosis of hypospadias was through the position of the urethral meatus on the surface of the ventrally located penis and the presence of ventral curvature. It was a nasogastric tube of 6-8 Fr (B. Braun, Germany) used as a stent based on the age of the patient. This is a common and low-cost stent option in many South Asian pediatric surgery units when standard pediatric silicone stents are not available, and its use has been described in earlier regional studies. In calculating hemostasis, lignocaine 0.5 percent with 1:200,000 adrenaline (Medicaine, Pakistan) was infiltrated. All procedures were performed under general anesthesia by the same pediatric surgeon. After marking and degloving, the urethral plate was tabularized in two layers. Both layers were closed with 6/0 polydioxanone using interrupted sutures in the first layer and a continuous suture in the second layer. A vascularized dartos flap was then placed over the neourethra for additional protection. Finally, the skin was closed with 5/0 polyglactin sutures. The steps and suture materials were the same in both groups. All patients received the same postoperative antibiotic regimen. Intravenous ceftriaxone was given once daily for 24 hours, followed by oral cefixime for five days. This protocol is the standard postoperative practice in our hospital. The patients undergoing stentless urethroplasty underwent discharge to allow them to go home on the second day after the operation. Patients who underwent a stent-assisted urethroplasty were discharged seven days after the removal of the stents. After surgery, follow-up visits were set at 2, 6, and 12 weeks. Formation of urethrocutaneous fistulas was measured at the 12-week follow-up with sterile normal saline injected into the neourethra and later clamped at the base of the penis. The escaping of saline between two points in the ventral surface of the penis was defined as a positive aspect [12]. Clinical information was all entered into a structured proforma that was designed for this study. The continuous and categorical variables were recorded. Age and duration of surgery were taken as continuous variables, and location of hypospadias, type of procedure, presence of chordee,

presence of infection, postoperative complications, and urethrocutaneous fistula were items under the categorical variables. Postoperative infection was assessed during the first 12 postoperative days. It was diagnosed when the wound showed redness, warmth, discharge, or when a fever above 38°C or a rise in CRP was present, leading to the start or change of antibiotics. All infections observed were wound infections; no urinary or catheter-associated infections occurred. Laboratory parameters were hemoglobin, serum creatinine, and C-reactive protein, as seen using a fully computerized analyzer (Roche Cobas C311, Switzerland). The cut-off was based on WHO pediatric values at less than 11 g/dL (anemia), greater than 1.0 mg/dL (elevated serum creatinine), and greater than 10 mg/L (elevated C-reactive protein). To reduce bias, all cases were standardized with respect to confounding variables, including surgeon experience, type of suture material, and infection control. Every operation was done by the same surgical doctor, with the same instruments, suture type, and postoperative care. Randomization served to adjust the bias of selection. Objective outcome evaluation, the data collector and the statistician were not informed of the group in which the study was conducted. Data collection began only with the approval of the ethics committee of the hospital. The patient information used in the study was confidential, and participation was voluntary. It was all done in accordance with the Declaration of Helsinki (2013 revision)(Figure 1).



**Figure 1:** CONSORT Diagram of the Included Participants in the Study

The age and duration of surgery were normally distributed continuous variables, which were researched by Shapiro-Wilk tests and further visual analysis of the histograms and Q-Q graphs. It was found that age and duration of surgery were normally distributed, whereas hemoglobin and serum

creatinine exhibited non-normal distributions. The normally distributed data were presented in terms of mean and standard deviation, and the non-normal data in terms of median and interquartile range.

Statistical analyses were done in Statistical Package of the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Demographic and clinical characteristics were summarized by descriptive statistics. Continuous variables such as age and duration of surgery were measured in terms of standard deviation and mean. Non-normally distributed laboratory values were quantified with median and inter-quantile range. Categorical variables like the location of hypospadias, the presence of infection, and the presence of urethrocutaneous fistula formation were checked as frequencies and percentages. The independent t-test was employed to provide the means of normally distributed variables between the two groups, e.g., age and length of surgery. The non-normally distributed continuous variables were tested by the Mann-Whitney U test. Categorical variables, such as type of hypospadias, infection status, and incidences of urethrocutaneous fistula, were compared through the chi-square test among the groups. The premise was to perform a logistic regression analysis to investigate the relationship that exists between the alleged risk variables (age, infection, duration of surgery) and the occurrence of fistula. The p-value of less than 0.050 was regarded as statistically significant. Age and type of hypospadias stratified confounders, and randomization, assessment blinding, and homogeneity of surgical and postoperative treatment minimized bias. Data were evaluated based on preset aims in order to understand whether the incidence of urethrocutaneous fistula varied significantly in the stented and the stentless urethroplasty groups.

## RESULTS

A total of 110 boys were enrolled and randomized, with 55 in each group. The mean age of the whole sample was  $5.9 \pm 2.8$  years. The mean age in the stent group was  $6.1 \pm 2.6$  years, and in the stentless group it was  $5.7 \pm 2.9$  years. The difference was not significant. All children received the assigned procedure. Follow-up at 12 weeks was completed by most participants. A small number had partial or no follow-up, and these cases were not included in the primary outcome analysis. Most continuous variables were normally distributed except for hemoglobin, serum creatinine, and CRP. The duration of surgery was similar in both groups ( $78.2 \pm 11.6$  minutes in the stent group vs  $76.4 \pm 12.3$  minutes in the stentless group;  $p=0.438$ ). Hospital stay was longer in the stent group ( $6.8 \pm 2.1$  days) compared with the stentless group ( $4.4 \pm 1.8$  days), and this difference was significant ( $p<0.001$ ). Postoperative infection occurred in 9 children (16.4%) in the stent group and in 4 children (7.3%) in

the stentless group. This difference was not statistically significant ( $p=0.158$ ). At 12 weeks, urethrocutaneous fistula (UCF) occurred in 8 children (14.5%) in the stent group and 3 children (5.5%) in the stentless group. This difference was significant ( $p=0.046$ ). No significant group differences were found for wound edema, hematoma, meatal stenosis, or laboratory values. In terms of postoperative outcomes, a significant difference was observed in hospital stay between the two groups. Children who underwent stentless urethroplasty had a shorter mean hospital stay ( $4.4 \pm 1.8$  days) compared to those who received stented repair ( $6.8 \pm 2.1$  days;  $p<0.001$ ), indicating earlier recovery and discharge in the stentless group. The use of a stent was also associated with a higher incidence of urethrocutaneous fistula (14.5 % vs 5.5 %;  $p=0.046$ ), suggesting that stent placement may increase the risk of fistula formation. Logistic regression analysis identified postoperative infection (OR 4.28; 95 % CI 1.22–14.99;  $p=0.023$ ) and prolonged operative duration greater than 90 minutes (OR 3.61; 95 % CI 1.03–12.61;  $p=0.044$ ) as independent predictors of fistula development. A moderate positive correlation was found between CRP levels and postoperative infection ( $\rho=0.46$ ;  $p<0.001$ ), confirming that higher inflammatory markers were associated with wound infection. Duration of surgery was also positively correlated with both patient age ( $r=0.29$ ;  $p=0.004$ ) and UCF occurrence ( $\rho=0.33$ ;  $p=0.006$ ), indicating that longer procedures in older children were more likely to result in fistula formation. Correlation analysis showed a weak positive relationship between age and duration of surgery ( $r=0.29$ ,  $p=0.004$ ). Infection was moderately correlated with higher CRP levels ( $\rho=0.46$ ,  $p<0.001$ ). Longer surgery time showed a moderate correlation with UCF ( $\rho=0.33$ ,  $p=0.006$ ). In the logistic regression analysis, postoperative infection (OR 4.28; 95% CI 1.22–14.99;  $p=0.023$ ) and surgery lasting more than 90 minutes (OR 3.61; 95% CI 1.03–12.61;  $p=0.044$ ) were the only independent predictors of UCF. Hospital stay and CRP level were not significant predictors. The overall UCF rate (10%) in this study is similar to reported South Asian rates. Most other variables showed no significant differences between groups. The study represents a report on the descriptive statistics of continuous variables: age, duration of surgery, hospital stay, hemoglobin, serum creatinine, and C-reactive protein (CRP) (Table 1).

**Table 1:** Comparison of Continuous Variables between Stent (n=55) and Stentless (n=55) Urethroplasty Groups

Variables	Shapiro-Wilk W (p)	Group A (Stent) Mean ± SD / Median (IQR)	Group B (Stentless) Mean ± SD / Median (IQR)	Test Statistic	p-value
Age (Years)*	0.983 (0.21)	6.1 ± 2.6	5.7 ± 2.9	5.7 ± at = 0.78	0.438
Duration of Surgery (min)*	0.978 (0.33)	78.2 ± 11.6	76.4 ± 12.3	t = 0.78	0.438
Hospital Stay (Days)*	0.981 (0.26)	6.8 ± 2.1	4.4 ± 1.8	t = 5.78	<0.001
Hemoglobin (g/dL)†	0.903 (0.012)	11.6 (11.0–12.1)	11.7 (11.2–12.3)	U = 1410.0	0.720
Serum Creatinine (mg/dL)†	0.912 (0.018)	0.62 (0.55–0.69)	0.61 (0.56–0.67)	U = 1432.5	0.810
CRP (mg/L)†	0.894 (0.009)	9.8 (6.3–12.6)	8.9 (5.9–11.7)	U = 1398.5 2.9	0.680

\*Data presented as Mean ± SD for normally distributed variables (independent t-test). †Data presented as Median (IQR) for non-normal variables (Mann-Whitney U test). Significance level p < 0.050

Results present the categorical variables and frequencies of both study groups (Table 2).

**Table 2:** Frequency Distribution of Categorical Variables between Stent (n=55) and Stentless (n=55) Urethroplasty Groups

Variables	Group A (Stent), n (%)	Group B (Stentless), n (%)	χ <sup>2</sup> (df)	p-value
<b>Hypospadias Location</b>				
Coronal	22 (40.0%)	20 (36.4%)	1.12 (2)	0.570
Subcoronal	19 (34.5%)	20 (36.4%)		
Mid-Penile	14 (25.5%)	15 (27.2%)		
<b>Chordee Severity</b>				
Mild	32 (58.2%)	30 (54.5%)	0.98 (2)	0.610
Moderate	18 (32.7%)	20 (36.4%)		
Severe	5 (9.1%)	5 (9.1%)		
<b>Other Factors</b>				
Post-Operative Infection	9 (16.4%)	4 (7.3%)	1.99 (1)	0.158
Wound Edema	15 (27.3%)	12 (21.8%)	0.45 (1)	0.500
Hematoma	3 (5.5%)	2 (3.6%)	Fisher	0.650
Urethrocutaneous Fistula (UCF)	8 (14.5%)	3 (5.5%)	3.97 (1)	0.046*
Meatal Stenosis	4 (7.3%)	3 (5.5%)	0.16 (1)	0.680

The chi-square test is applied unless Fisher's exact test is stated. \*p < 0.050 is considered significant

The study shows a multivariate binary logistic regression analysis identifying independent predictors of urethrocutaneous fistula formation (Table 3).

**Table 3:** Logistic Regression Model Predicting Urethrocutaneous Fistula Formation (n=110)

Predictor Variables	Adjusted OR (95 % CI)	Wald χ <sup>2</sup>	p-value
Post-Operative Infection	4.28 (1.22 – 14.99)	5.13	0.023*
Duration of Surgery > 90 min	3.61 (1.03 – 12.61)	4.08	0.044*
Hospital Stay > 5 Days	1.89 (0.61 – 5.84)	1.11	0.291
CRP > 10 mg/L	1.56 (0.43 – 5.66)	0.59	0.440

#Binary logistic regression analysis performed; reference category = no UCF. \*Significant at p < 0.050.

The analysis shows correlation and subgroup analyses between continuous variables (age, duration of surgery, hemoglobin, and CRP) and categorical variables such as infection and fistula presence. Pearson correlation was used for normally distributed data, and Spearman correlation for non-normal data (Table 4).

**Table 4:** Correlation and Subgroup Analysis of Continuous and Categorical Variables (n=110)

Variable Pair	Test Used	Correlation Coefficient (r/ρ)	95 % CI	Test statistic	p-value
Age vs Duration of Surgery*	Pearson	r = 0.29	0.10 – 0.46	t = 2.93	0.004*
CRP vs Infection Status†	Spearman	ρ = 0.46	0.29 – 0.61	Z = 4.22	<0.001*
Duration of Surgery vs UCF Occurrence†	Spearman	ρ = 0.33	0.11 – 0.52	Z = 2.81	0.006*
Hemoglobin vs Infection Status†	Spearman	ρ = -0.09	-0.28 – 0.11	Z = 0.92	0.360

\*Pearson correlation used for normally distributed variables. †Spearman correlation used for non-normal variables. p < 0.050 is considered significant

## DISCUSSION

The most important results of this study revealed that the incidence of urethrocutaneous fistula (UCF) was 10 percent in the cohort and that it was higher in the stent-assisted group (14.5 percent) than the stentless group (5.5 percent). There were no significant differences in age, type of hypospadias, chordee severity, hemoglobin, creatinine, and CRP levels by groups. In this trial, stentless urethroplasty was associated with a significantly shorter hospital stay, indicating faster recovery and reduced inpatient burden. The stented group had a higher fistula rate, suggesting that stent use may contribute to local irritation or impaired healing. Postoperative infection and prolonged operative time were independent predictors of fistula formation, emphasizing the need for strict infection control and minimizing surgical duration. CRP showed a meaningful correlation with postoperative infection, supporting its role as a useful inflammatory marker. Longer operative times were also associated with increasing age and the occurrence of UCF, implying that more complex repairs in older children may carry a higher risk of complications. Comparison of these results with national studies in Pakistan showed that in one randomized controlled trial involving 260 patients, the total incidence of UCF was 8%, though 13% in the stented and 2% in the stentless group (p=0.001). The overall rate of the current study (10%) could be due to the use of a slightly older age

group or possibly due to the limitation of resources in the hospital setting. An Indian single-centre cohort in the South Asian region did not find any significant difference in complication rates between distal hypospadias stented and unstented repairs (fistula rate of about 7%), and a study in Bangladesh observed similar results with shorter follow-up [12]. Studies in Europe and North America have reported that in unstented urethroplasty, there is no statistically significant risk increase in fistulas [13, 14]. Another recent North American study also indicated that the stent omission could reduce the hospital stay with no significant complication rate escalation ( $p=0.310$ ) [15]. Mechanistically, the higher UCF in the stented group may be due to the longer duration of catheterization, which leads to local irritation, bacterial colonization, and impaired neourethral healing [16]. The fact that it was largely related to operative time implies that more advanced anatomy or a more comprehensive dissection can lead to longer surgery time, which may compromise tissue integrity [17]. The intermediate association between infection and high CRP, the stands-alone consideration of inflammatory burden, could explain why urethral repair integrity is compromised [18, 19]. In this study, age was not a predictor of fistula development, possibly implying that there are greater influences of surgical factors than age of the patients when repair is performed [20].

Such a major methodological constraint is the inability to blind outcome assessors to detect UCF because of visible evidence of previous stent use. The issue with retrospective trial registration could be selective outcome reporting. Resource limitations (the use of nasogastric tubes as urethral stents) instead of conventional silicone pediatric stents can limit comparability with studies that used specialized urethral stents. The follow-up (12 weeks) is too short to evaluate such late complications as the meatal stenosis recurrence and long-term cosmetic results. Single-surgeon design is less variable, but less generalizable to other surgical teams having varied experience levels. Future studies should seek to compare long-term (24 to 36 months) results of stent and no-stent repairs in Pakistan or other low- and middle-income nations, and consider the cost-effectiveness and patient/parent-reported outcomes.

## CONCLUSIONS

In conclusion, the 12-week incidence of urethrocutaneous fistula was lower in the stentless group than in the stented group. Postoperative infection and longer operative time were the only factors linked with fistula formation. These findings suggest that stentless urethroplasty may be a safe option for selected distal and mid-penile cases. Larger studies with longer follow-up are needed to confirm these results.

## Authors' Contribution

Conceptualization: MZK

Methodology: MKC, AS, MAH

Formal analysis: MNK

Writing and Drafting: SS, SUR

Review and Editing: SS, MKC, AS, MAH, MZK, SUR, MNK

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



## Frequency of Fibroadenoma in Patients Presenting with Palpable Breast Lumps: A Cross-sectional Study

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## ABSTRACT

Palpable breast lumps are a common presentation in surgical practice, particularly among young women, and encompass a wide range of benign and malignant conditions. Fibroadenoma is the most frequently encountered benign breast tumor in this age group; however, local hospital-based data on its frequency with statistical precision remain limited. **Objectives:** To estimate the proportion of fibroadenoma among female patients presenting with palpable breast lumps at a tertiary care hospital. **Methods:** This descriptive cross-sectional study was conducted at the Department of General Surgery, Bilawal Medical College, Liaquat University of Medical and Health Sciences (LUMHS), Hyderabad, from January 2025 to June 2025. A total of 60 female patients aged 15–35 years with clinically palpable breast lumps were enrolled using non-probability consecutive sampling. All patients underwent triple assessment, including clinical evaluation, imaging (ultrasound ± mammography), and Tru-Cut biopsy with histopathological examination. Data were analyzed using SPSS version 23.0. Frequencies were reported with 95% confidence intervals (CIs). **Results:** The mean age was  $24.6 \pm 4.8$  years. Fibroadenoma was diagnosed in 22 patients, yielding a frequency of 36.7% (95% CI: 25.0–49.3%). The superolateral quadrant was the most commonly involved site. The proportion of fibroadenoma was consistent across age groups, BMI categories, marital status, breast laterality, and lump duration. **Conclusions:** Fibroadenoma constitutes over one-third of palpable breast lumps in young women presenting to a tertiary care hospital. These findings highlight the importance of structured diagnostic evaluation to guide appropriate management and avoid unnecessary surgical intervention.

## INTRODUCTION

Breast lumps are one of the most frequent presenting complaints in the outpatient surgery departments, and they form a broad range of benign and malignant breast pathologies. Even though most palpable breast lumps in young women are harmless, the clinical dilemma is how to distinguish between harmless lesions and those that may result in serious consequences, which may cause major psychological stress and negative consequences, especially in resource-limited environments where delay in diagnosis may cause severe consequences [1]. The most common benign breast tumor that is commonly diagnosed, particularly among adolescents and young females, is fibroadenoma, which is hormonally reactive and has a

generally favorable prognosis [2]. Fibroadenoma constitutes a variable proportion of palpable breast lumps that have been recorded in different populations with wide ranges of prevalence of one-third to over half of all of the benign breast lesions [3–6]. This heterogeneity is attributed to variations in age distribution, healthcare-seeking behavior, diagnostic facilities, and sociocultural factors. The age-related trends of fibroadenoma have been described by a number of regional and international studies that have uniformly shown a greater prevalence in women whose age is below 35 years [4–6]. Nevertheless, most of these are high-income country-based studies or selected tertiary centers, and their findings cannot be generalized



to the population of South Asian countries. The hospital-based statistics on the prevalence of fibroadenoma in patients presenting with palpable breast lumps are few in Pakistan and other low- and middle-income nations. Local research has concentrated on major trends in breast disease or heterogeneous groups that span extensive age groups without necessarily highlighting fibroadenoma as a preeminent result [6]. Further, most articles have reported associations with demographic and clinical factors without presenting accurate estimates, including confidence intervals, hence making their results less comprehensible and applicable in daily clinical practice. The correct estimation of the prevalence of fibroadenoma within a specified population of a hospital is necessary to inform the diagnostic strategy, maximize the use of imaging and biopsy, and educate patients about the prognosis and treatment choices [7]. This is especially crucial in younger women, where the unnecessary surgical intervention can be prevented in evidence-based decision-making. Also, insight into the local burden of fibroadenoma will help differentiate it more effectively against malignant and borderline fibroepithelial lesions, which could share similar clinical presentations, but would need very different management strategies [8-10].

This study is expected to add locally relevant evidence to inform clinical decisions and enhance the existing body of literature on the patterns of benign breast disease in South Asian contexts by presenting hospital-based prevalence data with an adequate level of statistical accuracy and stratification. Based on these gaps, the current study aimed to ascertain the prevalence of fibroadenoma among young female individuals between the ages of 15 and 35 years who presented with palpable breast masses in a tertiary care teaching hospital in Hyderabad, Pakistan.

## METHODS

It was a descriptive cross-sectional study that was carried out at the Department of General Surgery, Bilawal Medical College, Liaquat University of Medical and Health Sciences (LUMHS), Hyderabad, between January 2025 and June 2025. That study was carried out following the synopsis approval of the LUMHS and the ethical clearance given by the LUMHS Research Ethics Committee (Approval No: LUMHS/REC/-580). The WHO sample size calculator was used to compute the sample size of 60 patients at a 95% level of confidence, 12% margin of error, and an expected prevalence of fibroadenoma of 33.3% among patients with breast lumps. The sampling was the non-probability consecutive sampling [11]. The inclusion criteria were to be female patients aged 15 to 35 years with clinically palpable breast lumps and the readiness to sign an informed consent. The exclusion criteria consisted of patients who had a prior history of fibroadenoma, lumps due to trauma,

recurrent or ulcerated lumps, lumps that occurred during the menstrual cycle, male patients, metastatic breast cancer diagnosed during breast surgery, post-operative breast lump, or post-surgery breast cancer. Informed consent was signed by patients presenting to the General Surgery Outpatient Department after they had been given an elaborate explanation about the aim and advantage of the study. A detailed clinical test was performed in which the lump location, its size, shape, consistency, pain, swelling, nipple discharge, and its relation to the menstrual cycles were recorded. The preliminary lab tests consisted of a complete blood count and urinalysis. All patients received triple assessment, which included: Clinical (history and physical examination), Imaging studies such as ultrasound on all patients and mammography on patients above 30 years old, and Tru-Cut biopsy histopathological examination. A consultant general surgeon with more than five years of experience performed biopsies in aseptic conditions under local anesthesia. At least two samples of core tissues were taken in each lesion, labeled instantly, and stored in the histopathology lab. The samples were handled following standard procedures, and the histopathologist was blinded to the clinical information of the patients to minimize bias. Diagnosis was done through histopathological examination. The information was documented in the form of a structured proforma, which consisted of age, height, weight, BMI, marital status, breast site/ quadrant, lump duration, and the presence or absence of fibroadenoma. Selection bias and confounding were minimized by adhering to inclusion and exclusion criteria. Data were entered and statistically analyzed using SPSS version 23.0. The Shapiro-Wilk test was used to test the normality of the quantitative variables (age, BMI, and duration of breast lump). The summative statistics of normally distributed variables were reported as mean and standard deviation, whereas skewed variables were reported as median and interquartile range (IQR). Categorical variables such as marital status, location of breast involvement, and distribution by quadrant have been stated in frequencies and percentages. The main aim of the research was to establish the prevalence of fibroadenoma in patients who present with palpable lumps of the breast. To this end, results were provided in terms of 95% confidence interval estimates, which were made using the Wilson method to enhance accuracy. The stratification was done according to effect modifiers, which were set and included age, BMI, length of lump, marital status, location of breast involvement, and quadrant.

## RESULTS

A total of 60 patients presenting with palpable breast lumps were included in the study. The mean age of the participants was  $24.6 \pm 4.8$  years. The median duration of the breast lump at presentation was 3 months with an interquartile range (IQR) of 2–6 months. The mean height and weight were  $159.2 \pm 6.1$  cm and  $62.1 \pm 8.0$  kg, respectively, yielding a mean body mass index (BMI) of  $24.5 \pm 3.2$  kg/m<sup>2</sup>. Detailed demographic characteristics are summarized in table 1.

**Table 1:** Demographic Characteristics of Patients (n=60)

Variables	Mean $\pm$ SD / Median (IQR)
Age (years)	24.6 $\pm$ 4.8
Height (cm)	159.2 $\pm$ 6.1
Weight (kg)	62.1 $\pm$ 8.0
BMI (kg/m <sup>2</sup> )	24.5 $\pm$ 3.2
Duration of Lump (months)	3 (2–6)

Most participants were married (38; 63.3%, 95% CI: 50.4–74.7). Right-sided breast involvement was observed slightly more frequently (32; 53.3%, 95% CI: 40.1–66.3) compared with the left breast (28; 46.7%, 95% CI: 33.7–59.9). With respect to anatomical distribution, the superolateral quadrant was the most commonly involved (26; 43.3%), followed by the superomedial (12; 20.0%), inferolateral (12; 20.0%), and inferomedial quadrants (10; 16.7%). Clinical characteristics are detailed in table 2.

Stratified analysis of fibroadenoma frequency was performed according to age group, BMI, duration of lump, marital status, site of breast involvement, and quadrant. The proportion of fibroadenoma remained relatively consistent across all subgroups. As the primary objective of the study was estimation of frequency, interpretation focused on proportions and confidence intervals rather than hypothesis testing. Subgroup-specific estimates with 95% CIs are presented in table 4.

**Table 4:** Stratification of Fibroadenoma by Effect Modifiers (n=60)

Effect Modifier	Categories	Fibroadenoma, n (%)	95% CI	Other lesions, n (%)	95% CI
Age Group	15–25 Years	14 (40.0%)	27.0–54.1	21 (60.0%)	45.9–73.0
	26–35 Years	8 (32.0%)	17.9–50.1	17 (68.0%)	49.9–82.1
BMI	<25 kg/m <sup>2</sup>	10 (33.3%)	18.6–51.0	20 (66.7%)	49.0–81.4
	$\geq$ 25 kg/m <sup>2</sup>	12 (40.0%)	25.7–55.8	18 (60.0%)	44.2–74.3
Duration of Lump	<3 Months	9 (34.6%)	18.9–53.0	17 (65.4%)	47.0–81.1
	$\geq$ 3 Months	13 (38.2%)	24.0–54.3	21 (61.8%)	45.7–76.0
Marital Status	Married	14 (36.8%)	22.7–52.3	24 (63.2%)	47.7–77.3
	Unmarried	8 (36.4%)	18.0–57.5	14 (63.6%)	42.5–82.0
Site of Breast	Right	12 (37.5%)	22.7–54.2	20 (62.5%)	45.8–77.3
	Left	10 (35.7%)	21.1–53.1	18 (64.3%)	46.9–78.9
Quadrant	Superomedial + Superolateral	14 (36.8%)	22.7–52.3	24 (63.2%)	47.7–77.3
	Inferomedial + Inferolateral	8 (36.4%)	18.0–57.5	14 (63.6%)	42.5–82.0

## DISCUSSION

The overall percentage of fibroadenoma patients in this hospital-based study involving 60 cases of patients with palpable breast lumps was 36.7% (95% CI: 25.0–49.3%). The majority of the affected patients were young (15–25 years old), in line with the demographic profile of fibroadenoma,

**Table 2:** Clinical Characteristics of Patients (n=60)

Variables	Category	n (%)	95% CI
Marital Status	Married	38 (63.3%)	50.4–74.7
	Unmarried	22 (36.7%)	25.3–49.6
Site of Breast	Right	32 (53.3%)	40.1–66.3
	Left	28 (46.7%)	33.7–59.9
Quadrant of Breast	Superomedial	12 (20.0%)	11.0–32.4
	Superolateral	26 (43.3%)	30.8–56.5
	Inferomedial	10 (16.7%)	8.9–28.6
	Inferolateral	12 (20.0%)	11.0–32.4

Among the 60 patients, 22 (36.7%) were diagnosed with fibroadenoma, while 38 (63.3%) had other benign or malignant breast lesions. The 95% confidence interval (CI) for the frequency of fibroadenoma was 25.0–49.3%, calculated using the Wilson method. The assumed prevalence of 33.3% used for sample size estimation was derived from previous hospital-based studies of patients presenting with palpable breast lumps. The outcome distribution is shown in table 3.

**Table 3:** Frequency of Fibroadenoma in Patients with Palpable Breast Lumps (n=60)

Outcomes	n (%)	95% CI
Fibroadenoma	22 (36.7%)	25.0–49.3
Other benign/malignant lesions	38 (63.3%)	50.7–75.0

which is usually reported in previous hospital-based studies. Its distribution in both BMI groups, marital status, breast laterality, and quadrant involvement was quite balanced, indicating that these variables might not significantly affect the prevalence of fibroadenoma among

this group of patients [12, 13]. The frequency observed is quite consistent with that of other studies on hospitals that state the prevalence of fibroadenoma is between 30 and 40 percent in patients with palpable breast lumps [15]. In our cohort, histopathological analysis also revealed that fibroadenoma was the most frequent benign lesion of the breast, as it corresponded to the results of a study in Saudi Arabia and Nigeria [12-16]. Other rare presentations, including fibroadenoma in axillary accessory breast tissue, have also been reported, which underscores the value of careful clinical and imaging evaluation [11, 17]. To distinguish fibroadenoma among other fibroepithelial lesions and malignancies, imaging and radiologic-pathologic correlation are necessary [18]. The results are indicative of the greater global patterns of benign and malignant breast disease, with low- and middle-income countries showing the same epidemiologic patterns [19, 20]. Most of the patients in our study group were below the age of 35, and this age corresponded with the established age difference between benign lesions and carcinoma, affecting older women [20]. The stratification analysis did not demonstrate any significant relationship between fibroadenoma and BMI, marital status, breast laterality, or the involvement of the quadrant. Though other studies indicate these variables as possible modifiers, the non-significant differences in our study can indicate either the small sample size or the comparatively homogenous demographic population of the hospital patients [11, 17]. These results underscore the fact that the fibroadenoma is mostly associated with a young age but not lifestyle or demographic factors. The study supports the significance of early detection and proper diagnosis of fibroadenoma in younger women who show signs of palpable breast lumps. In areas with low breast cancer awareness, ultrasound and histopathology will continue to play a critical role in the differentiation between fibroadenoma and other benign and malignant lesions [18]. Clinicians must pay attention to risk stratification according to age and possibly conservative treatment or minimally invasive surgeries instead of surgical removal in the case of fibroadenoma, and they should reserve surgical intervention for cases that have symptoms or atypical.

The study has limitations, such as a single-center, hospital-based study design, which might be a limitation to generalizing. The size of the sample used is relatively small, which decreases the accuracy of subgroup analyses, as indicated in broad confidence intervals of certain categories. Also, the cross-sectional design does not permit the evaluation of longitudinal outcomes or risk of recurrence. In spite of these shortcomings, the study gives a good estimate of the prevalence of fibroadenoma among a hospital population and can inform future studies in similar contexts.

## CONCLUSIONS

Fibroadenoma was found in 36.7% of patients with palpable breast lumps in the hospital, with the highest rates observed in younger women between the ages of 15 and 25 years. There were no significant associations between the BMI, marital status, laterality of the breast, and quadrant involvement and fibroadenoma occurrence. The above findings underscore the fact that the age factor is still the major predictor of fibroadenoma, and the need to detect it early, have the right imaging, and conduct a histopathological study in order to have it managed properly. Such hospital-based data can be used to inform clinicians in risk stratification, patient counseling, and in making decisions regarding conservative versus surgical intervention, and to serve as a reference to future epidemiologic studies within such settings.

## Authors' Contribution

Conceptualization: SAS

Methodology: SAS, YR, DAS, AJ<sup>2</sup>

Formal analysis: SAS, DAS, AJ<sup>2</sup>

Writing and Drafting: SAS, YR, AJ<sup>1</sup>, BA

Review and Editing: SAS, YR, DAS, AJ<sup>1</sup>, AJ<sup>2</sup>, BA

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



## Cone Beam Computerized Tomographic (CBCT) Assessment of Buccal Bone Thickness in Maxillary Aesthetic Region

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## ABSTRACT

Buccal bone thickness (BBT) in the maxillary aesthetic region is a key determinant of ridge remodeling and the chances of recession of the mucosa following implantation. **Objectives:** To measure BBT at standardized levels around maxillary central incisors, lateral incisors, and canines on CBCT scans of patients from Peshawar, Pakistan. **Methods:** This cross-sectional study assessed 96 CBCT scans of patients aged 18-60 years obtained from the Department of Oral and Maxillofacial Radiology, Rehman Medical Institute/Rehman College of Dentistry, Peshawar, over six months from 3 February 2025 to 3 August 2025. BBT was measured on sagittal reconstructions at the crestal level (L0) and at 1 mm (L1), 3 mm (L3), and 5 mm (L5) apical to the crest. Descriptive statistics were reported; gender differences were explored using independent-samples tests and age associations using Spearman correlation ( $\alpha=0.05$ ). **Results:** At L0, BBT was <1 mm in 90.6% of central incisors, 90.7% of lateral incisors, and 84.3% of canines. Males showed greater BBT than females at selected levels (central incisors: L1 and L5; lateral incisors: L5). Age showed statistically significant but weak correlations with BBT at L1 for central incisors and at L5 for lateral incisors and canines. **Conclusions:** In this sample, the buccal plate in the anterior maxilla was predominantly thin (<1 mm), particularly for lateral incisors and at the crest. Preoperative CBCT assessment should guide implant positioning and the anticipated need for augmentation, with consideration of patient sex and age.

## INTRODUCTION

The key to the successful placement of the implants in the maxillary aesthetic area is maintaining the buccal plate and peri-implant soft tissues. When immediate implant placement is scheduled, a thin buccal bone wall is related to increased post-extraction remodeling and an increased likelihood of mid-facial recession. Conebeam computed tomography (CBCT) offers three-dimensional imaging, which allows the effective preoperative measurement of buccal bone thickness (BBT) and cemento-enamel

junctional alveolar crest (CEJAC) distance, which will determine the timing of implant creation, placement, and augmentation requirement. The measurement of the BBT in the maxillary aesthetic part is essential in dental implant placement as well as maintenance of oral aesthetics. CBCT has emerged as a preferred imaging technique, providing precise, three-dimensional representations of maxillofacial structures with reduced radiation exposure compared to traditional computed tomography [1, 2]. This

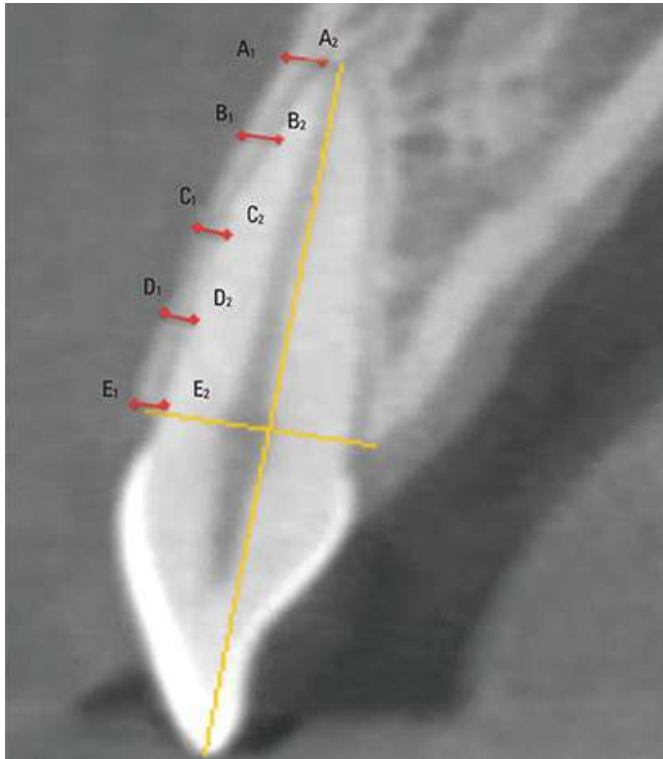
high-precision imaging allows clinicians to evaluate buccal bone dimensions that are vital for planning successful dental procedures, particularly in the maxillary aesthetic zone, where bone deficiency can significantly impact aesthetic outcomes and functional success [3, 4]. Previous studies underscore the importance of accurately measuring buccal bone thickness as it can greatly influence treatment strategies, particularly in post-extraction scenarios and in implantology [5, 6]. The ability to ascertain the morphology of buccal bone enhances treatment decision-making by identifying the volume available for implants and anticipating potential complications related to bone thickness [7, 8]. Notably, Fuentes et al. documented the effectiveness of CBCT in assessing buccal bone thickness, finding it essential for evaluating the anatomical considerations of extraction sites before implant placements [9]. Equally, research has noted that there have been thin buccal bone walls which are less softened than 1 mm at different anterior maxillary positions, posing a possible threat of resorption after implantation has been done [10, 11]. A difficulty for clinicians in placing dental implants in the anterior maxilla is the complex anatomical conditions coupled with the very high aesthetic demands of patients [12]. In the replacement of one anterior tooth in a region that does not have deficiencies of tissue, predictable results, such as esthetic results, may frequently be attained, primarily because of the soft-tissue support of the surrounding teeth. However, very few authors have covered the replacement of other surrounding absent teeth in the anterior maxilla with fixed implant restorations, and the cosmetic results cannot be predicted, especially when it comes to the preservation of natural soft tissue profiles [13]. This is the new trend of placing the implants within the aesthetic zone immediately after the removal of the failing tooth and then provisionalizing it immediately [14]. Provisionalization of implants in healed regions of the maxillary aesthetic area, which is temporary, yields the same outcomes as delayed provisionalization [15]. Treatment of the anterior maxilla with implants presents special problems due to the high aesthetic requirements and the morphology of the anatomy in this area. An adequate amount of bone in the bucca is one of the basic factors that dictate the stability of implants, proper placement, and success in the long-term aesthetics. There are significant dimensional changes that take place in the alveolar bone after the removal of the tooth, which commonly results in a loss of width and height of the ridge. The buccal plate thickness is especially important, as it is highly likely to be resorbed and, as such, disagrees with the hard and soft tissue support.

This study does not support a large sample size to define

the gap. This study aims to investigate the buccal bone thickness at standardized levels around maxillary central incisors, lateral incisors, and canines on CBCT scans of patients from Peshawar, Pakistan

## METHODS

The present cross-sectional study was done during the period from 3 February 2025 to 3 August 2025, and involved the analysis of 96 CBCT scans done at the Department of Oral and Maxillofacial Radiology, Rehman Medical Institute (RMI). The sampling technique of collecting the CBCT images of the patients attending Rehman College of Dentistry RCD was a convenience sampling procedure. The Institutional Review Board of Rehman College of Dentistry approved the ethical issue with the ref no: RCD-04-23-145. All the CBCT scans were performed by a trained technologist in the CBCT unit (CS9300CBCT, Carestream Dental, Atlanta, GA, USA) using the following parameters: 85 kV, 12 mA, a voxel size of 0.1 mm, and a field of view of 17 13 cm. The sample was established at 96, the basis of which was the prevalence rates of a previous study. CBCTs were also acquired on patients who had received dental services, including oral surgery, dental implants, and orthodontics, and were processed using the help of CS 3D software (Carestream Dental, Atlanta, GA, USA). Inclusion criteria were patients between the ages of 18 and 60 years, with intact maxillary central and lateral incisors and canines, no restorations, periodontal disease, or trauma. Scans that had clinical or radiographic signs of periodontal disease were eliminated. Gingival phenotype was not directly assessed on CBCT; therefore, residual confounding by soft-tissue phenotype cannot be completely excluded and is acknowledged in the limitations. Using EZ3D Plus software, sagittal reconstructions were obtained, and five lines were traced perpendicular to the tooth axis at standardized levels from the cemento-enamel junction (CEJ) to the apex. The thickness of the buccal bone was calculated at each level. The sagittal section of CBCT was compared at a particular parallel corresponding level in terms of the wall thickness of the buccal bone. Line A1-A2 was located in the very apical tooth, and line E1-E2 was located at the same level as the crests of the bone. Lines B, C, and D were drawn at an equal and parallel distance between A1-A2 and E1-E2 (Figure 1).



**Figure 1:** Buccal Bone Wall Thickness on Sagittal Sections of the CBCT Scans Using Standardized Parallel Reference Lines

Means, standard deviations, and frequency distributions were calculated. The independent samples T-test and ANOVA were used to assess differences across gender and age groups, with a significance threshold of  $p < 0.05$ .

## RESULTS

In this cross-sectional study, 96 CBCT scans from patients aged 18–60 years were assessed, with a mean age of  $36.8 \pm 10.9$  years. Participants were distributed across the 18–30 (35.4%), 31–45 (39.6%), and 46–60 (25.0%) year age groups. The sample included 28 males (29.2%) and 68 females (70.8%). CBCT indications comprised orthodontics (31.2%),

oral surgery (41.7%), and implant planning (27.1%). All scans were obtained from the Oral and Maxillofacial Radiology Department, Rehman Medical Institute/Rehman College of Dentistry, Peshawar, between 3 February 2025 and 3 August 2025 (Table 1).

**Table 1:** Demographic Characteristics of the Study Sample (n=96)

Characteristic	Value
Age (Years), Mean $\pm$ SD	36.8 $\pm$ 10.9
Age Groups, n (%)	18–30: 34 (35.4%); 31–45: 38 (39.6%); 46–60: 24 (25.0%)
Sex, n (%)	Male: 28 (29.2%); Female: 68 (70.8%)
Indication for CBCT, n (%)	Orthodontics: 30 (31.2%); Oral Surgery: 40 (41.7%); Implant Planning: 26 (27.1%)
CBCT Acquisition Period	3 February 2025 – 3 August 2025 (6 Months)

There was a buccal bone layer very thin (L0) at the crestal part in 28.1 per cent. of central incisors, 46.9 percent. of lateral incisors and 33.3 per cent. of canines. In 62.5 percent of central, 43.8 percent of lateral, and 51.0 percent of canines, a thickness of between 0.5mm and 1mm was observed. Only 9.4% of central incisors, 9.3% of lateral incisors, and 15.7% of canines had a heavier bone (12 mm). Thin apical buccal bone (0.5–1 mm) was observed at 1 mm apical to the crest (L1) in 65.6% of central incisors. On 13.6, 11.4, and 14.5 percent of central incisors, lateral incisors, and canines, respectively, a thickness of 1 to 2 mm was noticed. Very thin bone (<0.5 mm) occurred at 3 mm apical to the crest (L3) in 18.7% of central incisors, 35.4% of lateral incisors, and 19.8% of canines. Very thin bone (less than 0.5 mm) was present at 5 mm apical to the crest (L5) in 25.0 percent of central incisors, 53.1 percent of lateral incisors, and 22.9 percent of canines. Thickness of up to 0.5 mm to 1 mm was observed in 61.5 percent of central incisors, 41.7 percent of lateral incisors, and 59.4 percent of canines. The only central incisors, lateral incisors, and canines with a thickness of 1 to 2 mm were 13.5 percent, 5.2 percent, and 17.7 percent, respectively (Table 2).

**Table 2:** Buccal Bone Thickness Distribution Categories (<0.5 Mm, 0.5–1 Mm, 1–2 Mm) at Each Level (L0, L1, L3, L5) by Tooth Type

Level	<0.5 mm (%) CI	0.5–1 mm (%) CI	1–2 mm (%) CI	<0.5 mm (%) LI	0.5–1 mm (%) LI	1–2 mm (%) LI	<0.5 mm (%) C	0.5–1 mm (%) C	1–2 mm (%) C
L0	28.1	62.5	9.4	46.9	43.8	9.3	33.3	51.0	15.7
L1	20.8	65.6	13.6	31.3	57.3	11.4	23.0	62.5	14.5
L3	18.7	68.8	12.5	35.4	54.2	10.4	19.8	65.7	14.5
L5	25.0	61.5	13.5	53.1	41.7	5.2	22.9	59.4	17.7

The average distance of the CEJ to the alveolar crest was  $2.10 \pm 0.78$  mm in central incisors,  $2.18 \pm 0.82$  mm in lateral incisors, and  $2.25 \pm 1.10$  mm in canines. The last value of the mean BBT at the crest measured 0.68 bbcci, 0.61 bbcci, and 0.72 bbcci with crest in central incisors, lateral incisors, and canines, respectively. The mean thickness at 1 mm apical to the crest was  $0.81 \pm 0.20$  mm (central incisors),  $0.73 \pm 0.25$  mm (lateral incisors), and  $0.82 \pm 0.27$  mm (canines). Mean thicknesses at 5 mm were  $0.71 \pm 0.21$  mm (central incisors),  $0.50 \pm 0.22$  mm (lateral incisors), and  $0.66 \pm 0.26$  mm (canines) (Table 3).

**Table 3:** Mean BBT (mm) and CEJ-AC Distance (mm) by Tooth Type and Level

Tooth	Crest (L0)	1 mm (L1)	3 mm (L3)	5 mm (L5)	CEJ-AC
Central Incisor	0.68 ± 0.23	0.81 ± 0.20	0.75 ± 0.22	0.71 ± 0.21	2.10 ± 0.78
Lateral Incisor	0.61 ± 0.24	0.73 ± 0.25	0.65 ± 0.29	0.50 ± 0.22	2.18 ± 0.82
Canine	0.72 ± 0.26	0.82 ± 0.27	0.79 ± 0.28	0.66 ± 0.26	2.25 ± 1.10

Descriptive statistics for buccal bone thickness and CEJ-AC distance

Sex differences were initially explored using independent-samples tests within each tooth type and measurement level. To assess whether age confounded observed sex differences, we additionally fitted an age-adjusted multivariable model with buccal bone thickness as the outcome, sex as the main predictor, and age as a covariate,

accounting for within-subject clustering of repeated measurements. 1. BBT = BBT measured on sagittal CBCT reconstructions. 2. L1 = 1 mm apical to the alveolar crest; L5 = 5 mm apical to the alveolar crest. 3. Sex differences were tested using independent-samples comparisons; only statistically significant results are shown. 4. Age associations were assessed using Spearman's rank correlation (rs). 5. Statistical significance was set at alpha = 0.05 (two-sided). Although age showed statistically significant correlations with BBT at selected levels, the effect sizes were weak and had limited clinical predictive value. Clinical interpretation should prioritize absolute CBCT-measured thickness and whether sites approach commonly cited stability thresholds (~1.5–2.0 mm), noting that most sites in this cohort remained <1 mm (Table 4).

**Table 4:** Statistically Significant Associations of Sex and Age with BBT in the Anterior Maxilla (n=96)

Predictor	Tooth Type	Measurement Level	Direction of Association	Effect Estimate/Test Statistic
Sex (Male vs Female)	Central incisor	L1	Males Had Greater BBT Than Females	p=0.006
Sex (Male vs Female)	Central incisor	L5	Males Had Greater BBT Than Females	p=0.031
Sex (Male vs Female)	Lateral incisor	L5	Males Had Greater BBT Than Females	p<0.001
Age (Years)	Central incisor	L1	Increasing Age Was Associated with Thinner BBT	rs = 0.298, p<0.001
Age (Years)	Lateral incisor	L5	Increasing Age Was Associated with Thicker BBT	rs = 0.195, p=0.021
Age (Years)	Canine	L5	Increasing Age Was Associated with Thicker BBT	rs = 0.208, p=0.016

## DISCUSSION

This CBCT-based assessment shows that the buccal plate in the anterior maxilla is predominantly thin in this Peshawar cohort, especially at the crestal level. Most sites were <1 mm at L0 across all three tooth types, with lateral incisors demonstrating the least favourable distribution and the lowest mean thickness at deeper levels. This finding is clinically important because the anterior maxilla has high aesthetic demands and limited tolerance for post-extraction and post-implant hard- and soft-tissue changes. Even small losses of facial bone support can translate into mid-facial mucosal recession and compromised aesthetic outcomes in the long term [1, 2]. Current results align with the broader morphometric literature showing that the facial/buccal bone wall in the maxillary aesthetic region is frequently thin when evaluated on CBCT. Systematic reviews and meta-analyses of CBCT studies report a high prevalence of thin facial plates in the anterior maxilla, with substantial inter-individual variability but a consistent pattern of limited buccal thickness at many anterior sites [15, 16]. Multiple CBCT investigations similarly highlight that thin buccal walls are common around maxillary anterior teeth and should be anticipated during implant planning [17–20]. Recent CBCT work focusing on maxillary central incisors also supports that the buccal wall is often slender and morphologically variable, reinforcing the need for site-specific assessment rather than assumptions based on tooth type alone [21]. From a treatment-planning

perspective, thin buccal bone is relevant because it is more susceptible to resorption and dehiscence after extraction and during implant therapy. Evidence from experimental and clinical work suggests that a thicker peri-implant buccal wall is associated with more favourable hard- and soft-tissue stability. Experimental evidence has revisited the concept of a “critical” buccal wall thickness, with values around 1.5 mm frequently discussed as a clinically meaningful threshold for reducing remodeling-related risk compared with thinner walls [12]. Clinical trials in the aesthetic zone show that even with immediate implant placement and provisionalization, hard- and soft-tissue alterations occur and may require adjunctive approaches to mitigate aesthetic compromise [9, 10]. Where baseline buccal thickness is limited, augmentation strategies (e.g., guided bone regeneration and/or grafting approaches) may be needed to support appropriate three-dimensional implant positioning and soft-tissue contour stability [6, 7]. These considerations are consistent with classic aesthetic-zone principles that prioritize prosthetically driven implant placement and preservation of facial support [1, 2]. Sex-based differences in this dataset were statistically significant at selected sites/levels (central incisor L1 and L5; lateral incisor L5), with males showing higher BBT. However, the clinical implications of these differences should be interpreted cautiously. The absolute thickness values remained low overall, and the distribution analysis indicates

that most sites still fell below <1 mm, even where sex differences were present. Therefore, sex may contribute to anatomical variability but should not replace direct CBCT-based evaluation of the recipient site. Age showed statistically significant but weak correlations with BBT at specific measurement points. These effect sizes have limited clinical predictive value on their own. Interpreting the associations against anatomical thresholds is more informative than focusing on p-values. At the levels where age correlations were detected, most sites remained within thin-bone categories, meaning that small age-associated shifts are unlikely to move many patients into thicker, lower-risk ranges. Accordingly, treatment decisions in the aesthetic zone should prioritize the measured site-specific thickness and whether it approaches commonly cited stability thresholds ( $\approx 1.5$ – $2.0$  mm), rather than relying on age alone [15, 16]. Soft-tissue phenotype may also influence aesthetic risk and peri-implant remodeling, but it was not directly measured in this study. Prior work indicates relationships between gingival thickness, underlying bone morphology, and early peri-implant bone changes, suggesting that combined hard-soft tissue assessment is ideal when feasible [8, 14]. The use of convenience sampling from a single centre may also limit the generalizability of the findings. Nonetheless, the study's strengths include standardized CBCT acquisition parameters, defined inclusion/exclusion criteria to reduce confounding from pathology/restorations, and tooth- and level-specific measurements that reflect clinically relevant implant planning landmarks. CBCT remains a suitable modality for three-dimensional assessment in this setting, and diagnostic performance can be influenced by voxel size and reconstruction parameters, which were standardized in our protocol [13]. Overall, the present findings support routine preoperative CBCT assessment in the maxillary aesthetic region to guide implant positioning and to anticipate whether buccal augmentation may be required, particularly in lateral incisor sites and at crestal levels where thin plates are most prevalent [12, 16].

The findings of this study are confined by the single retrospective design that is limited to a single center and cannot support the outcomes to occur after treatment, nor can they be generalized to other populations. One of the weaknesses of the study is the lack of soft-tissue data, which is an essential aspect of the aesthetic results. Being solely a radiographic study, the outcomes are also not corroborated by real-life surgical results or by long-term patient outcomes. Further research ought to determine the direct clinical evidence by following the effect of thin buccal plates on the aesthetics of the implant in the long run. The studies need to foster both 3D bone evaluation and the gingivae phenotype to develop their full risk profile. Further, to enhance the generalizability, the same studies need to be done in multi-center populations that are diverse. Lastly, a

comparative analysis is required in order to assess the best bone augmentation methods to use in these high-risk and thin-wall locations.

## CONCLUSIONS

The study confirms that in our patients, most anterior maxillary sites have buccal bone thicknesses less than the ideal 2 mm for implant procedures. These findings advocate for routine CBCT assessment and individualized treatment planning in implant dentistry.

## Authors' Contribution

Conceptualization: SR, HMA

Methodology: MHA, HMA

Formal analysis: FM

Writing and Drafting: SR, MHA, NN, SS

Review and Editing: SR, MHA, NN, FM, HMA, SS

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



## Incidental Renal Artery Stenosis amongst a Cohort of Hypertensive Patients Undergoing Coronary Angiography: An Analytical Cross-Sectional Study

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## ABSTRACT

There has been less research on accidental RAS in patients with hypertension who have received coronary angiography. **Objectives:** To determine the prevalence rate of incidental renal artery stenosis (IRAS) in patients having coronary angiography. **Methods:** This analytical cross-sectional study was conducted at Khyber Teaching Hospital for six months between 1st April 2025 and 30th September 2025. Consecutive sampling was used to enroll 139 hypertensive patients under diagnostic coronary angiography as participants. Findings of coronary angiography and incidental evaluation of the renal artery were recorded, with stenosis of  $\geq 50\%$  seen as IRAS. The analysis of data was done with SPSS version 25.0. Odds ratios were estimated at 95% confidence intervals using univariate analysis. **Results:** Incidental renal artery stenosis was observed in 18.0% of patients, and in 13.7% and 4.3%, respectively, bilateral and unilateral renal artery stenosis. IRAS was significantly correlated with longer hypertension period and high serum creatinine ( $p < 0.05$ ). **Conclusions:** Nearly one-fifth of hypertension patients who had coronary angiography had incidental renal artery stenosis, most of which were unilateral. Chronic hypertension and high creatinine were identified as some of the most important associated factors, and it is important to evaluate renal arteries when the coronary arteries should be evaluated to be able to assess the cardiovascular and renal risks.

## INTRODUCTION

Hypertension is an important factor in cardiovascular morbidity and mortality, therefore being one of the largest global public health issues [1, 2]. Pharmacological treatment for hypertension has improved, yet a sizable portion of patients still have resistant or uncontrolled hypertension, suggesting other underlying etiological causes. Among these is renal artery stenosis (RAS), a clinically relevant disease that is frequently misdiagnosed [3, 4]. It is primarily induced by atherosclerotic disease, and it is closely linked to systemic vascular pathology and coronary artery disease (CAD) [5, 6]. The association of

RAS with CAD demonstrates diffuse atherosclerosis, and many patients who underwent a coronary angiography might have an asymptomatic or incidental involvement of the renal artery [7]. The occurrence of renal artery stenosis is reported to be widely variable based on the population of patients and the detection method, with 5%-40% prevalence being reported in cases where patients are undergoing coronary angiography or peripheral vascular assessment [7]. Additionally, compared to the general population, hypertensive patients with widespread atherosclerosis are far more likely to develop renal artery



stenosis [8]. Incidental RAS identified on coronary angiography has been of growing interest due to the possible effects it could have on blood pressure management, worsening of renal function, cardiovascular events, and therapeutic decision-making [9]. Early detection is especially important in hypertensive patients with resistant hypertension, unexplained renal dysfunction, or diffuse vascular disease, in which the preventive intervention at the initial stage can have an impact on the treatment plan and the outcome [10]. Although clinically important, incidental renal artery stenosis can be easily missed during standard cardiovascular assessment, particularly in the resource-constrained environment where renal artery imaging may not be conducted everywhere during coronary angiography [11].

Also, there is limited regional data regarding the burden of incidental RAS on hypertensive cohorts who have undergone coronary angiography. The production of local evidence is necessary to emphasize its magnitude, inform screening decisions, and facilitate risk-stratified assessment of hypertensive patients at risk. This research is thus conceptualized to close this knowledge deficit by measuring the incidence of incidental renal artery stenosis in hypertensive patients during coronary angiography and thus add essential information to the continuum of systemic involvement of atherosclerosis among the hypertensive patients. This study aims to determine the frequency of incidental renal artery stenosis (IRAS) in hypertensive patients undergoing coronary angiography.

## METHODS

The design of this study was analytical, cross-sectional, and carried out over the course of six months, from April 1, 2025, to September 30, 2025, at the Department of Radiology of the Khyber Teaching Hospital in Peshawar. The Institutional Research and Ethical Review Board (IREB) of Khyber Medical College in Peshawar granted ethical permission with approval number 280/DME/KMC. To calculate the sample size, the WHO sample size calculator was used using the formula  $n = Z^2 \times p \times (1 - p) / d^2$  [12], where  $n$  was the required sample size,  $Z$  was the standard normal variate at 95% (1.96),  $p$  was the anticipated prevalence of incidental renal artery stenosis (10%) [13], and  $d$  = margin of error (5%). The total calculated sample size was 139. A non-probability Consecutive sampling was used to recruit participants. The inclusion criteria involved patients aged 18–80 Years, both male and female, and hypertensive patients undergoing coronary angiography, as per operational definitions. Individuals who had previously been diagnosed with renal artery stenosis, had undergone renal interventions such as renal stenting or angioplasty, or had non-atherosclerotic causes of renal artery stenosis

such as fibromuscular dysplasia, were not allowed to participate in the study. Data collection was done after the IREB of KMC provided the ethical approval. The hypertensive patients undergoing diagnostic coronary angiography over the study period participated in the data collection. All patients who were admitted to the cardiac catheterization laboratory were screened consecutively, and those who met the inclusion criteria were enrolled with informed consent. Individuals having a history of hypertension, antihypertensive drug use, or a diagnosis of hypertension were all included. Individuals with a history of renal artery stenosis, renal artery revascularization surgeries, kidney transplants, or incomplete renal artery visibility were not included. To ensure confidentiality and eliminate duplication, each enrolled participant was given a unique study identification code. Baseline demographic and clinical parameters were gathered using a systematic review of medical records and structured interviews before the procedure of coronary angiography was performed. These parameters included age, sex, and years of hypertension, status of smoking, diabetes mellitus, dyslipidemia, serum creatinine level, and previous ischemic heart disease. All data were recorded using a standardized pro forma created for this investigation. Experienced interventional cardiologists utilized either radial or femoral arteries via aseptic coronary angiography using the Philips Allura Xper FD10 angiography system (Philips Healthcare, Netherlands) with Judkins 6F/7F catheters (Cordis Corporation, USA). An iodinated contrast agent, Iopamidol 370 mg/mL (Bayer Healthcare, Germany) has been used, and a standard coronary projection has been obtained following the institutional protocol. At the same time, the renal artery delineation, where feasible, was performed using the abdominal aortography or the spillover of contrast during the angiographic run, hence removing the unnecessary exposure to contrast. The angiographic images were checked in real-time and on the digital archive. Renal artery stenosis was determined by visual estimation of luminal constrictions. Renal artery stenosis of at least 50% in either or both of the renal arteries was referred to as incidental renal artery stenosis (IRAS) [14]. Angiographic evaluation was also done by two senior cardiologists, who independently assessed it in order to reduce bias in observers, and disagreements were solved using consensus. Additional angiography factors were also recorded, such as the number of coronary artery diseases and the existence of multivessel coronary artery disease. The second investigator made sure that every form was filled out completely and consistently. Angiography logs or patient records were used to double-check any missing or ambiguous entries.

The data were entered and analyzed using the Statistical Package of Social Sciences (SPSS) software, version 25.0.

The Shapiro-Wilk test was used to assess the normality of two continuous variables: age and the length of hypertension. Regularly distributed data were shown using the mean and standard deviation (SD), while non-normally distributed variables were shown using the median and interquartile range (IQR). Frequencies and percentages were used to describe the categorical variables, including gender, diabetes mellitus, smoking status, dyslipidemia, coronary artery disease pattern, and incidental renal artery stenosis (IRAS). The prevalence of IRAS in hypertensive individuals undergoing coronary angiography served as the primary outcome measure. The percentage of study subjects with  $\geq 50\%$  luminal constriction in one or both renal arteries during angiographic evaluation was used to calculate the prevalence. The purpose of the stratified analysis was to look at the differences in IRAS between the predefined subgroups, such as age groups, sex, duration of hypertension, diabetes, smoking, and severity of coronary artery disease. To ascertain the relationship between IRAS and categorical characteristics, the chi-square test was utilized. The Independent Samples t-test for normally distributed data and the Mann-Whitney U test for non-parametric data were used to compare continuous variables between patients with and without IRAS. The factors associated with IRAS were identified by univariate analysis, and the results were presented as crude odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as a p-value of  $\leq 0.05$ .

## RESULTS

The study included 139 male and 33.8 female hypertensive patients. The prevalence of diabetes mellitus was 45.3% and, dyslipidemia was 56.8, and current smokers were 34.5%. The participants had a history of ischemic heart disease in 41.7% and a median of 8 (5–12) years of hypertension. The majority of the patients had normal renal functions, with a median serum creatinine reading of 1.0mg/dL (0.9–1.3)(Table 1).

**Table 1:** Baseline Demographic and Clinical Characteristics (n=139)

Variables	Mean $\pm$ SD / n (%)	Median (IQR)
Age in Years	58.6 $\pm$ 9.8	–
Male	92 (66.2%)	–
Female	47 (33.8%)	–
Duration of Hypertension (years)	–	8 (5–12)
Diabetes Mellitus	63 (45.3%)	–
Dyslipidemia	79 (56.8%)	–
Current Smoker	48 (34.5%)	–
Creatinine in Serum (mg/dL)	–	1.0 (0.9–1.3)
History of Ischemic Heart Disease	58 (41.7%)	–

Coronary angiography showed that 29.5% of the patients had single-vessel coronary artery disease (CAD), 33.1% had

double-vessel disease, and 37.4% had triple-vessel disease. A total of 70.5% of the cohort possessed multivessel CAD (Table 2).

**Table 2:** Coronary Angiographic Findings (n=139)

Variables	n (%)
Single-vessel CAD	41 (29.5%)
Double-vessel CAD	46 (33.1%)
Triple-vessel CAD	52 (37.4%)
Multivessel CAD ( $\geq 2$ vessels)	98 (70.5%)

Incidental renal artery stenosis (IRAS) was present in 18.0% of the patients and was unilateral in 13.7% and bilateral in 4.3% of the patients. Most of the participants (82.0%) did not show any sign of renal artery stenosis by angiography. (Table 3).

**Table 3:** Frequency and Pattern of Incidental Renal Artery Stenosis (IRAS)

Outcomes	n (%)
Incidental RAS ( $\geq 50\%$ stenosis)	25 (18.0%)
Unilateral IRAS	19 (13.7%)
Bilateral IRAS	6 (4.3%)
No renal artery stenosis	114 (82.0%)

Stratified analysis revealed that the prevalence of IRAS was higher among patients aged  $\geq 60$  years (23.4%) than in patients aged  $< 60$  years. The IRAS was more prevalent in patients with diabetes (23.8%) than in non-diabetic patients (13.2%) ( $p=0.11$ ). There were 22.9% of smokers with IRAS compared to 15.4% non-smokers ( $p=0.29$ ). IRAS was more common in patients with multivessel CAD (20.4%) than in single vessel disease (12.2%), though this was not statistically significant ( $p=0.28$ ). In the univariate analysis, the presence of IRAS was significantly correlated with a longer history of hypertension ( $\geq 10$  years) and high serum creatinine ( $\geq 1.2$ mg/dl). Participants aged  $\geq 60$  years, those with diabetes, smokers, males, and those who had multivessel CAD had greater odds of IRAS; none of the relationships were found statistically significant (Table 4).

**Table 4:** Association of Clinical and Demographic Factors with Incidental Renal Artery Stenosis (IRAS)

Variables	IRAS		OR (95% CI)	p-value
	Present, n (%)	Absent, n (%)		
<b>Age</b>				
$\geq 60$ Years	15 (23.4%)	49 (76.6%)	1.99 (0.84–4.68)	0.12
$< 60$ Years	10 (13.2%)	65 (86.8%)	Reference	
<b>Gender</b>				
Male	17 (18.5%)	75 (81.5%)	1.11 (0.44–2.80)	0.84
Female	8 (17.0%)	39 (83.0%)	Reference	
<b>Diabetes Mellitus</b>				
Present	15 (23.8%)	48 (76.2%)	2.06 (0.89–4.78)	0.09
Absent	10 (13.2%)	66 (86.8%)	Reference	

Smoking Status				
Current Smoker	11 (22.9%)	37 (77.1%)	1.64 (0.71-3.79)	0.24
Non-smoker	14 (15.4%)	77 (84.6%)	Reference	
Coronary Artery Disease				
Multivessel CAD	20 (20.4%)	78 (79.6%)	1.83 (0.73-4.55)	0.19
Single-vessel CAD	5 (12.2%)	36 (87.8%)	Reference	
Duration of Hypertension				
≥10 Years	–	–	2.57 (1.09-6.07)	0.03*
<10 Years	–	–	Reference	
Serum Creatinine				
≥1.2 mg/dL	–	–	2.71 (1.18-6.21)	0.02*
<1.2 mg/dL	–	–	Reference	

\*Statistical significance at  $p \leq 0.05$

The mean age of patients with IRAS was somewhat greater than that of patients without IRAS, although this difference was not statistically significant ( $p=0.28$ ). People with IRAS had a longer median history of hypertension than people without, which was statistically significant ( $p=0.04$ ). Similarly, the serum levels of creatinine in the IRAS and non-IRAS groups differed statistically significantly ( $p=0.02$ )(Table 5).

**Table 5:** Comparison of Continuous Variables between Patients with and without IRAS

Variables	IRAS		p-value
	Present (n=25)	Absent (n=114)	
Age (Years), Mean $\pm$ SD	60.4 $\pm$ 9.2	58.2 $\pm$ 10.0	0.28 <sup>1</sup>
Duration of Hypertension (Years), Median (IQR)	10 (6-14)	8 (5-11)	0.04 <sup>2</sup>
Serum Creatinine (mg/dL), Median (IQR)	1.2 (1.0-1.5)	1.0 (0.9-1.2)	0.02 <sup>2</sup>

<sup>1</sup>p-value calculated using the Independent Samples t-test. <sup>2</sup>p-value calculated using the Mann-Whitney U test. \*Statistical significance at  $p \leq 0.05$

## DISCUSSION

The current study found that among hypertension patients having coronary artery angiography, the incidence of accidental renal artery stenosis (IRAS) was 18.0%. This incidence is consistent with previous findings showing high levels of RAS are not a rare occurrence in high-risk cardiovascular populations. In individuals undergoing coronary angiography, a meta-analysis of 31 studies involving over 31,000 patients revealed a total RAS frequency of roughly 13.4%. The ratio of severe to bilateral disease is comparable to our result of bilateral disease with primarily unilateral involvement [7]. The current study's prevalence rate is comparable to that of a multi-center study conducted in Iraq, which found that 15% of hypertensive individuals who had elective coronary angiography had RAS. RAS is strongly associated with abnormal coronary outcomes and inadequate blood pressure control [14]. These results support the idea that systemic atherosclerosis often affects both the coronary and renal arterial beds, especially in patients who have

chronic hypertension. A recent observational study in Indian patients receiving primary percutaneous coronary intervention has also shown RAS in 16% of patients, and older age and hypertension have a significant association with the prevalence of stenosis, which is consistent with our significant associations between duration of hypertension and increased creatinine levels [11]. Although previous studies have reported lower prevalence rates, ranging between 12-15% among the coronary artery disease patients, the estimates are generally in line with ours when they look at the variation in the population risk profiles, screening methods, and threshold of significant stenosis. According to a study on the prevalence of renal artery stenosis in CAD patients, the frequency was 12.9%, and one of the prognostic factors was female gender [15]. Similar to the patterns seen in our investigation, a different worldwide cohort also found that 11.9% of hypertensive patients with CAD had substantial RAS [16]. A systematic review revealed that the prevalence rates of RAS in hypertensive patients undergoing coronary angiography in the past were within the range of about 10-30%, depending on the unique cohorts and imaging modalities [7]. Current results are well within this range, which confirms the consistency of the estimates of RAS prevalence in recent studies. Correspondingly, systematic epidemiologic reviews have indicated that the prevalence of substantial RAS among patients with atherosclerotic vascular disease, including combined hypertension and CAD, is not uniformly distributed, something that further indicates the importance of context-specific screening approaches [17]. The incidence of RAS among relevant patient categories in South Asia is not well documented locally, although this usually indicates a significant burden. In hypertensive populations, a cross-sectional study conducted in Pakistan showed a strong correlation between RAS and coronary artery disease (CAD), supporting the notion that renovascular pathology frequently leads to systemic atherosclerosis in this group. However, the investigation's main findings did not include precise prevalence data [18]. The most recent study about RAS prevalence was published in a hospital-based cohort in Visakhapatnam, India, where it is reported that 19% where unilateral involvement, was 14%, and 5% had bilateral involvement [19]. These two studies indicate that RAS is a significant comorbidity among patients with hypertensive CAD in South Asia. These results are similar to those reported internationally, including a cohort study using multi-centers across South Asia in which extensive RAS prevalence near 24% was highly related to age, disease duration, and burden of comorbidity, confirming that metabolic and vascular risk factors increase the predisposition of developing renovascular affection [20].

There are various limitations to this research. First, because it is a cross-sectional, single-center study, the findings

cannot be extrapolated to other regions or the whole population of hypertension patients. Second, the sample size, though sufficient to estimate prevalence, might not have been powerful to determine statistically significant relationships with some risk factors, such as diabetes, smoking, and multivessel coronary artery disease. Third, analysis of the renal artery was conducted incidentally with coronary angiography and not with specific renal imaging, which might not have well reflected the actual prevalence of stenosis. Lastly, univariate analysis was applied only, and there was no control of potential confounding factors; therefore, one should interpret the observed associations with caution.

## CONCLUSIONS

Incidental renal artery stenosis was found in almost a quarter of hypertensive patients undergoing coronary angiography, and it was predominantly unilateral. Hypertension and serum creatinine were important predictors, with a longer period of hypertension and high levels of serum creatinine. These results underline the need to observe IRAS among high-risk hypertensive patients since early identification can be used to shape specific management plans and avoid the development of renal and cardiovascular issues. Routine monitoring of the renal arteries during coronary angiography may thus present a viable opportunity for early diagnosis and thorough risk classification, which falls between cardiac and renal care.

## Authors' Contribution

Conceptualization: ZUD

Methodology: ZUD, SI, JI, SDK

Formal analysis: ZUD, SN

Writing and Drafting: ZUD, SI, JI, SDK, HG

Review and Editing: ZUD, SI, JI, SDK, HG, SN, WHK

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



## Comparison of Post-Operative Port Site Pain after Gall Bladder Retrieval through Umbilical versus Epigastric Port in Patients Undergoing Laparoscopic Cholecystectomy

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## ABSTRACT

Port-site pain is a typical issue that occurs after laparoscopic cholecystectomy. When the gall bladder is to be retrieved, the site used could be umbilical or epigastric and could have an effect on the extent of pain, which would impact patient comfort and recovery. **Objectives:** To determine the difference in post-operative port-site pain between umbilical and epigastric ports during laparoscopic cholecystectomy in patients. **Methods:** It was a descriptive study done for six months at Khyber Teaching Hospital. Non-probability consecutive sampling was used to enroll 36 patients undergoing elective laparoscopic cholecystectomy and randomized them into umbilical and epigastric port groups. The Visual Analogue Scale (VAS) was used to measure post-operative pain at 6, 12, and 24 hours. The analyzed data were processed in SPSS v. 25. The chi-square test, independent samples t-tests, and multivariate linear regression were employed to measure the predictors of pain. The  $p$ -values  $\leq 0.050$  was considered significant. **Results:** The umbilical port also recorded lower VAS scores at each time point ( $p \leq 0.050$ ). Multivariable regression established port site as the significant predictor of pain with the only significant adjusted variable ( $p = 0.003$ ). **Conclusions:** The recovery of the gall bladder through the umbilical port would lead to much lower early post-surgery pain than through the epigastric port, regardless of patient demographics or comorbidities, and is an argument in favor of the umbilical port as the site of extraction.

## INTRODUCTION

Laparoscopic cholecystectomy has become the gold standard in the treatment of symptomatic cholelithiasis because, compared to open surgery, it offers the benefits of smaller incisions, shorter hospital stays, faster recovery, and less postoperative morbidity [1, 2]. The procedure is usually characterized by the removal of the gall bladder using one of the operating ports, most usually either the umbilical or the epigastric port [3]. Despite laparoscopic

surgery being viewed as a low-risk surgery, post-operative port site pain is one of the most common patient complaints, and it can affect early discharge, prescription of analgesics, length of stay, and overall patient satisfaction [4]. Thus, measures to reduce port site pain are of significant interest in enhancing post-operative results. Gallstone disease is one of the most prevalent gastrointestinal diseases in the world, with the number of

cholecystectomies in millions per year [5]. Cholelithiasis is most common in women, and it is more common as age, obesity, and metabolic disorders progress [6]. Laparoscopic cholecystectomy is widely utilized in developing countries, such as Pakistan, both in the public and private sectors, due to its favorable safety profile and good results [7]. The umbilical and epigastric ports were different in anatomical structure, size of incision, fascial manipulation, and manipulation of tissue, which can affect the intensity of pain after surgery [8]. Laparoscopic cholecystectomy causes port site pain that is multifactorial; this occurs due to fascial stretching, muscle fiber disruption, and traction during the retrieval of the laparoscopic specimen [9]. The epigastric port lies in a relatively less compliant region with denser musculofascial tissue compared to the umbilical port, which lies in a naturally weak scar region with little mass [10]. There are surgeons who like to use the epigastric port to retrieve specimens to minimize the risk of umbilical wound complications, and surgeons who like to use the umbilical route because of cosmetic advantages and complaints of less pain [11]. Despite the common practice of laparoscopic cholecystectomy, there remains no explicit agreement as to which of the umbilical or epigastric ports is the most suitable site for retrieving the gall bladder in relation to the post-operative pain. Anatomical differences between the two ports, which include more fascial and muscle manipulation at the epigastric location compared to the naturally less strong umbilical location, could lead to a clinically significant difference in pain magnitudes. In the resource-limited and high-volume surgical environment, determining which port is less painful will aid in maximizing recovery, decreasing the burden of the postoperative phase, and enhancing the quality of care. Thus, the study is necessary to have objective comparative evidence on post-operative port site pain between umbilical and epigastric retrieval ports.

Although there is increasing evidence on the effects of vitamin D on alopecia areata, there are still some significant gaps. There are no large, multicentric, randomized, controlled studies that assessed the efficacy of microneedling-assisted delivery of topical vitamin D3 in localized alopecia areata, and most of the studies had small sample sizes with limited follow-up periods. The best suitability of vitamin D3 level, the vehicle formulation, the dosing schedule, and the required number of microneedling sessions to achieve the highest therapeutic effect have not been determined. This study aims to compare post-operative port site pain after gall bladder retrieval through the umbilical port versus the epigastric port in patients undergoing laparoscopic cholecystectomy.

## METHODS

This was a descriptive study done in the Department of Surgery, Khyber Teaching Hospital, Peshawar, for six months from 1st October, 2024 to 31st March, 2025. Research and Ethical Review Board (IREB) of Khyber Medical College (KMC) approved the study with the following approval number: 617/DME/KMC. The sample size was estimated with the help of Open Epi software, and it was calculated on the basis of the reported mean post-operative pain scores. The mean score of pain associated with the retrieval of the gall bladder using an umbilical port was approximated to be  $4.00 \pm 1.537$ , and the mean score of pain with the retrieval using an epigastric port was approximated to be  $5.27 \pm 1.167$  [12]. The calculated minimum sample size was 36 patients, with a power of 80% and a confidence level of 95%, with 18 patients in each group. In the calculation, Open Epi assumes that the variances between the groups are equal, and the homogeneity of variance was later established by analysis with the Levene test prior to proceeding with the application of the parametric tests. A non-probability consecutive sampling method was used. The study included patients aged 18 to 60 years who underwent laparoscopic cholecystectomy according to the operation definitions of either gender. Patients were not included when they reported having acute cholecystitis, evidenced by a positive Murphy sign, elevated white blood cell count, pericholecystic edema, or the presence of raised gall bladder wall thickness on ultrasound. Patients who had cholangitis (fever, jaundice, and hypochondria to the right), had common bile duct stones on ultrasonography, or had had gallstone pancreatitis with elevated serum amylase levels were also excluded. Moreover, patients whose BMI exceeded 30 kg/m<sup>2</sup> and those who had undergone laparotomy in the past were excluded. Following the approval, data were gathered among patients hospitalized in the indoor Department of Surgery and who met the selection criteria. Eligible patients were approached and informed that written consent was acquired after being made aware of the purpose of the study, the potential risks, and the benefits that would be expected. The proforma included baseline demographic and clinical variables, such as age (years), gender, BMI (weight in kg/height in m<sup>2</sup>), place of residence (rural/urban), level of education, occupation, and socioeconomic status. Such clinical features as surgery indications and comorbidity were also recorded. The presence of diabetes mellitus was registered as detected when the level of fasting blood sugar was greater than 130 mg/dl, and hypertension when the blood pressure was more than 140/90 mmHg. Patients who had a laparoscopic cholecystectomy with the gall bladder removed via the umbilical port or the epigastric port were recruited into the study groups. All the

procedures were done under general anesthesia. The same surgical team performed the surgeries under the guidance of a seasoned consultant laparoscopic surgeon, and the principal researcher was involved in every surgery to maintain uniformity of the procedures and to reduce variability brought about by the operator. All patients were followed by standard procedures. The standardization of post-operative care was based on the departmental guidelines, such as the use of antibiotic prophylaxis, fluid replacement, and adequate analgesia. The assessment of pain was conducted on a post-operative basis with the help of the Visual Analogue Scale (VAS)[13]. The level of pain was measured with the help of the Visual Analogue Scale (VAS) after the operation. Pain measurements were done at port-sites 6 hours, 12 hours, and 24 hours post-operative, and the respective VAS scores of individual patients were documented. To guarantee the reliability of responses, the patients were educated on the interpretation of the VAS before the operation. Any post-operative complications that occurred immediately were also recorded where necessary.

Statistical Package of Social Sciences version 25 was used to enter and analyze all the collected data. Analysis of data was done after confirmation of its completeness and accuracy. Mean, median, and standard deviation were used to present quantitative variables like age, BMI, postoperative VAS pain scores at 6, 12, and 24 hours, and frequencies and percentages were used to present qualitative variables such as gender, residence, occupation, socioeconomic status, comorbidities, and indication of surgery. The Shapiro-Wilk test was used to determine the normality of quantitative data before inferential analysis, and homoscedasticity (equal variance of residuals) was evaluated based on the residual versus fitted value curves. The Levene test was used to determine the homogeneity of variances between the two groups. The Independent Samples t-test was used to compare the mean VAS pain scores between the umbilical port and epigastric port groups, when the variables followed a normal distribution. The Mann-Whitney U test was used as a non-parametric alternative to test variables that did not meet the assumptions of normality. A statistically significant  $p$ -value  $\leq 0.050$  was taken as significant. A multivariate linear regression model was developed with VAS pain score as the dependent variable and baseline factors, including age, BMI, gender, residence, diabetes mellitus, and hypertension as independent variables, to examine the possible confounding variables. Before the multivariable linear regression was conducted, some important assumptions were evaluated to guarantee that the model was valid. Scatterplots and residual plots verified that the dependent variable (12-hour VAS score) and the continuous predictors are linear. The dependent

variable used in the multivariate linear regression model was the 12-hour post-operative VAS pain score since pain is most intense during this period in the post-surgical stage of laparoscopic cholecystectomy, when anesthesia has been successfully finished and before the occurrence of any significant analgesic tapering. This is an early post-operation discomfort measurement that is also reliable and can be used to meaningfully compare the umbilical and epigastric port groups without much variation influenced by immediate post-anesthesia effects or slow recovery. The Multicollinearity between predictor variables was evaluated by using the Variance Inflation Factor (VIF), and variables with  $VIF > 10$  were deemed to be significant and thus excluded from the final model. The assumptions were all met satisfactorily, which justifies the suitability of the regression analysis. Adjusted mean differences, regression coefficients, and 95% confidence intervals were reported.

## RESULTS

The demographic and clinical characteristics of the patients in the umbilical and epigastric port groups were similar at baseline. There was no significant difference in mean age and BMI between the two groups and no significant difference in the gender distribution, with evenly represented males and females (Table 1).

**Table 1:** Baseline Demographic and Clinical Characteristics

Variables	Umbilical (n=18)	Epigastric (n=18)	p-value
<b>Age</b>			
(Years), Mean $\pm$ SD	42.1 $\pm$ 10.5	44.3 $\pm$ 9.8	0.520
<b>Gender</b>			
Male	10 (56%)	9 (50%)	0.680
Female	8 (44%)	9 (50%)	
<b>Residence, n (%)</b>			
Urban	11 (61%)	12 (67%)	0.720
Rural	7 (39%)	6 (33%)	
<b>Others, n (%)</b>			
BMI (kg/m <sup>2</sup> ), Mean $\pm$ SD	25.8 $\pm$ 2.9	26.4 $\pm$ 3.1	0.480
Diabetes Mellitus	3 (17%)	4 (22%)	0.670
Hypertension	5 (28%)	6 (33%)	0.710

The use of the Visual Analogue Scale (VAS) to measure post-operative pain revealed that the umbilical port group experienced a reduced level of pain compared to the epigastric port group at all the measured time points. The umbilical group complained of less pain at 6 hours after surgery, and this difference was still significant at 12 and 24 hours (Table 2).

**Table 2:** Post-operative VAS Pain Scores

Time Post-Surgery	Umbilical (Mean ± SD)	Epigastric (Mean ± SD)	Mean Difference (Umbilical - Epigastric)	95% CI	p-value
6 Hours	3.2 ± 1.1	4.5 ± 1.3	-1.3	-2.0 to -0.6	0.002
12 Hours	2.5 ± 1.0	3.7 ± 1.2	-1.2	-1.8 to -0.6	0.001
24 Hours	1.8 ± 0.8	2.4 ± 0.9	-0.6	-1.2 to -0.01	0.048

Note: Negative values indicate lower pain in the umbilical port group

All variables were port site, age, BMI, gender, residence, diabetes mellitus, and hypertension, the port site being the only variable that significantly predicted. During retrieval of the gall bladder using the umbilical port was linked to a reduction in 12-hour pain scores as opposed to the epigastric port (p=0.003)(Table 3).

**Table 4:** Stratified Analysis of Post-Operative VAS Pain(12h)

Variables	Subgroup	Umbilical (Mean ± SD)	Epigastric (Mean ± SD)	Mean Difference (Umbilical - Epigastric)	95% CI	p-value
Age (years)	≤40	2.5 ± 0.9	3.6 ± 1.0	-1.1	-1.8 to -0.4	0.003*
	>40	2.6 ± 1.0	3.7 ± 1.1	-1.1	-1.9 to -0.3	0.004*
Gender	Male	2.5 ± 0.9	3.6 ± 1.0	-1.1	-1.8 to -0.4	0.002*
	Female	2.6 ± 0.9	3.7 ± 1.0	-1.1	-1.9 to -0.3	0.003*
BMI (kg/m <sup>2</sup> )	<25	2.4 ± 0.8	3.5 ± 1.0	-1.1	-1.8 to -0.4	0.002*
	≥25	2.6 ± 0.9	3.7 ± 1.0	-1.1	-1.8 to -0.4	0.003*
Surgery Indication	Symptomatic Cholelithiasis	2.5 ± 0.9	3.7 ± 1.0	-1.2	-1.8 to -0.6	0.001*
Comorbidities	DM	2.5 ± 0.9	3.6 ± 1.0	-1.1	-1.9 to -0.3	0.004*
	HTN	2.6 ± 0.9	3.7 ± 1.0	-1.1	-1.9 to -0.3	0.003*
	None	2.5 ± 0.9	3.6 ± 1.0	-1.1	-1.8 to -0.4	0.002*

## DISCUSSION

In the present research, patients who experienced the retrieval of a gallbladder by the umbilical port had considerably reduced postoperative port site pain at various periods of time as opposed to patients who had their gallbladder retrieved by the epigastric port. This result is consistent with an accumulating literature of modern studies that indicates that umbilical port can be connected with less post-surgical pain. Other recent investigations have also noted a reduced VAS score of pain with umbilical port removal. The study led by a randomized controlled trial in 2025 indicated that patients who received umbilical port treatment had a reduced VAS score at different postoperative periods, and the preliminary data showed a lower level of pain in the umbilical port group than in the epigastric port group and no significant difference in port site complications between the two conditions [8]. Respectively, the comparative study released in 2024 has shown that umbilical retrieval was linked with much lower pain levels at 24 hours and reduced time of retrieval time, which proves the superiority of the umbilical method in terms of comfort and recovery [14]. In line with these, a study reported that umbilical port retrieval led to much lower VAS pain scores on the 1st and 2nd postoperative days

**Table 3:** Multivariable Regression Analysis for 12h VAS Pain

Predictors	Adjusted B	95% CI	p-value
Port Site (Umbilical vs Epigastric)	-1.1	-1.8, -0.4	0.003
Age (Years)	0.01	-0.05, 0.07	0.710
BMI (kg/m <sup>2</sup> )	0.03	-0.11, 0.17	0.650
Gender (Male vs Female)	-0.1	-0.6, 0.4	0.750
Residence (Urban vs Rural)	0.2	-0.3, 0.7	0.440
Diabetes Mellitus (Yes vs No)	0.3	-0.6, 1.2	0.490
Hypertension (Yes vs No)	0.2	-0.5, 0.9	0.590

In all subgroups, patients who used the umbilical port had significantly lower pain scores than those who used the epigastric port. The statistical significance of these differences was found to be significant across each of the subgroups studied (Table 4).

than when epigastric retrieval was used [15]. The distinction in pain was also filled by improved cosmetic satisfaction and reduced port site infections in the umbilical group, but operative times were similar [16]. On the contrary, there is some recent observational data to indicate that epigastric port extraction, in certain settings, can be linked to reduced immediate postoperative pain. The intervention study showed that the patients retrieved by the epigastric port experienced less pain at 6 hours after the surgery and showed tendencies to have lower overall pain scores and fewer port site complications, such as herniation and infection [17]. A systematic evaluation of randomized trials showed no significant difference in postoperative pain at 24 hours between umbilical and epigastric extraction, but there was an increase in the risk of port site hernia and a slight increase in the length of time spent in the operating theater [18]. The present study also finds that our findings are largely consistent with the literature. A 2022 study found that there was a significant reduction in immediate postoperative pain in the umbilical group at 24 and 48 hours, but the differences were reduced by one week. Previous RCT data also reported less umbilical port retrieval at various postoperative periods [12]. Nevertheless, not all

evidence can be aptly characterized as biased towards a particular port: there are reports of no significant differences in pain or other outcomes between groups in some comparative studies carried out in similar settings, though most of these usually lack enough power to identify subtle differences [19]. Other than pain alone, complication trends in the recent literature resonate with the need to have balanced decision-making: the 2025 trial did not establish any significant difference in port site complications between groups, and other studies demonstrate higher infection or herniation rates with an alternative port choice. These findings underscore the fact that pain is not the only aspect of the postoperative recovery [20].

There are a number of limitations to this study. To begin with, the sample size was comparatively small, and it might restrict the possibility of applying the results to a more general population. Second, the study was performed in one tertiary care center, and thus, differences in surgical or post-operative care in other jurisdictions could affect the study. Third, post-operative pain was assessed objectively with the help of VAS, which is a patient-reported outcome that could be affected by pain threshold or psychological issues. Fourth, the reduction of follow-up was to 24 hours after the pain assessment; no follow-up results on port-site complications, herniation, or persistent pain were conducted. Fifth, the researchers used non-randomized assignment to umbilical and epigastric port groups, which can result in the introduction of allocation bias in spite of characteristic similarity at the baseline and the correction of confounding factors. Randomized research should be conducted in the future to validate these results. Lastly, even with multivariate regression and stratified analyses to remove confounding, it is not possible to rule out residual confounding by unmeasured variables.

## CONCLUSIONS

Laparoscopic cholecystectomy is associated with a clear reduction in the occurrence of early post-operative port-site pain when the gall bladder is retrieved via the umbilical port than when it is retrieved via the epigastric port, regardless of patient age, sex, BMI, surgical indication, and comorbidities. Umbilical approach may thus be a better method to provide better patient comfort during the immediate post-operative period without risking complications. These results justify the consideration of the umbilical port as the most optimal location of gall bladder extraction, and the considerable importance of conducting larger multicenter studies to confirm and expand these findings.

## Authors' Contribution

Conceptualization: KN

Methodology: KN, MMI, AYK, MUK, MS

Formal analysis: KN, MMK, MUK, MS

Writing and Drafting: MMI, MMK, AYK, MUK

Review and Editing: KN, MMI, MMK, AYK, MUK, MS, HAK

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



## Comparison of Ultrasound-Guided Ilioinguinal and Iliohypogastric Nerve Block with and without Tramadol for Postoperative Pain in Patients Undergoing Caesarean Delivery

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## ABSTRACT

Maternal relief, early mobilization, and breastfeeding are dependent on the effective postoperative pain management following caesarean section. **Objectives:** To compare the analgesic effect of ultrasound-guided ilioinguinal-iliohypogastric nerve block with ropivacaine only versus ropivacaine with tramadol in patients who underwent elective cesarean delivery. **Methods:** A retrospective study was performed on a sample of 100 individuals, and the study was performed in two groups. Group A was given ropivacaine, and Group B was given ropivacaine and tramadol to relieve postoperative pain. Median [IQR] and mean  $\pm$  SD were estimated, and comparisons between them were done by Fisher's Exact test, Mann-Whitney U-test, and independent t-test, with  $p \leq 0.050$  taken as significant. **Results:** The combination of Ropivacaine and Tramadol gave better analgesia in patients who had a caesarean than when Ropivacaine was used. The combination group had a much longer pain-free period (20 vs. 14 hours,  $p=0.002$ ), and the overall pain scores were lower ( $1.0 \pm 0.7$  vs.  $1.8 \pm 1.0$ ,  $p=0.001$ ). The patients needed fewer rescue analgesics, and there was no difference in opioid side effects. **Conclusions:** The combination of Tramadol and Ropivacaine has a significant positive effect on postoperative analgesia in patients undergoing a caesarean section, extending pain-free periods and decreasing the intensity of pain, with minimal adverse effects, which makes it an effective and safe approach to enhancing patient comfort and satisfaction.

## INTRODUCTION

Cesarean section (CS) is one of the most prevalent surgical procedures globally, the rate of which has grown significantly over the past 30 years, rising from about 7% in 1990 to about 21% in 2021, with regional disparities still existing and some areas still increasing in use [1]. The global estimates are showing a rise in the rate of CS at the population level, with rates rising to 7% in 1990 to about 21% by 2021, and with more regional differences and increasing trends in most regions. The increased number of CS surgeries worldwide means that even minor changes in

perioperative pain management may lead to significant population-level benefits in maternal recovery, breastfeeding, mobility, and opioid exposure [2]. Despite the advances in obstetric anesthesia methods, clinically significant acute postoperative pain in a considerable percentage of women who have undergone CS has remained [3]. The first 24 hours following a CS have been associated with moderate to severe pain, with reported rates ranging from roughly 50% to even higher, depending on circumstances and analgesic treatments, according to



several research studies and systematic reviews [4, 5]. Improper nursing, delayed mobilization, disturbed mother-infant attachment, increased opiate intake, and a high risk of developing chronic pain all coexist with the phenomenon of uncontrollable acute postoperative pain following cesarean surgery [6]. As a result, these results bring forward the pressing need to implement effective, opioid-sparing analgesic measures implementable in the everyday obstetric environment [7]. Pfannenstiel incision-directed peripheral nerve blocks have been identified as useful adjuncts in multimodal analgesics after CS [5]. A bilateral ilioinguinal-iliohypogastric nerve block not only provides localized analgesia to the lower abdominal wall but also has been shown to reduce early postoperative pain scores and opioid consumption following lower abdominal surgeries, which include CS and gynecologic surgeries when performed under ultrasound guidance [8]. Ultrasound guidance increases block accuracy, reduces local anesthetic volume, and lowers complication rates compared with landmark-based methods, making these blocks attractive for routine practice in obstetric anesthesia. Observational trials and randomized controlled studies in the 2020s reported good analgesic and safety effects of ultrasound-guided ilioinguinal/iliohypogastric blocks [9]. Integration of adjuvants into local anesthetics (PA) used to block peripheral nerves has been widely studied to increase peripheral nerve block duration and decrease dependence on systemic opioids. Tramadol is a weak  $\mu$  opioid receptor agonist that also has monoaminergic effects and thus has been investigated as a co-administration agent with local anesthetics with a range of peripheral and truncal blockade methods [10]. A study reported that tramadol extends the duration of sensory blockade and reduces postoperative analgesic consumption of some types of blocks, although the effect size and the adverse-effect profile are dependent on dose and route of administration, and the type of surgery [11]. Modern studies also compare tramadol and other adjuvants in the form of dexamethasone and note that tramadol is effective in many of these environments; other adjuvants may have an extended action or a different side-effect profile. Since the use of opioid-sparing methodologies and tramadol has remained of intense interest, and due to the pharmacologic properties of tramadol, its use as an adjunct to truncal blocks during a caesarean section is a phenomenon that warrants specific study [12, 13]. The addition of a pharmacologic adjuvant such as tramadol with a highly selective, ultrasound-guided ilioinguinal and iliohypogastric nerve block can cause a clinically significant improvement in postoperative analgesia, a decrease in the requirement for opioid rescue, and a quicker recovery in mothers after CS [14].

However, the evidence that is specifically on caesarean patients on the comparative effectiveness of bilateral ultrasound-guided ilioinguinal/iliohypogastric blocks with and without tramadol is very limited and very variable. A well-planned comparative study will determine whether the addition of tramadol to the block will result in greater analgesic effect, stronger opioid-sparing effect, and a fair side-effect profile in mothers, and consequently, it will present an actionable solution immediately to improve post-caesarean outcome in accordance with the global targets to reduce the exposure of opioids in postpartum. This study aimed to compare ultrasound-guided ilioinguinal nerve block, iliohypogastric nerve block with and without tramadol in managing postoperative pain in individuals who undergo a CS.

## METHODS

The study was a retrospective observational study that was carried out in the Department of Anesthesiology, Rehman Medical Institute (RMI), Peshawar, Pakistan, for six months from 1st August 2025 to 1st January 2026. The approval was obtained from the Institutional Review Board and Ethical Committee (IRB-ERC) of RMI (Approval No: RMI/IRB-EC/Approval/264). Data were collected from July 2024 to July 2025. Since this was a retrospective observational study, the sample used was decided by the number of patients who fit the inclusion criteria based on the available records. Among 417 cesarean sections done in the study period, 100 patients who satisfied the eligibility criteria were incorporated in the analysis. A post-hoc power analysis was carried out based on the difference between the 12-hour difference in pain score between groups observed in order to ensure the adequacy to detect a difference in the postoperative pain. Written informed consent was taken. The study used 50 patients per group, an effect size of 0.6, and an alpha of 0.05, yielding a power of 85%, which shows that the sample size was adequate to reveal clinically significant differences in the pain outcomes. According to the 12-hour postoperative pain scores, the mean NRS of the ropivacaine-only group was  $3.0 \pm 1.2$ , and of the ropivacaine-tramadol group was  $1.8 \pm 1.0$ . The pooled standard deviation was calculated and is equal to 1.105, which becomes a large effect size (Cohen,  $d = 1.086$ ). The study had a power of more than 99 using an alpha of 0.05, and this indicates that the sample size was adequate to identify clinically significant differences in postoperative pain. All eligible patient records were screened using consecutive sampling. Additional data collected included a review of operative records and anesthesia charts available via the electronic medical record system of the hospital. Demographic variables (such as weight (kg), age (years), 'American Society of Anesthesiologists (ASA) status', gravida, and parity) were

noted in relation to each patient. Moreover, the history of previous surgeries and post-operative pain in previous surgeries was also inquired. The nerve block data included the, the local anaesthetic used (ropivacaine 0.375%), the volume (20mL each side), and the use or non-use of tramadol(1mg/kg per each side)as needed. For all the nerve blocks, a 21G 80mm short beveled blunt tip needle (Stimuplex® Ultra 360® Needle) was used. These parameters were carefully recorded on a Performa. After data collection, patients were categorized into two groups based on the nerve block they had received during routine care. Group A consisted of patients who received a ropivacaine block, whereas Group B consisted of patients who received ropivacaine and tramadol in the nerve block. All the patients received IV paracetamol 1gm TID and IV ketorolac 30mg TID as part of multimodal analgesia. Patients were discharged from the hospital after the 2nd postoperative day. The post-operative pain data were collected in accordance with the unit's established guidelines, then entered into a structured data extraction sheet that was then imported into SPSS. The Numeric Rating Scale (NRS 0-10) was used to measure pain at the following time points: 0, 4, 8, 12, 16, 24, 30, 36, 42, and 48 hours [15]. The onset time of pain after the block, the use of rescue analgesia, the total amount of opioids consumed over 48 hours, and any adverse events related to opioids and local anesthesia were also recorded. Finally, patients' overall experience of pain relief and satisfaction was also extracted from the feedback forms. The level of patient satisfaction with pain control measurement was performed by utilizing a 5-point Likert scale, with 1 = very dissatisfied and 5 = very satisfied. SPSS (version 26.0) was used to conduct statistical tests. Initially, descriptive statistics were acquired. When continuous variables had normal distributions, they were reported as mean and standard deviation; when they did not, they were described as median with inter-quartile range; and when they were categorical, they were described as frequencies and percentages. The Shapiro-Wilk test was used to determine whether continuous variables were normal. Independent-samples t-tests were used for between-group comparisons of regularly distributed continuous data, whereas Mann-Whitney U tests were used for non-normally distributed data. Categorical variables, such as frequency and percentage of postoperative pain scores at various follow-up hours, were presented in terms of frequency and percentage. The pain scores were classified into No Pain (0), Mild Pain (1-3), Moderate Pain (4-6), and Severe Pain (7-10) to make them easy to interpret and compare. Since the Likert scale is ordinal in nature and the distribution of the responses in both groups is approximated to be normally distributed, mean + SD was deemed suitable to compare the responses using an independent t-test. The Fisher's

exact test was used to compare the two groups of patients (Ropivacaine only vs. Ropivacaine + Tramadol) at each following time points. The statistically significant p-value  $\leq 0.05$ .

## RESULTS

The average age of the participants was  $29.27 \pm 5.7$  years, and the average body weight was  $72.9 \pm 9.9$  kg. Most parturient (98%) were classified as ASA class 2. The median gravidity was 2 (IQR: 1-4), and the median parity was 1 (IQR: 1-3). The most common type of surgery was Caesarean section (42%), followed by repair of a 3rd-degree perineal tear (3%), anterior vaginal repair (1%), dilation and curettage (2%), and laparoscopic cholecystectomy (1%), with 51% having no prior surgery. The average time interval between the last surgeries was  $1.75 \pm 0.35$  years. On the issue of pain during prior surgeries, 3% had mild pain, 22% had moderate pain, 22% severe pain, and 3% had none; 50% of the respondents had no previous surgical procedures (Table 1).

**Table 1:** Baseline Characteristics of the Study Population (n=100)

Variables	Mean $\pm$ SD / n (%)
<b>Age</b>	
Years	29.27 $\pm$ 5.7
<b>Weight</b>	
kg	72.9 $\pm$ 9.9
<b>ASA Status</b>	
ASA II	98 (98%)
ASA III	2 (2%)
<b>Median (IQR)</b>	
Gravida	2 (1-4)
Parity	1 (1-3)
<b>Name of Previous Surgery</b>	
C-Section	42 (42%)
3rd-Degree Perineal Tear	3 (3%)
Anterior Vaginal Repair	1 (1%)
D&C	2 (2%)
Laparoscopic cholecystectomy	1 (1%)
None	51 (51%)
History of previous surgery	50 (50%)
<b>Time Since Last Surgery</b>	
Years	1.75 $\pm$ 0.35
<b>Pain in Previous Surgery</b>	
Mild	3 (3%)
Moderate	22 (22%)
Severe	22 (22%)
No Pain	3 (3%)
No Previous Surgery	50 (50%)

Baseline variables (demographic and clinical) were compared between Group A (ropivacaine) and Group B (ropivacaine + tramadol). There were no notable differences between the samples, which validated that the

two cohorts were similar before the analysis of the outcomes (Table 2).

**Table 2:** Baseline Characteristics of Study Groups (n=100)

Variables	Group A (Ropivacaine, n=50)	Group B (Ropivacaine + Tramadol, n=50)	p-value
Age (Years), Mean ± SD	29.4 ± 5.6	29.1 ± 5.8	0.780
Weight (kg), Mean ± SD	73.2 ± 10.0	72.6 ± 9.8	0.720
ASA II, n (%)	49 (98%)	49 (98%)	1.000
ASA III, n (%)	1 (2%)	1 (2%)	1.000
Gravida, Median (IQR)	2 (1-4)	2 (1-4)	0.850
Parity, Median (IQR)	1 (1-3)	1 (1-3)	0.920
History of Previous Surgery, n (%)	25 (50%)	25 (50%)	1.000

**Table 3:** Distribution of Static Pain Scores at Different Follow-up Hours in Patients Receiving Ropivacaine Alone in Block or Ropivacaine plus Tramadol in Block

Follow-up Hours	Patient Group	No Pain (0), n (%)	Mild Pain (1-3), n (%)	Moderate Pain (4-6), n (%)	Severe Pain (7-10), n (%)	p-value
0	Ropivacaine Only	50 (100%)	0 (0%)	0 (0%)	0 (0%)	-
	Ropivacaine + Tramadol	50 (100%)	0 (0%)	0 (0%)	0 (0%)	
4	Ropivacaine Only	47 (94%)	3 (6%)	0 (0%)	0 (0%)	0.360
	Ropivacaine + Tramadol	49 (98%)	1 (2%)	0 (0%)	0 (0%)	
8	Ropivacaine Only	43 (86%)	7 (14%)	0 (0%)	0 (0%)	0.373
	Ropivacaine + Tramadol	41 (82%)	9 (18%)	0 (0%)	0 (0%)	
12	Ropivacaine Only	19 (38%)	31 (62%)	0 (0%)	0 (0%)	0.008*
	Ropivacaine + Tramadol	33 (66%)	15 (30%)	2 (4%)	0 (0%)	
16	Ropivacaine Only	16 (32%)	34 (68%)	0 (0%)	0 (0%)	0.056
	Ropivacaine + Tramadol	22 (44%)	23 (46%)	5 (10%)	0 (0%)	
24	Ropivacaine Only	4 (8%)	46 (92%)	0 (0%)	0 (0%)	0.210
	Ropivacaine + Tramadol	1 (2%)	43 (86%)	6 (12%)	0 (0%)	
30	Ropivacaine Only	13 (26%)	37 (74%)	0 (0%)	0 (0%)	0.181
	Ropivacaine + Tramadol	7 (14%)	39 (78%)	2 (4%)	2 (4%)	
36	Ropivacaine Only	6 (12%)	44 (88%)	0 (0%)	0 (0%)	0.438
	Ropivacaine + Tramadol	5 (10%)	40 (80%)	3 (6%)	2 (4%)	
42	Ropivacaine Only	16 (32%)	34 (68%)	0 (0%)	0 (0%)	0.018*
	Ropivacaine + Tramadol	13 (26%)	33 (66%)	4 (8%)	0 (0%)	
48	Ropivacaine Only	27 (54%)	23 (46%)	0 (0%)	0 (0%)	0.079
	Ropivacaine + Tramadol	14 (28%)	34 (68%)	2 (4%)	0 (0%)	

Fisher's Exact Test to take out p-value, and \*p ≤ 0.05 is considered significant

The analgesic need and pain relief results revealed that the Ropivacaine + Tramadol group delayed the onset of pain significantly more than the Ropivacaine-only group (p=0.004). Though more patients in the combination group needed rescue analgesia, the difference was not significant (p=0.100). The Ropivacaine + Tramadol group performed significantly better than the Ropivacaine-only group (p=0.004). Also, the incidence of opioid related side effects was higher in the combination group (14%) compared with the Ropivacaine-only group (p=0.005). The two groups did not differ in patient satisfaction scores of pain control (p=0.351) (Table 4).

Independent t-test for continuous variables, Mann-Whitney U test for medians, Fisher's exact test for categorical variables. p ≤ 0.05 is considered significant

At baseline (0 hours), all patients in both groups reported no pain. At 4 and 8 hours, most patients experienced no or mild pain, with no significant differences between groups (p=0.360 and 0.373, respectively). At 12 hours, the combination group (Ropivacaine + Tramadol) showed a significantly higher proportion of no pain (p=0.008). At 16 hours, mild pain predominated in both groups (p=0.056). Later follow-ups (24-48 hours) showed mostly mild pain, with occasional moderate pain, and differences were not statistically significant except at 42 hours (p=0.018), favoring the combination group (Table 3).

**Table 4:** Analgesic Requirements and Pain Relief Outcomes (n=100)

Outcome Variables	Group A Mean ± SD/ n (%)	Group B Mean ± SD/ n (%)	p-value
The Onset of pain	14.0 ± 2.9	16.1 ± 4.0	0.004*
Rescue analgesic required, n (%)	3 (6.0%)	8 (16.0%)	0.100+
Timings of Rescue Analgesia Administration	19.6 ± 7.6	15.5 ± 6.2	0.004*
Opioid-Related Side Effects, n (%)	4 (8%)	7 (14%)	0.005+
Patient Satisfaction Score with Pain, Mean ± SD	4.8 ± 0.4	4.7 ± 0.5	0.351*

\*Independent t-test applied, and +Fisher Exact Test to take out p-value, and p ≤ 0.05 is considered significant

**Table 5:** Comparative Analysis of Postoperative Pain Relief between Ropivacaine Alone and Ropivacaine with Tramadol in Patients Undergoing Caesarean Delivery (n=100)

Primary Outcome	Group A (Ropivacaine)	Group B (Ropivacaine + Tramadol)	P-value
Duration of Pain Relief (Hours)	14 [12–16]	20 [18–24]	0.002*
Degree of Pain Relief (Overall MeanNRS)	1.8 ± 1.0	1.0 ± 0.7	0.001+

\*Man, Whitney U test, and Independent +-t-test applied to take out p-value, and  $p \leq 0.05$  is considered significant

## DISCUSSION

In this retrospective observational trial involving postsurgical analgesia with Ropivacaine and Tramadol versus Ropivacaine alone in patients undergoing elective caesarean surgery, we noted superior pain control, postoperative pain onset, and slight analgesia extension with Tramadol supplement. In particular, the combination group scored lower on the measure of static pain at several postoperative time-points, took a longer period to first request analgesics, and had a better profile of analgesics. Our results are consistent with the outcomes of a recent randomized controlled trial where II-IH block was found to be an effective postoperative analgesic in caesarean patients, leading to a significant decrease in pain scores and time to first rescue analgesic, compared to controls [16]. Similarly, a prospective RCT from a low-resource setting demonstrated II-IH block as a practical and efficacious method for post-CS analgesia, reducing both pain intensity and opioid consumption [17]. In addition, more comprehensive studies on the peripheral nerve blocks used in caesarean delivery (e.g., fascial plane, nerve blocks) indicate that blocks, either singly or in combination with neuraxial analgesia, are effective in reducing early postoperative rest pain and opioid needs [18]. Tramadol combined with Ropivacaine probably augmented the analgesic duration and quality of the block in our study. This is consistent with results obtained with upper-extremity surgical procedures that indicate that, when administered as an adjuvant to local anesthetics, Tramadol extends sensory blockage and general analgesia without augmenting events of adverse effects [13]. The reduced total pain scores and the delayed requirement of rescue analgesia in our combination group support the hypothesis that Tramadol is a useful adjuvant to local anesthetics in regional blocks of abdominal surgery. Although most prior studies use other adjuvants (e.g., dexmedetomidine, dexamethasone) to extend block duration, our findings with Tramadol are positive, indicating the potential of an opioid-sparing option of relevant clinical value, namely, Tramadol [19, 20]. Nonetheless, some studies also, to some extent, disagree with our results. As an example, meta-analyses comparing transversus abdominis plane (TAP) block with II IH block in the management of post-caesarean analgesia

show no significant difference in 24-hour opioid consumption or rest pain scores between the two techniques, whereas the use of an adjuvant such as Tramadol is important to improve outcomes [21, 22]. Variations in the local anesthetic concentration, volume, timing, block method (nerve block vs fascial plane), and adjunct choice are probably the reasons for differences in studies.

There are some limitations in this study. First, it was a single-centered study with a relatively small sample size that could limit the extrapolation of the findings. Second, the follow-up was limited to 48 hours, and pain outcomes in the long term were not measured. Third, personal pain tolerance and perception might affect subjective pain with the help of the numerical rating scale. Moreover, we have focused on tramadol as an adjuvant but have not compared other adjuvants. A multicenter prospective randomized controlled trial could address the limitations.

## CONCLUSIONS

Combining Tramadol with Ropivacaine in the use of postoperative nerve blocks in caesarean surgery is much more effective in reducing pain, extending analgesia, and decreasing the use of rescue analgesics without altering opioid-related adverse events. Such a combination is an easy, secure, and effective approach to patient comfort during the immediate postoperative period. The results indicate the use of Tramadol as an adjuvant in the regional anesthesia practice to ensure the best management of postoperative pain and patient satisfaction.

## Authors' Contribution

Conceptualization: SSS

Methodology: MYBK, AA

Formal analysis: MS

Writing and Drafting: SSS, FK

Review and Editing: SSS, MYBK, AA, MS, FK

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



## Frequency of Antenatal Depression in Obstetric Patients Attending Antenatal Clinic

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## ABSTRACT

Antenatal depression is a prevalent but poorly understood mental health disorder with adverse maternal and fetal outcomes. It is common in different populations, with its risk factors being different, especially among the low- and mid-income countries. Timely intervention requires early diagnosis. **Objectives:** To identify the prevalence of antenatal depression and the related sociodemographic and obstetric variables in women visiting the antenatal clinic. **Methods:** The study was cross-sectional and conducted between January 1, 2025, and July 30, 2025, among 278 pregnant women through consecutive sampling. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure antenatal depression, and a cutoff score of  $\geq 13$  was considered to be depressed. The analysis was performed with SPSS version 25.0, and descriptive statistics, a bivariate analysis, and binary logistic regression were applied to determine independent predictors ( $p \leq 0.05$  was taken to be significant). **Results:** Antenatal depression was found to be prevalent (27.3, 95% CI: 21.9–32.7%). Major independent predictors were low socioeconomic status (AOR = 2.41;  $p=0.002$ ), unplanned pregnancy (AOR = 1.94;  $p = 0.023$ ) and past adverse obstetric outcomes (AOR=1.72;  $p=0.048$ ). **Conclusions:** Depression occurred in more than a quarter of antenatal women in this tertiary care facility. The key risk factors are socioeconomic disadvantage, unintended pregnancy, and poor obstetric history. It is advised to conduct regular mental health screening and targeted interventions throughout the antenatal care to enhance maternal and fetal outcomes.

## INTRODUCTION

Pregnancy is conventionally seen as a time of happiness and emotional satisfaction, but in a significant number of women, it is filled with significant psychological distress [1]. Depressive symptoms arising in the course of pregnancy, which are now known as antenatal depression, have become a significant public health issue with significant effects on both maternal and fetal well-being [2]. It is marked by chronic depression, loss of interest, tiredness, sleep problems, anxiety, poor functioning, and lack of coping with life responsibilities [3]. Antenatal depression is not given due clinical attention compared to postpartum depression and is often under-identified and

undertreated despite comparable or even higher levels in a range of populations [4]. Antenatal depression is a global problem that has unequal distribution among regions and socioeconomic backgrounds [5]. It is reported that studies in high-income countries have a prevalence of 7%-15%, but much higher prevalence rates between 19-25% have been recorded in low- and middle-income countries [6]. Poverty, unintended pregnancy, lack of social support, partner abuse, stressful life events, and preexisting mental health conditions are some of the factors that contribute to these variations [7]. It is said that the incidence is very high, especially in the setting of South Asia, which is dominated



by cultural pressures, gender-based inequalities, financial strain, and inadequate access to mental health services [6]. Antenatal depression is closely linked with poor obstetric and neonatal outcomes such as preterm birth, low birth weight, intrauterine growth retardation, maternal poor nutrition, poor bonding, and risk of postpartum depression [8,9].

The increasing awareness that enhancing maternal mental health is essential towards the realization of optimal pregnancy outcomes is being supported, but limited evidence exists to date on the impact of antenatal depression on our local obstetric population. It will help to establish the level of the issue at this setting and demonstrate the necessity of routine psychological screening in addition to traditional obstetric evaluation. The research is thus carried out to produce context-specific indications that can guide clinicians, policymakers, and program planners towards mental health assessment inclusion in the antenatal care pathways. This study aimed to establish the prevalence of antenatal depression among obstetric patients visiting the antenatal clinic.

## METHODS

This cross-sectional study was conducted at the Antenatal Clinic of Hayatabad Medical Complex (HMC), Medical Teaching Institution (MTI), Peshawar, over six months from January 1, 2025, to July 30, 2025. Data collection commenced following approval from the Institutional Review and Ethics Board (IREB) of HMC-MTI (Approval No. 826/HEC/B&PSC/2022). The sample size required was computed using the OpenEpi (version 3.01) program, with expected prevalence (P) of antenatal depression taken as 20.7% based on the pooled prevalence estimates from systematic reviews of the global prevalence of antenatal depression (20.7%; 95% CI 19.4–21.9%) from various studies across the globe [10]. Using the formula for minimum sample size estimation for a given confidence level and margin of error:  $n = [Z^2 \times P \times (1 - P)] / d^2$  where d is the margin of error, Z is the confidence level, and P is the target proportion, the sample size at 95% confidence level (Z=1.96) and a margin of error (d) of 5% was calculated and obtained a minimum sample size of 253 participants. For response and item non-response, a 10% adjustment was made, bringing the final sample size to 278 participants. Non-probability consecutive sampling was used to recruit the participants. Women were included in the study if they were mentally alert and able to comprehend the information about the study, and if they agreed to participate voluntarily and signed the informed consent. Eligible participants included both primigravida and multigravida women across all the different socioeconomic strata and educational levels. Women were

excluded if they had a prior psychiatric diagnosis of any form of major depression, bipolar disorder, psychosis, or anxiety disorder, or if they were on any form of treatment, like antidepressants or any other psychotropic medication. Also excluded from the study were women who had severe obstetric or medical problems that would need them to be provided emergency services (like antepartum hemorrhage, pre-eclampsia/eclampsia or preterm labor), women who had chronic systemic conditions that would affect their mood or psychological status, women who had cognitive or language barriers that would limit them from understanding the questionnaire, women who opted out of the study, and women who withdrew their consent. To avoid duplicate enrollment, each eligible participant was included only once, and repeat clinic visits by the same individual were excluded through verification of clinic records. The data was collected by trained female assistants who were briefed about the research objectives, the administration of the questionnaires, and participant confidentiality. All antenatal patients visiting the clinic were screened for eligibility, and those meeting the criteria were spoken to courteously. The researchers provided the participants with the study's objectives in basic terms and assured them that their answers would be kept confidential and would not impact their medical treatment. Before participants were enrolled, they provided their written informed consent. In order to provide privacy, comfort, and the freedom to express themselves, interviews were held in one of the quiet and private counseling rooms in the antenatal clinic. Information regarding sociodemographic and obstetric factors was collected using a pre-designed structured proforma capturing the individual's age, level of education, job/status, marital status, socioeconomic status, adequate parity and gravidity, gestational age, prior pregnancy experiences, and any obstetric complications. Following the collection of baseline data, the level of antenatal depression was determined by the Edinburgh Postnatal Depression Scale (EPDS) [11]. The EPDS is composed of 10 questions, and the participants were instructed to reply based on their emotions during the past week. The scores on the EPDS were measured on a Likert scale (4 points) (0-3), and the overall score was 0-30 [12]. The scoring and review of the responses took place right after completing the questionnaire. Like in the published literature and validation studies of antenatal populations, a cutoff score of  $\geq 13$  was regarded as a positive screening in women, and a cutoff score of less than  $< 13$  was regarded as a negative screening. The data collected were checked for completeness and accuracy, and were entered, and the data were analyzed using the Statistical Package of the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA). The data was manually input into the software, and cross-checking of transcription was done twice to reduce

transcription errors. Normality of continuous variables like age and gestational age was evaluated through the visual examination of histograms and the Shapiro-Wilk test. These variables were summarized with mean  $\pm$  standard deviation (SD) when the data are normally distributed and median (interquartile range) when the data are skewed. Frequencies and percentages were used to present categorical variables. The main outcome variable was the antenatal depression, which was defined as a dichotomous variable according to the EPDS cutoff score ( $\geq 13$ =depressed,  $<13$ =not depressed). The antenatal depression prevalence (prevalence) was computed as the percentage of women who screened positive out of the total sample size of the study and reported with a 95% confidence interval(CI).

A bivariate analysis was conducted to evaluate the relationship between the independent variables and antenatal depression. Chi-square test was used in the case of categorical variables. The p-value  $\leq 0.05$  was taken to be significant. To do the exploratory analysis, the variables whose significance was identified at  $p < 0.20$  during the bivariate test were included in a binary logistic regression model to examine independent significant variables of antenatal depression, controlling for the possible confounding variables. Adjusted odds ratios (AOR) with 95% confidence intervals were provided. The Hosmer-Lemeshow goodness-of-fit test was used to test model fitness. The maternal age was analyzed both as a continuous variable and a categorical variable ( $\leq 25$  vs  $>25$  years) so as to be clinically interpretable and comparable to earlier regional research where similar age cutoffs are used.

## RESULTS

The average age of the participants was  $27.9 \pm 5.4$  years, with the median gestational age of 26 weeks (IQR: 20-32 weeks). The majority of the women were multigravida (58.6%), 41.4% primigravida. Almost 45.7% of the respondents had a low socioeconomic status, and 32.4% and 21.9% had middle and high socioeconomic status, respectively. Regarding education, 39.2% were not educated, 34.5% had secondary education, and 26.3% had college or greater education (Table 1).

**Table 1:** Sociodemographic and Obstetric Characteristics of Participants (n=278)

Variables	Mean $\pm$ SD / n (%)
Age (Years), Mean $\pm$ SD	27.9 $\pm$ 5.4
Gestational Age (Weeks), Median (IQR)	26 (20-32)
<b>Gravidity</b>	
Primigravida	115 (41.4%)
Multigravida	163 (58.6%)

<b>Parity</b>	
Nulliparous	102 (36.7%)
Multiparous	176 (63.3%)
<b>Socioeconomic status</b>	
Low	127 (45.7%)
Middle	90 (32.4%)
High	61 (21.9%)
<b>Education status</b>	
No Formal Education	109 (39.2%)
Secondary	96 (34.5%)
College or Higher	73 (26.3%)
<b>Pregnancy Status</b>	
Planned	181 (65.1%)
Unplanned	97 (34.9%)
<b>History of Adverse Obstetric Outcome</b>	
Yes	82 (29.5%)
No	196 (70.5%)

The average EPDS score of the study population was  $9.8 \pm 4.7$ . Based on the predefined cutoff score of  $\geq 13$ , 27.3% of women were found to be positive in the screening of antenatal depression. The means of the EPDS of women who screened positive ( $16.4 \pm 2.1$ ) were greater than those of women who screened negative ( $7.1 \pm 3.2$ ) (Table 2).

**Table 2:** EPDS Scores and Frequency of Antenatal Depression

Variables	Mean $\pm$ SD / n (%)
Mean EPDS Score	9.8 $\pm$ 4.7
Women Screening Positive for Depression (EPDS $\geq 13$ )	76 (27.3%)
Prevalence of Antenatal Depression (95% CI)	27.3% (21.9-32.7)
<b>Mean EPDS score</b>	
Depressed	16.4 $\pm$ 2.1
Non-depressed	7.1 $\pm$ 3.2

Antenatal depression was significantly linked on bivariate analysis to maternal age at conception (younger age of maternal age:  $p=0.032$ ), socioeconomic status (lower socioeconomic status:  $p=0.004$ ), unplanned pregnancy ( $p=0.008$ ), and previous adverse obstetric outcome ( $p=0.014$ ). It was noted that there was no statistically significant correlation between depression and parity ( $p=0.218$ ), the category of gestational age ( $p=0.147$ ), and the employment-no category ( $p=0.276$ ). Depressed women also had much lower mean age than non-depressed women ( $p=0.031$ ). The median EPDS-adjusted emotional distress score of women with antenatal depression was slightly higher than that of non-depressed women ( $p=0.015$ ) (Table 3).

**Table 3:** Bivariate Association between Maternal Factors and Antenatal Depression (n=278)

Variables	Depressed, n (%)	Not Depressed, n (%)	p-value
<b>Age group</b>			
≤ 25 years	34 (36.2%)	60 (22.8%)	0.032*
> 25 years	42 (63.8%)	142 (77.2%)	
<b>Socioeconomic status</b>			
Low	43 (56.6%)	84 (31.4%)	0.004*
Middle/High	33 (43.4%)	118 (68.6%)	
<b>Education status</b>			
No formal education	35 (46.1%)	74 (27.7%)	0.091
Secondary or higher	41 (53.9%)	128 (72.3%)	
<b>Pregnancy status</b>			
Unplanned	36 (47.4%)	61 (23.2%)	0.008*
Planned	40 (52.6%)	141 (76.8%)	
<b>Previous adverse obstetric outcome</b>			
Yes	28 (36.8%)	54 (20.8%)	0.014*
No	48 (63.2%)	148 (79.2%)	
<b>Parity</b>			
Nulliparous	25 (32.9%)	77 (30.4%)	0.218
Multiparous	51 (67.1%)	125 (69.6%)	

\*Statistically significant at  $p \leq 0.05$

Lower socioeconomic status was a significant independent predictor of antenatal depression after adjustment of confounders ( $p=0.002$ ). Women who gave birth to unplanned pregnancies had nearly twice the odds of screening positive ( $p=0.023$ ), and women with a history of adverse obstetric outcome also had much higher chances of experiencing depression ( $p=0.048$ ). The maternal age and level of education were not statistically significant in the final model. The logistic regression model showed satisfactory goodness of fit, based on the Hosmer-Lemeshow test ( $p=0.389$ ), which shows that the model was sufficient to explain the observed data (Table 4).

**Table 4:** Multivariable Logistic Regression for Predictors of Antenatal Depression

Predictor Variables	Adjusted OR (AOR)	95% CI	P-value
Low Socioeconomic Status	2.41	1.36-4.28	0.002*
Unplanned Pregnancy	1.94	1.09-3.46	0.023*
Previous Adverse Obstetric Outcome	1.72	1.01-2.95	0.048*
Younger Maternal Age (≤ 25 Years)	1.29	0.77-2.17	0.241
Lower Education	1.21	0.68-2.14	0.314

Model Fit: Hosmer-Lemeshow  $\chi^2 = 7.42$ ,  $p=0.389$  \*Statistically significant at  $p \leq 0.05$

## DISCUSSION

The incidence of antenatal depression in this cross-sectional study of 278 antenatal women was 27.3%, but it was determined using the Edinburgh Postnatal Depression Scale with a cutoff point of  $\geq 13$ . The estimate is in line with the past evidence that antenatal depression is a serious mental health issue in low and middle-income

environments. A detailed meta-analysis published a combined prevalence of perinatal depression of about 24.7%, with a greater prevalence in the lower middle-income nations, specifically in South Asia (27.6%), and such regional settings as our study area [13]. Our prevalence estimate compares with some of the more recent studies. Indicatively, a community-based survey carried out in rural Bangladesh indicated prevalences of antenatal depression between 18%-33% and, in certain situations, even 56%, which indicated high rates of intimate partner violence and gender inequalities [14]. Another more recent study in rural Bangladesh reported a prevalence of 39% and found the same predictors of unintended pregnancy and social stressors [15]. Conversely, a Malaysian-based, hospital-based study has noted lower prevalence rates of antenatal depression at 8.4%, with possible variations in the cultural attitude to mental health and methods of measurement, such as differences in cutoff scores on EPDS [16]. Some other research done in other international settings has also indicated a differing rate; a cross-sectional survey of China indicated that around 25.2% of women had antenatal depressive symptoms in the post-COVID-19 period, very similar to the present study [17]. In our research, the independent variables (low socioeconomic status, unplanned pregnancy, and history of adverse obstetric outcomes) were connected with increased odds of antenatal depression. These findings coincide with observations in Bangladesh, whereby psychosocial factors like intimate partner violence and perceived gender preference had a significant effect on increasing depressive symptoms [14]. Likewise, a study by Chala *et al.* has attributed increased antenatal depressive symptoms to unplanned pregnancy and socioeconomic stressors [18]. In contrast, a study by Kasujja *et al.* established that psychosocial adversity and instability were important factors in contributing to high antenatal depression rates, highlighting a cross-contextual trend [19]. An overview of Pakistani perinatal literature gave a high prevalence of prepartum depression (37%) under strong associations with low levels of income, marital tension, and inadequate social support [20]. A recent survey of adolescent women in Ghana indicated a rate of antenatal depression of more than 38%, with low education and social stress having a significant relationship with symptoms of depression [21]. Although the study is rigorous, it has several limitations. First, the cross-sectional design limited causal inference, as associations were established, but no temporal relationships between risk factors and antenatal depression were identified. Second, the study was conducted at a single tertiary care hospital, which may not be representative of rural or community-based populations, thereby limiting generalizability. Third, the use of self-reported scales, including the EPDS, could have resulted in social desirability bias, as some women may have underreported depressive symptoms due to cultural stigma or fear of judgment. Additionally, certain

psychosocial variables, such as family support, intimate partner violence, and a history of mental illness in first-degree relatives, were not fully represented, which may have under-addressed the role played by these factors. Lastly, although the EPDS is a validated screening instrument, it does not substitute for a formal psychiatric diagnosis, and cases of mild depression or subthreshold symptoms may have been misclassified. Although a formally revalidated local-language version of the EPDS was not used, the scale was administered in a language familiar to participants, and prior studies from Pakistan and South Asia support its reliability and validity.

## CONCLUSIONS

This research has shown that depression is present in more than one out of four antenatal women in a tertiary care clinic, which highlights the importance and lack of acknowledgment of antenatal depression as a social health issue. The prediction of maternal mental health as per the complex interaction of social, economic, and obstetric determinants was shown to be practical with the introduction of socioeconomic disadvantage, unplanned pregnancy, and the production of adverse obstetric outcomes. These results highlight the necessity to incorporate regular mental health assessment and counseling into antenatal care, especially among the high-risk groups.

## Authors' Contribution

Conceptualization: AS

Methodology: AS, KN, LB

Formal analysis: AS, KB, SS

Writing and Drafting: KN, LB

Review and Editing: AS, KN, LB, KB, SS, SA

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



## Frequency of Factors Leading to Elective Surgery Cases Postponement at Tertiary Care Hospital, Karachi

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## ABSTRACT

Delay of elective surgery is one of the ongoing issues in hospital systems that disrupts the operating room schedule, creates extra healthcare expenses, patient dissatisfaction, and wasteful use of resources. It is necessary to understand the root causes of these delays to make perioperative planning more effective, multidisciplinary coordination more robust, and patient safety more efficient. **Objective:** To identify the number of factors that cause the delay of the elective cases of surgeries in a Tertiary Care Hospital in Karachi. **Methods:** The study was a cross-sectional study carried out in Jinnah Postgraduate Medical Centre, Karachi. The data were gathered in the form of a structured proforma, which included demographic data that was divided into patient-related, surgeon-related, and anesthesia-related. Sampling involved consecutive sampling. Data analysis was done by use of SPSS version 20. Categorical variables were calculated by frequencies and percentages. The Fisher's exact test was used to determine relationships between postponement factors and demographic factors, where  $p \leq 0.05$  was regarded as significant. **Results:** The postponement of elective surgery occurred in 12.1% of patients, and patient-related issues (medication unavailability, refusal, not fasting) were the most common reasons. The causes associated with surgery and anesthesia were less prevalent. The delay was not significantly related to the age, sex, home, or ASA status. **Conclusions:** Patient-related factors were more effective in influencing elective surgery delays than surgeon or anesthesia-related issues. It can be strengthened by having preoperative assessment, enhancing scheduling coordination, and increasing communication within surgical teams to reduce the rate of postponement.

## INTRODUCTION

Elective surgeries form a significant part of surgical activities among hospitals in all parts of the world and play a significant role in enhancing the quality of life, decreasing disability, and preventing prolonged complications in patients [1]. Nevertheless, the delay of elective surgical operations has been a chronic problem both in developed and developing nations [2]. Elective surgery postponement is the delay of an operation that was planned to be carried out because of patient-related, administrative, anesthesia, or surgical reasons [3]. These delays not only hamper patient care but also cause emotional distress, augmented morbidity, extended stay in the hospital, and substantial economic drainage of both patients and the healthcare system [4]. The rates of

elective surgery delays have been reported globally to vary between 10% and 40%, according to the institute's efficiency, resources, and processes [5, 6]. In developed nations, the frequent causes are a shortage of operating room (OR) time, insufficient preoperative preparation, and staff or equipment shortage [7]. In low and middle-income countries (LMIC), including South Asian countries, the workload is even greater with such high postponement rates of up to 30% to 60% being reported [3]. Among the contributing factors in LMIC settings can be the overbooking of theatre lists, poor interdepartmental communication, unavailability of needed supplies, comorbidities of patients not optimized preoperatively, and infrastructural limitations. The issue is particularly



acute in Pakistan because of the large number of patients, the limited resources, and the lack of consistency in the hospital management systems. Elective surgery cancellation rates of 22% to 50% have been found in studies across different parts of Pakistan and represent a significant healthcare system problem that impacts governmental and privatized tertiary-care hospitals [8-10]. Karachi is a large metropolitan city hosting high surgical caseloads, which present a significant challenge in scheduling surgeries [11]. Delays not only decrease surgical productivity but also lead to psychological stress in patients and families, bed occupancy, and an increase in hospital costs.

Although the scale of the issue is large, up-to-date region-specific data on Karachi, particularly on the precise distribution of the factors that contribute to the delay in elective surgery, is limited. It is essential to comprehend these determinants in a tertiary-care environment to enhance the use of operating rooms, preoperative check-up, communication channels, and hospital regulations. The research fills a considerable gap by offering local evidence that can be used to inform administrative changes and address avoidable delays to eventually enhance patient satisfaction and surgical outcomes. The purpose of the current research was to establish the frequency and distribution of factors contributing to the delay of elective surgical cases in a tertiary-care hospital in Karachi.

## METHODS

The study was a cross-sectional research study conducted in the Department of Anesthesia, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The study was conducted from 1st April, 2025, up to 30th September, 2025, after the study synopsis was approved. The Institutional Review Board of JPMC approved the research under the approval number NO.F.2-81/2025-GENL/256/JPMC. The WHO sample size calculator was used to calculate the sample size. Taking a prevalence of surgeon unavailability as a cause of elective surgery postponement of 10.3%, a margin of error of 6%, and a confidence level of 95%, the sample size required was calculated to be 99 patients [12]. Surgeon unavailability was chosen as a parameter of reference since it is a clearly defined and objectively identifiable cause of postponement and offers a conservative estimation when it comes to calculating the sample size. The non-probability consecutive sampling method was used on all the eligible patients who fell within the scope of the study considered in the period of data collection, until the required sample size was reached. The participants were chosen according to preset inclusion and exclusion criteria. Eligible participants consisted of 20-80 years old patients who had elective surgery scheduled, also had at least 24 hours of preoperative planning time, and were

categorized as ASA physical status I or II [13]. Patients were excluded if they were having emergency operations or they had severe comorbidities (including connective tissue disorders, hemoglobinopathies, bleeding disorders, renal insufficiency or failure, coronary heart disease, congestive heart failure, acute coronary syndrome, chronic renal failure, or chronic liver disease). The study excluded patients who did not satisfy these requirements because it would introduce confounding variables that may contribute to surgical delays independently. All participants gave informed consent, in writing, before they were included in the study after being told about the purpose of the research, procedures, risks, and benefits. Participation was voluntary, and the study abided by the confidentiality of patient information. The structured proforma employed in data collection was specifically designed to carry out the study. The proforma was developed using a standardized checklist and guidelines provided by the World Health Organization (WHO) and tested by using highly qualified personnel with expertise to ensure content validity. The demographic data of each patient, surgical details, and postponement factors of elective surgery were documented. Data on administrative reasons, patient-related reasons, surgical or anaesthetic reasons, and resource constraints were gathered in an organized manner. Patient interviews, pre-operative evaluation, surgical scheduling records, and consultation with the anesthesia and surgical team were used to get data. Trained data collectors collected all the information to guarantee standardization and reduce bias of the interviewer.

SPSS 25 was used to analyze the data. Quantitative variables like age were analyzed using mean and standard deviation. The Shapiro-Wilk test was performed to determine the normality of the quantitative data, and the mean  $\pm$  SD was provided as the metric of central tendency in normally distributed variables, the median and the interquartile range (IQR) in quantitative variables that were not normally distributed. The quantitative variables of gender, residence status, ASA status, and the things that contributed to the postponement of elective surgery cases (yes/no) were computed in terms of frequencies and percentages. Stratification was done to control effect modifiers like age, gender, residence status, and ASA classification in order to assess their influence on the outcome variables. After stratification, Fisher's Exact test was used, and  $p \leq 0.05$  was regarded as statistically significant.

## RESULTS

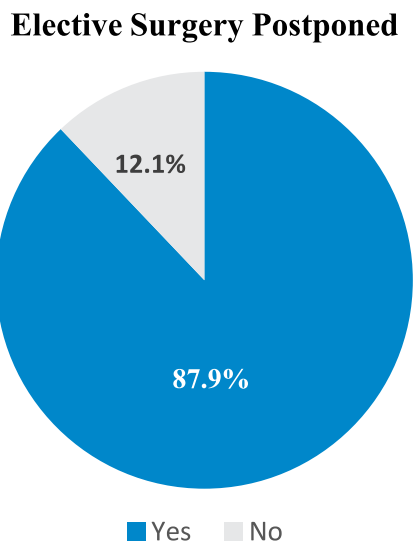
A total of 99 patients were included in the study. The participants were characterized by an average age of  $46.8 \pm 13.2$  years. The study population was split into 58.6% and

41.4% men and women, respectively. Most of them (82.9%) were residing in the rural setting, whereas the rest (17.1%) were in an urban setting. On clinical status, 52.5% of the patients were ASA I and 47.5% were ASA II (Table 1).

**Table 1:** Baseline Characteristics of Patients (n=99)

Variables	Category	n (%) / Mean ± SD
Age	Years	46.8 ± 13.2
Gender	Male	58 (58.6%)
	Female	41 (41.4%)
Residence Status	Urban	17 (17.1%)
	Rural	82 (82.9%)
ASA Status	ASA I	52 (52.5%)
	ASA II	47 (47.5%)

On the whole, 12.1% of elective surgeries were postponed (95% CI: 6.4% - 20.2%), and 87.9% of scheduled procedures were conducted smoothly (Figure 1).



**Figure 1:** A Pie Chart Showing the Frequency of Overall Postponement

The most common were patient-related factors among the 12 patients whose elective surgery was postponed. In particular, the reason why 41.7% of postponements were carried out was because of refusal to undergo surgery, 50.0% by unavailability of required medications, and 33.3% patients were not properly fasting. Factors relating to the surgeons were less prevalent, with surgeon unavailability leading to 25.0% of the postponements, change in diagnosis 8.3%, extra surgical workup 16.7%, and emergency scheduling 16.7%. The least common causes were associated with anesthesia, including the patient being unfit for anesthesia, abnormal laboratory results, anticipated difficult intubation, and equipment unavailability, all contributing 8.3% of the postponements (Table 2).

**Table 2:** Frequency of Factors Leading to Postponement of Elective Surgeries (n=12)

Variables	Factor	n (%)
Patient-Related Factors	Refusal to Surgery	5 (41.7%)
	Patient Medication Unavailable	6 (50.0%)
	Patient Not Fasting	4 (33.3%)
Surgeon-Related Factors	Surgeon Unavailability	3 (25.0%)
	Change in Diagnosis	1 (8.3%)
	Additional Surgical Workup Required	2 (16.7%)
	Emergency Scheduling	2 (16.7%)
Anesthesia-Related Factors	Patient Unfit for Anesthesia	1 (8.3%)
	Abnormal Lab Results	1 (8.3%)
	Anticipated Difficult Intubation	1 (8.3%)
	Equipment Unavailable	1 (8.3%)

The proportion of the total postponed cases is determined as percentages (n=12). There can be more than one cause related to the case; therefore, the percentages can be more than 100%

The stratification analysis was done to analyze the relationship between elective surgery postponement and demographic and clinical variables. The small number of postponed cases has led to using Fisher's exact test. The postponement and age group, gender, status of residence, and the ASA classification did not have statistically significant associations ( $p > 0.05$  at all comparisons), meaning that in the present study, elective surgery postponements were independent of these two patient characteristics (Table 3).

**Table 3:** Stratification of Elective Surgery Postponement by Demographic and Clinical Variables (n=99)

Variables	Category	Postponed, n (%)	Not Postponed, n (%)	p-value
Age Group	<40 years (n=32)	4 (12.5%)	28 (87.5%)	1.00
	≥40 years (n=67)	8 (11.9%)	59 (88.1%)	
Gender	Male (n = 58)	7 (12.1%)	51 (87.9%)	1.00
	Female (n = 41)	5 (12.2%)	36 (87.8%)	
Residence Status	Urban (n = 17)	1 (5.9%)	16 (94.1%)	0.69
	Rural (n = 82)	11 (13.4%)	71 (86.6%)	
ASA Status	ASA I (n = 52)	6 (11.5%)	46 (88.5%)	1.00
	ASA II (n = 47)	6 (12.8%)	41 (87.2%)	

The Fisher's Exact test was applied, and  $p \leq 0.05$  was considered statistically significant

## DISCUSSION

Postponement of elective surgery was experienced among 12.1% of the patients in the present study. This is higher than certain international reporting, though within the wide range as seen around the world and resource-constrained environments. Patient-related factors in the delayed cases were noted more than the surgeon or anesthesia-related factors. Nonetheless, the total amount of delayed cases was not high (n=12), and hence the proportionality of the distribution of individual causes is to be taken into consideration with care. These results

represent tendencies and not the strict predominance of certain postponement variables. Indicatively, a multicenter audit study conducted by Sarang et al. in India gave a cancellation rate of 9.7% on the day of elective surgery in a research consortium 'IndSurg' led by the 'World Health Organization Collaboration Centre' (WHOCC) for Research in Surgical Care Delivery in LMICs [5]. Similarly, a cross-sectional study conducted by Ozcan et al. in a higher academic institution in Turkey registered a very minimal cancellation rate of 0.9% in operated patients [14]. Conversely, a study conducted by Sukwana et al. in Nelson Mandela Academic Hospital (NMAH), a government-funded public hospital situated in Mthatha, Eastern Cape Province, South Africa, noted a 14.4% rate of cancellation (or postponement) [15]. Therefore, the present study's postponement rate is not as low as in certain high-efficiency centers but is similar to those in which resource limitations and socioeconomic considerations influence surgical scheduling. In terms of causes of delay, our results with patient-related causes (medication unavailability, refusal, and not fasting) are in the lead and replicate those of other similar studies. A study conducted by Feleke et al. in Ethiopia at Wolaita Sodo University Comprehensive Specialized Hospital found that patient-related factors were the most common contributors to elective surgery cancellations (31.3%), followed by administrative or facility-related factors; anesthesia-related factors were the least common contributors to cancellations [16]. Correspondingly, Sarang et al. in India found that a significant proportion (28%) were cancelled due to patient refusal or no show, and that a significant proportion of cancellations were avoidable preceding [5]. These similarities indicate that patient-level barriers continue to be a significant obstacle in most low- and middle-income countries (LMIC) environments. Conversely, a study conducted by Naderi et al. showed a cancellation rate of 6.3% in a large retrospective cohort of almost 30,000 elective cases at Namazi Teaching Hospital, a major referral center in southern Iran [17]. The most common cause was the patient being unfit to be operated on (37%), then patient non-compliance (10%), lack of time (10.5%), and equipment or supply (10%), representing a different ratio with clinical (fitness) and resource factors being more dominant in that study. Their reduced overall delay but higher proportion of anesthesia or facility-based causes could be due to superior preoperative assessment regimens or more rigid scheduling systems as compared to the present study. A study conducted by Spazzapan et al. in Princess Royal University Hospital, London, UK showed a quality improvement initiative in a hospital that was introduced in 2021 as a nurse-led preoperative assessment clinic. They showed that the cancellation rates decreased by 23.9% to 4.3% after structured preoperative evaluation [18]. That significant increase in performance highlights

the relevance of effective preoperative optimization and planning, which is justified in light of the large percentage of delays caused by patient-level causes, a significant number of which may be prevented. The present study's postponement rate is slightly higher in comparison to most national hospital-based data. Indicatively, a previous study conducted by Bashir et al. at the Department of Pediatric Surgery, King Edward Medical University / Mayo Hospital, Lahore, Pakistan, reported that the number of cancellations on the day of surgery was 4% [19]. Another study conducted by Zafar et al. in Ayub Teaching Hospital involved delay rates of between 5-6% [20]. Our relatively high delay might be caused by the differences in the population of the patients, rurality, lack of resources, or institutional scheduling policies. Another study conducted by Zaeem et al. at District Headquarters Hospital, Faisalabad, Punjab, reported that 6.1% cases were postponed from elective surgery [9]. The stratification analysis showed no important relationships between postponement and age, gender, residence, or ASA status. Conversely, the tertiary center prospective study (0.9% cancellation) revealed that older age and higher ASA class had a significant correlation with cancellations [14]. This difference could be explained by the fact that in our cohort, the number of postponed cases (n=12) is comparatively small, which limits the statistical power, or it might indicate that in the present study, case logistic and patient-related factors surpass clinical risk factors as the determinants of postponement. To conclude, the present study lies halfway between national and international statistics, not as efficient as high-resource optimized settings, but still better than in some rural or resource-limited settings. A majority of patient-related causes of delay are seen in most other similar studies in LMICs, suggesting an important point of improvement. This is contrary to the situation in studies where anesthesia or facility considerations were the main causes, and indicates that reinforcement of preoperative assessment and patient preparation can be the most beneficial in curbing the postponement. The analysis reveals that the most common reasons leading to the postponement of the elective surgery, despite the relatively low percentage of 12.1%, are patient factors, which include the unavailability of medication, refusal, and not fasting. The findings stress the need to conduct preoperative evaluation carefully, educate and counsel patients to be ready. Better coordination of scheduling and proper communication between surgical, anesthesia, and administrative teams can also help minimize delays, maximize operating room efficiency, reduce the anxiety of patients, and improve overall care quality. Hospitals can implement standardized preoperative practices and reminder systems to deal with preventable delays, especially within rural and resource-restricted groups. This research was conducted in a single tertiary care

hospital, and this factor may limit the generalizability of the results to other settings. The cross-sectional design can be used to determine associations but not causality. The information was based on hospital data and interviews with patients and may be subject to reporting bias or incomplete records. Also, the relatively low number of delayed cases (n=12) means that the statistical power to identify significant relationships between demographic variables or clinical variables is limited. These limitations notwithstanding, the study offers useful information about the determinants of elective surgery postponement and the room to enhance them. The unequal distribution of the rural participants could have affected stratified analyses and led to the lack of statistical power to determine the impact of residence status on elective surgery postponement.

## CONCLUSIONS

Elective surgery postponement was low but significant, with patient-related factors being the most prevalent cause. Problems of the surgeon and anesthesia were less common. Preoperative assessment, patient preparation, coordination of schedules, and effective communication with surgical teams can be used to significantly reduce the postponement rates. These interventions will enhance patient satisfaction, resource allocation, and the timely delivery of surgical care, making surgical care more efficient and improving the quality of hospital services.

## Authors' Contribution

Conceptualization: S

Methodology: S

Formal analysis: S

Writing and Drafting: S, SM

Review and Editing: SM

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



# Hypokalemia and Hyponatremia in Hepatic Encephalopathy and Its Distribution Across Age, Gender, and Grade of Hepatic Encephalopathy

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## ABSTRACT

Hepatic encephalopathy is a complication of cirrhotic liver disease precipitated by a variety of factors. One such factor is disturbance in the levels of sodium and potassium. **Objectives:** To determine the prevalence of hypokalemia and hyponatremia in patients of hepatic encephalopathy at a secondary care setting and its distribution in different age groups, gender, and grades of hepatic encephalopathy. **Methods:** This cross-sectional descriptive study with stratified analysis was held at the Department of Medicine, Tehsil Headquarter Hospital, Sarai Alamgir, Pakistan, from January 2024 to February 2025. In this study, a total of 127 patients who presented with hepatic encephalopathy were included. All these patients were assessed for the presence of hypokalemia and hyponatremia. **Results:** Mean age of hepatic encephalopathy sufferers was  $50.64 \pm 10.29$  years. There were 87 (68.50%) male and 40 (31.50%) female patients. The most common cause of cirrhotic liver disease was the hepatitis C virus found in 62 (48.80%) patients. Prevalence of hypokalemia and hyponatremia in HE patients was 24 (18.90%) and 49 (38.60%), respectively. There was no significant difference in the prevalence of hypokalemia in age groups ( $p=0.609$ ), gender ( $p=0.482$ ), or grades of hepatic encephalopathy ( $p=0.902$ ). Hyponatremia was significantly higher in older people ( $p=0.005$ ) while there was no significant difference in its prevalence based on gender ( $p=0.824$ ) or hepatic encephalopathy grade ( $p=0.621$ ). **Conclusions:** Hypokalemia and hyponatremia are highly common in patients with hepatic encephalopathy presenting at a secondary care hospital.

## INTRODUCTION

Cirrhotic liver disease (CLD) is a major global cause of morbidity and mortality [1]. Globally, this condition has been reported to have an incidence of 58.4 million [2]. In Pakistan, the exact incidence of this condition is not known; however, it has been found that the most common cause of this condition in the Pakistani population is hepatitis C infection, with a frequency of 47.6% [3]. Several complications can complicate the course of this chronic disease, including ascites, tremors, jaundice, bleeding, bruising, gynecomastia, multi-organ failure, cryoglobulinemia, and hepatocellular carcinoma [4]. Another important complication of this condition is hepatic encephalopathy (HE), with a reported prevalence of 40% [5]. Patients with CLD are at risk of electrolyte

disturbance due to a low salt diet, laxative use leading to recurrent diarrhea, and use of diuretics [6]. These disturbances can occur in almost all the electrolytes, but the most important ones are hypokalemia and hyponatremia, which in severe cases can be life-threatening due to their related neurologic and cardiac complications. [7, 8]. In previous literature, the prevalence of hyponatremia among patients with HE has been reported at 36.9% [9]. Similarly, in one study that included patients with HE, upon analysis of the presence of hypokalemia, it was found that the prevalence of this electrolyte disturbance was 30% [10].

When it comes to the prevalence of aforementioned electrolyte disturbances, results are primarily from high-



output tertiary care centers, where mostly complicated cases are referred, which may add bias to their results. In addition, most of the patient burden is catered to at secondary care hospitals as these are more accessible to the community and are usually the first places where patients present. Despite this, no such data regarding dyselectrolytemia is available from secondary healthcare centers. This study aims to determine the frequency of hypokalemia in patients with HE presenting at a secondary care hospital in Pakistan.

## METHODS

This descriptive analytical study was conducted at the Department of Medicine, Tehsil Headquarter Hospital, Sarai Alamgir, Pakistan, from January 2024 to February 2025 after obtaining approval from the ethical committee (Ref no: EC/001/02/). Sample size of 127 was calculated using WHO sample size calculator (developed by K. C. Lun, Peter Y. W. Chiam and Chuah Aaron of the W.H.O. Collaborating Centre for Health Informatics and the Medical Informatics Program of the National University of Singapore) by assuming confidence level of 95%, absolute precision of 8% and anticipated frequency of hypokalemia in patients of HE of 30% [10]. Patients who were between 25 and 75 years, who were either male or female, had CLD and presented in the Emergency Department with the diagnosis of HE was included. Patients who had concomitant chronic renal failure, acute fulminant hepatitis, hypoglycemia, diabetic ketoacidosis, hyperglycemic hyperosmolar state, stroke, and uremic encephalopathy were excluded. The study population was selected by using a non-probability consecutive sampling method. A written consent, which was signed by the study participants, was made an essential prerequisite. Baseline characteristics, including age, gender, duration of CLD, cause of CLD, and grade of HE based on West Haven criteria, were documented. Grade 0 or minimal HE (impaired neuropsychological functions that could only be assessed by the means of test but no clinically overt change in mental state of the patient), Grade 1 HE (minimal degree of lack of awareness, feelings of anxiety, poor and shorter span of attention, euphoria and impairment of ability to add or subtract), Grade 2 HE (apathic patient with symptoms of lethargy, change in personality of the patient, behavioral alterations and being disoriented in time), Grade 3 (excessive sleepiness, stupor but intact ability to respond to stimulus, severe disorientation and confusion) and Grade 4 (coma) [11]. After that, patients were assessed for the presence of hypokalemia and hyponatremia by taking a blood sample of 5ml, placing it in the serum vial, and sending the sample to the laboratory. Hypokalemia was defined as serum potassium levels  $< 3.5$  meq/l. Hyponatremia was defined as serum sodium levels  $< 135$

meq/l.

Statistical analysis of the collected data was performed by using Statistical Package for Social Sciences, IBM SPSS version 22:00, Armonk, New York, USA. Quantitative data (age and duration of CLD) were represented using the mean with standard deviation. Qualitative data (gender, cause of CLD, grade of HE, hypokalemia, and hyponatremia) were represented by using percentages and frequency. Stratification of the prevalence of hypokalemia and hyponatremia was based on age, gender, and grade of HE, and post-stratification comparative analysis was done using the Chi-square test. A p-value of  $\leq 0.05$  was statistically significant.

## RESULTS

In this study, the mean age of HE sufferers was  $50.64 \pm 10.29$  years. There were 87 (68.50%) male and 40 (31.50%) female patients. Mean duration of CLD was  $4.71 \pm 2.50$  years. The most common cases of CLD were HCV found in 62 (48.80%) patients, followed by NAFLD in 16 (12.60%), HBV in 15 (11.80%), and alcohol use in 13 (10.20%) patients. Demographic characteristics of patients with HE is given in table 1.

**Table 1:** Demographic Characteristics of Patients with HE (n=127)

Characteristic	Mean $\pm$ SD; n (%)
<b>Age</b>	
Years	50.64 $\pm$ 10.29
<b>Gender</b>	
Male	87 (68.50%)
Female	40 (31.50%)
<b>Duration of CLD</b>	
Years	4.71 $\pm$ 2.50
<b>Cause of CLD</b>	
HCV	62 (48.80%)
HBV	15 (11.80%)
NAFLD	16 (12.60%)
Alcohol Use	13 (10.20%)
No Cause Identified	21 (16.50%)
<b>Grade of HE</b>	
1	34 (26.80%)
2	30 (23.60%)
3	32 (25.20%)
4	31 (24.40%)

SD = Standard deviation, CLD = Cirrhotic liver disease, HCV = Hepatitis C virus, HBV = Hepatitis B virus, NAFLD = Non-alcoholic fatty liver disease, HE = Hepatic encephalopathy

Prevalence of hypokalemia and hyponatremia in HE patients was 24 (18.90%) and 49 (38.60%), respectively. In the younger age group (n=42), the prevalence of hypokalemia and hyponatremia was 9 (21.43%) and 9 (21.43%), while in the older age group (n = 85), it was 15 (17.65%) (p=0.609) and 40 (47.06%) (p=0.005), respectively. Stratification of the prevalence of dyselectrolytemia based

on age is demonstrated in table 2.

**Table 2:** Stratification of Prevalence of Dyselectrolytemia in HE Patients Based on Age (n=127)

Age Stratification	< 45 Years (n=42)	≥ 42 Years (n=85)	p-value <sup>a</sup>
Hypokalemia	9 (21.43%)	15 (17.65%)	0.609
Hyponatremia	9 (21.43%)	40 (47.06%)	0.005

In male patients (n=87), the prevalence of hypokalemia and hyponatremia was 15 (17.24%) and 33 (37.93%), while in female patients (n=40), it was 9 (22.50%) (p=0.482) and 16 (40.00%) (p=0.824), respectively. Stratification of the prevalence of dyselectrolytemia based on gender is demonstrated in table 3.

**Table 3:** Stratification of Prevalence of Dyselectrolytemia in HE Patients Based on Gender (n=127)

Age Stratification	Male (n=87)	Female (n=40)	p-value <sup>a</sup>
Hypokalemia	15 (17.24%)	9 (22.50%)	0.482
Hyponatremia	33 (37.93%)	16 (40.00%)	0.824

Across different grades of HE, there was no significant difference in the prevalence of hypokalemia (p=0.902) and hyponatremia (p=0.902). Stratification of the prevalence of dyselectrolytemia based on grade of HE is demonstrated in table 4.

**Table 4:** Stratification of Prevalence of Dyselectrolytemia in HE Patients Based on Grade of HE (n=127)

Grade of HE Stratification	1 (n=34)	2 (n=30)	3 (n=32)	4 (n=31)	p-value <sup>a</sup>
Hypokalemia	6 (17.65%)	7 (23.33%)	6 (18.75%)	5 (16.13%)	0.902
Hyponatremia	11 (32.35%)	14 (46.67%)	11 (34.38%)	13 (41.94%)	0.621

HE = Hepatic encephalopathy, a = Chi-square test, b = Pearson chi-square test

## DISCUSSION

HE is a life-threatening complication of the CLD, which is characterized primarily by impaired cognition and higher motor functions [12, 13]. The present study focused on an important aspect of this complication, i.e., hypokalemia and hyponatremia. The average age of the HE sufferers was 51 years. Similar to this, a study was conducted with a different aim in which patients suffering from HE was included; in this study, the average age of HE sufferers averaged between 48 and 52 years [14]. Proportion of male patients was higher than female patients with males making up 68.5% of the study population, thereby, exhibiting a male to female ratio of 2.2:1. Similar to this, a large-scale epidemiological survey revealed that at global scale, men were affected more from this chronic liver condition as compared to females with the incidence of CLD in both genders reported at 1.2 and 0.8 million, respectively [15]. In another study, a similar male predominance was reported in terms of having CLD [16]. The reason for this male predominance can be attributed to

higher chances of men to indulge in activities (like shaving outside, smoking, outdoor dining, and exposure to quack treatment) that can result in exposure to common causes of CLD. In the present study, the most common cause that led to the development of CLD was chronic viral hepatitis C infection. The reason for this trend could be attributed to the fact that HCV is highly prevalent in the Gujrat district of Pakistan, where this study was conducted. [17] This finding was congruent with what was described in a study conducted by Gonzalez-Chagolla *et al.* who stated that among all the factors that contribute to the etiology of CLD and cirrhosis, hepatitis C is a major contributor. [18] Contrarily, this was not the case in a global epidemiological survey conducted by Zhang *et al.* in which it was reported that although hepatitis C does contribute to the etiology of this progressive condition, major contributor to the rising prevalence of this progressive damage to the liver is now NAFLD which may be due to rising number of people across the globe who are becoming overweight and obese [19]. In this study, the prevalence of hypokalemia and hyponatremia in patients presenting with HE was 18.9% and 38.6%, respectively. Compared to this, a study found that the prevalence of hypokalemia among patients presenting at various tertiary care institutions across the globe with this complication of CLD was 35%, which was relatively higher than the present study [20]. In another study, conducted on a much larger scale, hypokalemia prevalence was even higher compared to the present study and was reported at 78% [21]. In one study, HE patients presenting at a tertiary care center were analyzed for the presence of dyselectrolytemia, and it was reported that the prevalence of deficient levels of sodium and potassium in these patients was 75% and 50%, respectively, with both proportions significantly higher compared to the present study [22]. Similarly, in another study, hyponatremia prevalence among HE patients presenting at a tertiary care hospital was reported at 58.28% [23]. Such major difference in the prevalence being reported in previous studies and what has been observed in present study could have occurred due to the differences in sample sizes, type of treatment being used by the patients (particularly the doses of laxatives and diuretics), level of disease awareness and dietary restrictions to be followed, progression of CLD, HE severity pattern and level of healthcare facility of presentation. Upon stratification of the prevalence of hyponatremia and hypokalemia by age, it was observed that there was no significant difference based on hypokalemia prevalence among age groups (p=0.609), but the prevalence of hyponatremia was significantly higher among HE patients who were in the older age group (p=0.005). One possible reason for higher hyponatremia prevalence in older patients could be

attributed to the physiological decline in kidney function as well as the use of medications that can alter sodium balance, both of which are common in older age [24]. Upon gender stratification of hyponatremia and hypokalemia, it was observed that there was no significant difference between male and female patients based on the prevalence of hyponatremia ( $p=0.482$ ) or hypokalemia ( $p=0.824$ ). This demonstrates that gender does not play any role in determining the occurrence of dyselectrolytemia in HE patients. Similarly, it was observed that there was no statistically significant association between HE severity (based on West Haven criteria) and prevalence of either hyponatremia ( $p=0.621$ ) or hypokalemia ( $p=0.902$ ). Based on the findings of the present study, it is evident that hypokalemia and hyponatremia are highly prevalent among CLD patients presenting with HE at a secondary care hospital, but as compared to those who were analyzed at tertiary care and teaching hospitals, this prevalence is relatively low. This indicates that patients may have dyselectrolytemia even at earlier stages of disease, where they are mostly managed at secondary care hospitals, and thus, this screening should be regularly performed once the diagnosis of CLD is made.

There were a few limitations of the present study, including the study being held at a single center, non-inclusion of the severity of CLD due to the unavailability of certain investigations required for determining Child-class, and inability to assess HE outcome since most patients were referred to the tertiary care level after diagnosis and laboratory investigations. Although referral of the patient may appear as a bias-causing factor, the patients were referred after they were already assessed for the outcome of the present study, i.e., presence of lower levels of either sodium or potassium levels or both, and they were kept part of the study irrespective of their referral since the data was collected before patient referral.

## CONCLUSIONS

In conclusion, dyselectrolytemia is highly common in patients with cirrhotic liver disease who present with hepatic encephalopathy, with the prevalence of hypokalemia and hyponatremia in these patients being 18.9% and 38.6%, respectively. This signifies that patients presenting with this complication of liver cirrhosis should always be screened for either of these disturbances in the electrolyte levels and should be considered as a possible precipitating factor of hepatic encephalopathy, even when other obvious precipitants are clinically apparent.

## Authors' Contribution

Conceptualization: TI

Methodology: TI

Formal analysis: TI

Writing and Drafting: TI

Review and Editing: TI

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



## Identifying Factors Associated with High-Risk Obstructive Sleep Apnea (OSA) among Hypertensive Patients: A Case-Control Study in A Tertiary Care Hospital in Pakistan

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## ABSTRACT

Obstructive sleep apnea (OSA) involves repeated upper-airway collapse and intermittent hypoxia. In hypertensive patients, particularly in developing regions, undetected OSA exist which significantly increases cardiovascular dangers. **Objective:** To identify factors associated with high-risk OSA in patients with raised blood pressure attending two tertiary hospitals in Peshawar. **Methods:** This case-control study (June 2025–September 2025) included 156 hypertensive adults (78 cases, 78 controls). Inclusion required a diagnosis of hypertension and a specific STOP-Bang score (cases  $\geq 3$ ; controls  $\leq 2$ ). Exclusion criteria involved prior OSA treatment, pregnancy, resistant hypertension, or severe mental health conditions. Data were collected via structured questionnaires and analyzed using multivariable logistic regression. **Results:** Mean age, BMI, and neck circumference were significantly higher in the high-risk group ( $p < 0.001$ ). Gender, BMI category, and ischemic heart disease were significantly associated. In crude regression, age, gender, BMI, neck circumference, and ischemic heart disease were significant predictors; however, after adjustment, only older age, male gender, and larger neck circumference remained independently associated with high-risk OSA. **Conclusions:** Older age, male gender, and increased neck circumference independently predict high-risk OSA in hypertensive patients. STOP-Bang proved useful as a screening tool, and the high prevalence of anxiety highlights the broader clinical burden. Incorporating neck circumference and age into routine hypertension care may aid earlier OSA recognition.

## INTRODUCTION

The most widespread sleep-related breathing condition is Obstructive Sleep Apnea (OSA), defined by cycles of breathing pauses and restarts during sleep. Unlike other forms, OSA happens when pharyngeal muscles relax excessively, resulting in transient airway blockage. Common symptoms include loud snoring, increased daytime sleepiness, and repeated nighttime episodes of upper-airway collapse. These repeated episodes of sleep fragmentation and hypoxia contribute to impaired daytime functioning and cognitive decline [1]. OSA prevalence

reaches 50% in the hypertensive population and up to 71% in resistant hypertensive cases [2, 3]. The intermittent hypoxia in OSA triggers sympathetic activation and oxidative stress, promoting cardiovascular diseases, diabetes mellitus, and increasing mortality risk if left untreated [1, 4]. Studies have shown that obesity and a larger neck circumference, typically  $\geq 35.5$  cm in males and  $\geq 32$  cm in females, are major factors linked with severe OSA risk [5-7]. The coexistence of OSA and hypertension is clinically critical, as both conditions share



pathophysiological mechanisms like inflammation and vascular remodeling, all contributing to elevated blood pressure [8]. Regional studies have demonstrated a high prevalence of OSA symptoms among hypertensive patients, with evidence consistently showing that OSA is significantly associated with elevated blood pressure and hypertension even after adjusting for demographic and lifestyle factors [9, 10]. For confirmatory diagnosis of OSA, polysomnography is the gold standard procedure, but its use remains restricted in settings like ours due to cost and availability [11]. Globally, almost 75%-80% of OSA cases remain undiagnosed [12], with particularly low awareness in regions like Karachi, where only 15% of respondents demonstrated adequate understanding of OSA [13]. Furthermore, up to 93% of moderate-to-severe OSA cases in women may go unrecognized [14]. A study conducted in a local tertiary setting showed a substantial burden of OSA, emphasizing the fact that OSA remains significantly unrecognized in the local population [15]. To address this diagnostic gap, the STOP-Bang questionnaire (SBQ) provides a validated, sensitive, and cost-effective screening instrument, offering high sensitivity for detecting moderate-to-severe OSA in low-resource environments [16, 17].

Despite the globally well-established link between OSA and cardiovascular diseases, there is still a significant lack of regional evidence regarding risk factors specific to hypertensive populations in Pakistan. While general predictors are known, local predictors such as specific neck circumference threshold remains unexplored among the high-risk group. This study addresses this literature gap. This study aims to focus on finding local determinants in a tertiary care setting in Peshawar to enable earlier clinical recognition of OSA. As identifying these determinants is crucial for developing targeted screening protocols and improving management outcomes in low-income settings.

## METHODS

This case-control study was conducted from 1st June to 1st September 2025 at Rehman General Hospital and Rehman Specialist Hospital in Peshawar, Pakistan. The participants were briefed on the study objectives and then signed informed consent forms. The research protocol was approved by the Institutional Review Committee on 15th May 2025 (Approval Letter Reference No: IRC-Approval-10-15-5-25). For this case-control study, the sample size was estimated using the formula,  $n = (Z\alpha/2 + Z\beta)^2 \times [p_1(1-p_1) + p_2(1-p_2)] / (p_1 - p_2)^2$ . The parameters used for the formula were 95% confidence level ( $Z\alpha/2=1.96$ ), 80% power ( $Z\beta=0.84$ ), and based on a reported smoking prevalence difference of 28.4% in cases ( $p_1$ ) versus 9.2% in controls ( $p_2$ ) [18]. Cases were defined as hypertensive adults (blood

pressure  $\geq 140/90$  mmHg or on antihypertensive medication) with a Snoring, Tiredness, Observed apnea, high blood pressure, Body mass index, Age, Neck circumference, and Gender (STOP-Bang) questionnaire score  $\geq 3$  and at least one additional high-risk feature. Controls were hypertensive adults with a STOP-Bang score  $\leq 2$  [19] was followed for these classification and exclusion criteria. Participants with prior OSA treatment, pregnancy, resistant hypertension, or severe mental health conditions were excluded. The STOP-Bang questionnaire is a well-recognized, reliable, and practical screening instrument; using a cutoff score of  $\geq 3$ , it demonstrates a sensitivity of 93% for moderate-to-severe OSA and 100% for severe OSA [16]. The tool consists of 8 questions with a possible score ranging from 0 to 8, and has a reported Cronbach's alpha of 0.72, showing good internal consistency [20]. Data were collected using interviewer-led structured questionnaires covering sociodemographic variables (age, gender, socioeconomic status, and education level) and health-related variables. Height was measured using a stadiometer, weight using a digital weighing scale, blood pressure using a sphygmomanometer, and neck circumference using a non-stretchable measuring tape. Body mass index was calculated as weight in kilograms divided by height in meters squared. Comorbidities, including diabetes mellitus, ischemic heart disease, stroke, and hypercholesterolemia, were verified based on documented diagnosis and current medication use. Psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS) with Urdu/Pashto verbal translation. HADS consists of two 7-item subscales, score of each range from 0 (minimum) to 21 (maximum); both subscales have demonstrated good internal validity with reported Cronbach's alpha ranging from 0.80 to 0.90 [21]. The scores of HADS-A and HADS-D were categorized as, a score of 0-7 was classified as Normal, a score of 8-10 was classified as Borderline, and a score of 11-21 was classified as abnormal [21].

All statistical analyses were performed using SPSS version 26.0. Quantitative variables were expressed as mean  $\pm$  standard deviation and compared using independent t-tests, while qualitative variables were analyzed using Chi-square or Fisher's exact tests. Predictors of high-risk OSA were identified using binary logistic regression, followed by multivariable logistic regression for variables with  $p \leq 0.20$  to calculate adjusted odds ratios. For all logistic regression models, the 'Low-Risk OSA' group (STOP-Bang score  $\leq 2$ ) served as the reference category. For categorical predictors, 'Female' was utilized as the reference category for Gender, and the 'Absence of comorbidity' served as the reference for clinical variables. Statistical significance was defined as  $p \leq 0.05$  at a 95% confidence level.

## RESULTS

A total of 156 hypertensive patients were analyzed, equally separated into high-risk (n = 78) and low-risk (n = 78) OSA classes using the STOP-BANG questionnaire. The overall mean age was 54.3 ± 13.1 years, mean BMI 27.3 ± 5.4 kg/m<sup>2</sup>, and mean neck circumference 15.0 ± 1.5 inches. Most participants were non-educated (65.4%) and belonged to the middle socioeconomic class (71.8%). Based on HADS scoring, anxiety symptoms were predominantly prevalent, with most participants in the abnormal anxiety range, while depressive symptoms were generally mild. In order to compare the quantitative variables among the two groups t-test was applied, which showed a significant difference between the groups. Mean age, BMI, and neck circumference were markedly elevated in the high-risk group (p<0.001 for all), as shown in Table 1.

**Table 1:** Comparison of Continuous Variables Between High- and Low-Risk OSA Groups

Variable	Low-Risk Mean ± SD	High-Risk Mean ± SD	t-value	p-value
Age (years)	48.2 ± 11.7	60.4 ± 11.6	-6.22	<0.001*
BMI (kg/m <sup>2</sup> )	25.8 ± 4.5	28.9 ± 5.9	-3.56	<0.001*
Neck Circumference (inches)	14.2 ± 1.0	15.9 ± 1.5	-7.63	<0.001*

BMI: Body mass index; SD: Standard deviation. \*Indicates statistical significance at p≤0.05

Chi-square was applied to assess the relationship between qualitative variables and that of OSA-risk (Table II). A significantly higher proportion of males was observed among high-risk OSA cases compared to controls ( $\chi^2 = 10.74$ , p=0.001). Similarly, BMI category showed a significant relationship with OSA risk ( $\chi^2 = 14.35$ , p=0.002), with obesity being more frequent in the high-risk group. Ischemic heart disease ( $\chi^2 = 10.26$ , p=0.001) was also significantly linked with high-risk OSA. A borderline association was noted for stroke ( $\chi^2 = 3.85$ , p=0.050; LR = 4.10, p=0.043; Fisher's exact 1-sided = 0.049). Observed counts and percentages within groups are presented in table 2.

**Table 2:** Association of Categorical Variables with OSA Risk (Chi-Square Test)

Variable	Category	Low-Risk, (n, %)	High-Risk, (n (%))	$\chi^2$	p-value
Gender	Male	15 (19.2%)	34 (43.6%)	10.741	0.001*
	Female	63 (80.8%)	44 (56.4%)		
BMI Category	Underweight (<18.5)	5 (6.4%)	2 (2.6%)	14.351	0.002*
	Normal (18.5-24.9)	26 (33.3%)	20 (25.6%)		
	Overweight (25-29.9)	35 (44.9%)	23 (29.5%)		
	Obese (≥30)	12 (15.4%)	33 (42.3%)		
Ischemic Heart Disease	Yes	13 (16.7%)	31 (39.7%)	10.256	0.001*
	No	65 (83.3%)	47 (60.3%)		
Stroke (History)	Yes	3 (3.8%)	9 (11.5%)	3.847	0.050*
	No	75 (96.2%)	69 (88.5%)		

All expected counts were ≥5 except for the stroke variable (minimum expected count = 3.25). Fisher's exact test was therefore additionally applied. \*Indicates statistical significance at p≤0.05

Binary logistic regression was applied for every potential predictor separately, and then multivariable regression was applied on the variables having a p-value up to 0.2, as shown in table 3.

**Table 3:** Crude Logistic Regression of Factors Associated with High-Risk OSA

Predictor	B	SE	Wald	OR (95% CI)	p-value
Age (years)	0.129	0.028	21.311	1.14 (1.06-1.21)	<0.001*
Gender (male)	1.177	0.367	10.291	3.25 (1.61-6.55)	0.001*
BMI (kg/m <sup>2</sup> )	0.115	0.045	6.570	1.12 (1.03-1.22)	0.010*
Neck circumference (inches)	1.041	0.274	14.424	2.83 (1.54-5.21)	<0.001*
Smoking Status	0.330	0.141	5.459	1.39 (0.84-2.33)	0.190
Cholesterol (Abnormal)	0.247	0.192	1.660	1.28 (0.92-1.79)	0.150
Stroke (History)	0.418	0.239	3.060	1.52 (0.95-2.42)	0.080
Ischemic Heart Disease	1.193	0.382	9.763	3.30 (1.55-7.02)	0.002*

OR: Odds ratio; CI: Confidence interval; SE: Standard error; BMI: Body mass index. Note: The Low-risk OSA group (STOP-Bang scores≤2) served as the reference category for the calculation of odds ratios. For categorical predictors, 'Female' served as the reference category for Gender, and 'No' (absence of the condition) served as the reference for all clinical comorbidities. \* Indicates statistical significance at p≤0.05

After adjustment, age, gender, and neck circumference remained independent predictors of high-risk OSA, whereas BMI and IHD lost statistical significance, as shown in table 4.

**Table 4:** Multivariable Logistic Regression of Factors Associated with High-Risk OSA

Predictor	B	SE	Wald	OR (95% CI)	p-value
Age (years)	0.122	0.031	15.44	1.13 (1.06-1.21)	<0.001*
Gender (male)	1.085	0.482	5.07	2.96 (1.22-7.18)	0.016*
Neck circumference (inches)	1.005	0.231	18.93	2.73 (1.55-4.83)	<0.001*

AOR: Adjusted odds ratio; CI: Confidence interval; SE: Standard error. Note: The Low-risk OSA group (STOP-Bang scores≤2) served as the reference category for the calculation of odds ratios. For categorical predictors, 'Female' served as the reference category for Gender, and 'No' (absence of the condition) served as the reference for all clinical comorbidities. \*Indicates statistical significance at p≤0.05

Older age, male gender, and increased neck circumference showed independent association with greater odds of high-risk OSA among hypertensive patients. Although BMI and ischemic heart disease were initially significant in crude models, their effects were no longer significant after adjustment, suggesting shared variance with anthropometric predictors.

## DISCUSSION

This case-control analysis assessed factors linked with high-risk OSA in hypertensive patients through the STOP-Bang tool. Older age, male sex, and greater neck circumference were confirmed as independent predictors, supporting trends described in previous regional and global studies. These findings align with the observations of Salim *et al.* who reported that men with older ages and higher BMI were found to have higher OSA risk among hypertensive patients in Kenya [11]. Similarly, the nationwide Korean analysis by Huh *et al.* confirmed age and male gender as robust predictors of OSA after full multivariable adjustment [18]. The contribution of male sex to OSA risk has also been described in broader epidemiological literature, emphasizing the influence of sex hormones and craniofacial morphology on airway collapsibility [22]. Neck circumference demonstrated a particularly strong and independent association with high-risk OSA in the present study. This finding supports evidence from the Salim *et al.* [11] and Huh *et al.* [18] cohorts, where neck circumference remained one of the most powerful predictors of OSA even after adjusting for confounders. Larger neck circumference indicates upper airway anatomical narrowing and increased soft tissue volume, factors that predispose individuals to pharyngeal collapse during sleep. In contrast, BMI, though widely recognized as an OSA risk factor, reflects general adiposity rather than regional fat distribution. Consequently, BMI's predictive strength often diminishes when neck circumference is included in multivariate models, as also noted by Salim *et al.* [11]. This suggests that regional adiposity (particularly around the upper airway) may play a more direct etiological role in OSA development than generalized obesity. These findings therefore support the study hypothesis that selected demographic and anthropometric characteristics are significantly linked to hypertensive patients who are at higher risk of OSA. The attenuation of certain variables in the adjusted model in the present study parallels patterns observed in earlier research. While BMI and ischemic heart disease (IHD) demonstrated an association that was statistically significant with high-risk OSA in unadjusted analysis, both lost statistical significance in the multivariable logistic regression. A similar attenuation was reported in the Korean population by Huh *et al.* [18], where hypercholesterolemia and chronic kidney disease (CKD) showed strong crude associations with high-risk OSA, but these associations disappeared after full adjustment. This loss of significance highlights that such comorbidities as hypercholesterolemia, CKD, IHD, and BMI may act as mediating or intermediary factors within a shared cardiometabolic pathway rather than as independent

determinants. In the current study, the multicollinearity between BMI and neck circumference likely contributed to BMI's non-significance, as both variables capture overlapping elements of obesity and airway morphology. Neck circumference thus emerged as the more specific anthropometric correlate of OSA risk in this hypertensive cohort. The high prevalence of anxiety among hypertensive participants in this study is noteworthy. Although no significant association was found between anxiety or depression and OSA risk, the frequency of abnormal anxiety scores suggests that psychological distress is prevalent among patients with chronic hypertension; studies conducted in the past have shown the prevalence of disorders like anxiety and depression among the OSA population [4, 11]. While mood disorders did not directly predict OSA status in this analysis, the coexistence of hypertension, anxiety, and sleep-related symptoms may collectively aggravate patient outcomes, underscoring the value of integrated screening and management approaches. Overall, these results indicate that the STOP-BANG is a practical and reliable instrument for screening OSA in hypertensive subjects in routine clinical practice. The identification of neck circumference, age, and male gender as strong predictors is clinically valuable, as these parameters are simple to measure and cost-effective. The observed attenuation of metabolic and cardiovascular factors (BMI, IHD, cholesterol) after adjustment reinforces the complexity of OSA's pathophysiology, emphasizing that structural and demographic determinants may hold greater predictive power in this population.

This study's strengths include a robust case-control design and standardized data collection, which ensured reliable measurements of anthropometric and clinical parameters. Potential confounders were statistically addressed through multivariable logistic regression, and the use of the validated STOP-Bang questionnaire provided a cost-effective approach for identifying OSA risk in a resource-limited setting. However, limitations include the single-center tertiary care design, which may restrict the generalizability of findings to broader populations. Furthermore, the high prevalence of diabetes among hypertensive patients complicated the recruitment of fully matched non-diabetic controls, and sociocultural factors may have influenced self-reported smoking status in females. Finally, while the STOP-Bang tool is a validated screening instrument, the absence of polysomnography—the diagnostic gold standard—may have introduced some degree of misclassification. Despite these constraints, the study provides valuable insights into clinical determinants of OSA risk, underscoring the necessity of integrated screening protocols in routine hypertensive care. Routine Screening: Integrate neck circumference measurements and the STOP-Bang questionnaire into standard

hypertension management for earlier OSA detection. Resource Optimization: Prioritize structural and demographic predictors, such as age and gender, in clinical settings where polysomnography is unavailable. Integrated Care: Screen hypertensive patients for psychological distress as part of a holistic management approach. Further Research: Conduct multicenter studies utilizing polysomnographic validation to refine these risk thresholds for the local population.

## CONCLUSIONS

This study demonstrates that older age, male gender, and increased neck circumference are independent predictors of high-risk obstructive sleep apnea (OSA) among hypertensive patients in Peshawar. The STOP-Bang questionnaire serves as a practical, high-sensitivity screening tool in resource-limited settings where polysomnography is unavailable. These findings suggest that incorporating routine neck circumference measurements into hypertension management can facilitate earlier OSA detection. Such integrated screening is vital for mitigating cardiovascular risks and addressing the significant psychological burden prevalent in this population.

## Authors' Contribution

Conceptualization: IUH

Methodology: IUH, HI, AB, AA, HH, TR

Formal analysis: IUH, AA

Writing and Drafting: IUH, HI, AB, AA, HH, TR

Review and Editing: IUH, HI, AB, AA, HH, TR

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



## Various Modes of Delivery After a Trial of Labor among Pregnant Women at Term with a Previous One Cesarean Section

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## ABSTRACT

The most crucial approach to lowering the increasing prevalence of cesarean sections and related maternal morbidity is vaginal birth after cesarean (VBAC). The need for local evidence to direct clinical practice is highlighted by the fact that TOLAC success varies across populations.

**Objectives:** To identify the rates of various delivery modalities: spontaneous VBAC, assisted VBAC, and repeat cesarean section among women who have undergone a trial of labor following one prior cesarean section and relate them to age, BMI, and parity. **Methods:** This study was conducted in the Department of Gynecology at Mohtarma Benazir Bhutto Shaheed Medical College/DHQ Teaching Hospital, Mirpur, Azad Kashmir. It was a descriptive cross-sectional study conducted over 6 months. The sample size was 160 with full-term pregnant women with one prior c-section. Consecutive sampling was applied for this study. Data were analyzed using SPSS version 25.0 with a chi-square test ( $p < 0.05$ ). **Results:** Spontaneous VBAC occurred in 57.5% of women, assisted VBAC in 20.6%, and repeat cesarean in 21.9%. Assisted VBAC was significantly associated with age  $\geq 30$  years ( $p = 0.030$ ) and parity ( $p = 0.026$ ), while spontaneous VBAC was significantly related to BMI ( $p = 0.041$ ). **Conclusions:** The VBAC success rate was 78.1%, indicating that TOLAC is a safe and effective option for most women with one previous cesarean section. Although age, BMI, and parity influenced modes of vaginal delivery, they did not significantly affect repeat cesarean rates, supporting planned TOLAC to reduce unnecessary repeat cesarean sections and improve maternal outcomes.

## INTRODUCTION

The increasing number of cesarean deliveries worldwide has led to a dire need to conduct a critical analysis of the available delivery modes for women who already had a cesarean [1]. A surgical approach to birth, named Caesarean delivery, or delivery of a child through an incision in the uterus [2], has gained more and more popularity during the last century, both in developed countries and in developing ones [3]. Advanced surgical

procedures, anesthetic skills, access to blood products, expansion of indications and awareness of fetus as a patient, and the possibility of vaginal birth following cesarean (VBAC) have played a part in this trend. The incidence of cesarean delivery among women has increased 4 times for 30 years [4]. Traditionally, once a cesarean, always a cesarean has been the motto of fear of disastrous uterine rupture in case of classical cesarean



delivery. Nonetheless, this solution was criticized as overwhelming the healthcare system and producing a high-risk group of women with scarred uteri [5]. Up-to-date obstetric care has lowered the occurrence of uterine rupture after lower segment cesarean section by a significant magnitude, but the high cesarean birth rates continue to have a high association with maternal and neonatal complications [6]. This has resulted in the introduction of trials of labor after cesarean (TOLAC) trial, and VBAC is becoming a viable and safe method [2]. The majority of women who have had one cesarean section are eligible to undergo VBAC, with reported success rates of between 72 and 89, with previous successful VBAC proving to be the best predictor of future successful VBAC [7]. VBAC has such advantages as less maternal morbidity, fewer postpartum complications and infection, less recovery time, and fewer costs of healthcare compared to the planned repeat cesarean section [8, 9]. However, failed TOLAC is accompanied by the risk of uterine rupture, which is why it is necessary to carefully select the patients, counsel them, and categorize risks [10, 11]. Past researches have reported VBAC success rates of 57.3 to 71.5, with assisted vaginal deliveries comprising another percentage, with repeat cesarean rates of between 28.5 and 29 [12]. The success rates of VBAC were also significantly greater in women with previous vaginal births (80.8% vs. 52.3%,  $p < 0.001$ ) [6]. These reasons highlight why it is important to consider maternal variables such as age, BMI, and parity when forecasting VBAC success.

Even though there is an increased call around the world to promote TOLAC to curb the increasing rates of cesarean section, gaps in evidence are still observed in low-resource contexts. The available research is mainly based on the high-income nations having various obstetric regimes, healthcare systems, and demographics of patients. This poses a challenge to local clinicians in areas such as AJK, Pakistan, who do not have strong population-specific data to inform the choice of patients, counseling, and intrapartum care of TOLAC. This study aimed to create local evidence by ascertaining the rates of different delivery modes, namely, spontaneous VBAC, assisted VBAC, and repeat cesarean section, which followed a trial of labor in women with one previous cesarean section at one of the tertiary care hospitals in Mirpur, AJK.

## METHODS

It was a cross-sectional descriptive study that was carried out at the Department of Gynecology, Mohtarma Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur, Azad Kashmir, over a minimum period of six months (January to July 2025) after the study synopsis was approved (Ref. No. 158/ Academic blocks Trauma Centers/Surgery/2025). A sample size of 160

women was taken, which was calculated using an effect size of 0.10 of cesarean section among women in labor, who had a previous cesarean section, an 80 percent power, and a 5 percent margin of error according to the WHO calculator sample size calculation [12], and chosen by non-probability sequence sampling. Inclusion criteria were women of 20-29 years and  $\geq 30$  years age who had one previous cesarean section, went to labor at full term with a singleton vertex fetus and no medical or obstetric complications [13], whereas the exclusion criteria were those with more than one previous cesarean section, obstructed labor, cephalopelvic disproportion, macrosomic infants, or umbilical cord about fetal neck to avoid confounding [14]. The data collection was conducted before obtaining ethical approval and written informed consent by use of a structured proforma. A senior obstetrician examined all the participants and reviewed their previous delivery history to identify possible risk factors. The prognostic factors, including engaged head, average fetal size, soft, central, and dilated cervix, and adequate pelvis (measured in terms of digital pelvimetry), were considered during the trial of labor. Patients were maintained at nil by mouth, properly hydrated by administration of intravenous dextrose 5% fluids, and partograms were used to measure the progress of labour. Systemic analgesia was in use, and the patients were observed for scar tenderness, maternal tachycardia, vaginal bleeding, presenting part loss, and fetal distress, such as fetal heart rate and meconium passage. The infusion of Oxytocin was applied to augment labor when there were not enough contractions. A senior house officer or trainee who was aware of the antenatal record of the patient ensured that the right monitoring was carried out. At least 1 pint of blood was typed and cross-matched, and a 16-18 gauge IV line was kept. There was information to the anesthetist and theatre staff about the possibility of cesarean delivery. There was a trial of spontaneous vaginal delivery, and vacuum or outlet forceps were applied where necessary, and emergency cesarean section was done in case of failure of vaginal delivery. After birth, a two-hour observation of the labor room was made of patients to detect postpartum bleeding after birth.

Data analysis was done on SPSS version 25.0 and continuous variables were represented by mean and standard deviation (i.e., age, parity, and BMI), and the categorical variables (i.e., modes of delivery) were represented by frequencies and percentages. Age, parity, and BMI stratified modes of delivery, and post-stratification chi-square was used with a p-value of less than 0.05 as significant.

## RESULTS

The study involved 160 pregnant women who already had one cesarean section. The participants were aged between 20 and 40 years, with a mean and SD of 28.51 ± 4.58 years. The body mass index (BMI) was between 16.10 - 35.00 kg/m<sup>2</sup>, and the mean BMI was 24.48 ± 4.70 kg/m<sup>2</sup>. Such attributes offer a preliminary knowledge of the study population before determining how many different modes of delivery have taken place after labor (Table 1).

**Table 1:** Sample Characteristics and Delivery Outcomes

Variables	Category	n (%)
Age Group	20-29	112 (70%)
	≥30	48 (30%)
BMI Category	Underweight	17 (10.6%)
	Normal weight	68 (42.5%)
	Overweight	56 (35.0%)
	Obese	19 (11.9%)
Parity	1	95 (59.4%)
	2	65 (40.6%)
Spontaneous VBAC	Yes	92 (57.5%)

**Table 2:** Association of Independent Variables with Mode of Delivery

Variables	Category	Spontaneous VBAC, n (%)	Assisted VBAC, n (%)	C-Section, n (%)	χ <sup>2</sup>	p-value
Age Group	20-29	70 (62.5%)	18 (16.1%)	24 (21.4%)	5.410	0.047
	≥30	22 (45.8%)	15 (31.3%)	11 (22.9%)		
BMI Category	Underweight	9 (52.9%)	2 (11.8%)	6 (35.3%)	2.974	0.041
	Normal Weight	39 (57.4%)	16 (23.5%)	13 (19.1%)		
	Overweight	32 (57.1%)	12 (21.4%)	12 (21.4%)		
	Obese	12 (63.2%)	3 (15.8%)	4 (21.1%)		
Parity	1	57 (60.0%)	14 (14.7%)	24 (25.3%)	5.412	0.051
	2	35 (53.8%)	19 (29.2%)	11 (16.9%)		

This research involved 160 pregnant women who had one cesarean section. The average age of the participants was 20-29 (70%, n=92), and most of the individuals were primiparous (59.4%, n=95). About the body mass index (BMI), 68 (42.5%) were of normal weight, 56 (35.0%) overweight, 19 (11.9%) obese, and 17 (10.6%) underweight. Still, 92 (57.5%) women gave birth without help, 20.6% (n=33) with the help of VBAC, and 35 (21.9%) repeated C-section, which showed that most of them could deliver a baby vaginally, even when they had a previous cesarean section. The women between the ages of 20 and 29 years (62.5%) found more spontaneous VBAC than older women (45.8%), with a near-significant difference (p=0.047), indicating that younger women are more likely to have a successful unassisted vaginal birth. The prevalence of assisted VBAC was also higher among women aged 30 years and above (31.3% vs 16.1%), which suggests the possibility of women aged above 30 years being more likely to have assisted vaginal delivery. The age did not have a significant difference in repeat cesarean section rates

Assisted VBAC	No	68 (42.5%)
	Yes	33 (20.6%)
Caesarean Section	No	127 (79.4%)
	Yes	35 (21.9%)
	No	125 (78.1%)

The study involved 160 pregnant women who had one past cesarean section. Most of the participants were between 20- 29 years (70.0%, n=112), and 30 years and above (30.0%, n=48). As to body mass index (BMI), 68 (42.5%) of women were normal, 56 (35.0%) of the women were overweight, 119 (1.9%) of women were obese, and 17 (10.6%) of women were underweight. Regarding parity, 95 (59.4%) were primiparous (parity 1), and 65 (40.6%) were multiparous (parity 2). Regarding delivery modes following a trial of labor, 92 (57.5%) had spontaneous VBAC, 33 (20.6%) had assisted VBAC, and 35 (21.9%) had repeat cesarean section. These results represent a vivid picture of the distribution of maternal features and delivery at bay, which is consistent with the aim of the study, which is to provide the frequency of the different modes of delivery in women with a prior cesarean section (Table 2).

(22.9% vs 21.4%), indicating that age was not a key factor in determining surgical birth. BMI analysis showed that the spontaneous VBAC rates were 52.9%, 57.4%, 57.1%, and 63.2% among underweight, normal weight, overweight, and obese women, respectively, which were not statistically different (p = 0.047), proving that vaginal delivery could occur in all BMI groups. The mode of delivery did not vary significantly with maternal weight in this cohort because assisted VBAC and repeat cesarean section did not have any significant association with BMI. The spontaneous VBAC was found in 60.0% and 53.8% of primiparous and multiparous women, respectively (p=0.051); this indicated no significant difference. The rates of assisted VBAC were higher in multiparous women (29.2%) than in primiparous women (14.7), and the rate of repeat cesarean section was 25.3% and 16.9%, respectively. This implies that multiparty might stimulate the necessity of assisted vaginal delivery, and not necessarily repeat cesarean. Overall, the results indicate that the majority of women who have had a prior cesarean

segment can deliver spontaneously, assisted VBAC is more probable among older women, or multiple pregnancies, and recidivism is fairly steady in respect to age, BMI, and parity, which is also in line with the research objective to define the frequency and determinants of various modes of delivery.

## DISCUSSION

This paper assessed the incidence and predictors of the different delivery modes in women who had had one previous cesarean delivery. All in all, spontaneous VBAC was obtained in 57.5% of the participants, assisted VBAC in 20.6%, and repeat cesarean section in 21.9%. These results are aligned with the global statistics indicating successful rates of vaginal birth between 57 and 77 percent following a cesarean operation [12]. As an example, a retrospective cohort study at Italian tertiary hospitals found a spontaneous VBAC rate of 57.3% of women, assisted VBAC of 9.2%, and a repeat of cesarean section of 29.4% [15]. On the same note, one study that conducted a study involving 235 women who attempted labor following a prior cesarean revealed that the VBAC success rate was 71.5% and the repeat cesarean rate was 28.5% [12]. The minor disparities in the levels of success in the research may be explained by the differences in the patient selection, obstetric practice, and organizational guidelines. Age appeared to influence the outcomes of birth in our cohort. Spontaneous VBAC was more common in women who were below 20 to 29 years of age (62.5%) compared to those who were 30 years and above (45.8%), which was almost close to the statistical significance ( $p=0.050$ ). Alternatively, assisted VBAC was significantly higher in those 30 years and above (31.3% vs 16.1;  $p=0.047$ ). These results are similar to other studies where maternal age was identified to have a stronger effect on successful unassisted vaginal delivery among young adults, but in older age, the likelihood of obstetric intervention may be significant [16]. It was found that there was no significant difference in age groups in terms of repeat cesarean rates, and thus, maternal age is not a determinant that dictates surgical delivery. The BMI analysis showed that spontaneous VBAC occurred across all categories: underweight (52.9%), normal weight (57.4%), overweight (57.1%), and obese (63.2%), with a significant association ( $p=0.041$ ). This indicates that BMI can influence spontaneous VBAC, although vaginal delivery remains possible even with higher BMI. These findings are consistent with previous studies, suggesting that women should not be excluded from TOLAC solely based on their weight [17]. Parity analysis showed that VBAC being spontaneous was 60.0 and 53.8 percent in the primiparous and multiparous women, respectively, and there was no statistically significant difference ( $p=0.051$ ). Assisted VBAC was also more common in multiparous women (29.2%) than

in primiparous women (14.7%), to support the idea that additional obstetric intervention may be needed in multiparous women who have a previous cesarean section. The repeat cesarean sections were not significantly different across the groups of parity (16.9% vs 25.3%;  $p=0.051$ ). These results are consistent with international data, which suggest that successful vaginal birth in the past is a significant predictor of successful VBAC, and parity may affect the probability of the necessity of assisted vaginal delivery [15, 16]. In this cohort, the general VBAC success rate (including both spontaneous and assisted) was 78.1%, and is at the upper end of the international reports [18, 19]. This can be explained by the systematic intrapartum procedure, high-quality staffing, and specific counseling offered during the trial of labor, which are in line with the research stressing the significance of institutional policies and patient education to promote VBAC [20, 21]. The reason is the relatively low repeat cesarean rate (21.9%) in our cohort, which implies a proactive approach to TOLAC instead of the setting where the previous cesarean section is nearly a certain precursor of repeat surgical delivery [22, 23]. In clinical terms, the advocacy of TOLAC has a great effect on maternal and neonatal health. Effective VBAC decreases risks related to the occurrence of a second or more cesarean sections, such as placenta accreta, and also improves maternal recovery and subsequent reproductive outcomes [14, 24]. These findings indicate that TOLAC is feasible and safe in well-selected women, even with higher BMI or multiparity, as long as it is closely monitored under the clinical guidelines. To sum up, our results confirm that spontaneous VBAC is possible in most of the women who have undergone one cesarean delivery, assisted VBAC has higher chances in older women or in those with multiple births, and repeat cesarean section is not any different in terms of age, BMI, and parity. These findings underscore the need to have structured TOLAC interventions, patient education, and excellent intrapartum care that can maximize VBAC outcomes and minimize unwarranted repeat cesarean sections.

The single-center and cross-sectional design has key limitations that restrict its generalizability, and the sample size is small, which could decrease statistical power. The researchers further failed to adjust some of the crucial confounders, such as the indication of primary cesarean or inter-delivery interval. We suggest setting up systematic TOLAC counseling interventions and undertaking more extensive, prospective multicenter investigations, which would encompass a broader spectrum of predictive variables in order to create a locally valid instrument to predict VBAC success.

## CONCLUSIONS

Spontaneous VBAC was possible in most women who had one previous cesarean section, and this indicates that vaginal birth following cesarean is a safe and viable procedure in most instances. More elderly women and high parity were found to have assisted VBAC, which implies that maternal age, BMI, and parity could be factors in obstetrical intervention during labor. The rates of repeat cesarean section were rather stable by age and parity, while BMI showed a significant association with spontaneous VBAC but not with repeat cesarean section, which led to the conclusion that these variables are not sufficient predictors of the necessity of the surgical delivery. In general, the strategic selection, observation, and counseling of patients may maximize the delivery results, minimize the needless repetitive cesarean section in women with a prior cesarean section, and present the evidence to support the local clinical practice with regard to managing labor among women with a prior cesarean section.

## Authors' Contribution

Conceptualization: FS

Methodology: HR, AJ

Formal analysis: HR, SP, SA

Writing and Drafting: FS, SP, AJ, UM

Review and Editing: HR, FS, SP, AJ, UM, SA, AJ

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



## Frequency of Giardiasis in Children Presenting with Chronic Diarrhea

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## ABSTRACT

Giardiasis, caused by *Giardia duodenalis*, is a common enteric protozoan infection in children, particularly in low-resource settings. It may present with chronic diarrhea, weight loss, and dehydration, though many infections remain asymptomatic. **Objectives:** To determine the frequency of giardiasis among children aged 1 to 5 years presenting with chronic diarrhea. **Methods:** This cross-sectional study was conducted in the Department of Paediatrics, Khyber Teaching Hospital, Peshawar, over six months. A total of 203 children with chronic diarrhea were enrolled using non-probability consecutive sampling. Stool samples were examined by direct microscopy with saline and Lugol's iodine staining, as well as formalin-ethyl acetate concentration. Giardiasis was diagnosed based on the presence of six or more cysts per coverslip at 40× magnification. Written informed consent was obtained from all parents/guardians. The study received ethical approval from the institutional review board (IRB Approval No: 935/DME/KMC). **Results:** Out of 203 children, 20 (9.9%) tested positive for *Giardia duodenalis*. No significant associations were found with age, gender, or weight. However, a statistically significant correlation was observed between giardiasis and duration of diarrhea. Children with symptoms lasting more than eight weeks had a higher prevalence (24.1%) compared to those with shorter duration (0.8%) ( $p=0.001$ ). **Conclusions:** Prolonged diarrhea may be a clinical indicator of giardiasis in paediatric patients. Early detection and improved diagnostic methods are essential for timely treatment, especially in endemic areas with limited resources.

## INTRODUCTION

*Giardia duodenalis*, sometimes referred to as *G. intestinalis* or *G. lamblia*, is the enteric protozoan that causes giardiasis. Flatulence and watery diarrhea are common symptoms, especially in children from low-resource homes. Cases are mostly documented among foreign visitors, outdoor explorers, and childcare providers in high-income nations like the US. Even while the illness is frequently asymptomatic, in those who do have symptoms, it can lead to serious morbidity, such as weight loss and dehydration. Nitroimidazole or other antiparasitic treatment usually works well and causes symptoms to go away quickly [1, 2]. The parasite spreads when cysts released by infected hosts contaminate water supplies. These cysts are long-lived in freshwater and immediately

become infectious upon excretion. Of the seven known genetic assemblages (A-G), only A and B are associated with human infection [3, 4]. Direct contact between people or the ingestion of contaminated water, particularly in unhygienic environments like daycare facilities, might facilitate the transmission of infection. When changing diapers, poor hand hygiene is one of the primary culprits in these situations. After consumption, the cysts excyst in the small intestine, releasing the pear-shaped, dual-nucleated motile trophozoites. Despite the wide variation in clinical presentation, over half of infected patients do not exhibit any symptoms. Within 1-2 weeks of infection, symptoms typically include gas, bloating, nausea, abdominal pain, and thick, greasy, foul-smelling feces. In addition to mild



diarrhea, children may experience stomachaches. Dehydration is common due to fluid loss. A study by Jethwa et al. found that 5% of kids with persistent diarrhea had a *Giardia* infection [5]. Mumtaz et al. however, discovered a prevalence of 25.3% in a similar cohort [6]. These discrepancies underscore the ongoing clinical and epidemiologic uncertainty regarding the role of *Giardia duodenalis* as a pathogenic cause of chronic diarrhea. Considering the disease's worldwide prevalence, this ambiguity is particularly serious. The World Health Organization (WHO) considers *Giardia* a neglected tropical illness, with an estimated 280 million infections per year and extended carriage in afflicted children, typically lasting more than six months [3]. The parasite is a chronic public health concern due to its environmental resilience, low infectious dosage (as little as 10 cysts), and dual transmission potential via people and animals [2, 6]. Foodborne outbreaks from contaminated seafood and leafy greens, clusters related to childcare, and seasonal surges associated with recreational water use have all been documented in resource-rich nations [3, 5]. Previous studies report highly variable prevalence of giardiasis in children with chronic diarrhea, and local data from Pakistani pediatric populations remain limited and inconsistent. In addition, many studies focus on acute diarrhea or asymptomatic infections rather than prolonged diarrheal cases and their clinical predictors. There is also insufficient evidence exploring the relationship between duration of diarrhea and confirmed Giardiasis using standardized diagnostic criteria. Therefore, this study addresses the need for region-specific data to clarify the frequency and clinical indicators of giardiasis among young children presenting with chronic diarrhea. This study aims to ascertain the prevalence of *Giardia duodenalis* infection in children who present with chronic diarrhea, taking into account the inconsistent epidemiological results and clinical ambiguity shown in previous investigations.

## METHODS

This cross-sectional study was conducted at the Department of Paediatrics, Khyber Teaching Hospital in Peshawar. The study was conducted between November 1, 2024, and May 1, 2025. The study received ethical approval from the institutional review board (IRB Approval No: 935/DME/KMC). The study involved 203 children in total. With a 95% confidence interval, a 3% margin of error, and an expected frequency of giardiasis of 5% based on prior research, the sample size was calculated using the WHO sample size calculator. Rephrased scientifically. Every child who met the inclusion criteria during the study period was recruited until the required sample size was reached using non-probability, consecutive sampling. Written informed consent was obtained from all parents or

guardians of participating children before inclusion in the study. Particular inclusion and exclusion criteria were used in the selection of participants. Children of either gender, aged 1 to 5, who had chronic diarrhea defined as having stool frequency of  $\geq 3$  times per day sustained for  $\geq 4$  weeks, were eligible. A history of hepatitis, respiratory infections, lactose intolerance, or the inability to produce a stool sample for analysis were among the exclusion criteria. Enrolment was limited to children who met all inclusion requirements and none of the exclusion criteria. Data collection started in the outpatient department following ethical approval. All participating children's parents or guardians provided written informed consent. Age, gender, weight, and the length of diarrhea were among the baseline demographic data that were documented. Parents or guardians received instructions on how to properly collect stool samples. To ensure an adequate sample for analysis, parents of children under two years old were recommended to use the nappy in reverse to prevent absorption of the faecal matter. Youngsters over two were instructed on how to gather the sample in a sterile container. All samples were promptly delivered to the laboratory for microscopic examination. Light microscopy was used to examine stool samples using Lugol's iodine staining, and direct saline smears were performed. The presence of protozoan cysts was further confirmed using the formalin-ethyl acetate concentration technique. According to the operational criteria, which required six or more *Giardia* cysts per coverslip to be inspected at 40 $\times$  magnification, Giardiasis was identified. On a specially created proforma, the results were recorded.

To analyse the data, IBM-SPSS version 20 was used. Frequencies and percentages were used to represent categorical characteristics like gender and Giardiasis presence. Means and standard deviations were used to analyse quantitative data such as age, weight, and length of diarrhea. To evaluate any correlations or patterns within subgroups, giardiasis was stratified by age, gender, and length of diarrhea.

## RESULTS

A total of 203 children with chronic diarrhea who were between the ages of 1 and 5 were included in this study. Participants' average diarrhea length was  $8.02 \pm 2.18$  weeks, and their average age was  $2.76 \pm 1.01$  years. The recorded mean weight was  $11.11 \pm 1.55$  kg. Of the patients who were enrolled, 72 (35.5%) were female, and 131 (64.5%) were male. Twenty (9.9%) of the 203 patients had a *Giardia duodenalis* infection, whereas 183 (90.1%) did not have the parasite. Despite the fact that females had a higher percentage of giardiasis (11.1%) than males (9.2%), this difference was not statistically significant ( $p=0.655$ ) (Table 1).

**Table 1:** Demographic Characteristics and Frequency of Giardiasis(n=203)

Variables	Mean ± SD / n (%)
Age (years)	2.76 ± 1.01
Duration of Diarrhea (weeks)	8.02 ± 2.18
Weight (kg)	11.11 ± 1.55
Gender (Male)	131 (64.5%)
Gender (Female)	72 (35.5%)
Giardiasis Positive	20 (9.9%)
Giardiasis Negative	183 (90.1%)

Giardiasis was slightly more common in children older than 3 years (14.3%) than in those younger than 3 years (8.7%), although the difference was not statistically significant ( $p=0.279$ ). With a positive rate of 11.3% in children weighing more than 10 kg and 7.6% in those weighing less than 10 kg ( $p=0.389$ ), weight-based stratification likewise did not reveal any significant correlation (Table 2).

**Table 2:** Stratification of Giardiasis by Demographic Variables

Variables	Subgroup	Giardiasis (+)	Giardiasis (-)	p-value
Age	1-3 Years	14 (8.7%)	147 (91.3%)	0.279
	>3 Years	6 (14.3%)	36 (85.7%)	
Gender	Male	12 (9.2%)	119 (90.8%)	0.655
	Female	8 (11.1%)	64 (88.9%)	
Weight	≤10 kg	6 (7.6%)	73 (92.4%)	0.389
	>10 kg	14 (11.3%)	110 (88.7%)	

Nonetheless, a statistically significant correlation between the length of diarrhea and giardiasis was discovered. Giardiasis was much more common in children whose diarrhea lasted longer than 8 weeks (24.1%) than in those whose diarrhea lasted between 4 and 8 weeks (0.8%) ( $p>0.001$ ). This implies that lengthier diarrheal episodes could be a significant sign of a paediatric *Giardia* infection. These findings emphasize the need to consider giardiasis in children presenting with prolonged diarrhea, even in the absence of significant weight or age-related trends (Table 3).

**Table 3:** Stratification of Giardiasis by Duration of Diarrhea

Duration of Diarrhea	Giardiasis (+)	Giardiasis (-)	p-value
4-8 Weeks	1 (0.8%)	123 (99.2%)	<0.001
>8 Weeks	19 (24.1%)	60 (75.9%)	

## DISCUSSION

Children with chronic diarrhea have a significant prevalence of *Giardia duodenalis* infection, according to this cross-sectional study, highlighting the pathophysiology of chronic gastrointestinal illness in this population. After three weeks of treatment, a considerable proportion of patients were still infected even though metronidazole was administered at the recommended dosage for children. Several reasons could be responsible

for this treatment failure, such as the quick reinfection brought on by close contact with other infected people in hospital settings [7] or the compromised immune responses frequently seen in undernourished children with chronic diarrhea and protein-energy malnutrition [8]. Indeed, prior research has documented recurring or persistent giardiasis in immunocompromised persons, especially those with weakened cell-mediated immunity [9]. Half of the children in our cohort who tested positive for giardiasis were not underweight, despite the fact that malnutrition is known to be a contributing factor to chronic giardiasis. However, several host defenses, including the release of stomach acid, can be compromised by starvation. Giardiasis is frequently linked to conditions like hypochlorhydria and achlorhydria, which can promote both the original infection and reinfection [10]. *Helicobacter pylori* co-infection, which is known to lower stomach acid levels and may lead to persistence or reinfection with *Giardia*, has also been linked to giardiasis [11, 12]. More research is necessary to determine whether eliminating *H. pylori* could lower the risk of giardiasis recurrence. Diagnostic methods and population selection have an impact on the variation in the background prevalence of giardiasis among children in low-resource settings who do not exhibit symptoms. Higher dosages or longer treatment periods, such 35 mg/kg/day for 10 days, would have been more beneficial even though we followed a typical metronidazole protocol. To improve outcomes for children with chronic giardiasis, it is important to investigate the effectiveness of an initial eradication strategy and the possible advantages of retreatment following nutritional rehabilitation. *Giardia* is endemic in many low-income areas, and almost all children are exposed to it, but not all of them develop symptoms [13]. Only the first infections in babies or children who have just been exposed (such as creche participants or tourists) usually cause acute diarrhea, whereas reinfections are usually asymptomatic because of partial immunity. However, persistent and severe forms of giardiasis are more common in malnourished children, especially those with underlying nutritional deficits [14]. Stunted growth, poor cognitive development, and severe nutritional status worsening can result from these infections [15-17]. *Giardia* trophozoites cause chronic intestinal injury and enduring symptoms by damaging villi, upsetting the intestinal epithelium, and possibly avoiding immune clearance through antigenic variation [18, 19]. Specific immunological weaknesses, including hypogammaglobulinemia, are significantly linked to chronic infection, even though overall immunosuppression does not always increase susceptibility, as demonstrated by its relatively low occurrence in HIV or chemotherapy patients [20]. Young children's adaptive immune system immaturity is probably

a major contributing cause to the greater incidence of Giardiasis symptoms following initial exposure.

Future studies should include multicenter designs with larger sample sizes and incorporate advanced diagnostic methods such as antigen detection or PCR to improve accuracy. Longitudinal research is also recommended to evaluate treatment outcomes, reinfection rates, and the role of nutritional status in chronic giardiasis among children. There are several restrictions on this study. The results might not apply to larger populations because the study was conducted at a single location and had a small sample size. Selection bias may be introduced when non-probability sampling is used. Furthermore, compared to more sophisticated molecular approaches, the sensitivity of relying solely on microscopy for diagnosis may be limited.

## CONCLUSIONS

The study found a high prevalence of *Giardia duodenalis* in children with chronic diarrhea lasting over eight weeks. Diarrhea duration was a key indicator, while age, gender, and weight showed no significant correlation. Metronidazole often failed to fully clear the infection, possibly due to reinfection or immune issues in underweight children. Early diagnosis and improved treatment strategies are critical in endemic, resource-limited areas.

## Authors' Contribution

Conceptualization: MHA

Methodology: MHA, W

Formal analysis: MHA, W

Writing and Drafting: MLK, MHA, MI, SK, W

Review and Editing: MLK, MHA, MI, SK, W

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

## Comparison of the Effectiveness of Palonosetron and Dexamethasone to Prevent Postoperative Nausea and Vomiting in Patients Undergoing Uncomplicated Laparoscopic Cholecystectomy

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## ABSTRACT

Postoperative nausea and vomiting (PONV), particularly in patients having laparoscopic cholecystectomy, continues to be a prevalent and distressing consequence after surgical operations. It leads to higher hospital stays and resource utilization, as well as patient dissatisfaction. PONV occurrences have been linked to a range of patient-specific, anesthesia- and surgery-related risk factors. **Objectives:** To determine the effectiveness of palonosetron compared to dexamethasone in preventing PONV in patients undergoing a laparoscopic cholecystectomy operation (uncomplicated). **Methods:** It was a quasi-experimental study that was conducted in the Department of Anesthesiology, Sir Ganga Ram Hospital, Lahore. The inclusion and exclusion criteria were met, and after that, 108 candidates were included and categorized into 2 groups. In patients of group A, 54 patients received 0.075mg Palonosetron (diluted in 5cc distilled water) intravenously in a single dose. In patients of group B, another 54 patients received 8mg dexamethasone intravenously. **Results:** Most of the patients included were female (66.7%), and the mean age of patients was  $52.82 \pm 8.80$  years. When compared, the efficacy of both the drugs for PONV using the chi-square test (significant  $p$ -value  $> 0.005$ ) showed that only 20 cases (37.0%) of the group palonosetron suffered from PONV. While 42 patients (77.8%) of the dexamethasone group suffered from PONV ( $p$ -value  $< 0.001$ ). This showed that Palonosetron is clearly a superior drug in terms of efficacy as compared to dexamethasone. **Conclusions:** This study concluded that palonosetron is more effective than dexamethasone in preventing PONV in patients undergoing uncomplicated laparoscopic cholecystectomy.

## INTRODUCTION

In laparoscopic surgeries, nausea and vomiting are the most frequently occurring postoperative complications after pain. Its consequences are delayed recovery, prolonged hospital stay, i.e., in the Post Anesthesia Care Units, pulmonary aspiration, wound dehiscence, electrolyte imbalance, dehydration, greater perception of pain, and esophageal rupture [1]. It has an incidence of 30% in all postoperative surgical cases, with the exception of high-risk cases in which it rises to 80% [2]. The female

gender, nonsmoking, obesity, and use of post-op opioids are common risk factors. Extended surgical duration is a significant contributing factor to postoperative nausea and vomiting (PONV) risk [3]. Laparoscopic surgeries like laparoscopic cholecystectomy require carbon dioxide insufflation, which causes distension of the peritoneum and dilates the intestinal loops. This distension triggers the gut wall's mechanoreceptors, leading to a surge in serotonin production. This elicits the chemoreceptor

trigger zone (CTZ) in the medulla, which receives vagal afferents from various parts of the body and produces emesis. The incidence of PONV ranges from 40% to 75% in laparoscopic surgeries without any antiemetic prophylaxis [4]. Drugs used to treat PONV include 5-Hydroxytryptamine antagonists such as ondansetron, Anticholinergics such as scopolamine, Histamine antagonists such as Dimenhydrinate, meclizine, etc. Dopamine antagonists such as Domperidone, metoclopramide, etc. Neurokinin antagonists like Aprepitant and corticosteroids such as dexamethasone [5]. Khan et al. affirmed that Dexamethasone is an effective antiemetic when used during anesthesia induction. Its mode of action is unfamiliar, but it is most likely to be the central blocking of the production of prostaglandins and result in the reduction of serotonin turnover in the central nervous system. It causes the stimulation of glucocorticoid receptors in the medulla and suppresses the synthesis of prostaglandins. It also prevents the emission of endogenous opioids [6]. Dexamethasone is very cheap [7]. It is a corticosteroid that has long-acting properties, and its half-life is 36-72 h [8]. Palonosetron is a 5-HT<sub>3</sub> receptor antagonist that has the highest receptor-binding affinity. It lasts half-life of 40h, and its slow excretion by the body eliminates PONV to a range of 48h [9]. Srivastava and colleagues in 2016 concluded that the combination of these two antiemetics doesn't significantly decrease PONV incidence in laparoscopic surgeries as compared to drugs alone (24.4% vs. 22.2%) [10]. A study done by Kim et al. included only female patients, while we will study drug efficacy in both genders. Similarly, there are a few studies done on the comparison of these two drugs alone [9].

In Pakistan, there are few comparative studies to assess the effectiveness of various antiemetic drugs to prevent postoperative nausea and vomiting (PONV), especially in laparoscopic cholecystectomy patients. The available literature presents contradicting results, and there has been a lack of local studies comparing palonosetron to dexamethasone. Postoperative nausea and vomiting is a frequent and uncomfortable problem that happens after laparoscopic surgeries, and it results in delayed recovery and high cost of health care. Nevertheless, it is still unclear which prophylactic drug is the best agent in preventing its occurrence in clinical practice. This study aimed to compare the efficacy of Palonosetron and Dexamethasone to prevent PONV, as very few studies are available in Pakistan, and due to conflicts in the conclusions of the literature reviews mentioned above.

## METHODS

This quasi-experimental study was conducted in the Department of Anesthesia, Sir Ganga Ram Hospital, Lahore, over a period of one year (November 2022 to

November 2025) following synopsis approval (20-MS-Anesthesia/IRB). 108 patients were included, with 54 patients in each group, based on clinician allocation. The sample size was calculated assuming an expected PONV incidence of 27.2% in the palonosetron group versus 56.1% in the dexamethasone group, with 95% confidence, 80% power, and a 20% anticipated dropout rate [2]. After taking the written informed consent, the patients aged 40-70 years, with ASA physical status I-II and BMI <35 kg/m<sup>2</sup>, were included. Patients were excluded if they had a history of nausea, vomiting, or motion sickness, were pregnant or lactating, had a BMI >35 kg/m<sup>2</sup>, ASA III-IV, allergy to study drugs, prior use of medications affecting PONV, immunocompromised status, complicated cholecystitis, nasogastric tubes, or refused to participate. Baseline assessment included age, gender, and BMI, and patients were kept nil per OS for 8 hours before surgery. Study drugs were administered one hour before induction of anesthesia, with the palonosetron group receiving 0.075 mg intravenously diluted in 5 mL distilled water, and the dexamethasone group receiving 8 mg intravenously. Standard intraoperative monitoring included ECG, noninvasive blood pressure, nasopharyngeal temperature, and pulse oximetry, with Ringer's lactate infusion initiated upon arrival to the operating room. Premedication consisted of midazolam 0.2 mg/kg IV, followed by induction with nalbuphine 0.1 mg/kg and propofol 2 mg/kg. Atracurium (0.5mg/kg) was used to attain neuromuscular blockade and an endotracheal tube was inserted into the patient with the correct endotracheal tube. Controlled ventilation of 1.2% MAC isoflurane in 50% oxygen and 50% nitrous oxide was used, and end-tidal CO<sub>2</sub> followed. Acetaminophen 15mg/kg was used as intraoperative analgesia, and neostigmine 0.04mg/kg and glycopyrrolate 10 µg/kg were used to reverse residual paralysis. The analgesia was postoperative IV paracetamol 1 g in 6h and ketorolac 30 mg in 6h IV as required. The main finding of the given research was the development of PONV during the first 6 hours of the surgical procedure. PONV was used to be characterized as an incidence of nausea, retching (involuntary vomiting), or vomiting (emergence of gastric contents). Complete response was defined as the absence of PONV without the need to use rescue antiemetic treatment. IV administration of metoclopramide 10mg was also administered as a rescue antiemetic. The intensity of PONV in the first 6 hours postoperatively was measured using a PONV scoring system in which a score of 1-4 was considered clinically important concerning PONV, and a score of 0 represented no PONV [11]. Structured forms were used to gather data. SPSS version 26.0 has been applied to analyze the data, where quantitative variables are in the form of mean and standard deviation, and qualitative variables are in the form of frequency and

percentage. Chi-square test/Fisher Exact Test of categorical variables and t-test of continuous variables, using the assistance of Mann-Whitney U test (non-normally distributed data with the help of Shapiro wilk test), were used to compare the palonosetron versus dexamethasone group with a p-value of 0.005 as the significant value.

## RESULTS

The average age of patients was  $52.82 \pm 8.81$  years, and the mean BMI was  $32.42 \pm 2.97$  kg/m<sup>2</sup>, which indicates a middle-aged cohort with moderately high body mass. Most of the respondents were women (66.7 percent), and males made up 33.3 percent of the sample population. Physical status: 72.2 percent of the patients were of the type ASA I, and 27.8 percent were of the type ASA II, which indicates that the majority of the participants were generally healthy with mild systemic disease, which was a smaller percentage (Table 1).

**Table 1:** Clinical and Demographics of Patients

Variables	Category	n (%)	Mean $\pm$ SD
Age	Years	108	52.82 $\pm$ 8.81
BMI (kg/m <sup>2</sup> )	–	108	32.42 $\pm$ 2.97
Gender	Female	72	66.7
	Male	36	33.3
ASA Score	I	78 (71.2%)	–
	II	30 (2.8%)	–

A significantly lower rate of PONV was observed in the palonosetron group (37.0%) relative to the dexamethasone group (77.8%) ( $p < 0.001$ ), demonstrating superior prophylactic efficacy. The need for rescue antiemetic therapy was also markedly lower in the palonosetron group across all postoperative intervals, with only 14.8% requiring intervention in the first 1–2 hours and none in the 3–6-hour periods. In contrast, dexamethasone-treated patients had a higher and more prolonged need for rescue therapy, with 59.3% at 1–2 hours, 61.1% at 3–4 hours, and 14.8% at 5–6 hours (all  $p < 0.005$ ). These results indicate that palonosetron is more effective than dexamethasone in preventing early PONV and reducing reliance on rescue antiemetics following laparoscopic cholecystectomy (Table 2).

**Table 2:** Comparison of PONV and Need for Rescue Antiemetic in Study Groups

Parameter	Palonosetron (n=54)	Dexamethasone (n = 54)	p-value
<b>Incidence of PONV</b>			
Yes	20 (37.0%)	42 (77.8%)	<0.001*
No	34 (63.0%)	12 (22.2%)	
<b>Need for Rescue Antiemetic</b>			
1–2 h	8 (14.8%)	32 (59.3%)	<0.001*
3–4 h	0 (0.0%)	33 (61.1%)	<0.001*
5–6 h	0 (0.0%)	8 (14.8%)	0.003*

\*Independent sample t-test

The mean PONV scores were consistently lower in the palonosetron group compared with the dexamethasone group across all postoperative intervals. At 1–2 hours, the palonosetron group had a mean score of  $0.43 \pm 0.63$  versus  $1.33 \pm 1.20$  in the dexamethasone group ( $p < 0.001$ ). At 3–4 hours, palonosetron-treated patients had no PONV ( $0.00 \pm 0.00$ ), and the dexamethasone group had a mean score of  $0.74 \pm 0.78$  ( $p < 0.001$ ). On the same note, the palonosetron group showed no PONV at 5–6 hours ( $0.00 \pm 0.00$ ) as opposed to the dexamethasone group that had a mean of  $0.26 + 0.71$  ( $p < 0.001$ ). Such results suggest that palonosetron gives much better control of postoperative nausea and vomiting at any given time interval after laparoscopic cholecystectomy, which is more effective in prophylaxis than dexamethasone (Table 3).

**Table 3:** Comparison of Mean PONV Scores Between Study Groups

Time Interval	Group	Mean $\pm$ SD	p-value
1–2 Hours	Palonosetron	0.43 $\pm$ 0.63	<0.001*
	Dexamethasone	1.33 $\pm$ 1.20	
3–4 Hours	Palonosetron	0.00 $\pm$ 0.00	<0.001*
	Dexamethasone	0.74 $\pm$ 0.78	
5–6 Hours	Palonosetron	0.00 $\pm$ 0.00	<0.001*
	Dexamethasone	0.26 $\pm$ 0.71	

\*Independent sample t-test

## DISCUSSION

The present study was done on the comparison of the efficacy of palonosetron and dexamethasone in preventing postoperative PONV in patients who have already undergone laparoscopic cholecystectomy without any complications. Palonosetron is a selective 5-HT<sub>3</sub> receptor antagonist that has demonstrated favorable propensity in inhibiting nausea and vomiting by means of central effects and peripheral effects, and the half-life is lengthy, approximated to 40 hours [12–14]. Conversely, dexamethasone, a corticosteroid, an anti-inflammatory and antiemetic agent, is a common PONV prophylaxis agent [14, 15]. The mean age of the participants in this study was 52.82280 years, with the majority being female (66.7%), which is similar to other past surveys like Chatterjee *et al.* where the mean age was 43.5711.74 years and females made up the majority. PONV was observed to be very low in the palonosetron group (37%) as compared to the dexamethasone group (77.8%). In the case of Chatterjee *et al.* it was 27.2% in the palonosetron group and 56.14% in the dexamethasone group [2]. On the same note, rescue antiemetics were also necessary to a much lower degree in the palonosetron group, with only 8 patients (14.8%) requiring treatment in the first 1–2 hours postoperatively and no patients requiring intervention

from 3–6 hours, whereas dexamethasone-treated patients showed a higher and more prolonged requirement. Previous studies have also demonstrated that combination therapy of palonosetron with dexamethasone (PD) can further reduce PONV rates compared to either drug alone. As an example, a study has indicated that PD was found to reduce PONV both in the initial 24–48 hours of the postoperative period and decrease the use of rescue antiemetics in comparison to dexamethasone [16]. Although our research was not an evaluation of combination therapy, these findings suggest it might be feasible to employ this strategy in high-risk countries of PONV. In line with our observation, Gupta et al. observed that palonosetron was more potent than other 5-HT<sub>3</sub> antagonists in managing PONV, with a response rate of 90 percent in all patients [17]. Other studies comparing palonosetron with granisetron demonstrated similar efficacy in preventing early PONV but showed superior prevention of late-onset nausea (2–48 hours) with palonosetron, likely due to its longer half-life and faster onset of action [18]. Dexamethasone is not as effective as palonosetron, but has been demonstrated to be as effective as ondansetron in PONV reduction in some surgery procedures, including pediatric strabismus repair, indicating it can be used as an alternative when palonosetron is not available [19]. Nevertheless, randomized trials comparing palonosetron with other such combinations like ondansetron plus dexamethasone or metoclopramide plus dexamethasone have continued to demonstrate palonosetron as a single agent to be a better PONV control and rescue antiemetic agent [20, 21]. In general, current results support the high-level of effectiveness of palonosetron over dexamethasone in the effectiveness of prophylaxis of PONV in patients after laparoscopic cholecystectomy. Palonosetron should be viewed as the agent of first choice due to its increased length of action, lower rates of PONV, and lower rates of antiemetic rescue use, but combination treatment should be used in high-risk situations where an agent alone might not be effective.

The quasi-experimental design applied in the research was not completely randomized and this can create selection bias. It was also a single-center study with a small sample size, which decreases the generalizability. Besides, short-term results (within the initial 6 hours after the operation) were evaluated. Randomized controlled trials using larger multi-center samples should be used in future research to enhance reliability. Long-term results should also be evaluated and combination therapy of antiemetics should be tested to improve the prevention of PONV.

## CONCLUSIONS

To sum up, this thesis offers profound information in regard to the efficiency of Palonosetron and Dexamethasone in

the prevention of PONV among patients who undergo uncomplicated Laparoscopic Cholecystectomy. The evidence provided herein lends credence to the fact that Palonosetron is by far better than Dexamethasone in lowering the occurrence of PONV. The clinical implications of these findings are immense because an effective PONV prophylaxis will result in better patient outcomes, a higher degree of satisfaction, and a decrease in healthcare expenditure. Hopefully, this research will also add to the existing literature in the area of anesthesia and perioperative care, which will eventually enable healthcare providers to make informed decisions when choosing the most relevant antiemetic regimen when employing uncomplicated Laparoscopic Cholecystectomy in patients.

## Authors' Contribution

Conceptualization: SA, SZA, YS

Methodology: SA, SZA, YS, AI

Formal analysis: SZA, YS

Writing and Drafting: MTC, FH

Review and Editing: SA, SZA, YS, MTC, AI

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



## Diagnostic Accuracy of Point of Care Ultrasound (POCUS) for Diagnosing Neonatal Pneumothorax Keeping Chest X-ray as Reference Standard

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## ABSTRACT

Neonatal pneumothorax needs immediate medical assessment because it poses a danger to life. Neonates face radiation risks from chest X-ray (CXR), which physicians frequently use, but it creates treatment delays. Point-of-care ultrasound (POCUS) offers a rapid, bedside, radiation-free alternative. **Objective:** To assess how accurately POCUS detects neonatal pneumothorax compared to CXR, which serves as the standard reference. **Methods:** The descriptive, cross-sectional study took place in the Combined Military Hospital's Neonatal Intensive Care Unit from October to December 2025 after researchers obtained permission through ethical approval (Ref No. 576/2024). The study enrolled one hundred neonates who were 28 days old or younger and showed clinical signs of pneumothorax. A trained radiologist performed bedside POCUS using a high-frequency linear probe. A radiologist who remained blinded to the study read the CXR results. Researchers computed sensitivity, specificity, PPV, NPV, and overall accuracy together with ROC-AUC values. **Results:** CXR confirmed pneumothorax in 35 neonates. POCUS showed sensitivity 91.6%, specificity 93.75%, PPV 89.18%, NPV 95.2%, and overall diagnostic accuracy 93%. The AUC measurement reached 0.93 while the 95% confidence interval ranged from 0.87 to 0.97. **Conclusion:** POCUS provides high diagnostic accuracy which makes it an effective NICU screening tool for detecting neonatal pneumothorax.

## INTRODUCTION

Neonatal pneumothorax (NP) is a critical condition that can lead to the death of the newborn and it has a global incidence of 0.05-2% in newborns and up to 9% in preemies that are extremely immature [1, 2]. The occurrence of NP in neonatal intensive care units (NICUs) is about 1-2%, but it is higher in babies on mechanical ventilation and having respiratory distress syndrome (RDS) [3]. In Pakistan and the neighboring countries, the rate of NP among NICU-admitted patients is approx. 0.8-1.02%, mostly seen in preterm boys with low Apgar scores [4, 5]. The standard radiological procedure, that is, chest X-ray (CXR), is the most sensitive and specific method for NP diagnosis, but it

also has the disadvantage of exposing babies to ionizing radiation and delaying diagnosis in places where resources are limited. POCUS, i.e., point-of-care ultrasound, at the bedside presents a way of detecting NP that is free from radiation and is at the same time superior in sensitivity (98%) and specificity (99%) to CXR (82% and 96%) in neonates. Meta-analyses have indicated POCUS pooled sensitivity of 74-98% and specificity exceeding 93% against CXR, while faster performance fits well with NICUs [6, 7]. This is a descriptive cross-sectional study that plans on evaluating the accuracy of POCUS by taking CXR as the reference in Pakistani neonates.



Nevertheless, there are not enough local data available about its effectiveness in the neonatal population in Pakistan, where resource scarcity and delayed imaging are the norm. The study hypothesized that point-of-care ultrasound technology would achieve the same level of diagnostic accuracy as chest X-ray for detecting neonatal pneumothorax. The device can function as an effective first evaluation tool for NICU patients. Thus, this study aims to evaluate the diagnostic accuracy of POCUS in comparison with chest X-ray, with the intention of supporting the evidence-based utilization of POCUS for the early and efficient diagnosis in neonatal intensive care units.

## METHODS

This descriptive, cross-sectional study was conducted in the Combined Military Hospital Neonatal Intensive Care Unit, Lahore, Pakistan, from October 2025 to December 2025, following ethical approval, No 576/2024. The sample size was calculated using the diagnostic accuracy formula for sensitivity estimation:  $n = (Z^2 \times Se(1 - Se)) / (d^2 \times P)$ . Where:  $Z = 1.96$  (95% confidence level). Expected sensitivity ( $Se$ ) = 0.90 (based on previous neonatal ultrasound studies). Absolute precision ( $d$ ) = 0.08. Estimated prevalence ( $P$ ) of neonatal pneumothorax in NICU = 0.35 (35%, based on anticipated suspected cases). The calculated minimum sample size was 94 neonates. After adjusting for possible incomplete data, a total of 100 neonates were enrolled [8]. The sample size was then rounded up to cover possible data loss and incomplete evaluations; finally, a total of 100 neonates with suspected pneumothorax were included in the study. Non-probability consecutive sampling was the technique chosen because neonatal pneumothorax is a critical but not very common emergency that needs to be evaluated without delay. Through this method, all the newborns who were eligible and showed signs of having a pneumothorax were admitted during the study period, which helped in quick recruitment without postponing treatment. Neonates aged  $\leq 28$  days with clinical signs suggestive of pneumothorax (e.g., respiratory distress, decreased breath sounds, chest asymmetry) were considered eligible after parental consent was obtained. Neonates with contraindications to ultrasound (e.g., severe skin conditions), a history of pneumothorax requiring surgical intervention, or severe comorbidities affecting the accuracy of ultrasound or chest X-ray (CXR) were excluded. Eligible neonates were enrolled after informed consent was obtained from parents or legal guardians. Privacy and confidentiality were ensured. POCUS was performed by trained radiologists using a GE LOGIQ P9 ultrasound system fitted with a 7–12 MHz high-frequency linear transducer. The chest was scanned in anterior, lateral, and subcostal views.

Pneumothorax was assessed by the presence of a lung point or by the combined absence of lung sliding and B-lines. Findings were documented on a predesigned proforma. Standard anteroposterior (AP) and lateral CXR images were obtained, and pneumothorax was diagnosed by visualization of the visceral pleural line along with absence of peripheral lung markings. All radiographs were interpreted by a radiologist blinded to POCUS findings. Pneumothorax diagnosis was confirmed by an expert consultant radiologist with at least 10 years of experience. Operator's knowledge, device's standard, and clinical stability of newborns were taken into account. A highly skilled consultant radiologist carried out all ultrasound examinations using machines produced in the last five years. Only those newborns whose condition was stable in hemodynamic terms underwent scans. All ultrasound tests were conducted by superior radiologists with recognized postgraduate diplomas in radiology and at least five years of practice in the area of neonatal and pediatric imaging. The readers of the radiological images had the benefit of prior training in point-of-care lung ultrasound, were accustomed to the standard diagnostic criteria for neonatal pneumothorax, and were unaware of each other's findings in order to maintain objectivity and reproducibility in the results. The data were gathered through a structured proforma that was used to record the demographic data, clinical signs, and POCUS and CXR findings. The patients' confidentiality was secured. Two different radiologists of the consultant level were hired: one to perform all POCUS and the other to interpret all CXRs. They were not aware of each other's results.

The accuracy of POCUS diagnosis was computed through SPSS version 23.0. The analyses carried out resulted in a combination of descriptive, comparative, and diagnostic accuracy analyses. The analysis of variables involved demographic variables (age in days, gender), perinatal variables (gestational age in weeks, birth weight in kilograms), and clinical variables (respiratory distress, decreased breath sounds, chest asymmetry), among others. The variables related to imaging included POCUS findings (loss of lung sliding, absence of B-lines, lung point) and chest X-ray features (visceral pleural line, absence of peripheral lung markings). The comparative analysis was performed using independent sample t-tests and chi-square tests. The variables for diagnostic accuracy consisted of sensitivity, specificity, PPV, NPV, and overall accuracy. ROC curve analysis was used to assess the diagnostic performance of POCUS. The area under the curve (AUC) with 95% confidence intervals was calculated using SPSS version 23.0. The optimal cutoff point was determined using the Youden index (sensitivity + specificity – 1).

## RESULTS

Out of the total of 100 neonates that were selected for the study, 35 had pneumothorax, and 65 did not. The average ages of both groups were practically the same, with pneumothorax ( $14.33 \pm 6.64$  days) and without pneumothorax ( $14.36 \pm 6.06$  days;  $p=0.710$ ). The male/female ratio was also found to be similar in both groups (22/13 vs. 36/29 male/female;  $p = 0.680$ ). The researchers did not find any significant difference in the mean gestational age ( $35.74 \pm 2.41$  vs.  $36.9 \pm 3.17$  weeks;  $p=0.420$ ) or in the birth weight ( $2.50 \pm 0.52$  vs.  $2.48 \pm 0.67$  kg;  $p=0.530$ ). Respiratory distress was a common condition in both groups (100% vs. 93.8%;  $p=0.130$ ). Decreased breath sounds (85.7% vs. 15.4%;  $p<0.001$ ) and chest symmetry (42.8% vs. 6.2%;  $p<0.001$ ) were two symptoms that occurred much more frequently among the neonates suffering from pneumothorax (Table 1).

**Table 1:** Baseline Demographic and Clinical Characteristics of Neonates with and without Pneumothorax (n=100)

Variables	Pneumothorax Present, (n=35)	Pneumothorax Absent, (n=65)	p-value
Days	14.33 ± 6.64	14.36 ± 6.06	0.710
<b>Gender</b>			
Male	22	36	0.680
Female	13	29	
<b>Others</b>			
Gestational Age (weeks)	35.74 ± 2.41	36.9 ± 3.17	0.420
Birth Weight (kg)	2.50 ± 0.52	2.48 ± 0.67	0.530
<b>Respiratory Distress</b>			
Yes	35 (100%)	61 (93.8%)	0.130
No	0 (0%)	5 (6.2%)	
<b>Decreased Breath Sounds</b>			
Yes	30 (85.7%)	10 (15.4%)	<0.001*
No	5 (14.3%)	55 (84.6%)	
<b>Chest Asymmetry</b>			
Yes	15 (42.8%)	4 (6.2%)	<0.001*
No	20 (57.2%)	61 (93.8%)	

Independent sample tests for continuous and chi-square tests for categorical variables \*Statistically significant at  $p \leq 0.05$ \*

In neonates diagnosed with pneumothorax through POCUS, the most common finding was the loss of lung sliding, which was seen in 30 cases (90.9%), and then the absence of B-lines in 28 cases (84.8%). The lung point, the most specific sonographic sign, was seen in 24 neonates (72.7%). The most common radiographic feature in chest X-ray was the visualization of visceral pleural line in 26 cases (74.2%), whereas peripheral lung markings were absent in 22 neonates (62.8%) (Table 2).

**Table 2:** Distribution of Point-of-Care Ultrasound (POCUS) and Chest X-Ray Features Among Neonates Diagnosed with Pneumothorax

POCUS Features	n (%)	Chest X-ray	n (%)
Loss of Lung Sliding	30 (90.9%)	Visceral Pleural Line	26 (74.2%)
Absence of B Lines	28 (84.8%)	Absence of Peripheral Lung Markings	22 (62.8%)
Lung Point Visualized	24 (72.7%)	–	–

POCUS was able to correctly identify 33 true-positive cases of neonatal pneumothorax, alongside giving 4 false positives and 3 false negatives, while also correctly categorizing 60 cases as true negatives. From these results, it could be said that POCUS had a sensitivity of 91.6% and a specificity of 93.75%. The positive predictive value was calculated to be 89.18%, while the negative predictive value was remarkable at 95.2%. In general, POCUS was found to have a diagnostic accuracy of 93% when assessed against chest X-ray as the reference gold standard. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the overall discriminatory performance of point-of-care ultrasound (POCUS) for detecting neonatal pneumothorax, using chest X-ray as the reference standard. The area under the ROC curve (AUC) for POCUS was 0.93 (95% CI: 0.87–0.97), indicating excellent diagnostic performance. An optimal operating point was identified based on the maximum Youden index, corresponding to a sensitivity of 91.6% and specificity of 93.75% (Table 3).

**Table 3:** Diagnostic Accuracy Parameters of Point-of-Care Ultrasound (POCUS) Compared with Chest X-Ray for Detection of Neonatal Pneumothorax

Diagnostic Parameter	Value	95% Confidence Interval
True Positives (TP)	33 (33.0%)	–
False Positives (FP)	4 (4.0%)	–
True Negatives (TN)	60 (60.0%)	–
False Negatives (FN)	3 (3.0%)	–
Sensitivity	91.6%	78.2% – 97.1%
Specificity	93.75%	85.0% – 97.5%
Positive Predictive Value (PPV)	89.18%	75.3% – 95.7%
Negative Predictive Value (NPV)	95.2%	86.9% – 98.4%
Overall Accuracy	93.0%	86.3% – 97.0%

## DISCUSSION

The study sensitivity (91.6%) is slightly lower when compared to meta-analyses, which reported 98–99% for lung ultrasound (LUS) in diagnosing neonatal pneumothorax. For example, the 2021 systematic review by Fei *et al.* encompassing eight prospective studies with a total of 529 neonates, reported a pooled sensitivity of LUS at 98%, specificity at 99%, and a diagnostic odds ratio (DOR) of 920 that was much higher than CXR's 82% sensitivity and 96% specificity [9]. One possible reason for

this difference could be related to our having a larger number of false-positive results (4 cases), which might be attributed to the operator's experience or to subtle artifacts mimicking absent lung sliding, a finding that was noted in 90.9% of our true positives. On the other hand, our specificity (93.75%) is in line with Ruoss *et al.* review (96.7–100%), where LUS consistently diagnosed pneumothorax in NICU environments [10]. The PPV (89.18%) and NPV (95.2%) obtained in our study are better than those reported in some adult-focused POCUS but are still inferior to neonatal-specific ones; a study reported a pooled sensitivity of 74.3% and a specificity of 93.6% with a total of 3,840 subjects from different age groups and attributed the variance to non-standardized protocols [11]. This study's detection of lung point (72.7%) resembles that of Wang *et al.* who declared a specificity of this sign (100% in their cohort) to be 94.28% [12]. Some CXR characteristics, like visceral pleural line (74.2% here), showed common ground, yet the immediacy of POCUS at the bedside serves to address the delays in CXR that were the subject of criticism in Liu *et al.* where LUS specificity was found to be 98% [13]. The POCUS signs that we observed in our group—absent lung sliding (90.9%), absent B-lines (84.8%), lung point (72.7%)—are consistent with recent validations; Dong *et al.* confirmed the so-called lung point's specificity in neonatal respiratory distress [14]. Nazir *et al.* made a similar comparison between ultrasonography and CT in the case of pneumothorax detection, noting that pleural line visualization was as high as our 74.2% CXR rate [15]. It should be emphasized that our false negatives (3 cases) were presumably due to tiny pneumothoraxes not detected during the initial POCUS, a difficulty that has been pointed out in preterm-heavy cohorts like ours (mean GA 36.3 weeks), whereas term neonates show a higher detection rate as reported by Liu [13]. There were no baseline differences (age, sex, GA, birth weight, respiratory distress) that could confound our results; thus, they are in agreement with the similar populations in the studies conducted post-2020. The assessment of reduced breath sounds (85.7% vs 15.4%,  $p < 0.001$ ) was a strong indicator of POCUS positives, giving further justification to the integrated clinical-ultrasound protocols in ESPNIC guidelines (as implied in recent POCUS endorsements) [16]. In Pakistan, where resources are scarce, our POCUS-first protocols were backed by 93% accuracy. The reduction in CXR radiation (0.01–0.1 mSv per view) is significant, especially considering the high respiratory distress burden. Our practical metrics (e.g., 91.6% sensitivity) confirm that the application of the technology is justified, even though there are minor discrepancies from the ideal pooled estimates [17, 18]. Compared to the 2021 meta-analyses, this study's results show that the integration of

symptoms allows for more precise diagnostics and therefore necessitates training according to the recent consensus [12, 19]. Among the strengths were the potential pairing of POCUS–CXR in 100 neonates, corresponding to the actual NICU workflows, and the high NPV allowing safe rule-out, which was reported by Indian cohorts with the 93.22% sensitivity [19–21]. Operator blinding reduced bias to a minimum, contrary to some reviews in which there was a lot of variability.

On the other hand, limitations included a small sample ( $n=100$ ), a single-center design that limited generalizability, and CXR as an imperfect gold standard that is susceptible to inter-observer variability (up to 20% in neonates). The lack of serial imaging missed the evolution of dynamic pneumothorax, and the preterm predominance (implied by GA) might have been responsible for the false positives from the atelectasis mimics being inflated. The absence of volume quantification restricts severity correlation as well as emerging air-fluid points. Operator dependency still exists, but our metrics are getting closer to expert benchmarks. The study demonstrates that POCUS technology provides exceptional diagnostic performance because it achieved a high AUC score of 0.93, which shows that it can identify different medical conditions.

## CONCLUSIONS

The research showed that POCUS tests achieve both high sensitivity and high specificity and demonstrate total diagnostic accuracy when used to identify neonatal pneumothorax through comparison with chest X-ray results. The test shows a high negative predictive value, which establishes its function as an accurate bedside tool for ruling out medical conditions. The study results cannot be applied to other situations because the research used a small number of participants and was conducted in one medical facility. The existing requirement for primary confirmation in neonatal intensive care units should remain until larger multicenter research studies are finished.

## Authors' Contribution

Conceptualization: SK

Methodology: SK, SA, AMA, HA

Formal analysis: SK, SA, SFAN

Writing and Drafting: SK, SA, SAHK

Review and Editing: SK, SA, AMA, HA, SFAN, SAHK

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



## Multidisciplinary Team Approach for Morbidly Adherent Placenta: Maternal Outcomes Compared with Standard Care

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## ABSTRACT

Morbidly adherent placenta (MAP), part of the placenta accreta spectrum, is a major cause of severe obstetric hemorrhage and may lead to massive transfusion, peripartum hysterectomy, ICU care, and maternal morbidity. Rising cesarean section rates are increasing the burden of MAP in Pakistan. Multidisciplinary team (MDT) management is proposed to improve preparedness, but outcome benefits remain uncertain. **Objective:** To compare maternal outcomes in patients with MAP managed by an MDT versus standard obstetric care. **Methods:** A comparative, non-randomized observational study was conducted at the Department of Obstetrics and Gynecology, Pakistan Navy Ship Shifa Hospital, Karachi, from February 2022 to July 2022, vide Ethical Committee PNS Shifa approval. A total of 151 women diagnosed with MAP were included. Outcomes included maternal morbidity, estimated blood loss (EBL), transfusion requirement, time to intervention, hospital stay, and surgical procedures. **Results:** Overall mean EBL was 512.24 mL, and mean transfusion requirement was 1.91 units. Compared with standard care, MDT management showed no significant differences in EBL ( $p=0.300$ ), transfusion units ( $p=0.237$ ), time to intervention ( $p=0.426$ ), or hospital stay ( $p=0.926$ ). Maternal morbidity and major surgical interventions were also comparable between groups. **Conclusions:** MDT-based care showed no significant improvement in blood loss, transfusion needs, or maternal morbidity compared with standard care

## INTRODUCTION

Morbidly adherent placenta (MAP), increasingly described under the broader term placenta accreta spectrum (PAS), represents a severe obstetric disorder linked to considerable maternal morbidity and mortality. PAS includes placenta accreta, increta, and percreta conditions characterized by abnormal placental adherence and/or invasion into the uterine wall, often resulting in severe postpartum hemorrhage and complex surgical challenges [1]. The rising incidence of PAS is primarily

attributed to increasing rates of cesarean delivery and prior uterine surgery, making management of PAS a growing concern in maternal healthcare [2]. Given its complexity, a multidisciplinary team (MDT) approach is widely emphasized in contemporary guidance for improving safety through planned delivery, coordinated surgical care, and preparedness for massive hemorrhage [3]. PAS is a leading cause of life-threatening obstetric hemorrhage and may require hysterectomy and large-



volume blood transfusion, contributing to increased maternal morbidity and occasional maternal death [2]. The unpredictable nature of PAS supports proactive, team-based care. MDT involvement, typically including obstetric surgeons/maternal-fetal medicine specialists, anesthesiologists, blood bank/transfusion services, and surgical subspecialties (e.g., urology) where indicated, facilitates early diagnosis, operative preparedness, and coordinated hemostatic control [3, 4]. Recent evidence also supports the clinical value of prenatal recognition and structured planning in PAS. A systematic review and meta-analysis found that prenatally diagnosed PAS is associated with more favorable perioperative outcomes compared with undiagnosed cases, supporting the importance of antenatal screening and referral pathways [5]. In parallel, contemporary consensus work has promoted standardized approaches to prenatal ultrasound evaluation and reporting of PAS markers to improve diagnostic consistency across settings [6]. Implementation tools and systems-readiness guidance have further highlighted that MDT care is strengthened when institutions use structured checklists, planning worksheets, and organized preparedness processes, particularly for emergencies and unanticipated PAS [7]. Institutional and regional reports continue to describe improved organization of care and perioperative management after establishing dedicated PAS/MDT services, especially when pathways incorporate imaging, planned delivery logistics, and coordinated operative roles [8, 9]. Regional initiatives and quality-focused efforts also report benefits such as improved planning, resource mobilization, and reductions in severe hemorrhage-related morbidity when MDT models are integrated into service delivery [10]. Finally, early detection and effective team collaboration have been highlighted as key components for preventing severe maternal outcomes, including maternal death, in PAS/MAP [11].

Morbidly adherent placenta (MAP), within the placenta accreta spectrum, remains a major obstetric challenge and is associated with severe maternal morbidity and mortality, largely due to massive hemorrhage, high transfusion requirements, and the need for peripartum hysterectomy. The increasing incidence of MAP is closely linked to rising cesarean section rates, making optimization of its management essential. Standard obstetric care may be limited by fragmented perioperative planning. In contrast, a multidisciplinary team (MDT) model integrating obstetricians, anesthesiologists, urologists, hematologists, interventional radiologists, and critical care specialists may improve coordination and surgical preparedness. However, published evidence regarding the impact of MDT-based care on maternal morbidity and

surgical outcomes remains inconsistent, particularly in low-resource settings. Therefore, this study aimed to compare maternal morbidity, surgical outcomes, and perioperative parameters (including estimated blood loss, transfusion requirement, time to intervention, and hospital stay) between women with MAP managed by MDT-based care and those managed with standard obstetric care.

## METHODS

This comparative, non-randomized observational study was conducted in the Department of Obstetrics and Gynecology, Pakistan Navy Ship Shifa Hospital, Karachi, a tertiary care referral center, vide Ethical Committee PNS Shifa approval no: ERC/2022/Gynae/45. The study duration was six months (February 2022 to July 2022). This study was used to compare outcomes of women with morbidly adherent placenta (MAP) managed with standard obstetric care versus multidisciplinary team (MDT) based care. Written informed consent was obtained from all participants. Data were de-identified to ensure privacy and confidentiality. Sample size was calculated using an anticipated maternal mortality of 4.4% from previous literature, with 95% confidence level and 3.2% precision, yielding a total sample of 151. This mortality-based calculation was selected because mortality is a key safety endpoint and because reliable local effect-size estimates for morbidity categories and perioperative parameters were not available. Accordingly, comparisons of morbidity components and perioperative outcomes were treated as comparative secondary analyses, and results are presented with p-values and effect estimates/95% confidence intervals where applicable. Women aged 18–45 years with a singleton pregnancy diagnosed with MAP (placenta accreta, increta, or percreta) were eligible. Women who did not provide informed consent, had multiple pregnancies, or had severe comorbidities (e.g., pre-eclampsia/eclampsia, renal disease) were excluded. Participants were categorized into two management groups based on the care pathway received: standard obstetric care and MDT-based care. In the standard care group, management was provided by consultant obstetricians with routine labor ward/operating theatre support staff. In the MDT group, care was coordinated by obstetricians in collaboration with relevant specialists, including anesthesiologists, hematologists/blood bank support, urologists, and intensive care specialists. Assignment to MDT-based care versus standard care was not randomized and was determined by the institutional service pathway during the study period (e.g., MDT availability/on-call roster/protocol-based scheduling/time period policy). Because allocation was non-random, the potential for selection bias and confounding by case severity was acknowledged, and findings were interpreted

as associations rather than causal effects. Baseline demographic and obstetric severity variables (e.g., age, parity, number of previous cesarean sections, and accreta subtype/severity) were not available in the anonymized dataset used for analysis; therefore, baseline comparability between groups could not be formally assessed, and residual confounding cannot be excluded. The primary outcomes were maternal morbidity and maternal mortality. Maternal morbidity was assessed as individual categorical outcomes, including hemorrhage, infection, and ICU admission, and was also summarized as a composite morbidity variable (no morbidity vs any morbidity). Maternal mortality was defined as any maternal death due to delivery-related causes or complications occurring during the study period and was compared between the MDT-based care and standard-care groups as a categorical outcome. Secondary outcomes included key perioperative measures of surgical blood loss and transfusion requirement, specifically estimated intraoperative blood loss (EBL, mL) and number of blood transfusion units, as well as delay to intervention (hours) and duration of hospital stay (days), which were compared between the MDT-based care and standard-care groups. Surgical outcomes were categorized as none, hysterectomy, and bladder repair, and compared between groups. Team structure (MDT vs standard) was recorded. A locally developed structured questionnaire/proforma was used for standardized data collection. Along with the extraction of perioperative and surgical variables from clinical records, the proforma captured patient safety indicators, including communication score, patient satisfaction, and post-treatment quality of life, and these were compared between MDT-based care and standard-care groups. Communication was recorded on a 5-point scale (1 = poor, 5 = excellent). Patient satisfaction was recorded on a 3-point ordinal scale (0 = low, 1 = medium, 2 = high). Post-treatment quality of life was recorded on a 4-point ordinal scale (0 = poor, 1 = fair, 2 = good, 3 = excellent). For these indicators, higher scores represented better outcomes. The questionnaire/proforma was completed at discharge and supplemented by review of clinical records. Follow-up requirements and long-term health outcomes were also documented from clinical records and the structured proforma. A validated named instrument was not used; therefore, these measures were treated as structured service-evaluation indicators rather than validated patient-reported outcome measures. Data were entered and analyzed using SPSS version 26.0. Continuous variables were assessed for normality using appropriate tests (e.g., Shapiro-Wilk) and/or graphical methods. Normally distributed continuous variables were summarized as mean  $\pm$  SD, and non-normally distributed variables as median (IQR). Categorical variables were

summarized as frequency and percentage. For comparisons between the MDT and standard care groups, continuous outcomes including EBL, transfusion units, delay to intervention, duration of hospital stay, and communication score were analyzed using an independent samples t-test for normally distributed data; otherwise, the Mann-Whitney U test was applied. Homogeneity of variances was assessed using Levene's test; when the equal-variance assumption was violated (Levene's  $p < 0.05$ ), Welch's t-test (SPSS "equal variances not assumed") was used. Associations between care group and categorical variables were assessed using the Chi-square test, and Fisher's exact test was used when expected cell counts were  $<5$ . Specifically, differences in maternal morbidity components (hemorrhage, infection, and ICU admission) and maternal mortality between MDT and standard-care groups were assessed using Chi-square/Fisher's exact test, as appropriate. Given that patient satisfaction and post-treatment quality of life were measured on ordinal scales, group comparisons were performed using the independent samples t-test as applied in the study analysis plan; where relevant, nonparametric testing (Mann-Whitney U) may be used if distributional assumptions are not met. Where relevant, effect estimates (risk ratio/odds ratio) with 95% confidence intervals were calculated. A  $p$ -value  $<0.05$  was considered statistically significant. In addition to  $p$ -values, effect estimates with 95% confidence intervals (CI) were reported to support clinical interpretation, including mean differences (95% CI) for continuous outcomes and risk ratios/odds ratios (95% CI) for dichotomous outcomes.

## RESULTS

The overall mean estimated blood loss (EBL) was  $512.24 \pm 283.43$  mL, and the mean transfusion requirement was  $1.91 \pm 1.39$  units. The mean time to intervention was  $2.07 \pm 0.49$  hours, and the mean hospital stay was  $5.13 \pm 2.16$  days. The mean communication score (5-point scale) was  $3.23 \pm 1.39$  (Table 1).

**Table 1:** Descriptive Statistics for Numerical Variables

Variables	n	Mean $\pm$ SD
Estimated Blood Loss (mL)	151	$512.24 \pm 283.43$
Transfusion Units	151	$1.91 \pm 1.39$
Time to Intervention (hours)	151	$2.07 \pm 0.49$
Hospital Stay (days)	151	$5.13 \pm 2.16$
Communication Score (1-5)	151	$3.23 \pm 1.39$

When continuous outcomes were compared between the standard-care and MDT groups, no statistically significant differences were observed. Mean EBL was  $477.63 \pm 300.46$  mL in standard care versus  $528.86 \pm 274.86$  mL in MDT care ( $p=0.300$ ). Mean transfusion requirement was  $1.71 \pm 1.47$  units versus  $2.00 \pm 1.34$  units ( $p=0.237$ ). Mean time to

intervention was  $2.11 \pm 0.54$  hours in standard care versus  $2.05 \pm 0.46$  hours in MDT care ( $p=0.426$ ). Mean hospital stay was  $5.10 \pm 2.44$  days versus  $5.14 \pm 2.03$  days ( $p=0.926$ ) (Table 2).

**Table 2:** Comparison of Continuous Outcomes Between Standard Care and MDT Groups

Variables	Group	n	Mean $\pm$ SD	p-value
Estimated Blood Loss (mL)	Standard	49	477.63 $\pm$ 300.46	0.300
	MDT	102	528.86 $\pm$ 274.86	
Transfusion Units	Standard	49	1.71 $\pm$ 1.47	0.237
	MDT	102	2.00 $\pm$ 1.34	
Time to Intervention (hours)	Standard	49	2.11 $\pm$ 0.54	0.426
	MDT	102	2.05 $\pm$ 0.46	
Hospital Stay (days)	Standard	49	5.10 $\pm$ 2.44	0.926
	MDT	102	5.14 $\pm$ 2.03	

Maternal morbidity components were compared between groups as categorical outcomes. Hemorrhage occurred in 26.5% of standard-care patients versus 25.5% of MDT patients ( $p=0.891$ ), infection in 12.2% versus 18.6% ( $p=0.323$ ), and ICU admission in 2.0% versus 5.9% ( $p=0.429$ , Fisher's exact test where applicable). Overall morbidity (any morbidity vs none) was also comparable between groups (40.8% vs 50.0%,  $p=0.290$ ). Additionally, maternal mortality was low and did not differ significantly between groups. Maternal deaths occurred in 1/49 (2.0%) patients in the standard-care group and 5/102 (4.9%) in the MDT group, with no statistically significant difference (Fisher's exact test  $p=0.664$ ). Neonatal mortality was not assessed in this study because neonatal outcome variables were not captured in the study dataset. Furthermore, patient safety indicators were also comparable between groups. Mean communication score (5-point scale) was  $3.06 \pm 1.41$  in standard care versus  $3.31 \pm 1.39$  in MDT care ( $p=0.298$ ). Mean patient satisfaction score (0–2 scale) was  $1.49 \pm 0.62$  versus  $1.36 \pm 0.73$  ( $p=0.294$ ). Mean post-treatment quality of life score (0–3 scale) was  $2.08 \pm 0.89$  versus  $1.94 \pm 0.95$  ( $p=0.387$ ). Overall, MDT-based management did not demonstrate a statistically significant improvement in these patient safety indicators compared with standard care (Table 3).

**Table 3:** Maternal Morbidity Components, Maternal Mortality, and Patient Safety Indicators by Care Group (Standard vs MDT)

Maternal Morbidity Outcome	Standard (n=49), n (%) / Mean $\pm$ SD	MDT (n=102), n (%) / Mean $\pm$ SD	p-value
<b>Maternal Morbidity Components</b>			
Hemorrhage	13 (26.5%)	26 (25.5%)	0.891
Infection	6 (12.2%)	19 (18.6%)	0.323
ICU Admission	1 (2.0%)	6 (5.9%)	0.429*
Any Morbidity (Hemorrhage/ Infection/ICU)	20 (40.8%)	51 (50.0%)	0.290
No Morbidity	29 (59.2%)	51 (50.0%)	–

<b>Maternal Mortality by Care Group</b>			
Maternal mortality (Yes)	1 (2.0%)	5 (4.9%)	0.664*
Maternal mortality (No)	48 (98.0%)	97 (95.1%)	
<b>Patient Safety Indicators</b>			
Communication score	3.06 $\pm$ 1.41	3.31 $\pm$ 1.39	0.298
Patient satisfaction	1.49 $\pm$ 0.62	1.36 $\pm$ 0.73	0.294
Quality of life post-treatment	2.08 $\pm$ 0.89	1.94 $\pm$ 0.95	0.387

\*Fisher's exact test applied where appropriate. Percentages are within each group. The p-values compare Standard vs MDT for each outcome. \*Fisher's exact test (2-sided). Fisher's exact test was reported due to small expected counts. Standard vs Extended (MDT) was compared using an independent samples t-test

Follow-up care requirements and long-term health outcomes were also similar between groups. Follow-up care was required in 57.1% of standard-care patients and 58.8% of MDT patients ( $p=0.845$ ). Long-term complications were reported in 30.6% of standard-care patients compared with 21.6% of MDT patients ( $p=0.226$ ), indicating no statistically significant association with team composition (Table 4).

**Table 4:** Association of Team Composition with Other Categorical Variables

Variables	Category	Standard (n=49), n (%)	MDT (n=102), n (%)	Total, (n=151)	p-value
Follow-Up Care	Not required	21 (42.9%)	42 (41.2%)	63 (41.7%)	0.845
	Required	28 (57.1%)	60 (58.8%)	88 (58.3%)	
Long-Term Health Outcomes	No complications	34 (69.4%)	80 (78.4%)	114 (75.5%)	0.226
	Complications	15 (30.6%)	22 (21.6%)	37 (24.5%)	

Percentages are within each group. The p-values are for the overall association within each variable

Major surgical intervention categories did not differ significantly between standard care and MDT care ( $p=0.570$ ). No major surgical intervention was required in 63.3% of standard-care patients versus 70.6% of MDT patients. Hysterectomy was performed in 20.4% versus 18.6%, and bladder repair was required in 16.3% versus 10.8%, respectively. Effect estimates also showed no statistically significant reduction in major interventions with MDT care: hysterectomy (RR 0.91; 95% CI 0.46–1.81) and bladder repair (RR 0.66; 95% CI 0.28–1.54), as confidence intervals crossed 1.0 (Table 5).

**Table 5:** Major Surgical Interventions by Care Group (with Effect Estimates)

Outcomes	Standard (n=49), n (%)	MDT (n=102), n (%)	RR (MDT vs Standard), (95% CI)	OR (MDT vs Standard), (95% CI)
Hysterectomy (Yes)	10 (20.4%)	19 (18.6%)	0.91 (0.46–1.81)	0.89 (0.38–2.10)
Bladder Repair (Yes)	8 (16.3%)	11 (10.8%)	0.66 (0.28–1.54)	0.62 (0.23–1.65)

Note: "None" category is not included in effect estimates because RR/OR are calculated for binary outcomes (Yes/No). Percentages are within each group. Effect estimates compare MDT vs Standard. CI = 95% confidence interval

## DISCUSSION

Morbidly adherent placenta (MAP), now more commonly described under the umbrella of placenta accreta spectrum (PAS), remains a significant challenge in obstetric care and is associated with major maternal morbidity due to severe hemorrhage, complex surgery, and potential need for hysterectomy and massive transfusion. Optimized management strategies are therefore essential to reduce maternal risk. The risk of MAP increases with the number of previous cesarean sections, and data from a tertiary care center reported a high burden of MAP among women with multiple prior cesareans [12, 13]. In tertiary care hospitals where multiple disciplines are available, coordinated involvement of different specialties through a multidisciplinary team (MDT) is widely recommended, particularly when care is centralized and supported by institutional preparedness. Evidence from protocol-oriented quality improvement and structured MDT service implementation suggests that MDT-based models can improve perioperative preparedness and may reduce bleeding and transfusion needs in PAS, especially when management is standardized and delivered by experienced teams [14, 15]. These findings support the potential advantages of MDT involvement in the care of MAP, but they also indicate that “MDT” is most effective when it functions as a consistent pathway rather than ad-hoc availability of multiple specialists. Beyond team availability, the effectiveness of MDT care may depend on protocolization and early identification of high-risk cases. When MDT pathways incorporate structured antenatal diagnosis, outcomes may improve because delivery can be planned, resources arranged in advance, and the surgical approach optimized. Recent ultrasound-based scoring approaches and structured imaging criteria have been proposed to improve prenatal identification and stratification of PAS severity, supporting timely referral to tertiary centers with MDT capability [16]. In addition, contemporary safety and preparedness resources emphasize systematic planning (e.g., standardized preoperative planning tools, readiness bundles, and structured communication) as key components for safer PAS care. Studies from tertiary centers have similarly reported reduced blood loss and transfusion needs with coordinated care and planned management [17]. Severe complications have also been evaluated in contemporary cohorts and improvement initiatives, where better outcomes are often seen after MDT protocols mature, teams gain experience, and pathways become standardized [14, 18]. Continuous collaboration, structured communication, and shared decision-making may also create a team-learning environment in which experience improves over time and is associated with better outcomes. For example, a large

cohort evaluating outcomes before and after implementation of a structured MDT protocol demonstrated improvements in perioperative outcomes after pathway adoption, consistent with the benefits of protocolization and team learning [18]. Furthermore, delivery in specialized “accreta centers” or expert settings has been associated with lower severe maternal morbidity compared with non-specialist care, reinforcing the importance of systems-level organization beyond individual clinician expertise [19]. Importantly, the absence of statistically significant differences in immediate clinical parameters does not exclude the possibility of improved long-term maternal safety when MDT care is implemented through standardized protocols. Standardized MDT pathways that incorporate early antenatal diagnosis and planned use of additional hemorrhage-control strategies (including interventional radiology where feasible and guideline-supported) may improve preparedness, facilitate hemorrhage control, reduce unplanned intraoperative events, and potentially improve longer-term recovery and safety [20]. Maternal mortality remains a critical concern in MAP/PAS. Contemporary summaries of evidence and guidance emphasize that MDT care and planned delivery in expert centers are key to reducing morbidity, while impact on mortality is harder to demonstrate consistently because maternal death is rare and studies may be underpowered for this endpoint [20]. Maternal mortality has been reported in MAP cohorts, emphasizing the need for continued efforts to improve safety and outcomes [12]. In this cohort, maternal mortality was low and did not differ significantly between groups; larger prospective studies may be required to detect differences in rare outcomes such as maternal death.

In contrast to much of the published evidence, this study did not demonstrate statistically significant differences between MDT-managed and standard-care groups in key short-term clinical parameters, including estimated blood loss, transfusion requirement, time to intervention, or duration of hospital stay. Maternal morbidity components and major surgical interventions were also comparable between groups. These differences from earlier reports may reflect variation in institutional expertise, non-standardized MDT protocols, differences in case mix and referral patterns, and the fact that MDT benefit may be most apparent when a structured pathway is implemented consistently. In this study, long-term outcomes were recorded; however, the dataset did not capture protocol components such as timing of antenatal diagnosis, standardized referral pathways, or interventional radiology utilization as discrete variables. Therefore, this study could not specifically evaluate whether protocolized MDT care with early diagnosis and additional adjunctive strategies

improves long-term maternal safety beyond short-term perioperative metrics. The clinical burden of MAP/PAS is increasing due to rising rates of primary and repeat cesarean delivery. Continuous upgrading of tertiary care protocols, consistent MDT coordination, and strengthening antenatal screening and referral pathways are essential for improving clinical outcomes. Future research should focus on prospective, protocol-based MDT implementation that explicitly measures antenatal diagnostic timing, planned delivery pathways, adjunctive interventions, and long-term maternal outcomes to determine whether standardized MDT models can improve long-term safety even when short-term differences are not immediately statistically significant. Because the sample size was based on mortality, and maternal death was rare, the study may be underpowered to detect small differences between groups in morbidity components and perioperative outcomes.

## CONCLUSIONS

In women with morbidly adherent placenta, MDT-based care did not demonstrate statistically significant improvement in perioperative outcomes—including estimated blood loss, transfusion requirement, time to intervention, hospital stay, maternal morbidity, or major surgical interventions compared with standard obstetric care. Future prospective studies should evaluate standardized MDT protocols, including early antenatal diagnosis and planned multidisciplinary pathways, to determine their impact on long-term maternal safety.

## Authors' Contribution

Conceptualization: BI

Methodology: BI, UIK, RA

Formal analysis: UIK, SRK

Writing and Drafting: BI, UIK, AT, SN, RA, SRK

Review and Editing: BI, UIK, AT, SN, RA, SRK

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



## Outcome of Modified Salter Osteotomy in Improving Acetabulum Index of Developmental Dysplasia of the Hip with Age Group of 2–10 Years

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## ABSTRACT

The modified Salter osteotomy is a widely utilized surgical intervention for treating developmental dysplasia of the hip (DDH). **Objectives:** To assess the outcome of modified Salter osteotomy in improving the acetabular index (AI) in children with DDH aged 2–10 years. **Methods:** This observational cohort study was conducted at the Department of Orthopedics, JPMC, Karachi, from December 2024 to September 2025. Sixty children aged 2–10 years with DDH undergoing modified Salter osteotomy were included. Baseline demographics, clinical examination, and preoperative radiographs for AI were recorded. Outcomes included change in AI, radiological grading by Severin classification, and clinical results by Modified MacKay criteria at 3 and 6 months. Data were analyzed using SPSS version 26.0 with non-parametric tests, Chi-square/Fisher's exact test, and Kappa statistic, taking  $p < 0.05$  as significant. **Results:** In a total of 60 children, 12 (20.0%) were boys, and 48 (80.0%) were girls, with a median age of 7 (5.5–9) years, and BMI 25 (23.0–27.0) kg/m<sup>2</sup>. The median AI decreased significantly from 39.00 (35.00–43.00) preoperatively to 21.00 (18.00–25.00) at 6 months ( $p < 0.001$ ). At 6 months, radiological outcomes were excellent in 24 (40.0%), good in 20 (33.3%), fair in 10 (16.7%), and poor in 6 (10.0%). Clinical outcomes were excellent in 22 (36.7%), good in 21 (35.0%), fair in 11 (18.3%), and poor in 6 (10.0%). Agreement between the two systems was substantial ( $\kappa = 0.71$ ,  $p < 0.001$ ). **Conclusions:** Modified Salter osteotomy resulted in a significant improvement in AI among children with DDH, accompanied by favorable radiological and clinical outcomes at six months.

## INTRODUCTION

The modified Salter osteotomy is a widely utilized surgical intervention for treating developmental dysplasia of the hip (DDH). The modified Salter osteotomy is primarily aimed at correcting acetabular dysplasia and enhancing the biomechanical alignment of the hip joint in pediatric patients. If left untreated, DDH can lead to early degenerative changes, resulting in pain, restricted mobility, and the necessity for additional surgical interventions in adolescence or adulthood. In early childhood, the acetabulum is relatively malleable, and surgical correction can significantly reshape the hip socket [1]. No formal studies are available estimating the

prevalence of DDH in Pakistan. Whatever local data exist, the incidence of DDH is estimated to be around 5/1000 hips [2]. A key indicator of acetabular dysplasia and treatment efficacy in DDH management is the acetabular index (AI), which measures the slope of the acetabular roof [3]. A high AI indicates insufficient acetabular coverage of the femoral head, increasing the risk of hip instability and progressive joint degeneration. Surgical procedures like the Salter osteotomy enhance acetabular coverage [3]. The traditional Salter osteotomy redirects the acetabulum by cutting through the ilium and rotating the acetabular fragment, utilizing a bone graft to improve coverage over



the femoral head and reduce the acetabular index [4–6]. Modifications to the Salter technique have been developed to optimize surgical outcomes and minimize complications in pediatric orthopedic surgery [7, 8]. Baghdadi et al., in a clinical evaluation based on the Modified MacKay criteria, noticed that 30% of cases were rated as excellent, 52% as good, 14% as fair, and 4% as poor following the Salter technique in DDH [9]. The DDH can result in persistent acetabular dysplasia, hip instability, and early degenerative changes if not corrected during childhood. In children, pelvic osteotomies are often required to improve femoral head coverage and allow further acetabular remodeling. The modified Salter osteotomy is a commonly performed redirection procedure aimed at correcting acetabular dysplasia, and improvement in AI is a key objective, a radiographic marker of treatment success. Although literature reports favorable outcomes after modified Salter osteotomy, local evidence in children aged 2–10 years remains limited, and radiographic outcome data are scarce in comparable settings.

The modified Salter osteotomy has been mostly applied in developmental dysplasia of the hip, but a local assessment of its radiographic outcome, especially the increase in the acetabular index, in children as young as 2–10 years is scarce. The absence of outcome data tailored to the population poses a gap in the objective evaluation of the surgical success in similar contexts. This research aimed to determine the result of modified Salter osteotomy through the evaluation of the change in the acetabular index of children with DDH.

## METHODS

This observational cohort study was conducted at the Department of Orthopedics, Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan, between December 2024 and September 2025. Ethical approval was granted by the Institutional Review Board of JPMC (letter number F.2-81/2024-GENL/166/JPMC). Informed written consents were sought from all study participants. The inclusion criteria were children of either gender, aged 2–10 years, diagnosed with DDH, and who underwent surgical intervention via modified Salter osteotomy. Children with neuromuscular disorders, syndromic etiologies of hip dysplasia, prior hip surgery, or incomplete medical records were excluded. DDH was defined as a developmental disorder of acetabular formation leading to hip instability and abnormal gait. Non-probability, consecutive sampling technique was adopted. A sample size of 60 was based on the WHO sample size calculator using an expected 4.0% frequency of poor outcomes in DDH [9], a 5% margin of error, and a 95% confidence level. At baseline, demographic data, including age, gender, and body mass index (BMI), were recorded. A detailed clinical examination

was performed to assess hip stability, range of motion, and gait. Preoperative anteroposterior pelvic radiographs were obtained, and AI were independently measured by two radiologists to ensure interobserver consistency. Intraoperative details, including osteotomy technique, fixation type, and perioperative complications, were documented. All patients underwent Modified Salter Osteotomy performed by an experienced pediatric orthopedic surgeon following standard operative protocols. The primary outcome was improvement in AI, while secondary outcomes included radiological classification of hip morphology by the Severin grading system and clinical outcomes using the Modified MacKay criteria, both categorized as excellent, good, fair, or poor. The AI, defined as the angle between Hilgenreiner's line and a line drawn from the triradiate cartilage to the lateral edge of the acetabulum, was used as a quantitative radiographic measure of acetabular coverage. Severin's classification system grades hip morphology on postoperative radiographs according to acetabular development, congruency of the femoral head, and the presence of degenerative changes. Severin grades I and II, representing a normal or nearly normal hip joint with adequate acetabular coverage, were categorized as excellent or good outcomes. Grades III and IV, which indicate dysplastic hips with insufficient coverage but without frank dislocation, were considered fair outcomes, while grades V and VI, denoting subluxated or redislocated hips and advanced degenerative changes, respectively, were classified as poor outcomes. The Modified MacKay criteria provide a standardized framework for assessing postoperative hip function. The criteria take into account hip stability, range of motion, presence or absence of pain, gait quality, and limb length equality. Patients with full stability, a normal pain-free gait, and a full range of motion were classified as having excellent clinical outcomes. Those with minor limitations in movement or gait disturbances without significant pain were graded as good outcomes. Patients with moderate restriction of movement, limping, or discomfort were placed in the fair outcome category, while those with persistent instability, severe stiffness, painful gait, or marked functional limitation were graded as poor outcomes. Participants were followed at 3 months and 6 months postoperatively. At each follow-up, clinical outcomes were assessed using the Modified MacKay criteria, while serial radiographs were obtained for acetabular index measurement and graded according to the Severin classification. Outcome assessment was performed by clinicians blinded to the initial preoperative measurements to reduce assessment bias. The completeness of follow-up was ensured through scheduled hospital visits and reminder calls to caregivers, with any loss to follow-up recorded.

All data were entered and analyzed using IBM-SPSS Statistics version 26.0. Categorical variables such as age group, gender, surgical side, BMI categories, and outcome grades were expressed as frequencies and percentages. Continuous variables, including the age, BMI, and AI, were assessed for normality using the Shapiro-Wilk test and were reported as median with interquartile range because the data were not normally distributed. The preoperative and postoperative AI were compared using the Wilcoxon signed-rank test for paired data. Radiological outcomes according to the Severin classification and clinical outcomes according to the Modified MacKay criteria were presented as categorical distributions, and agreement between the two outcome scoring systems was assessed using the Kappa statistic. Associations between outcome categories (excellent, good, fair, poor) and demographic or clinical variables were evaluated using the Chi-square test or Fisher's exact test where appropriate. Statistical significance was defined as a p-value of less than 0.05.

## RESULTS

In a total of 60 children, 12 (20.0%) were boys, and 48 (80.0%) were girls. The median age and BMI were 7 (5.5–9) years, and 25 (23.0–27.0) kg/m<sup>2</sup>, respectively. Surgical intervention was performed on the right side in 17 (28.3%), on the left side in 30 (50.0%), and bilaterally in 13 (21.7%) (Table 1).

**Table 1:** Characteristics of Children (n=60)

Characteristics		Frequency (%)
Age (Years)	2-5	21(35.0%)
	>5 to 10	39(65.0%)
Gender	Boy	12(20.0%)
	Girl	18(80.0%)
Surgical Site	Right	17(28.3%)
	Left	30(50.0%)
	Bilateral	13(21.7%)
Body Mass Index (kg/m <sup>2</sup> )	≤24	19(31.7%)
	>24	41(68.3%)

The AI showed a statistically significant improvement 6 months after modified Salter osteotomy, and the median preoperative AI was 39.0° (IQR 35.0–43.0), which decreased to 21.0° (IQR 18.0–25.0) at follow-up (p<0.001). Radiological outcomes at 6 months based on the Severin classification demonstrated that 24 (40.0%) hips were graded excellent, 20 (33.3%) good, 10 (16.7%) fair, and 6 (10.0%) were poor. Clinical outcomes at 6 months assessed using the Modified MacKay criteria showed that 22 (36.7%) hips were graded excellent, 21(35.0%) good, 11(18.3%) fair, and 6(10.0%) were poor. Comparison of outcome systems demonstrated substantial agreement with a Kappa statistic of 0.71 (p<0.001)(Table 2).

**Table 2:** Cross-Comparison of Radiological (Severin) and Clinical (Modified MacKay) Outcomes After 6-Months (n=60)

Severin Classification	Modified MacKay Criteria			
	Excellent	Good	Fair	Poor
Excellent	18	4	2	–
Good	3	13	3	1
Fair	1	2	6	1
Poor	0	2	0	4

Radiological outcomes by the Severin classification showed that in children aged 2 to 5 years, 11 (45.8%) were excellent, 6 (30.0%) good, 3 (30.0%) fair, and 1 (16.7%) poor, while in those aged 6 to 10 years, 13 (54.2%) were excellent, 14 (70.0%) good, 7 (70.0%) fair, and 5 (83.3%) poor (p=0.484). Among boys, 7 (29.2%) were excellent, 4 (20.0%) good, and 1 (10.0%) fair, with no poor outcomes, whereas in girls, 17 (70.8%) were excellent, 16 (80.0%) good, 9 (90.0%) fair, and 6 (100%) poor (p=0.336). With respect to the surgical side, excellent outcomes were observed in 5 (20.8%) right-sided, 15 (62.5%) left-sided, and 4 (16.7%) bilateral hips, while poor outcomes were seen in 1 (16.7%) right-sided, 3 (50.0%) left-sided, and 2 (33.3%) bilateral hips (p=0.791). In the BMI ≤24 kg/m<sup>2</sup> group, 9 (37.5%) were excellent and 2 (33.3%) poor, compared with 15 (62.5%) excellent and 4 (66.7%) poor in the BMI >24 kg/m<sup>2</sup> group (p=0.733)(Table 3).

**Table 3:** Association of Radiological Outcomes (After 6 Months) Based on Severin Classification with Demographic and Clinical Variables (n=60)

Variables	Excellent, n (%)	Good, n (%)	Fair, n (%)	Poor, n (%)	p-value	
Age (Years)	2 to 5	11(45.8%)	6(30.0%)	3(30.0%)	1(16.7%)	0.484
	>5 to 10	13(54.2%)	14(70.0%)	7(70.0%)	5(83.3%)	
Gender	Boy	7(29.2%)	4(20.0%)	1(10.0%)	–	0.336
	Girl	17(70.8%)	16(80.0%)	9(90.0%)	6(100%)	
Surgery Side	Right	5(20.8%)	7(35.0%)	2(20.0%)	1(16.7%)	0.791
	Left	15(62.5%)	8(40.0%)	6(60.0%)	3(50.0%)	
	Bilateral	4(16.7%)	5(25.0%)	2(20.0%)	2(33.3%)	
Body Mass Index (kg/m <sup>2</sup> )	≤24	9(37.5%)	8(40.0%)	2(20.0%)	2(33.3%)	0.733
	>24	15(62.5%)	12(60.0%)	8(80.0%)	4(66.7%)	

Chi-Square test applied

Clinical outcomes according to the modified MacKay criteria indicated that in children aged 2 to 5 years, 10 (45.5%) were excellent, 7 (33.3%) good, 3 (27.3%) fair, and 2 (33.3%) poor, whereas in those aged 6 to 10 years, 12 (54.5%), 14 (66.7%), 8 (72.7%), and 4 (66.7%) respectively were observed (p=0.734). In boys, 6 (27.3%) were excellent, 5 (23.8%) good, and 1 (9.1%) fair, with no poor outcomes, while in girls, 16 (72.7%) were excellent, 16 (76.2%) good, 10 (90.9%) fair, and 6 (100%) poor (p=0.357). Considering the surgical side, excellent outcomes were seen in 4 (18.2%) right-sided, 14 (63.6%) left-sided, and 4 (18.2%) bilateral hips, with poor outcomes in 1 (16.7%) right-sided, 3 (50.0%) left-sided, and 2 (33.3%) bilateral hips (p=0.380). In the BMI

≤24 kg/m<sup>2</sup> group, 8 (36.4%) were excellent and 2 (33.3%) poor, compared with 14 (63.6%) excellent and 4 (66.7%) poor in those with BMI >24 kg/m<sup>2</sup> (p=0.940)(Table 4).

**Table 4:** Association of Clinical Outcomes (After 6 Months) Based on Modified Mackay Criteria with Demographic and Clinical Variables(n=60)

Variables	Excellent, n (%)	Good, n (%)	Fair, n (%)	Poor, n (%)	p-value	
Age (Years)	2 to 5	10 (45.5%)	7 (33.3%)	3 (27.3%)	2 (33.3%)	0.734
	>5 to 10	12 (54.5%)	14 (66.7%)	8 (72.7%)	4 (66.7%)	
Gender	Boy	6 (27.3%)	5 (23.8%)	1 (9.1%)	–	0.357
	Girl	16 (72.7%)	16 (76.2%)	10 (90.9%)	6 (100%)	
Surgery Side	Right	4 (18.2%)	8 (38.1%)	2 (18.2%)	1 (16.7%)	0.380
	Left	14 (63.6%)	9 (42.9%)	7 (63.6%)	3 (50.0%)	
	Bilateral	4 (18.2%)	4 (19.0%)	2 (18.2%)	2 (33.3%)	
Body Mass Index (kg/m <sup>2</sup> )	≤24	8 (36.4%)	8 (38.1%)	3 (27.3%)	2 (33.3%)	0.940
	>24	14 (63.6%)	13 (61.9%)	8 (72.7%)	4 (66.7%)	

Chi-Square test applied

## DISCUSSION

The present study demonstrated a significant reduction in AI at six months after modified Salter osteotomy in DDH among children aged 2–10 years. Rehman and colleagues reported a reduction in mean AI from 32.25 ± 3.77° to 19.16 ± 5.25° at eight weeks following Salter osteotomy in children aged 18 months to 4 years, which was statistically significant (p<0.001) [10]. The larger reduction in AI observed in the present study may reflect the inclusion of older children up to 10 years, who presented with higher baseline AI values, thereby providing a greater potential for correction. Esmailnejad-Ganji *et al.* reported long-term outcomes of a modified Salter osteotomy in 90 hips with DDH, demonstrating a reduction in mean AI from 47.85° to 17.16° immediately postoperatively, with further remodeling leading to a mean AI of 11.24° at final follow-up [11]. The current study observed a similar significant reduction at six months, although the degree of correction was not as profound as reported in that study. The discrepancy likely reflects the relatively short follow-up duration in the present cohort, as long-term remodeling of the acetabulum is expected to enhance radiological improvement over time. Vasyly and Viktor, evaluating modified single pelvic osteotomy (SPO), also reported a reduction in AI from 39.5 ± 7° to 20.4 ± 5° at six months, with continued improvement to 14.5 ± 4° at longer follow-up [12]. Based on the Severin classification, the present study observed excellent or good radiological outcomes at six months. These results are in agreement with Baghdadi *et al.* who found radiological satisfaction rates of 86% and 85% in patients younger and older than three years, respectively, using the modified Severin score [9]. A study from Iraq reported good to excellent radiological outcomes in the majority of patients under six years of age

undergoing Salter osteotomy, with minimal complications [13]. Mahmud and colleagues, who evaluated a triple procedure including open reduction, varus derotation femoral osteotomy, and acetabular osteotomy, demonstrated a reduction in mean AI from 48.55 ± 7.63 to 23.68 ± 2.93, with Severin excellent or good outcomes in 16 (72.7%) hips [14]. The comparable rates of radiological success between the two studies suggest that modified Salter osteotomy alone, when properly indicated, may provide outcomes equivalent to more extensive combined procedures. In contrast, the long-term study by van Stralen *et al.* highlighted that 8% of hips required total hip arthroplasty at a median of 22 years following Salter osteotomy, and that the occurrence of avascular necrosis (AVN) significantly influenced radiological outcomes [15]. Clinically, the modified MacKay criteria revealed excellent or good results in the vast majority at six months. This proportion is consistent with the 82–83% satisfactory clinical outcomes reported by Baghdadi *et al.* in both age groups [9]. Jasim similarly documented favorable functional recovery, particularly in younger children [13]. Esmailnejad-Ganji *et al.* found excellent or good clinical outcomes in 94.5% of hips at final follow-up after a newly modified Salter osteotomy [11]. The slightly lower proportion in the present study is likely due to the shorter follow-up period, as functional recovery in DDH patients continues to progress with rehabilitation and growth [16, 17]. In the present study, radiological and clinical outcomes did not differ significantly between age groups. Baghdadi *et al.* also found no significant differences between children under and over three years in terms of clinical and radiological satisfaction [9]. In contrast, Koroglu *et al.* demonstrated that children operated before the age of four years achieved superior clinical outcomes and lower rates of AVN compared with those operated later [18]. The findings of this study support the role of modified Salter osteotomy as a reliable intervention for DDH in children between 2 and 10 years, producing both significant radiographic correction and functional improvement [19–21]. The substantial agreement between radiological and clinical outcome measures underlines the importance of combined assessment in postoperative evaluation [22–24]. The evidence from this and related studies suggests that surgical correction yields high proportions of satisfactory outcomes across a broad age range, provided that careful patient selection and surgical expertise are ensured [25].

Several limitations should be acknowledged. The short follow-up duration of six months restricts the ability to assess long-term acetabular remodeling, functional recovery, and the risk of late complications such as AVN, redislocation, or early degenerative changes. The single-

center design limits generalizability, and a multicenter collaborative approach would provide larger sample sizes and broader external validity. Moreover, the single-center study limits external validity; hence, multicenter research with a larger sample size and extended follow-up would be advised in the future to obtain stronger evidence and confirm the radiographic and clinical outcomes of modified Salter osteotomy.

## CONCLUSIONS

The use of modified Salter osteotomy increased the acetabular index (AI) of children with developmental dysplasia of the hip (DDH) significantly. This was accompanied by positive radiological and clinical outcomes at six months after surgery. Also, it was observed that Co concordance between various assessment systems was high, which proves the validity of the surgical outcomes.

## Authors' Contribution

Conceptualization: MA, PA

Methodology: MA, AGJ, FA, HA

Formal analysis: SS, AGJ, FA, HA

Writing and Drafting: MA

Review and Editing: MA, PA, SS, AGJ, FA, 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



## The Silent Guardian of Operating Room Patients' Knowledge and Perception About Anesthesia and Anesthetists at a Tertiary Care Hospital

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## ABSTRACT

The role of anesthesiologists in perioperative care is significant, but it is frequently neglected. The knowledge and perception of anesthesia and anesthesiologists can play a major role in influencing the experience and collaboration of patients during the perioperative period.

**Objective:** To evaluate the level of knowledge and perceptions toward anesthesia and the role of anesthesiologists among patients. **Methods:** It was a cross-sectional study that was conducted from December 2025 to January 2026 at Sindh Institute of Urology and Transplantation (SIUT) in Karachi. Non-probability consecutive sampling was applied to select the sample of 312 patients planned to receive elective surgery. The intrusion was collected by the face-to-face interview using a structured questionnaire that included demographic information and some specific questions that measured knowledge and perception. The analysis of the data was done with SPSS 25. Associations were determined using the chi-square test, and a p-value  $\leq 0.05$  was regarded as significant. **Results:** According to the research, 58.3% of the participants showed good knowledge, and 65.4% had a positive perception of anesthesiologists. The residence ( $p=0.021$ ) and education level ( $p<0.001$ ) were significantly related to knowledge status. Patients administered general anesthesia had a much better positive perception as compared to those administered with local anesthesia or regional anesthesia ( $p=0.041$ ). **Conclusions:** The general knowledge and perception turned out to be satisfactory, but there are still significant misunderstandings, especially in terms of the nature of the work of anesthesiologists.

## INTRODUCTION

The role of the anesthetist has transformed significantly over the past few decades, where the views held by the professionals concerned on the roles of the anesthetists in the perioperative units have changed to include the patients, including the minors, in their decision-making unit, considering their developmental abilities, and the medical complexities involved [1]. Guidelines provided by the professional societies in the field of anesthesia recommend that the anesthetists must be included in the decision-making unit of the perioperative units, which incorporates a variety of medical fields [2]. Anesthesiologists often have limited time to build trust

with patients, requiring effective preoperative visits and strong interpersonal skills to improve patient-physician relationships and reduce anxiety, preventing medical disasters and costly interventions [3-5]. Numerous patients undergo feelings of fear and anxiety in the preoperative phase, stemming from insufficient knowledge regarding the potential occurrences linked to anesthesia or surgical procedures. Various research works have illustrated the inadequate public understanding of anesthesia and the responsibilities held by anesthetists in nations at various stages of development [6]. Many people believe that anesthesiology is not as well-known as other



medical and surgical specialties, and they are also unaware of the differences between general and local anesthesia [7-9]. Patients' misconceptions about anesthesia can affect their decision to seek surgical consultation and their willingness to undergo anesthesia and surgical procedures, particularly in developing countries. These misunderstandings may result in delayed patient presentation, ultimately impacting healthcare outcomes and quality of care negatively [10, 11]. Previous international research on patients' level of knowledge of anesthesia and the role of anesthesiologists found that out of all participants, 28.3% had good knowledge, and the mean knowledge score was  $1.72 \pm 0.45$ . Participants with poor knowledge answered less than half of the questions correctly [6]. One of the studies showed the patients' perception of anesthesiologists' expertise, role, and responsibilities. The prevalence of correct perception regarding an anesthesiologist's role was found in different questions to be 84.5% [12]. In Pakistan, half of the patients are unaware of their surgery purpose and follow surgeons' advice to undergo pre-anesthetic assessment, highlighting the need for increased awareness about anesthesia risks and pre-anesthesia assessment [13].

Previous studies have highlighted inadequate patient knowledge regarding anesthesia and the role of anesthesiologists; however, limited local data exist to assess awareness within our population. This gap creates challenges, as poor understanding may increase preoperative anxiety and hinder effective utilization of anesthetic services. The study aimed to determine the frequency of patients' knowledge and perception regarding anesthesia and anesthesiologists in our setting to support improved patient education and healthcare planning.

## METHODS

This cross-sectional study was conducted in the Department of Anaesthesia, Sindh Institute of Urology and Transplantation (SIUT), Karachi, from December 2025 to January 2026, after obtaining approval from the Ethical Review Committee of SIUT (Approval No: SIUT-ERC-2025/A-619). Following ethical approval, data collection was conducted over a predefined short duration through consecutive face-to-face interviews and was completed within the approved study period. Although conducted under a single institutional framework, participants were recruited from multiple SIUT campuses comprising eight hospital buildings across four different cities, supported by a large multidisciplinary anesthesia department with over 100 anesthesiologists across all hierarchical levels. The sample size was calculated using the WHO sample size calculator by taking a prevalence of good knowledge level as 28.3%, a 5% margin of error, and a 95% confidence interval. The resulting sample size was 312 patients [6]. A non-

probability consecutive sampling technique was employed for participant recruitment. Patients aged 18 to 75 years of both genders, scheduled to undergo elective surgical procedures under both general or local anesthesia, and willing to provide informed consent, were included in the study. Patients with psychiatric disorders, a history of previous surgeries, hearing or speech impairments, or those unable to communicate (e.g., patients with tracheostomies or low Glasgow Coma Scale scores) were excluded. Informed consent was obtained from each patient before inclusion. Data collection was carried out, and information, such as age, gender, residence, marital status, education, occupation, type of anaesthesia, and previous anaesthesia history, was documented. Knowledge and perception regarding anesthesia and anesthesiologists were assessed using a structured questionnaire adapted from previously published studies. The questionnaire consisted of closed-ended items evaluating patients' understanding of anesthetic techniques and the roles of anesthesiologists, as well as their perceptions toward anesthetic care. Each correct response was assigned a score of 1, while incorrect or 'don't know' responses were assigned a score of 0. The total scores were summed and categorized into 'good' or 'poor' knowledge and 'positive' or 'negative' perception based on predefined cut-off values. A correct answer received 1 point, and an incorrect or no answer received 0 points. All knowledge and perception scores were added and typed. To achieve the accuracy and consistency of the data, the principal investigator had to collect all data using a predefined proforma. There was a reduction in bias because of the inclusion and exclusion criteria, which was observed to the letter, and due to stratification to control potential confounding factors.

Analysis was done using SPSS version 25. Qualitative variables like gender, residence, marital status, education, occupation, type of anesthesia, previous anesthesia received, and knowledge and perception status were calculated with frequencies and percentages. Normality of the quantitative variables was checked by the use of the Shapiro-Wilk test. The standard deviation and the mean were given in normally distributed data. Stratification was used to control the effect modifiers that included age, gender, residence, marital status, education, occupation, type of anaesthesia, and previous anaesthesia received. Chi-square test was used to associate the knowledge and perception with these stratified variables. A p-value of  $\leq 0.05$  was taken as a statistically significant value.

## RESULTS

The study involved 312 patients, though on a very thin margin, males outnumbered the females. Most of the participants lived in urban locations, with the majority

being married. There was also a variation in the educational levels, and a significant percentage of the population had attained secondary or higher levels of education, but a large number were illiterate. Housewives occupied the highest category of occupation, followed by people involved in business and students. The most used form was general anesthesia, and a lower number of patients were administered regional or local anesthesia. A little over 50 percent of the respondents had no previous experience with anesthesia. The average age of the research population was  $41.3 \pm 12.5$  years, which shows that the respondents were distributed across a wide range of ages (Table 1).

**Table 1:** Demographic and Clinical Characteristics of Participants (n=312)

Variables	Categories	n (%)
Gender	Male	166 (53.2%)
	Female	146 (46.8%)
Residence	Urban	198 (63.5%)
	Rural	114 (36.5%)
Marital Status	Single	98 (31.4%)
	Married	192 (61.5%)
	Divorced/Separated	14 (4.5%)
	Widowed	8 (2.6%)
Education	Illiterate	50 (16.0%)
	Primary	76 (24.4%)
	Secondary	92 (29.5%)
	Intermediate	56 (17.9%)
	Bachelors	38 (12.2%)
Occupation	Professional	54 (17.3%)
	Business	62 (19.9%)
	Housewife	102 (32.7%)
	Student	58 (18.6%)
	Others	36 (11.5%)
Type of Anesthesia	General	186 (59.6%)
	Regional	72 (23.1%)
	Local	54 (17.3%)
Previous Anesthesia Exposure	Exposed	144 (46.2%)
	Non-exposed	168 (53.8%)
Mean Age	41.3 $\pm$ 12.5 yrs	

Based on the assessment of knowledge and perception, a majority of the participants demonstrated a good level of knowledge regarding anesthesia and the role of anesthesiologists. Equally, a large percentage experienced a positive attitude towards anesthesiologists and their roles in patient care. Nevertheless, a significant number of them retained insufficient knowledge or negative attitudes, which means that the area of widespread awareness of the population and the education of patients could be enhanced (Table 2).

**Table 2:** Knowledge and Perception Scores of Participants

Status Types	Categories	n (%)
Knowledge Status	Good	182 (58.3%)
	Poor	130 (41.7%)
Perception Status	Positive	204 (65.4%)
	Negative	108 (34.6%)

In comparing the relationship between the status of knowledge among the participants with the demographic traits of the participants, there was no significant relationship between gender and exposure to anesthesia before. Nevertheless, there was a statistically significant correlation between knowledge status, residence, and education level. The percentage of good knowledge was increased among urban residents compared to rural residents. Equally, the education level secondary and higher education had more chances of possessing good knowledge, whereas those having no formal education had a majority possession of poor knowledge. These results indicate that education level and city life can have a positive effect on the patients' knowledge of anesthesia and the work of anesthesiologists (Table 3).

**Table 3:** Association between Knowledge Status and Demographic Variables

Variables	Good Knowledge, n (%)	Poor Knowledge, n (%)	p-value
<b>Gender</b>			
Male	98 (59.0%)	68 (41.0%)	0.317
Female	84 (57.5%)	62 (42.5%)	
<b>Residence</b>			
Urban	130 (65.7%)	68 (34.3%)	0.021*
Rural	52 (45.6%)	62 (54.4%)	
<b>Education Level</b>			
Illiterate	12 (24.0%)	38 (76.0%)	<0.001*
Primary	34 (44.7%)	42 (55.3%)	
Secondary	136 (74.7%)	46 (25.3%)	
<b>Previous Anesthesia</b>			
Exposed	90 (62.5%)	54 (37.5%)	0.068
Non-exposed	92 (54.8%)	76 (45.2%)	

The chi-square test was applied

\*Statistically significant at  $p \leq 0.05$

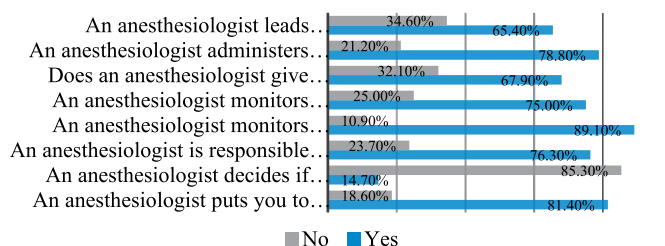
There was also a strong correlation between the perception of the patients of the anesthesiologists and the type of anesthesia that they had been administered ( $p=0.041$ ). The patients undergoing general anesthesia were more likely to have a positive perception than the patients undergoing regional or local anesthesia. It is important to note that a negative perception was observed in almost 50% of the patients undergoing local anesthesia. Such results imply that the level of interaction with patients and the type of anesthetic care could determine the perception of the role and significance of anesthesiologists by patients (Table 4).

**Table 4:** Association Between Perception Status and Type of Anesthesia

Type of Anesthesia	Perception n (%)		p-value
	Positive	Negative	
General	130 (69.9%)	56 (30.1%)	0.041*
Regional	46 (63.9%)	26 (36.1%)	
Local	28 (51.9%)	26 (48.1%)	

The number of participants who correctly identified that putting patients to sleep during general anesthesia is the role of anesthesiologists was 254 out of 312 (81.4%), and the number of individuals who correctly identified that their task is to wake patients after the operation was also 238 out of 312 (76.3%). Many of them, 278 respondents (89.1%) knew that anesthesiologists watch such parameters as blood pressure and breathing during surgery. Equally, 234 (75.0%) acknowledged that anesthesiologists pay attention to blood loss, and 212 (67.9%) understood that they have to administer blood in case of need, during the surgery. Moreover, 246 respondents (78.8%) correctly determined that anesthesiologists give drugs and fluids in an operating room, whereas 204 (65.4%) participants assumed that anesthesiologists took the lead in the post-operative care. Nonetheless, the perception of the preoperative role of anesthesiologists revealed the existence of a large disparity in perceptions between respondents, with 46 participants (14.7%) indicating that anesthesiologists are engaged in deciding on whether surgery should proceed, compared to the majority of 266 individuals (85.3%) (Figure 1).

### Patient Perception Regarding Anesthesiologists

**Figure 1:** A bar graph showing the Patient Perception Regarding Anesthesiologists

## DISCUSSION

In the current research, the researcher intended to measure the level of knowledge and perception of patients about anesthesia and the role of anesthesiologists. We found that 58.3% of the participants were good in terms of knowledge, and 65.4% were positive in their perception. The findings indicate that there is a moderate degree of awareness among surgical patients, and their awareness level can be improved, especially in the knowledge of the role played by the anesthesiologist during the preoperative and decision-making process. The present study found it

consistent with a study done in Saudi Arabia by Almutairi et al. in which 60% of participants had sufficient knowledge about anesthesia, and 63% had a positive attitude towards anesthesiologists [5]. A study by Arefayne et al. in Ethiopia showed that 28.3% of participants knew enough about anesthesiologists [6]. A different study conducted by Jouybar et al. in Iran reported that reduced awareness led to an awareness of the role of the anesthesiologist during the operation; only 38% of respondents were aware of this job intraoperatively [14]. In our work, good knowledge was significantly correlated with education level and urban living, which is also in line with the results of Zaihi et al. in Saudi Arabia, who claimed that higher education was the strongest predictor of better knowledge [15]. Likewise, Wang et al. stated that patients who had a higher education level and previous experience with surgery were more familiar with the facts related to anesthesia [16]. Our findings are also supported by a study carried out in China by Wu et al. who found that urban patients were more likely to have a positive perception than patients living in rural areas, which may be attributed to the fact that they had better access to information on the subject and services due to the presence of anesthetic technologies [17]. In addition, the necessary results obtained in the present study show that patients undergoing general anesthesia demonstrated a significantly greater positive perception than those undergoing regional or local anesthesia. A study in the USA by Pennington et al. supports this claim by finding that exposure to general anesthesia correlates with increased patient engagement and dependence on anesthesiologists [18]. In contrast to our results, a study conducted by Ebrahimi et al. indicated poor knowledge above 70% of respondents, which suggests that there are significant differences in the knowledge of the public regarding the practice of anesthesia between the regions and healthcare systems [19]. In a similar vein, a study by Renuka in India indicated that non-medical graduate professionals believed anesthesiologists did something more than administering anesthesia, and this is a major difference in what is known about their scope of practice [20]. The current paper highlights the urgent importance of organized patient education about anesthesia and the overall role of anesthesiologists. The introduction of anesthesia awareness modules in preoperative counselling, displaying educational posters in preoperative waiting bays, and asking anesthesiologists to introduce themselves and their role can contribute a great deal to patient trust and cooperation. Perioperative anxiety among patients can also be mitigated through the enhancement of patient understanding and shared decision-making in surgical care.

Despite being a cross-sectional study conducted within a

single institutional framework, the study population was drawn from multiple SIUT campuses located across different cities, which may partially enhance the representativeness of the sample. However, the single-center design limits the generalizability of the findings to other healthcare settings with different organizational structures and patient populations. There may be social desirability or recall bias in self-reported questionnaire responses. Also, our research did not evaluate the fears of patients or their psychological determinants of knowledge and perception. Future, longitudinal, and multicenter research using qualitative interviews would aid in delving deeper into these dimensions.

## CONCLUSIONS

Conclusively, although most of the patients portrayed good knowledge and positive attitude towards the anesthesiologists, there are still gaps, especially in how the patients perceive the anesthesiologists in deciding and leading them outside of the operating room. The results also highlight the importance of specific educational measures aimed at increasing patient awareness and, more specifically, the population of rural and less-educated people. Patients empowered with correct information about anesthesia will not only create trust and cooperation but will also enhance safer and more patient-oriented perioperative care.

## Authors' Contribution

Conceptualization: AAG

Methodology: SWU

Formal analysis: SMA, SK, MQA

Writing and Drafting: AAG, SMA, NN, SK, SWU

Review and Editing: AAG, SMA, NN, SK, MQA, SWU

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

## Diagnostic Performance of Magnetic Resonance Imaging for Vertebral Metastases in Routine Clinical Practice

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### ABSTRACT

Vertebral metastasis is a frequent complication of systemic malignancies and may cause pain, pathological fractures, and neurological compromise. MRI is commonly used for suspected spinal metastases; however, the diagnostic performance of routine 1.5-Tesla MRI interpreted using visual criteria in everyday practice remains unclear. **Objectives:** To determine the diagnostic accuracy of conventional MRI for the detection of vertebral metastases using histopathology and/or multidisciplinary clinic radiologic consensus as reference standards. **Methods:** This prospective cross-sectional study at MTI Bacha Khan Medical College and Mardan Medical Complex, Pakistan (15 Sept–15 Dec 2025), included 106 adults with suspected vertebral neoplastic lesions who underwent 1.5-Tesla MRI. Two blinded radiologists independently interpreted scans, resolving discrepancies by consensus. Histopathology and/or tumor board consensus served as the reference standard. Sensitivity, specificity, predictive values, accuracy, and ROC-AUC were calculated. **Results:** Of 106 patients, 64 (60.4%) had vertebral metastases by the reference standard. MRI sensitivity was 42.2% (95% CI: 30.1–54.3), specificity 54.8% (95% CI: 39.7–69.9), PPV 58.7% (95% CI: 44.5–72.9), NPV 38.3% (95% CI: 26.1–50.5), and overall accuracy 47.2% (95% CI: 37.7–56.7). The AUC was 0.515 (95% CI: 0.40–0.63). False positives were commonly due to hemangioma and infection, whereas false negatives were mainly related to poor image quality, small/early lesions, and reader variability. **Conclusions:** Conventional 1.5-Tesla MRI using routine visual criteria showed low sensitivity, modest specificity, and limited accuracy for vertebral metastases. Clinical correlation and reference-standard confirmation remain essential for equivocal cases.

### INTRODUCTION

Vertebral metastasis represents the most common form of malignant involvement of the skeletal system and constitutes a major cause of morbidity, chronic pain, neurological compromise, and reduced quality of life in patients with systemic malignancies [1]. The spine is particularly vulnerable to metastatic spread because of its rich vascular supply and high content of red marrow, making it a frequent site of secondary tumor deposits. Early and accurate detection of vertebral metastases is therefore critical, as delayed diagnosis may result in irreversible spinal cord compression, pathological fractures, and permanent neurological deficits. Timely

identification plays a central role in guiding therapeutic decisions, including surgery, radiotherapy, and systemic treatment, and directly influences patient outcomes [2]. Magnetic resonance imaging (MRI) is widely regarded as the imaging modality of choice for the evaluation of suspected vertebral metastases, owing to its superior soft-tissue contrast, multiplanar capability, and high sensitivity for detecting early bone marrow infiltration before cortical destruction becomes apparent on conventional radiography or computed tomography [3]. Typical MRI features of vertebral metastases include T1 hypointensity, T2/STIR hyperintensity, diffusion restriction, contrast

enhancement, and involvement of the pedicles or posterior elements. However, despite these established imaging criteria, considerable overlap exists between metastatic lesions and a range of benign conditions, including vertebral hemangiomas, infectious spondylitis, osteoporotic compression fractures, and degenerative Modic changes. This overlap often leads to diagnostic uncertainty and may result in inappropriate management if imaging findings are misinterpreted [4, 5]. In recent years, advanced techniques such as quantitative diffusion-weighted imaging, radiomics, and artificial intelligence-assisted image interpretation have shown promising improvements in the diagnostic performance of MRI [6, 7]. Nevertheless, in most low- and middle-income settings, including Pakistan, routine clinical practice continues to rely predominantly on conventional visual interpretation of standard MRI sequences. There is limited real-world evidence regarding the diagnostic accuracy of such routine MRI protocols in differentiating metastatic from non-metastatic vertebral lesions, particularly in South Asian populations, where patterns of primary malignancies and access to advanced imaging tools may differ from those reported in high-income countries [8]. This evidence gap is directly relevant to the scope of radiology-focused journals, which emphasize evaluating imaging performance in routine clinical practice. The study hypothesized that conventional MRI, when interpreted using standard visual criteria alone, has limited diagnostic accuracy for differentiating metastatic from non-metastatic vertebral lesions in routine clinical practice. Therefore, the present study was designed to evaluate the diagnostic accuracy of conventional 1.5-Tesla MRI for the detection of vertebral metastases using histopathology and multidisciplinary clinic radiologic consensus as reference standards, and to analyze the causes of diagnostic discordance in routine reporting. The study aimed to provide clinically relevant evidence aligned with the journal's focus on diagnostic imaging performance and quality of radiologic interpretation.

## METHODS

The study was a prospective cross-sectional diagnostic accuracy study (diagnostic test evaluation) conducted at the Department of Radiology, MTI Bacha Khan Medical College and Mardan Medical Complex, Mardan, Pakistan, over three months (15 September 2025 to 15 December 2025) after ethical approval by the Ethical Review Board of Bacha Khan Medical College, Mardan (Approval No. 929/BKMC). Ethical clearance was granted for the research project entitled "Diagnostic Accuracy of Magnetic Resonance Imaging for Vertebral Metastases." Written informed consent was obtained from all participants before enrollment, and the study was carried out in

compliance with the Declaration of Helsinki. The study was conducted and reported in accordance with the Standards for Reporting Diagnostic Accuracy Studies (STARD 2015) guidelines. All clinical and imaging data were anonymized and coded to ensure patient confidentiality. The eligible patients presenting during the study period were enrolled consecutively and underwent MRI followed by reference standard confirmation. Non-probability consecutive sampling was used to enroll one hundred and six (106) adult patients with suspected vertebral lesions on clinical or radiologic grounds between 15 September 2025 and 15 December 2025. Patients aged 18 years and older who presented with vertebral lesions suspicious for neoplastic pathology on initial imaging and proceeded to undergo MRI followed by confirmatory diagnostic reference investigations were eligible. Patients were excluded in case of recent vertebral trauma, a known history of primary spinal infection, poor-quality MRI scans that were non-diagnostic, or incomplete clinical or histopathological data. The sample size was calculated for estimation of MRI sensitivity using the standard single-proportion formula. The sample size was calculated for estimation of MRI sensitivity using the standard single-proportion formula:  $n = Z^2 \times S(1 - S) / d^2$ , where  $Z = 1.96$  for a 95% confidence interval,  $S$  was the anticipated sensitivity (70%) based on previously published meta-analytic data on skeletal metastases detection and  $d$  was the allowable margin of error (9%) [9]. Every patient underwent MRI examination on a 1.5-Tesla scanner using a standardized spine imaging protocol that comprised sagittal T1-weighted sequences, axial T1-weighted sequences, sagittal T2-weighted sequences, STIR sequences, diffusion-weighted imaging (DWI), and post-contrast fat-suppressed T1-weighted sequences. Two consultant radiologists (each with  $\geq 5$  years post-fellowship experience) independently interpreted all MRI examinations while blinded to the reference standard outcome. Disagreements were resolved in a joint consensus session to generate the final MRI classification used for analysis. Formal interobserver agreement statistics (e.g., Cohen's kappa) were not calculated, as the final diagnostic classification was based on consensus interpretation; therefore, quantitative assessment of interobserver reproducibility was not performed. MRI was classified as positive for vertebral metastasis when one or more predetermined imaging characteristics were detected, including T1 hypointensity, T2/STIR hyperintensity, diffusion restriction, contrast enhancement, heterogeneous enhancement, pedicle involvement, skip lesions, multiple non-contiguous vertebral involvement, marrow replacement patterns, or adjacent disc sparing. MRI positivity was intentionally defined as a composite visual criterion to mirror routine

reporting practice, where radiologists integrate multiple features into an overall impression. Consequently, the study did not perform feature-level diagnostic modeling or assess the independent predictive performance of individual MRI signs. The reference standard was defined as histopathology from vertebral biopsy whenever biopsy was clinically indicated and technically feasible. For patients without histopathology, final classification was determined by a multidisciplinary tumor board (radiology, oncology, spine surgery, and pathology) using a predefined consensus process incorporating imaging findings, clinical course, laboratory results, and follow-up information. This composite reference standard was selected to reflect routine clinical practice; however, it may introduce classification heterogeneity and potential verification bias in cases without tissue confirmation. A structured proforma was used to record demographic characteristics, clinical parameters, imaging features, and final reference standard outcome. Selection bias was minimized through consecutive patient recruitment. Observer bias was controlled by blinded dual-reader interpretation with consensus resolution. Verification bias was minimized by ensuring that all enrolled patients underwent reference standard assessment. However, because histopathology was not available for all participants, partial verification bias and classification heterogeneity cannot be completely excluded. An audit of discordant MRI examinations was performed to identify technical and interpretative factors contributing to false-positive and false-negative results. Statistical analysis was performed using IBM SPSS Statistics version 26.0. Normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were summarized as median and interquartile range, and categorical variables were expressed as frequencies and percentages. Pearson chi-square or Fisher's exact test and the Mann-Whitney U test were used to compare categorical and continuous variables, respectively. Diagnostic performance indices, including sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy, and 95% confidence intervals, were calculated. Receiver operating characteristic (ROC) curve analysis was performed to estimate the area under the curve (AUC), and effect sizes were reported using Cramer's V. A p-value < 0.05 was considered statistically significant.

## RESULTS

The two groups were comparable with respect to age and duration of symptoms, with no statistically significant differences observed. The female gender was significantly more frequent in the metastatic group, indicating a possible gender-related difference in disease distribution. No significant associations were identified for age group,

smoking status, presence of back pain, or neurological deficit between the two groups. The baseline demographic and clinical characteristics of patients with and without vertebral metastasis. Additionally, the overall pattern of primary tumors was similar in both metastatic and non-metastatic groups. No statistically significant difference was observed in the distribution of primary tumor types, suggesting that the underlying primary malignancy profile did not differ meaningfully between the two groups. The distribution of primary malignancy types stratified by gold-standard diagnosis. Further, there were no significant differences in vertebral region, number of vertebrae involved, posterior element involvement, paraspinal mass, or epidural extension. Pathological vertebral collapse demonstrated a borderline association with metastatic disease, suggesting a possible trend toward higher fracture risk in metastatic lesions, although this did not reach statistical significance. The comparison of vertebral level involvement and disease extent between the two groups (Table 1).

**Table 1:** Baseline Demographic and Clinical Characteristics of Patients with and Without Vertebral Metastasis, Distribution of Primary Malignancy Types Stratified and Vertebral Level Involvement and Disease Extent According to Gold-Standard Diagnosis (n=106)

Variables	Metastasis (n=64)	Non-metastasis (n=42)	p-value
<b>Baseline Demographic and Clinical Characteristics</b>			
Age (Years), Median (IQR)	52 (35-68)	53 (36-69)	0.436‡
Duration of Symptoms (Weeks), Median (IQR)	10 (=5-15)	10 (=5-15)	0.933‡
<b>Gender</b>			
Female	37 (57.8%)	16 (38.1%)	0.047*
Male	27 (42.2%)	26 (61.9%)	
<b>Age group</b>			
≤40	11 (17.2%)	12 (28.6%)	0.150
41-60	26 (40.6%)	10 (23.8%)	
>60	27 (42.2%)	20 (47.6%)	
<b>Smoking status</b>			
Smoker	38 (59.4%)	20 (47.6%)	0.234
Non-smoker	26 (40.6%)	22 (52.4%)	
Back pain present	38 (59.4%)	25 (59.5%)	0.988
Neurological deficit	32 (50.0%)	22 (52.4%)	0.810
<b>Primary Tumor Type</b>			
Breast	3 (4.7%)	7 (16.7%)	0.473
Gastrointestinal	8 (12.5%)	7 (16.7%)	
Hematological	10 (15.6%)	5 (11.9%)	
Kidney	7 (10.9%)	5 (11.9%)	
Liver	7 (10.9%)	4 (9.5%)	
Lung	8 (12.5%)	6 (14.3%)	
Prostate	8 (12.5%)	4 (9.5%)	
Unknown / Not detected	13 (20.3%)	4 (9.5%)	

Vertebral Region			
Cervical	11 (17.2%)	12 (28.6%)	0.451
Thoracic	20 (31.3%)	10 (23.8%)	
Lumbar	15 (23.4%)	7 (16.7%)	
Sacral	18 (28.1%)	13 (31.0%)	
Number of Vertebrae Involved			
Single	35 (54.7%)	24 (57.1%)	0.803
Multiple	29 (45.3%)	18 (42.9%)	
Posterior Element Involvement	34 (53.1%)	21 (50.0%)	0.753
Paraspinal Soft-Tissue Mass	33 (51.6%)	22 (52.4%)	0.934
Epidural Extension	36 (56.3%)	20 (47.6%)	0.384
Pathological Collapse/Fracture	26 (40.6%)	25 (59.5%)	0.057

\*Chi-square test ‡Mann-Whitney U test

None of the individual MRI features showed a statistically significant difference between the two groups, indicating substantial overlap in imaging appearances. A non-significant tendency toward higher prevalence of adjacent disc sparing was observed in non-metastatic lesions, but this finding did not reach statistical significance. The comparison of MRI signal and enhancement characteristics between metastatic and non-metastatic vertebral lesions, table 2.

ability, as reflected by an area under the curve close to 0.5, indicating that MRI performed only slightly better than chance in distinguishing metastatic from non-metastatic lesions (Table 3).

**Table 3:** Diagnostic Accuracy of MRI for Detection of Vertebral Metastases Using the Gold-Standard Reference (n=106)

Variables	Gold-standard Metastasis +	Gold-standard Metastasis -	Total	Estimate % (95% CI)
MRI Positive	27 (True Positive)	19 (False Positive)	46	–
MRI Negative	37 (False Negative)	23 (True Negative)	60	–
Total	64	42	106	–
Sensitivity	–	–	–	42.2 (30.1-54.3)
Specificity	–	–	–	54.8 (39.7-69.9)
Positive Predictive Value (PPV)	–	–	–	58.7 (44.5-72.9)
Negative Predictive Value (NPV)	–	–	–	38.3 (26.1-50.5)
Overall Accuracy	–	–	–	47.2 (37.7-56.7)
Area Under the Curve (AUC)	–	–	–	0.515 (0.40-0.63)

Values are presented as percentages with 95% confidence intervals in parentheses

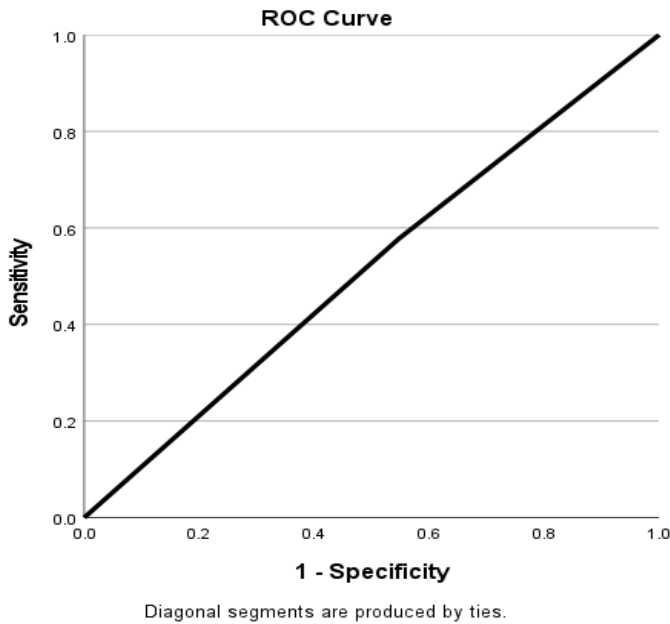
The area under the curve indicates poor discriminative performance, confirming the limited diagnostic utility of MRI when compared with the gold-standard reference. The receiver operating characteristic curve for MRI in the detection of vertebral metastases (Figure 1).

**Table 2:** Comparison of MRI Signal and Enhancement Characteristics between Metastatic and Non-Metastatic Vertebral Lesions (n=106)

MRI feature	Metastasis n (%)	Non-metastasis n (%)	$\chi^2$ value	p-value
T1 hypointensity	30 (46.9%)	16 (38.1%)	0.80	0.372
T2/STIR hyperintensity	34 (53.1%)	23 (54.8%)	0.03	0.869
Diffusion restriction (DWI)	34 (53.1%)	21 (50.0%)	0.10	0.753
Contrast enhancement present	37 (57.8%)	20 (47.6%)	1.06	0.303
Heterogeneous enhancement	33 (51.6%)	16 (38.1%)	1.85	0.174
Pedicle involvement	32 (50.0%)	24 (57.1%)	0.52	0.471
Skip lesions	28 (43.8%)	21 (50.0%)	0.40	0.528
Multiple non-contiguous lesions	37 (57.8%)	22 (52.4%)	0.30	0.582
Adjacent disc sparing	28 (43.8%)	25 (59.5%)	2.52	0.112
Marrow replacement pattern	34 (53.1%)	20 (47.6%)	0.31	0.579

All comparisons were performed using the Pearson Chi-square test

MRI demonstrated low sensitivity and moderate specificity for the detection of vertebral metastases, resulting in poor overall diagnostic accuracy. Receiver operating characteristic analysis confirmed limited discriminative



**Figure 1:** Receiver Operating Characteristic (ROC) Curve Showing the Diagnostic Performance of MRI for Detection of Vertebral Metastases. The Area Under the Curve (AUC) was 0.515 (95% CI: 0.40-0.63), Indicating Poor Discriminative Ability Compared with the Gold-Standard Reference

False-positive interpretations were most commonly

attributed to benign vertebral conditions such as hemangioma and infection, whereas false-negative results were mainly related to poor image quality, reader variability, and small or early marrow lesions. These findings indicate that both technical limitations and interpretative factors contributed substantially to diagnostic errors (Table 4).

**Table 4:** Analysis of Discordant MRI Results and Audit Findings (n=56)

Categories	n	Common reasons (Audit Findings)
False positives (FP)	19	Hemangioma (26.3%), Infection (21.1%), Other benign lesions (21.1%), Trauma (10.5%), Osteoporosis (10.5%), Modic changes (10.5%)
False negatives (FN)	37	Poor image quality (32.4%), Reader variability (21.6%), Small lesions (18.9%), Early marrow infiltration (16.2%), Other causes (10.8%)

No significant differences were observed between the metastatic and non-metastatic groups with respect to neurological deficit, need for urgent surgery, or radiotherapy planning. Length of hospital stay was also comparable between the two groups, indicating that short-term clinical outcomes did not differ significantly according to metastatic status. Effect sizes were negligible for all assessed clinical outcomes (Table 5).

**Table 5:** Clinical Outcomes and Management According to Vertebral Metastatic Status (n=106)

Parameters	Metastasis, n (%)	Non-metastasis (%)	Test	$\chi^2$ (df)	p-value	Cramer's V
Neurological Deficit	32 (50.0%)	22 (52.4%)	$\chi^2$	0.058 (1)	0.810	0.023
Need For Urgent Surgery	29 (45.3%)	21 (50.0%)	$\chi^2$	0.224 (1)	0.636	0.046
Radiotherapy Planned	29 (45.3%)	20 (47.6%)	$\chi^2$	0.054 (1)	0.816	0.023
Hospital Stays (Days), Median (IQR)	10 (8%)	11.5 (7%)	Mann-Whitney U	—	0.142	—

## DISCUSSION

The present study evaluated the diagnostic performance of conventional 1.5-Tesla MRI interpreted by routine visual criteria for detecting vertebral metastases using histopathology and/or multidisciplinary tumor board consensus as the reference standard. MRI demonstrated low sensitivity (42.2%) and modest specificity (54.8%), with an AUC of 0.515 (95% CI: 0.40-0.63), indicating poor discriminative ability. Taken together, these findings suggest that when routine MRI interpretation is reduced to a binary "metastasis vs non-metastasis" decision based on multiple overlapping features, diagnostic separation becomes limited in real-world reporting conditions. Harlianto et al. reported that meta-analytic evidence suggests that, under optimized protocols and standardized assessment, MRI can achieve substantially higher pooled sensitivity and specificity for spinal metastases, indicating that the poor performance observed in the present cohort likely reflects real-world methodological and interpretative constraints rather than intrinsic limitations of MRI as a

modality [10]. A clinically important observation in this cohort was the high proportion of discordant scans (n=56), with more false-negative (n=37) than false-positive results (n=19). This pattern indicates that missed metastases were a larger contributor to diagnostic error than overcalling, which is relevant because false-negative interpretations may delay oncologic staging and timely intervention. The audit findings in Table 6 further clarify the mechanisms of error: false positives were commonly related to benign entities with overlapping marrow signal and enhancement (e.g., hemangioma and infection), while false negatives were linked to technical limitations (poor image quality), subtle/early marrow infiltration, small lesions, and reader-related variability. This supports the interpretation that the limited accuracy observed was not driven by a single imaging sign, but rather by the cumulative effect of overlap between benign and malignant marrow patterns under routine clinical constraints. Similar sources of diagnostic error, particularly overlap with benign marrow conditions

and limitations of visual assessment, have also been reported in comparative imaging reviews, reinforcing that misclassification remains a common challenge in routine spinal MRI interpretation [11]. When compared with contemporary literature, the performance observed in our study is lower than that reported in studies using more structured quantitative approaches or broader protocols. For example, Mijaljevic *et al.* reported very high discrimination for benign versus malignant vertebral lesions when diffusion and chemical-shift parameters were integrated, achieving an AUC close to 1.0 with high sensitivity and specificity [12]. Zhang *et al.* and Sanker *et al.* reported that, unlike our study, their diagnostic strategy relied on quantitative thresholds in addition to morphology; therefore, their results cannot be directly extrapolated to routine visual interpretation alone, but they do highlight the potential value of measurement-based workflows, and radiomics-based models have shown moderate-to-high discrimination in differentiating spinal metastases from other vertebral pathologies [13, 14]. In addition, MRI-based radiomics nomograms have demonstrated significantly improved discrimination compared with conventional morphological criteria, further supporting the concept that feature extraction beyond routine visual assessment is necessary for reliable lesion characterization [15]. Another key methodological point raised by the reviewers relates to grouping multiple MRI features into a single binary MRI outcome. In this study, MRI positivity was defined pragmatically as the presence of one or more predefined features, which mirrors real reporting practice but may dilute the individual predictive contribution of each sign. This is supported by table 4, where no single MRI feature significantly distinguished metastatic from non-metastatic lesions, suggesting substantial overlap across commonly used signal and enhancement characteristics. Therefore, the findings should be interpreted as an evaluation of routine “overall impression” MRI reporting, rather than the diagnostic power of any individual MRI parameter. This limitation of composite binary classification has also been highlighted in recent artificial intelligence and automated detection studies, where individual feature weighting and multivariate models achieved superior diagnostic separation compared with unweighted visual criteria [16, 17]. From a clinical standpoint, table 7 showed no significant difference between metastatic and non-metastatic groups in neurological deficit, urgent surgery, radiotherapy planning, or length of hospital stay. This likely reflects that treatment decisions and short-term outcomes in this cohort were influenced by multiple clinical factors (symptom burden, stability, oncologic plan), not solely by MRI classification [18]. Importantly, the

absence of group differences in these outcomes does not negate the need for accurate imaging; rather, it emphasizes that diagnostic imaging must be interpreted within a broader clinical pathway and corroborated with reference standards when uncertainty persists. Beyond initial diagnosis, MRI also plays an established role in treatment response assessment after targeted therapies such as stereotactic body radiotherapy, underscoring its broader clinical relevance in the longitudinal management of spinal metastases [19, 20].

The main strength of this study is its focus on real-world diagnostic accuracy using standard MRI protocols and routine interpretive workflows, which aligns with the journal's emphasis on practical radiology performance. This pragmatic evaluation of routine MRI performance directly aligns with the journal's scope, which emphasizes assessment of diagnostic imaging accuracy, reproducibility, and quality of radiologic interpretation in everyday clinical practice. However, several limitations should be considered. First, this was a single-center study with a moderate sample size, which may limit generalizability. Second, although MRI examinations were initially interpreted independently by two blinded radiologists, formal interobserver agreement statistics (e.g., Cohen's kappa) were not calculated; therefore, quantitative assessment of reproducibility was not performed, which may limit extrapolation to non-consensus or single-reader clinical settings. Third, the reference standard incorporated both histopathology and multidisciplinary tumor board consensus to reflect routine clinical practice; while pragmatic, this approach may introduce classification heterogeneity and partial verification bias, particularly in cases without tissue confirmation. Fourth, MRI positivity was defined using a composite visual criterion rather than feature-level diagnostic modeling; consequently, the independent predictive value of individual imaging features was not assessed, which may limit generalizability to structured or quantitative reporting frameworks. Future multicenter studies incorporating formal reproducibility analysis and feature-level modeling are warranted to validate these findings.

## CONCLUSIONS

Conventional 1.5-Tesla MRI interpreted using routine visual criteria demonstrated poor diagnostic accuracy for vertebral metastases in this cohort, with low sensitivity (42.2%), modest specificity (54.8%), and poor discrimination (AUC 0.515; 95% CI: 0.40–0.63) compared with histopathology and/or multidisciplinary reference standards. Diagnostic discordance was driven predominantly by false-negative interpretations and by overlap between benign and malignant marrow patterns,

compounded by technical factors and reader variability. These findings support careful correlation with clinical context and reference standard confirmation when MRI appearances are equivocal, and they provide practice-relevant evidence aligned with the journal's scope in diagnostic radiology.

### Authors' Contribution

Conceptualization: LK

Methodology: ZJO, MS

Formal analysis: TB, HB, SN

Writing and Drafting: LK, ZJO, TB, SN, MS

Review and Editing: LK, ZJO, TB, HB, SN, MS

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

### Conflicts of Interest

All the authors declare no conflict of interest.

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## Original Article



## Postoperative Ileus After Exploratory Laparotomy

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## ABSTRACT

Postoperative ileus is a common and significant complication following abdominal surgery, particularly after exploratory laparotomy. It is characterized by a temporary impairment of gastrointestinal motility leading to delayed passage of bowel contents, abdominal distension, nausea, vomiting, and prolonged hospital stay. Identifying the frequency of postoperative ileus after exploratory laparotomy is essential for understanding its clinical burden and for improving perioperative management strategies aimed at reducing postoperative morbidity. **Objectives:** To determine the frequency of postoperative complications in patients undergoing emergency exploratory laparotomy for non-traumatic ileal perforation. **Methods:** This Analytical cross-sectional study was conducted from 15th July 2025 to 16th October 2025 at the Department of Surgery, Lady Reading Hospital, Peshawar. A total of 115 patients, aged 18–65 years, undergoing exploratory laparotomy were included using non-probability consecutive sampling. **Results:** The mean age was  $41.08 \pm 14.05$  years, and 64.3% were male. Wound infection was the most frequent postoperative complication observed in 33 patients (28.7%), followed by peristomal excoriation in 19 (16.5%), postoperative ileus in 18 (15.7%), wound dehiscence in 13 (11.3%), and fistula formation in 3 patients (2.6%). **Conclusions:** Postoperative ileus remains a considerable complication after exploratory laparotomy. Diabetes, hypertension, obesity, and older age are important predictors.

## INTRODUCTION

Postoperative ileus is a common complication occurring after exploratory laparotomy. [1] It is defined as a temporary impairment of bowel motility following surgical intervention, resulting in delayed passage of flatus and stool, abdominal distension, nausea, and vomiting [1]. After exploratory laparotomy, handling of bowel loops, exposure of the peritoneal cavity, and tissue trauma lead to neurogenic and inflammatory responses that suppress coordinated peristalsis [2]. The condition is usually transient but can significantly prolong hospital stay and increase patient discomfort. Clinically, patients present with a bloated abdomen, absent or hypoactive bowel sounds, intolerance to oral intake, and sometimes nasogastric aspirate persistence [3]. The pathophysiology of postoperative ileus is multifactorial. Surgical stress

activates the sympathetic nervous system, which inhibits gastrointestinal motility [4]. In addition, inflammatory mediators such as cytokines and prostaglandins are released due to bowel manipulation, causing smooth muscle dysfunction [4]. Use of opioid analgesics further worsens ileus by acting on  $\mu$ -receptors in the gut wall, decreasing peristaltic activity [5]. Electrolyte imbalance, especially hypokalemia, and intra-abdominal infection may also contribute to prolonged ileus. [6] Small intestine motility usually recovers within 24 hours, stomach within 24–48 hours, while colonic activity may take 48–72 hours or longer after major abdominal surgery [7]. Management of postoperative ileus is mainly supportive and preventive. Early mobilization, early enteral feeding when tolerated, and minimizing opioid use are important strategies [8].



Multimodal analgesia and the use of epidural anesthesia can help reduce opioid requirements. Nasogastric decompression is not routinely recommended but may be required in patients with persistent vomiting or severe distension [9]. Correction of fluid and electrolyte imbalance is essential. Enhanced Recovery After Surgery (ERAS) protocols have shown a reduction in duration of ileus and hospital stay by promoting early ambulation, early feeding, and optimal pain control [10, 11]. Careful surgical technique with minimal bowel handling during exploratory laparotomy also plays a significant role in prevention [12]. Despite its clinical relevance, limited regional data are available regarding the frequency and associated factors of postoperative ileus in patients undergoing exploratory laparotomy in Peshawar. Variations in demographic characteristics, comorbidity profiles, nutritional status, and perioperative management may influence the occurrence of postoperative ileus. This study aimed to determine the frequency of postoperative ileus after exploratory laparotomy and to assess its association with selected demographic and clinical factors in a tertiary care hospital setting.

## METHODS

This analytical cross-sectional study was conducted from 15th July 2025 to 16th October 2025 at the Department of Surgery, Lady Reading Hospital, Peshawar. Ethical approval was obtained from the Ethics Review Board of Lady Reading Hospital (Ref No: 217/LRH/MTI) and the CPSP no: CPSP/REU/SGR-2021-022-13041. The sample size was calculated using the standard formula for estimation of a single population proportion:  $n = Z^2 \times P \times (1 - P) / d^2$ , where  $n$  is the required sample size,  $Z$  is the standard normal deviate corresponding to a 95% confidence level ( $Z = 1.96$ ),  $P$  was the expected frequency of postoperative ileus (25.5%) [13], and  $d$  was the absolute precision (8%). Based on these parameters, the calculated sample size was 115 patients. Participants were enrolled using a non-probability consecutive sampling technique. Inclusion criteria comprised male and female patients aged 18–65 years who had non-traumatic ileal perforation and had undergone emergency laparotomy and were part of this study. Exclusion criteria included pregnant patients, those with known gastrointestinal motility disorders, a history of previous major abdominal surgery, pre-existing mechanical bowel obstruction, inflammatory bowel disease, malignancy-related obstruction, and patients requiring re-exploration within 72 hours postoperatively. All patients received standardized preoperative preparation according to departmental protocols, including overnight fasting, clinical assessment of nutritional status, and routine laboratory investigations. Preoperative nutritional and electrolyte status was

assessed clinically and through serum electrolyte measurements, and identified abnormalities were corrected before surgery. All procedures were performed under standardized general anesthesia. Perioperative use of prokinetic agents was not routine and was reserved for selected postoperative cases based on clinical judgment. Surgeries were conducted by consultant surgeons or senior surgical residents under direct consultant supervision. The degree of intraoperative bowel manipulation was documented as minimal or extensive based on operative findings. Operative details, including bowel resection, anastomosis, or stoma formation, were recorded. The term emergency laparotomy here meant a surgical opening of the abdominal cavity done quickly to manage sudden and life-threatening illness. Non-traumatic ileal perforation is a condition where the lower small intestine is perforated without external injury, presenting with abdominal pain above 3 on the visual analog scale, with tenderness, rigidity, and a gas shadow seen under the diaphragm on X-ray. Before starting data collection, every patient had been informed about the purpose and safety of the study, and a written consent had been taken from them or their attendant. They were assured that no extra harm or risk would come because of participation. After surgery, each patient was assessed by a consultant surgeon with more than five years of post-fellowship experience. The assessment involved full medical history, physical check, and inspection of the operative wound at regular intervals up to 45 days after surgery. Wound infection was considered when discharge with pus, along with redness, warmth, swelling, and pain of more than 3 on the pain scale, was observed. Peristomal excoriation was identified when the skin around the stoma showed irritation, ulcer, or wet lesion. Wound dehiscence was noted when the wound edges got separated or opened. Prolonged ileus was recognized if X-ray showed dilated intestinal loops with fluid levels, together with a distended abdomen and less bowel sound. Fistula formation was recorded when any abnormal opening was seen discharging continuously with irritation of the nearby skin. These were the outcome variables of the research and were observed as per the definitions mentioned.

All data were analyzed using SPSS version 23.0. Variables like age, BMI, and duration of surgery were shown as Mean  $\pm$  SD. And qualitative variables were presented in the form of frequency and percentage. Demographic variables were stratified, and the results were analyzed by using the Chi-square test, with a p-value equal to or less than 0.050 taken as significant.

## RESULTS

The trial involved 115 patients aged  $41.08 \pm 14.05$  years who underwent exploratory laparotomy, with a mean BMI of  $25.67 \pm 2.94 \text{ kg/m}^2$ . The mean duration of surgery was  $77.40 \pm 20.51$  minutes. The study population included 74 males (64.3%) and 41 females (35.7%). Comorbidities included controlled chronic diabetes mellitus in 25 patients (21.7%) and controlled chronic hypertension in 28 patients (24.3%), as documented in preoperative medical records. Postoperatively, 59 patients (51.3%) received intravenous morphine at standard analgesic doses (2–4 mg per dose) administered at 6–8-hour intervals, based on pain assessment and institutional analgesia protocols (Table 1).

**Table 1:** Baseline Demographic and Clinical Characteristics

Demographics	Mean $\pm$ SD / n (%)
Age (Years)	41.08 $\pm$ 14.05
BMI (kg/m <sup>2</sup> )	25.67 $\pm$ 2.94
Duration of Surgery (Minutes)	77.40 $\pm$ 20.51
<b>Gender</b>	
Male	74 (64.3%)
Female	41 (35.7%)
<b>Diabetes</b>	
Yes	25 (21.7%)
No	90 (78.3%)
<b>Hypertension</b>	
Yes	28 (24.3%)
No	87 (75.7%)
<b>Morphine Use</b>	
Yes	59 (51.3%)
No	56 (48.7%)

Enteric fever was the most common cause of perforation, accounting for 77 patients, which was 67.00% of total cases, followed by tuberculosis in 27 patients, that represent 23.50% cases, while adhesions were responsible for only 11 patients, making 9.60% of the studied sample (Table 2).

**Table 2:** Cause of Perforation among Patients

Cause of Perforation	n (%)
Enteric Fever	77 (67%)
Tuberculosis	27 (23.5%)
Adhesion	11 (9.6%)
Total	115 (100%)

Regarding postoperative complications that were observed in patients after exploratory laparotomy, wound infection was the most frequently encountered complication, and it was seen in 33 patients, which corresponds to 28.70% of all cases. Peristomal excoriation was noted in 19 patients, which making 16.50% of complication cases, and postoperative ileus was also among the significant findings and was observed in 18

patients, that represent 15.70% of the total. Furthermore, wound dehiscence was recorded in 13 patients, which accounted for 11.30% of cases, whereas fistula formation was the least commonly occurring complication, which was only presented in 3 patients, corresponding to 2.60% of the total studied patients (Table 3).

**Table 3:** Number of Postoperative Complications among Patients

Postoperative Complications	n (%)
Postoperative Ileus	18 (15.70%)
Wound Infection	33 (28.70%)
Peristomal Excoriation	19 (16.50%)
Wound Dehiscence	13 (11.30%)
Fistula Formation	3 (2.60%)

Age stratification showed ileus occurred in 7 patients (9.7%) aged  $\leq 45$  years compared to 11 patients (25.6%) aged  $> 45$  years ( $p=0.024$ ). Gender distribution showed 11 males (14.9%) and 7 females (17.1%) developed ileus with no significant difference ( $p=0.755$ ). BMI analysis demonstrated ileus in 4 patients (7.7%) with BMI  $\leq 25 \text{ kg/m}^2$  versus 14 patients (22.2%) with BMI  $> 25 \text{ kg/m}^2$  ( $p=0.040$ ). Surgery duration showed 1 patient (3.6%) with ileus in procedures  $\leq 60$  minutes compared to 17 patients (19.5%) in surgeries  $> 60$  minutes ( $p=0.069$ ). Diabetes showed the strongest association with 15 diabetic patients (60.0%) developing ileus compared to only 3 non-diabetic patients (3.3%) ( $p<0.001$ ). Hypertension was present in 10 patients (35.7%) with ileus versus 8 normotensive patients (9.2%) with ileus ( $p<0.001$ ). Morphine use showed 11 patients (18.6%) with ileus among morphine users compared to 7 patients (12.5%) among non-users ( $p=0.365$ ) (Table 4).

**Table 4:** Association of Postoperative Ileus with Demographic and Clinical Factors

Demographic Factors	Postoperative Ileus, n (%)	No Ileus, n (%)	p-value
<b>Age (Years)</b>			
$\leq 45$	7 (9.7%)	65 (90.3%)	0.024*
$> 45$	11 (25.6%)	32 (74.4%)	
<b>Gender</b>			
Male	11 (14.9%)	63 (85.1%)	0.755
Female	7 (17.1%)	34 (82.9%)	
<b>BMI (kg/m<sup>2</sup>)</b>			
$\leq 25$	4 (7.7%)	48 (92.3%)	0.040*
$> 25$	14 (22.2%)	49 (77.8%)	
<b>Duration of Surgery (Minutes)</b>			
$\leq 60$	1 (3.6%)	27 (96.4%)	0.069
$> 60$	17 (19.5%)	70 (80.5%)	
<b>Diabetes Mellitus</b>			
Yes	15 (60.0%)	10 (40.0%)	$<0.001^*$
No	3 (3.3%)	87 (96.7%)	
<b>Hypertension</b>			
Yes	10 (35.7%)	18 (64.3%)	$<0.001^*$
No	8 (9.2%)	79 (90.8%)	

Morphine Use			0.365
Yes	11 (18.6%)	48 (81.4%)	
No	7 (12.5%)	49 (87.5%)	

\* $p < 0.050$  considered statistically significant

When analyzing the association between clinical variables and the development of postoperative ileus, several findings emerged. In terms of symptom duration, patients with symptom duration more than 48 hours were showing postoperative ileus in 14 patients (18.2%) compared to 4 patients (10.5%) with symptom duration less than or equal to 48 hours; this difference was not reaching statistical significance ( $p=0.415$ ). Similarly, when comparing emergency versus elective cases, postoperative ileus occurred in 16 patients (16.7%) of emergency cases and 2 patients (10.5%) of elective cases, with no statistically significant difference between groups ( $p=0.733$ ). Looking at surgical indication, perforation was associated with postoperative ileus in 7 patient (14.0%), obstruction in 5 patient (14.7%), trauma in 2 patients (14.3%), ischemia in 1 patient (16.7%), sepsis in 2 patient (22.2%), and other cause in 1 patient (50.0%). Despite these variations, no statistically significant association was found between surgical indication and postoperative ileus ( $p=0.853$ ). When examining procedure type, stoma creation was showing the highest rate of postoperative ileus with 7 patients (20.6%), followed by adhesiolysis in 3 patients (23.1%), repair in 3 patients (20.0%), resection and anastomosis in 4 patients (10.0%), and drainage in 1 patient (8.3%). The palliative procedure was not associated with any case of postoperative ileus. However, these differences across procedure type were not statistically significant ( $p=0.662$ ) (Table 5).

**Table 5:** Association of Surgical Indications and Procedures with Postoperative Ileus

Clinical Variables		Postoperative Ileus		p-value
		Yes, n (%)	No, n (%)	
Symptom Duration	≤48 Hours	4 (10.5%)	34 (89.5%)	0.415*
	>48 Hours	14 (18.2%)	63 (81.8%)	
Urgency	Emergency	16 (16.7%)	80 (83.3%)	0.733*
	Elective	2 (10.5%)	17 (89.5%)	
Indication	Perforation	7 (14.0%)	43 (86.0%)	0.853*
	Obstruction	5 (14.7%)	29 (85.3%)	
	Trauma	2 (14.3%)	12 (85.7%)	
	Ischemia	1 (16.7%)	5 (83.3%)	
	Sepsis	2 (22.2%)	7 (77.8%)	
	Other	1 (50.0%)	1 (50.0%)	
Procedure Type	Resection Anastomosis	4 (10.0%)	36 (90.0%)	0.662*
	Stoma	7 (20.6%)	27 (79.4%)	
	Repair	3 (20.0%)	12 (80.0%)	
	Drainage	1 (8.3%)	11 (91.7%)	
	Adhesiolysis	3 (23.1%)	10 (76.9%)	
	Palliative	0 (0.0%)	1 (100.0%)	

\*Fisher's Exact Test

## DISCUSSION

In the present study, enteric fever was found to be the most common cause of perforation in 77 patients (67.00%). This may be because enteric fever caused by *Salmonella typhi*, which produced inflammation and necrosis in the Peyer's patches of the terminal ileum, leading to perforation. Wound infection was the most frequently seen postoperative complication and was observed in 33 patients (28.70%). This is because during emergency laparotomy, bowel content is spilled into the peritoneal cavity, that causing contamination and increases the risk of surgical site infection. Postoperative ileus was noted in 18 patients (15.70%), which is also a significant complication. This occurs because handling of the bowel during surgery causes inhibition of normal peristalsis due to activation of the sympathetic nervous system and release of inflammatory mediators. Prolonged ileus further complicates the recovery and increases the hospital stay of patients. Peristomal excoriation was also observed in 19 patients (16.50%), which occurred due to continuous contact of bowel content and digestive enzymes with the peristomal skin, causing skin breakdown and irritation in these patients. The incidence of postoperative ileus observed in the present study lies within the range reported in previous literature. Vather *et al.* reported that postoperative ileus occurs in approximately 10–30% of patients undergoing abdominal surgery, indicating that it is a common complication following laparotomy [14]. Similarly, Chapman *et al.* analyzed postoperative outcomes after abdominal operations and reported an incidence of postoperative ileus of about 15.4%, which is comparable with the findings of the present study [15]. Differences in the reported frequency of postoperative ileus across studies may be attributed to variations in patient populations, type of surgical procedures performed, perioperative management, and criteria used to define postoperative ileus. The wound infection rate of 28.70% observed in the present study is comparable with several previous studies evaluating postoperative complications after emergency laparotomy. Siddiqui *et al.* reported higher morbidity, including wound infections, in patients without defunctioning ileostomy, suggesting that contamination from enteric contents plays a major role in surgical site infections [16]. Chauhan *et al.* reported a lower wound infection rate of 12.28% in emergency laparotomies [17], while Chaudhary *et al.* and Murtaza *et al.* reported infection rates of 22.2% and 21.6%, respectively [18, 19]. Anwar F *et al.* reported a surgical site infection rate of 28.2%, which is very close to the 28.70% observed in the present study [20]. Higher infection rates of 47% and 47.2% were reported by Nazir *et al.* and Gangamma *et al.* respectively [21, 22]. Begum *et al.* also identified wound infection as the most common postoperative complication among patients

with ileal perforation, supporting the findings of the present study [23]. Peristomal excoriation was observed in 19 patients (16.50%) in this study. Similar findings were reported by Rajper *et al.* who documented peristomal skin excoriation in 14.08% of patients undergoing ileostomy for ileal perforation [24]. These findings indicate that stoma-related skin complications are common, particularly in emergency settings where proper stoma site selection and patient education may be limited. Wound dehiscence was noted in 13 patients (11.30%) in the present study. A comparable rate of 11.43% was reported by Rajper *et al.* [24]. However, lower rates of 4.8% and 5.3% were reported by Murtaza B *et al.* and Chaudhary SH *et al.* respectively [18, 19]. The relatively higher rate observed in perforation cases may be attributed to severe peritoneal contamination, delayed presentation, and poor nutritional status, which impair wound healing and increase the risk of fascial separation after surgery.

The present study also has several limitations. The results obtained may not necessarily be generalizable to other settings because it is a single-center trial, and there might be differences with respect to patient mix and surgical and postoperative care practices. A sample size of 115 cases might also affect the sensitivity to detect correlations with certain identified risk factors, particularly those with low prevalence rates. The absence of uniform definitions regarding postoperative ileus diagnoses across different providers could also affect outcomes. The study could not take into account identified potential sources of confusion, which could affect postoperative ileus incidence, such as bowel prep performed preoperatively, distinct anesthetic approaches, fluid management approaches during surgery, and pain management approaches postoperatively, including those excluding morphine administration. The duration and specific definitions regarding postoperative ileus resolution could also affect measurements.

## CONCLUSIONS

This research has shown that the problem of postoperative ileus persists after exploratory laparotomy, and diabetes mellitus is found to be the most significant predictor of postoperative ileus, followed by hypertension, body mass index, and age, while gender and morphine administration are not found to have any significant relationship.

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## Authors' Contribution

Conceptualization: BUD

Methodology: BUD, AN

Formal analysis: BUD

Writing and Drafting: BUD

Review and Editing: BUD, AN

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



## Identification of Genetic Variants Associated with Chronic Kidney Disease Using Restriction Fragment Length Polymorphism

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## ABSTRACT

Chronic kidney disease (CKD) is one of the most common kidney diseases that poses serious health risks. **Objective:** To identify the genetic variants associated with CKD. **Methods:** A cross-sectional study was conducted among 183 participants at Ibn-e-Sina Hospital, Multan, from Nov 2023 to May 2024. *Klotho (KL)*, *Catalase (CAT)*, *Cyclophilin (Cyp)*, tumor protein p53 (*p53*), and *Superoxide dismutase 1 (SOD1)* were selected for polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Primers were designed via Primer3Plus and confirmed through SnapGene. *In-silico* RFLP involved NEBcutter and SnapGene for the construction of the sequence map and the mutated band. Wet lab RFLP involved DNA cleavage by restriction enzymes. After PCR incubation, samples were visualized via gel electrophoresis. The T-Coffee tool aligns sequences, enabling the identification of variations in amino acids. **Results:** The target genes were successfully amplified in the CKD patients before proceeding to RFLP analysis. *TaqI*, *EcoRI*, *AluI*, and *AccI* restriction enzymes were selected from *in-silico* Sequence Maps to cut the band of *SOD1*, *Cyp*, *KL*, and *p53* genes, respectively. Cleaved bands of mutated sequences were obtained. The alignment of wild-type to mutated with T-Coffee tool revealed six amino acid substitutions in *CAT* (*Asp/Asn*, *Asp/Gly*, *Tyr/Asp*, *Lys/Arg*, *Gln/Ser* and *Ala/Val*) and single amino acid substitutions in *KL* (*Phe/Val*), *Cyp* (*Ser/Thr*), *SOD1* (*Gly/Arg*) and *p53* (*Leu/unknown*). **Conclusions:** The current study identified genetic variants in *KL*, *CAT*, *Cyp*, *p53*, and *SOD1* genes that may influence CKD progression and therapy.

## INTRODUCTION

Chronic kidney disease (CKD) is a common and serious medical condition affecting millions of people worldwide [1]. It is characterized by a progressive loss of kidney function over time, leading to complications such as hypertension, anemia, bone disease, and cardiovascular disease [2]. The best available indicator of overall kidney function is glomerular filtration rate (GFR), measuring the

fluid filtered through functioning nephrons [3]. CKD is a non-communicable disease strongly associated with chromosome 22 [4]. CKD patients experience heightened genomic instability, leading to increased genetic and chromosomal damage from radiation and impaired DNA repair. This genetic damage may be both cause and consequence of CKD [5]. Several genes associated with



CKD have been identified, affecting the risk and progression of the condition [6]. Genetic variations can have various effects on the body, ranging from no noticeable effect to serious health conditions [7]. It may impact protein function and lead to organ damage that influences disease development and progression [7]. For example, variations in the *klotho* gene can lead to a reduction in the expression of the *klotho* protein, which has been associated with a higher risk of age-related diseases, including CKD and Alzheimer's disease [8]. Genomic studies are critical in finding a correlation between a normal genome and its variations, as the genomic variant of a diseased person is present in non-coding regions [7]. Understanding the effects of specific variations in genes can help researchers to develop targeted treatments and therapies that address the underlying genetic causes of disease [9]. The use of molecular biology techniques in genetic research has contributed significantly to the identification of genetic variations associated with CKD [10]. Restriction Fragment Length polymorphism (RFLP) analysis is a key technique for identifying genetic variations. It can detect DNA sequence variations that alter DNA fragment lengths produced by restriction enzymes [11]. In addition to identifying genetic variations, RFLP analysis has several advantages over other genetic analysis methods. RFLP analysis can detect variations in genes even when the specific mutation is unknown. It can also be used to detect multiple variations (haplotype) in a single gene simultaneously [11]. Previously, RFLP has been successfully identified as an association of several polymorphisms in *IL-6*, *GPX1*, *SOD2*, and *NRF2* genes in patients with CKD and end-stage renal disease (ESRD) [12, 13].

Pakistan does not have any extensive genetic association studies that focus on the contribution of *KL*, *CAT*, *Cyp*, *p53*, and *SOD1* gene variants to chronic kidney disease, and the bulk of local research is conducted on clinical and biochemical parameters but not regarding the molecular genetic phenotype. This study aimed to identify genetic variants associated with CKD by analysis of PCR-RFLP, which may help in creating targeted therapies and personalized treatment plans through the functional implications of detected polymorphisms.

## METHODS

This cross-sectional study was conducted among 183 participants at Ibn-e-Siena Hospital and Research Institute, Multan, Pakistan, from Nov 2023 to May 2024. CKD was defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Ethical approval was obtained from Ibn-e-Siena Hospital and Research Institute, Multan, with the IRB/IEC number of C-70-1021-03. Informed consent was obtained from all participants

according to the Declaration of Helsinki. Participants were eligible for inclusion based on the following criteria. Above the age of 18 years and willing to provide written informed consent were selected for this study. Along with this, for cases, confirmed CKD patients were selected with one of the following comorbid conditions associated with increased risk of CKD, such as diabetes, hypertension, cardiovascular disease, arthritis, and glomerulonephritis. While for the control age of 18 years, without CKD and associated risk factors, was included in this study. Participants were excluded from the study if they required dialysis therapy, were undergoing specific immune or steroid therapies, or had been diagnosed with uterine fibroids or cancer. Additional exclusion criteria included clinical histories of rheumatoid arthritis, systemic lupus erythematosus, acute infection, septic shock, hypotension, or a positive diagnosis of COVID-19. The present study included 183 participants. The sample size was determined to estimate the population parameter with a 95% confidence level and 5% absolute precision. The sample size was determined using Cochran's formula with finite population correction as described by Shemsu et al. [14]. The formula of Cochran's formula with Finite Population Correction is given below.  $n = N^2 P(1-P) / d^2(N-1) + Z^2 P(1-P)$ , where  $n'$  = sample size with finite population correction (183),  $N$  = population size (349),  $Z$  = Z-value (1.96 for a 95% confidence level),  $P$  = expected proportion (0.5) and  $d$  = margin of error or precision (0.05). Whole blood sample (5mL) was collected from all participants in EDTA tubes. DNA extraction from blood samples was performed using a mammalian genomic DNA extraction kit (Axygen Biosciences, California, USA), following the manufacturer's recommendations, and stored at  $-80^{\circ}\text{C}$  till the assay was performed. *Klotho* (*KL*), *Catalase* (*CAT*), *Cyclophilin* (*Cyp*), *tumor protein p53* (*p53*), and *Superoxide dismutase 1* (*SOD1*) genes were selected for polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). The genetic sequences of selected genes were retrieved from NCBI (<http://www.ncbi.nlm.nih.gov/nucleotide>). The primer3Plus web interface (<https://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi>) was used for designing the primers. Designed primers were confirmed via the computer software SnapGene (<https://www.snapgene.com/>). For in-silico RFLP, firstly, a sequence map of the coding DNA sequence (CDS) was extracted by NEBcutter (<http://nc2.neb.com/NEBcutter2/>), and then SnapGene software was used to cleave the bands of the mutated sequences. In wet lab RFLP, restriction enzymes cleave DNA into fragments. The mixtures were incubated at  $37^{\circ}\text{C}$  for 1–2 hours to allow for DNA cleavage, followed by visualization on a 1% agarose gel electrophoresis. DNA sequencing by the Sanger Sequencer was employed to determine the precise nucleotide sequence (A, T, C, G) of

the targeted genes within participants. For alignment of DNA sequences, the T-Coffee tool (<https://www.ebi.ac.uk/Tools/msa/tcoffee/>) was used. Identified nucleotide variations among samples and reference sequences, with variations highlighted in the obtained sequences.

SPSS version 25.0 and Microsoft Excel were used for data analysis. Quantitative variables (e.g., Age and Weight) were represented as mean  $\pm$  standard deviation (SD) and statistically analyzed with the independent samples t-test, while qualitative variables were represented with frequency (n) and percentage (%) and statistically analyzed by Chi-square test and Fisher's Exact Test. To evaluate the association between genetic variants and CKD risk, genotype and allele frequencies were compared between groups. To determine the strength of the association, Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated. To account for the presence of zero values in the control group, the Haldane-Anscombe correction was applied by adding 0.5 to all cells in the 2x2 contingency tables. Statistical significance for all genotype and allele distributions was assessed using Fisher's Exact Test. p-values were reported to determine the statistical significance, with values less than 0.05 ( $p < 0.05$ ) indicating a significant association.

## RESULTS

Out of 183 participants, 113 were CKD patients, and 70 were healthy controls. The average age was  $46 \pm 15$  years within the CKD participants, while  $42 \pm 17$  years within the control. The male-to-female ratio in the CKD group was 30:70, while in the control group, it was 40:60. CKD participants had a mean weight of  $57 \pm 15$  kg, while controls had  $58.5 \pm 13$  kg. The p-values for age, gender, and weight were greater than 0.05; these parameters were not statistically significant. The clinical and demographic characteristics of participants are given (Table 1).

**Table 1:** The Clinical and Demographic Characteristics of Participants

Parameters	CKD Patients (n=113), Mean $\pm$ SD/n (%)	Controls (n=70), Mean $\pm$ SD/n (%)	p-value
Age (Years)	46 $\pm$ 15	42 $\pm$ 17	0.05
Male	34 (30.1%)	28 (40.0%)	0.05
Female	79 (69.9%)	42 (60.0%)	0.05
Weight (kg)	57 $\pm$ 15	58.5 $\pm$ 13	0.05
Smoking	79 (69.9%)	10 (14.3%)	0.05
Ischemic Heart Disease	76 (67.3%)	22 (31.4%)	0.05
Family History	47 (41.6%)	34 (48.6%)	0.05
Hypertension	73 (64.6%)	0 (0%)	0.05
Type 2 Diabetes Mellitus	41 (36.3%)	0 (0%)	0.05
Hepatitis-B	7 (6.2%)	0 (0%)	0.05
Hepatitis-C	9 (8.0%)	0 (0%)	0.05

The genetic sequences of the *KL*, *CAT*, *Cyp*, *p53*, and *SOD1*

genes were retrieved from NCBI, and their FASTA sequences were obtained for primer designing through Primer3Plus. The specificity and high efficiency of primers were achieved through the optimization of GC content, melting temperatures ( $T_m$ ), and primer lengths. Because GC content and length are critical determinants of specificity and hybridization stability, these parameters were strictly controlled to ensure robust amplification during both PCR and DNA sequencing (Table 2).

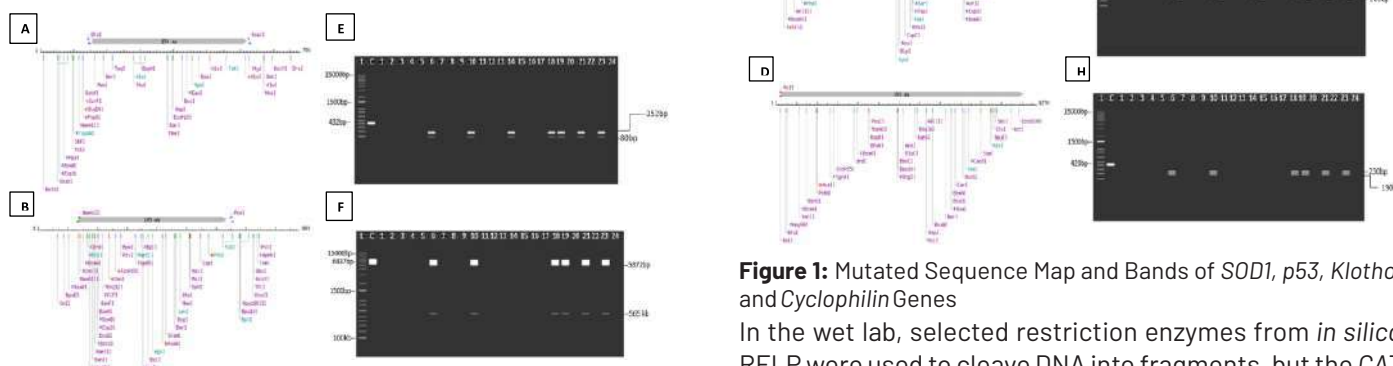
**Table 2:** The Primers Used for Genotyping

Genes	Primer sequence	GC%	$T_m$	Restriction Enzyme
<i>SOD1</i>	F: CCAGTGCAGGGCATCATCAA	55	60.7	TaqI
	R: CAAGCCAAACGACTTCCAGC	55	60	
<i>p53</i>	F: TGAAGCTCCCAGAATGCCAG	55	60	AclI
	R: CAGTCAGAGCCAACCTCAGG	60	60	
<i>CAT</i>	F: AGTGATCGGGGATTCCAGA	55	60	HinfI
	R: CCACCCGTGATTGTCTGCAT	55	60	
<i>KL</i>	F: TACAACAACGTCTTCCGCGA	50	60	AlwI
	R: GCTTAGGGCAATGGACACCT	55	60	
<i>Cyp</i>	F: CCGTGTCTTCGACATTGCC	55	59.8	EcoRI
	R: TCGAGTTGTCCACAGTCAGC	55	60	

F: Forward; R: Reverse

Designed primers were confirmed via the computer software SnapGene. Successful amplification of genes was confirmed via gel electrophoresis. For in-silico RFLP, the sequence map of selected genes was obtained from the NEBcutter tool. The sequence maps have different mutation sites and different enzymes (A-D). For mutation identification, TaqI, EcoRI, AlwI, and AclI restriction enzymes were selected from these Sequence Maps to cut the band of *SOD1*, *Cyp*, *KL*, and *p53* genes, respectively. Instead of performing the actual laboratory experiments, in silico RFLP software or online tools were utilized to simulate the digestion patterns based on the known recognition sites of the chosen restriction enzymes. To cleave the bands of the mutated genomic sequences, the current study created 1% gel, a 1 kb ladder, and used several enzymes via SnapGene software. Specific bands were obtained, indicating that DNA fragments were cleaved by the selected restriction enzyme. TaqI enzyme cut the bands at 1 side, and two bands of 352bp and 80bp were obtained in the *SOD1* gene (E). The study cut the bands at 1 side, and two bands of 230 bp and 190 bp were obtained in the *p53* gene (F). The AlwI enzyme cut the bands at 1 side, and two bands of 691bp and 263bp were obtained in the *KL* gene (G). EcoRI enzyme cut the bands at 1 side, and two bands of 5872bp and 565bp were obtained in *Cyp* gene (H). The presence of cut bands suggests that the recognition site for the restriction enzyme is present in the DNA region of interest in the samples of CKD patients. A-D illustrate mutated sequence maps for the *SOD1*(A), *p53*(B), *KL*(C), and

Cyp (D) genes, while E to H display the bands of mutated sequence *SOD1* (E), *p53* (F), *KL* (G), and *Cyp* (H) genes, respectively. L: Ladder, C: control, and Well 1-24: samples in E to H (Figure 1).



**Figure 1:** Mutated Sequence Map and Bands of *SOD1*, *p53*, *Klotho*, and *Cyclophilin* Genes

In the wet lab, selected restriction enzymes from *in silico* RFLP were used to cleave DNA into fragments, but the *CAT*

gene failed to provide restriction enzymes from *in silico* RFLP. Therefore, we utilized the *HinfI* restriction enzyme for the *CAT* gene analysis. DNA sequencing was used to determine the precise nucleotide sequence (A, T, C, G) of the targeted genes within the CKD cohort. This approach allows for the identification of specific genetic variants that may serve as markers for disease susceptibility, phenotypic severity, and individualized treatment response. DNA sequencing revealed several distinct genetic variations within the CKD cohort. Among them, significant polymorphisms were observed in the *KL* (T/G; n=60), *SOD1* (G/C; n=22), and *p53* (unknown; n=17) genes; none of them were present in the control group. Conversely, polymorphisms in the *Cyp* (T/A; n=10 vs. n=2 in controls) and *CAT* (haplotype; n=4) genes were observed but did not reach statistical significance (Table 3).

**Table 3:** Frequency Distribution among CKD Patients and Control Groups

Genes	Genotype Frequency			Allele Frequency			Odd Ratio	95% CI	p-value
	Genotype	CKD (n=113)	Control (n=70)	Allele	CKD (n=113)	Control (n=70)			
<i>SOD1</i>	G/C	22 (19%)	0 (0%)	G	204 (90.3%)	140 (100%)	34.67	2.08-584.6	<0.05
				C	22 (9.7%)	0 (0%)			
<i>p53</i>	CTG/ NNN	17 (15%)	0 (0%)	CTG	209 (92.5%)	140 (100%)	25.57	1.52 - 428.37	<0.05
				NNN	17 (7.5%)	0 (0%)			
<i>CAT</i>	Multiple (Haplotype) (G/A, A/G, T/G, A/G, C/T, C/T)	4 (3.5%)	0 (0%)	Non-Haplotype	222 (98.2%)	140 (100%)	5.80	0.31-109.95	>0.05
				Haplotype	4 (1.8%)	0 (0%)			
<i>KL</i>	T/G	60 (53%)	0 (0%)	T	166 (73.5%)	140 (100%)	159.45	9.68-2617.49	>0.05
				G	60 (26.5%)	0 (0%)			
<i>Cyp</i>	T/A	10 (8.8%)	2 (2.8%)	T	216 (95.6%)	138 (98.6%)	2.68	0.66-10.84	>0.05
				A	10 (4.4%)	2 (1.4%)			

NNN indicates a non-specific variant fragment length detected by *AccI*

Based on the CLUSTAL W alignment, the mutated proteins exhibited specific amino acid substitutions. Among them, alignment of wild-type to mutated catalase protein sequences revealed six amino acid substitutions (A). The amino acid substitutions in *CAT* are: aspartic acid to asparagine, aspartic acid to glycine, tyrosine to aspartic acid, lysine to arginine, glutamine to serine, and alanine to valine (A). The CLUSTAL W alignment of wild-type to mutated *KL*, *Cyp*, *SOD1*, and *p35* protein sequences revealed single amino acid substitutions. *KL* shows an amino acid substitution of phenylalanine to valine (B). *p53* shows an amino acid substitution of leucine to unknown (C). *Cyp* show the amino acid substitution of serine to threonine (D). *SOD1* shows an amino acid substitution of glycine to arginine (Figure 2E). The observed variations differed in

their structural impact; single substitutions (*SOD1*, *p53*, *KL*, *Cyp*) involve a point-specific residue change within a conserved sequence, whereas the multiple substitutions in *CAT* represent a complex haplotypic variation. Even a single amino acid substitution can significantly disrupt the protein function by altering structural stability or impairing enzymatic activity. T-Coffee alignment clearly shows substitutions in CKD patients, allowing researchers to pinpoint variations that may lead to functional loss or drug resistance (Figure 2).



**Figure 2:** Variations in the Sequence by Protein Alignment via the T-Coffee tool. A-D Shows Mutation in the Sequence of *CAT*(A), *KL* (B), *p53*(C), *Cyp*(D), and *SOD1*(E)Proteins, Respectively

**DISCUSSION**

The current study investigation identified several genetic variations within the *KL*, *CAT*, *Cyp*, *p53*, and *SOD1* genes that demonstrate a strong association with CKD pathogenesis. Overall, our findings emphasize the importance of considering genetic factors in the development of CKD, as evidenced by genetic mutation analysis using RFLP analysis and SnapGene software. Researchers utilized in silico RFLP analysis to investigate genetic variations in CKD, employing bioinformatics tools to simulate enzymatic digestion patterns of DNA sequences from CKD patient samples with specific restriction enzymes [15]. This in silico method predicts fragment patterns and identifies genetic variations linked to CKD susceptibility or progression. By integrating *in silico* RFLP analysis with experimental validation and clinical data, researchers seek to understand genetic factors influencing CKD diagnosis and treatment [16]. The current study used the BLAST tool on the NCBI database to identify mutated sequences in the genes of interest and then used SnapGene software to analyze the sequences and cut them with different enzymes to identify mutations. Researchers identified specific polymorphisms within the *CAT* and *SOD1* genes in CKD patients. *CAT* and *SOD1* gene polymorphisms in CKD

patients were also observed by Crawford *et al.* who reported that the *SOD2* Val/Val genotype increased end-stage renal disease (ESRD) risk, which was even higher in combination with the GpX1 polymorphism [17]. These findings are parallel with the existing research of Kidir *et al.* on acute kidney injury (AKI), where polymorphisms in *SOD*, *GpX1*, and *CAT* have also been observed [18]. AKI is marked by a rapid decline in glomerular filtration rate, leading to significant morbidity and possible chronic kidney disease onset. The overlap of antioxidant genes across both CKD and AKI underscores the critical role of oxidative stress as a common driver in the progression of various forms of renal disease [19]. Researchers' analysis found a strong association between *KL* gene variations and CKD, aligning with previous studies [20, 21]. The polymorphism of the *KL* gene was most prevalent among detected CKD patients compared to other genes in our study. Hassan *et al.* also found a polymorphism of the *KL* gene within CKD patients that shows the association of the *KL* gene with CKD [21]. The current study analysis revealed that genetic variation in the *Cyp* gene was also strongly associated with CKD, but the results of *Cyp* gene polymorphism were non-significant in our study and were also observed in 2 control patients, which suggests that this gene may play a role in the development and progression of CKD. Based on previous findings, *Cyp* genes play a critical role in protein folding and are significantly upregulated during kidney injury, acting as a stress response mechanism [22, 23]. The association of these genetic variants with decreased renal function highlights the potential of *Cyp* genes not only as markers of injury but as key players in the progression of renal dysfunction, supporting the hypothesis that dysregulated protein folding contributes directly to the pathogenesis of chronic renal failure. Recent studies have suggested that variations in the *p53* gene may be associated with CKD development [24]. This is particularly underscored by the work of Wu *et al.* who demonstrated that targeting the Tp53RK pathway can effectively mitigate renal fibrosis. Collectively, these results suggest that *p53*-mediated pathways, specifically those governing apoptosis and fibroblast activation, are central to the maladaptive repair processes that drive CKD progression [25]. The consistency between current results and earlier reports strengthens the understanding of the pathogenesis of CKD and highlights the significance of these genetic factors in the disease. The current study enhances the understanding of the genetic basis of CKD and reveals genetic variants that have potential for personalized interventions based on genetic profiles to improve patient outcomes. The study successfully identified genetic variants in target genes using cost-effective RFLP analysis, known for its specificity and sensitivity.

However, limitations include a relatively small sample size that may hinder the detection of all variations and a cross-sectional design that prevents establishing causal relationships between the variations identified and CKD. Despite these limitations, our findings have important clinical implications. Future research should explore the significance of these genetic variants and validate findings in diverse populations. Additionally, methods like RFLP analysis should investigate further genetic variants related to CKD, potentially impacting prevention and treatment strategies.

## CONCLUSIONS

The current study identified genetic variants related to CKD using RFLP analysis, including variations in the *KL*, *p53*, *CAT*, *SOD1*, and *Cyp* genes. The current findings suggest that these genetic variants may influence CKD development and progression, suggesting that targeting them could offer new therapeutic strategies.

## Authors' Contribution

Conceptualization: ZHQ

Methodology: ZHQ, AJ

Formal analysis: ZHQ, MI, AI, BF

Writing and Drafting: ZHQ, MI, AI, AJ, SA, MJK

Review and Editing: ZHQ, MI, AI, BF, AJ, SA, MJK

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



## Comparing the Efficacy of Oral Fluconazole versus Oral Itraconazole in Treating Resistant Tinea Corporis

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## ABSTRACT

Dermatophytosis, particularly tinea corporis, has become challenging due to rising antifungal resistance, notably *Trichophyton indotinea*. Comparative efficacy data for oral fluconazole versus itraconazole in resistant cases in local populations remain limited. **Objectives:** To compare the efficacy and safety of oral fluconazole versus oral itraconazole for resistant tinea corporis. **Methods:** This single-blind randomized controlled trial (trial reference CPSP/REU/EDR-2023-253-19306) was conducted at Capital Hospital CDA, Islamabad, from June to October 2025. 126 adults with clinically and KOH microscopy-confirmed resistant tinea corporis were randomized 1:1 to receive oral itraconazole 200 mg daily or fluconazole 150 mg every other day for 4 weeks. The primary outcome was complete clinical cure (erythema=0, scaling=0, pruritus=0, no visible lesions) at week 4. Secondary outcomes included percentage improvement in clinical signs and adverse events. **Results:** Complete clinical cure was achieved in 79.4% (50/63) with itraconazole versus 66.7% (42/63) with fluconazole ( $p=0.109$ ; risk difference 12.7%, 95% CI -2.8 to 28.2). The primary endpoint did not reach statistical significance. However, mean percentage improvements were significantly higher with itraconazole for erythema (45.3% vs 36.4%;  $p=0.027$ ), scaling (39.5% vs 30.2%;  $p=0.041$ ), pruritus (52.6% vs 43.3%;  $p=0.038$ ), and elevated borders (38.3% vs 31.6%;  $p=0.015$ ). Itraconazole remained an independent predictor of cure (adjusted OR 2.12, 95% CI 1.04-4.31;  $p=0.037$ ). Mild adverse effects occurred in 9.5% vs 14.3% ( $p=0.581$ ). **Conclusions:** Although the difference in complete clinical cure rates (primary endpoint) was not statistically significant, itraconazole showed greater clinical improvement across secondary endpoints and was independently associated with higher odds of cure compared to fluconazole.

## INTRODUCTION

Dermatophytes are the leading cause of fungal infections in the world, impacting millions of individuals each year. These are filamentous fungi that can infect keratinized tissue such as skin, hair, and nails, which are classified into three genera, *Trichophyton*, *Epidermophyton*, and *Microsporum* [1]. Another method is to classify dermatophytosis clinically based on site of infection from head to toe, i.e., tinea corporis, tinea capitis, tinea barbae, tinea facies, tinea manuum, tinea unguium, tinea cruris, and tinea pedis [2]. Irrespective of classification, these fungi have exhibited an increase in resistance towards various anti-fungal agents, and this problem is growing

with each passing day, creating a therapeutic conundrum for treating physicians [3, 4]. Here are numerous host defensive mechanisms that prevent the spread of infection, including skin type, UV exposure, dryness, and warm temperature [5]. However, when the infection ensues, it becomes very difficult to treat in some cases due to its resistant and relapsing nature, for which numerous strategies are employed, like using various formulations and combinations of anti-fungal [6, 7]. In this instance, a study was conducted with the aim of comparing the efficacy of multiple oral anti-fungal agents for managing resistant cases of tinea infection, including the tinea



corporis. Fluconazole and itraconazole were part of this study, and upon comparison, it was found that oral itraconazole was significantly better than oral fluconazole in terms of frequency of complete clinical resolution (72.2% versus 16.7%, respectively)[8]. Similarly, in another study, it was found that the frequency of complete clinical resolution of resistant tinea of all types of superficial dermatophytosis was much higher with itraconazole as compared to fluconazole (84% versus 62%, respectively) [9]. When it comes to previous studies regarding the efficacy of oral itraconazole and fluconazole in managing resistant tinea, studies have not focused on any specific type, and data regarding this in the local population is also lacking. Additionally, the skin type of populations is different in different geographical regions, and the pattern of anti-fungal resistance is also highly variable with changing demographics[10,11].

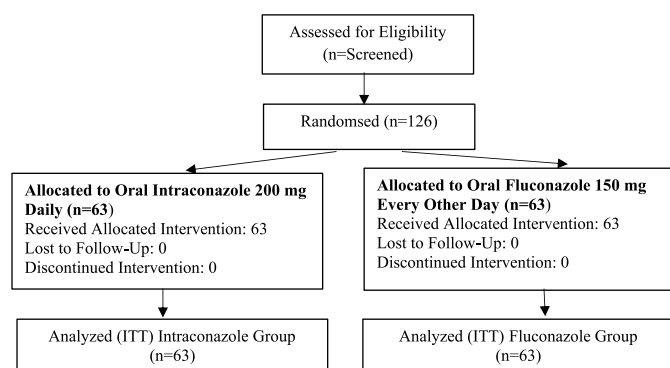
Pakistan does not have quality comparative data on oral fluconazole versus itraconazole of resistant tinea corporis specifically, and most studies conducted locally involved mixed dermatophytosis types or non-resistant case. None of the previous randomized controlled trials have undergone the use of these azoles in the Pakistani population in KOH-confirmed resistant tinea corporis. This study aimed to compare the efficacy of oral fluconazole versus oral itraconazole in treating resistant tinea corporis, specifically in the local population.

## METHODS

This randomized trial was carried out at the Capital Hospital's Department of Dermatology, which is governed by the Capital Development Authority (CDA) in Islamabad, Pakistan. The randomized trial was approved by the College of Physicians and Surgeons, Pakistan, CPSP, with reference number CPSP/REU/EDR-2023-253-19306, after receiving ethical approval for the study from the Institutional Research Board and Ethics Committee, Capital Hospital, CDA, under reference number IRB-89-8-2-25. The trial reference number was NCT07342153. The study was conducted from June 25, 2025, to October 1, 2025. A total of 126 patients who met the eligibility requirements were recruited from the dermatology outpatient department. Both male and female patients with clinically and mycologically verified resistant tinea corporis between the ages of 18 and 70 were included. Resistant tinea corporis was defined as persistent clinical lesions for six months or more despite adequate topical antifungal therapy, confirmed by positive 10% potassium hydroxide (KOH) microscopy demonstrating fungal hyphae from skin scrapings taken from the active border. Fungal culture and species identification were not performed owing to resource and logistical constraints in our setting. Recent (within three months) use of systemic antifungal

therapy, antibiotic treatment for a superadded bacterial infection within the previous month, known immunosuppressive conditions like diabetes mellitus or cancer, immunosuppressive medication use, or azole antifungal hypersensitivity were among the exclusion criteria. Before enrollment, all individuals provided written informed consent. Following baseline evaluation, patients were randomly assigned in a 1:1 ratio to the itraconazole or fluconazole group using computer-generated random numbers via a mobile randomizer application with block randomization (block size of 4) to ensure balance. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes prepared by an independent person not involved in the study. This was a single-blind randomized controlled trial in which participants were blinded to treatment allocation, while the clinical investigators were aware of group assignment due to the nature of the intervention. A 4-week treatment duration was chosen based on standard recommended regimens for systemic azoles in dermatophytosis and previous comparative trials [12-14]. Although longer courses are sometimes required in highly resistant cases, this duration allowed evaluation of standard therapy, with the option of extension outside the protocol for non-responders. Age, sex, body mass index (BMI), length of skin lesions, residence location, and educational attainment were among the baseline variables that were documented. The Dermatophyte Severity Scale (Annexure A), which rates erythema and scaling on a 4-point clinician-rated scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), and pruritus on a 0-10 patient-rated visual analog scale, was used to measure clinical severity at baseline by a consultant dermatologist. Complete clinical cure, which was defined as erythema = 0, scaling = 0, pruritus = 0, and the absence of visible lesions after 4 weeks, was the main outcome. Along with side effects, secondary outcomes were the percentage improvement in erythema, scaling, pruritus, and elevated borders compared to baseline. Outside of the trial protocol, patients who did not fully recover were given the option of extended or alternative therapy at the consultant's discretion. To minimize inter-observer variability, the same dermatologist conducted all clinical evaluations at 4 weeks. During follow-up visits, all adverse events were noted and categorized according to their severity. Considering the established safety profile of these medications, no severe side effects necessitating stopping were expected. Sample size calculation was based on expected complete clinical cure rates of 84% with itraconazole versus 62% with fluconazole from a previous study [9]. Assuming 80% power and a two-sided alpha of 0.05, the WHO sample size calculator determined that 126 patients (63 per group) were required. This gave enough power to identify group differences that were clinically

significant. All analyses were performed on an intention-to-treat basis, including all randomized participants. The study is reported according to the CONSORT 2010 statement. The participant flow is presented in a CONSORT diagram. A CONSORT flow diagram shows flow of participants in the randomized controlled trial. Overall 126 subjects were randomly divided into two groups in the ratio of 1:1 who were to receive oral itraconazole (200mg/day) or oral fluconazole (150mg/day) as a treatment of resistant tinea corporis. Every participant in each group (n=63) received his/her treatment and did not lose follow-up or stop treatment. The two groups were examined on the basis of the intention-to-treat (ITT) principle and shown in figure 1.



**Figure 1:** CONSORT flow diagram of the Randomized Controlled Trial

SPSS version 25.0 was used to analyze the data. Depending on the distribution determined by the Shapiro-Wilk test, continuous data such as age, BMI, and lesion duration were reported as mean  $\pm$  standard deviation or median (interquartile range). Frequencies and percentages were used to represent categorical characteristics, including sex, residence, education, and treatment response. Primary analysis used the Chi-square test or Fisher's exact test, as applicable, to compare the percentage of patients who experienced a full clinical cure at 4 weeks between groups. Secondary analyses used independent-samples *t*-tests to compare mean percentage improvements in pruritus, erythema, scaling, and elevated borders. Results were stratified by age, sex, BMI, and length of lesion in subgroup analyses, and exploratory forest plots of absolute differences were produced. Using treatment group, age, sex, BMI, lesion duration, and place of residence as factors, multivariable logistic regression was used to find independent predictors of cure. For all analyses,  $p < 0.050$  was the threshold for statistical significance, and 95% CIs were provided.

## RESULTS

Itraconazole (n=63) and fluconazole (n=63) were the two equally randomized groups into which 126 individuals with resistant tinea corporis were divided. The groups' baseline

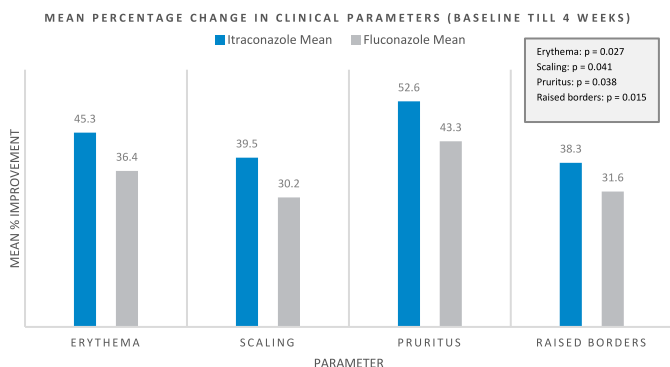
clinical and demographic traits were evenly distributed. The itraconazole group's mean age was  $32.4 \pm 8.7$  years, while the fluconazole group was  $34.9 \pm 9.3$  years ( $p = 0.212$ ). Between the two groups, the percentage of male participation was similar (55.6% vs. 52.4%;  $p = 0.712$ ). BMI, lesion duration, residency area, and baseline clinical severity levels for pruritus, scaling, and erythema did not differ significantly (all  $p > 0.050$ ). The distribution of primary outcomes and the specific baseline parameters are shown in table 1.

**Table 1:** Baseline Demographic and Clinical Characteristics of Patients Receiving Itraconazole or Fluconazole and Primary Clinical Outcomes At 4 Weeks

Variables		Itraconazole, (n=63)	Fluconazole, (n=63)	p-value
Age (years), mean $\pm$ SD		32.4 $\pm$ 8.7	34.9 $\pm$ 9.3	0.212
Male sex, n (%)		35 (55.6%)	33 (52.4%)	0.712
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD		24.4 $\pm$ 3.4	24.7 $\pm$ 2.4	0.613
Lesion duration (weeks), median (IQR)		46 (39-61)	43 (38-52)	0.314
Urban residence, n (%)		35 (55.6%)	46 (73.0%)	0.054
Education $\geq$ primary, n (%)		38 (60.3%)	41 (65.1%)	0.571
Erythema score, median (IQR)		2 (1-3)	2 (1-3)	0.944
Scaling score, median (IQR)		2 (1-3)	2 (1-3)	0.891
Pruritus VAS, median (IQR)		6 (5-8)	6 (5-8)	0.905
Clinical Outcomes at 4 weeks	Complete clinical cure (all scores 0)	50/63 (79.4%)	42/63 (66.7%)	0.109
	Partial improvement	6/63 (9.5%)	9/63 (14.3%)	0.409
	Clinical failure	3/63 (4.8%)	7/63 (11.1%)	0.187

At 4 weeks, complete clinical cure was achieved in 79.4% (50/63) of patients in the itraconazole group versus 66.7% (42/63) in the fluconazole group ( $p = 0.109$ ; risk difference 12.7%, 95% CI -2.8 to 28.2). Although the primary endpoint did not reach statistical significance, the absolute difference favored itraconazole. Lesion duration was compared using the Mann-Whitney U test as the data were non-normally distributed. Clinical failure was seen in 4.8% vs. 11.1% of patients, and partial improvement in 9.5% vs. 14.3% of patients ( $p > 0.050$  for both). After 4 weeks of treatment, both therapies produced clinically significant decreases in erythema, scaling, pruritus, and elevated borders; however, the itraconazole group's improvement was consistently larger across the board. With itraconazole, the average percentage improvement in erythema was  $45.3 \pm 12.4\%$ , while with fluconazole, it was  $36.4 \pm 13.8\%$  (mean difference 8.9%, 95% CI 1.2-16.6;  $p = 0.027$ ). The improvement in pruritus was  $52.6 \pm 13.1\%$  vs.  $43.3 \pm 14.7\%$  (mean difference 9.3%, 95% CI 1.5-17.1;  $p = 0.038$ ), and the improvement in scaling was  $39.5 \pm 11.2\%$  vs.  $30.2 \pm 12.1\%$  (mean difference 9.3%, 95% CI 1.1-17.5;  $p = 0.041$ ). Similarly, the itraconazole group's elevated borders improved by  $38.3 \pm 14.9\%$ , whereas the fluconazole group's improved by  $31.6 \pm 36.8\%$  (mean difference 6.7%,

95% CI 1.5–11.9;  $p=0.015$ ). Although the standard deviation in the fluconazole group was large, normality was confirmed by the Shapiro–Wilk test, and the independent-samples t-test was therefore appropriate (Figure 2).



**Figure 2:** Mean Percentage Improvement from Baseline to Week 4 in Erythema, Scaling, Pruritus, and Raised Borders for Itraconazole and Fluconazole Groups

The two regimens were both highly received. Nine out of sixty-three patients (14.3%) receiving fluconazole and six out of sixty-three (9.5%) receiving itraconazole experienced mild adverse effects (Fisher's exact test,  $p=0.581$ ). There were no significant side effects or treatment discontinuations; the most common symptoms were headache, dizziness, and gastrointestinal distress, as shown in table 2.

**Table 2:** Multivariable Logistic Regression Analysis for Predictors of Complete Clinical Cure at 4 Weeks

Predictor Variables	Adjusted OR	95% CI	p-value
Itraconazole vs Fluconazole	2.12	1.04 – 4.31	0.037
Age (per year increase)	0.98	0.95 – 1.02	0.271
Male sex	1.11	0.57 – 2.16	0.759
BMI (per kg/m <sup>2</sup> )	0.96	0.89 – 1.04	0.298
Lesion duration $\geq$ 1 year	0.83	0.41 – 1.69	0.614
Urban vs rural	1.27	0.64 – 2.53	0.496

The two regimens were both highly received. Nine out of sixty-three patients (14.3%) receiving fluconazole and six out of sixty-three (9.5%) receiving itraconazole experienced mild adverse effects (Fisher's exact test,  $p = 0.581$ ). There were no significant side effects or treatment discontinuations, however the most common symptoms were headache, dizziness, and gastrointestinal distress.

## DISCUSSION

Both oral itraconazole and fluconazole produced clinically significant improvements at four weeks in this randomized controlled study assessing resistant tinea corporis. Itraconazole, on the other hand, was independently linked to a larger chance of a full clinical cure and consistently resulted with better decreases in erythema, scaling, pruritus, and elevated borders. These results are in line with recent clinical studies that emphasize the improved pharmacokinetic characteristics of itraconazole over

fluconazole, such as its longer tissue persistence, stronger keratin affinity, and wider range of activity [12, 13]. These benefits have been supported by a number of recent randomized trials, which have demonstrated that itraconazole is either clinically superior or non-inferior to other systemic antifungals, such as fluconazole, especially in cases of resistant infections [14, 15]. The complete clinical cure rates observed in the present study (79.4% with itraconazole versus 66.7% with fluconazole) align with findings from previous comparative trials, although the absolute difference was smaller than previously reported. Koregol et al. documented complete clinical resolution rates of 72.2% with itraconazole versus only 16.7% with fluconazole in resistant tinea cases [8]. Similarly, Tyagi et al. reported cure rates of 84% versus 62%, respectively, across various types of superficial dermatophytosis [9]. The narrower gap in our trial is likely attributable to our stricter inclusion criteria (clinically and mycologically confirmed resistant tinea corporis only) compared with the broader populations studied earlier. Nevertheless, the consistent direction of benefit favoring itraconazole, together with the significantly greater mean percentage improvements in erythema (45.3% vs 36.4%), scaling (39.5% vs 30.2%), pruritus (52.6% vs 43.3%), and elevated borders (38.3% vs 31.6%), further strengthens the evidence of itraconazole's superior clinical response in resistant cases. With more and more resistant infections being documented in Asia, Europe, and North America, Trichophyton indotineae's advent has altered the epidemiological landscape of dermatophytosis worldwide [16, 17]. Clinical failures are frequently linked to changes in ERG genes and other resistance mechanisms, and this pathogen is linked to decreased sensitivity to fluconazole [18–20]. The direction and consistency of the treatment effect seen in this trial, however, can be explained by the fact that itraconazole usually maintains efficacy against these resistant isolates. Serum level investigations that reveal therapeutic cut-offs connected with cure further support the pharmacologic justification for itraconazole usage in resistant tinea [21]. Clinical outcomes and medication exposure have improved due to the introduction of super-bioavailable formulations and optimized dosage regimens [22, 23]. Fluconazole, on the other hand, has demonstrated decreasing response rates over the past ten years, particularly in resistant T. indotineae infections, despite its historical effectiveness [12, 19]. Similar to results from other RCTs, subgroup analysis in this trial demonstrated a consistent itraconazole advantage across age, sex, BMI, and lesion-duration strata [14, 22]. Unlike previous comparative trials that included heterogeneous superficial dermatophytoses or non-resistant cases [8, 9], the present study specifically

focused on clinically and mycologically confirmed resistant tinea corporis in the local Pakistani population. Multivariable modeling demonstrated itraconazole's therapeutic significance by confirming it as an independent predictor of cure, even if the absolute difference in complete cure was not statistically significant in unadjusted analysis. The global resistance epidemic must also be taken into consideration when interpreting these findings, as treatment guidelines and expert consensus statements increasingly promote itraconazole as the preferred systemic azole [16-20]. In disseminated disease, adjuvant topical treatments as luliconazole may improve results even more [24, 25].

This research has limitations. First, the follow-up was limited to a single 4-week endpoint; longer treatment and follow-up may be necessary for resistant infections and to capture recurrence data. Second, the primary outcome was clinical cure rather than mycological cure. Third, fungal culture, species identification, and antifungal susceptibility testing were not performed. Fourth, the sample size may not have been adequate for robust multivariable modeling. Fifth, the single-center design may limit generalizability. Multicenter trials with extended follow-up, mycological endpoints, and susceptibility testing are required. The future studies must concentrate on multicenter randomized trials and bigger sample sizes with longer follow-up to determine the long-term outcomes, recurrence, and long-term efficacy. Fungal culture incorporation, identification of the species (particularly *Trichophyton indotineae*) and antifungal susceptibility testing is suggested to provide a more accurate directive in targeted therapy. Furthermore, the future trials of combinations and dose optimization can help even more to enhance the outcomes of treatment in resistant dermatophytosis.

## CONCLUSIONS

In cases of resistant tinea corporis, itraconazole showed better clinical improvement and higher adjusted odds of cure than fluconazole. These results are consistent with new worldwide data on antifungal resistance and changing therapeutic approaches.

## Authors' Contribution

Conceptualization: UF

Methodology: SK

Formal analysis: UA

Writing and Drafting: DHA, RR, AJ

Review and Editing: UF, UA, SK, DHA, RR, AJ

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



## Frequency of Hypothyroidism among Patients with Chronic Kidney Disease at a Tertiary Care Hospital in Pakistan

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## ABSTRACT

Patients with Chronic kidney disease (CKD) suffer from endocrine axis disruption as a part of the complications involving several other organ systems. Hypothyroidism is one of the imbalances seen in patients with CKD, both in clinical practice and research. Thyroid dysfunction remains undiagnosed due to its non-specific symptoms and lack of routine screening, especially in resource-limited settings. **Objectives:** To determine the frequency of hypothyroidism among patients with CKD and to differentiate its clinical and subclinical forms. **Methods:** This cross-sectional (descriptive) study was conducted over a period of six months in the Department of Medicine, Mardan Medical Complex, Khyber Pakhtunkhwa. 131 CKD patients (18-70 years) were recruited by non-probability consecutive sampling. Serum levels of thyroid-stimulating hormone (TSH), free T3, and free T4 were used to evaluate the patient's thyroid status. Based on serum hormone levels, the patients were categorized into hypothyroidism, subclinical hypothyroidism, or euthyroid states. The data were analysed through SPSS (version 26.0). **Results:** Out of 131 CKD patients, clinical hypothyroidism was found in 24 (18.3%), while 27 (20.6%) of the patients had subclinical hypothyroidism. Thyroid dysfunction was more common in patients above 60 (p=0.003) and females (p=0.041). A significant association was also found with dialysis status (p=0.006). **Conclusions:** Hypothyroidism is a prevalent complication in CKD, especially among older and female patients. The study emphasizes the value of routine thyroid screening in all stages of CKD to facilitate early diagnosis and treatment, especially in dialysis-dependent people.

## INTRODUCTION

Chronic Kidney Disease (CKD) is a chronic and progressive disease characterized by a progressive decline in renal function. Among the top ten causes of death globally in developed countries, CKD affects approximately 10–16% of the adult population worldwide and has become a major public health concern. In Pakistan, the prevalence of CKD is continuously increasing; however, many healthcare settings fail to recognize it. Alongside its widely recognized cardiovascular, hematologic, and metabolic complications, CKD is also associated with many endocrine

abnormalities, including disturbances in thyroid function [1, 2]. The kidneys and thyroid glands are linked in a complicated and interdependent relationship. The kidneys play an essential role in the metabolism, clearance, and excretion of thyroid hormones, while thyroid hormones have a major impact on the renal blood flow, glomerular filtration rate (GFR), and electrolyte homeostasis. As the kidney functions decline gradually, changes in thyroid hormone levels become more prominent, often resulting in either clinical or subclinical hypothyroidism. However, the



symptoms of hypothyroidism, such as fatigue, cold intolerance, and weight gain, can resemble the general symptoms of uraemia, making early diagnosis challenging in patients with CKD [3, 4]. Several international studies have documented the high prevalence of thyroid dysfunction in patients with CKD; however, there is a dearth of regional data, especially from clinical settings in Pakistan [5, 6]. Moreover, subclinical hypothyroidism remains overlooked most of the time due to the absence of its common clinical signs, despite its potential influence on disease progression and cardiovascular risk in CKD.

Therefore, this study aimed to find out the frequency of clinical and subclinical hypothyroidism in CKD patients who were admitted to a tertiary care hospital in Mardan. The results will help in early detection and customized therapeutic interventions by raising clinical awareness and highlighting the importance of routine thyroid function screening in clinical practice. Moreover, finding out how common it is among CKD patients at a Pakistani tertiary care hospital offers crucial information for early screening, prompt intervention, and better patient management, all of which improve the quality of treatment for this high-risk group.

## METHODS

This cross-sectional study (descriptive) was conducted in the Medical Unit of Mardan Medical Complex (MMC), Mardan, Khyber Pakhtunkhwa, from August 2024 to January 2025. The study aimed to determine the frequency and pattern of hypothyroidism, including both clinical and subclinical forms, in patients diagnosed with chronic kidney disease (CKD). The study was conducted after receiving ethical clearance from two official bodies. Approval was obtained from the Ethical Committee of Bacha Khan Medical College, Mardan, under approval number 229/BKMC, dated May 30, 2022. Additionally, the study was reviewed and approved by the Research Evaluation Unit of the College of Physicians and Surgeons Pakistan (CPSP) with reference number CPSP/REU/MED-2020-028-16933, dated August 10, 2024. Informed written consent was taken from all participants or their legal guardians. Confidentiality and privacy of patient data were strictly maintained. One hundred and thirty-one patients were recruited using a non-probability consecutive sampling technique. The sample size was calculated using the WHO sample size calculator based on an anticipated prevalence of hypothyroidism in CKD of 14.2%, with a 95% confidence interval and a 6% margin of error [7]. Inclusion criteria consisted of patients aged 18 to 70 years, admitted with a confirmed diagnosis of CKD. CKD was diagnosed based on any two or more of the following [8]: Urinary albumin-to-creatinine ratio (ACR) > 30 mg/g [9], abnormal findings on renal ultrasound (e.g., increased cortical echogenicity, loss

of corticomedullary differentiation, renal length < 8 cm, or cortical thickness < 6 mm), estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m<sup>2</sup> [10]. Exclusion criteria included patients with a prior diagnosis of hyperthyroidism, those already on thyroid hormone replacement therapy, and individuals with comorbid conditions that could affect thyroid function, such as infections, malignancies, or autoimmune diseases. After taking informed consent, demographic details like age, gender, address, educational status, and socioeconomic class were recorded. Blood samples were taken from the cubital vein aseptically and sent to the hospital laboratory for the analysis of free serum triiodothyronine (FT3), free serum thyroxine (FT4), and thyroid-stimulating hormone (TSH). Based on these test results, the patients were categorized into clinical hypothyroidism, defined as elevated serum TSH (>4.0 mIU/L) with low levels of serum free T3 and free T4 hormones [9]. Subclinical hypothyroidism is defined as elevated serum TSH (between 4.0 and 10.0 mIU/L) with normal levels of serum Free T3 and Free T4 hormones. Euthyroid state was defined as having all three hormone values within the normal range.

Data were entered and analysed using SPSS version 26.0. The Shapiro-Wilk test was used for checking the normal distribution of numerical variables like age and hormone levels, and the data were presented in the form of mean ± standard deviation or median with interquartile range as appropriate. Frequencies and percentages were used to describe the categorical variables such as gender, thyroid status, and comorbidities. For categorical variables, Chi-square or Fisher's exact tests were used to find the associations between thyroid dysfunction and demographic or clinical factors. A p-value of <0.05 was considered statistically significant. To identify potential effect modifiers, stratification of data was performed for age group, gender, educational status, and dialysis status of the patients.

## RESULTS

The mean age of the study participants was 55.6 years, indicating that most patients with chronic kidney disease were in the middle to older adult age group. Male patients slightly outnumbered female patients; however, this difference was not statistically significant. Nearly 60% of the participants belonged to urban areas. The majority of patients were from a lower socioeconomic background. Educational status varied among participants, with a considerable proportion being illiterate or having education limited to primary schooling. The Demographic characteristics of CKD patients are represented (Table 1).

**Table 1:** Demographic Characteristics of CKD Patients(n=131)

Variables	Category	n (%)	p-value
Age (years)	Mean ± SD	55.6 ± 10.4	—
Gender	Male	72 (54.9%)	0.341
	Female	59 (45.1%)	
Residence	Urban	78 (59.5%)	0.228
	Rural	53 (40.5%)	
Socioeconomic Status	Low	64 (48.9%)	0.172
	Middle	51 (38.9%)	
	High	16 (12.2%)	
Education Level	Illiterate	42 (32.1%)	0.087
	Primary/Secondary	58 (44.3%)	
	Higher	31 (23.6%)	

Abnormal thyroid function tests were observed in a substantial number of patients with chronic kidney disease. Subclinical hypothyroidism was more frequently identified than overt hypothyroidism. Overall, more than one-third of the study population had some form of hypothyroidism. The thyroid status of the CKD patients is shown (Table 2).

**Table 2:** Thyroid Status Among CKD Patients

Thyroid Status	n (%)	95% Confidence Interval
Clinical Hypothyroidism	24 (18.3%)	11.7% – 25.0%
Subclinical Hypothyroidism	27 (20.6%)	13.7% – 27.5%
Euthyroid (Normal)	80 (61.1%)	52.7% – 69.4%

Biochemically, higher levels of serum TSH were observed in patients with chronic kidney disease upon testing for thyroid functions, along with comparatively lower levels of free serum T3 and free T4. This hormonal pattern was demonstrated by a larger proportion of the study population, pointing towards a higher prevalence of subclinical hypothyroidism than clinical hypothyroidism. The mean biochemical parameters of thyroid functions are reported (Table 3).

**Table 3:** Mean Biochemical Parameters of Thyroid Function

Parameters	Normal range	Mean ± SD
TSH (mIU/L)	0.4–4.5 mIU/L	5.98 ± 3.21
Free T3 (pg/mL)	2.3–5.0 pg/mL	2.31 ± 0.76
Free T4 (ng/dL)	0.93–1.7 ng/dL	0.84 ± 0.22

The study represents the stratification of hypothyroidism by demographic factors. Hypothyroidism was more prevalent among patients over 60 years of age. Moreover, thyroid dysfunction was also more frequently observed in female patients compared with male patients. Likewise, patients with lower literacy levels and those residing in rural areas exhibited a higher occurrence of thyroid dysfunctions, although these associations were not statistically significant. The data were analysed row-wise (Table 4).

**Table 4:** Stratification of Hypothyroidism by Demographic Factors

Variables	Hypothyroidism Present, n (%)	Hypothyroidism Absent, n (%)	p-value
Age >60 Years	28 (50.9%)	19 (23.7%)	0.003
Female	31 (54.4%)	28 (35.0%)	0.041
Rural Residence	25 (43.9%)	28 (35.0%)	0.291
Low Socioeconomic	29 (50.9%)	35 (43.8%)	0.432
Illiterate	22 (38.6%)	20 (25.0%)	0.089

The association of hypothyroidism with clinical comorbidities is shown. There was a significant association of the dialysis status with the presence of hypothyroidism among patients with chronic kidney disease, with a highly significant p-value. Moreover, a higher proportion of comorbidities such as cardiovascular disease and diabetes mellitus were observed among patients with hypothyroidism; although, these associations were not statistically significant (Table 5).

**Table 5:** Association of Hypothyroidism with Clinical Comorbidities

Comorbidity	Hypothyroidism Present, n (%)	Hypothyroidism Absent, n (%)	p-value
Diabetes Mellitus	26 (45.6%)	30 (37.5%)	0.314
Cardiovascular Disease	21 (36.8%)	19 (23.8%)	0.081
On Dialysis	18 (31.6%)	10 (12.5%)	0.006

## DISCUSSION

Thyroid hormones have a direct and indirect effect on both tubular function and glomerular filtration rate, which are important components of renal hemodynamics. Multiple studies have demonstrated that thyroid dysfunction and chronic renal disease have a direct interaction; a Nepalese study found a significantly increased frequency of thyroid dysfunction in CKD patients. There is strong evidence of the reciprocal association between thyroid and kidney function, as thyroid hormones are directly involved in renal development, kidney structure, and hemodynamic performance [11, 12]. There is a widely acknowledged recognition of the clinical importance of thyroid dysfunction in individuals with renal disease, as data show a significant correlation with cardiovascular morbidity and mortality [13]. The implications of our study for healthcare are particularly relevant in the Pakistani context, where access to specialized endocrine treatment is varied, and healthcare resources may be limited. The current findings are supported by a recent Pakistani study that also demonstrated a larger frequency of hypothyroidism among patients with chronic kidney disease in tertiary care settings, highlighting the local relevance of this clinical issue [14]. The current findings are also supported by new international research that has shed further light on the thyroid-kidney relationship. The impact of thyroid status on initial renal failure and CKD progression in a nationally

representative population was shown in large US cohort research [6]. Subclinical thyroid dysfunction is clearly linked to chronic renal disease, according to population-based studies conducted in South Korea [4]. This study found a high prevalence of both subclinical and clinical hypothyroidisms in patients with chronic kidney disease. Among the 131 patients studied, roughly 39% had some form of thyroid abnormality. This finding is consistent with the previous global and local research, supporting a clear association between progressive kidney damage and impaired thyroid hormone metabolism [15, 16]. The most notable aspect of this study was the slightly higher frequency of subclinical hypothyroidism (20.6%) than clinical hypothyroidism (18.3%). This result is in line with a comparable study from a tertiary care hospital in Saudi Arabia, in which the prevalence of clinical hypothyroidism in CKD patients was 34.9%, while subclinical hypothyroidism accounted for a larger fraction of the total. Similarly, the pattern of biochemical abnormalities, such as increased serum TSH with either normal or low levels of serum free T3 and T4, further supports the slight but common nature of thyroid dysfunction in patients with CKD [17-19]. Thyroid disturbance has also been linked to chronic kidney disease in a variety of demographic groups, according to research from northeastern Indian communities [20]. Most encouragingly, new research from Pakistan indicates that patients with end-stage renal illness may benefit from therapeutic intervention for thyroid dysfunction, underscoring the potential advantages of early identification and therapy. This reversibility concept offers hope for better patient outcomes through targeted therapy and supports the clinical significance of routine thyroid hormone screening in CKD patients [21]. Another significant aspect of this study was that hypothyroidism was more common in the older adults and female patients with CKD, which is also supported by the existing literature. The higher prevalence of hypothyroidism in older adults is explained by the age-related decline in thyroid function, which is frequently made worse in CKD due to impaired hormone clearance and altered peripheral conversion of T4 to T3, a fact supported by a study in a tertiary care hospital with similar demographics. The higher incidence of hypothyroidism in females as compared to males is consistent with broader endocrine trends, because females are usually at a greater risk for thyroid dysfunctions, including autoimmune-associated causes [22, 23]. Serum albumin is an important factor in the significant frequency of subclinical hypothyroidism in patients with end-stage renal disease, according to earlier studies from South India [24]. One of the notable deductions from this study was the statistically significant association between hypothyroidism and dialysis status ( $p=0.006$ ). Patients undergoing dialysis were

about three times more likely to have thyroid dysfunction than those not on dialysis. This relationship may be explained by the effect of hemodialysis on the thyroid hormone physiology, including altered protein binding, metabolic changes, and increased hormone clearance. In addition, the hypothalamic-pituitary-thyroid axis is also disrupted by the uremic environment in patients on dialysis, leading to dysregulation without obvious symptoms [25, 26]. Although comorbid conditions such as diabetes and cardiovascular diseases were frequently observed in hypothyroid patients, the differences were not statistically significant. Nevertheless, their clinical importance cannot be overlooked. As shown by the studies, hypothyroidism significantly exacerbates cardiovascular risk, promotes fluid retention, and worsens anaemia, all of which are the well-known risk factors for the progression of CKD. Further longitudinal studies are needed to clarify these causal relationships and the potential benefits of early screening and replacement of thyroid hormones in this population [27, 28]. The strength of this study is that it provides important local data on the Pakistani population, helping to address a significant lack of regional evidence available on thyroid dysfunction in patients with chronic kidney disease. The existing literature heavily depends upon the Western or Gulf studies, which may not accurately reflect the Pakistani healthcare setting because of differences in iodine levels, healthcare access, socioeconomic factors, and awareness regarding thyroid disorders. Consequently, this study offers essential, context-specific evidence to improve diagnostic and treatment protocols in local nephrology and internal medicine practice. Our results are in favour of routinely screening CKD patients for thyroid function in Pakistani healthcare facilities. Early thyroid dysfunction identification may enable prompt care, thereby lowering cardiovascular consequences and slowing the progression of chronic kidney disease. Healthcare professionals who treat patients with chronic kidney disease (CKD) should be aware of the high incidence of thyroid dysfunction and consider comprehensive screening procedures. The creation of regional clinical guidelines that include thyroid monitoring could enhance patient outcomes and care in general.

This study has several limitations; despite the important insights it provides. Because of its cross-sectional study design, it cannot assess changes in thyroid status over time and cannot establish causality between hypothyroidism and CKD. In addition, due to financial limitations, autoimmune markers such as anti-thyroid peroxidase (anti-TPO) antibodies were not evaluated, which could be helpful in differentiating the underlying cause of hypothyroidism. Future studies should consider longitudinal study designs to monitor changes in thyroid

function over time and clarify causal associations. Studies involving larger and more diverse populations would improve the generalizability of findings. Furthermore, the inclusion of autoimmune markers such as anti-TPO antibodies and other relevant investigations may provide a deeper understanding of the pathophysiology and causes of hypothyroidism in patients with CKD. Multicentre collaboration and the use of advanced diagnostic approaches may further strengthen the quality and scope of future studies.

## CONCLUSIONS

Patients with CKD have a high prevalence of thyroid dysfunction, particularly subclinical hypothyroidism. The findings of this study provide an evidence-based need to screen all patients with CKD for the presence of thyroid abnormalities regularly, especially among females, older adults, and those receiving dialysis. The overall health of these patients can be improved, and the complications can be prevented through early detection and timely management of thyroid dysfunction. We highly recommend incorporating endocrine evaluation in routine nephrology practices for providing a comprehensive patient-centred approach to care.

## Authors' Contribution

Conceptualization: AA<sup>1</sup>

Methodology: AA<sup>1</sup>, MH, MA, SS, HI, AA<sup>3</sup>, AA<sup>4</sup>

Formal analysis: AA<sup>2</sup>

Writing and Drafting: AA<sup>1</sup>, HU, MH, AA<sup>2</sup>, MA, AA<sup>3</sup>, AA<sup>4</sup>

Review and Editing: AA<sup>1</sup>, HU, MH, AA<sup>2</sup>, MA, SS, HI, AA<sup>3</sup>, AA<sup>4</sup>

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



## Comparative Outcomes of Traditional Versus High-Definition Liposuction in the Surgical Management of Gynecomastia: A Prospective Study

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## ABSTRACT

The prevalence of male patients seeking surgical treatment for gynecomastia has increased in recent years. While traditional liposuction with or without gland excision remains a standard approach, high-definition (HD) liposuction has emerged as a technique that offers improved aesthetic outcomes through enhanced chest contouring. **Objectives:** To compare the early and late clinical outcomes of traditional liposuction versus high-definition liposuction in the surgical management of gynecomastia. **Methods:** This prospective, comparative study was conducted at Jinnah Burn Reconstruction Surgery Centre, Allama Iqbal Medical College, Lahore. Sixty patients aged 18-55 years were enrolled and divided into two groups: Group A (traditional liposuction) and Group B (high-definition liposuction). **Results:** In this study, the mean age of the cases was  $25.33 \pm 4.14$  in Group A, while  $26.63 \pm 3.88$  in Group B. The mean operation time was  $86.33 \pm 18.38$  in Group A, while  $52.60 \pm 25.75$  in Group B, with a statistically significant  $p=0.001$ . Patient satisfaction after 3 months (86.7% vs 96.7%,  $p$ -value=0.161) and 1 year (66.7% vs 93.3%,  $p$ -value<0.001) was higher in Group B. The comparison of seroma, infection, and asymmetry showed insignificant differences  $p$ -value > 0.005. **Conclusions:** High-definition liposuction appears to offer superior aesthetic results and greater patient satisfaction compared to traditional liposuction, without an increase in complications. It represents an effective alternative in the surgical management of gynecomastia.

## INTRODUCTION

Gynecomastia refers to benign growth of glandular breast tissue in men, and occurs in about 30-70% of males during their lifetime [1]. Can be due to hormonal imbalance, systemic disease, physiological changes, or the use of some medications. Most commonly, it will present as a rubbery or solid mass that is symmetrical below the nipple [1, 2]. While pseudo-gynecomastia may have some impact on body image and psychological well-being, true

gynecomastia can have a significant effect on the psychological health and body image of the patient, particularly in teens and young adults [2]. Treatment options may range from medicinal treatment and monitoring for early or moderate cases to surgical treatment for long-standing, symptomatic, and cosmetically troublesome cases [2, 3]. Over the years, various classification systems have been developed, such



as Simon's grading, to guide treatment decisions based on the amount of glandular and fatty tissue and the degree of ptosis [3]. Typical surgical interventions are usually direct excision of the glands or liposuction. There have been advancements in cosmetic surgery to allow for more cosmetic surgery procedures, such as newer technologies like laser lipolysis, radiofrequency-assisted contouring, and ultrasound-assisted liposuction [4, 5]. However, one of them, high-definition (HD) liposuction, has emerged as a promising technique that can enhance the contour and give more athletic results by sculpting superficial and deep fat compartments to minimize the effect of the fat and increase the muscle beneath it [6, 7]. Another technique that could be employed is intramuscular or submuscular fat grafting to enhance areas that may be deficient [8].

Although more and more patients are seeking HD liposuction, there is a lack of comparative clinical studies that examine the results of this procedure versus those of traditional liposuction in patients with gynecomastia. Specifically, there is limited data on the duration of operation, volume of aspirated fat, complications, and patient satisfaction between these two methods. Moreover, most of the current literature consists of case series or descriptive reports lacking standardized outcome assessment. This study was therefore designed to prospectively compare early and late clinical outcomes of traditional versus high-definition liposuction in the surgical treatment of gynecomastia. By analyzing objective intraoperative metrics, postoperative complications, and long-term patient-reported satisfaction, we aim to provide evidence to guide the choice of technique for optimal aesthetic and functional results.

## METHODS

This prospective, comparative study was conducted at Jinnah Burn Reconstruction Surgery Centre, Allama Iqbal Medical College, Lahore (6116/ED/JB&RSC, Date: 27 August 2024). This study was conducted from September 2024 to August 2025. A total of 60 male patients were enrolled in this study after taking informed written consent. The sample size of 60 patients (30 in each group) was calculated using the WHO sample size calculator by comparing two proportions, assuming an expected difference of 30% in patient satisfaction between the groups based on previous literature [7], with a confidence level of 95% and a study power of 80%. They were allocated into two groups: Group A underwent traditional liposuction, and Group B underwent high-definition (HD) liposuction. A simple random sampling technique was employed. Male patients between 18 and 55 years of age, diagnosed with gynecomastia, with a body mass index (BMI) of 35 kg/m<sup>2</sup> or less, and generally good health, were eligible for inclusion. Patients with a BMI greater than 35 kg/m<sup>2</sup> or those with a

history of bariatric surgery were excluded from the study. The study protocol was approved by the Institutional Ethical Review Committee. Data were collected by using a structured proforma. All patients who were admitted to either of the participating hospitals were evaluated, and data were obtained. The objectives, methodology, cost sources, potential conflict of interest, institutional affiliations, potential benefits, risks, and post-study arrangements were presented to all participants in accordance with the Declaration of Helsinki. They were also reminded that they could leave at any time without penalty. All subjects were informed in writing about the permission. The number of days needed for the patient to resume their normal daily activities or occupational function was defined as the time of work. Traditional Liposuction Technique: The procedures were performed using general anesthesia, supine position, and arms spread to 90 degrees. After routine skin preparation and draping, a 4 mm stab incision was made in the anterior axillary fold. A tumescent solution was placed in the gland and surrounding tissue using a blunt-tipped 4-mm Klein infiltration cannula. Following a 7-minute latency interval, a second incision was performed along the anterior axillary line along the inframammary fold. Liposuction was executed with a 3.5-mm blunt-tipped Coleman cannula with vibration-assisted liposuction (VAL) following established methods. Patients with remaining glandular tissue received immediate excision. Drains were inserted via the inferior port location, and compression dressings were administered postoperatively. High-Definition Liposuction Technique: Preoperative markings were performed with the patient in the standing position, outlining muscle borders and negative anatomical triangles (latissimus dorsi-pectoralis major region) where both superficial and deep liposuction were planned. Resection zones were demarcated, and areas of pectoralis muscle definition were identified for potential fat grafting. Following tumescent infiltration, VASER-assisted emulsification was performed for 3-5 minutes per side, after which liposuction and glandular excision were carried out. VASER is done at a low setting, and fat accumulation is done in a sterilized container. Fat was prepared by gravity and Sedimentation in 50 ML Syringes. Fat Grafting with the ratio of 1:3 done into muscle & submucular plane respectively. Closed-suction drains were placed, and compression garments were applied. Drains were removed after 24 hours, patients were discharged, and dressings were changed on the 4th postoperative day. Then patients were followed up at 6th day, 15th day, 1 month, and 6th month.

Data were analyzed using SPSS version 23.0. Quantitative variables were expressed as mean  $\pm$  standard deviation, while qualitative variables were presented as frequency

and percentages. An independent sample t-test was applied to compare means between groups, and a chi-square test was used for categorical variables. A p-value of <0.005 was considered statistically significant.

## RESULTS

In this study, the mean age of the cases was 25.33 ± 4.14 in Group A, while 26.63 ± 3.88 in Group B. The mean operation time was 86.33 ± 18.38 in Group A, while 52.60 ± 25.75 in Group B, with a statistically significant p<0.001. The mean amount of aspirated fat was 493.00 ± 32.60 ml in Group A and 450.67 ± 55.26 in Group B, with p<0.001. The comparison of hospital stays hours and time of work showed insignificant p-values, i.e., 0.386 and 0.650, respectively. Simon's grades of gynecomastia were found to be insignificant between the two groups (Table 1).

**Table 1:** Demographic and Operative Characteristics

Variables	Group A, Mean ± SD/ n (%)	Group B, Mean ± SD/ n (%)	p-value
Age	25.33 ± 4.14	26.63 ± 3.88	0.215
Operation Time (Minutes)	86.33 ± 18.38	52.60 ± 25.75	<0.001
Hospital Stay Hours	8.73 ± 2.05	9.20 ± 2.09	0.386
Amount of Aspirated Fat (ml)	493.00 ± 32.60	450.67 ± 55.26	<0.001
Weight of Excised Glandular Tissue Bilaterally (g)	165.33 ± 74.59	167.83 ± 72.25	0.896
Time of Work (days)	5.40 ± 2.43	5.70 ± 2.67	0.650
<b>Grade</b>			
I	17 (56.7%)	18 (60%)	0.598
Ila	9 (30%)	6 (20%)	
Ilb	4 (13.3%)	6 (20%)	
III	0 (0%)	0 (0%)	

In this study, 14 (46.7%) patients in Group A and 8 (26.7%) patients in Group B received general anesthesia. Pseudo-gynecomastia was found in 5 (16.7%) patients in Group A and 3 (10%) in Group B. Patient satisfaction after 3 months (86.7% vs 96.7%, p 0.161). Patient satisfaction at 1 year (66.7% vs 93.3%, p=0.001) was higher in Group B with a statistically significant difference (Table 2).

**Table 2:** Anesthesia and Patient Satisfaction

Study Groups		Group A, n (%)	Group B, n (%)	p-value
Type of Anesthesia	General	14 (46.7%)	8 (26.7%)	0.108
	Local	16 (53.3%)	22 (73.3%)	
Pseudo-gynecomastia	Yes	5 (16.7%)	3 (10%)	0.448
	No	25 (83.3%)	27 (90%)	
Patient Satisfaction After 3 Months	Yes	26 (86.7%)	29 (96.7%)	0.161
	No	4 (13.3%)	1 (3.3%)	
Patient Satisfaction After 1 Year	Yes	20 (66.7%)	28 (93.3%)	0.001
	No	10 (33.3%)	2 (6.7%)	

The comparison of seroma, infection, and asymmetry showed insignificant differences p>0.005 (Table 3).

**Table 3:** Comparison of Early and Late Outcomes

Study Groups		Group A	Group B	p-value
Seroma	Yes	2 (6.7%)	1 (3.3%)	0.554
	No	28 (93.3%)	29 (96.7%)	
Infection	Yes	1 (3.3%)	1 (3.3%)	1.00
	No	29 (96.7%)	29 (96.7%)	
Asymmetry	Yes	1 (3.3%)	0 (0%)	0.313
	No	29 (96.7%)	30 (100%)	

Composite frontal and bilateral oblique views at six months following high-definition liposuction of the male chest, demonstrating stable pectoral contour, well-defined negative spaces, and sustained muscular delineation, were analyzed (Figure 1).



**Figure 1:** Composite Frontal and Bilateral Oblique Views at Six Months

Oblique view after high-definition chest sculpting showing refined transition zones between the pectoralis major, axillary fold, and upper abdomen with maintained surface definition (Figure 2).



**Figure 2:** Oblique View After High-Definition Chest Sculpting  
Postoperative result following conventional chest liposuction illustrating volume reduction with comparatively smoother contours and limited muscular delineation (Figure 3).



**Figure 3:** Postoperative Result Following Conventional Chest Liposuction

## DISCUSSION

This study is a prospective comparative study that shows that high-definition (HD) liposuction offers better long-term patient satisfaction than traditional liposuction in the treatment of gynecomastia and has a similar safety profile. While there were no significant differences noted at 3 months, the aesthetic results of HD liposuction continued to improve over time at the 1-year visit, when edema subsided and final contouring stabilized. One of the important conclusions of this study is that the time for the operation of HD lipo is significantly shorter. This might seem paradoxical considering the extra contouring procedures, but the reasoning for this is that energy-assisted technologies like VASER enable emulsification of the fibrofatty tissue and help to get rid of fat more efficiently. This decreases the surgeon's workload and fatigue, and the length of the surgery. Previous studies using ultrasound- or power-assisted liposuction have reported similar results, with enhanced efficiency without affecting results. Adverse events such as seroma, infection, and asymmetry were rare and similar between groups, and the extra contouring involved with HD did not raise the risk of these complications [8, 9]. This is partly due to the fact that the technique is focused on removing fat selectively and sculpting the contours of the body, in lieu of debulking the fat in bulk, which could account for the slightly lower aspirated fat volume observed in the HD group. HD Liposuction is not just about fat removal like traditional liposuction; it is about strategically preserving and redirecting fat for an enhanced muscular definition. This focused technique could be the reason for the higher satisfaction level, even though the volumes of aspirated fat were lower; patient satisfaction is more dependent on the quality of the contour rather than the total amount of fat removed. The efficiency of energy- and power-assisted platforms (VASER and PAL), which emulsify fibrofatty tissue and facilitate extraction, is the plausible explanation for a shorter operative time in the HD group [10-13]. This increase in satisfaction with HD may be due to its ability to

achieve selective fat definition in both superficial and deep fat compartments, as well as fat grafting in those where warranted, to improve the borders of the pectoral [7, 8]. These results are in accordance with previous studies that found liposuction alone is an effective treatment for lower-grade disease and a combination of treatments will enhance contour reliability in denser or higher grades of gynecomastia. Technique selection is based on classification- and algorithm-based strategies based on tissue character and ptosis [14, 15]. Importantly, there were low incidence rates of seroma, infection, and asymmetry in both groups. This discovery strengthens the safety of HD liposuction and suggests that both the extra sculpting maneuvers and fat grafting do not add to the risk of complications when done by an experienced surgeon. The findings confirm those of previous studies that report a low rate of complications with both traditional and innovative liposuction techniques. Comparative series and reviews report low complication rates across modalities, with technique-specific nuances; combined or energy-assisted techniques may allow the preservation of low modality complication rates and increase contour, particularly in difficult cases [11, 9]. For some patients, the minimally invasive and/or endoscopic approach can provide further options for scar concealment and cosmesis [16-18]. It is possible that the lack of significance in satisfaction level is due to sample size, subjective outcome evaluation, and surgeon expertise reducing intergroup variability. Results can also be affected by heterogeneity in the grade, tissue density, and skin quality. Though longer follow-up is warranted, prospective and multicenter studies with VASER, PAL, and hybrid energy techniques report excellent outcomes with low complication rates, and the use of standardized outcome measures and long-term evaluation is emphasized [19, 20]. To sum up, HD liposuction confers the aesthetic benefits and does not have any more complications than traditional liposuction, especially for the male chest area. The results are consistent with the safety and efficacy of HD as a technique for correcting gynecomastia, particularly for those wanting an athletic contour. Larger multicenter studies, with grade-stratified comparisons versus objective aesthetic metrics and longer follow-up to confirm these benefits and optimize patient selection criteria [18, 19].

There are several limitations to this study. First, the sample size was small, and thus may have limited power to detect differences in less common complications. Second, subjective measures, like patient satisfaction, may be subject to response bias if they are not standardized, validated scoring systems used. Third, the duration of follow-up (one year) might not be long enough to evaluate very long-term outcomes and recurrence. Furthermore, the study took place in two centers where there was the

possibility of different surgical procedures and perioperative management. Lastly, non-probability sampling limits external validity. Larger, multicenter, randomized controlled trials with standardized outcome measures such as validated aesthetic scoring systems and objective photo analysis should be conducted in the future. More extended follow-up periods are required to evaluate the long-term effectiveness. Incorporating cost-effectiveness analysis and stratification by grade of gynecomastia would further enhance clinical decision-making and guideline development.

## CONCLUSIONS

High-definition chest contouring shows an evident benefit in shaping, definition, and patient-reported satisfaction compared with standard liposuction, with comparable safety, and is therefore a valuable and reliable tool for the surgical treatment of gynecomastia.

## Authors' Contribution

Conceptualization: MB, MAY

Methodology: MB, MAY, KK, BB

Formal analysis: FAK

Writing and Drafting: MB, KK, AR, JA

Review and Editing: MB, MAY, KK, FAK, AR, BB, JA

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



## The Frequency of Raised Liver Enzyme in Patients on Anti-Tuberculosis Drugs

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## ABSTRACT

Anti-tuberculosis therapy is associated with hepatotoxicity, which may manifest as elevation of liver enzymes and can affect treatment adherence and outcome. **Objective:** To determine the frequency of raised liver enzymes in patients receiving anti-tuberculosis therapy. **Methods:** This prospective observational study was conducted at the Department of Medicine, AIMS Muzaffarabad, from May 2025 to December 2025. A total of 200 patients aged 18 to 70 years with pulmonary tuberculosis were enrolled through consecutive non-probability sampling. Patients with pre-existing liver disease, viral hepatitis, HIV, pregnancy, alcohol use, or concurrent hepatotoxic medications were excluded. All patients received standard first-line anti-tuberculosis therapy. Liver function tests were performed at baseline, 2 weeks, 4 weeks, 2 months, 4 months, and 6 months. Data were analyzed using SPSS version 30. **Results:** The mean age was  $44.17 \pm 15.55$  years, and 59% were male. Elevated ALT was observed in 29.0%, AST in 39.0%, and ALP in 7.0% patients. Overall, hepatotoxicity was observed in 57% patients. Elevated enzyme concentration was more common among subjects aged over 50 and subjects with a BMI over 25 kg/m<sup>2</sup>; nevertheless, no statistical significance was reached for these observations. The levels of enzymes significantly increased during the follow-up periods ( $p < 0.001$ ). **Conclusion:** Antitubercular therapy is commonly associated with a considerable frequency of raised liver enzymes, emphasizing the need for proper monitoring in antitubercular therapy.

## INTRODUCTION

Anti-tuberculosis drugs form the cornerstone of tuberculosis management, a chronic and potentially life-threatening infectious disease caused by *Mycobacterium tuberculosis* [1]. If left untreated, tuberculosis can severely damage the lungs and other organs, and its ability to spread through airborne droplets makes it a major public health concern worldwide [2]. The standard treatment regimen generally consists of a carefully designed combination of drugs such as isoniazid, rifampicin, pyrazinamide, and ethambutol [3]. These drugs act on the bacterium in different ways, and their combined effect works synergistically in eliminating the bacterium from causing infections, while at the same time avoiding the formation of

resistant strains [4]. Like all powerful drugs, there is a risk involved when using antituberculosis drugs. This is due to their side effects, which can affect different body organs. While some of the adverse effects are lesser and include gastrointestinal symptoms, vomiting, and dermatitis, other severe side effects are also common [5]. Adverse effects associated with these important medications should be carefully considered. These include the aspect of hepatotoxicity, which is well-known and common, especially when the medicines are either isoniazid, rifampicin, or pyrazinamide [6]. These medications, which are highly effective, cause considerable liver distress and can disrupt the metabolism of the liver. This adverse effect



is particularly common among patients having underlying factors such as advanced age, existing liver disease, excessive alcohol intake, malnutrition, and exposure to additional liver-toxic medications [7]. Hepatotoxicity as a result of an elevation in liver enzymes is a major sign of toxicity in patients receiving anti-TB medications, and it signifies damage or distress to the liver [8]. In some patients, the level of ALT, AST, and bilirubin is noted to be elevated [9]. In mild cases, there are no symptoms, but the elevation is reversible upon adjustment of the medication dose and termination of the therapy. In more severe cases, there might be rapid progression of hepatotoxicity, which can result in jaundice and an inability of the liver to work effectively. It can even cause liver failure in some cases. This would hamper the efficiency and success of the tuberculosis control program. Improper adjustment of the anti-TB drugs would reduce efficacy [10]. This is why the routine testing of liver functions should be done periodically, especially in the intensive stage of treatment. The study conducted by Shaikh et al revealed the incidence rate of ALT elevation was 29.6%, AST elevation was 39%, and ALP elevation was 7.4% in patients taking anti-tuberculosis drugs [11].

TB has been one of the health issues in Muzaffarabad for many years, with a high number of patients who need treatment with TB medicines. It should be noted that although it is very effective, its side effect is that this treatment produces adverse effects on the liver, especially an increase in enzyme levels in the liver. Since little literature is available in this regard locally, it becomes difficult to calculate the risk involved. This study, which has been carried out in Muzaffarabad, will be of great help in that respect.

## METHODS

This Prospective observational study was carried out in the Department of Medicine, AIMS Muzaffarabad, Azad Jammu and Kashmir, from May 2025 to December 2025. A total of 200 patients diagnosed with pulmonary tuberculosis were included. The sample size was calculated through the WHO sample size determination software, applying a 95% confidence interval, a 3.7% margin of error, and an anticipated frequency of raised alkaline phosphatase of 7.4% among individuals receiving anti-tuberculosis therapy [11]. A non-probability consecutive sampling technique was employed for patient recruitment. Ethical approval for the study was obtained from the Institutional Review Board of AIMS Muzaffarabad (IRB No. 8810/AIMS/2025). The subjects selected had to be within the age range of 18 to 70 years of either gender, and must have satisfied the diagnosis requirements of tuberculosis. Diagnosis of tuberculosis was based on the presence of pulmonary consolidation on the chest radiographs and

Mantoux reaction positivity with induration of  $\geq 10$ mm recorded after 48-72 hours. Individuals suffering from pre-existing hepatic disorders, associated infections like hepatitis B, hepatitis C, or HIV, alcoholism, use of hepatotoxic drugs, pregnancy, or lactation amongst women were excluded from the study. Informed consent was obtained from all the subjects before the commencement of the experiment. Basic demographic details were noted, such as age, gender, body mass index, socioeconomic status, education, residency, and the duration of presenting complaints. Detailed history and physical examination were performed, and standardized anti-tuberculosis therapy was initiated. During the intensive phases, the patients were put on isoniazid (5 mg/kg, maximum 300 mg/day), rifampin (10 mg/kg, maximum 600 mg/day), pyrazinamide (25 mg/kg/day), and ethambutol (15 mg/kg, maximum 1.5 g/day) for two months. This was followed by the continuation phase, which was continued for four months and involved the administration of isoniazid and rifampin at the same doses. The doses were individualized based on age and weight. Liver function test was planned at the start of the therapy during the second week, fourth week, and the second and fourth months. After the sixth month of therapy, 5 mL of venous blood was taken using Vacutainer tubes by an experienced fourth-year resident and analyzed for biochemical values. ALT  $>42$  U/L, AST  $>42$  U/L, and ALP  $>120$  U/L were considered elevated based on standard laboratory reference ranges [12]. Elevated levels were considered to be raised liver enzymes.

All of the data were entered and analyzed using SPSS 30.0. Quantitative variables like age, BMI, and duration of symptoms were expressed as mean and standard deviation. Categorical data, including sex, socioeconomic class, residence, educational background, and frequency of raised liver enzymes, were expressed as frequencies and percentages. Raised ALT, AST, and ALP were stratified against demographic and clinical variables, and statistical significance was determined using chi-square or Fisher's exact test where appropriate, with a p-value  $\leq 0.005$  considered significant.

## RESULTS

In this study evaluating the frequency of raised liver enzymes in patients on anti-tuberculosis therapy, the mean age was  $44.17 \pm 15.55$  years, and the mean BMI was  $23.22 \pm 2.98$  kg/m<sup>2</sup> (as shown in Table-1). Of the 200 patients, 118 (59.0%) were male, and 82 (41.0%) females; 138 (69.0%) were rural residents, and 62 (31.0%) were urban dwellers. Socioeconomically, 120 (60.0%) belonged to the low-income group, 58 (29.0%) to the middle-income group, and 22 (11.0%) to the high-income group (Table 1).

**Table 1:** Patient Demographics

Demographics	Mean ± SD
Age (Years)	44.17 ± 15.55
BMI (kg/m <sup>2</sup> )	23.22 ± 2.98
<b>Gender</b>	
Male n (%)	118 (59%)
Female n (%)	82 (41%)
<b>Residence</b>	
Rural n (%)	138 (69%)
Urban n (%)	62 (31%)
<b>Socioeconomic Status</b>	
Low n (%)	120 (60%)
Middle n (%)	58 (29%)
High n (%)	22 (11%)

The mean ALT, AST, and ALP levels were 41.42 ± 29.69, 48.90 ± 34.43, and 91.56 ± 35.71 U/L, respectively. Among 200 patients on anti-tuberculosis drugs, raised ALT was observed in 58 (29%), raised AST in 78 (39%), and raised ALP in 14 (7%) patients. Overall hepatotoxicity was recorded in 114 (57%) patients (Table-2).

**Table 2:** Frequency of Raised Liver Enzymes in Patients on Anti-tuberculosis Drugs

Liver Enzyme	Mean ± SD
ALT (U/L)	41.42 ± 29.69
AST (U/L)	48.90 ± 34.43
ALP (U/L)	91.56 ± 35.71
Liver Enzyme	<b>n (%)</b>
Raised ALT	58 (29%)
Raised AST	78 (39%)
Raised ALP	14 (7%)
Overall Hepatotoxicity	114 (57%)

Stratified analysis of raised ALT showed that among patients aged ≤50 years, 30 (24.2%) had raised ALT compared to 94 (75.8%) without, while in those >50 years, 28 (36.8%) had raised ALT versus 48 (63.2%) normal (OR=1.83, p=0.077). Among males, 34 (28.8%) had raised ALT and 84 (71.2%) normal, while among females, 24 (29.3%) had raised ALT and 58 (70.7%) normal (OR=0.98, p=0.944). In patients with BMI ≤25, 40 (26.3%) had raised ALT compared to 112 (73.7%) normal, while patients with BMI > 25 had 18 (37.5%) raised versus 30 (62.5%) normal (OR=1.68, p=0.137). By residence, 38 (27.5%) rural patients had raised ALT and 100 (72.5%) normal, compared to 20 (32.3%) urban patients with raised and 42 (67.7%) normal (OR=1.25, p=0.496). According to socioeconomic status, 36 (30.0%) low-income patients had raised ALT, while 84 (70.0%) were normal, 16 (27.6%) middle-income raised vs. 42 (72.4%) normal, and 6 (27.3%) high-income raised vs. 16 (72.7%) normal (OR=1.14 for low vs high, p=0.929). For AST, among ≤50 years, 46 (37.1%) patients had raised levels, while 78 (62.9%) were normal, compared to >50 years,

where 32 (42.1%) had raised levels, and 44 (57.9%) were normal (OR=1.23, p=0.481). Male patients had 46 (39.0%) raised AST vs. 72 (61.0%) normal, and females had 32 (39.0%) raised vs. 50 (61.0%) normal (OR=1.00, p=0.995). In the BMI ≤25 group, 56 (36.8%) had raised AST vs. 96 (63.2%) normal, while the BMI >25 group had 22 (45.8%) raised vs. 26 (54.2%) normal (OR=1.45, p=0.266). By residence, 56 (40.6%) rural patients had raised AST, and 82 (59.4%) had normal, compared to 22 (35.5%) urban patients raised and 40 (64.5%) normal (OR=0.80, p=0.494). Socioeconomic status showed 50 (41.7%) raised vs. 70 (58.3%) normal in low, 18 (31.0%) raised vs. 40 (69.0%) normal in middle, and 10 (45.5%) raised vs. 12 (54.5%) normal in high group (OR=0.86 for low vs high, p=0.318). For ALP, among ≤50 years, 8 (6.5%) had raised ALP vs. 116 (93.5%) normal, while >50 years had 6 (7.9%) raised vs. 70 (92.1%) normal (OR=1.24, p=0.698). Male patients showed 8 (6.8%) raised vs. 110 (93.2%) normal, while females had 6 (7.3%) raised vs. 76 (92.7%) normal (OR=0.92, p=0.884). In the BMI ≤25 group, 8 (5.3%) had raised ALP vs. 144 (94.7%) normal, compared to the BMI >25 group with 6 (12.5%) raised vs. 42 (87.5%) normal (OR=2.57, p=0.087). By residence, 12 (8.7%) rural patients had raised ALP vs. 126 (91.3%) normal, while only 2 (3.2%) urban patients had raised vs. 60 (96.8%) normal (OR=0.35, p=0.233). Socioeconomic differences were significant: 6 (5.0%) low-income patients had raised ALP vs. 114 (95.0%) normal, 8 (13.8%) middle-income raised vs. 50 (86.2%) normal, and none in the high-income group (0.0% vs. 100%) (OR=3.04 for middle vs low, p=0.040) (Table-3).

**Table 3:** Association of Raised Liver Enzymes with Demographic Factors

Demographic Factors		Raised ALT			OR	p-value
		Yes, n (%)	No, n (%)	Total		
Age (years)	≤50	30 (24.2%)	94 (75.8%)	124	1.83	0.077
	>50	28 (36.8%)	48 (63.2%)	76		
Gender	Male	34 (28.8%)	84 (71.2%)	118	0.98	0.944
	Female	24 (29.3%)	58 (70.7%)	82		
BMI (Kg/m <sup>2</sup> )	≤25	40 (26.3%)	112 (73.7%)	152	1.68	0.137
	>25	18 (37.5%)	30 (62.5%)	48		
Residential Status	Rural	38 (27.5%)	100 (72.5%)	138	1.25	0.496
	Urban	20 (32.3%)	42 (67.7%)	62		
Socioeconomic Status	Low	36 (30.0%)	84 (70.0%)	120	1.14	0.929
	Middle	16 (27.6%)	42 (72.4%)	58		
	High	6 (27.3%)	16 (72.7%)	22		
<b>Raised AST</b>						
Age (years)	≤50	46 (37.1%)	78 (62.9%)	124	1.23	0.481
	>50	32 (42.1%)	44 (57.9%)	76		
Gender	Male	46 (39.0%)	72 (61.0%)	118	1.00	0.995
	Female	32 (39.0%)	50 (61.0%)	82		
BMI (Kg/m <sup>2</sup> )	≤25	56 (36.8%)	96 (63.2%)	152	1.45	0.266
	>25	22 (45.8%)	26 (54.2%)	48		
Residential Status	Rural	56 (40.6%)	82 (59.4%)	138	0.80	0.494
	Urban	22 (35.5%)	40 (64.5%)	62		

Socioeconomic Status	Low	50 (41.7%)	70 (58.3%)	120	0.86	0.318
	Middle	18 (31.0%)	40 (69.0%)	58		
	High	10 (45.5%)	12 (54.5%)	22		
<b>Raised ALP</b>						
Age (years)	≤50	8 (6.5%)	116 (93.5%)	124	1.24	0.698
	>50	6 (7.9%)	70 (92.1%)	76		
Gender	Male	8 (6.8%)	110 (93.2%)	118	0.92	0.884
	Female	6 (7.3%)	76 (92.7%)	82		
BMI (Kg/m <sup>2</sup> )	≤25	8 (5.3%)	144 (94.7%)	152	2.57	0.087
	>25	6 (12.5%)	42 (87.5%)	48		
Residential Status	Rural	12 (8.7%)	126 (91.3%)	138	0.35	0.233*
	Urban	2 (3.2%)	60 (96.8%)	62		
Socioeconomic Status	Low	6 (5.0%)	114 (95.0%)	120	3.04	0.040*
	Middle	8 (13.8%)	50 (86.2%)	58		
	High	0 (0.0%)	22 (100.0%)	22		

\*Fisher's Exact Test

Binary logistic regression analysis demonstrated no statistically significant interaction between gender and duration of therapy in relation to overall hepatotoxicity ( $p = 0.238$ ) (Table 4).

**Table 4:** Logistic Regression Analysis for Interaction Between Gender and Duration of Therapy in Relation to Overall Hepatotoxicity

Variables	B	SE	OR (Exp B)	p-value
Gender	1.402	1.186	4.063	0.237
Duration	3.563	1.066	35.265	<0.001
Gender × Duration	-0.827	0.701	0.438	0.238

## DISCUSSION

Present study values are similar proportions as recorded by Sehar *et al.* which were 11.33%, which were lower compared to our study, possibly because the study had strictly applied their biochemical abnormality definition ( $>3 \times$  ULN) compared to our study that recorded elevated enzymes despite modest elevations [13]. Our findings are more aligned with the study conducted by Malik *et al.* which revealed the presence of hepatotoxicity in 36.8% of patients, corresponding to the total percentage of enzyme elevation observed in our study [14]. This correspondence could be due to similarities possibly existing between both study populations, mainly the preponderance of middle-aged patients on standard therapy. However, the study conducted by Shahid *et al.* observed an alarming proportion of 55%, especially in patients undergoing thrice-weekly combination therapy of INH, RIF, and PZA, which produced 100% hepatotoxicity [15]. This observed discrepancy could be attributed to the smaller study population and possibly the use of more hepatotoxic drug combinations, as well as regional factors. Mansoor *et al.* observed marked increases in levels of ALT, AST, bilirubin, and alkaline phosphatases during the intensive phase, thus validating the corresponding observation that subclinical

hepatotoxicity occurs commonly and the monitoring of enzymes is necessary. Compared to Akkahadsee *et al.* who had an incidence of 14.45% for anti-tuberculosis drug-induced liver injury (ATDILI) in Thailand, our study had significantly higher figures for the elevation of enzymes [16, 17]. This may be attributed to the fact that Akkahadsee *et al.* included participants with normal baseline liver function and applied stricter diagnostic criteria, unlike the present study, which looked for any increase above the normal values. Furthermore, their identification of malnutrition, comorbidities, and alcohol as key risk factors is consistent with our observation of higher risk in patients with older age and higher BMI, suggesting that multiple patient-related factors contribute to susceptibility [17]. Tariq *et al.* reported 8% hepatotoxicity with only 0.2% mortality, which is much lower than our observed frequency, which may again be attributed to regional variation and difference in case definition [18]. Memon *et al.* demonstrated a 16.93% frequency of hepatotoxicity in patients with HCV co-infection, a lower rate compared to ours, but their much higher ALT and AST values at peak toxicity suggest more severe liver injury likely due to underlying hepatic compromise [19]. Overall, our findings are comparable with regional data that demonstrate a higher burden of ATT-related hepatotoxicity compared to international reports, which may reflect population-based risk factors, including nutritional status, comorbidities, and monitoring practice [16-18]. This association of longer duration of therapy and elevated enzymes observed in our study further emphasizes the significance of liver function monitoring, which has been advised in various investigations [20]. No significant interactions between gender and duration were observed, indicating that the effects of treatment duration on hepatotoxicity do not differ between males and females. The study was a single center study using an observational prospective study design that may limit the applicability of the findings in the general population. The prospective observational design allowed assessment of temporal changes in liver enzyme levels during therapy; however, it does not permit inference of causal relationships, and the findings should be interpreted as associations only. Importantly, important confounders like nutritional factors, pre-existing subclinical hepatic dysfunction, and genetic factors were not considered in the study design. The study has extensively used biochemical markers, but has not clinically validated the degree of liver toxicity suffered by patients. The duration of therapy was not quantitatively analyzed, which limits understanding of time-dependent hepatotoxic effects.

There are some limitations that need to be considered in this study. This is a single-center prospective

observational study done in a tertiary care hospital, and this could limit its applicability to a larger population. As an observational study, it can only determine associations but cannot prove any cause and effect, and the temporality in the exposure to drugs and the increase in enzyme levels must not be assumed as being causal. Some confounders, such as nutrition, the presence of asymptomatic liver disease, and genetic predisposition, which may have affected the outcome of the study, were not determined in this study. No relation to the biochemical indices was made to the clinical manifestations of hepatotoxicity. In addition, no quantitative correlation of the cumulative duration of treatment with increased enzyme levels was made in this study. Therefore, it may not be concluded from this study that there is a drug-related effect, since uncontrolled confounding variables might have influenced the outcome of this study.

## CONCLUSIONS

The study found that patients on anti-tuberculous medication developed frequent abnormal liver enzymes. This was associated with those who have had long-term treatment, older patients, higher body mass index, and low socioeconomic class, though there is no cause-and-effect relationship. Monitoring of the liver function during medication is very necessary.

## Authors' Contribution

Conceptualization: AT

Methodology: MM, MAS

Formal analysis: AT, AK, MH

Writing and Drafting: AT

Review and Editing: AT, AK, MM, MH, MAS

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



## Clinical Accuracy of Intraoral Scanner Impressions Compared with Conventional Impressions in Fixed Partial Prostheses: A Systematic Review

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## ABSTRACT

The use of digital impression systems in prosthodontics has gained greater acceptance, but issues surrounding their clinical accuracy compared to traditional elastomeric impressions still exist, particularly for fixed partial prostheses. This comparison is crucial as many practices transition to digital workflows. **Objectives:** The primary objective of this review was to evaluate the clinical accuracy of intraoral scanner (IOS) impressions versus conventional impressions for fixed partial prostheses. **Methods:** A systematic search was conducted in PubMed, Scopus, and Cochrane Library for comparative clinical studies published between January 2018 and January 2024. Eligible studies included human trials comparing IOS and conventional impressions for tooth- or implant-supported fixed prostheses. Methodological quality was assessed using a modified QUADAS-2 tool. **Results:** Fifteen clinical studies met the inclusion criteria. Quantitative analysis revealed marginal gaps for digital workflows ranging from 30 to 90 µm, comparable to the 35-100 µm range observed for conventional methods. Digital impressions demonstrated superior time efficiency and patient comfort. For short-span restorations, IOS accuracy was equivalent to conventional methods; however, conventional techniques showed slightly better stability in long-span implant cases. **Conclusions:** Current clinical evidence suggests that intraoral scanners provide accuracy comparable to conventional impressions for most fixed partial prostheses, with added benefits in efficiency and patient experience. While caution is advised for complex full-arch cases, IOS can be reliably integrated into routine practice.

## INTRODUCTION

Digital technology has significantly transformed the modern practice of dentistry, and one area where this transformation has been particularly notable is impression making [1]. Previously regarded as an emerging supplementary technology, intraoral scanners have now become integral components of most restorative workflows. Their increasing adoption reflects broader trends toward enhanced chairside efficiency, seamless

digital workflow integration, and streamlined laboratory communication [2]. Regardless of this development, the fundamental clinical question remains: What is the accuracy of these digital impressions in comparison with the long-established conventional elastomeric materials traditionally used for fixed partial prostheses? [3, 4]. The success of any fixed restoration is fundamentally dependent on impression accuracy. Marginal fit, internal



adaptation, and three-dimensional precision are critical determinants of long-term outcomes such as biological compatibility, prosthesis longevity, and patient comfort [5]. While intraoral scanners are expected to achieve enhanced efficiency and improved patient acceptance, their clinical performance can be influenced by multiple factors, including clinical context, the extent of the restoration, scanner technology capabilities, and operator proficiency. Traditional materials, especially polyvinyl siloxane and polyether, have demonstrated a long history of consistent performance, thereby establishing a high benchmark for digital systems to achieve comparable standards [6-8]. A substantial body of clinical research has emerged in recent years comparing digital impressions with traditional methods. Findings from these investigations generally suggest that digital scanning can serve as a viable alternative for most routine prosthodontic procedures, although controversies persist regarding more complex clinical scenarios, particularly long-span implant restorations [9]. The objective of this systematic review was to synthesize the latest evidence from clinical studies published between 2018 and 2024. By critically evaluating studies that directly compare intraoral scanners with conventional impressions in human participants, this review seeks to provide a comprehensive and contemporary understanding of their relative accuracy and clinical implications for prosthodontic care.

Although intraoral scanners have become widely-used, it is not clear how accurately they can be compared to the traditional elastomeric impressions, especially in more complicated restorations and the placement of implantable prostheses. This is a challenge in attaining optimal marginal fit, internal adaptation, and long-term success of the prosthesis. This study aimed to conduct a meta-analytic review of recent clinical research findings to assess and compare the validity of digital and traditional impression methods in the study of prosthodontic care.

## METHODS

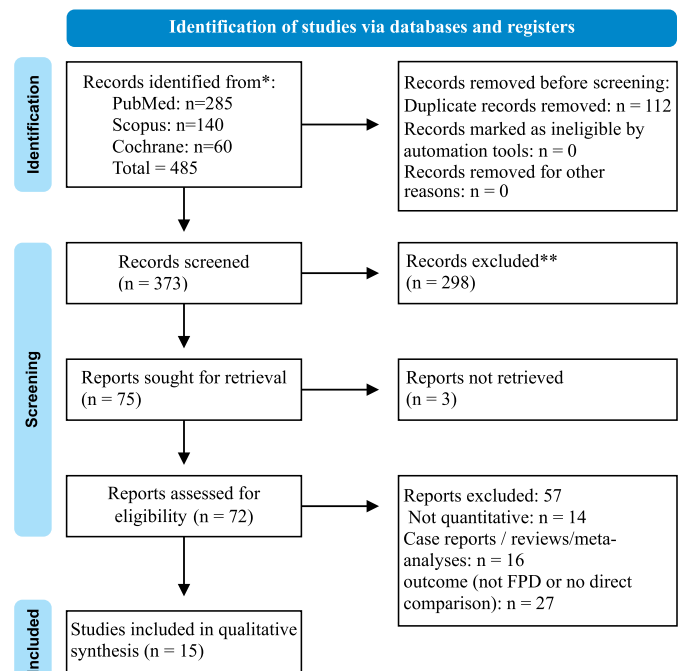
To ensure methodological clarity, the following PICO framework was defined for this review: Population: Patients requiring fixed partial prostheses (tooth-supported or implant-supported). Intraoral scanner (IOS) digital impressions, Comparator: Conventional elastomeric impressions (polyvinyl siloxane, polyether). Marginal fit, internal adaptation, clinical accuracy, treatment time, patient comfort. This systematic review was conducted to evaluate the clinical accuracy of intraoral scanner impressions compared with standard conventional impressions for fixed partial prostheses. The review methodology adhered to the established principles of the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to ensure

methodological rigor, clarity, and transparency throughout the selection process. Given that the primary focus was clinical accuracy, particular attention was directed toward identifying studies that directly compared both techniques under actual patient conditions. A comprehensive electronic search was conducted across PubMed, Scopus, and Cochrane Library. PubMed search strategy: "(intraoral scanner OR digital impression AND (conventional impression OR elastomeric impression AND (fixed partial prosthesis OR fixed dental prosthesis OR crown OR bridge OR implant AND (accuracy[Title/Abstract] OR fit[Title/Abstract] OR adaptation[Title/Abstract] OR clinical AND (2018/01/01:2024/01/31[Date - Publication]))" Scopus search strategy: ((intraoral AND scanner) OR (digital AND impression)) AND ((conventional AND impression) OR (elastomeric AND impression)) AND ((fixed AND partial AND prosthesis) OR (fixed AND dental AND prosthesis) OR crown OR bridge OR implant) AND (accuracy OR fit OR adaptation OR clinical) AND PUBYEAR > 2017 AND PUBYEAR < 2025" Cochrane Library search strategy: (intraoral scanner): OR (digital impression): (conventional impression): OR (elastomeric impression): (fixed partial prosthesis): OR (fixed dental prosthesis): OR crown: OR bridge: OR implant: accuracy OR adaptation: OR clinical: with publication year from 2018 to 2024. The search was temporally restricted to studies published between January 2018 and January 2024, as this period represents the timeframe during which modern intraoral scanners and updated CAD-CAM workflows became broadly accessible in clinical practice. No restrictions were applied to geographical location or clinical setting. Reference lists of included articles were manually screened to identify any additional potentially relevant studies. Inclusion Criteria: Study Design: Randomized controlled trials (RCTs), prospective clinical studies, crossover clinical trials, split-mouth randomized clinical studies, and comparative clinical trials conducted in human participants Participants/Population: Adult patients ( $\geq 18$  years) requiring fixed partial prostheses, including tooth-supported single crowns, multi-unit fixed dental prostheses (FDPs), and implant-supported restorations (single or multiple units) Intervention (Index Test): Intraoral scanner (IOS) digital impressions using any commercially available scanner system with complete digital workflow for prosthesis fabrication Comparator (Reference Standard): Conventional elastomeric impression techniques (polyvinyl siloxane, polyether, or other elastomeric materials) with traditional analog workflow Outcomes: Quantitative accuracy metrics including marginal fit/gap measurements ( $\mu\text{m}$ ), internal adaptation measurements ( $\mu\text{m}$ ), 3D positional deviations, clinical fit assessments; and/or clinical efficiency outcomes

including treatment time, chairside adjustment time, patient comfort/preference scores, need for impression repetition. Language: Studies published in English Publication Period: January 2018 to January 2024 Publication Type: Full-text peer-reviewed journal articles. Exclusion Criteria: Study Design: Study design was laboratory-based in vitro studies, case reports, case series, review articles (systematic reviews, narrative reviews, umbrella reviews), meta-analyses, editorials, commentaries, letters to the editor, conference abstracts, and technique description articles. Participants: Studies involving complete dentures, removable partial dentures, or pediatric populations. Intervention: Studies evaluating only digital design software, CAD-CAM milling accuracy, or digital workflows without actual clinical impression comparison. Comparator: Studies without direct comparison between digital and conventional impression techniques (single-arm studies). Outcomes: Studies reporting only subjective outcomes without quantitative accuracy or clinical fit data; studies limited to time/cost analysis without accuracy assessment. Language: Non-English publications Publication Type: Unpublished studies, dissertations, gray literature, and studies with incomplete or inaccessible data. Retrieved citations underwent a two-stage screening process. Initially, titles and abstracts were reviewed to exclude studies unrelated to prosthodontics or lacking comparative methodology. Subsequently, full-text articles were assessed for eligibility. Study characteristics including design, sample characteristics, prosthesis type, impression protocol, and outcome measures were extracted and organized in a structured table to facilitate comparative analysis. When data were ambiguous or incomplete, clarification was sought through supplementary materials or consultation of related publications. Methodological quality was assessed using a modified version of the QUADAS-2 tool, specifically adapted for prosthodontic accuracy studies where both impression techniques function as measurement procedures rather than diagnostic interventions. Modifications included evaluation of impression protocol standardization, operator calibration, and outcome measurement consistency. This approach enabled systematic appraisal of potential bias across multiple domains: patient selection, index test (digital impression) execution, reference standard (conventional impression) application, and flow and timing of outcome assessment. The risk of bias in each domain was classified as low, high, or unclear. This review was not prospectively registered in PROSPERO, which represents a limitation in terms of methodological transparency and should be acknowledged.

A total of 485 records were retrieved through database searches, and 112 duplicates were removed before screening. After

reviewing 373 titles and abstracts, 298 records were excluded for not meeting the study objective. Seventy-five full-text articles were assessed, of which three could not be retrieved. Following detailed eligibility evaluation of 72 full-text reports, 57 were excluded on the basis of study design, lack of quantitative data, or an unsuitable population or outcome measure. Ultimately, 15 studies fulfilled the inclusion criteria and were incorporated into the qualitative synthesis (Figure 1).



**Figure 1:** Flow diagram outlining the selection of studies included in this systematic review

## RESULTS

Fifteen clinical trials comparing intraoral scanner impressions with traditional impression techniques for fixed partial prostheses met the inclusion criteria and were analyzed. The included studies encompassed a variety of clinical scenarios, including tooth-supported crowns, three-unit fixed dental prostheses, and implant-supported reconstructions. Despite variability in prosthesis types, several consistent themes emerged. Multiple trials demonstrated that digital impressions offered significant advantages in terms of time efficiency, patient comfort, and reduced chairside adjustments. In studies assessing marginal or internal fit, digital workflows consistently produced outcomes that were either comparable to or slightly superior to those achieved with traditional elastomeric materials. Quantitative analysis across included studies revealed the following ranges: marginal gap measurements for digital workflows ranged from 30 to 90  $\mu\text{m}$  (mean:  $58 \pm 15 \mu\text{m}$ ), while conventional methods demonstrated ranges of 35-100  $\mu\text{m}$  (mean:  $62 \pm 18 \mu\text{m}$ ). Internal adaptation discrepancies ranged from 45 to 120  $\mu\text{m}$  for digital impressions compared with 50-135  $\mu\text{m}$  for

conventional techniques. Treatment time was reduced by 15-40% with digital workflows, and patient comfort scores (VAS) were significantly higher for IOS groups ( $8.2 \pm 0.9$  vs  $6.8 \pm 1.2$ ,  $p < 0.05$ ). This trend was particularly evident in studies investigating lithium-disilicate crowns and zirconia restorations. Implant-focused trials demonstrated similar patterns; digital impressions frequently matched the accuracy of open-tray techniques and were associated with fewer adjustments during prosthesis delivery. Only a limited number of studies reported marginal differences favoring conventional methods, and these differences were generally modest and lacked clinical relevance. Collectively, findings from the 15 included studies suggest that intraoral scanners have achieved a level of clinical reliability sufficient to support their routine use in most fixed prosthodontic procedures (Table 1).

**Table 1:** Characteristics of Clinical Studies Comparing Intraoral Scanner Impressions with Conventional Impressions for Fixed Partial Prostheses (2018-2024)

Sr. No.	References	Country	Study design/sample	Fixed prosthesis type	Intraoral scanner/digital workflow	Conventional impression/analog workflow	Main accuracy-related outcomes	Key conclusion on clinical accuracy
1	[10]	Switzerland	Randomized controlled clinical trial; patients requiring 3-unit zirconia-ceramic FDPs	Tooth-supported 3-unit FDPs	Complete-arch digital scan (TRIOS, 3Shape) with CAD-CAM workflow	Conventional complete-arch polyether impression and cast-based workflow	Time to obtain arch records, need to repeat impression, clinician, and patient perception of scan quality	Complete-arch digital scans were not superior in clinical performance to conventional impressions but showed similar accuracy with different time profiles and preferences
2	[11]	Switzerland	Randomized controlled clinical trial (Part III); same patient cohort as Sailer; n=20 FDPs	Tooth-supported zirconia 3-unit FDP frameworks	Fully digital workflow based on intraoral scanning and CAD-CAM zirconia frameworks	Conventional impressions with cast and metal frameworks	Marginal and internal fit (sectioned silicone replica and microscopic analysis)	Fit of CAD-CAM zirconia FDPs based on digital impressions was comparable to metal FDPs based on conventional impressions; both within clinically acceptable ranges
3	[12]	Italy	Randomized clinical trial; 24 patients with edentulous maxillae	Full-arch screw-retained implant-supported FDPs ("all-on-4")	Intraoral scan-based digital workflow (IOS + CAD-CAM)	Conventional open-tray elastomeric implant impressions	Passive fit (clinical and radiographic evaluation), complications, chairside adjustment	Digital and conventional workflows produced similar clinical fit and success, with reduced chairside time in the digital group
4	[13]	China	Double-blind self-controlled clinical trial; immediate vs conventional impressions after single implant placement	Single posterior implant-supported crowns	Immediate intraoral digital impression (IOS) and fully digital workflow	Conventional open-tray implant impression followed by lab analog procedures	Prosthesis fit occlusal adjustment time, patient comfort	Immediate digital impressions provided comparable or better clinical fit and shorter adjustment time, with high patient acceptance
5	[14]	China	Prospective clinical study; n=20 single implants	Single implant-supported crowns	Intraoral scanner-based impression after implant placement	Conventional implant impression with elastomeric material	Time efficiency, prosthesis fit, patient-reported outcomes	Digital impressions were more time-efficient with comparable clinical accuracy of single-implant crowns compared with conventional impressions
6	[15]	Denmark	Prospective split-mouth randomized clinical study; 20 patients, 40 lithium-disilicate crowns	Tooth-supported single crowns	IOS (TRIOS, 3Shape) with fully digital CAD-CAM crowns	Polyvinyl siloxane (PVS) conventional impressions and cast-based CAD-CAM	Marginal and internal fit (micro-CT/sectioning), clinical CDA scores at 6 and 12 months	IOS-based crowns showed significantly better marginal and internal adaptation before cementation, but similar clinical marginal ratings to conventional crowns

7	[16]	Lithuania	Comparative clinical study; 16 patients with 3-unit implant-supported FPDs	Implant-supported 3-unit FPDs	IOS (TRIOS) with scanbodies, digital models	Conventional open-tray implant impressions with polyether	3D positional and angular deviation between clinical and reference datasets	Digital implant impressions showed accuracy comparable to conventional impressions, with deviations below clinically relevant thresholds for short-span FPDs
8	[17]	South Korea	Parallel-group clinical trial; 60 lithium-disilicate single crowns	Tooth-supported posterior single crowns	Digital impression with IOS (Trios 3) and CAD-CAM LD crowns	Conventional PVS impression and cast-based LD crowns	Marginal/internal gap (silicone replica), chairside adjustment time, total treatment time	Digital impressions yielded similar or smaller marginal gaps, less time for adjustments, and shorter overall treatment time than conventional impressions
9	[18]	Taiwan	Randomized clinical trial; 40 posterior teeth needing interim crowns	Tooth-supported interim single crowns	Digital sextant scan, virtual design and CAD-CAM interim crowns	Conventional elastomeric impressions and chairside-fabricated interim crowns	Production time, internal fit, marginal discrepancy	Digital workflow showed shorter total treatment time and comparable or improved fit of interim crowns compared with conventional workflow
10	[19]	Netherlands	Randomized clinical trial; 32 patients, 45 posterior implants	Single posterior screw-retained monolithic zirconia implant crowns	IOS (3M™ True Definition) with scanbodies and CAD-CAM crowns	Conventional polyether open-tray pick-up impressions	Time required for occlusal and proximal adjustment, proportion of crowns needing no adjustment	IOS-based crowns required significantly shorter adjustment time and more crowns required no adjustment, indicating high clinical accuracy of digital impressions
11	[20]	Bulgaria	Controlled clinical trial; 36 patients needing 3-unit FPDs	Tooth-supported 3-unit zirconia bridges	Digital impression of whole arch (TRIOS, 3Shape)	Two-stage two-viscosity silicone impression (PVS) for abutments and antagonists	Total clinical time for impression procedures, need to repeat impressions	Digital impressions were significantly faster than conventional impressions while maintaining clinically acceptable results for bridge fabrication
12	[21]	Iran	Prospective crossover clinical trial; 15 patients, three-unit posterior ISFDPs	Implant-supported three-unit posterior FDPs	Fully digital workflow: IOS with scanbodies, CAD-CAM zirconia frameworks	Conventional open-tray implant impressions with elastomeric material and cast-based fabrication	Framework misfit (screw resistance, radiographs), chairside adjustment, patient satisfaction	Fully digital workflow produced clinically acceptable and comparable fit to conventional workflow, with less chairside adjustment and higher patient comfort
13	[22]	South Korea	Crossover clinical study; patients with multiple implants	Multi-unit implant-supported fixed prostheses	Intraoral scanning with implant scanbodies, digital design	Conventional elastomeric implant impressions (open-tray)	Impression time, perceived difficulty, framework fit, need for adjustment	Digital implant impressions showed similar clinical fit to conventional impressions, with reduced working time and improved operator preference
14	[23]	Switzerland / Turkey	Prospective crossover clinical trial; 12 patients, 14 three-unit FDPs	Tooth-supported 3-unit posterior FDPs (monolithic zirconia vs PFM)	Complete-digital workflow (Trios 3 IOS, model-free monolithic zirconia FDPs)	Complete-analog workflow (conventional impression, face-bow, semi-adjustable articulator, PFM FDPs)	Volumetric occlusal adjustment (mm <sup>3</sup> ) using pre-/post-adjustment scans, patient and operator VAS ratings	Complete digital workflow showed lower (though not statistically significant) occlusal adjustment volume and was strongly preferred by patients and operators; considered to provide high occlusal accuracy for short-span FDPs

15	[24]	Egypt	Randomized clinical trial; bilateral distal extension implant cases	Implant-supported fixed partial prostheses in Kennedy Class I situations	IOS-based digital implant impressions with scanbodies	Conventional open-tray elastomeric implant impressions	3D deviations (linear and angular) between clinical casts and reference, impression time	Digital implant impressions showed trueness and precision comparable to or better than conventional impressions in distal extension situations, with reduced impression time
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Most trials provided clear descriptions of patient selection processes, employed appropriate comparison methods, and maintained consistent clinical workflows for both digital and conventional impression techniques. The index test (digital impression procedure) was typically performed by trained clinicians using standardized scanning protocols, thereby minimizing the likelihood of performance bias. The reference standard (conventional impressions) was similarly applied using widely accepted techniques and materials (Table 2).

**Table 2:** Risk of Bias Assessment of Included Clinical Studies Based on Modified Quadas-2 Criteria

Sr. No.	References	Patient Selection	Index Test (Digital)	Reference Standard (Conventional)	Flow & Timing	Overall Risk of Bias
1	[10]	Low	Low	Low	Low	Low
2	[11]	Low	Low	Low	Low	Low
3	[12]	Low	Low	Low	Low	Low
4	[13]	Low	Low	Low	Low	Low
5	[14]	Low	Low	Low	Low	Low
6	[15]	Low	Low	Low	Low	Low
7	[16]	Low	Low	Low	Low	Low
8	[17]	Low	Low	Low	Low	Low
9	[18]	Low	Low	Low	Low	Low
10	[19]	Low	Low	Low	Low	Low
11	[20]	Low	Low	Low	Low	Low
12	[21]	Low	Low	Low	Low	Low
13	[22]	Low	Low	Low	Low	Low
14	[23]	Low	Low	Low	Low	Low
15	[24]	Low	Low	Low	Low	Low

## DISCUSSION

The predominant pattern emerging from this review is that intraoral scanner (IOS) impressions consistently yield clinical outcomes equivalent to those of conventional elastomeric techniques. This consistency across diverse prosthesis types reflects substantial improvements in optical systems, algorithmic refinement, and software calibration in contemporary scanners. This observation is corroborated by recent literature; for instance, a 2023 clinical trial evaluating partial edentulous maxillary defects found that digital impressions generated linear deviations within clinically acceptable ranges, findings consistent with those of the present review [25]. In early 2025, another study reported positive patient-reported outcomes and similar clinical accuracy when comparing digital and conventional workflows for implant-supported fixed restorations [26]. The finding that IOS demonstrates favorable performance in short-span tooth-supported restorations is consistent with previous findings, including a 2021 study comparing digital scanning to conventional impressions for interim crowns, where only minimal

differences in marginal adaptation and overall fit were observed [27]. Similar results were documented in a 2020 investigation of lithium disilicate crowns produced via digital and analog pathways, which demonstrated reduced clinical time and comparable fit accuracy with digital workflows [28]. The reliability of IOS for single-unit restorations appears to be a well-established finding supported by multiple clinical comparisons of posterior single-crown restorations [14]. Digital impressions for implant-supported prostheses have yielded similarly promising results. A 2022 clinical trial investigating posterior implant bridges found that digital workflows generated framework fits equivalent to traditional methods while requiring less adjustment time [21]. Comparable findings were apparent in a crossover study of multiple-implant prostheses using IOS impressions, which demonstrated nearly equivalent framework fit with operator preference strongly favoring digital techniques [29]. An additional 2021 randomized clinical trial also confirmed IOS efficacy for posterior screw-retained

implant crowns, demonstrating shorter adjustment times with digital impressions [30]. Nonetheless, the literature suggests that as restoration complexity increases, the potential for digital errors may also rise [31, 32]. A 2024 systematic review on full-arch scanning identified increased dimensional distortion with long-span digital scans relative to conventional impressions [32]. This finding is consistent with a second 2024 investigation that emphasized variability in long-span digital implant impressions and suggested that conventional open-tray techniques may provide more predictable accuracy in certain full-arch cases [33]. Clinical evidence published in 2023 regarding occlusal adjustment volumes in three-unit tooth-supported prostheses also indicated that digital workflows could potentially minimize adjustment volume, although these differences were not statistically significant [23]. Contemporary research provides additional insight. A 2023 assessment of IOS trueness and accuracy confirmed that scan length, angulation, and intraoral geometry may influence digital accuracy, particularly in extended scans [34]. A comparative study of digital versus analog techniques for three-unit zirconia prostheses in 2022 reinforced these findings, reporting that while both workflows achieved clinically acceptable precision, digital techniques demonstrated significantly greater time efficiency [20, 35]. A 2021 clinical investigation of implant scan body accuracy highlighted that IOS accuracy depends not solely on scanner specifications but also on scan body design and clinician scanning technique [16].

Throughout the literature reviewed, the prevailing theme is that digital impressions offer substantial benefits in efficiency and patient comfort without compromising accuracy in most routine fixed prosthodontic cases. While traditional impressions may still outperform IOS in certain long-span and complex implant cases, the overall body of evidence points toward increased reliability and clinical acceptability of digital systems. This review was not prospectively registered in PROSPERO, which represents a limitation in terms of methodological transparency and should be acknowledged. Further research and trials are necessary in the future by investigating IOS performance in complex restorations, randomized trials, standardization of assessment protocols, as well as the accuracy under mixed clinical circumstances, to further outline evidence-based guidelines.

## CONCLUSIONS

The cumulative evidence from recent clinical studies indicates that intraoral scanner-based impressions provide clinical accuracy comparable to conventional elastomeric techniques for most fixed partial prostheses. Digital workflows exhibit clear advantages in efficiency,

patient comfort, and procedural simplicity, particularly for single crowns and short-span restorations. While certain complex cases may still benefit from traditional impressions due to their proven dimensional stability, the growing consistency of IOS performance supports its routine use in modern prosthodontic practice. Future research focusing on full-arch and multi-implant restorations, as well as long-term clinical outcomes, would further strengthen the evidence base for broader digital adoption.

## Authors' Contribution

Conceptualization: SS

Methodology: SS, SN

Formal analysis: GW, ZI

Writing and Drafting: SN, GS, MW, ZI

Review and Editing: SS, SN, GW, GS, MW, ZI

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



## Platelet-Rich Plasma and Er: YAG Laser Therapy for Female Stress Urinary Incontinence: A Systematic Review

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## ABSTRACT

In female, stress urinary incontinence (SUI) is widely encountered and has a notable negative impact on daily living and overall well-being. Even though surgery is a good treatment, issues of morbidity and patient resistance have made the treatment of minimally invasive surgery more interesting. **Objectives:** To systematically evaluate clinical evidence on the effectiveness and safety of platelet-rich plasma (PRP) injections and 'non-ablative Er:YAG' vaginal laser interventions in women with SUI. **Methods:** This is a systematic review that adhered to PRISMA 2020. PubMed/MEDLINE, Scopus, and Cochrane Library were searched to identify studies published between January 2018 and March 2025. Randomized controlled trials and prospective interventional cohort studies that included adult women with SUI were included. Data were extracted on validated symptom scores, objective outcomes, adverse events, and treatment effects. Cohen Cochrane RoB-2 and NIH tools were used to assess the risk of bias. Because of heterogeneity, synthesis of results was in the form of narratives. **Results:** Ten studies (six randomized trials and four cohort studies) were included. Both PRP and Er: YAG laser therapy demonstrated improvement in symptom severity using validated patient-reported and objective measures. Sham-controlled trials generally favored active treatment, while combined PRP and pelvic floor muscle training showed greater benefit. Most randomized trials had some risk of bias, and cohort studies were of fair quality. **Conclusions:** PRP injections and Er: YAG vaginal laser therapy (NA Er:YAG laser) are promising minimally invasive options for selected women with mild to moderate SUI, though further high-quality trials are needed to confirm long-term effectiveness.

## INTRODUCTION

Stress urinary incontinence (SUI) is one of the most prevalent conditions of the pelvic floor in women in all nations of the world and has been a significant source of physical, psychological and social morbidity [1]. It is an involuntary urine leakage during activities that raise intra-abdominal pressure, such as physical activity, coughing, sneezing, or laughing, and is caused by urethral hypermobility and/or intrinsic sphincter deficiency. Epidemiological statistics show prevalence rates of 10-40

percent in adult women, and more prevalence in parous, postmenopausal, and obese groups. SUI is the involuntary leakage of urine during physical activity, coughing, or sneezing, and is disproportionately prevalent in parous and postmenopausal women and is generally underreported due to stigma surrounding it and lack of access to specialized care [2, 3]. The present therapeutic environment of SUI includes conservative treatment, pharmacological and surgical treatment. Mid-urethral sling



surgeries, have been developed as gold-standard surgical interventions with long-term effectiveness and objective cure rates of 60-85% at 5-10 years [4]. However dyspareunia, and urinary retention, have caused regulatory warnings and market recalls in a number of countries, with a significant effect on the rates of surgical utilization. Also, operative intervention has its own risks, such as anesthesia morbidity, infection, bleeding, and recovery time, which play a significant role in causing high patient reluctance, especially in younger women, those with mild-moderate severity, or those with medical comorbidities who should not undergo surgery [5, 6]. The main conservative first-line intervention is PFMT, which moderately, alleviating severity symptoms and achieving better continence outcomes with appropriate technique and supervision. Nevertheless, inconsistent patient compliance, inconsistent quality of training, need to continue treatment over a long period (usually 3-6 months to achieve maximum effect), and slow re-emerging symptoms after withdrawal are major factors that limit the clinical efficacy of PFMT. Additionally, PFMT is best applied in mild cases of SUI and shows decreasing returns in moderate-to-severe cases, which underscores the necessity of intermediate-intensity therapeutic strategies between conservative care and invasive surgery [7, 8]. Advances in regenerative and energy-based medicine have introduced PRP injections and non-ablative Er: YAG vaginal laser therapy as potential minimally invasive treatment options for female SUI [9-11]. PRP is rich in growth factors that promote angiogenesis, fibroblast proliferation, and tissue remodeling, while Er: YAG laser therapy induces controlled photothermal effects leading to collagen contraction and nucleogenesis, potentially improving urethral support and vaginal wall integrity [12].

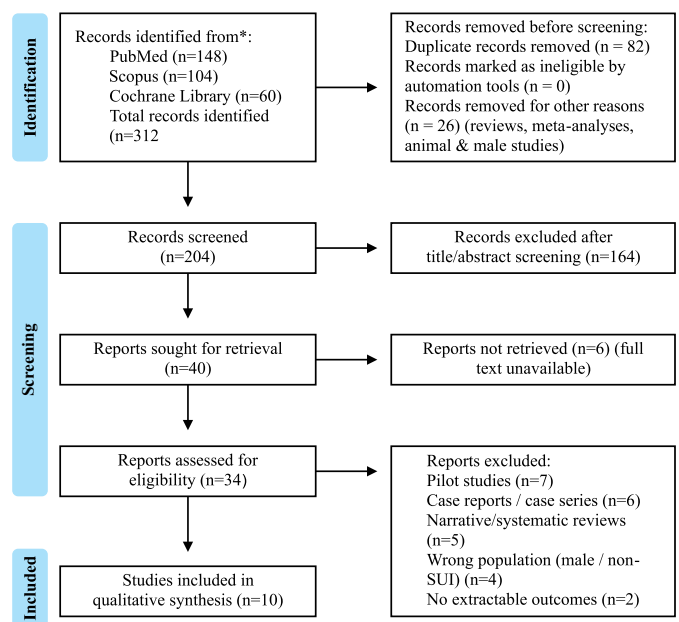
Despite increasing clinical use, evidence regarding the efficacy, durability, and comparative benefit of these modalities remains heterogeneous, with variable outcomes reported across studies. Therefore, a contemporary systematic synthesis of high-quality clinical evidence is required to better define their therapeutic role and support evidence-based clinical decision-making. This study aims to determine the clinical evidence on the effectiveness and safety of PRP injections and NA Er:YAG laser in women with SUI.

## METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. An electronic literature search was conducted in PubMed/MEDLINE, Scopus, and Cochrane Library, to find out the relevant clinical studies published between January 2018 and March 2025. The reason behind the selection of these databases

is that they cover a wide area of urogynecology, pelvic floor disorders, regenerative therapies, and interventional clinical trials. Both controlled vocabulary (MeSH terms) and free-text keywords were used, combined with Boolean operators. The search strategies were adapted to the indexing structure of each database to ensure optimal retrieval. The PubMed/MEDLINE search syntax was ("Stress Urinary Incontinence" [MeSH] OR "female stress urinary incontinence" OR SUI) AND (("Platelet-Rich Plasma" OR PRP OR "autologous platelet rich plasma") OR ("Er: YAG laser" OR "erbium: YAG laser" OR "vaginal laser")). The Scopus search strategy was: TITLE-ABS-KEY ("stress urinary incontinence" OR "female stress urinary incontinence" OR SUI) AND (TITLE-ABS-KEY ("platelet rich plasma" OR PRP OR "autologous PRP") OR TITLE-ABS-KEY ("Er: YAG laser" OR "erbium: YAG laser" OR "vaginal laser"). The Cochrane Library search syntax was ((stress urinary incontinence): OR (female stress urinary incontinence): OR SUI:) AND ((platelet rich plasma): OR PRP: OR (Er:YAG laser): OR (erbium: YAG laser): OR (vaginal laser). All the included studies also had their reference lists screened manually to identify any other eligible publications that might not have been identified by electronic searching. Inclusion criteria were that the studies were human clinical studies that included adult women diagnosed with stress urinary incontinence and that they were assessed with PRP injection therapy and/or Er: YAG vaginal laser therapy. Included studies comprised randomized trials along with prospective interventional cohorts and controlled clinical studies. The studies had to present validated clinical outcomes, including the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), pad test data, urodynamic data, or quality-of-life data. Pilot studies, case reports, case series, narrative reviews, systematic reviews, and meta-analyses were excluded. Studies that were animal or in-vitro, studies that used men exclusively, conference abstracts that were not available in full-text, and studies that did not provide extractable clinical outcome data were also excluded. Despite the large number of PRP and laser studies using relatively small cohorts, pilot studies and case series were excluded because of the lack of methodological strength and the lack of reporting comparative outcomes. All retrieved records were screened by two reviewers who independently screened the titles and abstracts. Predefined inclusion and exclusion criteria were then used to evaluate the full-text articles of potentially eligible studies. Any differences among reviewers were solved by discussion and consensus. A PRISMA 2020 flow diagram was used to document the study selection process, including the number of identified records, duplicates eliminated, records screened, full-text articles reviewed,

exclusion reasons, and included final studies. A standardized, pre-defined data extraction form was used to extract data, covering study identifiers, design, population demographics, intervention protocols (PRP and Er: YAG laser), comparator, follow-up, outcome measures, adverse events and quantitative efficacy data. Quantitative outcomes were baseline and post-intervention, within- and between-group, effect estimates with confidence intervals where reported, and p-values. In the case where there were many follow-up points, the longest follow-up was considered first in order to determine durability. Moreover, direction and magnitude of treatment effects such as reported mean changes, between-group differences, and statistical significance were also extracted where they were available. Two reviewers independently extracted data and cross-checked the data to validate accuracy and completeness. Randomized controlled trials were evaluated using the Cochrane Risk of Bias-2 (RoB-2) tool to assess their methodological quality and prospective and observational interventional studies were assessed using the National Institutes of Health (NIH) Quality Assessment Tool. Two reviewers independently rated each study and disagreements in quality ratings were addressed by consensus. The reason why meta-analysis was not conducted was that there was a significant clinical and methodological heterogeneity, which included differences in PRP preparation protocols, injection sites, Er: YAG laser parameters, treatment protocols, outcome measures, comparator groups, and follow-up periods. The lack of numerical reporting in studies also did not allow effective pooling of effect estimates. Based on this, a systematic narrative synthesis was developed, which summarized the nature of the studies, clinical effectiveness, response duration, and the quality of the methods. The protocol of the review was not registered in the International Prospective Register of Systematic Reviews (PROSPERO). Available literature was systematically compiled and analyzed retrospectively of recently published clinical studies, but all methodological steps were predetermined and strictly adhered to following PRISMA 2020 guidelines to reduce the risk of reporting bias and guarantee transparency (Figure 1).



**Figure 1:** PRISMA 2020 Flow Diagram of Study Selection

This figure illustrates the systematic identification, screening, eligibility assessment, and inclusion of studies evaluating PRP injection therapy and Er: YAG vaginal laser therapy for female stress urinary incontinence. After removal of duplicate records ( $n = 82$ ) and records excluded for predefined reasons ( $n = 26$ ), 204 records underwent title and abstract screening. Among them, 164 records were eliminated. Forty full-text articles were identified to be retrieved, and six were not retrieved because of the unavailability of the full text. Eligibility was evaluated on 34 full-text articles, with 24 being excluded with reported reasons (pilot studies, case reports or case series, narrative or systematic reviews, wrong population, or no extractable outcomes). Finally, 10 studies met the inclusion criteria and were included in the qualitative synthesis.

## RESULTS

A total of ten clinical studies published between 2018 and 2025 fulfilled the eligibility criteria and were included in the qualitative synthesis. These include of six Rcts and four prospective observational interventional cohort studies. The studies that were included were carried out in different geographic areas and clinical environments, which increases the external validity. The majority of the studies assessed non-ablative Er: YAG vaginal laser therapy, and three studies were assessing autologous PRP injections as a single intervention or combined with PFMT. The follow-up time in the studies was between 3 and 24 months. The studies included all used validated outcome measures with the most common outcome measure being the ICIQ-SF and objective pad test. The specific features of the studies included are described (Table 1).

**Table 1:** Characteristics of Included Clinical Studies on PRP & Er: YAG Laser Therapy for Female SUI (2018–2025)

References	Country	Sample Size	Population	Intervention	Comparator	Follow-Up	Outcome Tools
<b>Randomized Controlled Trials</b>							
[13]	Slovenia	114	Female SUI	Er: YAG laser (IncontiLase)	Sham laser	3 Months	ICIQ-UI SF, perineometer
[7]	China	144	Adult women SUI	Er: YAG laser (2 sessions)	Sham laser	6 Months	ICIQ-SF, pad test
[14]	Multicenter	120	Female SUI	Er: YAG laser (3 sessions)	Sham laser	3 Months	ICIQ-SF, Incontinence QoL
[15]	Multicenter	86	Urodynamic SUI	Er: YAG laser	Sham laser	~6 Months	Pad test, QoL
[16]	Thailand	72	Female SUI	PRP + PFMT	PFMT alone	6 Months	ICIQ-SF, pad test
[17]	Greece	60	Female SUI	Periurethral PRP	Sham injections	6 Months	ICIQ-SF
<b>Prospective &amp; Observational Interventional Studies</b>							
[8]	Taiwan	40	Female SUI	PRP sphincter injections	–	12 Months	ICIQ-SF
[18]	Portugal	43	Female SUI	Er: YAG laser (3 sessions)	–	18 Months	Pad test, ICIQ-SF
[19]	Switzerland	96	Female SUI	Er: YAG laser (multiple sessions)	–	24 Months	1-hr pad test, ICIQ-SF
[20]	China	50	Female SUI (± MUI)	Er: YAG laser (3 sessions)	–	6 Months	QoL questionnaires

Across the included studies, both PRP and Er: YAG laser therapy were associated with measurable improvements in stress urinary incontinence symptoms. In randomized controlled trials evaluating Er: YAG laser therapy, reductions in ICIQ-SF scores and pad test leakage were consistently reported at short-term follow-up (3–6 months) when compared with sham treatment. Where numerical data were available, studies reported statistically significant within-group reductions from baseline and between-group differences favoring active treatment, with p-values generally <0.05. In PRP-based interventions, periurethral or urethral sphincter injections resulted in reductions in symptom severity scores over follow-up periods of 6 to 12 months. Studies combining PRP with PFMT demonstrated greater magnitude and durability of improvement compared with PFMT alone, indicating a potential additive effect. Although effect sizes and confidence intervals were inconsistently reported, the direction of effect was uniformly favorable across PRP studies. Longer-term observational studies with follow-up extending to 18–24 months demonstrated persistence of treatment benefit for both modalities, as reflected by maintained reductions in pad test weights and sustained enhancement in health-related 'quality of life' domains. However, magnitude benefit varied between studies, likely reflecting heterogeneity in intervention protocols, baseline disease severity, and patient characteristics. A structured summary of reported effectiveness outcomes is presented (Table 2).

**Table 2:** Reported Effectiveness of PRP and Er: YAG Laser Therapy in Female Stress Urinary Incontinence

References	Intervention	Outcome Measures Reported	Follow-Up	Direction of Effect vs Comparator	Statistical Significance
[13]	Er: YAG laser	ICIQ-UI SF, perineometry, sexual function	3 months	Significant improvement vs sham	p<0.001
[7]	Er: YAG laser	ICIQ-SF, pad test	6 months	Modest improvement vs sham	Significant
[14]	Er: YAG laser	ICIQ-SF, I-QoL	3 months	Significant improvement vs sham	Significant
[15]	Er: YAG laser	Pad test, QoL	6 months	Significant improvement vs sham	Significant
[16]	PRP + PFMT	ICIQ-SF, pad test	6 months	Superior to PFMT alone	Significant
[17]	PRP	ICIQ-SF	6 months	Superior to sham injections	Significant
[8]	PRP	ICIQ-SF	12 months	Sustained symptom improvement	Significant
[18]	Er: YAG laser	Pad test, ICIQ-SF	18 months	Sustained improvement	Significant
[19]	Er: YAG laser	Pad test, ICIQ-SF	24 months	Sustained improvement	Significant
[20]	Er: YAG laser	Pelvic floor QoL domains	6 months	Significant symptom & QoL improvement	Significant

Evaluation of the quality of methods showed that the majority of randomized controlled trials were rated as having some concerns of bias based on Cochrane Risk of Bias-2 (RoB-2) tool. These issues are mainly related with the incomplete reporting of allocation concealment, difficulties in preserving the blinding, and absence of prespecified statistical analysis plans (Table 3).

**Table 3:** Risk of Bias Assessment of Randomized Controlled Trials Using the Cochrane RoB-2 Framework

References	Study (Year)	Randomization Method	Blinding & Intervention Fidelity	Completeness of Data	Outcome Measurement	Selective Reporting	Overall Risk
[13]	2018	Moderate concerns	Minor limitations	Adequate	Adequate	Moderate concerns	Moderate
[7]	2025	Minor limitations	Adequate	Adequate	Adequate	Moderate concerns	Moderate
[14]	2025	Minor limitations	Adequate	Moderate concerns	Adequate	Moderate concerns	Moderate
[15]	2024	Minor limitations	Adequate	Moderate concerns	Adequate	Moderate concerns	Moderate

[16]	2024	Moderate concerns	Moderate concerns	Moderate concerns	Adequate	Moderate concerns	Moderate
[17]	2024	Moderate concerns	Moderate concerns	Moderate concerns	Adequate	Moderate concerns	Moderate

Across randomized controlled trials, overall risk of bias was predominantly rated as “some concerns”, mainly due to incomplete reporting of allocation concealment procedures, partial blinding, and limited pre-specification of analysis plans, while outcome measurement and data completeness were generally assessed as low risk.

The National Institutes of Health (NIH) Quality Assessment Tool was used to rate prospective observational interventional studies as fair quality. Typical weaknesses were single-arm study designs, lack of confounder adjustment, and unreported participation rates and attrition. Nevertheless, outcome measures were validated and the follow-up time was mostly adequate to lend internal validity to the reported results. Risk-of-bias assessments (randomized and observational) are provided in detail (Table 4).

**Table 4:** Risk of Bias for Prospective/Observational Studies (NIH Quality Assessment Tool)

References	Clear Research Question	Defined Population	Participation Rate Adequate	Exposure Measured Reliably	Outcome Measures Valid /Reliable	Follow-Up Sufficient	Loss to Follow-Up ≤20%	Confounders Adjusted	Overall Quality
[8]	Yes	Yes	NR	Yes	Yes	Yes (12 months)	NR	NR	Fair
[18]	Yes	Yes	NR	Yes	Yes	Yes (18 months)	NR	NR	Fair
[19]	Yes	Yes	NR	Yes	Yes	Yes (24 months)	NR	NR	Fair
[20]	Yes	Yes	NR	Yes	Yes	Yes (6 months)	NR	NR	Fair

Due to heterogeneity, GRADE assessment was not feasible, although overall evidence was considered moderate based on study quality, consistency, and follow-up duration. The certainty of evidence regarding long-term durability is still low because most evidence is of the observational nature and the reporting of effect sizes and confidence intervals is not consistent.

## DISCUSSION

This systematic review included 10 clinical studies (six randomized controlled trials and four prospective interventional cohorts) to determine the effectiveness of PRP injections and non-ablative Er: YAG vaginal laser therapy on female SUI. Overall, both modalities demonstrated improvements in validated patient-reported outcomes, particularly ICIQ-SF scores, and objective measures such as pad test results. Randomized trials under Sham control tended to prefer active intervention to controls, whereas observational cohorts indicated that benefit persisted in patients. But quantitative pooling of effect estimates was constrained by methodological and clinical heterogeneity. There is mixed evidence on the use of non-ablative vaginal laser therapy, such as Er: YAG and CO<sub>2</sub> systems, but it indicates a short-term symptomatic effect. Sham-controlled randomized trials were included that showed statistically significant reductions in leakage and symptom severity at 3-6 months. These results are in agreement with other external randomized and multicenter trials which demonstrated an improvement in pad test results and quality-of-life indicators after laser therapy [21-23]. However, long-term follow-up has not been consistent and some studies have not shown long-term superiority over sham at 12 months or longer [7, 24]. The inconsistency in the results is probably caused by variability in treatment protocols, such as wavelength, fluence, the number of sessions, and the intervals between treatment. Laser-induced collagen remodeling and tissue tightening are proposed by external mechanistic and imaging studies but the extent and sustainability of these

changes differ significantly [25-28]. Other patient-related variables like the severity of SUI at baseline, menopause and body mass index have also been found to predict treatment response, making cross-study comparisons more difficult [8, 16]. Interventions based on PRP showed encouraging yet inconsistent results. Randomized and prospective studies that reported a reduction in symptom severity after periurethral or urethral sphincter injection were included, especially those that used PRP in several sessions or in conjunction with pelvic floor muscle training (PFMT). External pilot and cohort studies also indicate a regenerative effect of PRP in enhancing sphincter activity and pelvic support, but the effect sizes were reported to be different [28, 29]. Notably, a randomized trial with placebo control showed no significant effect after a single PRP injection, indicating that the intensity of treatment and the standardization of protocols are key factors of effectiveness [27]. On the other hand, the studies with repeated injections or adjunct PFMT showed a higher and longer-lasting improvement, which suggests the possibility of an additive effect [15]. External evaluations point to a high degree of heterogeneity in PRP preparation methods, platelet concentration, amount of injection, and the anatomical location, which hinder reproducibility and generalizability [29-31]. PRP injections and non-ablative vaginal laser therapies were both found to have a generally positive safety profile. Adverse events reported were mostly mild and temporary such as local pain and temporary urinary symptoms [32-34]. Most serious complications were infrequent but have been reported,

underscoring the need to select patients properly, use standard-based protocols, and clinician skills. External safety audits always suggest cautious counseling and prevention of exaggerating the efficacy assertions due to the changing evidence base [35]. A moderate level of evidence was observed, reflecting differences in study quality, potential bias, consistency of findings, and outcome precision regarding short-term effectiveness of Er: YAG laser therapy and low to moderate regarding PRP interventions, especially when it comes to long-term durability. There is limited evidence after 12 months and much of it is based on observational evidence [18, 19].

The limitations of the review are high levels of heterogeneity in treatment regimens (e.g., PRP preparation, laser settings, number of sessions), mainly short-term follow-up data, and methodological shortcomings of the studies included in the review (e.g., lack of blinding, small sample sizes), which cannot be used to make conclusive conclusions concerning long-term efficacy and comparative effectiveness. To effectively test the long-term safety and efficacy of SUI and identify the best treatment regimes, future studies must focus on large, multi-centric, sham-controlled randomized trials, longer follow-up (at least two years), and stratified research based on SUI severity and patient functions (e.g., menopausal status).

## CONCLUSIONS

Platelet-rich plasma injections and non-ablative Er: YAG vaginal laser therapy demonstrate clinically meaningful short-term improvements in female stress urinary incontinence with acceptable safety profiles. However, heterogeneity in intervention protocols, variable durability of effect, and methodological limitations restrict definitive conclusions regarding long-term efficacy. Based on current evidence, these therapies may be considered in carefully selected women with mild to moderate SUI, particularly those seeking non-surgical options or adjuncts to pelvic floor muscle training. Future research should focus on adequately powered, sham-controlled, multicenter randomized trials with standardized treatment protocols, harmonized outcome measures, and extended follow-up to better define comparative effectiveness and durability.

## Authors' Contribution

Conceptualization: MUR

Methodology: WA, SI, ZL

Formal analysis: ZL

Writing and Drafting: MUR, WA, SI, WN, RK

Review and Editing: MUR, WA, SI, WN, RK, ZL

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



# Impact of Burnout on Academic Performance and Well-Being among Medical Students: A Systematic Review

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## ABSTRACT

Medical student burnout has become a significant issue in the global community, with growing evidence of its negative implications on academic performance and mental health. Although there is an increasing body of research in this field, unified data on the extent and implications of burnout is scarce in the low- and middle-income contexts. **Objective:** To systematically review the impact of burnout on academic performance and well-being among undergraduate medical students. **Methods:** The systematic literature search was performed in PubMed, Scopus, Google Scholar, and Cochrane Library to identify research published from 2018 to 2024. Original English-language observational studies assessing burnout with validated measures and reporting academic or well-being outcomes were found. The selection of studies was done in accordance with PRISMA. The quality of methodology was determined with the help of the NIH Quality Assessment Tool. A narrative synthesis approach was used. **Results:** The qualitative synthesis included 15 studies. The prevalence of burnout was between 34.3% and 63.5. The most affected domain was emotional exhaustion. Increased burnout was always correlated to lower GPA/CGPA, worse examination results, lower learning motivation, worse quality of life, worse anxiety, depression, sleep problems, and stress. **Conclusions:** Burnout is highly prevalent among medical students and significantly compromises both academic performance and mental well-being. Institutional strategies focusing on workload regulation, mental health support, and improvement of learning environments are urgently needed.

## INTRODUCTION

Medical education is generally considered one of the most rigorous academic training programs with long working hours, high exams, competitive orientation, as well as early exposure to emotionally stressful clinical conditions [1]. Such stresses expose medical students to a significant risk of psychological pressure, especially burnout. Burnout is a multidimensional condition characterized by emotional weariness, depersonalization, and a decrease in individual

achievement. Being undetected, it may have an adverse impact on the ability to learn, professional growth, and the sustainability of a career in the future. Burnout is an issue that has been increasingly important in medical establishments across the globe in recent years [2, 3]. Burnout among medical students has been reported to occur in different geographical regions, and research has shown an increasing prevalence rate and growing

psychological morbidity [4, 5]. The most prominent aspect is always emotional exhaustion, likely to be followed by anxiety, depressive symptoms, and sleep disorders. There is also a correlation between burnout and a lack of concentration, motivation, and academic activity. These expressions not only undermine the mental health of students but can also lead to poor academic performance and clinical outcomes. Burnout is, therefore, a major problem in the sustainability of educational quality and the healthcare workforce [6]. Student progress and professional readiness are monitored through academic performance. There is new evidence that burnout can greatly disrupt learning outcomes such as GPA, examination performance, and academic motivation [7]. Students having high levels of burnout can exhibit a low level of study efficiency, rise cases of absenteeism, and a decrease in academic confidence. At the same time, burnout leads to a state of worse well-being, which is expressed not only through psychological distress but also through low quality of life and sleep problems. The presence of academic deficiency and the deterioration of well-being highlight the challenge of the multidimensionality of burnout [8, 9].

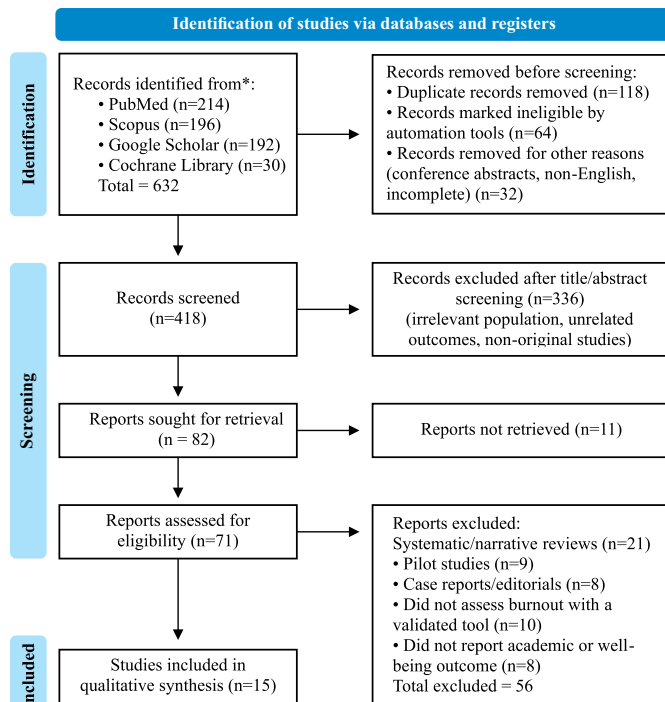
Although a growing interest exists across the world, the scale of burnout and its outcomes among medical students are not sufficiently documented, especially in the context of low- and middle-income countries. Differences in the measures of an outcome, the tools of assessment, and the institutional environment have restricted the generalizability of individual studies. Therefore, this study aims to synthesize recent evidence on the impact of burnout on academic performance and well-being among medical students, with the rationale of informing targeted institutional strategies to improve student mental health, academic success, and overall educational quality.

## METHODS

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and methodological rigor. The review synthesized evidence on the effects of burnout on academic performance and well-being among undergraduate medical students.

A systematic electronic literature search was conducted across PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Library. Articles published between January 2018 and December 2024 were identified using Medical Subject Headings (MeSH) terms and free-text keywords combined with Boolean operators (AND/OR). The main search terms included: burnout, medical students, academic performance, quality of life, depression, anxiety, sleep quality, and well-being. Reference lists of relevant

articles were manually screened to identify additional eligible studies. Original observational studies published in English between 2018 and 2024 were included. Studies were eligible if they: (1) assessed burnout among undergraduate medical students using validated instruments, and (2) reported at least one academic performance outcome (e.g., GPA, CGPA, examination results, academic success, or learning motivation) or well-being outcome (e.g., quality of life, depression, anxiety, psychological distress, or sleep quality). Only full-text articles involving human participants were considered. Database filters and reference management software were used to automatically exclude non-English records and conference abstracts. Non-original publications, animal studies, and duplicate citations were excluded. Additionally, systematic reviews, meta-analyses, narrative reviews, pilot studies, editorials, conference abstracts, and studies involving non-medical student populations were excluded. A total of 632 records were identified. After eliminating duplicates and ineligible records, titles and abstracts of 418 studies were screened. Subsequently, 71 full-text articles were assessed for eligibility, and 15 articles that met all inclusion criteria were included in the qualitative synthesis. Data were extracted independently using a standardized proforma that incorporated: author name, year of publication, country, study design, sample size, academic level, burnout assessment tool, academic performance outcomes, well-being outcomes, burnout prevalence, and key results. The NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies were used to assess methodological quality. The following domains were evaluated: clarity of objectives, definition of study population, validity of burnout measurement tools, justification of sample size, control of confounding variables, and validity of outcome measures. Studies were classified as having low risk of bias, some concerns, or high risk of bias. Due to heterogeneity in burnout measurement tools and outcome definitions, a narrative synthesis approach was employed. Results were summarized and described qualitatively in organized tables presenting burnout prevalence, severity, and effects on academic performance and well-being (Figure 1).



**Figure 1:** The Analysis of Studies

## RESULTS

Among the records that were initially identified, 64 were filtered automatically before being subjected to manual

title and abstract screenings. The studies included in the study were mostly cross-sectional studies that were held in various geographical locations such as Asia, Africa, Europe, and North America, with a wide international coverage of the medical student population. The 15 included studies were conducted across diverse geographical settings, including Ethiopia, Uganda, Serbia, Thailand, Pakistan, Mexico, Saudi Arabia, Indonesia, the USA, and Egypt. Sample sizes ranged from 144 participants [11] to 3,400 participants, with a median sample size of 400 students. Most studies (n=12) included mixed academic levels encompassing both preclinical and clinical years, while three studies focused specifically on preclinical students. The Maslach Burnout Inventory-Student Survey (MBI-SS) was the most commonly used assessment tool (n=10), followed by other validated instruments, including the Academic Burnout Inventory, MBI, and various burnout scales. Academic performance outcomes were assessed as primary outcomes in 6 studies, measuring indicators such as GPA, CGPA, examination performance, academic success, and learning motivation. Well-being outcomes were reported as primary outcomes in 9 studies, examining quality of life, depression, anxiety, psychological distress, and sleep quality. The remaining studies reported these outcomes as secondary variables. The study presents the detailed characteristics of all included studies (Table 1).

**Table 1:** Characteristics of Included Studies (2018–2024)

Sr. No.	References	Country	Study Design	Sample Size (n)	Academic Level	Burnout Instrument	Academic Performance Outcome	Well-Being Outcome
1	[10]	USA	Cross-sectional	315	Mixed	MBI-SS	Not primary	Wellness/burnout levels
2	[11]	Ethiopia	Cross-sectional	144	Mixed	MBI	Not primary	Not primary
3	[12]	Uganda	Cross-sectional	355	Mixed	MBI-SS	Not primary	Not primary
4	[13]	Serbia	Cross-sectional	760	Mixed	Burnout Scale	Not primary	Not primary
5	[14]	Thailand	Cross-sectional	1,095	Mixed	MBI-SS	GPA assessed	Depression assessed
6	[15]	Pakistan	Cross-sectional	400	Mixed	Academic Burnout Inventory	CGPA assessed	Not primary
7	[16]	Pakistan	Cross-sectional	318	Mixed	MBI	Not primary	Sleep quality assessed
8	[17]	Mexico	Cross-sectional	231	Pre-clinical	MBI-SS	Not primary	Psychological distress
9	[18]	Serbia	Cross-sectional	760	Mixed	Burnout Scale	Performance assessed	Not primary
10	[19]	Serbia	Cross-sectional	812	Mixed	MBI-SS	Performance assessed	Not primary
11	[20]	Pakistan	Cross-sectional	3,400	Mixed	Burnout Inventory	Not primary	Quality of life
12	[21]	Saudi Arabia	Cross-sectional	444	Mixed	MBI-SS	Academic performance assessed	Anxiety/ depression
13	[22]	Indonesia	Cross-sectional	385	Pre-clinical	Academic Burnout Scale	Learning motivation assessed	Not primary
14	[23]	Pakistan	Cross-sectional	1100	Mixed	MBI-SS	Not primary	Burnout prevalence + determinants
15	[24]	Various	Cross-sectional	385	Mixed	MBI-SS	Not primary	Not primary

MBI-SS = Maslach Burnout Inventory, Student Survey. Academic performance outcomes include GPA, CGPA, exam results, and other academic indicators. Well-being outcomes include quality of life, depression, anxiety, sleep quality, distress, etc.

The prevalence of burnout among medical students ranged from 34.3% to 63.5% across all included studies, demonstrating considerable variation influenced by geographical context, measurement tools, and cut-off criteria. The lowest prevalence

(34.3%) was reported by Haile et al. in Ethiopia using the MBI with standard cut-offs [11], while the highest prevalence (63.5%) was documented by Aljadani et al. in Saudi Arabia using validated local cut-offs for the MBI-SS. Emotional exhaustion consistently emerged as the most severely affected burnout domain across studies, with prevalence rates ranging from 49.5% to over 60% in several cohorts. Depersonalization was reported in 32% to 45% of students, while low personal accomplishment affected 40% to 50% of participants. Several studies identified significant demographic and contextual risk factors for burnout, including female gender (reported in studies by Haile et al. [11], Ilić et al. [13], and Baqai et al. [23]), clinical-year status [12], sleep deprivation (Irshad et al.), psychological distress [17], and poor learning environments [20]. The COVID-19 pandemic was noted as an exacerbating factor in studies conducted during 2020-2022, with Jezzini-Martinez et al. reporting elevated burnout rates (58.2%) during this period [17]. The results provide a comprehensive overview of burnout prevalence, severity across domains, assessment methods, and key observations from each study (Table 2).

**Table 2:** Prevalence and Severity of Burnout among Medical Students (2018-2024)

Sr. No.	References	Burnout Tool	Burnout Domain Assessed	Cut-off / Definition Used	Prevalence of Burnout	Key Observations
1	[10]	MBI-SS	EE, DP, PA	High EE ≥ 14, High DP ≥ 6, Low PA ≤ 22	Overall burnout 52.7%	Emotional exhaustion was the most prevalent domain
2	[11]	MBI	EE, DP, PA	High EE ≥ 27, High DP ≥ 10, Low PA ≤ 33	Overall burnout 34.3%	Higher burnout among female students
3	[12]	MBI-SS	EE, DP, PA	Standard MBI-SS cut-offs	Overall burnout 54.0%	Higher prevalence in clinical years
4	[13]	Burnout Scale	Overall burnout risk	Author-defined high-risk criteria	High burnout risk 41.2%	Females had significantly higher burnout
5	[14]	MBI-SS	EE, DP, PA	Thai validated cut-offs	EE: 49.5%, DP: 32.0%, Low PA: 40.4%	Burnout strongly associated with depression
6	[15]	Academic Burnout Inventory	Overall burnout	Scale-specific cut-off	Overall burnout 47.8%	Burnout inversely correlated with CGPA
7	[16]	MBI	EE, DP, PA	Standard MBI cut-offs	Overall burnout 38.1%	Sleep deprivation predicted burnout
8	[17]	MBI-SS	EE, DP, PA	Standard MBI-SS cut-offs	Overall burnout 58.2%	Higher burnout during COVID-19
9	[18]	Burnout Scale	Overall burnout	Author-defined	Overall burnout 36.9%	Burnout significantly reduced academic success
10	[19]	MBI-SS	EE, DP, PA	Standard cut-offs	High burnout risk 44.3%	Strong association with anxiety symptoms
11	[20]	Burnout Inventory	Overall burnout	Author-defined	Overall burnout 46.0%	Poor learning environment increased burnout
12	[21]	MBI-SS	EE, DP, PA	Saudi validated cut-offs	Overall burnout 63.5%	Burnout predicted poor academic performance
13	[22]	Academic Burnout Scale	Exhaustion, cynicism	Author-defined	Moderate-severe burnout 51.0%	Burnout inversely related to learning motivation
14	[23]	MBI-SS	EE, DP, PA	Pakistani validated cut-offs	Overall burnout 61.2%	Burnout is higher in females
15	[24]	MBI-SS	EE, DP, PA	Egyptian validated cut-offs	Overall burnout 45.8%	Burnout is associated with anxiety and depression

The association between burnout and academic performance was consistently negative across all studies that assessed this relationship. Five studies directly measured academic outcomes and demonstrated statistically significant inverse correlations between burnout severity and academic indicators. Puranitee et al. found that higher levels of emotional exhaustion and depersonalization were significantly associated with lower GPA ( $p < 0.01$ ) among Thai medical students [14]. Similarly, Saeed et al. reported that overall burnout significantly reduced CGPA among Pakistani students ( $p = 0.002$ ), with students in the highest burnout tertile showing markedly lower cumulative academic performance [15]. Ilić and Ilić demonstrated that burnout was a strong predictor of poor academic success ( $p < 0.001$ ) in Serbian students, even after controlling for demographic variables [18]. Aljadani et al. found that burnout, particularly emotional exhaustion and depersonalization domains, negatively affected examination performance ( $p < 0.05$ ) in Saudi medical students [21]. Felaza and Findyartini reported that academic burnout, specifically the exhaustion component, significantly decreased learning motivation among Indonesian preclinical students ( $p < 0.001$ ), which subsequently affected academic engagement and performance [22]. Regarding well-being outcomes, burnout showed strong and consistent associations with multiple adverse mental health indicators. Shahzad and Wajid documented that overall burnout significantly reduced quality of life ( $p < 0.001$ ) in a large Pakistani cohort, with burned-out students reporting substantially lower physical, psychological, social, and environmental quality of life scores [20]. Jezzini-Martinez et al. found that emotional exhaustion and depersonalization were positively associated with increased psychological distress ( $p < 0.01$ ) among Mexican first-year students during the COVID-19 pandemic [17]. Puranitee et al. reported that burnout strongly predicted depression ( $p < 0.001$ ), with emotional exhaustion showing the strongest correlation [14]. Irshad et al. identified that burnout, particularly emotional exhaustion,

was significantly linked to poor sleep quality ( $p < 0.05$ ) among Pakistani students in integrated modular curricula [16]. Baqai et al. demonstrated that emotional exhaustion and depersonalization increased psychological stress levels ( $p < 0.01$ ) [23], while Ilić et al. found that high burnout risk strongly predicted anxiety symptoms ( $p < 0.001$ ) in Serbian medical students [19]. These findings collectively indicate that burnout exerts detrimental effects on both academic performance and comprehensive mental health and well-being outcomes. Table 3 systematically presents the specific associations between burnout domains and academic and well-being outcomes across all included studies (Table 3).

**Table 3:** Impact of Burnout on Academic Performance and Well-Being among Medical Students

References	Outcome Domain	Outcome Measured	Burnout Domain Associated	Direction of Association	Statistical Significance	Key Finding
[14]	Academic	GPA	EE, DP	Negative	$p < 0.01$	Higher burnout is associated with lower GPA
[15]	Academic	CGPA	Overall burnout	Negative	$p = 0.002$	Burnout significantly reduced CGPA
[16]	Well-being	Sleep quality	EE	Negative	$p < 0.05$	Burnout linked to poor sleep quality
[17]	Well-being	Psychological distress	EE, DP	Positive	$p < 0.01$	Burnout increased distress
[18]	Academic	Academic success	Overall burnout	Negative	$p < 0.001$	Burnout predicted poor academic performance
[19]	Well-being	Anxiety symptoms	Overall burnout	Positive	$p < 0.001$	High burnout strongly predicted anxiety
[20]	Well-being	Quality of life	Overall burnout	Negative	$p < 0.001$	Burnout significantly reduced the quality of life
[21]	Academic	Exam performance	EE, DP	Negative	$p < 0.05$	Burnout significantly reduced exam scores
[22]	Academic	Learning motivation	Exhaustion	Negative	$p < 0.001$	Burnout decreased learning motivation
[14]	Well-being	Depression	EE, DP	Positive	$p < 0.001$	Burnout strongly predicted depression
[23]	Well-being	Psychological stress	EE, DP	Positive	$p < 0.01$	Burnout increases stress levels

Methodological quality assessment using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies revealed that 6 studies (40%) demonstrated low risk of bias, while 9 studies (60%) raised some concerns. All 15 studies had clearly defined research objectives and well-defined study populations. All studies employed validated burnout assessment instruments, ensuring measurement reliability. However, only 6 studies, like Puranitee et al. [14], Ilić and Ilić [18], Ilić et al. [13], Shahzad et al. [20], Aljadani et al. [21], and Baqai et al. [23], provided adequate justification for sample size calculation, while the remaining 9 studies did not report formal power analysis or sample size determination methods. Regarding confounding variables, 6 studies adequately adjusted for potential confounders, including age, gender, academic year, socioeconomic status, and mental health history through multivariate analysis. The remaining 9 studies only partially controlled confounders, typically through stratified analysis or univariate comparisons, raising some concerns about residual confounding. All studies used reliable and validated outcome measures for both academic performance (GPA, CGPA, standardized examinations) and well-being indicators (validated depression, anxiety, and quality of life scales). The predominance of cross-sectional study designs across all included studies limits causal inference, though the consistency of findings across diverse settings strengthens the evidence base. No studies were classified as high risk of bias. Table 4 presents the detailed risk of bias assessment for each included study across all evaluated domains (Table 4).

**Table 4:** Risk of Bias Assessment of Included Studies (NIH Quality Assessment Tool)

Sr. No.	References	Clear Objective	Defined Population	Valid Burnout Tool	Sample Size Justified	Confounders Adjusted	Outcome Measures Reliable	Overall Risk of Bias
1	[10]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
2	[11]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
3	[12]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
4	[13]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
5	[14]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
6	[15]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
7	[16]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
8	[17]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
9	[18]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
10	[19]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
11	[20]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
12	[21]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
13	[22]	Yes	Yes	Yes	No	Partial	Yes	Some concerns
14	[23]	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
15	[24]	Yes	Yes	Yes	No	Partial	Yes	Some concerns

## DISCUSSION

This systematic review shows that the prevalence of burnout among medical students is a global phenomenon and adversely affects the academic performance and psychological well-being of these students. In multiple countries, increased emotional exhaustion and depersonalization have correlated with lower GPA, CGPA, exam performance, academic success, and learning motivation. This evidence is consistent with international evidence [25-27]. An investigation from Indonesia, which used the MBI-SS to assess burnout, found that burnout significantly reduced academic performance amid the COVID-19 pandemic [28]. Similarly, an investigation from Iraq found that burnout reduced students' academic functioning and satisfaction with well-being [29]. First, the pooled burnout prevalence across 15 international studies (2018-2024) ranged from 34.3% to 63.5% (median 47%). Emotional exhaustion was the consistently dominant domain, affecting 49.5-60% of students, followed by low personal accomplishment (40-50%) and depersonalization (32-45%). This hierarchical pattern remained consistent across Asia, Africa, Europe, and North America, indicating emotional exhaustion as the primary manifestation of medical student burnout globally. Second, burnout demonstrated consistent statistically significant associations with adverse academic performance. Five studies reported significant inverse correlations: higher burnout predicted lower GPA ( $p < 0.010$ ) [14], reduced CGPA ( $p = 0.002$ ) [15], poorer examination performance ( $p < 0.05$ ) [21], decreased academic success ( $p < 0.001$ ) [18], and diminished learning motivation ( $p < 0.001$ ) [22]. This consistency across different educational systems and cultural contexts confirms that burnout meaningfully impairs academic functioning. Third, burnout domains, particularly emotional exhaustion and depersonalization, showed strong correlations with adverse mental health outcomes: depression ( $p < 0.001$ ) [14], anxiety ( $p < 0.001$ ) [13], poor sleep quality ( $p < 0.05$ ) [16], psychological distress ( $p < 0.01$ ) [17], elevated stress ( $p < 0.01$ ) [23], and reduced quality of life ( $p < 0.001$ ) [20]. These relationships indicate burnout as a central mediating factor connecting academic stressors to comprehensive health deterioration. Fourth, regarding methodological quality, 40% of studies ( $n = 6$ ) demonstrated low risk of bias with adequate sample size justification and comprehensive confounder adjustment, while 9 (60%) raised some concerns due to lack of formal sample size calculation and partial confounder control. All 15 studies utilized validated burnout instruments and reliable outcome measures. However, universal reliance on cross-sectional designs limits causal inference, necessitating cautious interpretation. Studies listing academic or well-being

outcomes as "not primary" were included because: (1) all reported statistical analyses examining burnout-outcome relationships using validated instruments; (2) primary/secondary designation reflected authors' research priorities, not methodological rigor; (3) studies with primary outcomes ( $n = 6$  academic,  $n = 9$  well-being) demonstrated the most robust associations, receiving greater interpretive weight; (4) inclusion of non-primary findings enabled triangulation across broader evidence, strengthening confidence in observed patterns. The findings correlate burnout with adverse mental health outcomes consistent with recent global literature. Saudi Arabian research demonstrates significant associations between burnout, anxiety, and depression affecting academic performance and quality of life [21]. Croatian and Spanish studies reported a high prevalence of poor sleep quality, psychological distress, and depressive symptoms among medical students, strongly correlated with burnout [30, 31]. Adesola *et al.* reported exceptionally high burnout prevalence (81.1%) in Nigeria [32], substantially exceeding our 34.3-63.5% synthesis range. This discrepancy reflects: (1) resource-constrained environment with large classes ( $> 200$  students), limited faculty, inadequate infrastructure, and frequent academic disruptions; (2) national economic instability and healthcare system strain; (3) locally adapted cut-off criteria potentially more sensitive than standardized international thresholds; (4) cultural factors including high family expectations where medical education represents substantial socioeconomic investment; (5) COVID-19 pandemic impact involving prolonged closures, inadequately resourced online learning, and clinical exposure anxiety. These converging factors, systemic resource limitations, socioeconomic pressures, cultural expectations, and pandemic disruptions plausibly explain markedly elevated burnout in low-resource settings, underscoring the need for context-specific interventions. Recent data indicate that emotional disengagement and burnout worsened during the COVID-19 pandemic, highlighting medical students' susceptibility during higher academic and psychological stress periods [33-35]. The COVID-19 pandemic represents a significant confounder requiring deeper analysis. Four studies conducted during 2020-2022 [16, 17] reported elevated burnout (38.1-58.2%) compared to pre-pandemic estimates. The pandemic introduced unmeasured confounders: (1) abrupt online learning transitions with variable technological access; (2) social isolation and disrupted peer support; (3) heightened health anxiety with clinical exposure; (4) economic hardship; (5) academic progression uncertainty. As noted in Table 4, 60% of studies demonstrated only partial confounder control, meaning pandemic-related variables were frequently

unaccounted for in analyses. These limits isolate burnout's independent effect, as observed associations may partially reflect pandemic-related stress. Additional inadequately controlled confounders included baseline mental health status (only 4 studies adjusted), socioeconomic status (5 studies), academic aptitude (3 studies), and family support (rarely measured). These unmeasured confounders, particularly during the global health crisis, suggest pandemic-era studies may overestimate burnout's independent impact. Future research should employ longitudinal designs with comprehensive confounder measurement, particularly pandemic-related stressors, to accurately quantify burnout's causal role. The convergence of findings from Asia, Africa, Europe, and the Middle East demonstrates that burnout is multidimensional with negative impacts on medical students' academic performance and mental health globally. These findings highlight the need for structured institutional measures, including workload management, early psychological screening and support, mentorship programs, sleep hygiene education, and coping skills training to mitigate burnout and protect students' well-being.

English-language limitations may exclude relevant non-English studies. Cross-sectional study prevalence limits causal interpretation of burnout-outcome relationships. Incomplete confounder adjustment, particularly for pandemic-related stressors, affects effect size interpretability. Heterogeneity in burnout measurement tools and outcome definitions precluded meta-analysis. Inclusion of studies with non-primary outcomes may introduce measurement bias, though sensitivity consideration of primary-outcome studies confirmed the consistency.

## CONCLUSIONS

Burnout among medical students is a widespread and serious concern that significantly compromises academic performance and mental well-being. Emotional exhaustion and depersonalization are the most affected domains and are consistently associated with poorer academic outcomes, reduced quality of life, and increased psychological distress. Targeted institutional interventions focusing on academic workload management, mental health support, and learning environment improvement are urgently required to enhance both academic success and student well-being.

## Authors' Contribution

Conceptualization: HI

Methodology: FMK

Formal analysis: MTE, BH, FMK

Writing and Drafting: HI, MTE, BH, SS, FMK, SSF

Review and Editing: HI, MTE, BH, SS, FMK, SSF

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



## Performance of Graphene-Reinforced Dental Materials in Restorative and Prosthodontic Applications: A Systematic Review

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## ABSTRACT

Mechanical fatigue, marginal degradation, microbial biofilm formation, and low long-term durability are persistent challenges associated with dental restorative and prosthodontic materials. The integration of graphene and its variants is an effective approach to enhance the structural and biological properties of conventional dental biomaterials. **Objective:** To systematically evaluate the performance of graphene-reinforced dental materials in restorative and prosthodontic applications. **Methods:** This systematic review was performed in accordance with PRISMA-2020 guidelines and involved searches of PubMed/MEDLINE, Scopus, and Cochrane Library to identify original research published between January 2019 and March 2025. Sixteen original in-vitro studies examining graphene-modified dental materials were included. Case reports, reviews, and animal studies were excluded. Meta-analysis was not performed due to substantial heterogeneity in graphene types, concentrations, base materials, and outcome measures. Narrative synthesis of data was performed on mechanical, physical, antimicrobial, and biocompatibility results. **Results:** Sixteen original in-vitro studies were included. Graphene derivatives, mainly graphene oxide and graphene nanoplatelets, were incorporated into resin composites, PMMA denture base materials, glass ionomer cements, dental adhesives, and CAD/CAM polymers. The majority of studies exhibited improved flexural strength, hardness, fracture resistance, and antimicrobial properties against *Streptococcus mutans* and *Candida albicans*. However, higher concentrations of graphene in certain formulations resulted in increased surface roughness and a lower degree of conversion. **Conclusions:** Graphene-reinforced dental materials exhibit promising mechanical reinforcement and antimicrobial properties in laboratory settings. However, formulation-dependent trade-offs and the lack of long-term clinical data necessitate further standardized experimental and clinical investigations before routine clinical adoption.

## INTRODUCTION

Modern oral rehabilitation relies on dental restorative and prosthodontic materials, which are limited in long-term clinical performance due to mechanical degradation, marginal wear, microbial colonization, and susceptibility to secondary caries and prosthesis-associated infections [1]. Resin-based composites, polymethyl methacrylate (PMMA) denture base resins, glass ionomer cements, and modern CAD/CAM polymers are frequently utilized, yet they still exhibit diminished durability and resistance to oral

biofilm environments under functional loading conditions [2]. Recent developments in nanotechnology have introduced new nanofillers aimed at enhancing the mechanical and biological properties of dental materials [3]. Among these, graphene and its derivatives such as graphene oxide (GO), reduced graphene oxide (rGO), and graphene nanoplatelets (GNPs) have gained significant interest due to their superior mechanical strength, high elastic modulus, high surface area, and antimicrobial



properties. These unique physicochemical properties offer opportunities to strengthen polymeric frameworks, increase interfacial bond strength, and prevent microbial attachment [4, 5]. There has been an increase in experimental research utilizing graphene in dental composites, adhesives, glass ionomer cements, PMMA denture bases, and ceramic-polymer hybrid materials [6, 7]. Preliminary evidence suggests that graphene can enhance flexural strength, wear resistance, fracture toughness, and antibacterial performance. However, the outcomes remain heterogeneous, and concerns regarding surface roughness, polymerization efficiency, and long-term biocompatibility continue to be debated [8].

Although increased attention has had an impact on graphene-reinforced dental materials, the study has not been thoroughly and up-to-date synthesis of its applications in both the field of restorative and prosthodontic dentistry, with stringent eligibility requirements. Available evidence is yet to be assembled, and therefore, it is still hard to make definite conclusions regarding their overall performance and their clinical relevance. This systematic review aims to critically assess and synthesize the recent original research on the mechanical, physical, antimicrobial, and biological properties of graphene-modified dental materials in order to present a cohesive evidence base to the future development and translational application of dental materials.

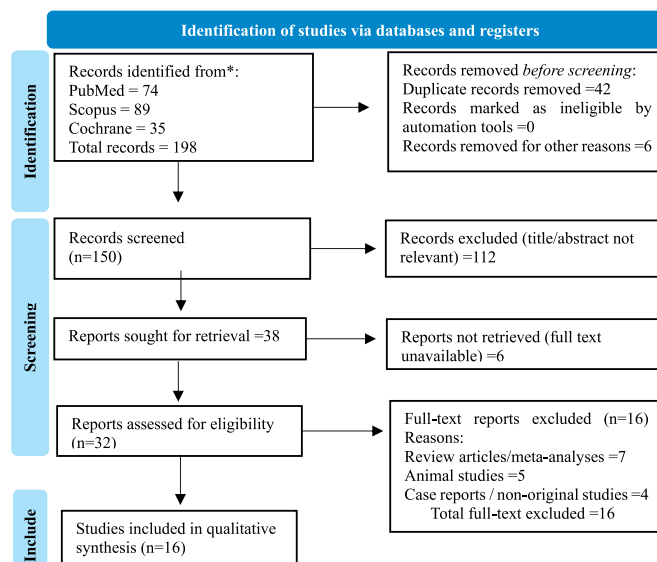
## METHODS

This systematic review was designed to adhere to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to assess the current evidence on the performance of graphene-reinforced dental materials in restorative and prosthodontic applications. The objective of the review was to synthesize findings from original experimental studies evaluating the mechanical, physical, antimicrobial, and biocompatibility properties of dental biomaterials modified with graphene. An electronic search of PubMed/MEDLINE, Scopus, and Cochrane Library was conducted to retrieve relevant studies published between January 2019 and March 2025. Both free-text keywords and Medical Subject Headings (MeSH) terms were combined using Boolean operators. The core PubMed search strategy included: ("graphene" OR "graphene oxide" OR "reduced graphene oxide" OR "graphene nanoplatelets") AND ("dental materials" OR "resin composite" OR "PMMA" OR "glass ionomer cement" OR "denture base" OR "ceramic" OR "adhesive" OR "prosthodontic"). Similar search strings were adapted for Scopus and Cochrane Library databases. The final search was completed on March 15, 2025. Full reproducible search strings for all databases are provided

in Appendix 1. In addition, reference lists of eligible articles were manually screened to identify further relevant publications. Studies were included if they were original in-vitro experimental investigations examining graphene-reinforced restorative or prosthodontic dental materials and reporting mechanical, physical, antimicrobial, or biocompatibility outcomes. Articles that were reviews, systematic reviews, meta-analyses, animal studies, case reports, editorials, conference abstracts, and articles evaluating non-graphene nanomaterials were excluded. All retrieved records were uploaded into reference management software (Mendeley Desktop, Elsevier), and duplicate records were removed. Two independent reviewers (Initials to be added) screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were then independently assessed against the inclusion criteria. Any disagreement was resolved by discussion until a consensus was reached. A third reviewer was available for arbitration if needed, though this was not required. A standardized data extraction form was developed and pilot-tested on three studies to ensure consistency. Data extracted included: authorship, year of publication, country of study, sample size, study design, type of dental material, type of graphene derivative and its concentration, and mechanical, physical, antimicrobial, and biological outcomes reported. Two reviewers independently extracted data from all included studies, and discrepancies were resolved through discussion. This dual extraction process minimized extraction errors and ensured data accuracy. The methodological quality of the included studies was assessed using a modified version of the Joanna Briggs Institute (JBI) critical appraisal checklist for quasi-experimental studies. The modified tool evaluated six domains: (1) random allocation of specimens to experimental groups, (2) use of standardized testing protocols, (3) inclusion of appropriate control groups, (4) blinding of outcome assessment, (5) completeness of data reporting, and (6) appropriateness of statistical analysis. Each domain was rated as "Yes," "No," or "Unclear." Studies were classified as low risk of bias (all or most domains rated "Yes"), moderate risk (one or two domains rated "No" or "Unclear"), or high risk (three or more domains rated "No"). Scoring thresholds were defined a priori: low risk => 5 "Yes" ratings; moderate risk = 3-4 "Yes" ratings; high risk = <= 2 "Yes" ratings. Two reviewers independently appraised each study, and disagreements were resolved by consensus. The claim that random allocation was clearly reported in all studies is supported by explicit statements in the materials and methods sections of each included article, where specimen allocation to control and experimental groups followed randomized assignment protocols using random number generators or block randomization techniques. In

cases where randomization methods were not explicitly detailed, the domain was marked as "Unclear" rather than "Yes." Quantitative meta-analysis could not be performed because of substantial heterogeneity in graphene type, concentration, base material composition, and outcome measures among the studies. Therefore, a narrative synthesis was conducted, and findings were summarized in structured evidence tables organized by material type and outcome domain. Flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of studies for this systematic review on graphene-reinforced dental materials. A total of 198 records were identified through PubMed (n=74), Scopus (n=89), and Cochrane (n=35). After removal of duplicates (n=42) and other ineligible records (n=6), 150 records were screened. Thirty-eight full-text articles were sought for retrieval, of which six were not retrievable. Thirty-two full-text articles were assessed for eligibility, and sixteen were excluded due to review design (n=7), animal studies (n=5), and case reports or non-original studies (n=4). Finally, sixteen original studies were included in the qualitative synthesis. Meta-analysis was not performed due to

methodological heterogeneity (Figure 1).



**Figure 1:** The Identification, Screening, Eligibility Assessment, and Final Inclusion of Studies on Graphene-Reinforced Dental Materials

## RESULTS

A total of 198 records were identified through database searching: PubMed (n=74), Scopus (n=89), and Cochrane Library (n=35). After the removal of 42 duplicates, 156 records remained. Six additional records were excluded due to being non-English language publications (n=4) or lacking full-text availability despite contact with authors (n=2), leaving 150 records for title and abstract screening. Following this screening, 112 records were excluded as irrelevant. Thirty-eight full-text articles were sought for retrieval; six could not be retrieved despite institutional access and author contact attempts. Thirty-two full-text articles were assessed for eligibility. Sixteen articles were excluded for the following reasons: review articles or meta-analyses (n=7), animal studies (n=5), case reports or non-original research (n=4). Finally, 16 original in-vitro studies met the inclusion criteria and were included in the qualitative synthesis. Meta-analysis was not performed due to methodological heterogeneity in graphene types, concentrations, base materials, and outcome measures. The 16 included studies were all laboratory-based in-vitro investigations published between 2019 and 2025. Studies originated from diverse geographical regions, including Europe (Romania, Portugal, UK, Italy, Spain, Turkey), Asia (China, India, Saudi Arabia), the Middle East (Iran), and Latin America (Brazil, Mexico). The majority of investigations focused on incorporating graphene derivatives into PMMA-based denture systems (n=7) and resin-based restorative materials (n=6), reflecting high research interest in enhancing prosthodontic durability and restorative longevity. The most commonly studied graphene derivatives were graphene oxide (GO) and graphene nanoplatelets (GNP), with reported loading concentrations ranging from 0.01 wt% to 2 wt%. All included studies employed standardized laboratory testing protocols with appropriate control groups, supporting methodological consistency and reliability of the qualitative synthesis (Table 1).

**Table 1:** Characteristics of Included Studies (2019–2025)

References	Study location	Sample size (n)	Study design	Material type	Graphene type	Concentration /loading	Application
[9]	Romania	n=180	In-vitro	PMMA denture base resin	Graphene-silver (Gr-Ag)	1 wt%, 2 wt%	Prosthodontic
[10]	Portugal	n=80	In-vitro	3D-printed PMMA resin	GNP	0.01, 0.1, 0.25, 0.5 wt%	Prosthodontic
[11]	UK	n=60	In-vitro	3D-printed dental resin	GNP	Not reported	Restorative/Prosthodontic
[12]	Saudi Arabia	n=40 clasps	In-vitro fatigue	CAD/CAM clasp materials	Graphene-based polymer	Not reported	Prosthodontic
[13]	Brazil	n=120	In-vitro	Resin-based composite	GO-MMt hybrid	0.3%, 0.5%	Restorative
[14]	Italy	n=90	In-vitro	CAD/CAM PMMA resin	G-PMMA	Commercial material	Restorative
[15]	Iran	n=100	In-vitro	CGIC & RMGIC	nano-GO	Not reported	Restorative

[16]	Romania	n=96	In-vitro	Resin-based cement	GO (with HA-Ag)	0.1%, 0.2% GO	Restorative
[17]	Brazil	n=80	In-vitro	Resin-modified GIC	GO	Not reported	Restorative
[18]	China	n=72	In-vitro	PMMA	ZnO/GO nanocomposite	Not reported	Prosthodontic
[19]	Spain	n=60	In-vitro	Photocurable acrylic resin	Graphene + GO	Not reported	Restorative/Prosthodontic
[20]	Saudi Arabia	n=90	In-vitro	PMMA	nGO ± hBN	Not reported	Prosthodontic
[21]	Turkey	n=96	In-vitro	Self-etch adhesive	GO-ZrO <sub>2</sub>	Not reported	Restorative
[22]	Iran	n=75	In-vitro	Dental composite	nanosized GO	0.2% GO	Restorative
[23]	Mexico	n=48 cell cultures	In-vitro	PMMA + GO	GO	Not reported	Prosthodontic/regenerative
[24]	India	n=40 FDP units	In-vitro	FDP material	Graphene vs zirconia	Not reported	Prosthodontic

Graphene reinforcement demonstrated consistent improvements in key mechanical properties across multiple material systems. Flexural strength, surface hardness, fracture resistance, and bond strength were enhanced in resin composites, PMMA denture base materials, and luting cements. For example, Bacali *et al.* reported significant improvements in flexural, tensile, and compressive properties of PMMA denture base resin reinforced with 1–2 wt% graphene-silver nanocomposites [9]. Similarly, Velo *et al.* demonstrated that the incorporation of 0.3–0.5% graphene oxide-montmorillonite hybrid fillers enhanced the mechanical performance and bioactive potential of resin-based composites [13]. However, formulation-dependent trade-offs were also evident. Salgado *et al.* observed increased surface roughness with higher graphene nanoplatelet concentrations in 3D-printed PMMA, although antimicrobial benefits were maintained [10]. Alahmad *et al.* reported that while microhardness and wettability increased with nano-graphene oxide incorporation, surface roughness also increased, and the degree of conversion decreased, indicating potential polymerization interference [20]. Prodan *et al.* identified an optimal GO/hydroxyapatite-silver formulation that balanced the degree of conversion, mechanical properties, and water sorption characteristics [16]. In prosthodontic applications, Hussein found that graphene-based polymer clasps exhibited lower retention force and greater deformation compared to PEEK after 10,000 fatigue cycles, suggesting performance limitations in certain high-stress applications [12]. Conversely, Angelis *et al.* reported that graphene-reinforced PMMA restorative resins demonstrated flexural strength comparable to controls with variations in compressive strength and Vickers hardness depending on formulation [14]. These findings collectively suggest that while graphene incorporation offers substantial mechanical reinforcement potential, careful optimization of graphene type, concentration, and dispersion is essential to avoid unintended adverse effects on physical properties (Table 2).

**Table 2:** Mechanical and Physical Performance

References	Material Type	Key Mechanical Outcomes	Direction of Effect
<b>Mechanical Performance Summary</b>			
[9]	PMMA Denture Base	Flexural, tensile, compressive strength	Improved at tested loadings
[10]	3D-Printed PMMA	Surface roughness	Increased with higher GNP concentration
[11]	3D-Printed Resin	Mechanical properties	Enhanced
[12]	CAD/CAM Clasp	Retention force, deformation	Lower retention, more deformation vs PEEK
[13]	Resin Composite	Mechanical properties	Improved at 0.3–0.5% GO-MMt
[14]	CAD/CAM PMMA	Flexural, compressive strength, and hardness	Flexural similar; compressive/hardness varied
[15]	CGIC/RMGIC	Shear bond strength	Altered by nGO
[16]	Resin Cement	Degree of conversion, mechanical properties	Optimal formulation identified
[17]	RMGIC	Mechanical properties	Improved with GO
[18]	PMMA	Mechanical properties	Enhanced with ZnO/GO
[19]	SLA Resin	Crosslinking, mechanical properties	Influenced by graphene/GO
[20]	PMMA	Microhardness	Increased
[21]	Adhesive	Bond strength, stability	Enhanced
[22]	FDP Material	Flexural/compressive strength, hardness	Graphene: higher hardness; Zirconia: higher strength
<b>Physical Performance Summary</b>			
[6]	PMMA	Water absorption	Assessed
[10]	3D-Printed PMMA	Surface roughness	Increased with GNP
[16]	Resin Cement	Degree of conversion, water sorption	Optimal formulation balanced properties
[19]	SLA Resin	Crosslinking	Influenced by graphene/GO
[20]	PMMA	Wettability, roughness, degree of conversion	Wettability ↑; roughness ↑; conversion ↓

The majority of included studies reported significant antimicrobial activity of graphene-functionalized materials against

clinically relevant oral pathogens, particularly *Streptococcus mutans* and *Candida albicans*. Salgado et al. demonstrated effective antimicrobial activity in graphene-doped 3D-printed PMMA specimens against both organisms, although surface roughness increased with graphene concentration [10]. Alahmad et al. (2025) found that nano-graphene oxide combined with hexagonal boron nitride significantly reduced *Candida albicans* attachment compared to control PMMA [20]. Fakoori et al. reported up to 40% antibacterial efficacy at 0.2% graphene oxide concentration in dental composite formulations targeting *S. mutans* [22]. Biocompatibility assessments revealed generally favorable cytotoxicity profiles. Ruan et al. evaluated zinc oxide/graphene oxide nanocomposite-reinforced PMMA and found that the material exhibited acceptable cytotoxicity levels alongside enhanced antibacterial and mechanical properties [18]. Vega-Quiroz et al. investigated the effects of graphene oxide-enriched PMMA on human dental pulp stem cells and reported that the material met ISO 10993-5 cytotoxicity thresholds ( $\geq 75\%$  cell viability), although effects on cellular differentiation were also observed [23]. Serfözö et al. developed a self-etch adhesive incorporating graphene oxide-functionalized zirconia, designed to enhance bond strength, biocompatibility, and long-term stability [21]. These findings indicate that graphene derivatives possess dual functionality, mechanical reinforcement, and antimicrobial activity, while maintaining acceptable biocompatibility within tested concentration ranges. However, the long-term biological safety, potential nanoparticle release, and tissue responses in clinical environments require further in-vivo validation (Table 3).

**Table 3:** Biological / Antimicrobial and Biocompatibility Outcomes

References	Organism/Cell Model	Key Biological Outcome
[10]	<i>Candida albicans</i> , <i>Streptococcus mutans</i>	Antimicrobial activity was achieved for graphene-doped specimens; roughness increased with concentration
[11]	Antimicrobial activity (drug-free)	Antimicrobial activity is reported along with mechanical enhancement
[16]	Antibacterial testing included	Antibacterial activity assessed alongside conversion/sorption/mechanics
[18]	Cytotoxicity + antibacterial testing	ZnO/GO-PMMA evaluated for cytotoxicity, antibacterial, and mechanical performance
[20]	<i>Candida albicans</i>	nGO+hBN group showed less <i>Candida</i> attachment; conversion decreased; roughness increased
[21]	Biocompatibility + stability tests	Adhesive designed for improved bond strength, biocompatibility, and stability
[22]	<i>S. mutans</i> antibacterial report	Up to ~40% antibacterial efficacy at 0.2% GO reported (composite context)
[23]	Human dental pulp stem cells (hDPSC)	PMMA+GO met ISO cytotoxicity threshold ( $\geq 75\%$ viability); differentiation effects reported

The overall methodological quality of the included studies was high. Fifteen of the 16 studies (93.8%) were classified as low risk of bias, demonstrating consistent use of standardized testing protocols, appropriate control groups, complete data reporting, and adequate statistical analysis. All included investigations clearly reported random allocation of specimens to experimental groups and employed homogeneous laboratory testing conditions. The single study classified as moderate risk of bias lacked explicit blinding of outcome assessment, though all other methodological criteria were met. Blinding status was unclear in the majority of studies (n=15), as outcome assessment blinding is less commonly reported in in-vitro experimental designs. These findings indicate that the synthesized evidence is derived predominantly from methodologically sound experimental studies, strengthening confidence in the reliability of the review conclusions (Table 4).

**Table 4:** Risk of Bias Assessment (Modified JBI Tool)

References	Random allocation	Standardized testing	Control group	Blinded assessment	Complete reporting	Overall risk
[9]	Yes	Yes	Yes	Unclear	Yes	Low
[10]	Yes	Yes	Yes	Unclear	Yes	Low
[11]	Yes	Yes	Yes	Unclear	Yes	Low
[12]	Yes	Yes	Yes	No	Yes	Moderate
[13]	Yes	Yes	Yes	Unclear	Yes	Low
[14]	Yes	Yes	Yes	Unclear	Yes	Low
[15]	Yes	Yes	Yes	Unclear	Yes	Low
[16]	Yes	Yes	Yes	Unclear	Yes	Low
[17]	Yes	Yes	Yes	Unclear	Yes	Low
[18]	Yes	Yes	Yes	Unclear	Yes	Low
[19]	Yes	Yes	Yes	Unclear	Yes	Low
[20]	Yes	Yes	Yes	Unclear	Yes	Low
[21]	Yes	Yes	Yes	Unclear	Yes	Low
[22]	Yes	Yes	Yes	Unclear	Yes	Low
[23]	Yes	Yes	Yes	Unclear	Yes	Low
[24]	Yes	Yes	Yes	Unclear	Yes	Low

## DISCUSSION

This systematic review synthesized current evidence on the laboratory performance of graphene-reinforced dental materials in restorative and prosthodontic applications. Overall, graphene derivatives (GO, GNP, nGO, and hybrids) demonstrated a consistent pattern of enhancing mechanical performance and antimicrobial activity in PMMA, resin composites, adhesives, and glass ionomer systems. However, material-specific trade-offs such as elevated surface roughness and reduced degree of conversion were also observed, indicating that the advantages of graphene are formulation-dependent. These findings are supported by recent external studies. Wang *et al.* demonstrated that the incorporation of SiO<sub>2</sub>@GO fillers significantly enhanced the physicochemical properties of resin composites, consistent with the mechanical performance improvements observed in the present review [25]. Sharafeddin *et al.* showed that GO-reinforced glass ionomer cements exhibited enhanced flexural strength, supporting the positive mechanical trends identified [26]. Sari and Ugurlu (2023) found that GO-modified RMGIC was characterized by greater hardness and strength but also greater surface roughness, which corresponds to the trade-off pattern identified in our synthesis [27]. In prosthodontic applications, Swaroop *et al.* reported reduced flexural strength associated with poor dispersion of graphene, potentially explaining the variable improvement observed in some of the reviewed prosthodontic formulations [28]. Conversely, Bacali *et al.* demonstrated enhanced microbial inactivation with graphene-silver PMMA in denture wearers, supporting the antimicrobial benefits of graphene incorporation identified in our review [29]. In adhesive dentistry, Williams *et al.* and Sawan *et al.* reported formulation-specific improvements in antibacterial activity with inconsistent bonding performance, aligning with our findings of materials that demonstrated biological benefits without consistently superior mechanical performance in adhesive systems [30, 31]. Graphene's potential extends to implant dentistry, with evidence of enhanced biocompatibility and antimicrobial properties. Jang *et al.*, Sun *et al.*, and Tan *et al.* reported improved osteogenic and antibacterial responses on graphene-modified titanium surfaces [32–34]. More recently, You *et al.* demonstrated that GO-based multilayer coatings resulted in a significant reduction of pathogenic colonization with low cytotoxicity [35]. Collectively, these studies reinforce the findings of the current review, indicating that graphene incorporation can enhance dental biomaterial performance; however, careful attention to formulation variables is essential for optimal outcomes. The principal source of heterogeneity identified across

studies is variation in graphene type, functionalization, concentration, dispersion methods, and base material chemistry. Poor dispersion can result in agglomeration, compromised polymerization, and increased surface roughness, whereas effective functionalization enhances filler-matrix bonding and antimicrobial action. The majority of the included studies demonstrated satisfactory cytocompatibility and antimicrobial activity, with graphene-based systems typically meeting ISO biocompatibility standards. However, long-term clinical safety data remain limited, and additional in-vivo studies are needed to assess long-term tissue responses, degradation behavior, and potential nanoparticle release in the oral environment. Graphene-reinforced PMMA and resin-based restorative systems demonstrate potential for enhanced wear resistance, microbial inhibition, and surface durability in laboratory settings. These properties may contribute to reduced risks of secondary caries and prosthesis-associated infections, particularly in high-risk patient populations. However, clinicians should be aware of possible increases in surface roughness and effects on polymerization that may occur with certain formulations. At present, graphene-reinforced materials are not yet commercially available for routine clinical use. Future research should focus on developing standardized graphene formulations, conducting clinically relevant aging protocols, and performing well-designed randomized controlled clinical trials to establish long-term safety, performance, and cost-effectiveness before clinical adoption. Strengths of this systematic review include adherence to PRISMA 2020 guidelines, comprehensive searches of multiple databases, rigorous dual screening and data extraction processes, and systematic quality assessment using a modified JBI tool. The review provides a focused synthesis of recent evidence (2019–2025) specifically addressing graphene-reinforced materials in restorative and prosthodontic dentistry, filling a gap in the current literature. Limitations include the exclusive inclusion of in-vitro studies, which limits the ability to conclude clinical performance and long-term outcomes in patients. Substantial methodological heterogeneity in graphene types, concentrations, dispersion techniques, base material compositions, and outcome measures precluded quantitative meta-analysis. Variability in the reporting of graphene loading concentrations and functionalization methods across studies further complicated direct comparisons. Additionally, the lack of standardized aging protocols and long-term degradation testing limits the applicability of findings to clinical scenarios. Publication bias may also be present, as studies with positive outcomes are more likely to be published. Future research

should prioritize standardized experimental protocols, clinically relevant aging simulations, and prospective clinical trials to validate laboratory findings.

## CONCLUSIONS

Graphene-reinforced dental materials exhibit promising mechanical reinforcement and antimicrobial properties in laboratory settings, supporting their potential future use in restorative and prosthodontic dentistry. However, clinical translation requires standardized formulations, long-term safety evaluations, and controlled clinical trials to confirm durability and biocompatibility before routine clinical adoption can be recommended.

## Authors' Contribution

Conceptualization: MN, ZQ

Methodology: SY

Formal analysis: MP, KM

Writing and Drafting: MN, AA, ZQ

Review and Editing: MN, SY, AA, MP, KM, ZQ

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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