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Editorial

Open Access

Building a Sustainable Research Culture in Pakistani Medical Universities

Iqbal Hussain Udaipurwala

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Medical research is widely recognized as a fundamental driver of innovation and evidence-based clinical practice. Nations that have developed strong research culture consistently demonstrate better healthcare outcome and superior academic influence.[1,2,3] Despite a growing academic infrastructure and medical universities in Pakistan, its contribution to global scientific literature remains relatively low and accounts for only 0.5–0.6% of global research output[4]. However, Pakistan's scientific productivity has expanded considerably over the past two decades, with a more than 300% increase in publications indexed in international databases between 2010 and 2019, it is still reflecting a substantial gap[5]. This development indicate that Pakistan possesses significant intellectual potential, but the sustainability and impact of this progress depend largely on the development of a strong and enduring research culture within the medical institutions. Locally generated research is particularly important because many healthcare challenges are context-specific and require solutions tailored to regional epidemiology and healthcare infrastructure.

There are many barriers that had led to comparatively slow development of research culture in medical institutions of Pakistan.[6] Among it, the most significant challenges are inadequate infrastructure and scanty research funding. High-quality medical research requires well-equipped laboratory with access to modern technology, reliable database and institutional support, but unfortunately many institutions in Pakistan lack these essential facilities. Insufficient funding opportunity with limited research grant further discourage researcher from pursuing good quality large-scale research project. Without constant investment in infrastructure, it is difficult for an institution to produce high impactful and internationally competitive research.

Another important factor for low research productivity is the limited integration of research training within undergraduate and postgraduate medical training.[7] Although research methodology with biostatistics is included in our under-graduate medical curriculum, the teaching often remains theoretical and does not adequately prepare student for practical research. As a result, many medical graduates lack confidence in designing research study, analyzing data or writing scientific manuscript. Early exposure to practical research during medical education is indispensable for cultivating analytical thinking and scientific curiosity. Many studies conducted in Pakistan have shown that medical students frequently report limited opportunity for research involvement due to inadequate mentorship, lack of structured training and insufficient institutional support[8].

Mentorship is widely recognized as one of the most critical factors in developing successful research careers. In established academic environment, experienced researcher guides junior colleague or student through the process of formulating research question, designing a study, interpreting its result and publishing manuscript. This type of mentorship is lacking in most of our institutions and thus strengthening it could significantly improve research among young investigators. Student research society, elective research rotation and structured undergraduate research program have been shown to enhance research interest and productivity in many countries. Encouraging students to undertake supervised research projects during their under-graduate medical training can improve scientific literacy with greater likelihood of future involvement.

Institutional and government policies for academic promotion also greatly influence research culture. In recent years, different academic regulatory bodies in Pakistan have increasingly emphasized research publication as a requirement for faculty promotion and annual appraisal. While this policy has encouraged research activity in many ways, it has also led to certain unintended consequences. The pressure to publish for career advancement may lead some researcher to prioritize quantity over quality which results in submission to low-impact or predatory journal. Concerns regarding plagiarism, duplicate publication and research misconduct have also been raised within the academic community due to it. Strengthening institutional review board and promoting training in research ethics and scientific integrity are therefore essential for maintaining the credibility of research produced in Pakistani institutions[9]. Universities and teaching hospitals should establish dedicated research support offices that should provide all types of assistance to researcher. This office must provide facility of a biostatistician, research methodologist and data analysts. Collaboration among institutions also has the potential to enhance research capacity where multicenter research studies

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can generate larger dataset. It can produce more robust and generalizable finding than a single center study. Establishing national research networks can facilitate data sharing, promote interdisciplinary collaboration and address important public health challenges through coordinated research efforts. Such collaborative initiatives are particularly important in low- and middle-income countries where resources may be limited.[10,11,12]

Faculty members often face heavy clinical workloads and administrative responsibilities, leaving limited time for research supervision. As a result of time constraint most clinicians either do low quality basic research including retrospective or basic epidemiologic study or they ask for guest authorship from their colleagues to add their name in any ongoing research to fulfill promotion requirement. Providing protected research time for faculty members can enable clinicians to balance their clinical responsibilities with academic and scholarly activities. In addition, a strong research culture also requires a broader cultural shift within academic and clinical communities. Research should not be perceived merely as a requirement for academic promotion but rather as an integral component of professional responsibility for healthcare providers. Clinicians offen encounter numerous clinical challenges and unanswered questions in their daily practice, many of which can form the basis for valuable research investigations.

National regulatory bodies and government policy makers can play an important role in shaping the research environment of the country. Strategic investment in research infrastructure can significantly enhance national research productivity. Continued support for research capacity-building program and international academic partnership will be essential for strengthening Pakistan's research ecosystem. Advancement in digital healthcare technology also present new opportunity for expanding good research culture. Use of electronic health record with AI application can facilitate large-scale studies. By leveraging this technology, researcher can generate high-quality evidences to form clinical practice and national health policies. International collaboration has increased significantly in recent years, enabling our researchers to participate in multinational research projects and gain exposure to advanced research methodology. Collaborative research partnership with international institution not only enhance the visibility of local research but also facilitate knowledge transfer and capacity building. Such collaboration can play a crucial role in improving the quality and impact of research produced in Pakistani medical institution.

In conclusion, strengthening the research culture in Pakistani medical institution is a mandatory need for enhancing the country's global academic standing. Although Pakistan has made significant progress in increasing its research output during recent years, substantial challenges remain in terms of infrastructure, funding, mentorship, regulatory policies, faculty burn-out and training. Addressing these challenges requires coordinated efforts from academic institutions, policymakers, regulatory bodies and healthcare professionals. By investing in research education, promoting mentorship programs, strengthening ethical oversight and encouraging collaborative research initiatives, Pakistan can develop a sustainable research ecosystem that may contribute meaningfully to global medical knowledge.

Authors Contribution:
Iqbal Hussain Udaipurwala: Conception, writing, literature search, proof reading

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Original Article

Open Access

Comparison of T-Loop vs Opus Loop in Canine Retraction Efficacy and Anchorage Loss Control – A Split- Mouth Randomized Clinical Trial

Ayesha Ashraf Khan, Sarah Irfan, Tabassum Ahsan, Maria Moin

Abstract:

Objective: The primary aim was to compare the rate of canine retraction between T loop and Opus loop. The secondary objectives were to compare the angulation of canine, anchorage loss and molar rotation for the two loops used.

Study Design and Setting: A Split- Mouth Randomized Clinical Trial done at Department of Orthodontics, Bahria University of Health Sciences Campus Karachi

Methodology: This study conducted including 14 participants who received both the Opus loop and T-loop in different quadrants. The primary outcome assessed was rate of canine retraction which was measured clinically at every appointment using calibrated calliper. Secondary outcomes included changes in canine angulation, anchorage loss and molar rotation. Canine angulation was measured using periapical radiographs of maxillary canine to 1st molar taken by DIGORA™ Optime at the start of canine retraction and after completion of canine retraction. Anchorage loss and molar rotation was measured by model analysis. For statistical analysis non-parametric test Wilcoxon signed-rank test was used to compare the treatment changes between Opus loop and T-loop.

Result: rate of canine retraction was higher in Opus loop (1.5 mm/month) compared to T-loop (1.45 mm/month) however no statistically significant differences between was found in rate of canine retraction, angulation change, anchorage loss, or molar rotation ($p > 0.05$), indicating comparable clinical performance of both mechanics during space closure.

Conclusion: Both loops showed similar efficacy during canine retraction.

Keywords: anchorage loss, angulation, canine retraction, Opus loop, T-loop

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INTRODUCTION:

Space closure is considered a biomechanically challenging procedure in orthodontics. The goal of the clinician is to identify methods that enable efficient canine retraction. The basis of biomechanics is important for clinicians to determine anchorage requirements, treatment prognosis, and final outcomes. The choice of biomechanics depends on the requirements of extraction space closure, the patient's age, compliance, and the expertise of the orthodontist.[1,2]

Extraction spaces can be closed using two methods: (1) frictional/sliding mechanics and (2) non-frictional mechanics. In sliding mechanics, the canine is retracted using NiTi coil springs or elastomeric chains, and friction occurs at the bracket–archwire interface, thereby increasing the overall duration of tooth movement and requiring greater anchorage.[3,4] In contrast, non-sliding mechanics, also known as loop mechanics, involves no friction. It can be achieved using either continuous or segmental mechanics.[5] The continuous method involves fabricating loops in the main archwire, connected to each tooth, which moves around its center of rotation.[5] In the segmented arch technique, the arch is divided into three segments, i.e., two posterior and one anterior, and both posterior and anterior segments are connected through loops.[6] Both segments can be controlled by changing the degree of gable bends and the position of the retraction loops placed between the anterior and posterior segmented arches.[6]

Load–deflection, M: F (moment-to-force) ratio, and vertical force are the main properties of mechanical loops. The M:F ratio is the most significant factor dictating the type of tooth movement. M:F ratios of 7:1 and 10:1 mm are suggested

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in the literature for controlled tipping and translation, respectively. These M:F ratios can be altered by changing the height of the loop, adding wire horizontally, incorporating a helix, and adjusting the placement of loops and gable bends. Different loop designs such as Gjessing, Ricketts retraction, L-loops, delta loops, T-loop springs (TLSs), and Opus loops have been studied in terms of moment-to-force ratio.[7]

The most important factor affecting the M:F ratio is the height of the closing loop. According to Burstone and Koenig et al[8] a 4 mm loop had an M:F ratio of 1.3, a 6 mm loop had 2.2, and a 10 mm loop had 4. T-loops include a gingival horizontal component that results in a comparatively consistent M:F ratio, a constant optimum force, and a low load–deflection rate throughout the loop's activation range.[5]

Siatkowski invented the Opus loop, an L-shaped helical loop. The helix in the apical region of the L-shape increases the M:F ratio.[7] Studies on Opus loops have demonstrated that they consistently exhibit a 10:1 M:F ratio, enabling bodily tooth movement. However, studies comparing the T-loop and Opus loop in terms of canine retraction rate, angulation of the canine, and anchorage loss are limited. Therefore, our study aims to compare the Opus loop and T-loop in terms of tooth movement and associated side effects.

The primary objective of this split-mouth randomized controlled trial (RCT) was to compare the canine retraction rate of the T-loop with the Opus loop. The secondary objectives were to evaluate canine angulation and changes in the position of the first molar in terms of anchorage loss and molar rotation for the two loops used. Our study was conducted based on the null hypothesis that there would be no significant difference in the rate of canine retraction, angulation of the canine, molar rotation, and anchorage loss between the T-loop and the Opus loop.

METHODOLOGY:

Our split-mouth RCT was conducted with a 1:1 allocation ratio between the right and left quadrants. ERC approval was obtained from the Institutional Review Board (IRB#018/23), and no changes were made after the trial commencement. The trial was registered in (No: NCT06945575). Recruitment begin in February 2025 and data collection was completed in July 2025.

All patients reporting to the department of Orthodontics were assessed for eligibility after record collection and finalization of their Orthodontic treatment plans. Participants included in the study were 1) aged between 14 to 40 years, 2) planned extractions of maxillary first premolars, 3) Class 1, 1/4th, ½, and 3/4th unit Class II molar relation 4) presence of all teeth up to second molar 5) good oral hygiene. Exclusion criteria were 1) full cusp Class II 2) developmental, medical or genetic problems 3) patients taking bisphosphonates 4) spacing in dentition 5) grossly carious upper molars which cannot be restored 6) patients with active periodontal disease, and 7) severe crowding. Patients who agreed to participate in the trial signed an informed consent. Consecutive sampling technique was used to enroll patients.

A total of 14 participants were included, who received both Opus loop and T-loop in different quadrants. Group 1: Opus loops 14(n) Group 2: T-loop 14(n). Randomization was performed using a simple lottery method, where allocation (right/left quadrant) was determined using sealed opaque slips to ensure allocation concealment. Half of the participants received Opus loop on right and T-loop on left side, while reverse was true for the other half.

After banding of first and second molars, bonding was done using brackets with MBT prescription (slot 0.022"×0.028", Orthocare UK) along with extractions of first premolars. 0.014" Niti was used for the initial levelling and alignment, and wires were progressed to 0.017"×0.025" Niti in the same sequence for all participants. Second molar, first molar, and second premolar were held by 0.017"×0.025" stainless steel (S.S) and colligated using steel ligature wire. Opus and T-loop were fabricated with 0.017"×0.025" S.S wires. The loops were placed midway within the extraction space. (Figure 1) A single experienced clinician fabricated and inserted the loops. Pre-activation bends of 30° and anti-rotational bends were given in the T-loops. Opus loop was inserted without any pre-activation bends. Each loop was activated 2 mm at each appointment, and it was continued till completion of canine retraction.

Rate of canine retraction was the primary outcome and was calculated by "the amount of canine retraction (in millimetres) divided by the time interval". Amount of canine retraction was assessed by measuring the distance from canine cusp tip to the mesiobuccal (MB) cusp tip of the 1st molar with a calibrated calliper at the time of placement of loops and at every month by a single calibrated clinician. The duration was measured as time interval and each time interval was 4 weeks. Even though the canine cusp tip and first molar mesiobuccal cusp are capable of orthodontic movement, this approach was chosen as it represents net change experienced by the canine–molar segment, which forms as a clinically relevant unit to retraction. An examiner, calibrated each 4-week period, made the measurement to avoid variability. Anchorage loss was also independently measured via cast analysis so that we could evaluate whether linear tooth movement was a result of canine retraction or mesial movement of the molars.

Secondary outcomes were change in angulation of canine, anchorage loss, and molar rotation. Periapical radiographs of maxillary canine to 1st molar were taken by DIGORA™ Optime at the start of canine retraction and after completion of canine retraction. X-ray film holders were used while taking periapical radiographs for standardization of x-ray. A single calibrated examiner analysed angulation of canine by measuring an angle formed between vertical line drawn

from buccal cusp tip of canine till root apex in reference with long axis of 2nd premolar. (Figure 2)

Anchorage loss and rotation of molar was measured by performing model analysis. Impression of patient was taken with alginate material before and after canine retraction. Figure 3. shows that the left and right third rugae were taken as reference points to measure anchorage loss. A horizontal line was constructed from mesiobuccal cusp tip of right and left first molar till mid palatal raphe. Distance between the horizontal line and the third rugae was measured on both sides at start and at end of the canine retraction. The difference between pre and post value represented anchorage loss.

Figure 4. shows that rotation of molar was measured as a difference between angle formed between line passing through distobuccal cusp tip and mesiopalatal cusp tip of 1st molar to mid palatal raphe was measured before and after canine retraction. To assess intra-observer reliability, all measurements were repeated after two weeks. Sample size was calculated with Open Epi software, Version 3.0, using the findings of Davis et al.[5] who reported the mean of tipping of the canine using Marcotte spring 6.645°± 2.744 and while using T-loop 1.229° ± 5.124. Keeping á = 0.05, a power of 80% and a confidence interval of 95%, the software calculated a sample size of 14 participants for each group with total 28 sides allocated. Due to the nature of the intervention in this split-mouth study, blinding of the operator and patients was not possible. However, all radiographic and model-based outcome assessments were carried out by a blinded independent examiner who was unaware of group allocation, minimizing potential measurement bias.

Data were analyzed using SPSS (IBM Corp, Version 23.0, NY, USA). Descriptive analysis was applied for the qualitative data. The intraclass correlation coefficient (ICC) was used to check intra-observer reliability. The Kolmogorov-Smirnov test was performed to test normality of the data and indicated that data were non-normal. Therefore, the treatment changes between Opus and T-loop were compared with a non-parametric Wilcoxon signed-rank test. A p-value = 0.05 was considered statistically significant.

RESULT:

Figure 5 shows the Consolidated Standards of Reporting Trials flowchart demonstrating 50 participants were analyzed for eligibility out of which 28 participants were included in study. Each group was allocated with 14 participants and there was no lost to follow-up. No participants were excluded from analysis. ICC value showed that measurements for angulation of canine (ICC: 0.91), anchorage loss (ICC:0.88) and molar rotation (ICC:0.96) were reliable.

Table 1 shows total of 14 participants, out of which 11 were females with a mean age of 17.73 ± 2.27 years and 3 were males with a mean age of 18.00 ± 2.36 years were included.

Table 2 shows canine retraction rate, angulation of canine, rotation of molar, and anchorage loss. Wilcoxon signed-rank test showed no statistically significant difference between the Opus loop and T-loop in any of the evaluated parameters. The median rate of canine retraction was comparable between the Opus loop (1.5 mm/month) and T-loop (1.45 mm/month) (p = 0.834). Similarly, no significant difference was observed in angulation change (p = 0.271), anchorage loss (p = 0.857), or molar rotation (p = 0.953).

DISCUSSION:

Several closing loops have been designed to provide a high M:F ratio and low force deflection rate enabling optimal retraction, bodily translation, minimal anchorage loss, and reduced rotation.[5,9] M:F ratio can be altered by changing the length, diameter, or material of the wire, addition of a helix,

Figure 1: T-loop and Opus loop placed for canine retraction

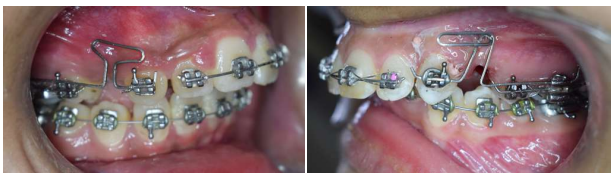

Figure 2: Canine angulation measured with reference to 2nd premolar

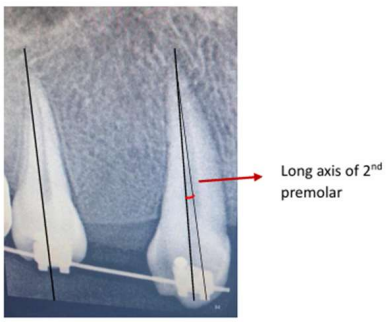

Figure 3: A horizontal line was drawn from mesiobuccal cusp tip of right 1st molar to left 1st molar. Anchorage loss was measured from mesial point of third rugae to the horizontal line. “A” measures anchorage loss from right molar. “B” measures anchorage loss from left molar

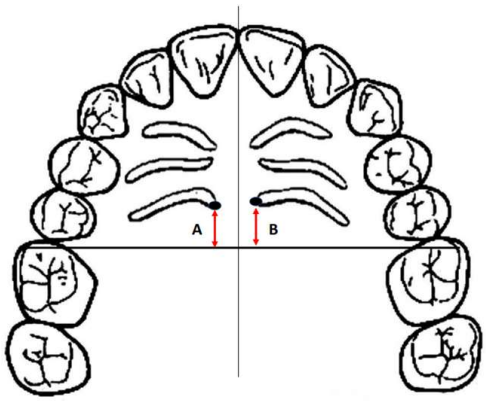

Figure 4: A diagonal line was drawn from distobuccal cusp tip to mesiopalatal cusp tip of 1st molar till mid palatal raphe. An angle formed between midpalatal raphe and diagonal line was measured as molar rotation. "C" measures right molar rotation. "D" measures left molar rotation.

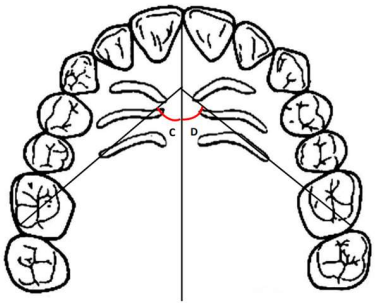

Figure 5: CONSORT diagram showing flow of patients through the trial

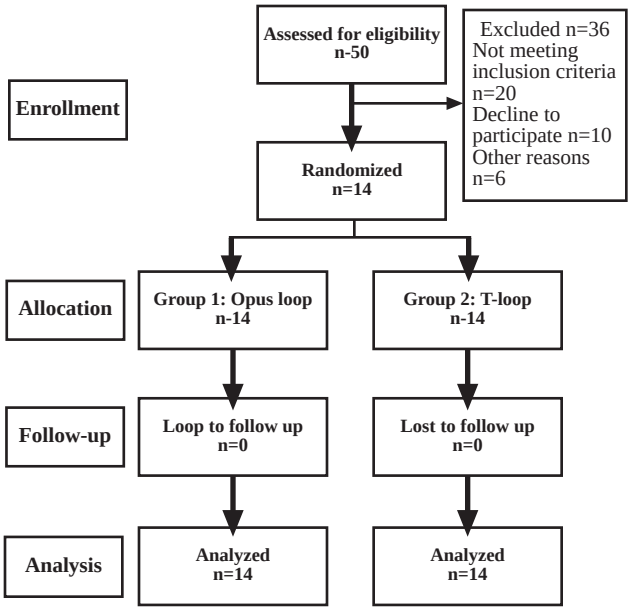

Table 1: Demographic Data

Gender	Female n=11	Male n=3
Mean age ± STD (years)	17.73±2.27	18.00±2.36

N=14, STD: Standard Deviation

Table 2: Comparison of Opus loop and T-loop

Variable	Opus Loop (Median [IQR])	T-loop (Median [IQR])	p-value*
Rate of retraction	1.5[0.44]	1.45[0.62]	0.834
Angulation change	1.0 [10.0]	0.5 [6.5]	0.271
Anchorage loss	-0.5 [1.25]	-1.0 [1.63]	0.857
Molar rotation	0.0 [2.0]	0.0 [5.0]	0.953

Wilcoxon signed-rank test for comparison of Opus loop and T-loop, $p<0.05$*

and pre-activation bends.[7,10] M:F ratio of 10:1 is required for bodily translation, whereas 7:1 is required for controlled tipping. [12] Different loops such as vertical closing, bull loop, snail loop, T-loop, L-loop, Opus loops have been designed to achieve the highest M:F ratio. According to Techalertpaisarn P et al.[7] M:F ratio is increased by increasing the height of the loop, however due to soft tissue limitation no loop can reach optimum height. The horizontal component of T-loop increases M:F ratio but then levels off. To achieve high M:F ratio Siatkowsk iet al.[13,14] designed an Opus loop by changing loop design by incorporating a helix in a L shaped loop. In their study they reported that Opus loop provides constant force delivery without pre-activation bends. Finite element model (FEM) showed that loops with helix had three times greater M:F ratio as compared to loops without helix. [9] Safavi MR et al.[15] who compared vertical helical closing loops, L-loops, and T-loops with pre-activation bends against Opus loops without pre-activation bends reported that pre-activation bends increased the M:F ratio at 0.1mm of activation.

In our study, it was found that Opus loop had faster rate of retraction than the T-loop however, there was no significant difference between them. Our result was in accordance with Obaidi H et al.[16] who compared rate of retraction, tipping and rotation of 8 different loops. He found that rate of space closure was insignificantly higher in opus loop(0.734mm) as compared to T-loop(0.711mm).

Findings based on this study, degree of tipping was greater in the Opus loop than in the T-loop, but the difference was not statistically significant. Our findings were similar to Obaidi et al.[16] however he found statistically significant difference in canine angulation between Opus loop and T-loop he stated that this difference was due to the change in the angle between the vertical portion (i.e., pre-activation bends), which alters the force distribution. The reason for increased tipping of the canine with Opus loop in our study may be due to absence of pre-activation bends in the Opus loop .Safavi MR et al.[15] stated in his study that T-loop and Opus loop without pre-activation bends have similar mechanical behavior whereas incorporating pre-activation bends in both loops increased M:F ratio and the Opus loop had slightly increased M:F ratio (7.6mm) as compared to the T-loop (7.26mm). Similarly, Davis S et al.[5] compared Marcotte loop with T-loop and he found that T-loop had lower degree of tipping than Marcotte. In his study only anti-extrusion bends were placed in Marcotte loop whereas pre-activation bends were only placed in T-loop, these pre-activation bends provided greater control of tooth movement with the T-loop. In contrast to our study Barot M et al.[17] in his study compared segmented T-loop, mushroom loop and Opus loop and concluded that segmented T-loop showed greatest distal movement of canine and controlled tipping compared to mushroom loop and Opus loop.

One of the major considerations during canine retraction is

preservation of the anchorage. Anchorage can be increased by increasing M:F ratio in posterior segment. This is usually done by placing pre-activation bend in beta arm i.e. in posterior segment, that creates a moment which tips crown distally or by asymmetric loop positioning which generates moment on the segment closer to loop. The findings revealed that less anchorage loss was seen in Opus loop compared to T-loop however the difference was not statistically significant. Less anchorage loss in Opus loop can be due to addition of helix, or an increased length of wire which increase the M:F ratio. However, result of our study contradicted with Barot M et al.[17] who suggested that T-loop is the most efficient loop for canine retraction as it has minimum intrusive effect and anchorage loss, maximum canine retraction in a single activation compared to mushroom and Opus loop. According to Masaes et al.[18] who compared T-loop with Ricketts maxillary canine retractor in term of anchorage loss control found T-loop had better anchorage control than Ricketts maxillary canine retractor. The rigid wire design of T-loop stabilizes the posterior segment which redistribute stress level to large surface and decreases force in the reactive unit.

Molar rotation was found to be less in Opus loop than T-loop but showed no significant difference. Masaes et al.[18] in their study also found no significant difference in molar rotation when he compared T-loop with Ricketts maxillary canine retractor.

In literature greater emphasis has been shown to biomechanics of space closure and biological response to forces. For predictable tooth movement adequate force system, loop geometry and positioning of loops plays a critical loop. Finding of these study shows that when all biomechanics principles are followed, different loop will yield similar clinical outcome. [19,20,21]

Limitations of the study: Periapical radiographs used in study provide two-dimensional assessment and may be affected by magnification, distortion, and superimposition of anatomical structures. Measurement of canine retraction using the mesiobuccal cusp tip of the first molar as a reference may introduce bias due to possible molar movement (anchorage loss). Rotation of the canines was not evaluated; however, rotation may affect the linear retraction measurement. Our radiographic focus was on angulation, and thus this factor is a methodological limitation of the study. For future research, more consistent and complete evaluation of canine movement with CBCT or other 3D methods is recommended that includes larger number of subjects, with a narrower age span, as well as balanced sex distribution and more consistent malocclusion characteristics to enhance external validity and increase the overall robustness of findings

CONCLUSION:

There is no significant difference between Opus loop and T-loop in terms of canine retraction rate, canine angulation, anchorage loss and molar rotation. Owing to similar efficiency of both loops either can be used in clinical setting according to clinicians' choice.

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Authors Contribution:
Ayesha Ashraf Khan: Concept and design, data collection, analysis, interpretation, manuscript writing
Sarah Irfan: Conceptualization, reviewing and editing supervision
Tabassum Ahsan: supervision, final approval of manuscript
Maria Moin: supervision

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Original Article **Open Access**

Calculation of Total Dose Delivered to Carcinoma Cervix Patients Treated with Volumetric Modulated Arc Therapy (VMAT) and Image-Guided Brachytherapy (IGBT)

Sana Naeem, Ayesha Anees, Ahmad Farooq, Tahir Sheikh, Rub Nawaz Maken

Abstract

Objective: To calculate the total radiation dose delivered to carcinoma cervix patients treated with Volumetric Modulated Arc Therapy (VMAT) and MRI-guided brachytherapy (IGBT), and to evaluate cumulative EQD2 to tumor and organs-at-risk.

Study Design and settings: This Descriptive, cross-sectional study was conducted at Department of Radiotherapy, INMOL Hospital, Lahore, from 1st August 2024 to 10th January 2025.

Methodology: Fifty patients with histologically confirmed carcinoma cervix, ECOG 0–II, aged 45–65 years, receiving VMAT-based external beam radiotherapy (45 Gy/25 fractions) followed by MRI-guided brachytherapy were included. EQD2 values for the high-risk target volume and organs-at-risk (bladder, rectum, sigmoid) were calculated using DVH parameters.

Results: The mean age of patients was 55.1 ± 5.8 years, with Stage IIIB being the most common stage (50%). A total of 64% received three brachytherapy insertions, while 36% required four. The mean cumulative tumor EQD2 was 84.9 ± 2.8 Gy. Mean bladder, rectum, and sigmoid EQD2 values were 78.1 ± 4.3 Gy, 67.3 ± 4.4 Gy, and 62.5 ± 4.2 Gy, respectively. More than 90% of patients met internationally recommended tumor and OAR dose constraints.

Conclusion: It is concluded that VMAT combined with MRI-guided brachytherapy delivers adequate cumulative tumor dose while maintaining organ-at-risk exposure within acceptable limits.

Keywords: Cervical cancer, patients, population, Radiotherapy, VMAT, MRI

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INTRODUCTION

Cervical cancer is the fourth most common cancer among women globally, with an estimated 601,000 new cases and 342,000 deaths in 2020.[1] In Pakistan, about 5,000 women in the country are diagnosed with cervical cancer every year and more than 3,000 of these women die (WHO).[1,2] The HPV infection is attributed to over 90 percent of the cases and other demographics that put individuals at risk are smoking, immunocompromised conditions, history of sexually transmitted diseases, young age at first intercourse, multiple sexual partners, and multiparty.[3] The patients may remain asymptomatic and be identified during screening, but the symptoms include, abnormal vaginal discharge, post-coital bleeding, dyspareunia, and pelvic pain. The workup involves a focused history, physical exam, and a gynecological examination of local and lymph node extension, smoking cessation counselling.[4] It also entails pertinent lab tests including complete blood count, full metabolic profile, pregnancy test, and HIV testing and diagnostic tests including colposcopy utilizing biopsy, cold-knife conization, and examination under anesthesia when necessary. PET-CT and pelvic MRI imaging studies determine the disease extent and fertility.[5]

Early-stage treatment consists of surgery, and the treatment of the locally advanced cervical cancer consists of concurrent chemo-radiotherapy (CCRT) and an external tumor boost with brachytherapy (BT). Image guided adaptive

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brachytherapy (IGABT) through MRI or CT imaging employs three-dimensional imaging which enhances the target area coverage through conformity, dose escalation, and reduction to the normal organs at risk (OARs). Main OARs of the greatest significance are the rectum and the bladder since there is a higher chance of radiation toxicity.[6] The constraints of dosage are necessary to prevent such complications as proctitis and cystitis. A 3-dimensional approach is obtained based on the 2cc volume on DVH (D2cc).[7] Dose higher than 80 Gy of rectum is known to cause rectovaginal fistula and higher than 2cc bladder volume causes 5-20% toxicity. The treatment methods such as IMRT and IGABT have facilitated compliance with these limitations.[8] IGABT and VMAT have been effective in enhancing the treatment of locally advanced cervical cancer, with the median dose of approximately 90.6 Gy to the area at risk being precisely delivered, and the dosage to the nearby organs is well controlled.[9] The multicenter study of Retro EMBRACE revealed the use of VMAT, IMRT and MRI-guided IGABT in patients with good long-term outcome. Mean dose of EBRT 46 +- 2.5 Gy, 77.4 percent underwent concurrent chemotherapy and mean total dose of IGBT-CTV was 87 ±15 Gy. The mean values of D2cc were bladder 81±22Gy, rectum 64±9Gy, sigmoid 66±10Gy, and bowel 64±9Gy (all EQD2). Cervical cancer is one of the big health issues that are experienced particularly in low- and middle-income countries where radiotherapy is a major treatment modality.[10] Such techniques as VMAT and IGABT can assist to obtain superior results as they provide functional, focused radiation with low toxicity. The correct dosage of delivered dose to the tumor and adjacent organs is an important factor in the successful treatment and reduction of complications.[11]

METHODOLOGY

This Descriptive, cross-sectional study was conducted at Department of Radiotherapy at INMOL Hospital, Lahore from 1st August 2024 to 10th January 2025. A total sample size of 50 patients was calculated with 95% confidence level, 5% margin of error, and expected response rate of 50%, ensuring adequate study power. A non-probability consecutive sampling technique was used to enroll eligible patients who fulfilled the inclusion criteria and consented to participate. Patients were eligible for inclusion if they had histologically confirmed carcinoma of the cervix and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–II. Only patients receiving external beam radiotherapy (EBRT) followed by MRI-guided brachytherapy were included in the study. Participants were required to be between 45 and 65 years of age and to have no history of contrast allergy to ensure safe administration of imaging protocols. Patients were excluded if they had a history of autoimmune disease or connective tissue disorders, severe comorbid conditions, or evidence of metastatic disease. Those who had previously received pelvic radiotherapy were also excluded. Additionally, patients who refused to provide informed consent or had contraindications to radiotherapy, such as psoriasis or xeroderma pigmentosum, were not considered eligible for participation. Approval from the ethical committee was obtained. Eligible patients who participated in the study after 2019 were identified and recruited. The baseline staging was conducted using MRI pelvis with contrast giving clear information on the extent of tumor before planning the treatment. The radiotherapy was applied as external beam radiotherapy based on CT-simulation without contrast, with regularized bladder-filling procedure and regular weekly image guidance to guarantee reliability and accuracy. VMAT to patients was administered at 45 Gy in 25 fractions, and then a boost as required by the institution. At the end of EBRT, MRI pelvis was repeated to determine tumor response. Depending on their response, patients underwent three insertions of the 7 Gy dose (of MRI-guided brachytherapy) in three locations (good responders) or four injections of the same dose (partial responders). On a case-by-case basis, the high-risk clinical target volume dose distribution, dose-volume histogram (DVH) parameters, and equivalent dose in 2 Gy fractions (EQD2) of the high-risk clinical target volume and the organs at risk, such as the bladder, rectum, and sigmoid colon, were calculated. Data were analyzed using SPSS version 20.0. Descriptive statistics were applied, with means and standard deviations calculated for quantitative variables such as age, tumor dose, and EQD2 parameters, while categorical variables such as stage and ECOG status were summarized as frequencies and percentages. Stratification by age and disease stage was performed to assess potential confounding effects. Post-stratification comparisons were carried out using independent sample t-tests for continuous variables and chi-square tests for categorical variables, with a p-value = 0.05 considered statistically significant.

RESULTS

Data were collected from 50 patients, with a mean age of 55.1 ± 5.8 years. Most patients presented with stage IIIB disease (50%), followed by stage IIIA (20%), while stage IIB and IVA accounted for 16% and 14% respectively. ECOG performance status was generally favorable, with 56% of patients having ECOG 1, 20% ECOG 0, and 24% ECOG 2. Regarding brachytherapy, 64% of patients required 3 insertions, whereas 36% required 4 insertions, reflecting differences in tumor response after external beam radiotherapy. Cumulative tumor dose delivery was consistent, with a mean tumor EQD2 of 84.9 ± 2.8 Gy, ranging from 80.1 to 89.9 Gy. Organ-at-risk doses stayed within acceptable tolerance limits: bladder EQD2 averaged 78.1 ± 4.3 Gy, rectum EQD2 averaged 67.3 ± 4.4 Gy, and sigmoid EQD2 averaged 62.5 ± 4.2 Gy. Patients receiving 3 insertions (n = 32) had a mean tumor EQD2 of 83.4 ± 2.1 Gy, whereas those receiving 4 insertions (n = 18) achieved a higher mean tumor EQD2 of 87.1 ± 1.8 Gy, with a p-value of <0.001 indicating statistical significance. Bladder EQD2 averaged

77.2 ± 4.4 Gy in the 3-insertion group and 79.7 ± 3.8 Gy in the 4-insertion group (p = 0.08). Rectum EQD2 averaged 66.4 ± 4.2 Gy in the 3-insertion group and 68.9 ± 4.5 Gy in the 4-insertion group (p = 0.09). Sigmoid EQD2 averaged 61.7 ± 4.1 Gy for 3 insertions and 63.9 ± 4.3 Gy for 4 insertions (p = 0.12). Patients with stage IIB (n = 8) received a mean tumor EQD2 of 83.6 ± 2.3 Gy, bladder EQD2 of 76.9 ± 4.2 Gy, rectum EQD2 of 66.2 ± 3.9 Gy, and sigmoid EQD2 of 61.1 ± 4.1 Gy. Stage IIIA patients (n = 10) had tumor EQD2 of 84.3 ± 2.6 Gy, bladder EQD2 of 77.5 ± 4.1 Gy, rectum EQD2 of 66.7 ± 4.5 Gy, and sigmoid EQD2 of 61.9 ± 4.0 Gy. Stage IIIB patients (n = 25) showed tumor EQD2 of 85.6 ± 2.7 Gy, bladder EQD2 of 78.9 ± 4.4 Gy, rectum EQD2 of 67.8 ± 4.3 Gy, and sigmoid EQD2 of 62.9 ± 4.3 Gy. Stage IVA patients (n = 7) had the highest doses, with tumor EQD2 of 86.2 ± 3.0 Gy, bladder EQD2 of 79.3 ± 4.0 Gy, rectum EQD2 of 68.4 ± 4.8 Gy, and sigmoid EQD2 of 63.4 ± 4.2 Gy. ECOG 0 patients (n = 10) received a mean tumor EQD2 of 84.1 ± 2.5 Gy, with 8 receiving 3 insertions and 2 receiving 4 insertions. ECOG 1 patients (n = 28) received a mean tumor EQD2 of 84.8 ± 2.9 Gy, with 20 receiving 3 insertions and 8 receiving 4 insertions. ECOG 2 patients (n = 12) received a mean tumor EQD2 of 85.6 ± 2.7 Gy, with 4 receiving 3 insertions and 8 receiving 4 insertions. The association between ECOG status and number of insertions was statistically significant (p = 0.04), reflecting the higher likelihood of requiring dose escalation in patients with poorer performance status.

Table 1. Baseline Demographic and Clinical Characteristics (N = 50)

Variable	Category	n (%) / Mean ± SD
Age (years)	—	**55.1 ± 5.8**
Stage	IIB	8 (16%)
	IIIA	10 (20%)
	IIIB	25 (50%)
	IVA	7 (14%)
ECOG Status	0	10 (20%)
	1	28 (56%)
	2	12 (24%)
IGBT Insertions	3 fractions	32 (64%)
	4 fractions	18 (36%)

Table 2. Treatment and Dosimetric Parameters

Parameter	Mean ± SD	Range
Tumor EQD2 (Gy)	**84.9 ± 2.8**	80.1 – 89.9
Bladder EQD2 (Gy)	78.1 ± 4.3	70.3 – 84.8
Rectum EQD2 (Gy)	67.3 ± 4.4	60.2 – 74.9
Sigmoid EQD2 (Gy)	62.5 ± 4.2	55.4 – 69.7

Table 3. Comparison of EQD2 by Number of IGBT Insertions

Variable	3 Insertions (n = 32) Mean ± SD	4 Insertions (n = 18) Mean ± SD	p-value
Tumor EQD2 (Gy)	83.4 ± 2.1	87.1 ± 1.8	**<0.001**
Bladder EQD2 (Gy)	77.2 ± 4.4	79.7 ± 3.8	0.08
Rectum EQD2 (Gy)	66.4 ± 4.2	68.9 ± 4.5	0.09
Sigmoid EQD2 (Gy)	61.7 ± 4.1	63.9 ± 4.3	0.12

Table 4. Stage-Wise EQD2 Distribution

Stage	Tumor EQD2 Mean ± SD	Bladder EQD2 Mean ± SD	Rectum EQD2 Mean ± SD	Sigmoid EQD2 Mean ± SD
IIB (n=8)	83.6 ± 2.3	76.9 ± 4.2	66.2 ± 3.9	61.1 ± 4.1
IIIA (n=10)	84.3 ± 2.6	77.5 ± 4.1	66.7 ± 4.5	61.9 ± 4.0
IIIB (n=25)	85.6 ± 2.7	78.9 ± 4.4	67.8 ± 4.3	62.9 ± 4.3
IVA (n=7)	86.2 ± 3.0	79.3 ± 4.0	68.4 ± 4.8	63.4 ± 4.2

Table 5. ECOG-wise Comparison of Treatment Parameters

ECOG	n	Tumor EQD2 Mean ± SD	IGBT Insertions (3/4)	p-value
0	10	84.1 ± 2.5	8 / 2	0.31
1	28	84.8 ± 2.9	20 / 8	0.28
2	12	85.6 ± 2.7	4 / 8	**0.04**

DISCUSSION

This study evaluated the cumulative radiation dose delivered to carcinoma cervix patients treated with VMAT followed by MRI-guided brachytherapy at a major oncology center in Pakistan. The results prove that the integrated treatment in the form of the combination therapy method attained the internationally recommended levels of the tumor dose and kept the organ-at-risk doses (OAR) within the reasonable tolerances of a considerable majority of patients. These findings underscore the usefulness of its contemporary radiotherapy methods in practice in the real world based on the purpose of modern radiotherapy, especially in limited resource areas where the lack of variation in the treatment, high patient load, and late-stage appearance is likely to make the delivery of the optimal dose a complicated affair. The average accumulated dose in the high-risk target volume up to 85 Gy was quite in line with GEC-ESTRO and ABS guidelines, which propose a minimum tumor dose of 80 Gy to ensure maximum local control.[12] Almost 80% of the patients had gone above the criterion mark of 84 Gy that has been linked to increased tumor response and reduced chances of local recurrence. The dose escalation in patients who are given four brachytherapy fractions is in line with international practice in that those patients with a suboptimal response of tumor may need extra fractions to counteract the remnant parametrial disease or the high-risk volumes of CTV. Notably, this escalation did not culminate into overdose of OAR, which supports the importance of MRI-based planning in the safe customization of fractions.[13]

The quality of the treatment delivery is also highlighted in the OAR dose distribution of this study. The average values of Bladder EQD2 were 78 Gy, and virtually no patient received a higher dose of 80-90 Gy which is the accepted

tolerance. Rectal and sigmoid doses were also well managed with a mean EQD2 of 67 Gy and 62 Gy respectively and a very low number of patients having an EQD2 of above 75 Gy- the level of EQD2 that is linked to more late gastrointestinal toxicity.[14] These results suggest that there is a standard aiding in the compliance to the accuracy of contours, the most adequate location of applicators and the correct utilization of volumetric optimization in the process of brachytherapy planning. They also point out the advantages of MRI guidance that can enable a better outline of the target and to define the dwell positions that would be more precise and would cause less exposure to the pelvic structures.[15] This distribution of stages in the Pakistani cohort of Stage III disease would represent the typical trend of late diagnosis in South Asians, which is usually ascribed to low levels of screening, socioeconomic, and cultural delaying health-seeking behavior. Regardless of this burden of advanced disease experience, cumulative doses met in this study were similar to that achieved in high-volume cancer centers in Europe and East Asia.[16] This confirms the use of VMAT with MRI-guided brachytherapy in the provision of high-quality radical therapy in even those population with larger tumors with larger parametrial involvement.

There is significant correlation between ECOG performance status and the risk of having to take up extra units of brachytherapy. Patients with ECOG 2 were more inclined to get four insertions and maybe there is some correlation between the poorer general health and slower tumor regression, or it may have been related to the tumor biology which responds differently to EBRT.[17] Nevertheless, OAR doses were employed even higher, but the effect was acceptable, which implied that a personalized planning ensured safety without affecting tumor coverage. The benefit of VMAT as the EBRT method of interest in cervical cancer is also highlighted by these findings. VMAT offers excellent conformity, shorter treatment time and dose distribution that is highly reproducible especially when minimization of bowel and bladder doses is required in treatment of the pelvis. When combined with MRI-guided brachytherapy, it constitutes a synergistic therapy, which increases the precision and therapeutic ratio.[18] One of the strong points of the given study is that it is a real-life clinical dosimetry study in Pakistan where the literature on much of the modern image-guided brachytherapy is scanty.[19,20]

Limitations: This research has a number of limitations that should be considered when analyzing the results. To begin with, it was carried out in only one tertiary care institution and the sample size of the study is very small (50 patients); thus, its results might not be applicable to the general population in Pakistan. Second, the study failed to correlate dosimetric adequacy with clinical outcomes, since cumulative values of EQD2 in the tumor and organs at risk had been well analyzed, but there were no clinical endpoints (e.g., local control rate, late toxicity, disease-free survival, and/or overall survival) to correlate the two. Thirdly, in all cases, MRI-guided brachytherapy was employed, which is a higher imaging level that is not evenly distributed across the regional centers; thus, dose distributions could vary in environments with CT-based or 2D brachytherapy planning. Fourth, the analysis was based on retrospective data retrieval that can induce documentation bias particularly in the treatment planning parameters. Also differences in applicator type, tumor regression patterns and individual anatomical differences may have an impact on dose distribution but were not stratified in this analysis. Lastly, there is no inter-observer variability assessment of contouring and planning, so there is no possibility of comparing reproducibility of clinicians. These limitations imply that bigger, multicenter projects that include clinical outcome measures and standardized planning protocols are necessary to verify these results and generalize them.

CONCLUSION

It is concluded that the combination of VMAT-based external beam radiotherapy and MRI-guided brachytherapy provides an effective and safe treatment approach for patients with carcinoma of the cervix. The cumulative EQD2 delivered to the high-risk target volume met internationally recommended dose thresholds in nearly all patients, ensuring adequate tumor coverage even in a population dominated by advanced-stage disease. Organs-at-risk, including the bladder, rectum, and sigmoid, consistently remained within acceptable tolerance limits, reflecting high-quality planning, accurate applicator placement, and the benefits of MRI-based optimization.

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Authors Contribution:
Sana Naeem: Conception, data collection, manuscript drafting
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Ahmad Farooq: Methodology development, data validation, statistical support
Tahir Sheikh: Data acquisition, literature search, editing
Rub Nawaz Maken: Project administration, resource provision, final approval

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Original Article **Open Access**

A Randomized Control Trial Comparing Effectiveness of Cross K-Wire and Lateral K-Wire Fixation Techniques in Reducing Gartland Type 3 Supracondylar Fractures of Children

Muhammad Junaid Khan, Shahid Mahmood, Muhammad Naeem Malik, Irfan Ali Shujah, Zahid Iqbal, Muhammad Arslan Ghori

Abstract

Objective: To compare the effectiveness of cross K-wire fixation versus lateral entry K-wire fixation in maintaining postoperative reduction of Gartland type III supracondylar humerus fractures in children.

Study Design and Settings: A randomized control trial was conducted at Orthopaedics Department, Bahawal Victoria Hospital, Bahawalpur, from 25th June 2025 to 10th December 2025.

Methodology: Ninety children aged 2–13 years with closed Gartland type III supracondylar fractures were randomly allocated into two groups: cross K-wire fixation (n = 45) and lateral entry K-wire fixation (n = 45). All patients underwent closed reduction and percutaneous pinning under general anesthesia. Standardized 1.5 mm K-wires were used in both groups.

Results: Loss of reduction occurred in 20% of patients in the cross-pin group compared to 71.1% in the lateral entry group ($p < 0.01$). Baumann's angle remained more stable in the cross-pin group ($p = 0.01$), and anterior humeral line integrity was preserved 73.3% patients of Cross K-Wire group as compared to 55.5% of Lateral Entry K-Wire group. No permanent ulnar nerve injuries were reported in either group, although transient postoperative concerns were slightly higher in the cross-pin group.

Conclusion: Cross K-wire fixation was more effective than lateral entry K-wire fixation in maintaining postoperative reduction in Gartland type III supracondylar fractures in children.

Keywords: Humeral fractures, Postoperative complications, Treatment outcomes

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INTRODUCTION

Supracondylar fractures just above elbow joints are one of the most prevalent injuries of distal humerus, affecting substantial proportion of all elbow fractures in children. Occurrence of these injuries have been increased dramatically during last decades accounting for 3 to 15% of all fracture types particularly among children aged between 5 and 7 years.[1] These injuries underscore immediate requirement of surgical intervention among affected population.

A consistent pattern of these injuries has been observed across different population around the globe. A Brazilian study of 197 children, having mean age 5.4 years, reported humeral supracondylar fractures in 56.9% male children with left sided fracture in 51.8%.[2] Similarly, A south African study of 266 children having mean age 6.3 years, documented supracondylar fractures in 71.8% male children with 64.3% injuries on left side. Extension type humeral supracondylar fractures were predominant ones.[3] Moreover, in New Zealand, a 10-year retrospective data-based research of 1563 pediatric patients documented 73.7% per 100,000 incident rate with substantial number of 5 to 9 years old children.[4]

Distal humerus elbow fractures account 85% and among these 55-75% comprises of supracondylar injuries, making 3.5% of all pediatric fractures [4]. Supracondylar fractures of the humerus cause high rates of neurovascular injury due to falls on non-dominant limbs, often resulting from falls during play or stairs.[5] Achieving and maintaining reduction are one of the major challenges faced while managing supracondylar fracture as they usually present to emergency department with variations in soft tissue swelling.[6]

Rates of nerve injury and vascular injury on presentation range from 5% to 19% and 5% to 17%, respectively.[7] These injuries can be difficult to treat due to immediate complications like compartment syndrome, neurovascular damage, and late complications like Volkman's ischemic contracture and malunion. Supracondylar humerus fractures are most often classified according to Gartland and his colleagues, who classified the fracture using the degree of displacement. Type I fractures are non-displaced, Type II fractures are displaced, but have a preserved posterior cortex, and Type III fractures are completely displaced without any contact of the posterior cortex. Type III fractures, especially, are more difficult and may require surgery because of their inherent instability and potential for neurovascular compromise.[8] Traditionally these fractures have been treated with either closed reduction and casting or open reduction with the use of fixation. Closed reduction and percutaneous pinning with Kirschner wires (K-wires) have become the standard of care, however, because of the evolution of pediatric orthopedic practice and the increased emphasis on minimally invasive techniques for displaced fractures.[9] In orthopedics, especially in the paediatric field, minimally invasive surgery is increasingly being used, as it is associated with quick recovery times, minimal scarring and better cosmesis, which are especially significant in young people. Lateral pinning and crossed pinning are two commonly employed fixation techniques for pediatric supracondylar humerus injuries. The lateral K wire configuration is superior over crossed K wire configuration in terms of avoiding iatrogenic ulnar nerve injury but comparatively less stable biochemically.[10] Balakumar B, et al. conducted a study including 29 children with lateral entry pins. Among these 10 (34.5%) revealed postoperative loss of reduction. Configurations with at least one medial pin were (c) crossed pins in 28 cases and (d) two lateral pins and one medial pin in 20 cases. In the groups which included at least one medial pin, 4 (8.3%) out of 48 cases lost reduction.[11] Another previous study conducted by Abubeih H, at final follow-up, there were no statistically significant differences (P>0.05) between group A and group B with respect to the average Baumann's angle (P=0.081), change in the Baumann angle (P=0.121), range of elbow motion (P=0.795), Flynn's grade (P=0.541), or Skaggs criteria (P=0.548).[12]

METHODOLOGY

This randomized control trial was carried out in the Orthopedics Department of Bahawal Victoria Hospital, Bahawalpur. The study was registered at ClinicalTrials.gov under the identifier NCT07266038. The study duration extended from 25 June 2025 to 10 December 2025, following ethical approval and synopsis clearance. Rules of Declaration of Helsinki and CONSORT guidelines were followed while conducting intended research. A total 90 patients (45 each group) were included in this study. Sample size was calculated using OpenEpi software at a 5% significance level and 95% power. The calculation was based on previously published findings reporting postoperative loss of reduction of 34.5% in lateral-entry pin configurations compared with 8.3% in configurations involving at least one medial pin. Patient enrollment was by a non-probability consecutive sampling technique. In order to achieve target sample, all patients visiting emergency department who met the eligibility criteria were approached. Patients of both genders having age less than 13 years with closed Gartland type III supracondylar humerus fractures no older than 7 days were included in this research. Those with open fractures, neurovascular injuries, medial column comminution, fractures older than 7 days, ipsilateral fractures of the radius, ulna or humeral shaft, and/or pathological fractures due to abnormal bone density, previous surgery on same elbow and allergic to metal implants were excluded. Parents/legal guardians signed informed consent before enrolling the child. Informed consent contained information about randomization process, both surgical procedures, associated risk factors (infection or nerve injury) and follow-up details. Those who met the criteria were placed under and initially treated with splinting, elevation, and appropriate analgesia. Ethical approval was obtained and eligible patients were put under and initially treated as follows: splintage, elevation and appropriate analgesia. Basic demographic and clinical parameters, including age, sex, side involved, and neurovascular assessment (radial pulse and motor function of median, radial, and ulnar nerves) were noted on a proforma. Patients were randomly allocated to either study group by lottery method. A research assistant having no involvement in clinical trial performed random sequence via computer based random number table. Allocation concealment was ensured by a closed opaque envelop which was opened by surgeon revealing group allocation. Blinding of the surgeon was not possible in view of the type of surgeries performed.

All surgery was performed under general anesthesia, with fluoroscopic guidance for reduction and pin placement by experienced orthopedic surgeons. All patients had standardized 1.5 mm K-wires and uniform pin-spread distance. A group of 45 patients received cross-K-wire fixation (Group A), and another group of 45 patients received lateral-entry K-wire fixation (Group B). Postoperative care consisted of pain management, instructions for immobilization and advice on the hygiene of pin sites. Patients were discharged on the 2nd day after operation.

Follow up visits were performed at 1st, 3rd and 6th postoperative weeks to evaluate the maintenance of reduction using Baumann angle and anterior humeral line. SPSS version 20 or later was used for data analysis. The quantitative data such as age, Baumann's angle, pin spread distance and ratio of pin spread were analyzed by the mean and standard deviation. Qualitative data (gender, side of fracture, integrity of anterior humeral line) were coded and the frequencies and percentages calculated. Loss of reduction was defined as a substantial change in the angle of Baumann and/or misalignment of the anterior humeral line. Age, gender, side, Baumann's angle, pin spread distance and pin spread ratio were stratified as effect modifiers. Paired-samples t-test was used for quantitative variables and chi-square test was used for categorical variables in the post-stratification analyses. The p-value < 0.05 was regarded as statistically significant.

RESULTS

Data were collected from 90 patients, with a mean age of 7.52 ± 3.44 years. Females were slightly more represented (52.2%) than males (47.8%). The distribution of fracture laterality was even, as 45 patients (50%) presented with right-sided injuries and 45 (50%) with left-sided injuries. Most patients (74.4%) had intact neurovascular status at presentation, while a smaller proportion demonstrated median nerve deficits (8.9%), radial nerve deficits (7.8%), or ulnar nerve deficits (8.9%). Preoperative measurements averaged 72.94 ± 1 °; immediate postoperative measurements were 73.5 ± 4.3 °, and a gradual decline to 72.4 ± 4.8 ° by week 6 was observed radiologically. After surgery, the alignment of the anterior humeral line significantly improved, rising from 42.2% preoperatively to 72.2% immediately postoperatively and remaining aligned in 64.4% by week 6. Postoperative outcomes showed that reduction was maintained in 49 patients (54.4%), whereas 41 patients (45.6%) experienced postoperative loss of reduction. Complications were not uncommon, with swelling reported in 23.3% of children, pin tract infections in 21.1%, postoperative stiffness in 20%, and cubitus varus in 18.9%. Alignment of the anterior humeral line immediately after surgery was higher in the cross-pin group (80.0% vs. 64.4%), and the trend persisted at week 6 (73.3% vs. 55.6%), although these differences were not statistically significant. The lateral-entry group experienced significantly more loss of reduction (71.1%) than the cross-pin group (20.0%), which is a significant difference. Swelling, infections of the pin tract, stiffness, and cubitus varus all occurred at similar rates in both groups. However, the lateral-entry group had a significantly higher overall complication rate (66.7% vs. 37.8%).

Table 1. Demographic and Clinical Characteristics of Patients (n = 90)

Variable	Category / Statistic	Value (n = 90)
Age (years)	Mean ± SD	7.52 ± 3.44
Gender	Male	43 (47.8%)
	Female	47 (52.2%)
Side Involved	Right	45 (50.0%)
	Left	45 (50.0%)
Fracture Age (days)	Mean ± SD	3.9 ± 1.8
Randomization Group	Cross K-wire (Group A)	45 (50.0%)
	Lateral-entry K-wire (Group B)	45 (50.0%)
Neurovascular Status at Presentation	Overall intact	67 (74.4%)
	Median nerve deficit	8 (8.9%)
	Radial nerve deficit	7 (7.8%)
	Ulnar nerve deficit	8 (8.9%)

Table 2. Radiological Characteristics of Patients (n = 90)

Variable	Statistic / Category	Value (n = 90)
Baumann's Angle	Preoperative (mean ± SD)	72.9 ± 4.1
	Immediate postoperative	73.5 ± 4.3
	Week 1	73.1 ± 4.5
	Week 3	72.8 ± 4.6
	Week 6	72.4 ± 4.8
Anterior Humeral Line Alignment	Pre-op aligned	38 (42.2%)
	Immediate post-op aligned	65 (72.2%)
	Week 6 aligned	58 (64.4%)
Pin Spread Distance (mm)	Mean ± SD	12.7 ± 3.4
Pin Spread Ratio	Mean ± SD	0.47 ± 0.11

Table 3. Postoperative Outcomes and Complications (n = 90)

Variable	Category / Statistic	Value (n = 90)
Maintenance of Reduction	Maintained	49 (54.4%)
	Loss of reduction	41 (45.6%)
Postoperative Complications	Swelling	21 (23.3%)
	Pin tract infection	19 (21.1%)
	Stiffness	18 (20.0%)
	Cubitus varus	17 (18.9%)
Neurovascular Complications	Any postoperative nerve injury	0 (0%)
Overall Complication Rate	Any complication	47 (52.2%)
	No complication	43 (47.8%)

DISCUSSION

Main objective of this research as to compare the efficacy of two different fixation techniques in the maintenance of reduction in children with Gartland type III supracondylar humerus fractures, the cross K-wire fixation and the lateral entry K-wire fixation. The result clearly demonstrated that postoperative alignment was significantly better with cross wire fixation (20.0%) than with lateral entry fixation (71.1%) with a significantly lower loss of reduction and rate of overall

Table 4. Comparison of Radiological Outcomes between Cross K-Wire and Lateral Entry K-Wire Groups (n = 90)

Radiological Parameter	Group A: Cross K-wire (n = 45)	Group B: Lateral Entry K-wire (n = 45)	p-value
Baumann's Angle (°)			
Immediate postoperative (mean ± SD)	73.8 ± 4.4	73.1 ± 4.2	0.42
Week 1	73.3 ± 4.6	72.9 ± 4.5	0.58
Week 3	72.9 ± 4.7	72.6 ± 4.6	0.70
Week 6	72.6 ± 4.9	72.2 ± 4.7	0.64
Anterior Humeral Line Alignment			
Immediate postoperative aligned, n (%)	36 (80.0%)	29 (64.4%)	0.11
Week 6 aligned, n (%)	33 (73.3%)	25 (55.6%)	0.07
Pin Spread Distance (mm)			
Mean ± SD	–	12.7 ± 3.4*	–
Pin Spread Ratio	–	0.47 ± 0.11*	–

*Pin spread parameters apply only to lateral-entry group

Table 5. Comparison of Postoperative Complications between Groups (n = 90)

Complication	Group A: Cross K-wire (n = 45)	Group B: Lateral Entry K-wire (n = 45)	p-value
Loss of Reduction, n (%)	9 (20.0%)	32 (71.1%)	<0.001
Swelling, n (%)	9 (20.0%)	12 (26.7%)	0.45
Pin Tract Infection, n (%)	7 (15.6%)	12 (26.7%)	0.19
Postoperative Stiffness, n (%)	10 (22.2%)	8 (17.8%)	0.61
Cubitus Varus, n (%)	6 (13.3%)	11 (24.4%)	0.18
Any Complication, n (%)	17 (37.8%)	30 (66.7%)	0.004

complications. The findings of the present study can be contextualized within the broader literature through comparison with published meta-analyses. A systematic review and meta-analysis by researchers who analyzed 13 studies including 1,158 patients (seven randomized controlled trials and six prospective comparative cohorts) reported that loss of reduction occurred in 27 (11.6%) of 232 patients treated with crossed K-wires and in 35 (12.4%) of 282 patients treated with lateral entry K-wires. According to Flynn criteria, there was no difference in functional outcome between the two K-wire configurations (relative risk 1.07). Regarding nerve complications, 20 (4.1%) of 493 patients in the crossed group were diagnosed with iatrogenic ulnar nerve injury, compared with only 2 (0.3%) of 666 patients in the lateral entry group. The overall incidence of persistent ulnar nerve-related complaints was 3.5 per 1,000. The authors concluded that crossed and lateral entry pin fixation result in similar construct stability and functional outcome, and that if the surgeon wishes to avoid all potential risk of iatrogenic ulnar nerve injury, the lateral K-wire approach is safest.[13] The results affirm the long-held belief within the pediatric orthopedic literature that adding a medial pin provides construct stability and biomechanical benefits, especially in unstable fracture patterns. Similar findings have been previously reported with the use of lateral pinning configuration, and the present results are in good agreement with these findings, suggesting that lateral entry fixation alone might not be sufficient in high-grade fractures. Cross pinning was also superior with respect to radiological results.[14] While both groups had reasonable Baumann's angle values at follow-up, the lateral entry group had a greater drop over time indicating an ongoing, albeit small, loss of alignment over time. A higher percentage of patients with an anterior humeral line aligned with the K-wire also had good alignment at 6 weeks, which was also favourable for cross K-wire fixation. These minor differences in the radiographs are of clinical significance as they can lead to deformity in childhood, particularly cubitus varus, which may be lifelong.[15]

Although there are concerns about potential iatrogenic ulnar nerve damage with the medial pin, the study found no such issues, possibly due to the use of safe surgical techniques and/or proper intraoperative imaging. The rates of postoperative complications in the lateral entry group were greater than in the other groups but were not significantly different, and included pin tract infection, swelling, stiffness, and cubitus varus.[16] Nevertheless, this trend implies an indirect biomechanical inferiority of two lateral pins which could be a possible source of malalignment-related problems, thus making careful selection of patients for this technique very important. Results are compatible with previous reports

that lateral entry configurations are linked to increased instability, especially if the fracture obliquity or comminution decreases lateral buttress support. In the present study, cross K-wire fixation has proven biomechanically superior against rotational, varus and valgus stresses, which is the reason for its superiority.[16-18] In cases comparable to those in Pakistan, where follow-up compliance and postoperative care can be inconsistent, a more stable setting, such as cross pinning, could reduce the need for subsequent interventions and the risk of long-term deformity.[19,20]

Limitations: This research has several limitations that are needed to be acknowledged for future studies. This is a single center study conducted only at Bahawal Victoria Hospital, Bahawalpur, which might limit the generalizability and reliability of the results for different population having different demographic or clinical parameters and fracture types. Non probability consecutive sampling technique was employed instead of random sampling, leading to selection biasness. Lack of blinding was another limitation of this study as it was not feasible to blind surgeons to allocation technique. Moreover, follow-up duration was limited to just 6 weeks which was sufficient for early complications but inadequate for long term postoperative complications, functional recovery and cosmetic outcomes. In conclusion, multi central studies employing random sampling with follow-ups for at least 12 months are recommended.

CONCLUSION

The study concludes that both the cross K-wire is found to be more effective as compared to lateral entry K-wire fixation techniques for treating Gartland type III supracondylar fractures in children, but there are significant differences in efficacy. The results showed that cross pinning had better mechanical stability as it maintained the reduction more effectively, while postoperative displacement was significantly less. Although lateral entry pinning did not increase the risk of iatrogenic ulnar nerve injury, it did increase the risk of loss of reduction when adequate pin spread and technique were used.

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Authors Contribution:
Muhammad Junaid Khan: Data collection, literature review, drafting of manuscript
Shahid Mahmood: Study supervision, methodology design, critical revision
Muhammad Naeem Malik: Surgical input, patient management data, manuscript review
Irfan Ali Shujah: Data interpretation, results validation, editing of manuscript
Zahid Iqbal: Statistical analysis support, quality assurance, proofreading
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Original Article

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Clinical Utility of Pleural Fluid Protein in Differentiating Tuberculous and Malignant Pleural Effusion in a Resource-Limited Setting

Bushra Arif, Sada Saeed, Hamid Nisar Khan, Sabeen Sajjad, Muhammad Mamoon, Fazal Mustan

Abstract

Objective: To evaluate the diagnostic performance of pleural fluid protein in differentiating tuberculous pleural effusion (TBPE) from malignant pleural effusion (MPE).

Study Design and Setting: This cross-sectional analytical study was conducted at the Department of Pulmonology, Ayub Teaching Hospital, Abbottabad, Pakistan, from October 2020 to March 2021.

Methodology: A total of 109 patients aged 20–75 years with pleural effusion were enrolled through consecutive non-probability sampling. Patients with end-stage renal, hepatic, or cardiac failure, terminal illness, or psychiatric disorders were excluded. Pleural biopsy with histopathological examination was used as the reference standard for diagnosing TBPE or MPE. Pleural fluid total protein was measured and categorized as <5 g/dL or =5 g/dL. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated.

Results: The mean age was 45.65 ± 15.34 years, with a near-equal gender distribution. Histopathology confirmed TBPE in 61 (56.0%) patients and MPE in 48 (44.0%). Pleural fluid protein levels =5 g/dL were observed in 46 (42.2%) patients, while 63 (57.8%) had levels <5 g/dL. Using a cutoff value of =5 g/dL, pleural fluid protein demonstrated a sensitivity of 81.97%, specificity of 72.92%, PPV of 79.37%, NPV of 76.09%, and diagnostic accuracy of 77.98% for identifying TBPE.

Conclusion: Pleural fluid protein estimation shows acceptable diagnostic performance in differentiating TBPE from MPE and may serve as a useful adjunct in resource-limited settings. Although histopathology remains the gold standard, pleural fluid protein measurement can support earlier clinical decision-making when interpreted with clinical and radiological findings.

Keywords: Diagnostic accuracy; Malignant pleural effusion; Pleural effusion; Pleural fluid protein

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INTRODUCTION

Pleural effusion is a common problem that doctors who treat breathing issues and other doctors see all the time everywhere. It happens a lot with people who have lung problems, heart problems, infections, inflammation and cancer. Pleural effusion uses up a lot of resources that hospitals and doctors have. People who have effusion might feel like they cannot breathe very well they might have chest pain and they might have a cough. They usually cannot do physical activity, which makes it really hard for them to do things they need to do every day and be comfortable[1].

Since pleural effusion can be caused by a lot of things it is very important for doctors to figure out what is causing the pleural effusion so they can treat it correctly and help people who have it feel better. When doctors check out an effusion the first thing they do is try to find out if the fluid, in the pleural effusion is transudative or exudative.[2]

Pleural fluid problems can be caused by diseases that affect how much fluid forms and gets absorbed. This includes things like heart failure, liver cirrhosis, nephrotic syndrome or hypoalbuminemia. In these cases the pleura itself is not the problem. We just need to treat the issue that is causing the trouble.[3] On the hand sometimes the pleura has local

problems. This can be due to vascular permeability, poor lymphatic drainage, inflammation or a disease that directly affects the pleura. Figuring out what caused these problems usually needs tests.

We can often tell when someone has an effusion just by looking at some clinical findings and lab tests. But working out what is behind an effusion is much harder. It is very important to make sure it is not tuberculosis or metastatic cancer. These are two of the causes of exudative effusions, in many parts of the world. We need to rule out effusions caused by tuberculosis and metastatic cancer because these diseases are big causes of exudative effusions.[3] Disease processes can cause pleural effusion in many parts of the body. This happens because of infections, cancer and problems with the system and also because of blockages in the lymphatic system blood clots in the lungs and other kinds of inflammation. Figuring out what caused the exudative pleural effusion is really tough because there are many things that can cause it. Doctors need to use their experience and knowledge. They also need to use tests like imaging tests and they need to look at the fluid from the pleura and sometimes they even need to do biopsies.[4] With new technology it is still hard to find the exact cause of the exudative pleural effusion especially in places that do not have a lot of resources.[4] In Pakistan and lots of developing countries exudative pleural effusion is a big problem for healthcare systems. A study from a hospital in Peshawar, Pakistan found that about 9 percent of patients each year had exudative pleural effusion. This shows how important it is to create affordable diagnostic methods, for regular use so doctors can diagnose exudative pleural effusion easily.[5]

Tuberculosis and cancer are the reasons people get fluid in the lungs in Pakistan just like in other parts of the world. Tuberculosis is the cause of this problem in countries where it is common. This shows that Tuberculosis is an issue for public health. When parts of the bacteria that cause Tuberculosis get into the space around the lungs it causes a reaction that leads to building up. This reaction is slow to happen. On the hand cancer is often the cause of fluid in the lungs when it is related to cancer. This type of buildup can come from cancer that started in the lungs or from cancer that spread to the lungs from other parts of the body. It can also come from types of cancer like lymphomas. Now even though Tuberculosis is the common cause of fluid in the lungs overall in places where Tuberculosis is not common and in people who are over sixty years old cancer is more likely to be the cause. Tuberculosis is still a problem but cancer is a bigger issue, in these cases.[6]

It is really important to tell the difference between malignant pleural effusions because the way we treat them and the results are very different. If we can find out someone has tuberculosis on we can start treating them right away which helps to stop the disease from spreading. When we find out someone has pleural effusion doctors can take a close look at the cancer and come up with a plan to treat it.[7] To figure out if someone has tuberculosis we usually look for Mycobacterium tuberculosis in the fluid or tissue around the lungs. However this can be very hard to do in a doctors office. The problem is that pleural tuberculosis does not have a lot of bacteria in the fluid so we call it paucibacillary. This makes it tough for tests to find the bacteria. They often do not work well. In fact these tests only work 30% of the time when we look at the fluid and about 50% of the time when we use tissue samples. This is a problem because the old way of testing, which is called a culture can take up to 60 days to get the results. This means that people have to wait a time to find out what is wrong, with them before they can start treatment.[7,8]

Over the years several tests for diagnosing pleural effusion have become really important. These include ADA, interferon-ã assays, lysozyme measurements, PCR-based methods and antibody tests.[9] Also tuberculous pleural effusions usually show several lymphocytes which is also helpful. Although these tests have made diagnoses more accurate many low-resource areas cannot access them. The problem is these tests need special lab equipment, expert technicians and financial constraints. Closed pleural biopsy to diagnose tuberculous pleural effusion and lung cancer is efficient. However biopsies are a very invasive in nature, they might not work for everyone, leading the doctors to start with tests for tuberculous pleural effusion.[10] Usually tests for protein and LDH levels are checked in the fluid. This helps to see wether fluid buildup is transudative or exudative which can indicate problems like tuberculosis or lung cancer.[11,12] In areas where doctors do not have access to tests, it is really important to find chemical markers. These markers help doctors make diagnoses while they wait for the final test results. For example one common test is to check the protein levels in the fluid. This study is about how useful those protein levelsre at telling the difference, between tuberculous and malignant pleural effusions in a large hospital. The goal of the research is to support decisions in places where advanced tools are not available.

METHODOLOGY

This cross-sectional analytical study was conducted in the Department of Pulmonology, Ayub Teaching Hospital, Abbottabad, which is acknowledged as a tertiary teaching institution. The time span covered in the given data is from October 2020 to March 2021. Patients who presented to the Pulmonology unit with pleural effusions and were sourced from the outpatient or emergency department. The departments and private practice clinics. A detailed historical and clinical examination was done. Patients with exudative pleural effusion underwent an Abrams needle biopsy, after obtaining written, informed consent. The biopsy material obtained was submitted for histopathological examination. The result of the biopsy was recorded and put on the structural proforma developed for the study. To ensure that there were

no confounding factors, the following steps were done: (a) There was one standardized laboratory used for the pleural fluid analyses, and the pleural tissue analyses were done by one histopathologist. (b) The pleural biopsy procedure in the patients was done by the researcher, using one standardized Abrams needle. Common tubes and bottles, with commonly used lab chemicals, were used. Patients who fit the inclusion criteria were recruited for this trial after they had given their consent. Baseline clinical details such as age, gender, and pleural fluid protein concentration were collected and documented with the help of a proforma. In an attempt to determine the significant difference in pleural fluid concentrations between cases of tuberculous and malignant pleural effusion, three groups were developed: Category 'A' with pleural fluid protein concentrations measuring from 3-4g/dl, Category 'B' with concentrations measuring from 4-5g/dl, and Category 'C' with concentrations above 5g/dl. A total of 109 patients with eligible characteristics were obtained through sequential non-probability sampling. The study was approved by the Institutional Ethics Committee of Ayub Teaching Hospital, Abbottabad, Pakistan (Approval No. 17-19 Dated 11-08-2020).

After approval from Institutional Ethics Committee the study was done in accordance with Declaration of Helsinki. We informed each participant about the study, benefits, and risks. After getting written consent, people could join the study. It was made sure that participants' information would remain confidential and they could drop out anytime without impacting their medical care. Demographics like age, gender, were collected. The lead researcher recorded everyone's history when they became ill, their current issues, and their exam results. Plus, we screened the participants for signs of tuberculosis or malignant pleural effusion and took note of any additional health complications they faced.

Thoracentesis, which is the process of removing fluid from the chest, was carried out carefully by the medical team in a sterile environment and stored. In the lab, they observed the fluid's appearance, color, and clarity. Next up, they performed tests to count the various types of white blood cells and ran some biochemistry and protein tests with standard procedures. Tissue samples were stored in a preserving solution called 10% buffered formalin and then sent off to the lab. There, expert pathologists checked the tissue for signs of tuberculosis, cancer, or other diseases. Using their expertise, the pathologists figured out the diagnosis and sorted the patients into the tuberculous pleural effusion group or the malignant pleural effusion group. The software used for the analysis of the results was SPSS version 24. The continuous variables such as age were presented using mean and standard deviation, while the categorical variables such as gender, the levels of proteins in the pleural fluid, and the histological diagnosis were presented using frequency and percentage. A 2x2 contingency table was formed in order to calculate the value of the sensitivity and specificity of the levels of proteins in the pleural fluid for the histological outcomes. The results will be analyzed in the context of the clinical utility of the measurement of proteins in the pleural fluid as a supplementary diagnostic method for the differentiation of tuberculous and malignant effusions.

RESULTS

In all, 109 subjects were involved. Table 1 shows the demographic information of interest. The mean age was 45.65 years, with a standard deviation of 15.34 years. There was thus a good representation across virtually all age spectrums. There was also near parity in the gender distribution, with 54 males constituting 49.5% and 55 females making up 50.5%. This indicates that pleural effusion occurred with relatively equal frequency in both sexes. Histopathological diagnosis revealed that 61 patients (56%) had TBPE and 48 patients (44%) had MPE, which are summarized in Table 2. The protein level in the pleural fluid was varied among the subjects. 57.8% of the patients had less than 5 g/dL, while 42.2% had 5 g/dL or higher. Table 2 illustrates the variations in protein concentration that coincide with the individual's aging. The highest levels of protein, =5 g/dL, were more incident in individuals between 20 to 40 years of age at 21 cases, while older age brackets were inclined towards a low protein level. The trend exhibited here shows that the pleural protein concentration also oscillates with age; however this variation itself is incapable of being an independent predictor sans histological correlation.

Table 3 presents a higher incidence of TBPE in young patients, ie, between ages 20 and 40 years, with a total of 30 cases recorded. Patients above 60 years showed a higher tendency to develop MPE. Table 3 shows a marginal rise in the incidence of malignant effusions in men, with a total of 28 cases, whereas a higher incidence of tuberculous effusions was observed in women with a total of 35 cases. Table 4 illustrates the diagnostic validity criteria for protein concentration in pleural fluid, taken above 5 g/dL. The trial showed a sensitivity of 81.97%, which indicates its effectiveness in diagnosing TBPE, and specificity of 72.92%, which indicates its ability to exclude malignancy. The positive predictive value was fixed at 79.37%, while the negative predictive value was determined to be 76.09%. The overall value for diagnosis was found to be 77.98%. The following Table 5 shows the association between the protein levels and histological indexes. Of the 63 patients having protein levels of 5g/dL and above, 50 were found to be suffering from tuberculous pleural effusion and 13 from malignant pleural effusion. In contrast, 35 out of 46 patients with protein levels below 5g/dL were found suffering from malignant pleural effusion, thereby revealing a stronger link between reduced levels of proteins and malignancy.

Table 1. Baseline Characteristics of the Study Population

Variable	Mean ± SD
Age (years)	45.65 ± 15.34
Gender	**n (%)**
Male	54 (49.5%)
Female	55 (50.5%)

Summary of demographic characteristics including age and gender distribution among patients with pleural effusion

Table 2. Histopathological Diagnosis and Distribution of Pleural Fluid Protein Levels

Diagnosis	Frequency (n)	Percentage (%)
Tuberculous Pleural Effusion	61	56
Malignant Pleural Effusion	48	44
Protein Level (g/dL)		
< 5 g/dL	63	57.8
= 5 g/dL	46	42.2
Age Group (years)	**<5 g/dL (n)**	**=5 g/dL (n)**
20–40	23	21
41–60	24	16
>60	16	9

Frequency and percentage of biopsy-confirmed tuberculous and malignant pleural effusions, and distribution of pleural fluid protein levels across age groups

Table 3. Age and Gender Distribution According to Histopathological Diagnosis

Age Group (years)	TBPE (n)	MPE (n)
20–40	30	14
41–60	21	19
>60	10	15
Gender		
Male	26	28
Female	35	20

Distribution of TBPE and MPE across age groups and gender

Table 4. Diagnostic Validity of Pleural Fluid Protein Level (Cutoff =5 g/dL)

Parameter	Value (%)
Sensitivity	81.97
Specificity	72.92
Positive Predictive Value (PPV)	79.37
Negative Predictive Value (NPV)	76.09
Overall Accuracy	77.98

Sensitivity, specificity, predictive values, and overall accuracy of pleural fluid protein for distinguishing TBPE from MPE

Table 5. Cross-Tabulation of Pleural Fluid Protein Level vs. Histopathology

Protein Level	TBPE (n)	MPE (n)	Total
=5 g/dL	50	13	63
<5 g/dL	11	35	46
Total	61	48	109

Distribution of TBPE and MPE across protein level categories

DISCUSSION

Pleural effusion is affecting people globally. Knowing whether it's caused by tuberculosis or cancer is crucial, especially in regions where both are major concerns. Quick diagnosis is essential since each illness needs a specific treatment. Our study found that 56% of patients had pleural effusion from tuberculosis, while 44% had the cancerous kind. This is what other studies have shown in developing countries, where TB remains a top cause of pleural effusion due to the widespread Mycobacterium tuberculosis infection. The high rate of TBPE in this study shows how much tuberculosis still affects low- and middle-income countries. This really makes you think about how important it's to have easy and cheap ways to diagnose tuberculosis early on so people can start treatment right away. The study found that patients with pleural effusion have a lot more protein in their pleural fluid compared to those with malignant pleural effusion.[13] For example the study says that a pleural fluid protein level of least 5 g/dL is a good way to diagnose TBPE. It correctly identifies about 81.97 percent of cases and rules out malignant causes around 72.92 percent of the time.[14] This means that measuring the protein in the fluid could be very helpful for telling TBPE apart from malignant pleural effusion especially in places that do not have access to advanced lab tests. The test is also good at finding TBPE in patients with tuberculous pleural effusion and it is fairly reliable, at ruling out malignant pleural effusion. The results are very similar to what we have seen before in studies. These studies have shown that people with pleural effusion have more protein in the fluid around their lungs than people with malignant effusion. This is what we would expect because tuberculosis causes a lot of inflammation. When someone gets tuberculosis their body reacts strongly to the infection.

The bodys reaction happens mostly in the area around the lungs. This reaction makes the tiny blood vessels in that area more permeable. As a result a lot of fluid that is rich in protein gets into the space around the lungs. Tuberculous pleural effusion also leads to a buildup of cells that are very active and other substances that cause inflammation. This buildup increases the amount of protein in the fluid more. The protein levels in the fluid of patients, with tuberculous pleural effusion are higher because of all these things.[15] On the hand malignant pleural effusions happen when tumors block lymphatic drainage. These effusions are also exudates.. Research shows they do not always have very high protein levels like tuberculous effusions do. Because of these biological processes checking protein levels in pleural fluid can help figure out what kind of infection someone has. Malignant pleural effusions and tuberculous effusions have protein levels, in pleural fluid. This difference can help doctors diagnose the infection.[16,17] The study also shows how age is important when it comes to the type of effusion people get. Younger people are more likely to get pleural

effusion while older people are more likely to get the malignant type. This is what other studies from around the world have found too. Tuberculosis tends to affect people when they're young and working and it spreads through the community. On the hand cancer-related pleural effusions usually affect older people because they have been around harmful things for a long time.[19]

Past studies have shown that people with pleural effusion are usually younger than those with the malignant type. Knowing these patterns is very helpful when doctors first see patients with effusion. The current study found that there were equal numbers of men and women. This means that pleural effusion affects both men and women equally. However there might be some differences because of things like job hazards, smoking, money and access to doctors. These things might cause some differences, between men and women sometimes.. Since the numbers are almost equal it is probably not a good idea to use gender to figure out if someone has tuberculous or malignant pleural effusion. The diagnosis of effusion is still a problem in many healthcare systems especially where they do not have a lot of resources. Doctors can use tests like adenosine deaminase and interferon-ã to diagnose tuberculosis with accuracy.. These tests are not used all the time because they are expensive and need special equipment and laboratory support. The same thing happens with tests to detect cancer in the fluid these tests are not always available in smaller hospitals. So doctors usually rely on fluid tests to make a diagnosis.[20] In these cases simple biochemical tests of the fluid are very helpful for a quick and affordable diagnosis. Things like protein, lactate dehydrogenase, glucose and cell makeup give doctors clues, about what is causing the problem. Protein tests are especially useful because they are cheap and easy to do. Our study shows that using protein levels is a way to tell if the fluid problem is caused by tuberculosis or cancer before getting the final diagnosis. If doctors can diagnose tuberculosis early they can start treatment faster which can prevent the disease from spreading. If cancer is suspected this allows doctors to take the steps to deal with the pleural effusion and the cancer.[21,22] This study could have impacts on health policy and how doctors work in developing countries. Using biochemical tests in regular fluid checks from the lungs can help doctors diagnose patients faster and start treatment sooner. While checking protein levels in the fluid is not enough on its own to make a diagnosis using it along with signs, X-rays and test results can make the diagnosis more accurate. This supports doctors in making decisions based on evidence. Even though the findings are promising we need to consider some limitations. The protein levels in the fluid can be affected by things like what a person eats other infections, overall inflammation and how bad the disease is. Because of this relying on one test might not always give us complete certainty. Future research could look at groups of people and more hospitals. Adding tests like checking for certain proteins and inflammation markers could also help. All of this could lead to ways to diagnose and tell apart different types of fluid buildup in the lungs. This study shows how checking the fluid in the lungs can really help diagnose buildup especially in places where tuberculosis is common and resources are limited. The results show that measuring protein in the fluid is a easy and affordable way to tell if the fluid buildup is due to TB or something else like cancer. Adding these tests to procedures could lead to earlier detection, better patient care and more efficient use of health resources in areas, without advanced diagnostic tools.

CONCLUSION

Pleural fluid protein estimation is not a standalone diagnostic test but serves as a practical and accessible adjunct in differentiating tuberculous from malignant pleural effusions. With a cutoff level of =5 g/dL, reasonable sensitivity and specificity were observed, supporting its use in early clinical assessment, particularly in resource-constrained settings. In spite of the availability of advanced diagnostic tools in developed countries, the diagnosis of tuberculous or malignant pleural effusion is a challenge. The data obtained from this study revealed that the level of protein in the pleural fluid is an adjunct useful criterion. The values were considerably higher in tuberculous and lower in malignant effusions. With the cutoff level of = 5 g/dL, considerable sensitivity, specificity, and performance of this method were observed in diagnosing TPE. The two causes prevail as the major unrecognised causes of lymphocytic exudative pleural effusion till date. Being one of our developing countries, the major diagnostic procedure utilised is closed pleural biopsy, as no modern and costly investigations have been included, though its sensitivity is suboptimal. With the above limitations in mind, the level of total protein in the pleural fluid, in association with clinical correlation, might help in distinguishing whether it is tuberculous or malignant.

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Bushra Arif: Study conception, data collection, interpretation of results, and manuscript drafting.
Sada Saeed: Study supervision, methodology design, statistical oversight, critical revision of the manuscript, and correspondence with the journal.
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Original Article **Open Access**

Comparison of Intra-Operative Hemorrhage by Blunt and Sharp Expansion of Uterine Incision at Caesarean Section

Summaira Shabbir, Syeda Maryam Batool, Arooj Naseem

ABSTRACT

Objective: To determine the difference in mean drop in post-operative haemoglobin level after caesarean section with blunt and sharp expansion of uterine incision during the operation.

Study Design and Setting: The study design was a randomized controlled trial, which was carried out at the Department of Obstetrics and gynecology, CMH Rawalakot, between 01- October-2024 and 31-March-2025.

Methodology: 130 women who had elective lower segment caesarean section were recruited and randomly divided into two equal groups: blunt expansion (n=65) and sharp expansion (n=65). Females between 20 and 40 years old with singleton pregnancies of 37 weeks and above with hemoglobin of 10 g/dL and above were included. Haemoglobin was determined before and after the operation (24 hours later). A decrease of more than 1.5 g/dL was regarded as a clinical significance. Analysis of data was done in SPSS version 22; independent-sample t-test was used.

Results: The mean haemoglobin drop in the blunt expansion group (1.37+0.79 g/dL) was significantly less than in the sharp expansion group (1.72+0.85 g/dL; p=0.016). Stratified analysis showed that there were significant differences in favor of blunt expansion in women aged >30 years (p=0.003), gestational age >39 weeks (p=0.008), and parity >2 (p=0.002).

Conclusions: Blunt expansion of the uterine incision is related to much less intraoperative blood loss than sharp expansion, which is why it should be used as a safer method of reducing blood loss during a caesarean section, especially in more at-risk subgroups.

Keywords: Caesarean section; Haemorrhage; Hemoglobin; Uterine incision; Uterotomy

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INTRODUCTION

Caesarean section is among the most common surgical procedures conducted in obstetrics where vaginal birth is deemed to be a risk to the mother or the baby. It entails opening of the abdominal wall and the uterus to provide safe delivery of the baby. This procedure over the years has been critical in minimizing maternal and neonatal morbidity and mortality especially in complex pregnancies and includes obstructed labour, fatal distress, and placenta previa.[1] Although it is lifesaving, caesarean section is a major surgical procedure and comes with inherent risks.[2] As such, the decision to use a particular surgical method is critical in determining short-term operative success and long-term maternal health.[3] The process of the procedure has different stages, the method of the uterine incision extension being one of the most crucial. This measure may have a crucial impact on intraoperative blood loss, level of tissue injury, and postoperative recovery.[4] Intraoperative bleeding is one of the most common complications experienced in caesarean birth and may be caused by factors like uterine atony, placental abnormalities, maternal comorbidities, and differences in surgical technique.[5]

Reducing blood loss intraoperative is thus a major goal when performing a caesarean section. Several measures have been considered to accomplish this aim such as pharmacological interventions, enhanced surgical expertise and optimization of operative procedures, but handling of uterine incision during its extension has been established as a crucial measure in minimizing unnecessary bleeding.[6] Appropriate technique during this phase may assist in maintenance of vascular integrity, minimise injury to the surrounding tissues and better overall surgical outcomes.[7] Both blunt and sharp extensions are very common in obstetric surgery, where the uterine incision may be extended by either the fingers or a scalpel. In blunt extension, the tissues

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are separated by hand, typically with the fingers, and allowed to part along their natural lines. This procedure is believed to reduce the destruction of blood vessels and other structures around. Sharp extension, on the contrary, can be done with the instruments of surgery (scissors or scalpel) and provide a more controlled and accurate enlargement of the incision, but it can be accompanied by a higher risk of vascular trauma and consequent bleeding.[8] Clinical research indicates that blunt extension might be linked to less blood loss during surgery than the sharp approach.[9] As an example, in one study (a randomized controlled trial) by Faiza et al., women undergoing lower segment caesarean section were compared between the two techniques.[10] The research showed that the average decrease in postoperative hemoglobin levels, which is a surrogate endpoint of blood loss, was less in the blunt extension group (1.47 ± 1.08 g/dl) than in the sharp extension group (1.95 ± 0.85 g/dl). The results of this study correspond with the idea that blunt extension can be a more effective and safer method of reducing the amount of hemorrhage during surgery.[11] Such findings are even more relevant in such areas as Azad Kashmir and other resource-constrained environments where the proportion of caesarean births is constantly growing.[12] The availability of blood transfusion services, sophisticated surgical centers, and competent medical professionals in these regions might be low. The adoption of less risky surgical procedures that cause less blood loss can thus be significant in enhancing patient safety and resource optimization.[13] Finally, the approach to extending uterine incision in a caesarean section is one of the most important factors that determine the results of operations both intraoperative and postoperative. Although both blunt and sharp techniques are widely used, the existing evidence indicates that blunt extension can benefit in terms of less blood loss and the decreased risk of complications. Implementing evidence-based surgical care that suits local health care environments can assist in leading to better maternal outcomes and safer obstetric care.

METHODOLOGY

This randomised controlled trial was conducted in the Department of Obstetrics and Gynecology, CMH Rawalakot, from 01-October-2024 to 31-March-2025 (six months). Ethical approval was obtained from the Institutional Ethics and Research Committee prior to initiation of data collection (ERC Approval No: 1105/Dated 01-08-2023). The study was conducted in accordance with the Declaration of Helsinki and applicable institutional guidelines. The required sample size was calculated using the WHO sample size calculator with a 5% level of significance (two-tailed) and 80% statistical power. Using published reference values of mean postoperative haemoglobin drop of 1.47±1.08 g/dL with blunt expansion and 1.95±0.85 g/dL with sharp expansion, a minimum of 60 participants per group was determined.[14] To account for potential dropouts, 65 participants were enrolled in each group, yielding a total sample of 130. Participants were recruited using a non-probability consecutive sampling technique. Inclusion criteria were: women aged 20–40 years; singleton pregnancy with gestational age =37 weeks confirmed by first-trimester ultrasonography; elective lower segment caesarean section; parity of =4; placenta located in the upper uterine segment on antenatal ultrasound; and preoperative haemoglobin =10 g/dL. Exclusion criteria were: multiple gestation; preoperative haemoglobin <10 g/dL; uterine fibroids identified on ultrasound; personal or family history of thromboembolic disease; and any contraindication to regional anaesthesia.

Written informed consent was obtained from each participant after a detailed explanation of the study objectives, procedures, potential risks, and benefits. Participants were assured that their decision regarding participation would not affect the quality of care received. Demographic data including age, gestational age, parity, residence, socioeconomic status, and baseline haemoglobin were recorded on a structured proforma. Computer-generated block randomisation was used to randomise the study groups. Abdominal entry was done through Pfannenstiel incision with blunt subcutaneous dissection in both groups. On the lower part of the uterus, a transverse incision 12 cm was made. In the blunt expansion group, this was extended laterally by traction of the fingers in bilateral directions along the natural tissue planes. Lateral extension under direct vision was performed using Mayo scissors in the sharp expansion group. Controlled cord traction was used to achieve placental delivery and 10 IU oxytocin (syntocinon) was given intravenously to actively control the third stage. Incision of the uterus was stitched in two layers using chromic catgut sutures; extra haemostatic sutures were added where necessary. Standard technique was used to complete closure of peritoneum, rectus sheath and skin. Intraoperative haemoglobin drop, which was determined as the difference between the preoperative haemoglobin and the haemoglobin 24 hours after the surgery was considered the primary outcome measure. Clinically significant blood loss was considered to be a haemoglobin reduction of more than 1.5 g/dL at 24 hours. The information was keyed into SPSS version 22. Mean ± standard deviation is used to show continuous variables. The independent-sample t-test was used to measure the difference in the mean haemoglobin drop between groups. A p-value =0.05 was considered statistically significant. The frequencies and percentages are used to summarise categorical variables. Stratification was used to control potential confounders such as age, gestational age and parity, and post stratification independent-sample t-tests were conducted on each sub-group.

RESULTS

The demographics of patients were comparable at baseline, with a mean age of 30.31 ± 6.35 years in the blunt expansion group compared to 28.74 ± 5.57 years in the sharp expansion group. The mean gestational age was 38.91 ± 1.48 weeks

in the blunt expansion group versus 38.80 ± 1.52 weeks in the sharp expansion group. There was no significant difference in the distribution of residence and socioeconomic status between the groups (Table 1). There was no significant difference in pre-operative haemoglobin levels (11.88 ± 1.11 g/dL in the blunt group vs 11.94 ± 1.08 g/dL in the sharp group). Postoperatively, haemoglobin levels were 10.50 ± 1.11 g/dL in the blunt group and 10.22 ± 1.32 g/dL in the sharp group (Table 2). The primary outcome analysis demonstrated a statistically significant difference in haemoglobin drop: the blunt expansion group showed a mean decrease of 1.37 ± 0.79 g/dL compared to 1.73 ± 0.86 g/dL in the sharp expansion group (t = -2.446, p = 0.016), as demonstrated. Age-, gestational age-, and parity-based stratified analyses demonstrated that the advantage of blunt expansion was statistically significant in higher-risk subgroups: patients aged >30 years (p = 0.003), gestational age >39 weeks (p = 0.008), and parity >2 (p = 0.002). No statistically significant difference was observed in the lower-risk subgroups (Table 4)

Table 1: Patient Demographics in Both Groups

Variables	Blunt Expansion n=65	Sharp Expansion n=65
	Mean ± SD	Mean ± SD
Age (years)	30.31 ± 6.35	28.74 ± 5.57
Gestational Age (weeks)	38.91 ± 1.48	38.80 ± 1.30
Parity	2.49 ± 1.28	2.22 ± 1.23
Residence	n (%)	n (%)
Rural	25 (38.5%)	28 (43.1%)
Urban	40 (61.5%)	37 (56.9%)
Socioeconomic Status		
Low	26 (40.0%)	32 (49.2%)
Middle	25 (38.5%)	28 (43.1%)
High	14 (21.5%)	5 (7.7%)

DISCUSSION

In the current research, blunt expansion of uterine incision during caesarean section was related to a significant decrease in intraoperative haemorrhage in comparison to sharp expansion. This was evidenced by a smaller mean decline in haemoglobin levels (1.37 ± 0.80 g/dL vs 1.73 ± 0.86 g/dL; p = 0.016). These results confirm the hypothesis that the method of extension of uterine incision has a quantifiable effect on maternal blood loss during caesarean section. This reduced bleeding through blunt expansion may be attributed to preservation of tissue structure and vascular integrity since this technique does not cut tissues but instead cuts them along the natural body lines. This enables the myometrial fibres to spontaneously recede around interrupted vessels to enable effective haemostasis.

Stratified analysis also revealed that there were significant tendencies in the riskier subgroups, including women aged >30 years, gestational age >39 weeks, and parity >2. This higher advantage in the older patients could be due to age-

Table 2: Pre- and Post-operative Haemoglobin Levels in Both Groups

Hemoglobin Levels	Blunt Expansion n=65	Sharp Expansion n=65
Pre-op Hb (g/dL)	11.88 ± 0.72	11.94 ± 0.81
Post-op Hb (g/dL)	10.50 ± 1.11	10.22 ± 1.32

Table 3: Comparison of Mean Drop in Haemoglobin between Groups

	Blunt Expansion n=65	Sharp Expansion n=65	t	P value
Drop in Hb (g/dL)	1.3718 ± 0.79546	1.7266 ± 0.85732	-2.446	0.016

Table 4: Stratified Analysis of Mean Haemoglobin Drop by Demographic Factors

Demographic Factor	Stratum	Group	Mean Drop in Hb (g/dL) Mean ± SD	n	p Value
Age (years)	=30	Blunt	1.4709 ± 0.77213	33	0.327
		Sharp	1.6855 ± 0.85657	38	
	>30	Blunt	1.2697 ± 0.81835	32	0.003
		Sharp	1.7844 ± 0.87129	27	
Gestational Age (wks)	=39	Blunt	1.5197 ± 0.84934	38	0.356
		Sharp	1.7017 ± 0.84077	42	
	>39	Blunt	1.1637 ± 0.67381	27	0.008
		Sharp	1.7722 ± 0.90411	23	
Parity	=2	Blunt	1.4784 ± 0.71534	31	0.193
		Sharp	1.7367 ± 0.89353	33	
	>2	Blunt	1.2747 ± 0.86115	34	0.002
		Sharp	1.7163 ± 0.83248	32	

associated variations in uterine vascularity and less tissue elasticity making them more prone to vascular damage during sharp dissection. Similarly, the pregnancies which extend beyond 39 weeks are often associated with increased uterine vascular engorgement and tissue fragility and blunt expansion would be more useful in maintaining vascular integrity. The multiple stretching and remodelling of uterine tissues in multiparous women could be a predisposing factor to vascular disruption; hence, blunt separation along natural tissue planes could be used to reduce excessive bleeding in this population.

These results are in line with the previous studies. Shaukat et al. showed a much less haemoglobin reduction with blunt expansion (0.79 ± 0.19 vs 1.21 ± 0.19 g/dL; $p < 0.05$).[15] Similarly, previous trials demonstrated reduced haemoglobin drop with the blunt technique (1.47 ± 1.08 vs 1.95 ± 0.85 g/dL; $p = 0.031$). These observations were further supported by a meta-analysis by Saad et al. which reported lower rates of blood transfusion and fewer unintended uterine extensions with blunt expansion.[16] All these studies confirm the notion that vascular structures are saved using blunt techniques with the assistance of natural tissue planes.

Nevertheless, there are studies that have indicated the opposite. Fatima et al. have found more changes in haematocrit using blunt expansion.[17] Tahir et al. also reported similar findings.[18] These inconsistencies could be explained by the differences in surgical experience, dissimilarity in the methods of operation, or the dissimilarity in patient groups. Blunt expansion is a procedure that is greatly reliant on the surgeon to properly identify and trace the natural tissue planes, which can affect the results. In addition, conflicting results of surrogate markers such as unintended uterine extensions are also found. Jayasundara et al. did not observe a significant difference in haematocrit drop >10% between methods, but found higher rate of blood transfusion in the blunt group.[19] In the same manner, El-Berry et al. did not find any significant difference in haemoglobin drop >2 g/dL between the two methods.[20] These results indicate that although significant haemorrhagic events might be similar, a cumulative minor bleeding, as indicated by changes in mean haemoglobin, may be more appropriate to indicate the haemostatic benefit of blunt expansion.

A significant value of the current study is the identification of certain subgroups that might be more benefited by blunt expansion especially women who are older than 30 years, gestational age of more than 39 weeks and those with more than 2 parity. The stratified analysis has not been well researched in the literature with the majority of the past studies not examining the patient specific factors. This shows that there is a great evidence gap when it comes to individualized surgical methods. Future research should incorporate stratified analyses to assist in offering more evidence-based and patient-specific obstetric care by helping to determine the patient groups that are most benefited by each approach.

Limitations: The research was carried out in one centre (CMH Rawalakot), and this might not be generalisable to other healthcare facilities that have different patient populations, resource base, or surgical skills. The sample size was sufficient to identify the difference in mean haemoglobin drop observed, but might not be enough to identify smaller, but clinically significant differences in the secondary outcomes or infrequent complications. The authors have not taken into consideration potential confounding variables such as the experience of individual surgeons, intra-group variations in surgical technique or variations in anaesthetic management that could influence intraoperative blood loss. Blood loss was also not assessed on a volumetric basis but on a basis of changes in haemoglobin and this might not be able to fully capture the entire haemorrhagic morbidity. Also, the operating surgeon could not be blinded due to the characteristics of the intervention, which would introduce some performance bias.

CONCLUSION

This paper finds that blunt expansion of the uterine incision during lower segment caesarean section is related to much less intraoperative haemorrhage than sharp expansion, as indicated by a reduced mean postoperative haemoglobin drop in the blunt expansion group (1.37 ± 0.79 vs 1.72 ± 0.86 g/dL; $p=0.016$). The advantage of blunt expansion was the greatest in women of age >30 years, gestational age of over 39 weeks and multiparous women of parity >2, which is directly proportional to the main study aim. These results justify the use of blunt uterine incision expansion as the technique of choice in reducing blood loss in caesarean birth, especially in subgroups of patients with increased risks.

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Authors Contribution:
Summaira Shabbir: Study design, conception statistical analysis, data collection
Syeda Maryam Batool: Literature review, proof reading
Arooj Naseem: Data collection, data interpretation

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Original Article

Open Access

Outcomes and Complications of Early Cholecystectomy versus Conservative Management in Diabetic Patients with Asymptomatic Gallstones

Waseem Ullah, Muhammad Daud, Aahan Attaullah, Faseeh Muhammad, Fazal Ahmad, Muneeb Ur Rehman

Abstract

Objective: To compare gallstone-related complication rates, emergency cholecystectomy conversions, morbidity, mortality, hospital stay duration, and 30-day readmissions between early laparoscopic cholecystectomy and conservative management in diabetic patients with asymptomatic gallstones.

Study design and setting: This was a prospective, comparative cohort study in which participants were recruited from the Department of General Surgery, Lady Reading Hospital, Peshawar, between January 2024 and December 2024. Those meeting inclusion criteria were allocated to either early laparoscopic cholecystectomy or conservative management groups, and outcomes were assessed at 3, 6, and 12 months.

Methodology: A total of 170 diabetic patients with ultrasound-confirmed asymptomatic gallstones were allocated equally into early cholecystectomy and conservative management group. The primary outcomes included gallstone-related complications, emergency cholecystectomy, and 30-day readmissions. Secondary outcomes included length of hospital stay and morbidity rates.

Results: The early cholecystectomy group showed significantly lower rates of complications (7.1% vs. 18.8%; $p = 0.02$) and emergency cholecystectomy (0% vs. 10.6%; $p = 0.001$) compared to the conservative group. Readmissions were also reduced in the early surgery group (2.4% vs. 8.2%; $p = 0.04$), and the mean hospital stay was shorter (2.5 ± 1.1 vs. 5.2 ± 1.8 days; $p < 0.001$). No mortality was observed in either group.

Conclusions: This study suggests that early cholecystectomy in diabetic patients with asymptomatic gallstones significantly lowers the risk of complications and healthcare utilization compared to conservative management, supporting the adoption of early elective surgery in high-risk populations.

Keywords: Cholecystectomy, Laparoscopic; Diabetes Mellitus; Gallbladder Calculi; Gallstones; Pancreatitis, Biliary

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INTRODUCTION

Diabetes mellitus is a well-recognized risk factor for gallstone formation and is associated with an increased risk of gallstone-related complications, even in asymptomatic cases.[1] Cholelithiasis affects approximately 20% of the global population, but diabetic patients exhibit a disproportionately higher prevalence and complication rate, attributed to impaired biliary motility, autonomic neuropathy, and dysregulated lipid metabolism.[1,2,6,7]

Many people with diabetes develop gallstones without any pain or warning signs. This makes it difficult for doctors to decide between watchful waiting and early surgery. If stones are left alone, they can suddenly cause infections, blocked bile ducts, or pancreatitis. These conditions affect diabetic patients more often than others. Surgery, however, brings its own costs and small operative risks. A balanced plan is to monitor the gallbladder with regular ultrasound, keep blood glucose well controlled, and discuss patient goals clearly. When new symptoms appear or overall risk rises, timely laparoscopic removal can prevent severe complications and protect long-term health.

The relationship between metabolic disorders and gallbladder function is increasingly being acknowledged in clinical research. Gallstone disease displays significant geographical variation, with a rising incidence being observed in South Asia, including India, where lifestyle changes and metabolic syndromes are on the rise.[3,8] Virk et al. note the lack of consensus among surgeons in India regarding the appropriate management of asymptomatic gallstones, highlighting variability in clinical decision-making and calling for standardized guidelines.[3]

This growing disparity in clinical approaches reflects a broader uncertainty regarding treatment thresholds in asymptomatic populations. Although up to 80% of gallstone carriers remain asymptomatic, diabetic patients face an elevated risk of progression to serious complications such as acute cholecystitis, choledocholithiasis, and gallstone pancreatitis.[1,2,4] These complications not only increase morbidity and mortality but also result in substantial healthcare utilization and cost burdens.[1,6] Kousgaard et al. reported a high short-term complication risk in symptomatic uncomplicated gallstone disease, suggesting that early surgical intervention may be beneficial in selected populations.[5] Thangaraj et al. similarly reported a prevalence of asymptomatic gallstones discovered during routine ultrasonography suggests the potential for silent disease progression.[2]

Clinical vigilance is therefore crucial in populations known to be at higher risk of disease progression, such as diabetics. The standard of care for symptomatic gallstone disease is laparoscopic cholecystectomy, which offers definitive treatment with low morbidity.[3,7,10] However, the management of asymptomatic gallstones, particularly in diabetic patients, remains contentious. While conservative management is generally accepted for asymptomatic gallstones in non-diabetic populations due to a low annual complication risk (1-4%),[3,5] diabetic patients are frequently considered a "high-risk" group, potentially warranting a more proactive surgical approach.[3]

Deciding between surgery and observation often requires weighing patient comorbidities, age, and long-term health outcomes. Conservative management could be viable for certain low-risk patients but emphasized considering individual risk profiles.[5] Cirocchi et al. reviewed management strategies in high-risk patients, noting the importance of tailored surgical approaches based on patient-specific risks and clinical presentation.[10]

As evidence accumulates, it becomes increasingly important to revise current clinical frameworks to better align with patient needs. New evidence obtained from prospective cohorts shows that uncomplicated symptomatic Gall Stone Disease carries a short-term risk, with up to 81% of patients developing complications within two years if left untreated.[4] Diabetics, due to their vascular fragility and immuno-compromised state, may be more susceptible to adverse outcomes.[1,2,4,9] Accordingly, Mencarini et al.[8] highlight the need beyond recognizing this heightened risk, clinicians must adopt individualized diagnostic and therapeutic strategies to optimize acute cholecystitis management in high-risk groups.

In spite of these issues, there are no firm recommendations in the present guidelines, such as those of the Society of American Gastrointestinal and Endoscopic Surgeons, on early cholecystectomy in asymptomatic diabetic patients.[3,7] The absence of consensus highlights an important gap in literature and is a source of variation in clinical practice.[3]

Addressing this gap through high-quality comparative research may help establish uniform protocols. Thus, the primary objective of this study was to determine whether the risk of natural disease progression in asymptomatic diabetic patients (progression to acute cholecystitis, pancreatitis, or cholangitis) outweighs the perioperative morbidity associated with elective laparoscopic cholecystectomy. This remains a controversial topic because surgical intervention carries inherent risks, such as bile duct injury or anesthesia-related events, which must be carefully weighed against the natural progression of cholelithiasis. In diabetic populations, this balance is particularly delicate due to their unique physiological vulnerabilities.

METHODOLOGY

This prospective, comparative cohort study was conducted in the Department of General Surgery, Lady Reading Hospital from 1st January 2024 to 29th December 2024 after the approval from the Institutional Review Board, Lady Reading Hospital, Peshawar (IRB Ref: No. 389/LRH/ MTI). The sample size was calculated through WHO sample size calculator. Using a 95% confidence level and 70% power, and assuming a 20% complication rate in the conservative management group and a 10% complication rate in the early cholecystectomy group, the calculated minimum sample size was 154 participants (77 in each group). To compensate for potential dropouts, the final sample size was increased to approximately 170 participants. Adult patients (=18 years) with a confirmed diagnosis of Type 1 or Type 2 diabetes mellitus and ultrasound-confirmed asymptomatic gallstones were included. To ensure a fair comparison between the “natural history” and “surgical risk,” all perioperative complications in Group A were recorded as “gallstone-related complications” for statistical parity. Only patients without prior history of gallstone-related complications and those who were fit for surgery (ASA I-III) were enrolled. Patients presenting with symptomatic gallstone disease, previous cholecystectomy, severe comorbid conditions contraindicating surgery, or pregnancy were excluded. Written informed consent was obtained from all participants. Group A included patients who underwent elective early laparoscopic cholecystectomy within four weeks of diagnosis.

Group B included patients who received conservative management with observation and symptomatic treatment as required. Participants were followed at 3 months, 6 months, and 12 months to assess for gallstone-related complications throughout the given period. The primary outcome was the incidence of gallstone-related complications, including acute cholecystitis, pancreatitis, cholangitis, and the need for emergency cholecystectomy. Secondary outcomes included morbidity and mortality rates, conversion from conservative management to emergency surgery, length of hospital stay, readmission rates, and healthcare costs. Patient demographics, clinical parameters (e.g., HbA1c, BMI, lipid profile), ultrasound findings, management strategy, and clinical outcomes were recorded using a structured data collection sheet. Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation and compared using Student's t-test or Mann-Whitney U test, depending on normality. Categorical variables were presented as frequencies and percentages and compared using the Chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

RESULT

A total of 170 diabetic patients with ultrasound-confirmed asymptomatic gallstones were enrolled in the study and allocated equally into two groups: 85 patients underwent early laparoscopic cholecystectomy (Group A), and 85 patients were managed conservatively (Group B). The mean age of patients was 57.4 ± 9.8 years in Group A and 58.1 ± 10.2 years in Group B, with no statistically significant difference ($p = 0.56$). The majority of patients in both groups were female, accounting for 61.2% in Group A and 64.7% in Group B ($p = 0.48$). Baseline clinical characteristics, including mean body mass index (BMI), glycosylated hemoglobin (HbA1c), and prevalence of comorbidities such as hypertension, dyslipidemia, and ischemic heart disease, were comparable between the two groups without statistically significant differences (Table 1).

During the one-year follow-up period, gallstone-related complications occurred in 6 out of 85 patients (7.1%) in Group A (early cholecystectomy) and 16 out of 85 patients (18.8%) in Group B (conservative management), showing a statistically significant difference ($p = 0.02$). Among the complications, the most common was acute cholecystitis, followed by gallstone pancreatitis and cholangitis, all of which were more frequent in the conservative group. Additionally, 9 patients (10.6%) in Group B required emergency cholecystectomy due to the onset of complications, compared to none in Group A ($p = 0.001$). No mortality was reported in either group during the study period.

Patients in the conservative management group (Group B) had a significantly longer mean hospital stay compared to those in the early cholecystectomy group (Group A**)** **(**5.2 ± 1.8 days vs. 2.5 ± 1.1 days; $p < 0.001$**).** The 30-day readmission rate was also higher in Group B, with 7 patients (8.2%) requiring readmission compared to 2 patients (2.4%) in Group A ($p = 0.04$). The overall morbidity rate was 14.1% in Group B and 4.7% in Group A ($p = 0.03$), primarily related to gallstone-related complications and postoperative issues. No mortality was recorded in either group during the one-year follow-up period. In Group A, the complications (7.1%) were primarily minor postoperative wound infections and transient ileus, whereas in Group B, the complications (18.8%) were systemic and severe, including gallstone pancreatitis and acute cholangitis.

When evaluating the types of gallstone-related complications, acute cholecystitis was the most common in both groups, occurring in 4 patients (4.7%) in Group A and 10 patients (11.8%) in Group B ($p = 0.05$). Gallstone pancreatitis occurred in 1 patient (1.2%) in Group A and 4 patients (4.7%) in Group B ($p = 0.17$). Cholangitis was observed in 1 patient (1.2%) in Group A compared to 2 patients (2.4%) in Group B ($p = 0.56$). The overall complication rate remained significantly higher in the conservative management group ($p = 0.02$), supporting the benefit of early elective surgery in diabetic patients with asymptomatic gallstones. Figure 1 shows a comparison of clinical outcomes between patients who underwent early cholecystectomy (Group A) and those who were managed conservatively (Group B). The complication rate was significantly higher in Group B (18.8%) compared to Group A (7.1%). Emergency cholecystectomy was performed in 10.6% of conservatively managed patients, while no such cases were reported in the early surgery group. Similarly, the 30-day readmission rate was greater in Group B (8.2%) than in Group A (2.4%).

Figure 2 illustrates the distribution of complication types in the conservative management group, with acute cholecystitis being the most frequent complication, followed by gallstone pancreatitis and cholangitis. Figure 3 shows cumulative incidence of gallstone-related complications at 3, 6, and 12 months. The conservative management group consistently showed a higher complication rate compared to the early cholecystectomy group.

DISCUSSION

Diabetic patients with asymptomatic gallstones face a higher risk of developing severe gallstone-related complications; however, the recommended management approach for this population remains a topic of ongoing debate. Our findings demonstrate that early cholecystectomy significantly reduces complication rates, emergency surgical interventions, and healthcare resource utilization compared to conservative management, supporting the role of timely surgical intervention in this high-risk group. The increased risk of complications in diabetics with asymptomatic gallstones has been widely discussed in the literature. Gupta et al.[1]

Table 1: Baseline Characteristics of Study Participants

Variable	Early Cholecystectomy (n = 85)	Conservative Management (n = 85)	p-value
Age (years), mean ± SD	57.4 ± 9.8	58.1 ± 10.2	0.56
Sex, n (%)	Female: 52 (61.2%) Male: 33 (38.8%)	Female: 55 (64.7%) Male: 30 (35.3%)	0.48
BMI (kg/m²), mean ± SD	29.5 ± 3.2	29.7 ± 3.4	0.62
HbA1c (%), mean ± SD	7.8 ± 0.4	7.9 ± 0.5	0.44
Hypertension, n (%)	Yes: 45 (52.9%) No: 40 (47.1%)	Yes: 46 (54.1%) No: 39 (45.9%)	0.87
Dyslipidemia, n (%)	Yes: 53 (62.4%) No: 32 (37.6%)	Yes: 51 (60%) No: 34 (40%)	0.73
Ischemic Heart Disease, n (%)	Yes: 15 (17.6%) No: 70 (82.4%)	Yes: 14 (16.5%) No: 71 (83.5%)	0.82

Notes: BMI = Body Mass Index; HbA1c = Glycosylated Hemoglobin; SD = Standard Deviation

Table 2: Comparison of Clinical Outcomes

Outcome	Early Cholecystectomy (n = 85)	Conservative Management (n = 85)	p-value
Gallstone-related complications, n (%)	6 (7.1%)	16 (18.8%)	0.02
Emergency cholecystectomy, n (%)	0 (0%)	9 (10.6%)	0.001
Morbidity, n (%)	4 (4.7%)	12 (14.1%)	0.03
Mortality, n (%)	0 (0%)	0 (0%)	-
Mean hospital stay (days)	2.5 ± 1.1	5.2 ± 1.8	<0.001
Readmission within 30 days, n (%)	2 (2.4%)	7 (8.2%)	0.04

$p < 0.05$ considered significant

Figure 1: Bar chart comparing complication rates, emergency surgeries, and readmissions between groups

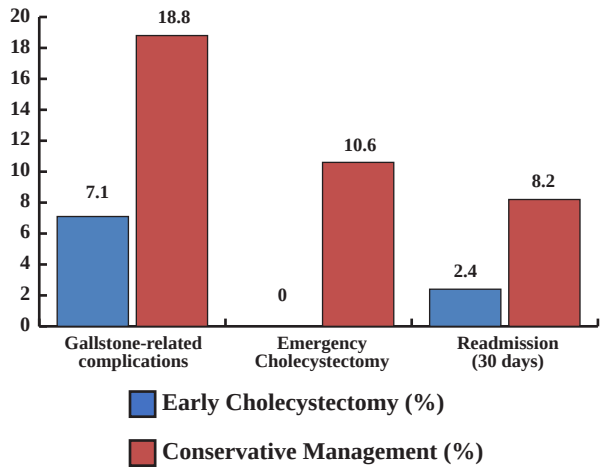
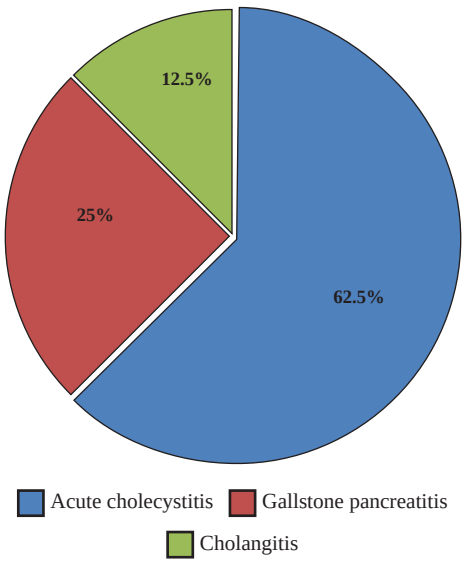
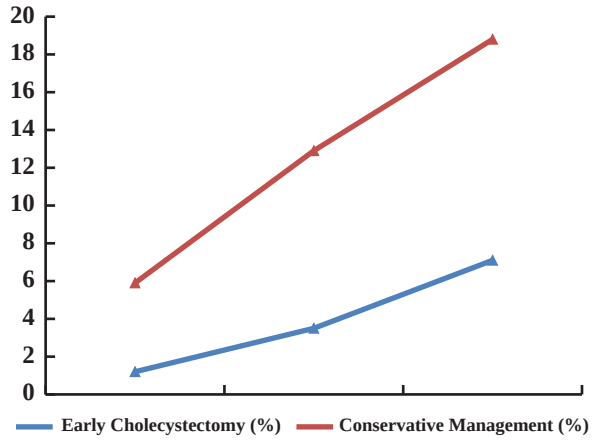


Figure 2: Pie chart showing distribution of complication types in the conservative management group



highlighted that gallstone disease in diabetics is associated with higher morbidity due to autonomic neuropathy and immune dysfunction, increasing the likelihood of progression to symptomatic disease. Our study supports this by showing that diabetic patients managed conservatively experienced a nearly three-fold higher complication rate compared to those who underwent early surgery. These findings highlight

Figure 3: Early cholecystectomy = surgery within 4 weeks; conservative management = observation without surgery; $p < 0.05$ considered significant.



the need to re-evaluate standard management strategies in diabetic populations, particularly those traditionally deemed safe to observe. However, recent European guidelines on bile duct stone management continue to reflect variations in practice patterns.[19] The prevalence of asymptomatic gallstones is substantial, particularly in high-risk populations. Thangaraj et al.[2] found a significant association between diabetes, obesity, and asymptomatic gallstones in a cross-sectional study. This underscores the importance of routine screening and consideration of long-term outcomes even in patients without symptoms. While asymptomatic gallstones are often left untreated, emerging evidence including that from Virk et al.[3] suggests early intervention may prevent complications, especially in diabetics where disease progression may be silent but severe. However, practice variations continue to exist across regions, often due to a lack of unified guidelines and differing perceptions of surgical risk.

Our findings also correlate with recent cohort studies that observed short-term complications in conservatively managed patients. Kousgaard et al.[4] reported that even uncomplicated symptomatic gallstones have a high risk of complications within one year, echoing our result of an 18.8% complication rate in the conservative group. The C-GALL trial similarly noted that laparoscopic cholecystectomy reduces recurrent symptoms and complications compared to non-surgical management, reinforcing the value of surgical intervention in carefully selected patients.[5] The significantly lower incidence of emergency cholecystectomy in the early surgery group supports the hypothesis that proactive intervention can prevent escalation of disease. Emergency surgical interventions in diabetic patients often present with higher perioperative risks due to underlying comorbidities and delayed clinical presentation. By reducing the need for urgent procedures, early surgery not only improves patient outcomes but also allows for better surgical planning, including optimization of glycemic control and perioperative risk mitigation.

Unexpectedly, our study recorded no mortality in either group during the one-year follow-up. This contrasts with literature reporting small but notable mortality rates in diabetic populations undergoing conservative management.[6] This discrepancy may be attributed to strict inclusion criteria, close monitoring, and early escalation of care in deteriorating patients within our study cohort. The structured follow-up schedule (3, 6, and 12 months) likely played a role in timely identification of complications and may serve as a model for surveillance in conservative approaches. Our results are also consistent with a meta-analysis by Cirocchi et al.[10], which demonstrated that early cholecystectomy lowers mortality and readmission rates compared to percutaneous drainage or delayed surgery in high-risk patients. The strong correlation between our data and those findings supports the external validity of our results. Furthermore, the conservative group's elevated emergency cholecystectomy rate mirrors findings from Nogueiro et al.[11] and Sneineh et al.[16], who observed late complications necessitating urgent surgery post-bariatric procedures. The literature also highlights key predictors for recurrent cholecystitis in non-surgical management, particularly among elderly patients with comorbidities. Some studies report recurrence rates ranging from 30% to 40%, most occurring within the first year. This suggest the rationale for considering early surgery in diabetic patients, who frequently present with overlapping risk factors such as age, dyslipidemia, and cardiovascular disease.[12,17] In terms of surgical approach, laparoscopic cholecystectomy remains superior to open surgery, as highlighted by Mannam et al.[13] due to its association with lower morbidity, shorter operative time, and reduced length of hospital stay. The preference for laparoscopic intervention in our study is based on both safety and efficiency. Additionally, in patients with complex bile duct stones, advances such as single-operator cholangioscopy and ERCP offer minimally invasive alternatives and reduce the need for more extensive surgery.[20] The shorter hospital stay in the early surgery group (2.5 ± 1.1 days vs. 5.2 ± 1.8 days; $p < 0.001$) is clinically relevant, reflecting smoother perioperative recovery and fewer complication-related admissions. Readmission rates were also significantly lower in this group. From a health economics perspective, these differences translate into meaningful cost savings. In resource-limited settings, strategies that reduce readmissions and emergency procedures are not only clinically sound but financially advantageous.

A central point of controversy in modern surgery is whether we should interfere with the natural history of a silent disease. Critics argue that surgical complications can be more debilitating than the stones themselves. However, our data suggests that in the diabetic subset, the "natural history" is frequently aggressive. While surgical risks exist, they were predominantly minor (Clavien-Dindo Grade I-II) in our

cohort, whereas the complications in the conservative group often required emergency intervention and longer stabilization. New emerging findings suggest that diabetic autonomic neuropathy may mask the early "warning" symptoms of biliary colic, leading to a late and more dangerous presentation of complications. This supports the shift toward elective surgery before the patient enters a high-risk emergency state. Although no statistically significant difference in baseline demographics was found between the two groups, the conservative group exhibited a higher morbidity rate, emphasizing the limitations of observational management in this population. Complications such as acute cholecystitis, gallstone pancreatitis, and cholangitis were more common in Group B. These conditions can evolve rapidly in diabetics due to impaired immune responses, making early elective surgery a safer option.

The increased rate of emergency cholecystectomy observed in the conservative group (10.6%) reflects the unpredictability of disease progression in diabetics. Emergency surgeries often occur in suboptimal conditions and are associated with greater risk of bile duct injury, longer recovery, and increased patient distress. Therefore, the timing of surgery plays a critical role not only in clinical outcomes but also in the overall surgical experience for the patient.

Additionally, our findings contribute to the growing recognition of the rising burden of gallstone-related complications in diabetic and general populations, as emphasized by Peery et al.[18] This burden extends beyond individual outcomes and impacts hospital admissions, costs, and care delivery efficiency. Li et al.[14] noted an increasing trend of choledocholithiasis and cholangitis, particularly in urban healthcare settings. Similarly, the RELAPSTONE study by Velamazán et al.[15] highlighted relapse rates up to 20% within six months of delayed surgery, supporting the rationale for early intervention in at-risk groups. Our findings are consistent with this broader body of evidence and contribute region-specific data to inform clinical decision-making. Importantly, the data support a nuanced approach to management. While early surgery appears favorable, it is essential to consider patient-specific factors including surgical fitness, comorbidity burden, and personal preference. Individualized care remains a cornerstone of high-quality management. For low-risk patients, particularly those with contraindications to surgery or limited access to surgical care, structured conservative management with close monitoring may still be appropriate. These considerations underpin our decision to standardize laparoscopic procedures in the early cholecystectomy group. These results support the view that tailored management strategies, guided by clinical risk profiles and regular follow-up, can help reduce adverse outcomes. Clinicians should assess both short-term surgical risks and long-term complication potential when making decisions in asymptomatic diabetic patients.

While this study provides valuable insights, certain limitations must be acknowledged. First, as a single-center study with a one-year follow-up, it may not capture very late surgical complications or the lifelong natural history of gallstones. Second, the study did not utilize a randomized controlled trial (RCT) design, which may introduce selection bias. Finally, while we categorized minor surgical issues as complications, a more granular quality-of-life (QoL) assessment would provide a more holistic view of the "surgery vs. observation" trade-off.

CONCLUSION

In conclusion, this study supports early cholecystectomy as a safer and more effective approach compared to conservative management for diabetic patients with asymptomatic gallstones. Our findings reinforce current guidelines advocating for early surgical intervention in high-risk populations, with significant implications for reducing morbidity, emergency surgery, and healthcare resource utilization. Future multicenter randomized trials with longer follow-up periods are recommended to further validate the benefits of early cholecystectomy in diabetic patients with asymptomatic gallstones. Research focusing on cost-effectiveness analysis and patient-reported outcomes could also offer deeper insights.

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Authors Contribution:
Waseem Ullah: data collection, initial draft writing
Muhammad Daud: concept, supervision, manuscript review
Aahan Attaullah: data collection and literature review
Faseeh Muhammad: statistical analysis and tables
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Original Article **Open Access**

Hormone Receptor Status in Breast Cancer Patients and Its Association with Age and Histopathological Grade in a Tertiary Care Setting

Manal Afzal, Rashid Ali, Tashaba Qaiser Faizi, Madiha Masood Khan, Mansah Ali, Surrendar Dawani

Abstract

Objective: Hormone receptor testing plays a central role in the classification and treatment planning of breast cancer. This study aims to assess the frequency of estrogen receptor (ER) and progesterone receptor (PR) expression in breast carcinoma and examine their association with age and histopathological grade in a tertiary care setting.

Study design and setting: This study design is cross-sectional, and it took place at Jinnah Postgraduate Medical Centre, Karachi.

Methodology:. A total of 175 breast carcinoma cases diagnosed at a tertiary care center were reviewed. Information regarding patient age, tumor characteristics (type, size, lymph node status, metastasis, histological grade), and ER/PR expression was recorded. Associations between receptor status and clinicopathological parameters were examined using the chi-square test.

Results: The majority of patients (59.4%) were aged 51–80 years. Most tumors were of ductal type (55.4%) and hormone receptor–negative, with 64.6% ER-negative and 70.3% PR-negative. ER and PR positivity were significantly higher in older patients ($p = 0.02$ and $p = 0.04$, respectively). However, no significant association was found between histopathological grade and either ER or PR status.

Conclusion: Hormone receptor negativity was prevalent, especially in younger women: ER and PR expression increased with age and showed no association with tumor grade. These findings support the routine use of hormone receptor testing for informed treatment decisions.

Keywords: Breast Neoplasms, Receptors, Progesterone, Immunohistochemistry, Receptors, Estrogen, Prognosis

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INTRODUCTION

Breast carcinoma is the most frequently diagnosed cancer affecting women globally and stands as the second leading cause of cancer-related deaths among females.[1] In Pakistan, breast cancer represents approximately 24.4% of all cancers diagnosed in women, compared to 23% in western countries. Research indicates that one in every nine women in Pakistan is affected by this disease.[2] Breast carcinoma is a complex and varied disease, characterized by a wide range of histopathological subtypes as well as distinct molecular and clinical profiles. The outcome and effectiveness of treatment in affected individuals are influenced by multiple contributing factors.[3] The prognosis of breast cancer is primarily determined by several critical factors, including the histological subtype, tumor size, presence of necrosis, involvement of the skin, nipple, or chest wall, lymphovascular invasion, tumor grade and stage, and the expression status of biomarkers such as estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2), and the cell proliferation marker Ki-67, along with the type of treatment administered.[4-6]

Prognostic indicators in breast cancer are generally classified into two main groups: those based on pathophysiological

characteristics and those identified as biological markers. [7] Key pathophysiological factors influencing prognosis include the patient's age, tumor size (T), the specific type of tumor tissue, the tumor's histological grade, the extent of lymph node involvement (N), and the presence of distant metastasis (M). Estrogen and progesterone receptors function as ligand-activated transcription factors within target cells, playing a crucial role in regulating gene expression. [8] Research has demonstrated that patients with tumors positive for both estrogen and progesterone receptors tend to have lower mortality rates and show a better response to hormonal treatments. Anti-hormonal therapies are effective in over half of the cases where both receptors are present. In contrast, tumors expressing only one of the receptors are associated with a mortality rate of approximately 33%, while those lacking both receptors have a mortality rate of less than 10%. [8-9]

Research findings have consistently shown that breast tumors expressing both estrogen and progesterone receptors are generally associated with a lower histological grade and a more favorable prognosis. Patients with hormone receptor–positive tumors tend to demonstrate improved survival outcomes across all individual stages of the disease, highlighting the prognostic significance of receptor status in breast carcinoma.[10] This favorable biological behavior is often attributed to the less aggressive nature and better treatment responsiveness of hormone receptor–positive tumors. To date, only a limited amount of research has explored the correlation between tumor histological grade and the expression of estrogen and progesterone receptors. Ayadi et al. found an inverse relationship, indicating that higher-grade tumors tend to show lower levels of ER and PR expression. [6] In a study conducted by Sohail et al, estrogen receptor (ER) and progesterone receptor (PR) positivity were reported in 45.4% and 36.9% of breast carcinoma cases, respectively.[11] Similarly, another study evaluating receptor expression across tumor grades found ER positivity in 19% of grade I, 38% of grade II, and 33% of grade III tumors, while PR positivity was observed in 17.9%, 36%, and 28.3% of the respective grades.[12] These findings further support the association between hormone receptor expression and tumor differentiation, underscoring the importance of ER and PR evaluation in prognostication and therapeutic decision-making.

Given the biologically heterogeneous nature of breast carcinoma disease, in which therapeutic decisions and prognostic expectations increasingly depend on a tumour's molecular profile, the routinely assayed biomarkers, estrogen receptor (ER) and progesterone receptor (PR) statuses are pivotal because they identify tumours likely to respond to endocrine therapy and carry distinct prognostic implications. However, reported receptor-positive frequencies vary widely across regions and populations, and it remains unclear to what extent ER and PR expression patterns correlate with histopathological grade. Establishing the local distribution of ER and PR positivity across the full spectrum of histological grades will therefore not only benchmark our population against global data but also clarify whether receptor testing can refine risk stratification beyond conventional grading. Such evidence is essential for optimising adjuvant treatment algorithms, allocating limited healthcare resources more rationally, and ultimately improving patient outcomes.

METHODOLOGY

This cross-sectional study was conducted to determine the frequency and expression pattern of estrogen and progesterone receptors in patients presenting with breast carcinoma. Further, they were evaluated to find an association between receptor statuses and age and histopathological grade. This study was carried out in the Department of Surgery, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The study started from February 2025 and ended in July 2025, spanning over a six-month period. A total of 175 patients were included in the study following a formal sample size calculation. The sample size was calculated using WHO sample size software, based on a previously reported prevalence of estrogen receptor positivity of 32%, a margin of error of 8%, and a confidence level of 95%.[12] The calculated sample size was considered adequate to detect meaningful associations between hormone receptor expression and histopathological variables. Patients were recruited using a non-probability consecutive sampling method. All eligible patients presenting during the study period and meeting the inclusion criteria were enrolled until the required sample size was achieved. The ethical approval for this study was obtained from the institutional review board of Jinnah Postgraduate Medical Centre (No. E.2-81/2024-GENL/184/JPMC) before the commencement of data collection. All procedures were conducted in accordance with institutional ethical standards. Written informed consent was obtained from all the participants after explaining the purpose of the study. The confidentiality of patient information was strictly maintained throughout the research process.

Patients aged between 20 and 80 years with histopathologically confirmed breast carcinoma were included in the study. Both newly diagnosed and surgically managed cases fulfilling the eligibility criteria were considered. Patients were excluded if their records lacked complete histopathological details, operative findings, or hormonal receptor status data, as incomplete data could affect the validity of receptor correlation analysis. Data were collected from patients admitted and managed surgically at JPMC who fulfilled the study criteria. Demographic and clinicopathological information was recorded using a structured proforma specifically designed for this study. Information collected included patient age, tumor type, tumor size, lymph node status, distant metastasis, histopathological grade, and hormone receptor status.

All surgical breast specimens were subjected to histopathological examination and immunohistochemical analysis for estrogen receptor (ER) and progesterone receptor (PR) expression. Immunohistochemistry was performed using the streptavidin immunoperoxidase technique with monoclonal antibodies, following standard laboratory protocols. Hormone receptor expression was assessed using the H-score method, a semi-quantitative scoring system that combines the proportion of positively stained tumor nuclei and staining intensity. The H-score was calculated by multiplying the percentage of positively stained tumor cells by staining intensity scores ranging from 0 to 3, producing a total score from 0 to 300. Tumors with an H-score greater than 50 were categorized as positive for hormone receptor expression in accordance with previously published criteria.

Histological grading of tumors was performed using the Bloom-Richardson grading system on hematoxylin and eosin–stained sections. Tumors were classified into grade I, grade II, or grade III based on tubule formation, nuclear pleomorphism, and mitotic activity. As they reflect increased degrees of aggressiveness and differentiation. This grading system was used to evaluate any potential relationship between receptor status and tumor grade. Additional tumor-related variables were also documented. Tumor type was classified into ductal, lobular, ductal-lobular, medullary, and mucinous carcinoma based on pathological diagnosis. Tumor size was categorized according to TNM criteria as T1 (=2 cm), T2 (2–5 cm), T3 (>5 cm), and T4 (with skin or chest wall involvement). Lymph node involvement was recorded as N0 to N3 according to the number and extent of involved regional lymph nodes. The metastatic status was categorized as M0 for absence and M1 for presence of distant metastasis. Tumor staging was cross-verified using imaging findings, including ultrasound and mammography where applicable, along with pathology reports to ensure diagnostic consistency.

All collected data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 22. Quantitative variables such as age were assessed for normality using the Kolmogorov–Smirnov test. For normally distributed variables, mean and standard deviation were calculated, whereas median and interquartile range were reported for non-normally distributed data. Categorical variables, including tumor characteristics, receptor status, and histopathological grades, were summarized as frequencies and percentages. To minimize the effect of potential confounding factors, stratification by age was performed during analysis. Associations between estrogen and progesterone receptor expression and clinicopathological variables, particularly histopathological grade and age groups, were evaluated using the chi-square test or Fisher's exact test where appropriate. A p-value of =0.05 was considered statistically significant for all the analyses.

RESULTS

The study analyzed data from 175 patients diagnosed with breast carcinoma. Most participants (59.4%) were between 51 and 80 years of age, while the remaining 40.6% fell within the 20 to 50 age group. Among the histological subtypes, ductal carcinoma appeared most frequently, accounting for 55.4% of cases. Ductal-lobular carcinoma represented 20%, followed by lobular (14.9%), medullary (5.1%), and mucinous types (4.6%). Tumor size varied across the cohort: 45.1% of patients presented with T1 tumors, 20% with T2, 15.4% with T3, and 19.4% with T4. With respect to lymph node involvement, 45.1% of patients were classified as N1, and 39.4% as N2. A smaller proportion fell into N3 (10.3%) and N0 (5.1%) categories. Most patients (90.3%) had no distant metastases at diagnosis (M0), whereas 9.7% had metastases (M1).

Analysis of histological grading showed that Grade II tumors were the most common (38.9%), closely followed by Grade III (38.3%), while Grade I tumors comprised 22.9% of cases. Regarding hormone receptor expression, 35.4% of tumors tested positive for estrogen receptors (ER), while 64.6% were ER-negative. Progesterone receptor (PR) positivity was noted in 29.7% of tumors, with the majority (70.3%) lacking PR expression. Further analysis explored associations between age and receptor status. ER positivity was significantly more frequent among patients aged 51–80 years ($p = 0.02$). Similarly, PR positivity showed a statistically significant association with older age ($p = 0.04$). However, no significant relationship emerged between histological grade and either ER ($p = 0.79$) or PR status ($p = 0.79$).

DISCUSSION

Hormone receptor status remains one of the most important biological markers in breast carcinoma because it provides valuable information regarding tumor behavior, prognosis, and response to therapy. Estrogen receptor (ER) and progesterone receptor (PR) expression are routinely assessed because of their established role in guiding endocrine treatment and predicting clinical outcomes. Given the variability in receptor expression across different populations and age groups, evaluating their distribution and association with clinicopathological parameters remains essential. In the present study, we examined the pattern of ER and PR expression in relation to patient age and histopathological grade.

A considerable proportion of tumors in our cohort lacked hormone receptor expression, with 64.6% testing negative for estrogen receptor (ER) and 70.3% negative for progesterone receptor (PR). This predominance of hormone receptor–negative tumors is noteworthy, as it may reflect a tendency toward more aggressive tumor biology. It also has important implications for prognosis and treatment planning, particularly in settings where endocrine therapy options are guided by receptor status. Our findings are in agreement

Table 1: Distribution of baseline characteristics among the study participants

Variables	n (%)
Age	
20 to 50 years	71 (40.6)
51 to 80 years	104 (59.4)
Tumor type	
Ductal	26 (14.9)
Lobular	97 (55.4)
Ductal-lobular	35 (20)
Medullary	09 (5.1)
Mucinous	08 (4.6)
Tumor size	
T1	79 (45.1)
T2	35 (20)
T3	27 (15.4)
T4	34 (19.4)
Lymph node	
N0	09 (5.1)
N1	79 (45.1)
N2	69 (39.4)
N3	18 (10.3)
Metastasis	
M0	17 (9.7)
M1	158 (90.3)
Histopathological grade	
Grade I	40 (22.9)
Grade II	68 (38.9)
Grade III	67 (38.3)
ER status	
Yes	62 (35.4)
No	113 (64.6)
PR status	
Yes	52 (29.7)
No	123 (70.3)
Total	175 (100)

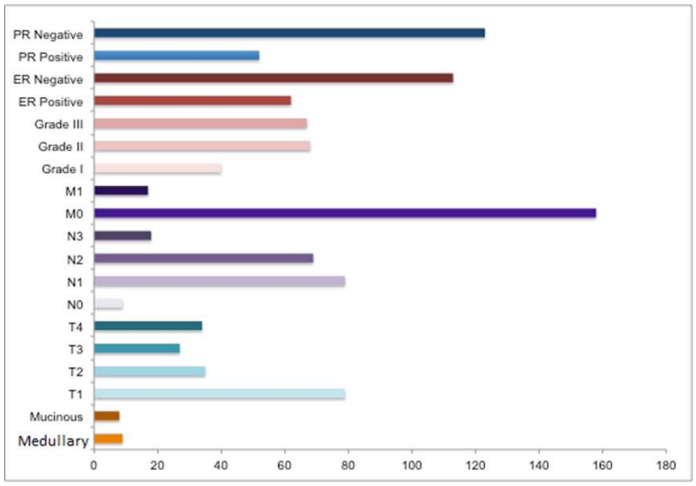
Table 2: Distribution of patient characteristics according to the ER status

Variables	ER status Yes n (%)	ER status No n (%)	P value
Age			
20 to 50 years	18 (25.4)	53 (74.6)	0.02
51 to 80 years	44 (42.3)	60 (57.7)	
Histopathological grade			
Grade I	15 (37.5)	25 (62.5)	0.79
Grade II	22 (32.4)	46 (67.6)	
Grade III	25 (37.3)	42 (62.7)	

Table 3: Distribution of patient characteristics according to the PR status

Variables	PR status Yes n (%)	PR status No n (%)	P value
Age			
20 to 50 years	27 (38)	44 (62)	0.04
51 to 80 years	25 (24)	79 (76)	
Histopathological grade			
Grade I	13 (32.5)	27 (67.5)	0.79
Grade II	21 (30.9)	47 (69.1)	
Grade III	18 (26.9)	49 (70.3)	

Figure 1: Distribution of baseline clinic-pathological characteristics among patients diagnosed with breast cancer



with earlier reports from South Asian populations, where hormone receptor–negative breast cancers have been observed more frequently than in Western cohorts.[13–14] This regional variation may be influenced by differences in tumor biology, genetic predisposition, environmental exposures, delayed presentation, or disparities in screening and diagnostic practices.

In the present study, ER and PR positivity were found to be significantly more common among older patients, particularly those between 51 and 80 years of age. This age-related pattern is consistent with previous literature and may reflect the influence of hormonal and biological changes associated with advancing age, especially in postmenopausal women.[15–16] Several studies have suggested that tumors arising in older women are more likely to exhibit hormone receptor positivity and may therefore show a more favorable response to endocrine-based therapies. The higher prevalence of receptor-positive tumors in this age group further emphasizes the possible role of hormonal milieu in influencing receptor expression and tumor characteristics.

Despite this clear association with age, neither ER nor PR status demonstrated a statistically significant relationship with histopathological grade in our analysis. Although receptor positivity appeared across different tumor grades,

no consistent trend was observed to support a significant correlation. This finding differs somewhat from earlier studies that reported a stronger inverse relationship between hormone receptor positivity and increasing tumor grade, suggesting that well-differentiated tumors are more likely to express ER and PR, whereas poorly differentiated tumors tend to be receptor negative.[14] This discrepancy may be attributable to differences in sample size, tumor distribution, population characteristics, or methodological variations between studies. Nevertheless, our findings suggest that in this cohort, age appeared to have a more prominent association with hormone receptor expression than histological grade.

Our results also contribute to the growing discussion around the clinical relevance of the ER-negative/PR-positive (ER-/PR+) phenotype. This receptor profile was once considered an artifact of testing variability. However, accumulating evidence supports its recognition as a biologically distinct entity with unique clinical behavior. [17-18] Other studies have shown that ER-/PR+ tumors, while rare, often present with aggressive features and worse outcomes than their ER+/PR+ counterparts. [18-19] Importantly, the presence or absence of progesterone receptor (PR) expression appears to carry significant biological and clinical implications, even among tumors that are estrogen receptor (ER) positive. While ER positivity has traditionally been regarded as a favorable prognostic marker and an indicator of responsiveness to endocrine therapy, recent evidence suggests that PR expression provides additional insight into the functional integrity of estrogen signaling pathways. PR negativity in ER-positive tumors has often been interpreted as a marker of impaired or dysregulated ER signaling and has been associated with more aggressive tumor nature, increased cellular proliferation, and relative resistance to endocrine-based treatment.[17,20] This has led to growing recognition that PR status should not be viewed merely as a secondary marker, but rather as an important prognostic and predictive factor. In our dataset, PR-negative tumors constituted the majority of cases, a finding that is noteworthy and consistent with reports linking PR negativity to less favorable prognostic profiles.[15–17] The predominance of PR-negative tumors in our population may partly explain the more aggressive clinicopathological features often reported in similar regional cohorts. Several larger studies have demonstrated that loss of PR expression may be associated with poorer outcomes, including higher recurrence rates and reduced responsiveness to hormonal therapies, particularly when compared with tumors retaining both ER and PR positivity[8,11]. Our findings, while observational, lend support to these previously reported associations.

Further emphasizing the importance of PR expression, researchers have proposed a PR positivity threshold of 10% as a clinically meaningful cutoff for prognostic stratification, particularly in luminal breast cancer subtypes. According to these studies, patients whose tumors exhibit PR expression below this threshold may derive comparatively less benefit from endocrine therapy and may have outcomes more closely resembling those of biologically aggressive disease.[17] Although our study was not powered to validate or challenge this specific cutoff value, our results support the broader concept that PR assessment contributes meaningful prognostic information beyond ER status alone. This reinforces the view that evaluating ER positivity in isolation may not fully capture the biological heterogeneity of hormone receptor–positive breast cancers.

Additionally, our findings are comparable to those of other studies demonstrating that hormone receptor negativity, particularly absence of PR expression, may correlate with adverse pathological features such as lymph node involvement and increased tumor burden.[14] These relationships further underscore the clinical value of assessing both ER and PR routinely, not only for subtype characterization but also for risk stratification and therapeutic planning. Incorporating both receptors into diagnostic evaluation allows for a more nuanced understanding of tumor biology and may assist clinicians in identifying patients who could require closer surveillance or alternative treatment strategies. The importance of PR assessment is also reflected in current international recommendations. The American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) continue to endorse routine evaluation of PR alongside ER because of its recognized predictive role in therapeutic decision-making and prognostic assessment.[21–22] In this context, our findings add to the growing body of evidence supporting the continued relevance of PR testing, particularly in populations where hormone receptor–negative disease appears relatively common.

Our findings further reinforce the inherent biological heterogeneity of breast cancer, highlighting that it cannot be viewed as a single uniform disease entity. The variability observed in hormone receptor expression within our cohort reflects the complex interplay of tumor biology, patient demographics, and possibly regional or environmental influences. In this context, our results strongly underline the importance of comprehensive hormone receptor profiling in all cases of breast carcinoma. While estrogen receptor (ER) status remains a central determinant in guiding endocrine therapy decisions, progesterone receptor (PR) expression provides additional and clinically meaningful information that contributes to a more refined understanding of tumor behavior.

The significance of PR becomes even more apparent when considered alongside ER expression, as it may help identify biologically distinct subgroups within hormone receptor–positive breast cancers. Our findings suggest that reliance on ER status alone may overlook important prognostic nuances that are captured through PR evaluation. This is particularly relevant in resource-limited healthcare

settings, where advanced genomic assays and molecular profiling techniques may not be readily available. In such contexts, routine immunohistochemically assessment of ER and PR remains a practical, cost-effective, and valuable tool for guiding clinical decision-making and treatment planning. Limitations: This study has certain limitations that should be acknowledged when interpreting the findings. First, the study was conducted with a relatively modest sample size, which may limit the statistical power and restrict the generalizability of the results to a broader population. A larger multi-center study would be better suited to confirm and expand upon these observations. Second, the cross-sectional nature of the study and the lack of follow-up data represent an important limitation. As a result, we were unable to assess the impact of hormone receptor status on long-term outcomes such as disease-free survival, recurrence rates, or overall survival. Consequently, the prognostic implications suggested by receptor patterns in this study remain indirect and cannot be fully established without longitudinal evaluation.

CONCLUSION

In conclusion, this study demonstrated that hormone receptor–negative breast cancer was relatively common in our population, particularly among younger patients. Although both ER and PR expression tended to increase with age, neither showed a statistically significant association with histopathological grade. These findings highlight the biological heterogeneity of breast carcinoma and reinforce the importance of routine ER and PR testing in all cases to support accurate prognostication and guide endocrine therapy decisions, especially in resource-limited settings where advanced molecular profiling is not widely available.

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Authors Contribution:
Manal Afzal Conceptualization, study design, data collection, statistical analysis, manuscript drafting.
Rashid Ali Assisted in study design, methodology supervision, data interpretation, critical manuscript review.
Tashaba Qaiser Faizi Data collection, data entry, statistical support, contributed to manuscript writing.
Madiha Masood khan Patient management/data acquisition, literature review, drafting sections of the results
Surrendar dawani Critical revision of the manuscript, contribution to discussion writing, approval of final draft.
Mansab Ali Overall supervision, guidance throughout study, final approval of the version to be published, guarantor of the work

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Original Article

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Safety and Efficacy of Mini Percutaneous Nephrolithotomy Using Smaller Nephroscope for Kidney Stones in Children

Firasat Majid, Mumtaz Rasool, Muhammad Usman

Abstract

Objective: To evaluate the safety and effectiveness of mini percutaneous nephrolithotomy (mini PCNL) with a smaller nephroscope in children aged 12 years and under with kidney stones

Study Design and Setting: It is a Prospective Cohort Study conducted at the department of Paediatric Urology, Bahawal Victoria Hospital Bahawalpur from 11th August 2020 to 10th August 2024.

Methodology: This study included 52 children (=12 years) with kidney stones =2.5 cm. Exclusions were children with non-functional kidneys, positive urine cultures, or coagulation disorders. After obtaining parental consent and assessing anaesthesia fitness, MPCNL was performed under general anaesthesia. A rigid 8/9.8 Fr nephroscope, 12 Fr amplatz sheath, and 1.5 mm pneumatic lithoclast probe were used. A supra-costal tract (above the 12th rib) was made in 36 patients and sub-costal in 16. Postoperative care included nephrostomy tube, ureteric catheter, and set tube removal protocol. Outcome measures included operative time, hospital stay, blood transfusion need, and stone clearance on follow-up ultrasound.

Results: The mean age was 5.2 years. Thirty two (61%) were male, with a male-to-female ratio of 1.6:1. Average hospital stay was 48 hours, and mean operative time was 42 minutes. Stone clearance was complete in 69.23% of cases, with 36.76% having >85% clearance. Blood transfusions were needed in 19.23%, with no pleural effusions or chest tube placements.

Conclusion: Mini PCNL is safe and effective for well-selected pediatric patients. Additional comparative studies are recommended for further validation.

Keywords: Percutaneous Nephrolithotomy; Nephrolithiasis; Pediatrics; Minimally Invasive Surgical Procedures; Lithotripsy; Kidney Calculi; Treatment Outcome

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INTRODUCTION

Kidney stones have become an increasingly common condition across all age groups, including pediatric populations worldwide.[1] Although historically considered rare among children, recent epidemiological data suggests a noticeable rise in pediatric kidney stone cases, likely due to changes in diet, lifestyle, and environmental factors.[2] In Pakistan, the prevalence of pediatric nephrolithiasis has also been on the rise, driven by both genetic and environmental influences such as high temperatures, low water intake, and specific dietary patterns prevalent in the region. With urolithiasis affecting the lives and renal health of young patients, there is a critical need for effective, minimally invasive treatment options tailored to the unique anatomical and physiological characteristics of pediatric patients. Percutaneous nephrolithotomy (PCNL) has long been established as an effective intervention for large or complex kidney stones. However, when it comes to children, especially those under the age of 12, traditional PCNL poses risks due to the relatively large instruments and tract size but still gaining popularity due to good outcomes.[3]

The introduction of mini PCNL has marked a significant advancement in pediatric urology. Mini PCNL involves the use of smaller nephroscopes, typically under 18 French, allowing for a reduced tract size, which is beneficial in minimizing the potential complications associated with PCNL, such as renal trauma, hemorrhage, and injury to surrounding tissues.[4] International studies, particularly those from Europe and North America, have demonstrated that mini PCNL can achieve comparable stone-free rates to traditional PCNL, with significantly reduced morbidity and improved recovery times in pediatric patients.[5] For Pakistani children, mini PCNL offers particular promise given the

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relatively high incidence of pediatric nephrolithiasis and limited access to advanced healthcare in some regions. By minimizing hospitalization and recovery times, mini PCNL could provide a more accessible and feasible solution for young patients across different socioeconomic backgrounds.[6]

Despite these potential advantages, there are still considerable concerns regarding the overall safety and efficacy of mini PCNL, especially when applied to children younger than 12 years. In pediatric patients, the kidney is smaller and more delicate, and the possibility of long-term impacts on renal growth and function from miniaturized instruments remains a key consideration. While mini PCNL is associated with fewer complications, the reduced size of nephroscope may limit visualization and access to larger stones, potentially affecting stone clearance rates and increasing the risk of residual fragments.[7] Studies from international centers have shown varied results, with some research indicating high stone-free rates and low complication rates, while other studies point out potential limitations, including residual stone fragments and the possibility of repeat procedures in complex cases. In Pakistan, recent small-scale studies have explored the outcomes of mini PCNL, generally reporting favorable outcomes but emphasizing the need for broader research to validate these results across diverse pediatric populations.

One of the main alternative treatments for pediatric urolithiasis is extracorporeal shock wave lithotripsy (ESWL), which, while effective for smaller stones, often proves insufficient for larger, more complex stones or for stones that are difficult to access anatomically. ESWL's reliance on multiple sessions and its potential for incomplete stone fragmentation present limitations, particularly for larger stones frequently observed in Pakistani children due to late presentations. Ureteroscopy, another minimally invasive option, also poses challenges, especially for very young patients due to their smaller uretral and renal anatomy. Therefore, mini PCNL stands out as a promising option in such cases, offering a more direct approach to stone removal and thus reducing the need for multiple treatments.[8]

This study aims to evaluate the safety and efficacy of mini PCNL specifically in children aged 12 years and younger, utilizing smaller nephroscopes that are better suited to the pediatric anatomy. By assessing postoperative outcomes, complications, and stone-free rates, this research seeks to fill the gap in existing knowledge regarding mini PCNL's applicability in younger populations, particularly within the Pakistani context.[9] As this age group often presents unique challenges in terms of anatomical considerations and stone composition, the findings from this study could contribute valuable insights into optimal treatment approaches for pediatric kidney stones.[10] In a healthcare system with variable access to advanced urological procedures, evidence supporting the safety and effectiveness of mini-PCNL can play an important role. It may encourage its adoption as a standard and accessible treatment for children with kidney stones in Pakistan and beyond. Despite improvements in minimally invasive techniques, considerable variation still exists in operative outcomes and postoperative recovery following mini-PCNL, especially in resource-limited settings. Therefore, locally generated evidence is essential to guide clinical decision-making and ensure patient safety. This study aims to address this gap by systematically evaluating perioperative outcomes in our population.

This study provides locally generated evidence on the safety and feasibility of mini-PCNL in pediatric patients within a resource-limited setting. The findings may help guide clinical decision-making and promote adoption of minimally invasive stone management strategies in similar healthcare environment.

METHODOLOGY

After the ethical approval by ethical review committee of Bahawal Victoria Hospital Bahawalpur (ERC NO 345/DME/QAMC Bahawalpur), Department of Paediatric Urology B.V Hospital Bahawalpur from 11th August 2020 to 10th August 2024. written informed consent was obtained from the parents or legal guardians of all the pediatric participants prior to enrollment patient data was anonymized , and confidentiality maintained throughout the study.

This study included patients aged 12 years and belowdiagnosed with kidney stones. The selection done by convinient purposive sampling , and met specific inclusion and exclusion criteria. Eligibility for the study required that patients have kidney stones with a maximum size of 2.5 cm, as determined by ultrasound and/or non-contrast computed tomography (CT) scan of the kidney, ureter, and bladder (KUB).

Patients with larger stones (>2.5 cm) or those with non-functional kidneys were excluded from the study. Additionally, patients with a positive urine culture or those with coagulation disorders were excluded.

In total, 52 patients who fulfilled the predefined inclusion criteria were enrolled in the study. All participants underwent a comprehensive preoperative evaluation, which included clinical examination, anesthetic assessment, and review of laboratory investigations, to ensure they were medically fit for general anesthesia. To minimize the risk of perioperative infections, prophylactic antibiotics were administered pre-operatively, following established institutional protocols and, when available, tailored according to culture and sensitivity results. This standardized approach ensured uniformity in preoperative care across all patients.

The mini-percutaneous nephrolithotomy (MPCNL) procedure was performed under general anesthesia in every case. A rigid nephroscope measuring 8/9.8 French (Fr) was employed for visualization, allowing effective access to the renal collecting system while maintaining a minimally invasive

tract size. Along with this, a 12 Fr Amplatz sheath facilitated tract stabilization, and a pneumatic lithotripter with a 1.5 mm probe was used for stone fragmentation, enabling efficient disintegration of calculi with reduced thermal injury risk.

In 36 patients, an upper-pole puncture was carried out through a supra-costal approach, entering the kidney above the 12th rib. This route was selected to provide improved access to stones located within the upper calyx or renal pelvis, especially in cases where lower-pole or mid-pole access would have resulted in suboptimal alignment with the targeted calyces. Although supra-costal entry may increase the theoretical risk of pleural injury, it often offers a more direct channel for complete stone clearance in anatomically challenging cases.

In the remaining 16 patients, a sub-costal approach was utilized, with puncture performed below the 12th rib. This technique is generally considered safer with respect to pleural complications and is preferred when the stone burden is located more inferiorly or when upper-pole access is not required. However, sub-costal access may provide comparatively limited maneuverability for upper calyceal stones, which was taken into account during tract selection based on individual stone characteristics. The tract size and choice of approach were individualized based on stone location, size, and the patient's anatomy, as visualized pre-operatively through imaging studies.

Postoperative drainage and tube placement followed a standardized protocol. A 10 Fr nephrostomy tube was placed through the tract site to allow drainage of urine and any residual stone fragments. Additionally, a 4 Fr ureteric catheter was inserted to ensure unobstructed urinary flow from the kidney to the bladder, and a 10 Fr silicone Foley catheter was placed per urethra for bladder drainage. These tubes were removed based on a set protocol to allow gradual adjustment of the urinary tract and prevent urinary stasis.

The primary variables recorded included the total operative time from the initial puncture, the length of the hospital stay, and the requirement for blood transfusion if the postoperative hemoglobin level fell by more than 2g/dl. Postoperative imaging, primarily via ultrasound, was conducted on the second postoperative day to assess the immediate stone clearance. A follow-up ultrasound was then performed one week after surgery to confirm the absence of residual fragments and to monitor for any delayed complications. In cases where residual stones were observed, additional follow-up or alternative management strategies were considered based on patient symptoms and stone characteristics.

Complications such as pleural injury requiring chest tube placement, postoperative infection, and pain requiring analgesic administration were meticulously documented. The incidence of these complications helped assess the procedure's safety profile, providing insight into potential risks associated with the supra- and sub-costal approaches in a pediatric population. Pain was managed with a standardized analgesic protocol, and the total analgesic requirement was recorded for each patient.

All recorded variables, including demographic profiles, detailed operative parameters, and postoperative clinical outcomes, were systematically analyzed using standard statistical techniques. Data entry and processing were performed using IBM SPSS Statistics, version 24, ensuring accuracy and consistency throughout the analysis. Descriptive statistics were applied to outline the baseline characteristics of the study population and to summarize intra-operative and postoperative performance indicators.

Data accuracy was maintained through a structured double-entry verification process, in which all variables were independently entered and cross-checked to minimize typographical or transcription errors. Any discrepancies identified during this process were resolved by referring back to the original clinical records, ensuring that the final dataset reflected the most reliable and consistent information. To protect patient privacy, all identifying details were removed, and each case was assigned a unique study code, allowing analysis to be conducted without compromising confidentiality

Continuous variables, such as operative time, duration of hospital stay, and patient age, were expressed as means with corresponding standard deviations to reflect both central tendency and variability within the data-set. Categorical variables, including overall complication rates, distribution of Clavien–Dindo grades, and the requirement for peri-operatively blood transfusion, were presented as frequencies and percentages to provide a clear representation of proportional outcomes. This structured statistical approach allowed for a comprehensive assessment of the safety and effectiveness of mini-PCNL within the studied cohort.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 24. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent sample t-test and chi-square test were applied where appropriate. A p-value of =0.05 was considered statistically significant.

RESULTS:

In this study of 52 patients, the average age of the participants was just over five years, reflecting the predominantly paediatric nature of the cohort. Males made up a larger share of the sample, with nearly two-thirds of the children being boys, resulting in a male-to-female ratio of approximately 1.6:1. Hospital stay after the procedure averaged about two days, although there was some variation among individuals. Following the puncture, the operative duration was a little over 40 minutes on average, again with noticeable variation depending on case complexity. Regarding treatment

outcomes, the procedure was largely successful. Overall success rate, defined as complete clearance plus clinically insignificant residual fragments (<3 mm), was 85.9%.Complete stone clearance was achieved in more than two-thirds of the patients, and when the criterion was broadened to include those with only minimal residual fragments (less than 3 mm), the rate of satisfactory clearance rose substantially, reaching nearly 85%.

The summarized results are presented in the following table.

Table 1: Preoperative Variables

Variable	Value
Mean Age	5.2 ± 2.2 years
Gender	32 Male (61%), 20 Female (38%)
Mean Stone Size	1.8 ±0.2 cm

Table 2: Operative and Postoperative Outcomes

Variable	Value
Operative Time	42 ± 8.78 min
Hospital Stay	48 ± 10.48 hrs
Complete Clearance	69.23%
Overall Success (CIRF included)	85.9%
Blood Transfusion	19.23%
Pleural Complications	0

DISCUSSION

This study explored the safety and efficacy of mini PCNL in children aged 12 years and under, with results indicating a favorable outcome in terms of stone clearance rates and a manageable complication profile. The mean age of 5.2 years, with a male predominance (male-to-female ratio of 1.6:1).[9] It is consistent with the demographic patterns observed in pediatric nephrolithiasis. Globally, studies have reported a higher prevalence of Urolithiasis in males, which may be due to gender-based anatomical or physiological differences influencing stone formation risk factors.[10] This trend aligns with previous studies in South Asia, where males have been more frequently affected.

The mean operative time after puncture, recorded at 42 minutes, falls within the typical range reported in pediatric mini PCNL procedures. Studies have shown that, in experienced hands, mini PCNL can achieve effective stone clearance within a similar operative time frame, which helps to minimize anesthesia exposure in young patients and contributes to an overall safer procedure.11 The choice of equipment, such as the 8/9.8 Fr nephroscope and 12 Fr amplatz sheath, facilitated an effective miniaturized approach, allowing for reduced trauma to the renal parenchyma.[12] This aligns with reports that advocate miniaturized tracts to reduce complications like bleeding and parenchymal damage, both crucial considerations in pediatric patients with smaller anatomical structures.

Stone clearance rates in this study were also notable, with 69.23% of patients achieving complete stone clearance, and 36.76% achieving more than 85% clearance with residual calculi less than 3 mm in size.[13] This aligns well with international studies on mini PCNL in children, where complete or near-complete stone clearance rates typically range between 65% and 85%, depending on stone size, composition, and surgeon expertise.[14] Residual fragments smaller than 3 mm are considered clinically insignificant (clinically insignificant residual fragments or CIRF).[15]

A key finding in this study is the low complication rate associated with the mini PCNL procedure.[16] Notably, there were no instances of pleural effusion or chest tube placement, complications that are often associated with supra-costal access, particularly in pediatric patients. Studies have shown that with appropriate imaging guidance and surgical experience, the risk of major complications such as pleural injury can be minimized in mini PCNL. The use of a supra-costal approach in 69% of patients without resulting in pleural complications highlights that, with careful planning, upper pole access can be safely achieved in pediatric patients to maximize stone clearance, especially for stones located in challenging upper calyces or renal pelvis.[17]

Blood transfusions were required in 19.23% of cases, a rate that aligns with other pediatric studies, which report transfusion rates ranging from 10% to 20% depending on operative factors such as tract size, stone burden, and patient age.[18] Although blood loss remains a concern in mini PCNL, the minimized tract size and refined techniques employed here contributed to maintaining this complication within manageable limits as compared to standard PCNL.[19]

The average hospital stay post-surgery was approximately 48 hours, which is consistent with recovery periods in similar studies where mini PCNL has been shown to allow for shorter hospitalizations due to its minimally invasive nature. Shortened hospital stays contribute positively to patient outcomes by reducing healthcare costs and decreasing the risk of hospital-acquired infections.[20]

This study has several important limitations that warrant consideration when interpreting the findings. First, it reflects the experience of a single center with a relatively small sample size, which restricts the external validity of the results and may not accurately represent outcomes in institutions with different case loads, surgical setups, or levels of endourological expertise. Second, the selection of patients for mini-PCNL versus standard PCNL was not randomized; instead, it may have been influenced by surgeon preference, stone characteristics, or anatomical considerations. This introduces a degree of selection bias that could affect the comparability of the two groups. Additionally, the follow-up duration was limited, preventing evaluation of long-term endpoints such as stone recurrence, renal growth, renal scarring, and preservation of renal function—factors that

are particularly important in the pediatric population.

Another limitation is the heterogeneity of the included cases, as variations in stone burden, location, composition, and degree of hydronephrosis could have influenced intraoperative difficulty and postoperative outcomes. The study also relied on ultrasonography and plain radiography for postoperative assessment, which are known to be less sensitive than CT imaging. This may have resulted in underestimation of clinically insignificant residual fragments or low-volume residual stones. Furthermore, metabolic evaluation—which plays a critical role in identifying the underlying etiology of pediatric urolithiasis—was not comprehensively performed, limiting the ability to correlate stone type with recurrence risk or tailor preventive strategies.

The study also did not incorporate cost analysis, patient-reported outcomes, or quality-of-life measures, all of which are increasingly recognized as essential components of evaluating surgical interventions in children. Despite these limitations, the study contributes meaningful preliminary data on the safety, feasibility, and outcomes of mini-PCNL in the local pediatric population and provides a platform for the development of larger, multicenter, prospective trials across Pakistan and the broader South Asian region..

Based on the findings of this study, several recommendations can be made to improve clinical practice and guide future research. Larger, multicenter studies with standardized operative protocols are needed to validate the safety and efficacy of mini-PCNL across diverse surgical settings in Pakistan. Randomized or well-matched comparative trials would help minimize selection bias and provide more reliable evidence on when mini-PCNL should be preferred over standard PCNL in children. Longer follow-up is essential to evaluate long-term renal function, recurrence rates, and the impact of residual fragments, especially in growing kidneys. Incorporating low-dose CT protocols or other advanced imaging techniques may improve the accuracy of postoperative stone-free assessment. Routine metabolic evaluation should be integrated into pediatric stone management pathways to better understand etiology and optimize recurrence prevention. Future studies should also explore the cost-effectiveness, parental satisfaction, and quality-of-life outcomes associated with mini-PCNL, enabling a more holistic assessment of its role within pediatric urolithiasis care. Collectively, these steps will help refine treatment algorithms and enhance the overall management of pediatric stone disease in the region.

Although all procedures in this study were performed in the prone position, recent literature suggests that supine PCNL may offer advantages such as reduced cardiopulmonary compromise and simultaneous retrograde access. However, surgeon familiarity and institutional protocols continue to influence positioning choice. Recent studies (2021–2025) have emphasized further miniaturization techniques such as ultra-mini and micro-PCNL, aiming to further reduce morbidity while maintaining efficacy. However, concerns remain regarding visualization and operative efficiency, highlighting the need for balanced technique selection.

This study's findings underscore that mini PCNL can be a safe and effective option for managing kidney stones in pediatric patients, provided that cases are carefully selected based on stone size, patient health status, and anatomical considerations. However, The findings should be interpreted cautiously due to the descriptive nature of the analysis and absence of a comparative group. More comparative studies are essential to substantiate these findings. Randomized controlled trials comparing mini PCNL with other minimally invasive techniques like extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) in pediatric patients could provide further evidence on the ideal treatment choice based on stone characteristics and patient factors.[21] Additionally, a comparative analysis between mini PCNL and ultra-mini PCNL could reveal valuable insights into whether further reduction in nephroscope size might offer benefits or present limitations in terms of visualization and stone clearance.

CONCLUSION:

Mini PCNL is safe and effective in children when performed in well selected patients. However comparative studies are required for more evidence.

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Authors Contribution:
Firasat Majid: Objective, surgery data collection, write up
Mumtaz Rasool: write up, data analysis, result interpretation final approval
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Original Article

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Clinical Outcomes of Magnesium Sulphate Nebulization in Acute Bronchiolitis Patients Admitted in a Tertiary Care Hospital

Nadia Iqbal, Khurram Fayyaz, Nadeem Sadiq, Saadia Karim, Ehsan Qadir, Imrana Atta

ABSTRACT

Objective: The objective of this research is to analyze the treatment results of nebulized magnesium sulphate for acute bronchiolitis patients requiring hospital admission at a tertiary care medical facility.

Study design and Setting: After the ethical approval from the institutional review board of PNS Shifa, this prospective observational study was conducted at PNS Shifa hospital, Karachi, from December 2024 to May 2025.

Methodology: This prospective observational study was conducted at PNS Shifa Hospital, Karachi (Dec 2024–May 2025; ERC/2023/Paeds/25-A). One hundred children (1–24 months) with acute bronchiolitis were enrolled; exclusions were congenital heart or lung disease, immunodeficiency, bacterial pneumonia, or prior intubation. Patients received either standard supportive care or standard care plus nebulized magnesium sulphate (150 mg in 2 mL NS every 6 hours for 24–48 h). Respiratory parameters, ICU admission, ventilator need, and hospital stay were assessed. Data were analyzed in SPSS v25 using paired t-test/chi-square with significance at $p<0.05$.

Results: A total of 100 children were enrolled (33 standard nebulization, 67 magnesium sulphate). Baseline demographics, weight, respiratory rate, and oxygen saturation were comparable between groups ($p>0.05$). Post-treatment oxygen saturation improved significantly with magnesium sulphate (97.2% vs. 95.8%, $p=0.003$), while respiratory rate reduction was similar ($p=0.666$). ICU admissions were lower with magnesium sulphate (15% vs. 30%, $p=0.017$). Length of stay, number of nebulization, need for ventilation, and mortality showed no significant differences.

Conclusions: Nebulized magnesium sulphate in addition to standard care significantly improved oxygen saturation and reduced ICU admissions in children with acute bronchiolitis.

Keywords: Bronchiolitis, Children, Magnesium Sulphate, Nebulization.

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INTRODUCTION

Acute bronchiolitis is one of the leading lower respiratory tract infections in infants younger than 2 years and accounts for a considerable proportion of pediatric morbidity and hospitalizations worldwide. It is most commonly the result of Respiratory Syncytial Virus (RSV), but other pathogens such as parainfluenza virus, adenovirus, human metapneumovirus and rhinovirus have also been identified. Inflammation, edema of the smaller airways and mucus plugging occur as a consequence of infection, making airflow obstruction secondary to gas exchange disturbances and respiratory distress.[1,2] In low-income countries bronchiolitis presents an additional formidable challenge owing to restricted access to intensive care units (ICUs), higher rates of viral transmission in crowding living environments, and a higher prevalence of malnutrition and comorbid respiratory conditions.

Although etiologies are well known after many years of research, acute bronchiolitis is managed mostly with supportive therapies.[2] Standard therapy involves euvolumia, oxygen supplementation for hypoxemia and ventilator support as required. Pharmacological interventions (e.g., bronchodilators, corticosteroids, epinephrine and antiviral

agents) are not without conflicting evidence in reducing duration of symptoms, time spent in hospital or the requirement for intensive care facilities.[2] The 2014 AAP guidelines do not recommend routine bronchodilator or corticosteroid use in the treatment of bronchiolitis, and they highlight role management.[2] Nevertheless, given the high worldwide prevalence and cost limitations of current therapy options, there is an urgent need for low-cost pharmacological alternatives that are accessible to all patients everywhere and can achieve better clinical results.

One such candidate treatment under investigation is magnesium sulphate (MgSO4), a drug with established smooth muscle relaxant and anti-inflammatory properties. Physiologically, magnesium acts as a calcium antagonist by blunting calcium influx into smooth muscle cells and curtailing the release of acetylcholine at neuromuscular junctions.[3] This effect leads to bronchodilation, diminished airway hyperactivity and potential reversal of bronchospasm in obstructive airway diseases. Second, magnesium is an anti-inflammatory agent and has membrane-stabilizing properties. This might reduce airway mucosal edema and oxidative damage in bronchiolar epithelium.[4]

Magnesium sulphate has a recognized beneficial effect in acute severe asthma, and is known to improve peak expiratory flow rate, oxygen saturation, and the hospitalization of individuals.[5-7] With these advances for the treatment of asthma, there has been clinical interest in whether similar benefits could be derived for bronchiolitis, because of some shared pathogenic pathways of airway obstruction and inflammation.

However, studies of MgSO4 in acute bronchiolitis have yielded conflicting results. Some RCTs investigating the nebulized strategy of MGSO4 in children have showed several advantages including lower clinical severity score, good improvement in oxygenation and less length of hospital stay.[3-5] For example, Sharma et al. (2013) and Gadomski et al. (2016) found that respiratory rate and oxygen saturation improved remarkably in children treated nebulized $MgSO_4$ as compared to those given normal saline. These findings indicated that magnesium would increase the airway relaxation and mucociliary clearance, accelerating the recovery.[4-5]

On the other hand, other studies have been unable to confirm these results. In researchers studies that presented by Modaresi et al. (2017) and Ralston et al. (2018) observed that severity scores of clinical, oxygen requirements and duration of hospital stay were not significantly different between the magnesium-treated and control groups.[6] Furthermore, a small number of studies have implied or reported potential negative aspects of this practice, such as incomplete readiness for departure from the hospital and high readmission rate in some subgroups treated with intravenous magnesium sulphate.[6-8]

A Cochrane review on the use of magnesium in bronchiolitis concluded that available evidence is scarce, its quality heterogeneous and it cannot be supported for clinical practice routinely.[1] The studies ranged greatly in terms of sample size, method of administration (neb vs IV), dose, outcome measurements and enrollment criteria. Likewise, a recently published network meta-analysis in 2023 has retired that magnesium sulphate is a bloomer as bronchodilator while evidences are unsounded to support standard therapy in bronchiolitis.[9]

Notwithstanding these caveats, magnesium sulphate is still a promising candidate to study further. Inexpensive, readily available even in resource-limited conditions, and generally safe in pediatric patients when used within recommended therapeutic boundaries.[8] Side effects such as hypotension, bradycardia, and hyporeflexia are uncommon at nebulized doses except with very high intravenous concentrations. Furthermore, the anti-inflammatory, vasodilatory and mucolytic effects could reasonably support effectively due to the supportive treatment of children with bronchiolitis that might lead to a distinct decrease of the airway obstruction rate and an increase in O2.

In this context, we conducted the present study to assess the therapeutic effectiveness of nebulized magnesium sulphate in infants with acute bronchiolitis. In particular, clinical severity scores, oxygen saturation and hospital length of stay versus standard supportive therapy. Through studying clinical as well as biochemical parameters in a tertiary care hospital, this study aims to establish if magnesium sulphate can make a difference to patient outcomes and join the divide that exists between hope on paper and applicability at bedside.

In this manner, the trial supports an evolving evidence base on management of bronchiolitis and helps frame future large trials that may define the role of $MgSO_4$ in pediatric respiratory practice. If successful, nebulized magnesium sulphate might provide a cheap, safe and easily available option to facilitate recovery in the young infants suffering from acute bronchiolitis by expediting their discharge from hospital—especially at resource-limited settings where pharmacological alternatives are far-fetched.

METHODOLOGY

This is a prospective comparative cohort study conducted in the Department of Paediatrics PNS Shifa Hospital, Karachi, with approval from the Institutional Review Board (Approval No. ERC/2023/Paeds/25-A). The study was done following the ethical principles of the Declaration of Helsinki. Before enrolling, written informed consent was obtained from all parents/legal guardians. Participants' confidentiality and anonymity were kept throughout the study and they could drop off at any point of the study without impacting their medical management.

During the study period, a consecutive sample of 150 eligible children aged 1–24 months with acute bronchiolitis was

admitted. A consultant paediatrician confirmed the diagnosis based on World Health Organization (WHO) clinical criteria and the Respiratory Distress Assessment Instrument (RDAI) was used to assess the diagnosis. Diagnostic features were cough, wheezing, tachypnea, nasal flaring, and chest retractions after an upper respiratory tract infection. The study excluded children with congenital heart disease, chronic lung disease, immunodeficiency syndromes (including HIV infection), bacterial pneumonia, previous endotracheal intubation or mechanical ventilation for respiratory failure, and those undergoing any of the investigational treatment for bronchiolitis.

After enrolment, the participants were divided into two groups based on the treatment plan decided by the treating pediatrician. The comparison group included patients who received standard supportive treatment and the intervention group included patients who received standard supportive treatment plus nebulized magnesium sulphate ($MgSO_4$).

Standard supportive care consisted of humidified oxygen therapy, fluid management as appropriate and inhaled normal saline and/or bronchodilators (salbutamol or epinephrine) if clinically indicated. Neubulized $MgSO_4$ was given as an intervention along with standard care. Nebulizations consisted of 150 mg of $MgSO_4$ in 2 mL of normal saline and were given every six hours for 24–48 hours as dictated by the patient's clinical response and the physician's discretion. All treatments were provided under trained paediatric supervision and oxygen saturations and heart rate monitored using pulse oximetry. Antibiotics and other adjunctive treatment were not routinely administered unless clinically indicated.

At the baseline and during hospitalization until discharge, clinical and demographic data were recorded. The main outcome variables were difference in clinical severity score, respiratory rate and oxygen saturation after treatment. Secondary outcome measures were number of nebulization sessions required, length of hospital stay, need for intensive care unit (ICU) admission and need for mechanical ventilation, adverse events and survival to discharge.

The severity of respiratory distress was determined by a validated clinical scoring system, based on respiratory rate, severity of wheezing, chest retractions and feeding intolerance. Hypoxemia was defined as oxygen saturation < 92% on room air. Active surveillance and management of possible side effects of magnesium sulphate treatment such as facial flushing, bradycardia and hypotension were undertaken.

All the demographic and clinical data were documented on a predesigned structured proforma. Completed forms were checked daily for completeness and correctness of data by the principal investigator. Standardized equipment and uniform assessment procedures were used throughout the study, thereby minimizing variability in measurements. Prior training of the nursing and clinical staff was provided on the study procedures and data collection techniques.

SPSS version 25.0 was used for data analysis. The continuous data were presented as mean ± standard deviation (SD) and the categorical data as frequencies and percentages. Independent-samples t-test and Chi-square or Fisher's exact test was used to compare the standard nebulization and magnesium sulphate nebulization groups as appropriate. A p-value <0.05 was considered statistically significant.

All participant identifiers were coded using coded numbers and the information was kept in electronic databases with password protection so as to maintain confidentiality. The Institutional Review Board was contacted with any adverse or unexpected events. The ethical principles of beneficence, respect for persons, autonomy and confidentiality were respected at all phases of the study.

RESULTS

A total of 100 children with acute bronchiolitis were enrolled, comprising 33 in the standard nebulization group and 67 in the nebulized magnesium sulphate group. The mean age was 13.5 ± 6.4 months in the standard group and 11.6 ± 6.4 months in the magnesium sulphate group (p=0.374). Male patients constituted 51% (n=17) in the standard group and 61% (n=41) in the magnesium sulphate group, while females accounted for 49% (n=16) and 39% (n=26), respectively (p=0.475). Mean weight was 7.03 ± 2.25 kg in the standard group compared to 7.8 ± 2.5 kg in the magnesium sulphate group (p=0.263). The demographic details are shown in Table 1. Table 2 shows the comparison of respiratory parameters in the two treatment groups. There was no difference between the standard nebulization and the magnesium sulphate group regarding RR at baseline (60.87 ± 10.6 vs. 62.9 ± 11.1 breaths/min, p=0.146). Similarly, no significant differences existed between the groups with regard to baseline oxygen saturation (91.3 ± 4.0% vs. 90.8 ± 4.06%, p=0.755). After treatment, post treatment respiratory rates were similar in both groups (43.3 ± 9.4 vs. 42.02 ± 8.5 breaths/min, p=0.666). But post-treatment oxygen saturation was much better in kids who were nebulized with magnesium sulphate than in those who were nebulized without magnesium sulphate (97.2 ± 1.91% vs. 95.8 ± 2.4%, p=0.003). The clinical outcomes are reported in Table 3. The mean number of nebulization sessions was similar in both groups (2.78 ± 1.49 vs. 2.98 ± 1.5, p=0.392). There was no statistically significant difference in the length of hospital stay between the two groups (5.4 ± 2.1 vs. 6.0 ± 2.1 days, p=0.760) though it was slightly shorter in the magnesium sulphate group. There were fewer admissions in the magnesium sulphate group than the standard nebulization group (15% vs. 30%, p=0.017). The need for mechanical ventilation was reduced in the magnesium sulphate group; however, it was not statistically significant (p=0.103). There was a low mortality rate in both groups (p=0.572), two deaths (6%) in the standard nebulization

group and one death (1%) in the magnesium sulphate group. In sum, nebulized magnesium sulphate was more likely to be associated with better oxygen saturation and to have a reduced need for admission to the intensive care unit than standard nebulization therapy.

DISCUSSION

Bronchiolitis continues to be a major cause of morbidity, hospitalization and healthcare utilization in young infants in early winter months. There are few useful pharmacological treatments despite decades of research (management is largely supportive with measures aimed at trying to maintain oxygenation, hydration and nutrition). It is most commonly caused by infection with respiratory syncytial virus (RSV), which results in inflammation, mucosal edema and airway obstruction from plugging of bronchi and bronchioles by mucus. Based on this pathophysiology, recent efforts have been poured into investigating the potential role of bronchodilator and anti-inflammatory agents, such as magnesium sulphate (MgSO4), as adjunctive therapy to decrease airway obstruction and enhance ventilation in acute bronchiolitis.[11]

Table 1: Demographic profile of study participants

Variables	Standard Nebulization (n=33)	Magnesium Sulphate Nebulization (n=67)	p-value
Age (months)	13.5 ± 6.4	11.6 ± 6.4	0.374
Gender			
• Male	17 (51%)	41 (61%)	0.475
• Female	16 (49%)	26 (39%)	
Weight (kg)	7.03 ± 2.25	7.8 ± 2.5	0.263

Table 2: Between-group comparison of respiratory rate and oxygen saturation before and after treatment

Variables	Standard Nebulization (n=33)	Magnesium Sulphate Nebulization (n=67)	p-value
Baseline respiratory rate (breaths/min)	60.87 ± 10.6	62.9 ± 11.1	0.146
Baseline oxygen saturation (%)	91.3 ± 4.0	90.8 ± 4.06	0.755
Post-treatment respiratory rate (breaths/min)	43.3 ± 9.4	42.02 ± 8.5	0.666
Post-treatment oxygen saturation (%)	95.8 ± 2.4	97.2 ± 1.91	0.003*

* Significant at $p < 0.05$

Table 3: Clinical outcomes of study participants

Variables	Standard Nebulization (n=33)	Magnesium Sulphate Nebulization (n=67)	p-value
Number of nebulization sessions	2.78 ± 1.49	2.98 ± 1.5	0.392
Length of hospital stay (days)	6.0 ± 2.1	5.4 ± 2.1	0.760
ICU admission	10 (30%)	10 (15%)	0.017*
Mechanical ventilation	6 (18%)	4 (6%)	0.103
Outcome			
• Expired	2 (6%)	1 (1%)	0.572
• Discharged	31 (94%)	66 (99%)	

* Significant at $p < 0.05$

Magnesium is crucial as a calcium antagonist in smooth muscle relaxation with resultant reduced calcium inward flow into cells and decreased acetylcholine release at neuromuscular junctions. These effects have a synergistic beneficial impact on bronchodilation and airway hyperactivity-administered as nebulized combination products.[12] In addition, magnesium has anti-inflammatory and membrane-stabilizing effects and could work to reduce airway oedema and hypersecretion of mucus. These physiologic characteristics have established its potential role in the treatment of acute severe asthma and generated interest for its use in bronchiolitis, particularly among infants with moderate to severe respiratory distress who do not improve with traditional therapies.

Recent studies evaluating the clinical efficacy of magnesium sulphate in children with respiratory diseases, especially bronchiolitis, have yielded contradictory data. [a]1k et al. observed that intravenous $MgSO_4$ significantly increased clinical scores, oxygen saturation and reduced hospital stay in children with acute bronchiolitis, indicating potential benefit in moderate–severe cases of the disease where an airway obstruction and airway inflammation are more intense.[13] Similarly, Guruprasad et al. demonstrated the efficacy of $MgSO_4$ nebulization for moderate bronchiolitis, but also found that it was only minimally effective with no reduction in length of stay. This indicated that magnesium may alleviate the symptoms for mild cases or when mechanical supportive therapy is already effective, but not produce significant changes in disease development.[12]

However, there are also studies that have shown no or equivocal effect. In a RCT, compared nebulized $MgSO_4$ with nebulized salbutamol and saline; they also noticed no difference between the groups in clinical improvement or time to discharge. Their results reinforced the need for interpretive caution with respect to presumed efficacy of $MgSO_4$ agent, since studies differed in patient populations, doses and severity of illness.[13] However, these findings should not completely rule out a potential therapeutic benefit of magnesium but underscore the need to identify subgroups of patients in whom it may be justified.

Credible evidence from high risk pediatric populations also offers tempered optimism. Yasin et al. found beneficial effects of intravenous $MgSO_4$ on respiratory outcomes and the need for mechanical ventilation in acute pediatric respiratory conditions, such as bronchiolitis. Their results corroborate the theory that magnesium could prevent an increased need for care by enhancing bronchial smooth muscle relaxation and diminishing inflammatory damage. Similarly, nebulized magnesium sulphate with hypertonic saline and reported that clinical scores were better, respiratory distress was improved faster with magnesium but there was no significant reduction in length of stay or requirement for ICU. These results indicate that magnesium may shorten the symptom duration and does not necessarily reduce total disease length.[14-15]

Additional perspective may be obtained from the use of magnesium in pediatric asthma, a disease with similar pathophysiology that includes bronchoconstriction and airway inflammation. The trial protocol of the MagNUM PA trial and the subsequent report by Schuh and colleagues found modest benefit from adding nebulized $MgSO_4$ to albuterol in pediatric refractory asthma, further supporting the idea that magnesium's efficacy can be small and indication-specific. However, study conducted a meta-analysis pooled both intravenous and nebulized $MgSO_4$ led to improved oxygenation and decreased hospitalization of children with acute exacerbations of asthma. Such similarities of asthma and bronchiolitis pathophysiology provide an indirect support regarding the potential role of magnesium as a therapeutic agent in correcting small airway obstruction and ventilation-perfusion mismatch in bronchiolitis.[16-17]

The discrepancies have also been addressed by large-scale reviews and meta-analyses. In a 2024 systematic review, found that nebulized magnesium sulphate was a safe and well-tolerated adjunct for treatment of asthma, but efficacy differed between studies.[18] The variability in outcomes was primarily attributable to variations of the dosing schedule, duration of treatment, nebulation methodology and the degree of initial disease severity in included subjects. More recently, study showed that early intravenous magnesium administration in acute childhood asthma decreased the severity of symptoms, length of hospital stay and improved clinical outcome and provided further justification for studying its use in other pediatric airway disease such as bronchiolitis.[19]

Our evidence fits within this emerging evidence base. We also saw a statistically significant elevation in oxygen saturation and a drop in the number of patients requiring ICU admission for those who received nebulized magnesium sulphate vs alone with standard therapy. These findings indicate that magnesium might be of benefit in moderate-to-severe bronchiolitis by promoting bronchodilation, increasing ventilation and possibly reducing the risk of clinical deterioration requiring intensive care support. The absence of significant adverse effects in our series confirms the outstanding safety profile of nebulized magnesium if cautiously used under clinical control.[20]

Nevertheless, despite these promising results, there are some limitations to be taken into account. The amount of benefit in such studies is, however, significant rather than spectacular and may not always represent a clinically important difference, especially regarding time to hospital discharge or total recovery time. Besides, the difference in causative agent, viral strains and immune responses of patients may affect therapeutic effects. Magnesium treatment, therefore, should not be substituted for established supportive care measures but rather may be an adjunct in a subgroup of patients who present with moderate respiratory distress. The totality of the evidence, based on the current literature suggests that despite being safe, low-cost and physiologically justified adjuvant therapy magnesium sulphate is not consistently effective in bronchiolitis. Variations in study populations, size of the sample studied, route of administration, dosing schedule and severity of disease may explain the discrepancy between trials. Our results of a beneficial effect for oxygenation and reduced ICU requirement, also lend support to targeted use in specific pediatric populations. However, further large-scale multicenter randomized controlled trials with standardized protocols are required to clarify the best-dosing regimen, duration of treatment and patient selection who will likely benefit from magnesium therapy. Until such evidence arrives, magnesium sulphate ought to be viewed more as a welcome adjunct than the treatment of choice in acute bronchiolitis.

CONCLUSION

Our observational study suggests that adjunctive nebulized magnesium sulfate may enhance oxygenation and reduce ICU transfer in pediatric acute bronchiolitis, with potential but as yet unconfirmed benefits in other outcomes. Given the limited and heterogeneous body of existing evidence, high-quality randomized trials are essential to define the role, dosage and patient populations in which magnesium therapy could be beneficial.

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Authors Contribution:
Nadia Iqbal: Conception and design of study, data collection, drafting of manuscript, and final approval.
Khurram Fayyaz: Study supervision, methodology refinement, and critical review of manuscript.
Nadeem Sadiq: Data interpretation, technical guidance, and literature review
Sadia Karim: Assistance in manuscript writing, literature search, and referencing.
Ehsan Qadir: Statistical analysis, interpretation of results, and preparation of tables/figures.
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Original Article **Open Access**

Comparison between the Retrieval of the Gallbladder by the Direct Extraction Method and the Bag Method in Laparoscopic Cholecystectomy

Amjad Gul, Zaki Hussain Salamat, Muhammad Rashid Husnain, Najam Shabbir, Syeda Sanila Aijaz, Shireen Sabir Ansari

Abstract

Objective: This study aimed to compare the complications associated with direct versus endobag retrieval methods in laparoscopic cholecystectomy.

Study design and setting: A prospective cohort study was conducted at PNS Shifa Hospital, Karachi, from 1st June 2024 to 30th June 2025.

Methodology: A total of 270 patients with ultrasound-proven cholelithiasis undergoing laparoscopic cholecystectomy were included. Patients were divided into two groups: Group A (direct retrieval, n=114) and Group B (Endo bag retrieval, n=156). Postoperative complications, including port-site pain, infection, hernia, sinus formation, and intraperitoneal contamination, were assessed and statistically analyzed using SPSS v21.

Results Direct retrieval was associated with significantly higher intraperitoneal contamination (15% vs. 5.6%, $p<0.05$). Endo bag retrieval showed a higher rate of port-site pain (14.5% vs. 22.3%). Rates of surgical site infection and port-site hernia were comparable between both groups.

Conclusion Endo bag use significantly reduced intraperitoneal contamination and stone spillage. However, it increased postoperative port-site pain due to larger fascial incisions. Direct retrieval remains cost-effective but carries higher contamination risk. Choice of retrieval technique should balance patient safety, surgical outcomes, and resource availability.

Keywords: bile spillage, gallbladder removal, laporoscopic cholecystectomy, port site infection, specimen bag

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INTRODUCTION

The gallbladder is a small, pear-shaped, hollow viscus situated in the right upper quadrant of the abdomen. It forms an integral component of the biliary system—also referred to as the biliary tree or biliary tract—which comprises a network of ducts originating from the liver, gallbladder, and pancreas, collectively draining into the small intestine. Anatomically, the gallbladder is positioned on the inferior surface of the liver, within the gallbladder fossa, and is connected to the extrahepatic biliary apparatus through the cystic duct.[1]

Cholelithiasis is characterized by the formation of gallstones, which result from an imbalance in the chemical composition of bile. Gallstones are usually composed of bile, cholesterol and bilirubin. They are not always symptomatic, but with contraction of gall bladder upon stimulation may result in classic biliary pain. This happens as the stone slips into cystic duct and causes obstruction in bile flow. The obstruction of bile flow if sustained for few hours results in inflammation of gall bladder and commonly known as cholecystitis.[2] It is the most frequent reason for hospitalization in the setting of abdominal pain in affluent countries. In the UK alone, gallstones affect 5.5 million people, with 50,000 cholecystectomies being performed annually.[3]

Obesity is one of the major modifiable risk factors for cholelithiasis, and South Asians are one of the communities showing an increasing prevalence of overweight.[4] This changing pattern of body composition can predispose to the pathogenesis of cholesterol gallstones. Recent data suggest a prevalence rate of 10-15 percent in Western countries, while 3-4% in South Asian communities. In Pakistan, it's found to be 8% and 20% in the population over 40 years and 60 years, respectively.[5] However, cholelithiasis in South Asians is mostly underexplored, with limited data available.[6]

For symptomatic patients, cholecystectomy has become the standard treatment. The first cholecystectomy was done in 1882 on an 83-year-old patient. Cholecystectomy has changed significantly since then, including the introduction of the laparoscopic technique, single-port laparoscopic cholecystectomy, and robotic-assisted cholecystectomy. Laparoscopic cholecystectomy was first performed in 1987, a century after the introduction of cholecystectomy. This method of surgery became mainstream just 20 years after it was initiated.[7] This minimally invasive procedure offers several benefits over open surgery, including reduced postoperative pain, lower analgesic requirements, shorter recovery times, and decreased hospital stays.[8] Although laparoscopic procedures are more expensive in terms of operating costs compared to the conventional open approach, the reduced hospital stay and the quicker return to normal work and activities provide both direct and indirect financial benefits, making laparoscopy a preferred option.[9]

A standard laparoscopic cholecystectomy involves the following steps: the patient is prepared and given general anesthesia in the supine position. Pneumoperitoneum is created using a Veress needle or Hasson technique, and four ports are inserted. The peritoneal cavity is inspected. During laparoscopic cholecystectomy, the gallbladder itself is used as a retractor to elevate the right lobe of the liver and to gain visualization of the porta hepatis. This is done by securing gallbladder with grasping forceps and pushing it in a cephalad direction. Calot's triangle is dissected to identify the cystic duct and artery, achieving the critical view of safety (CVS). The CVS consists of three essential component or steps. Firstly, dissection of the hepatocystic triangle. Secondly, exposure of at least lower one third of the cystic plate and lastly demonstration of only two tubular structures (cystic duct and cystic artery) that remain attached to the gallbladder after the first two components have been achieved. All these three steps must be completed before claiming that CVS has been achieved. Next, cystic artery and cystic duct are clipped and cut respectively. The gallbladder is removed from its hepatic bed using thermal energy, either laser or electrocautery. specimen is retrieved outside the abdomen. Finally, the pneumoperitoneum is released, ports are removed, and the wounds are closed and dressed.[10]

While operating in the setting of an inflamed gall bladder, obese men, elderly, non-virgin abdomen, patients with pigment stones, or in patients who have positive bile cultures, it is not uncommon to encounter gall bladder perforation during surgery. This is usually experienced while the gall bladder is being dissected from gall bladder fossa or during essential traction of gall bladder while dissecting Callot,s triangle.[11] Soon afterwards, another crucial step includes the retrieval of the gallbladder after its dissection, which is usually done via the epigastric port. Perforation of gall bladder during surgery or while extraction has its dire consequences like biliary peritonitis, intra-abdominal abscess formation, adhesions leading to intestinal obstruction later on etc. Multiple ways to retrieve the gall bladder are in use to ensure ease of retrieval and to minimize complications, which include direct retrieval via grasper and the use of an endo bag for retrieval.[12] It is the choice of the primary surgeon to determine the method of retrieval.

Limited data is available comparing the complications associated with each method of retrieval. Use of the Endo bag for retrieval is apparently a safe surgical practice to prevent surgical site infection, but it adds to the cost and is an added burden in low-resource countries. Whereas the direct retrieval method is associated with its own set of complications, like intra-peritoneal contamination and port site inflammation.[13] This study aims to compare the frequency of complications associated with gallbladder retrieval using the endo glove technique versus conventional methods during laparoscopic cholecystectomy for cholelithiasis. The results will inform surgical practice and promote infection control strategies, ultimately reducing postoperative morbidity and healthcare burden.

METHODOLOGY

This prospective cohort study was conducted in PNS Shifa Hospital, Karachi, from 1st June 2024 to 30th June 2025, spanning a period of 12 months (12 months for data collection and 2 months of data analysis). The ethical clearance was taken from the Institutional Ethics Committee, PNS Shifa, before the commencement of the study with form number ERC/2024/SURG/112. Written informed consent was obtained from each study subject before enrolment. The study included all patients who had a laparoscopic cholecystectomy, both with and without the use of a retrieval drain bag. Patients were divided into two groups according to the method of gall bladder retrieval. The choice of method was based completely on the surgeon's preference. Group A contains those patients in which direct retrieval method was used. In these patients after identifying the Callots triangle and achieving critical view of safety, cystic artery and cystic duct were secured. Gall bladder was dissected from liver bed and the specimen was handled by a non traumatic grasper and retrieved from the 10mm epigastric port directly without an endobag. Group B contains those patients in which endobag has been used. In these patients, after dissection of callots triangle an sterile endobag is introduced in abdominal cavity which was prepared

beforehand by following method: a sterile glove was securely tied at the wrist using vicryl suture and shaped like a bag by cutting the fingers. The bag was submerged in saline and then inserted into the abdomen with a non traumatic grasper through the epigastric port, positioning it on the superior surface of the liver. The gallbladder, along with any spilled stones, was placed inside the glove, and the ends of the glove was grasped with a toothed grasper through the axillary port before being removed via epigastric port. Our Study consisted of 12 months of data collection and 2 months of data analysis. All data was collected on a pre-formed questionnaire. Sample size was calculated using an online sample size calculator, considering a 800-bedded hospital with 5% margin of error and an 95% confidence level.[14,15] The total sample size was 270, which was randomly divided into two groups as mentioned. The inclusion criteria was designed including patients of any gender in the 20–60 age range. Every individual who underwent laparoscopic cholecystectomy having ultrasound-proven cholelithiasis was included and consented to take part in the research.[7]

Patients having any gall bladder complications like gangrenous gall bladder, perforated gall bladder, gallbladder cancer, patient undergoing hybrid procedure i.e. laparoscopic converted to open cholecystectomy, or patient having any terminal illnesses were excluded from the study, to ensure unbiased results. Patients who were unable to keep follow-ups were also excluded. Regarding postoperative assessment, severity of port site pain on different post-operative days was noted using the pain score (VAS score). Patients were also examined for surgical site infection. Regular followups were ensured after discharge for port site hernia and sinus formation etc. The data was transferred to an Excel sheet. All statistical analyses were done on advanced Excel and relevant tools. Statistical analysis using SPSS-21 data analysis software& Chi square test.

RESULTS

The study consisted of 270 patients who underwent laparoscopic cholecystectomy, 96 patients were in the age bracket of 20-40 years, 107 patients belonged to the 40-60 years age bracket, and 57 patients were aged greater than 60. 64.4 percent of total patients were female, and 35.6 percent were male. Out of all patients, direct retrieval of the gall bladder was done in 114 patients and an Endo bag was used in 156 patients, contributing to the percentages of 42.22% and 57.77% respectively. In the case of direct retrieval, 69 patients were female and 45 were male, whereas via Endo bag retrieval, 93 patients were female and 63 were male. Only intra-peritoneal contamination show statistically significant results. The rest doesn't show any significance

DISCUSSION

Laparoscopic cholecystectomy has emerged as a successful alternative to the open technique and gained popularity due to its merits of shorter hospital stay, significantly smaller incision size, and lower number of complications than the open technique.[16] It comes with its own set of demerits that include bile leakage, iatrogenic injury, bile peritonitis, postoperative bleeding, etc.[17] A few absolute contraindication

Table 1: Presenting complaint

	Frequency (n=)	Percentage
asymptomatic cholelithiasis	32	11.8%
Epigastric pain	22	8%
Fever	14	5.2%
RUQ pain	193	71.5%
Vomiting	9	3.5%
Total	270	100

Table 2: Complications encountered after the retrieval of the gall bladder via direct retrieval

	Frequency	Percentage
epigastric port site hernia	1	1.2%
epigastric port site infection (pod 7th)	5	4.4%
epigastric port site pain	17	14.5%
epigastric port site sinus	0	0%
intraperitoneal contamination	17	15%
No complications	73	64.9%
Total	114	100

Table 3: Complications encountered after retrieval of the gall bladder via endobag

	Frequency	Percentage
epigastric port site hernia	00	0%
epigastric port site infection (pod 7th)	3	2%
epigastric port site pain	34	22.3%
epigastric port site sinus	0	0%
intraperitoneal contamination	9	5.6%
No complications	109	70.1%
Total	156	100

Table 4: Comparison of complications encountered in both techniques

Complications	While direct retrieval via grasper (n=114)	While using a sterile endobag (n=156)	P value
epigastric port site hernia	1.2% (n=1)	00%	0.42
epigastric port site infection (pod 7th)	4.4% (n=5)	2% (n=3)	0.29
epigastric port site pain	14.5% (n=17)	22.3% (n=17)	0.36
epigastric port site sinus	00%	00%	1.00
intraperitoneal contamination	15% (n=17)	5.6% (n=9)	0.02 ($p<0.05$)

to laparoscpic cholecystectomy includes, uncontrolled coagulopathy, severe chronic obstructive pulmonary disease, congestive cardiac failure (ejection fraction <20%) and inability to tolerate anesthesia.[18]

Our study included 162 female patients, (93 and 69 in direct retrieval group and endo bag group respectively), whereas 108 male candidates participated in the study (45 and 63 in direct retrieval group and endo group, respectively). This is in accordance to the well-established fact that cholelithiasis is more prevalent in females as also discussed in study by Lazarchuk I. et al. Reasons include, hormonal changes in reproductive years, hormone replacement therapy, usage of oral contraceptive, rapid weight loss, and predisposition to high carbohydarate and low protein diet etc. Hormones particularly estrogen impair the contraction of gall bladder that augment stone formation.[19]

71.5 percent of our total inclusion criteria presented to hospital with complain of right upper quadrant pain either in out patient department or in emergency room. As stated by Martin Wt, in his study any right upper quadrant pain that is lasting for greater than four hours is an indication of pathological cholecystitis and warrants urgent cholecystectomy. Clinical examination by a skilled physician is a more reliable parameter to detect cholecystitis than ultrasound in this setting.[20] An additional consideration is that our study includes 11.8% patients that present with asymptomatic cholelithiasis, as incidental finding on abdominal ultrasound. Routine cholecystectomy for subjects with silent gallstones is an aggressive management option, not indicated for most subjects with asymptomatic cholelithiasis.[21] However, we consider cholecystectomy for asymptomatic gallstone patients include gallstones > 3 cm, concurrent gallbladder polyps, concomitant cholecystectomy during bariatric surgery, existing comorbidities such as diabetes as backed by studies. Prophylactic cholecystectomy is also indicated in patients of sickle cell anemia and hereditary spherocytosis.[22]

Retrieval of the gall bladder is one of the most crucial steps during the surgery. Direct retrieval of the gall bladder was attempted in 114 patients in our study. The merits of direct retrieval are its significance in being cost-effective, decreased intraoperative time, and lower rates of postoperative port site pain.[12] In our study, the prevalence of intra-peritoneal contamination in the direct retrieval group is significant, i.e.15%. This result is similar to the studies by Kuldeep Singh et al., which also showed increased bile spillage in the case of direct retrieval.[12] Spillage of bile into the peritoneal cavity during gallbladder extraction can precipitate biliary peritonitis, a potentially severe inflammatory response triggered by the caustic nature of bile on the peritoneum.[23] Complications reported from gallstone spillage include peritoneal–cutaneous sinus formation, intra-abdominal and hepatic abscesses, subhepatic inflammatory masses, persistent trocar site discharge, micro-abscesses, retroperitoneal collections, granulomas, cholelithoptysis, small bowel obstruction, enteric and colonic fistulae, as well as bowel perforation and ileus caused by adherence of the intestine to abscess walls. Retained gallstones may remain asymptomatic within the peritoneal cavity for extended periods, but can later become infected following septicemic episodes, leading to abscess formation.[24]

Direct extraction of the gallbladder markedly increases the risk of port-site spillage as well. This occurs because the resistance of the abdominal wall compresses the edematous and fragile gallbladder, causing it to tear during withdrawal or allowing bile and stones to escape through the narrow incision. This can lead to the formation of port site sinus later on, in accordance with the study by Faridi SH et al.[25] However, no case of port site sinus was reported in our study. These results are also in accordance with the study by Kuldip Singh et al, which had no reported port sinus cases.[12] One possible reason could be the shorter duration of follow-up in our study.

In our study, we used sterile glove of size 7.5-8.0 as an endobag which was uneventful for any mishap. We found it to be cost-effective, easily available, and easier to replicate for young residents in training and assistants. Worldwide, commercially available endobags are used for this purpose, examples including EndoCatch bag and Endopouch (Ethicon); Pleatman Sac (Abbot Medicals); and Ponsky Endosac (US Endoscopy). These endobags are easy to use, but the main demerit is the huge cost, which limits their use in the developing countries like Pakistan where patients usually pay for their surgeries. The other commonly used inexpensive alternatives include sterile male condoms, recloseable zipper bags, Nadiad bags. Out of all these sterile glove is the most common entity as backed by studies.[26] A few studies also implied using sterile empty polythene drain bags as endobag.[7,12]

Endo bags have been introduced in the setting of gall bladder retrieval with the benefit of a decrease in prevalence of surgical site infections, a decreased rate of intra-peritoneal contamination during retrieval, avoiding spillage of stones, and a decrease post-operative pain in Visual analog scales. An endo bag is also very helpful when used in suspected cases of GB cancer to reduce the risk of tumor cell seedlings and in situations of acute cholecystitis and GB empyema to prevent the wound from becoming contaminated with infected bile or stones when the GB is being removed. [27,28,29]Our study proves a very significant role of Endo bag in preventing intraperitoneal contamination in laparoscopic cholecystectomy, with statistically significant results.

A further point of interest is the fact that 22.3% experienced port site pain with Endo bag use compared to 14.5% incase of direct retrieval method. One possible explanation for this is the need to increase the fascial incision during the retrieval of the gall bladder,[30] which later on becomes a reason for

increased epigastric port site pain. This is further augmented by a study conducted in 2001 by Lomanto D et al, which proved that there is a significant reduction in post operative pain in VAS when 5mm trocar was replaced by 2mm trocar ultimately resulting in smaller fascial incision.[31] Increased fascial incision later on may lead to epigastric port site hernia, which may become a life-threatening complication if ignored and would require another surgery, adding to cost and liability. There have been cases of Richter`s hernia that occurred at a port site after laparoscopic surgery, reported, and its incidence is found to be 0.2% to 3%.[12] Our study didn't report any port site hernia in the Endo bag group, and one patient was reported to have a port site hernia in the direct retrieval group. Not performing fascial closure at the time of surgery could be one of the reasons for port site hernia later on, and this was taken care of in all of our patients indigenously.[12]

Several studies have also reported iatrogenic injury to the gut during manipulation and increased operative time while using the Endo bag.[23] However, it is subjective to the surgical skills of the operating surgeon.[32] For determining port site infection, we assessed the patients between their 7^{th} to 10^{th} post operative day, i.e. on their first follow up visit. Our results indicate 4.4% of the patients exhibiting port site infection in direct retrieval group while percentage reduced to 2% incase of endobag. As discussed above endobag has been successful in preventing port site spillage and thereby reducing contamination. It has been explained in study by Divya et al., the source of microorganisms in surgical site infections can be internal or external. Hollow viscera flora, patients' skin, subcutaneous fat, positive bile cultures are considered endogenous sources whereas any contaminated object or instrument, inadequate sterile techniques by surgeons and assistants are the exogenous pools.[7] In our study there was no morbidity reported in either of the groups. The cosmesis and total cost of surgery was similar for all the patients. Limitations: Although this study provides valuable insights regarding retrieval methods of the gall bladder during laparoscopic cholecystectomy, there are few limitations that need to be addressed. Firstly, variability of surgical skills might affect the results of the study as patients were operated by multiple surgeons. Moreover, our study being a single-centre study with a shorter duration of follow-up might prove to be a bias. To address this, further multicenter prospective trials, with longer duration of follow-up and decreased variability in surgical skills, will add to the benefit of masses.

CONCLUSION

Laparoscopic cholecystectomy is a safe and effective alternative to open surgery, but gallbladder retrieval remains a critical step associated with risks of bile spillage and contamination. Our study demonstrated that the use of an endobag significantly reduced intraperitoneal contamination and gallstone spillage compared to direct retrieval. Overall, while both techniques yielded comparable SSI outcomes, the use of endobags remains valuable in minimizing intraperitoneal contamination and preventing stone-related complications. In addition to this our study, proves the efficacy of sterile surgical glove as an innovative, cheap and safe alternative to the traditional specimen retrieval endobag for gall bladder extraction during laparoscopic cholecystectomies.

Authors Contribution:
Amjad Gul: Conception, Design and collection of data
Zaki Hussain Salamat: Data analysis, interpretation and writing
Muhammad Rashid Husnain: Conception, Design and collection of data
Najam Shabbir: Conception, data analysis, Approval of final draft
Syeda Sanila Aijaz: Interpretation of data and analysis
Shireen Sabir Ansari: Revision and finalization of manuscript

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Original Article **Open Access**

Comparison of Metformin and Insulin in the Management of Non-Obese Gestational Diabetes Mellitus Patients

Naimatullah Khan, Waheed Iqbal, Heema, Nizamuddin, Syed Hasnain Ali Shah, Noor Ul Ain

ABSTRACT

Objective: This study will aim to determine the effects of metformin and insulin in the management of non-obese GDM.

Study Design and setting: This Cohort study was carried out in the department of gynecology, Healthways Hospital Khyber Pakhtunkhwa (KPK) Pakistan. The duration of the study was 6 months started from May 2024 to Dec 2024.

Methodology: Total 160 GDM patients were recruited which were divided equally in to two groups. To one group metformin 500mg thrice daily were prescribed while insulin (mixtard 70/30) was prescribed to insulin group. The target fasting blood sugar (FBS) was set <95mg/dl. All the patients were followed for 2 months with FBS after 1st week, 2nd week, 14 days and 1 month interval**.**

Results: In metformin group, 32.5% patients were in 1st trimester, 41.25% were in 2nd trimester while 41.25% were in 3rd trimester while in insulin group the frequency of 1st, 2nd and 3rd trimester was 33.75%, 52.5% and 13.75% respectively. The mean age, BMI and FBS in metformin group were 26.74±3.5 years, 24.18±2.21 and 135.16±9.74 mg/dl respectively. There were no statistical differences observed between mean values of both group with p-values 0.96, 0.73 and 0.87 respectively. However, in insulin group there was statistically significant difference achieved in controlling the FBS after two months with p-value 0.04.

Conclusion: Insulin significantly controls the FBS but metformin also shows comparable results. Thus, metformin is a good first line drug in terms of cost and compliance to GDM patients especially in financially deprived area.

Keywords: Gestational Diabetes Mellitus, Hyperglycemia, Insulin, Metformin

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is referred to as hyperglycemia among women during pregnancy.[1] There is also increase probability of type 2 diabetes mellitus after pregnancy. GDM not only poses threats at maternal level but also there is an increased risk of adverse outcomes at fetal level as well. At maternal level, there is an increased risk of caesarean section (C-section), macrosomia, preeclampsia and intrauterine growth retardation. The fetal abnormalities are not limited to delay brain maturity, lower intelligence that normal delivered babies, language impairments and poor attention.[2] Thus an early diagnosis and treatment prevent both mother and child from adverse outcomes.[3] Unlike obese women with GDM, in whom insulin resistance predominates, GDM in lean women is believed to result primarily from impaired insulin secretion. The risk factors related to the development of GDM included family history of diabetes, low physical activity, advanced maternal age, BMI >30kg/m^2, inadequate diet and antenatal depression were reported by many researchers around the world.[4] This pathophysiological distinction underscores the need to evaluate whether management strategies should differ based on BMI.[5] Globally, the prevalence of GDM ranges from approximately 1% to 14%. Higher rates are

observed in populations with risk factors such as advanced maternal age, obesity, and specific ethnicities. Regional data indicate variability, with some regions reporting as low as 1–2%, while others, especially in South Asia and the Middle East, report a prevalence exceeding 10%. According to a study published in Australia, Asian women are at higher risk of developing GDM the Australian women.[6] South Asian countries reported higher prevalence of GDM as compared to rest of the world. In Pakistan, studies have reported a GDM prevalence ranging from approximately 7% to 14%, reflecting regional and methodological differences. This aligns with the higher prevalence of GDM observed in South Asia[2] However, according to a recent meta-analysis, the prevalence of GDM was reported to be 16.7%, thus posing treat to the rising burden of GDM in this subcontient.[7] The pathophysiology of GDM is complex and involved multiple complex mechanisms of hormonal, metabolic and cellular that leads to impairment of glucose regulation during pregnancy. These factors include insulin resistance, dysfunction in beta cells, and alteration in inflammatory biomarkers, genetic and environmental factors. The diagnosis of GDM is easy and cost effective thereby checking the fasting and random blood sugar during initial consultation. Diagnosis is typically established using a 75-g oral glucose tolerance test (OGTT), with plasma glucose thresholds of =92 mg/dL (5.1 mmol/L) fasting, =180 mg/dL (10.0 mmol/L) at 1 hour, or =153 mg/dL (8.5 mmol/L) at 2 hours.[7,8] The treatment options for the management of GDM are very limited and pharmacotherapy is required alongside diet modifications. The pharmacotherapy includes primarily insulin. However, metformin and glyburide are also considered as an alternative therapy in the management of hyperglycemia. Despite the role of pharmacotherapy, diet modification is as effective as pharmacotherapy in the management of hyperglycemia related to GDM. The ultimate goal of pharmacotherapy and diet modification in GDM is to manage hyperglycemia thereby preventing the mother as well as the fetus from adverse outocomes.[9] Usually metformin is employed in the treatment of GDM and if the hyperglycemia persists, insulin is added. The diverse mechanism of action of metformin beyond its gluco-regulatory and insulin sensitizing properties, makes metformin as a suitable candidate in the management of hyperglycemia associated with GDM. Metformin is also safe and effective in decreasing gestational weight gain, macrosomia and neonatal hypoglycemia.[10] Some randomized control trial reported insulin as more effective in the management of GDM while others found no statistical differences between both drugs while some published reports prefer metformin over insulin in the management of GDM. Studies on the long-term effects of metformin and insulin were also conducted and reports contradicting finding related to both metformin and insulin.[11-13] Thus further studies demanded to evaluate efficacy of both drugs in the management of GDM. Kohat being the fourth most populous city in Khyber Pakhtunkhwa with over 220,000 people, with limited resources and finances, research studies on such population are very impactful to explore these patients. Therefore, this study represents the people of Kohat with GDM and aims to compare the efficacy of metformin and insulin in the management of hyperglycemia related to GDM in Kohat Khyber Pakhtunkhwa.

METHODOLOGY

This quasi-experimental study was conducted in the department of gynecology and obstetrics, Health Ways hospital (HWH) Kohat, Khyber Pakhtunkhwa. The duration of the study was 6 months started from 2nd May 2024 to 30th Dec 2024. Total 160 GDM patients were included in the study which was calculated using openepi () taking power of study 80, 95% confidence interval, 5% margin of error and 11.8% prevalence [2] of GDM in Pakistan. Newly diagnosed GDM patients willing to participate in the study as per World Health Organization (WHO) criteria (FBS>92mg/dl, 1 hour RBS>180mg/dl or 2 hour RBS>153mg/dl) were included using non-probability convenient sampling.[14] The patients were properly enrolled after issuance of ethical approval letter from HWH via letter no. HWH-109 dated 13-05-2024. All the GDM patients were verbally informed in their local language regarding our research project and GDM patients whose showing willingness to participate in the study; proper consent was signed from each patient. Patients not consenting, having metabolic illness, and having pre-gestational diabetes were excluded from the study. After fulfillment of the inclusion criteria, the enrolled patients were thoroughly undergoing a detailed interview process where the demographics including age, parity, trimester, and BMI were initially recorded in a predesigned proforma. The patients were then categorized into two groups (group A and group B). Group A were prescribed metformin while group B was prescribed insulin. There was drop-off of 4 patients in metformin group and 7 patients in insulin group which were compensated by recruiting additional patients to meet the criteria of 80 patients in each group. To metformin group, metformin 500mg thrice daily was prescribed to maximum of 750mg thrice a day while insulin (mixtard70/30) were prescribed to insulin group as per gestational age and body weight. The target FBS was set to be <95mg/dl for which the dose was titrated after 72 hours till the target was achieved. All the patients were followed for 2 months with FBS after 1st week, 2nd week, 14 days and 1 month interval. If the target FBS was not achieved after two weeks in metformin group, the dose was increased to maximum (750mg), small doses of insulin were added to metformin group if the target FBS was not achieved with maximum dose. The criteria were adopted as per previous report published with slight modifications.[15] all the data was analyzed using SPSS version 26.0. The numerical variables were presented in mean ±

standard deviation (SD) while categorical variables were shown in frequency and percentages. To determine the possible association between categorical variables, chi-square test was used. For numerical variables, mean differences in both groups were observed using independent sample t-test. The considered test values were two-tailed and p-value <0.05 was considered significant. The graphs were constructed using MS-excel version 2013.

RESULTS

The clinical presentation of the patients is summarized in table 1. In metformin group primigravidas were present in 47.5% GDM patients while 52.5% were in insulin group. Similarly, multigravidas were prevalent in 52.5% and 47.5% in metformin and insulin group respectively. There were no statistically significant differences observed between both groups with p-value 0.31 reflecting a balanced enrollment of patients in both groups. In metformin group, 32.5% patients were in 1st trimester, 41.25% were in 2nd trimester while 41.25% were in 3rd trimester while in insulin group the frequency of 1st, 2nd and 3rd trimester was 33.75%, 52.5% and 13.75% respectively. Chi-square test reveals no statistical differences between both groups with p-value 0.12. The overall frequencies of trimester presentation are graphically shown in figure 1.

Table 1: Presentation of GDM patients and its association between groups

Variables	Groups	Metformin group (n=80)	Insulin group (n=80)	p-value
Obs. status	Primigravida	38 (47.5%)	42 (52.5%)	0.31
	Multigravida	42 (52.5%)	38 (47.5%)	
Trimester	1st trimester	26 (32.5%)	27 (33.75%)	0.12
	2nd trimester	33 (41.25%)	42 (52.5%)	
	3rd trimester	21 (26.25%)	11 (13.75%)	

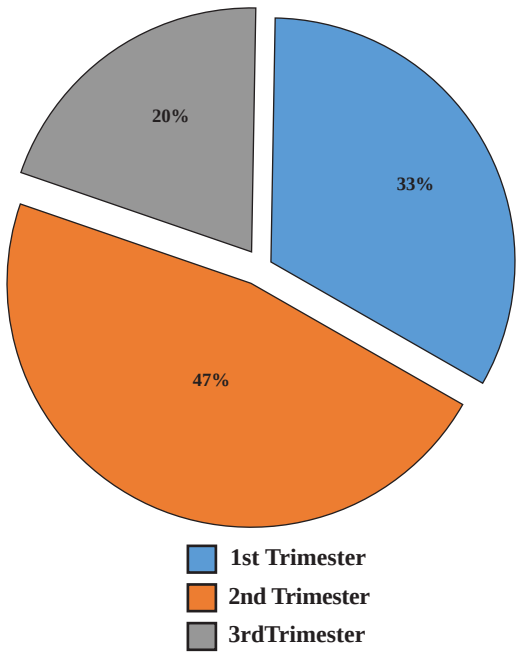
Table 2: determination of mean differences between both groups (n=160)

Variables	Groups	Mean±SD	p-value	95%CI
Age (years)	Metformin	26.74±3.5	0.96	-1.18-1.13
	Insulin	26.76±3.1		
BMI (kg/m^2)	Metformin	24.18±2.2	0.73	-0.83-0.58
	Insulin	24.30±2.3		
FBS (mg/dl)	Metformin	135.16±9.7	0.87	-3.12-2.65
	Insulin	135.46±8.7		
FBS after 1 week	Metformin	91.28±10.4	0.73	-2.76-3.91
	Insulin	91.70±10.9		
FBS after 2nd week	Metformin	87.98±8.8	0.12	-4.9-0.59
	Insulin	90.14±8.7		
FBS after one month	Metformin	88.16±8.9	0.16	-0.72-4.1
	Insulin	86.48±6.2		
FBS after two months	Metformin	86.94±8.0	0.04	0.02-4.0
	Insulin	84.89±4.4		

In order to determine the mean differences between both groups, independent sample t-test was used. The mean age, BMI and FBS in metformin group were 26.74±3.5 years, 24.18±2.21 and 135.16±9.74 mg/dl respectively. Similarly, in insulin group, the mean age was 26.76±3.1 years, mean BMI was 24.30±2.3 kg/m^2, and mean FBS was 135.46±8.7mg/dl. After 1st week of follow-up, the mean FBS in metformin and insulin group was 91.28±10.4mg/dl and 91.70±10.9mg/dl respectively. In 2nd follow-up after 2 weeks, the mean FBS in metformin group was 87.98±8.8mg/dl and in insulin group it was 90.14±8.7mg/dl. After 3rd follow-up (one month), both mean FBS levels were comparable (88.16±8.9mg/metformin group vs. 86.48 ± 6.2mg/dl in insulin group). There were no statistical differences observed between mean values of both group with p-values 0.96, 0.73 and 0.87 respectively. This proves that both drugs are helpful in controlling the blood glucose in GDM patients. However, after two months of follow-up the mean FBS levels in metformin and insulin group were 86.94±8.0mg/dl and 84.89±4.4mg/dl respectively, showing that insulin group provides statistically significant reduction in controlling the FBS after two months as compared to metformin with p-value 0.04. Further details of the demographic and biochemical variables are summarized in table 2.

The insulin group achieved the targeted FBS after two months follow up while only 5% patients in metformin group does not achieve targeted FBS levels and insulin were added to their regimen.

Figure 1: Trimester presentation of GDM patients



DISCUSSION

The prevalence of DM in our country is up surging at alarming rate creating financial burden on developing country like Pakistan. Though the exact prevalence of GDM in our country is yet to known but city based small studies reports high prevalence of GDM in Pakistan. This condition poses high risk to both mother and child leading to high rate of morbidity and mortality. To limit the adverse outcomes, proper screening is necessary to diagnose GDM early in pregnancy and provide effective treatment to properly control the hyperglycemia related to GDM. In general, the studies focusing on the use of metformin in GDM are very limited as compared to insulin. This study compared the efficacy of metformin and insulin in controlling FBS levels in non-obese GDM patients. Such studies are not conducted particularly in Kohat Khyber Pakhtunkhwa and we are the 1st to report such studies from the peripheries.

In this experimental study, we enrolled 160 GDM patients who were equally divided into two groups (group A and group B) and were followed for 2 months at four follow-up intervals. Group A were prescribed metformin 500mg thrice daily to maximum of 750mg thrice a day while insulin (mixtard70/30) were prescribed to insulin group as per gestational age and body weight. The target FBS was set to be <95mg/dl in both groups. The demographics of our study participants in both groups including age, BMI, gestational age and clinical presentation were similar and does not differ significantly (p-value >0.05), suggesting that patients in both groups were enrolled with extreme cautions and the differences observed in FBS control were more likely due to different treatment modalities rather than underlying patient factors.

In our study, both metformin and insulin provide effective control in managing targeted FBS (<95mg/dl) in GDM patients. Metformin manages hyperglycemia in GDM patients primarily by reducing hepatic glucose production and improving peripheral insulin sensitivity. It also decreases the production of glucose in the liver, which lowers the amount of glucose released into the bloodstream. Additionally, metformin also facilitates the transport of glucose in the muscle and adipose tissue, thereby increasing glucose utilization and reducing blood glucose levels. Unlike insulin, metformin does not stimulate insulin secretion but improves the body's response to existing insulin, making it effective in managing hyperglycemia in GDM without causing hypoglycemia. On the other hand, insulin controls hyperglycemia in gestational diabetes mellitus (GDM) patients primarily by facilitating glucose uptake and utilization, thereby lowering elevated blood glucose levels. In GDM, insulin resistance increases due to placental hormones, leading to impaired glucose regulation. Administered insulin compensates for this resistance by enhancing cellular glucose uptake, especially in muscle and adipose tissues. Suppress the hepatic glucose production, reducing endogenous glucose release into the bloodstream. Promote glycogen synthesis and storage in the liver and muscles. Inhibit the lipolysis, which reduces free fatty acid levels that can worsen insulin resistance. The advantage of metformin over insulin is that metformin does not cause hypoglycemia while insulin may cause hypoglycemia so patient education is very necessary.[16] Our findings are similar with the studies published previously. According to a randomized control trial (RCT) by Tertti et al reported that both metformin and insulin provides comparable results in treating GDM patients reflecting our initial findings that both metformin and insulin manage the glucose levels effectively in GDM patients.[17] A meta-analysis published by Xin Bao et al also reported potential benefits of metformin for pregnant women and babies with no adverse effects, showing the safety and efficacy of metformin and insulin to both mother and child in a long run.[18] Based on determination of adverse events, a study published by Paavilainen et al reported no differences between metformin and insulin in neuropsychological and cognitive outcome in children whose mother were treated with metformin and/or insulin, showing comparable results of metformin and insulin related to prospective child health.[18] Similarly, another randomized control trials (RCT) published by Sheng et al related to the neonatal adverse outcome in GDM patients on metformin versus insulin found no short term adverse outcome in metformin group suggesting that metformin is safe and effective alternative to inuslin.[20]

Our study demonstrated a statistically significant difference in controlling FBS levels after two months. These findings are in line with Ainuddin et al who showed that insulin therapy was more effective than metformin in achieving glycemic control in GDM patients.[21] The superior glycemic control with insulin as compared to metformin may be attributed to its direct action on glucose metabolism, allowing for more precise control of blood glucose levels. A most recent meta-analysis published by Wu et al also reported that metformin may also reduce adverse outcome related to both mother and child as compared to insulin, however long-term follow-up in necessary.[22] However, contradicting findings related the effects of metformin and insulin was also reported. A study conducted by Cesar et al, reported metformin provides better control of post prandial sugar as well as lower episodes of hypoglycemia and maternal weigh gain as compared to insulin.[23] Similarly, a meta-analysis summarizes fifty RCTs representing Chinese population also reported that metformin provides better picture in controlling maternal hyperglycemia and glycated hemoglobin levels as compared to insulin.[24]

The findings of our study have important implications for clinical practice in the management of GDM patients especially in financially deprived area, Kohat Khyber Pakhtunkhwa. As our findings report comparable results of both metformin and insulin, metformin may be considered

as the first line drug for non-obese GDM patients where insulin therapy may be challenging due to cost or access constraints. Studies related to the cost and effectiveness were also done and according to a study published by Ainuddin et al, reported that metformin is an effective and cheap treatment option for patients with GDM [21] with no potential harm or adverse outcomes to both mother and child.[25]

From the previous published reports, it has been summarized that both insulin and metformin show comparable results in the management of hyperglycemia associate with GDM. Furthermore, studies on long term follow-up to evaluate the efficacy and adverse outcomes also reported comparable results of both metformin and insulin. In a net shell, though most of the studies were in favor of insulin but metformin cannot be subsided because of its cheap price, no hypoglycemia effects as well as no short- and long-term adverse outcome both maternal and fetal. Thus, metformin is safe and effective alternate for insulin in the management of GDM especially in our vicinity.

Limitation of the study: This study was limited to single ethnic group and one center. Enrollment of patients from different ethnic groups, urban and rural as well as involving multiple centers with large sample size would provide a better picture of the current study. Furthermore, a longer maternal follow-up duration as well as studies focusing children born from GDM mothers will present a better picture for both drugs.

CONCLUSION

In our study both metformin and insulin show promising results in the management of FBS in non-obese GDM patients. However, insulin provides a slightly better control but given to its cost effectiveness and comparable efficacy, metformin is a better first line therapy option for non-obese GDM patients. Further research is needed to determine the long-term outcomes and potential benefits of combination therapy in GDM management.

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Authors Contribution:
Naimatullah Khan: Conception, Design and collection of data
Waheed Iqbal: Data analysis, interpretation and writing
Heema: Conception, Design and collection of data
Nizamuddin: Conception, data analysis, Approval of final draft
Syed Hasnain Ali Shah: Interpretation of data and analysis
Noor ul Ain: Revision and finalization of manuscript

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Original Article **Open Access**

Comparison of the Outcome of Coblation Tonsillectomy versus Cold Dissection Tonsillectomy

Aqsa Yaqub, Muhammad Zeeshan Ashraf, Sarfraz Latif, Sadaf Zafar, Laraib Abro, Arslan Liaqat

ABSTRACT:

Objectives: To compare the outcome of coblation tonsillectomy versus cold dissection tonsillectomy.

Study design & settings: Randomized controlled trial from 26th September 2025 to 25th December 2025 at ENT Department at Sheikh Zayed Hospital, Lahore.

Methodology: All patients with chronic tonsillitis of duration >3 months, age 20 to 60 years of either gender were included. Tonsillar cancer, known bleeding disorders (INR >1.5), and a history of peritonsillar abscess were excluded. Patients in a group Group B's tonsils are removed via cold dissection, while group A's tonsils are removed by coblation. Seven days following the operation, the mean post-operative pain was assessed. There were additional reports of initial bleeding, secondary bleeding, and secondary infection. The postoperative discomfort in both groups was compared using the independent "t" test, and the primary, reactionary, and secondary hemorrhages were compared using the chi square test; a p-value of =0.05 was deemed significant.

Results: In this study, mean intra-operative blood loss in Group A (coblation tonsillectomy) was 28.90 ± 7.78 ml while in Group B (cold dissection tonsillectomy) was 42.07 ± 4.77 ml (p-value = 0.0001). Mean post-operative pain in Group A was 2.20 ± 0.89 while in Group B was 4.87 ± 1.14 (p-value = 0.0001). Secondary hemorrhage was found in 3.33% patients in the cold dissection group and 0.0% in the coblation group.

Conclusion: Coblation tonsillectomy offers benefits such decreased intraoperative blood loss, shorter surgery time, and quicker return to a normal diet.

Keywords: Coblation, tonsillectomy, post-operative pain, blood loss, hemorrhage

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INTRODUCTION:

The tonsils are a component of the Waldayer's ring, an assembly of lymphoid tissue found in the oropharynx and nasopharynx at the aerodigestive tract's entry. It has a significant impact on children's immunology and defense mechanisms, antibody secretion, and most notably, secretory Ig A synthesis, which is crucial for the mucosal defense mechanism. Their defense system occasionally malfunctions and becomes the source of infection, resulting in recurring sore throats, fevers, and other problems for no apparent reason. This necessitates tonsillectomy, or the removal of the diseased tonsils.[1]

In 30 BC, Celsus was the first to describe tonsil removal. Since that time, numerous techniques of surgery and improved instruments have been created with this purpose.[2] The process should ideally be quick, painless, and bloodless. However, in practice, there are risks associated with every tonsillectomy technique. Even though tonsillectomy is the most common and straightforward surgery, the surgeon is constantly concerned about the high risk of complications, such as intraoperative and postoperative hemorrhage, which can cause shock and occasionally even death.[3]

The two most common postoperative outcomes after

tonsillectomy are discomfort and bleeding. The guillotine operation, cold dissection, electrocautery, harmonic scalpel, coblation, and laser surgery are only a few of the additional methods described in the literature.[3] One of the most traditional and tried-and-true methods is the traditional cold dissection method with metal tools. This leaves an open wound that can be healed by secondary intention. Initially employed for arthroscopic procedures, the coblation method is a relatively recent technique. In 1998, a new technique for tonsillectomy was introduced: radiofrequency-based dissection in the plasma field.[4] Coblation tonsillectomy was initially suggested as an efficient and safer method of tonsil removal in 2001. This technique ablates tissue at relatively low temperatures (4070 to C) by producing a plasma field at the surface of the probe. This is in contrast to diathermic coagulation which causes temperatures extending to 500 o C, this plasma field consisting of highly ionized particles examines and separates the molecular bonds of restricted tissue, significantly reducing heat loss to adjacent tissues. Radiofrequency generator may also be used to perform coagulation in order to attain hemostasis.[5,6]

Concerning the different surgical procedures, the more critical issues when it comes to defining which modality is the best to use in this treatment are augmenting intra-operative effectiveness, and reducing post-operative morbidity. Pain and bleeding, which expose the wound to secondary intention healing, are two of the main postoperative problems associated with cold steel dissection tonsillectomy.[4,5] The quality of life following tonsillectomy can be assessed by tracking complications (hemorrhage), tonsillar fossa healing, postoperative pain, and return to a normal diet. The coblator reduces blood loss, shortens the time required for surgery, and lessens the possibility of damage to adjacent tissues like the uvula, posterior pillar, and anterior pillar.[6] Studies have demonstrated that the coblation strategy is better than conventional methods, however the results are often inconsistent. Coblation is associated with an earlier return to normal activity, despite the increased risk of recurrent bleeding.[7]

According to one study[8], patients treated with coblation tonsillectomy had an average operating time of 20.2 minutes, SD = 4.7, while those treated with traditional cold dissection tonsillectomy had an average operating time of 31.2 minutes, SD = 4.3. According to a similar study, the cold dissection group experienced higher mean post-operative pain after 7 days (1.84 ± 0.85) than the coblation group (1.24 ± 0.77).[8] There was secondary hemorrhage in 3.26% patients in the cold dissection group and 0.0% in the coblation group.[9]

I've decided to compare the outcomes of coblation and cold dissection tonsillectomy in the local community because there isn't much information available. In addition to adding significantly to the corpus of current literature, my study included local information.

METHODOLOGY:

After approval from institutional ethical review committee (Ref no. 02-TERC/NHRC-SZH/INT-SC/768 dated 26-6-2025), the ENT Department at Sheikh Zayed Hospital, Lahore conducted this Randomized controlled trial (ClinicalTrials.gov Identifier: NCT07488858) from 26th September 2025 to 25th December 2025. The WHO calculator was used to figure out the sample size for two population means. With a 95% confidence level, 80% research power, and a mean pain score in cold dissection as 1.84 ± 0.85 and coblation as 1.24 ± 0.77, the sample size of 60 cases—30 in each group—was set.[8]

All patients with chronic tonsillitis (Clinical examination of recurrent tonsillitis with four acute tonsillitis attacks in a year revealed a high grade fever (>101 F), red, swollen tonsils and anterior pillars, and a palpably sore jugulodigastric lymph node in each attack (at least three attacks in a year)) of duration >3 months, age 20 to 60 years of either gender were included. H/o peritonsillar abscess, known bleeding disorder (INR >1.5) and tonsillar malignancy were not included.

Every patient was asked for their informed permission. Demographic information (age, gender, and length of illness) were then taken. Each selected case was selected by lottery into either group A or B. In group A, the tonsils are removed using coblation and on group B, the tonsils are removed using cold dissection. Through the assistance of the researcher, all procedures have been performed by one surgical team.

General anesthesia was used for the procedure, and either nasal or oral endotracheal intubation was used. A appropriate Boyle Davis mouth gag with tongue blade was used to open the mouth while the head was positioned in Rose's position. Draffin's bipod, which is stabilized by the Maguran plate, then stabilizes the mouth. Tonsils are held in place with Dennis Brown tonsil retaining forceps. With this approach, a scissor was used to make an incision just medial to the anterior pillar. Once the capsule was identified, Gwynne-Evans's dissector was utilized to perform the dissection. In this plain, dissection was carried out until the lower pole was reached. Negus artery forceps crushed the lower pole, and then scissors severed the tonsil. Next, a Negus knot tier was used to press an outer knot made of No. 1 silk inside. The suture is severed after the knot below the lower end of the double-curved artery forceps is tightened, the Negus forceps are removed, and another knot is made. Lastly, a Mollisons anterior pillar retractor was used to examine the fossa and look for any bleeding. If a bleeder point was discovered, bipolar diathermy is used to either ligate or cauterize it. For the other site, the identical procedures are done. Both procedures require the same postoperative care and drugs. To prevent edema from forming, the patient's head was elevated above the level of the heart in the ward by resting it on a cushion. The jugulodigastric area can be

covered with ice packs wrapped in gauze. The patient can start taking cold beverages and ice cream on day 0. Patients are advised to begin eating semi-liquid foods on day one. A few days following surgery, antibiotics were recommended.

Following the device's setup, we employ an EVAC70 T&A (ArthroCare ENT, Sunnyvale, CA), which is configured to have an irrigation system linked. To determine the precise plane of dissection between the tonsillar capsule and its bed, we made an incision in the anterior pillar at the level of the tonsil's higher pole. From upper to lower pole, we start the process. To preserve the dissection in the interim, we alter how the tonsil is handled. Coagulation mode is used to control any bleeding. To enable the plasma field that is created at the wand's tip to work, we gently move the wand as if we were holding a pencil while maintaining a very little gap between the wand's tip and the tissue. Until the lower pole is located and separated, the process is repeated. For added security, the lower pole may be ligated in adults.

All patients received the same anesthesia and recovery room procedures. Mean post-operative pain was measured using a visual analoque scale 7 days after the procedure, with 0 representing no pain and 10 representing the severe pain. Secondary infection: presence of purulent discharge (thick and milky discharge from a wound) and resulting in opening of the skin wound within 2 weeks after operation. Primary hemorrhage: Bleeding during tonsillectomy procedure. It was quantified in milliliter (ml). Reactionary hemorrhage: Bleeding within 24 hours of tonsillectomy. Its occurrence was noted only. Secondary hemorrhage: Bleeding occurring between 24hrs – 2 weeks after tonsillectomy. Its occurrence was noted only. Pre-designed Performa will be used to gather the data.

The data was entered and analyzed using SPSS version 25.0. For age, length of sickness, and postoperative pain score, the mean and SD were shown. Gender, housing location (rural versus urban), hemorrhage, frequency and percentage were all shown. The postoperative pain was compared by independent t test and the chi square test of the hemorrhage; a p-value of =0.05 was considered significant. Age, gender, duration of sickness, and place of residence (rural vs. urban) were the factors used for stratification. The independent t-test was used following stratification, and a p-value of =0.05 was deemed significant.

Table-1: Distribution of different variables (n=60)

		Group A (n=30)	Group B (n=30)
		Number (%)	Number (%)
Age (years)	20-40	26 (86.67%)	25 (83.33%)
	41-60	04 (13.33%)	05 (16.67%)
Gender	Male	18 (60.0%)	19 (63.33%)
	Female	12 (40.0%)	11 (36.67%)
Duration of disease (months)	<6	11 (36.67%)	12 (40.0%)
	>6	19 (63.33%)	18 (60.0%)
Residence	Rural	11 (36.67%)	09 (30.0%)
	Urban	19 (63.33%)	21 (70.0%)

RESULTS:

Age was 31.90 ± 7.86 years on average. Patients in groups A and B had mean ages of 32.07 ± 7.92 and 31.73 ± 8.61 years, respectively. According to Table 1, the majority of the 51 patients (85.0%) were in the 20–40 age range. With a male to female ratio of 1.6:1, 37 (61.67%) of the 60 patients were men and 23 (38.33%) were women. Group A's mean illness duration was 7.50 ± 2.36 months, whereas group B's was 7.23 ± 2.21 months. Table 2 displays the distribution of several variables.

In this study, mean operative time in group A (coblation tonsillectomy) was 21.92 ± 6.83 minutes and in group B (cold dissection tonsillectomy) was 30.29 ± 8.67 minutes. Mean intra-operative blood loss in Group A (coblation tonsillectomy) was 28.90 ± 7.78 ml while in Group B (cold dissection tonsillectomy) was 42.07 ± 4.77 ml (p-value = 0.0001). Mean post-operative pain in Group A (coblation tonsillectomy) was 2.20 ± 0.89 while in Group B (cold dissection tonsillectomy) was 4.87 ± 1.14 (p-value = 0.0001) as shown in Table 2. There was no primary infection and reactionary hemorrhage in both groups. Secondary hemorrhage was found in 3.33% patients in the cold dissection group and 0.0% in the coblation group.

Stratification of intra-operative blood loss and post-operative pain with respect to effect modifiers is shown in Table 3 & 4 respectively.

DISCUSSION:

Even though tonsillectomy is a frequent procedure carried out by otolaryngologists, there are still hazards associated with it, including bleeding and post-operative pain.[10,11] To determine the best tonsillectomy procedure in terms of

Table-2: Comparison of outcome between both groups

Outcome	Group A (n=30)	Group B (n=30)	p-value
	Mean ± SD	Mean ± SD	
Operative time (min)	21.92 ± 6.83	30.29 ± 8.67	0.0001
Intra-operative blood loss (ml)	28.90 ± 7.78	42.07 ± 4.77	0.0001
Post-operative pain	2.20 ± 0.89	4.87 ± 1.14	0.0001

Table 3: Stratification of intra-operative blood loss with respect to effect modifiers

		Group A (n=30)	Group B (n=30)	P-value
		Blood loss (ml)	Blood loss (ml)	
		Mean ± SD	Mean ± SD	
Age (years)	20-40	28.81 ± 7.73	41.36 ± 5.91	**0.0001**
	41-60	29.50 ± 9.33	45.60 ± 8.68	
Gender	Male	28.94 ± 7.73	41.63 ± 5.53	
	Female	28.83 ± 8.20	42.82 ± 8.08	
Duration of disease (months)	=6	31.73 ± 5.59	39.83 ± 5.64	
	>6	27.26 ± 8.52	43.56 ± 6.71	
Residence	Rural	31.82 ± 7.08	39.0 ± 5.39	
	Urban	27.21 ± 7.84	43.38 ± 6.56	

Table 4: Stratification of postoperative pain with respect to effect modifiers

		Group A (n=30)	**Group B (n=30)**	**P-value**
		VAS score	**VAS score**	
		Mean ± SD	Mean ± SD	
Age (years)	20-40	2.15 ± 0.92	4.88 ± 1.20	**0.0001**
	41-60	2.50 ± 0.58	4.80 ± 0.84	
Gender	Male	2.28 ± 0.75	5.11 ± 1.05	
	Female	2.08 ± 1.08	4.45 ± 1.21	
Duration of disease (months)	=6	1.73 ± 0.65	5.25 ± 0.97	
	>6	2.47 ± 0.90	4.61 ± 1.20	
Residence	Rural	1.64 ± 0.81	4.89 ± 1.27	
	Urban	2.53 ± 0.77	4.86 ± 1.11	

cutting down on surgery time, limiting blood loss, and avoiding problems like discomfort and postsurgical hemorrhage, surgeons continuously evaluate different approaches. The purpose of this study was to compare tonsillectomy by coblation with the conventional dissection method in adult patients.

According to the current study, the mean duration of coblation tonsillectomy was much lower than that of cold dissection tonsillectomy. This result implies that lower intraoperative periods may be linked to coblation-assisted tonsillectomy, which could result in shorter surgical times and less anesthetic exposure. This result demonstrates a possible efficiency benefit of coblation-assisted tonsillectomies, which could help patients and surgical teams by cutting down on anesthetic duration and total surgical process time. In contrast to coblation-assisted instances, which required 4.2 minutes, the conventional approach required 7.2 minutes for the operation, according to Zainon et al.'s report.[12] The coblation-assisted tonsillectomy took 15 minutes to perform, while the usual procedure only took 11 minutes, according to a research by Rakesh et al.[13] In their investigation, Pachar K et al. came to the conclusion that the intraoperative times for the two procedures did not differ significantly.[14] When compared to other research, some concluded that the coblation-assisted method required surgical competence and took longer, while others found that the procedure's mean time was shorter.

According to the current study, compared to cold dissection tonsillectomy, coblation tonsillectomy showed a much decreased mean blood loss during the process. This result implies that, in comparison to traditional tonsillectomy, coblation-assisted tonsillectomy might result in less intraoperative hemorrhage. Specifically, the mean intra-operative blood loss in Group A (coblation tonsillectomy) was 28.90 ± 7.78 ml while in Group B (cold dissection tonsillectomy) was 42.07 ± 4.77 ml (p-value = 0.0001). This finding suggests that coblation-assisted tonsillectomy may help reduce intraoperative bleeding, which could improve surgical outcomes, cut down on hemostasis operating times, and hasten patient recovery. In their study, Nallasivam et al. found that patients who had tonsillectomy using the traditional technique lost more blood on average (43.4 ml) than those who had tonsillectomy with coblation assistance (18.7 ml).[15]

According to the results, patients who had coblation had consistently lower pain scores at all time periods and needed fewer analgesic doses during the first week following surgery. These results imply that, in comparison to the conventional method, coblation offers a more delicate surgical approach, leading to better patient comfort and a quicker recovery.

The current study's findings are consistent with a number of earlier studies that emphasized the benefits of coblation in lowering postoperative morbidity. Several studies have demonstrated that coblation is linked to fewer pain episodes, an earlier oral feeding resume, and a decreased requirement for medication. Goyal A et al[16] explained the positive effects of coblation by describing it as a technique that restricts heat injury to surrounding tissue. In a similar vein, individuals receiving coblation reported far lower pain levels than those having cold dissection, according to Muddaiah D et al.[17] However, not every study cites the same advantages. Due to variations in study populations, sample sizes, or the operating surgeon's experience, some researchers have not found statistically significant differences between the two methods. Coblation-assisted tonsillectomy patients had significantly greater postoperative pain assessments. According to Lavania A et al.'s research, patients undergoing coblation-assisted tonsillectomy used fewer analgesics, experienced less discomfort, and resumed their regular eating and activities faster than those undergoing dissection tonsillectomy.[18] In their investigation, Jat et al. also found that patients who had tonsillectomy using the traditional technique experienced much more postoperative pain.[19]

The current study indicates that there was no primary infection and reactionary hemorrhage in both groups. Secondary hemorrhage was found in 3.33% patients in the cold dissection group and 0.0% in the coblation group. Only one patient had a secondary hemorrhage on the right side on the seventh day, which resulted in delayed healing, according to a research by Karathia et al.[20]

In the same study, Mostafa et al. identified a reduced primary tonsillectomy hemorrhage rate compared to the dissection method and higher rate of secondary tonsillectomy hemorrhage (60 patients). The time to resume the normal activity (which was determined by resuming job activities) as well as the average time to resume normal diet was significantly less in the coblation group.[21]

In their prospective investigation, Muthubabu et al. came to the following conclusions: coblation is a rather simple procedure that produces a bloodless field with little tissue injury. Compared to the dissection approach, the coblation process needed more operating time. Neither higher intraoperative blood loss nor increased postoperative pain were brought on by the lengthier duration. Compared to the dissection and snare approaches, the coblation method resulted in a much lower intraoperative blood loss. The coblation approach helped the patient return to regular activities sooner since the postoperative pain scores were much reduced.[22] A meta-analysis also found that the coblation approach produced improved perioperative results.[23] Coblation is chosen over traditional methods since it allows for a quicker return to normal even at work.[24]

According to a different study[25], it took an average of 42.9 minutes for the dissection approach and 34 minutes for the coblation technique to achieve full hemostasis after making an incision. On average, 51.8 ml of blood was lost using the dissection approach, while 22.3 ml was lost using the coblation technique. It was determined that this difference was statistically significant. A visual analog scale was used to assess pain. After statistical analysis of the data collected from the two groups, the independent t-test was used to determine the "p" value. Over a ten-day period, the average pain score for the coblation technique was 2.72, while the average pain score for the dissection approach was 4.84.[25]

Notwithstanding the encouraging outcomes, it is important to recognize some of this study's shortcomings. Despite using a Visual Analog Scale, pain evaluation is intrinsically subjective and impacted by personal tolerance. Furthermore, the study was restricted to a single institution and had a small sample size, which limits how broadly the results may be applied. Multicenter, prospective randomized controlled trials with greater sample sizes should be a part of future research in order to assess a wider variety of clinical outcomes and give more robust data.

Limitations: Possible limitations to this Study are sample size, patient drop outs and the duration of the study. The Study has its limitation in the number of participants (n=60); it might be insufficient to identify the relatively uncommon hemorrhage complication and pain after tonsillectomy. Additionally, the patients who drop out may also affect the outcome and result in an overestimation of the risk of a particular treatment compared to the other. Finally, the study will be restricted to two weeks after operation. Follow-up would be a long term study that would enable investigations of long term results of the two techniques.

CONCLUSION:

In summary, the results show that, in comparison to traditional tonsillectomy, coblation tonsillectomy offers benefits such decreased intraoperative blood loss, shorter surgery time, and quicker return to a normal diet. The research highlights the potential advantages of coblation tonsillectomy in improving patient outcomes and accelerating recovery, even though traditional techniques may be favored for treating postoperative pain. However, when choosing the best tonsillectomy technique, it is essential to consider unique patient characteristics and surgical preferences. Even though coblation tonsillectomy has benefits including less intraoperative blood loss and quicker recovery, it's important to carefully weigh aspects like cost-effectiveness, surgeon experience, and patient-specific considerations.

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Aqsa Yaqub: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published
Muhammad Zeeshan Ashraf: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published
Sarfraz Latif: Conception, acquisition of data, critical revision of the manuscript
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Original Article **Open Access**

Anxiety and Depression in Rheumatoid Arthritis Patients and its Impact on the Quality of Life

Ishma Arif, Anila Nisar, Anum Rasheed, Aanum Misbah Hasanat, Amber Iltaf

Abstract:

Objective: To determine the frequency of depression and anxiety among patients with rheumatoid arthritis (RA) and to assess its impact on the quality of life.

Study Design and Setting: This cross-sectional study was conducted in KRL hospital Islamabad from 1-January-2025 to 31-July-2025.

Methodology: 115 patients aged 18 years or older with a confirmed diagnosis of RA were included. To evaluate disease severity, standardized criteria i.e. the Disease Activity Score involving 28 joints (DAS28) was employed. The Hospital Anxiety and Depression Scale (HADS), a validated instrument, was used to measure symptoms related to depression and anxiety. The impact on patients' quality of life was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI).

Results: 15 participants (13.0%) were male, while 100 participants (87.0%) were female. The mean duration of RA was 7.70 (±6.41) years. Among the participants, 30 patients (26.1%) were identified as experiencing depression, whereas 22 patients (19.1%) were found to have anxiety. Mean ESR, tender joint count (TJC), swollen joint count (SJC) and VAS score were significantly high in patients with depression and anxiety. The DAS-28 scores averaged 4.88 (±1.36) for those with anxiety/depression versus 3.85 (±1.26) for those without (P-value <0.0001) showing moderate disease activity in both groups. The HAQ-DI score averaged 1.33 (±0.84) for individuals with anxiety/depression as compared to 0.77 (±0.68) for those without (P-value <0.0001).

Conclusion: There is a considerably high prevalence of anxiety and depression among RA patients with a significant impact on the quality of life.

Keywords: Anxiety, DAS-28, depression, HADS, HAQ-DI, rheumatoid arthritis

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INTRODUCTION:

Rheumatoid arthritis (RA), a chronic systemic inflammatory disorder comprising of both articular and extra articular symptoms is an autoimmune condition resulting in progressive joint damage and impaired quality of life.[1] Despite ongoing research, the exact etiology of this condition remains unclear, though multiple studies show a complex interaction between various factors such as genetic susceptibility, environmental exposures, and aberrant autoimmune responses leading to disease onset and progression.[2] Autoantibodies present in rheumatoid arthritis such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can be detected years before the onset of the disease and are usually associated with more severe manifestations.[3] A variety of immune cells including T cells, B cells, macrophages, and dendritic cells, are involved in the immune dysregulation which leads to synovial inflammation and eventual joint damage.[4]

Even though RA can affect individuals of all ages, it is most commonly diagnosed in patients between 40 and 60 years of age, with a female-to-male predominance of

approximately 2–3:1.[5] The global prevalence of RA ranges from around 0.5% to 1%, with slight variations present due to differences in geographical regions, ethnicity, and study methodology.[6] In addition to joint inflammation and destruction, RA is a multisystem disease with extra-articular manifestations as well. These include cardiovascular complications, such as accelerated atherosclerosis and increased risk of myocardial infarction, pulmonary involvement, hematologic abnormalities, renal involvement and metabolic bone disease leading to osteoporosis.[7] Patients also report symptoms of fatigue, sleep disturbances, and chronic pain leading to significant functional impairment and reduced quality of life.[8] Psychological conditions such as anxiety and depression are commonly seen in RA population and these further contribute to the disease burden.[9]

Studies show that chronic inflammation is a major contributing factor to the increased incidence of depression seen in rheumatoid arthritis (RA), resulting in observation of a decline in the health-related quality of life (HRQoL).[10] Since there is a close relationship between mental health and RA disease activity, factors such as pain, functional limitations, and fatigue, have a major impact on the psychological well-being of the patient. Studies indicate that the prevalence of depression among patients with RA is estimated to be around two to three times greater than the normal population.[11] A recent meta-analysis reported that approximately 17.9% of patients with RA experience depressive symptoms, with lifetime prevalence reaching 32.4%, emphasizing on the persistent and substantial burden of mood disorders in this population.[12] Psychological comorbidities often emerge within a few years of disease onset. Within the initial five years of the disease, approximately 30% of RA patients develop depression, while 20% experience anxiety disorders, demonstrating a sequential relationship between the disease course and mental health complications.[13] Both depression and anxiety in RA have been consistently associated with higher levels of disease activity, greater amount of pain, reduced physical function, and poor HRQoL, emphasizing on the effect of psychological distress on patient outcomes.[14] Therefore, routine screening for the presence of features of depression and anxiety in patients with RA, is necessary for the introduction of mental health interventions into disease management strategies to ensure both physical and psychological well-being of patients.[13,14] Chronic diseases like RA, can significantly influence an individual's quality of life. Factors such as chronic pain, social and functional impairments, disability leading to unemployment, and adverse effects from medications all play a crucial role in this impact. Furthermore, systemic inflammation in RA has also been associated with impaired cognitive function, including deficits in attention, memory, and executive functioning, which can further deteriorate daily functioning and self-management of the disease.[15]

Apart from this, psychological comorbidities are also common in RA such that depression and anxiety frequently co-occur with the disease. This is linked to higher pain perception levels, greater functional impairment, and significantly lower health-related quality of life (HRQoL).[16]

Prospective cohort data suggests that the presence of depressive and anxiety symptoms in RA patients is linked with markedly decreased chances of achieving clinical remission over a two-year follow-up period. [17] This emphasizes on the bidirectional relationship between psychological health and RA disease activity, stressing that mental health not only affects patient well-being but also influences the long-term clinical outcomes. The present study aims to establish the prevalence of depression and anxiety among patients with RA and to evaluate their impact on health-related quality of life, thereby providing valuable insight into the complex nature of this disease.

METHODOLOGY:

This cross-sectional study was conducted at KRL Hospital, Islamabad, from 1st January 2025 to 31st July 2025 after approval of the synopsis by the Ethical Review Committee (KRL-HI-PUB-ERC/Feb25/60). The study aimed to evaluate the prevalence of depression and anxiety among patients suffering from rheumatoid arthritis (RA) and to assess their impact on health-related quality of life (HRQoL). An informed written consent was obtained by all participants before enrollment. A total of 115 individuals aged 18 years or more with a confirmed diagnosis of RA, based on the 2010 ACR/EULAR classification criteria, [18] were included from outpatient rheumatology department. Individuals were excluded if they had severe cognitive impairment, current psychiatric disorders under medical treatment, or had comorbid conditions resulting in physical disability, such as heart failure, decompensated chronic liver disease, or stage V chronic kidney disease requiring hemodialysis. Pregnant and breastfeeding females were also excluded. This ensured that physical or psychiatric comorbidities did not alter the assessment of psychological symptoms or quality of life. The study sample size was calculated using an estimated prevalence of anxiety 8.1%,[19] desired precision level 6.0% and confidence level 95%. Data collection was done through consecutive sampling, where all eligible patients attending the rheumatology OPD during the established study period were invited to participate. Clinical and demographic information, which included age, gender, duration of the disease, comorbidities, socioeconomic status, educational status and current medications, was collected using a well-structured questionnaire and patient medical records. Assessment of disease activity was done using DAS28-ESR score which included the swollen joint count (SJC), tender joint count (TDJ), patient global health assessment (VAS) and ESR. A score of <2.6 showed remission, 2.6–3.2 indicated

low disease activity, >3.2–5.1 signified moderate disease activity, and a score of >5.1 was classified as high disease activity. The Hospital Anxiety and Depression Scale (HADS), a validated 14-item questionnaire, was used to assess symptoms of anxiety and depression. A score of 0–7 was classified as normal, 8–10 as borderline abnormal (possible cases), and 11–21 as abnormal (probable cases). For estimation of prevalence, participants with scores =11 were considered to have probable anxiety or depression. Patients' functional status and quality of life were determined using the Health Assessment Questionnaire Disability Index (HAQ-DI score). Scores were categorized as =1 for mild disability, >1–2 for moderate disability, and =2 for severe disability.

Data was entered and analyzed by using SPSS version 29. Descriptive statistics was applied on the study population. Percentages and frequencies were included for categorical variables such as anxiety and depression. The Chi-square test was applied to assess association between psychological comorbidities (anxiety and depression) and clinical and demographic variables, such as disease activity (DAS28-ESR), functional limitations (HAQ-DI), socioeconomic status, and level of education. Additionally, odds ratios (ORs) with 95% confidence intervals were also used to calculate the strength of associations between risk factors and the presence of anxiety or depression. A p-value = 0.05 was considered statistically significant for the analyses. This allowed establishing potential predictors of psychological diseases in RA patients while accounting for the influence of various demographic factors.

RESULTS:

At baseline, the study population had a mean age of 49.1 ± 12.6 years, with age variation from 22 to 74 years, indicating that RA in this study predominantly affected middle-aged adults. The study was predominantly female, with 100 female participants (87.0%) as compared to 15 males (13.0%), strengthening the previously well-established higher prevalence of RA among women. The majority of the patients were married (n=106; 92.2%), while 9 (7.8%) were unmarried, suggesting that social support system may play a role in mental health outcomes. With regards to the socioeconomic status, the majority of participants belonged to the lower socioeconomic class (n=64; 55.7%), followed by the middle class (n=50; 43.5%), and only one participant (0.9%) was classified as upper socioeconomic class, highlighting a stark difference among the three subsets of income class. A substantial proportion of patients had associated comorbid conditions (n=64; 55.7%), whereas 51 participants (44.3%) had no other illnesses. The most prevalent comorbid conditions were hypertension (32.2%), dyslipidemia (20%), and type 2 diabetes mellitus (14.8%) [Figure 1], reflecting an association between RA, systemic inflammation, and metabolic disorders. Importantly, among participants with comorbidities, 25 individuals (39.1%) reported depression, and 24 individuals (35.8%) experienced anxiety, indicating that patients with comorbid conditions were particularly susceptible to psychological distress.

The average duration of rheumatoid arthritis (RA) among participants was 7.7 ± 6.4 years. Patients were classified as being seropositive if rheumatoid factor (RF) and/or anti–citrullinated protein antibodies (ACPA) were present, and seronegative if both of them were absent. The majority of participants turned out to be seropositive (n=109; 94.8%), with only a small fraction (n=6; 5.2%) classified as seronegative, consistent with the previously established predominance of seropositivity among RA patients. RA-related joint deformities were observed in 16 participants (13.9%), and only 2 patients (1.7%) had undergone total knee replacement, signifying that advanced structural damage was present in only a minority of cases. The average erythrocyte sedimentation rate (ESR) was 34.0 ± 21.1 mm/hr, representing ongoing systemic inflammation. Regarding functional capacity, 9.6% of patients were able to perform daily activities only minimally, 20.0% moderately, 31.3% mostly, and 39.1% were able to complete all tasks with no limitations. The mean DAS28-ESR in our patients was 4.15 ± 1.37, which showed moderate disease activity. The HAQ-DI score had an average of 0.94 ± 0.77, indicating mild to moderate functional impairment in our patients [Table 2]. A significant proportion of 30 (26.1%) out of a total of 115 patients were identified with depression, while 22 patients (19.1%) were found to have anxiety suggesting a considerable burden of mental health issues in RA patients.

Table 3 presents the association of various risk factors with the frequency of anxiety or depression among participants, including the means and standard deviations (SD) for each relevant variable. The duration of rheumatoid arthritis (RA) was slightly longer in individuals with anxiety/depression to those without but it was not found to be statistically significant averaging (P-value of 0.06). The erythrocyte sedimentation rate (ESR) was significantly higher in those with anxiety or depression, recording an average of 40.14 (±24.45) mm/hr versus 31.43 (±19.13) mm/hr in those without, with a P-value of 0.014. Additionally, the tender joint count and swollen joint count were both significantly higher in the anxiety/depression group, with TJC averaging 4.91 (± 6.03) compared to 2.06 (± 3.64) in those without (P-value of 0.04), and SJC averaging 3.58 (±4.52) compared to 1.85 (±3.17) in the non-anxious/depressed group (P-value of 0.02). The visual analog scale (VAS) score, reflecting perceived pain, was substantially higher in individuals experiencing anxiety/depression, averaging 73.23 (±19.65), compared to 49.01 (±30.92) for those without, with a highly significant P-value of less than 0.0001. Regarding the ability to carry out daily activities, among individuals with anxiety or depression, (23.5%) reported only being able to perform activities a little, as opposed to just 3.7% of those without

anxiety or depression (P-value of 0.002). The DAS-28 scores, indicating disease activity, averaged 4.88 (±1.36) for those with anxiety or depression versus 3.85 (±1.26) for those without, with a highly significant P-value of less than 0.0001. According to the DAS-28 score, there was moderate disease activity in both groups but there was a significant difference in the score between those having anxiety or depression as compared to those without them. Finally, the HAQ-DI score also showed a significant difference, averaging 1.33 (±0.84) for individuals with anxiety or depression compared to 0.77 (±0.68) for those without, again with a P-value of less than 0.0001. These findings highlighted a significant association between various risk factors and the occurrence of anxiety and depression in our patient population [Table 3].

DISCUSSION:

Approximately 18 million individuals worldwide were affected by rheumatoid arthritis (RA) by 2019, and the prevalence is expected to rise to 31.7 million by 2050, reflecting a drastic increase in the disease burden over time.[20] RA is a chronic, systemic inflammatory disorder which not only has a physical impact but it also places substantial burden on psychological and social functioning capacity of affected individuals. Patients frequently complain of severe pains, persistent fatigue, and joint deformities leading to limitations in daily activities. All of these factors have a negative impact on the occupational, personal and social life of individuals. [21]

Apart from these challenges, the chronic and incurable nature of RA also places significant psychological stress on these individuals. Studies reveal an increased prevalence of anxiety and depression in patients with RA, leading to reduced health-related quality of life (HRQoL).[21,22] According to another Indian cohort study, there is a strong correlation between psychological distress and poor overall functioning capacity of individuals, indicating that poor mental health can have a greater negative impact on physical disability.[21] Likewise, it has been suggested that there is an increased need for diagnosis and medical management of depression in RA patients for a better outcome of the disease.[22]

All these studies stress on the multifactorial burden of RA, where physical disability, chronic pain, and psychological comorbidities interact with each other to reduce the daily functioning of individuals. This results in patient dissatisfaction and an impaired quality of life. Hence, understanding the prevalence and impact of anxiety and depression in patient with RA is crucial to develop better individualized management strategies that are able to address both the physical and mental health needs of these patients.[20,21,22]

This study has a similar aim to establish the relationship between rheumatoid arthritis (RA) and mental health

Figure 1. Prevalence of comorbidities

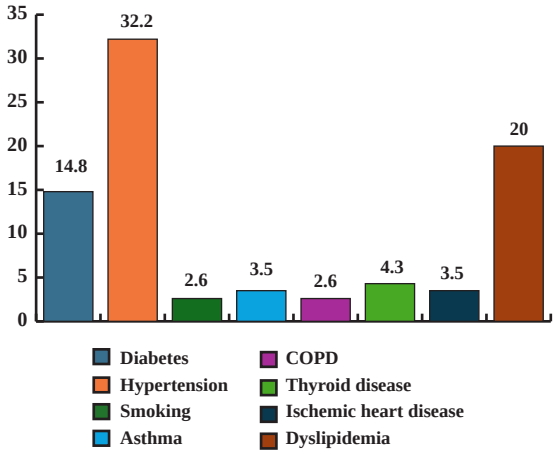

Table 2. Disease Characteristics of Study Patients

Duration of RA (mean ± SD)	7.70±6.41
Gender (%)	
Male	15 (13.0%)
Female	100 (87.0%)
Type of RA (%)	
Seropositive	109 (94.8%)
Seronegative	6 (5.2%)
RA Related Deformity (%)	16 (13.9%)
ESR (mean ± SD)	34.0±21.1
Able to Carry Out Activities	
A little	11 (9.6%)
Moderate	23 (20.0%)
Mostly	36 (31.3%)
Completely	45 (39.1%)
DAS-28 Score (mean ± SD)	4.15±1.37
HAQ-DI score (mean ± SD)	0.94±0.77

Table 3. Association of Risk Factors with Occurrence of Anxiety/Depression

	Anxiety/Depression		**P-value**
	Yes (N=34)	**No (N=81)**	
Age (Years)	49.85±11.18	48.81±13.24	0.68
Duration of RA (Years)	9.54±7.02	6.93±6.02	0.06
Gender (%)			
Male	5 (14.7%)	10 (12.3%)	0.73
Female	29 (85.3%)	71 (87.7%)	
ESR	40.14±24.45	31.43±19.13	0.014
VAS Score	73.23±19.65	49.01±30.92	<0.0001
Able to Carry Out Activities			
A little	8 (23.5%)	3 (3.7%)	0.002
Moderate	9 (26.5%)	14 (17.3%)	
Mostly	10 (29.4%)	26 (32.1%)	
Completely	7 (20.6%)	38 (46.9%)	
DAS-28 Score	4.88±1.36	3.85±1.26	<0.0001
HAQ-DI score	1.33±0.84	0.77±0.68	<0.0001

conditions, particularly depression and anxiety, with its main focus on the Pakistani population. As previously discussed, RA is a chronic disease that not only affects the physical health of individuals but also has a profound impact on their psychological and social well-being. Having established that, understanding the mental health burden in patients with RA is crucial since it has also shown to exacerbate pain perception in these individuals reducing their functional ability and diminishing their overall HRQoL.

In line with these objectives, the central idea of this study is to determine the prevalence of depression and anxiety among individuals living with RA in Pakistan, as the current data is quite limited. Additionally, this study was also conducted to assess the impact of these psychological conditions on the daily functioning of these individuals along with their coping strategies, providing insight into the interaction of mental health with chronic disease management. Through this, our study aims to contribute evidence for better patient care by integrating mental health screening into routine RA management whenever required. Understanding these dynamics is essential for improving the current management plans and providing better patient satisfaction leading to improved overall outcomes. It has been noted however that the rate of anxiety and depression among RA patients vary considerably across studies. This difference is mainly due to the variations in the assessment tools used along with their cutoff values. For example, when using the Hospital Anxiety and Depression Scale (HADS), the prevalence for depression has been estimated to range from approximately 14.8% to 48%, depending on the thresholds used to diagnose patients in different studies. Similarly, the prevalence of anxiety can also vary within a range in different studies and this reflects inconsistencies produced by using different assessment criterias and study methodologies.[19] For the purpose of our study, a HADS cutoff value of =11 was used to define probable depression and anxiety which is consistent with the widely accepted practice for diagnosing these conditions. Using this threshold, the prevalence of depression was found to be 26.1% in our study, while 19.1% of the patients were diagnosed with anxiety. This highlights a significant psychological burden in patients suffering from RA. In comparison, a cross-sectional study conducted by Ionescu et al. (2025) reported a prevalence of depression in only 10.0% of patients with RA and anxiety in 8.1%.[19] These differences signify the importance of using proper cutoff values and assessment tools based on demographic variables and geographical locations along with careful interpretation of data.

Another study carried out by Uda M et al. (2021) found the prevalence of anxiety to be 17.6% and 27.7% for depression in RA patients,[23] and these values are consistent with the findings of our study as well. The results show that a substantial proportion of RA patients experience psychological comorbidities, but the prevalence rates may differ depending on demographic characteristics and the study methodology used. Studies like Enginar and Nur have reported even higher rates of prevalence, with 50.3% experiencing depression and 25.3% of RA patients suffering from anxiety.[24] Similarly, research from Saudi Arabia by Alanazi et al. (2024) also found an increased prevalence of depression (42.4%) and anxiety (36.3%) in their study further strengthening the fact that these mental health issues are a global concern resulting in a greater disease burden.[25] Studies have also established that the severity of depression and anxiety in rheumatoid arthritis (RA) is closely linked to the underlying disease activity and this further creates a negative impact on the long-term outcomes. Fragoulis et al. (2020) evaluated depression and anxiety in an early RA cohort using the Hospital Anxiety and Depression Scale (HADS) and found a significant association between HADS scores and DAS28-CRP measurements at both six and twelve months, highlighting the importance of psychological symptoms on both objective and subjective disease activity.[26]

A systematic review and meta-analysis by Machin et al. (2020), which combined data from five studies, further revealed that symptoms of anxiety were associated with higher DAS28 scores and poor quality of life, showing the implications of psychological comorbidities on patient well-being.[27] Other evidence suggests that depression and anxiety in RA are often associated with greater tender joint counts and higher patient global assessment scores, reflecting the impact of mental health on the subjective components of disease activity assessment scores.[19] Our local data also support these global findings. A 2024 cross-sectional study conducted in Lahore by Haq et al. reported that patients with RA having a higher disease activity experienced significantly worse HRQoL, due to impairment in physical ability, pain, and associated anxiety and depression.[28] Overall, these studies highlight the complex relationship between RA disease activity and psychological health, emphasizing that mental health comorbidities not only influence disease outcomes but may also affect perception of disease severity. The primary purpose of our study was to establish the prevalence of anxiety and depression in the Pakistani population suffering from this autoimmune condition. The results of our study emphasize on the need for a multidisciplinary care and approach for integration of a better management plan in RA patients. Routine mental health screening may lead to early identification, diagnosis and management of psychological conditions alongside standard RA treatment. Our data also highlights a clear gap in early recognition and diagnosis of these illnesses due to which they are not properly addressed. This research adds to the existing body of knowledge by providing evidence on the psychological burden of RA in Pakistani population, a region where mental health conditions remain vastly under recognized so the data is also quite limited. By documenting the prevalence and impact of these mental health illnesses

in our population, the study offers insight into not only the extent of these conditions but also their impact on the daily functioning of individuals. The significance of these results should ensure patient education and understanding of their disease so measures can be taken to reduce disease burden and improve their quality of life.

However, there are also some limitations in our study. Selection bias may have been introduced as the participants were enrolled from specific clinical settings. Only diagnosed patients of RA were included in our study who came for their routine checkup. Hence the generalizability of these findings to the broader RA population may be limited which may affect the robustness of these conclusions. Additionally, our sample size was also relatively small so future research targeting larger and more diverse samples are required to validate these findings. All this may lead to more accurate results and guide the development of better care facilities.

CONCLUSION:

The prevalence of anxiety and depression among patients diagnosed with rheumatoid arthritis (RA), is quite high having a significant impact on the health-related quality of life. The severity of RA also appears to be affected with the presence of these psychological conditions.

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Authors Contribution:
Ishma Arif: Study design, conception statistical analysis, data collection
Anila Nisar: Literature review, proof reading
Anum Rasheed: Data collection, data interpretation
Aanum Misbah Hasanat: Proof reading
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Original Article **Open Access**

Safety and Efficacy of Racecadotril in Acute Watery Diarrhea: A Randomized Controlled Trial in Children Aged 3 –59 Months

Own Abbas, Ayesha Nousheen, Abdullah Ali, Syed Khuzaima Arslan Bokhari, Shazia Naz, Muhammad Ali Khan

Abstract

Objective: To evaluate the efficacy and safety of racecadotril (1.5 mg/kg thrice daily) in combination with standard oral rehydration therapy (ORT) and compare with placebo plus ORT in 3 - 59 months old hospitalized children with acute watery diarrhea

Study Design and Setting: A randomized controlled trial having registration number NCT07392931 was conducted with 200 children aged 3-59 months hospitalized with AWD at the Punjab Rangers Teaching Hospital in Lahore, as a prospective, double-blinded study. Participant enrolment and follow-up covered six consecutive months (1st June to 30th November 2025). The study protocol was approved by the Institutional Review Board (IRB) of Punjab Rangers Teaching Hospital, Lahore (Ref: PRTH/IRB/2023/63).

Methodology: Children either received Racecadotril (1.5mg/kg three times a day) or a placebo, with standard oral rehydration therapy. The key outcomes were the number of stools in 24 hours and the length of stay of the children in the hospital.

Results: Day 1 (3.1 vs. 4.8) Racecadotril reduced the stool count. The proportion of children who achieved treatment success (a decrease in stools) on the drug compared to placebo was 82% and 48%, respectively (NNT=3). The children who were administered Racecadotril spent 26.4 hours less in the hospital. The adverse effects were rare (8% vs. 12%) and no drug-related or serious problems were observed. The cost analysis showed a savings of 6,230 PKR per patient.

Conclusion: Racecadotril is safe, effective, and cost-effective. It promptly reduces stool output and hospital stay of children with AWD regardless of their age and dehydration condition.

Keywords: Racecadotril; Acute watery diarrhea; Antisecretory; Oral rehydration therapy; Randomized controlled trial

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INTRODUCTION

Acute watery diarrhea (AWD) is one of the main reasons why children are brought to emergency rooms and hospitals worldwide, with a major toll on children and health-care systems.[1] The World Health Organization estimated that children under five have about 1.7 billion episodes of diarrhea each year, and this leads to 525,000 deaths (around 1,400 per day), despite the availability of low-cost interventions.[2] Nearly 90% of all these deaths occur in low- and middle-income countries (LMICs), where lack of sanitation, overcrowding, low parental education and delayed seeking of care combine to increase risk.[3] In fact, AWD is one of the leading causes of health-care use even in high-income countries. In Europe, any episode of gastroenteritis represents 5-10% of pediatric emergency consultations and 132 hospitalizations per 100 000 children annually.[4]

Most deaths related to diarrhea are due to dehydration and electrolyte imbalance, but the long-term sequelae (including growth faltering, cognitive impairment, and greater susceptibility to infection) affect human capital development as well.[5] For more than 4 decades, the mainstay of diarrheal disease management has been oral rehydration therapy (ORT), a simple solution that contains glucose and

electrolytes that replaces fluid losses and corrects hypovolaemia.[6] The universal coverage of ORT could prevent up to 93% of diarrhea related deaths.[7] ORT does not alter stool frequency or consistency. Thus, there is a recognized need for a safe adjunctive agent that will shorten the duration of illness without compromising the safety profile of ORT.[8-9]

Racecadotril, an orally active prodrug of enkephalinase inhibitor thiorphan is a rational therapeutic approach. By selectively blocking membrane-bound neutral endopeptidase in the intestinal mucosa, it also conserves endogenous enkephalins which physiologically inhibit the cyclic adenosine monophosphate cAMP-mediated secretory cascade elicited by the enterotoxins.[10] Unlike opioids, racecadotril has no effects on gastrointestinal (GI) motility or crosses the blood-brain barrier, avoiding centrally-mediated effects.[11] In adult volunteer studies using jejunal perfusion chambers, the presence of racecadotril was shown to induce a 45% lower secretion of fluid following a dose of toxin derived from cholera, within 90 minutes.[12]

Trials in Europe and Latin America in the early years of treatment showed benefit. In a Peruvian study on 135 boys aged 3-35 months, 48 hour stool output was reduced by 45% ($p = 0.02$) and time to cure by 27 hours by racecadotril.[13] In a study, Racecadotril has a significant beneficial effect on acute gastroenteritis regardless of whether it is caused by rotavirus, with a number needed to treat (NNT) of about 3 to promote rapid clinical improvement (eg normalisation of stool frequency within 72 hours).[14] A randomised study (n=120, children 6 months-5 years) found that Racecadotril significantly decreased racecadotril significantly decreased the number of stools at 48 hours ($p=0.012$) and made the hospital stay shorter than placebo. The authors concluded that racecadotril is effective in the treatment of acute gastroenteritis in paediatric subjects.[15]

Pakistan has the fifth highest diarrheal mortality in the world with an estimated 41,000 under-five deaths every year.[16] National Demographic and Health Surveys show that only 46% of caregivers prepare ORT correctly, 38% withhold feeds during illness, and 28% first seek care from unqualified providers.[17] These factors may reduce the effectiveness in real-life practice in comparison to controlled trials. To date, the only open-label study from Karachi (n = 176) has evaluated the efficacy of racecadotril, revealing a reduction of 1 day of hospital stay; despite the lack of comparison with placebo and single center design, the study is limited. Therefore, high-quality evidence produced through the public-sector hospitals of Pakistan is necessary to inform decisions at the clinical and policy level.[18]

This study sought to assess the therapeutic benefit of racecadotril in routine clinical settings outside of the ambient conditions of tertiary care, but serving a population of low socio-economic standing and living in peri-urban areas. By using rigorous randomization, blinding the trials and using objective outcomes, it aims to offer actionable evidence for clinicians and policymakers. Demonstration of the benefits of an inexpensive oral adjunct safely reducing the duration of illness by 24 hours and resulting in hospital stay savings could improve child outcomes while also increasing hospital efficiency--an achievement with dual benefit in health systems under financial constraint.

METHODOLOGY

This prospective, double-blinded, placebo-controlled, parallel-group randomized controlled trial (RCT), with registration number NCT07392931, assessed the efficacy and safety of racecadotril as supplemental oral rehydration therapy (ORT) in children admitted for an episode of acute watery diarrhea (AWD). The study was conducted in the pediatric wards of the Punjab Rangers Teaching Hospital, Lahore.

Participant enrolment and follow-up covered six consecutive months (1st June to 30th November 2025). The participants were followed up until discharge; those hospitalized for longer than seven days were censured at seven days for length of stay analysis. Sample size was estimated using the WHO Sample Size Calculator (v2.0) assuming that the mean difference in stools per 24 hours (SD 3) in the racecadotril group compared to placebo would be two, $a = 0.05$ (two-tailed), 90% power and 5% attrition. Ninety-six participants were needed in each arm; the actual total was raised to 200 (100 in each group) for the potential for losses.

Simple randomization was achieved by lottery method. Two hundred opaque, sequentially numbered envelopes holding allocation cards on which the words "Racecadotril" or "Placebo" were printed as words were prepared by an independent statistician. Once eligibility confirmation and consent were obtained, the next envelope in sequence was opened by the study nurse. Allocation concealment was performed and blinding involved participants. Identical-appearing sachets that contained racecadotril 15 mg (Hidrasec(R)) or placebo (microcrystalline cellulose) were dispensed in sequentially numbered drug boxes. The participant flow through the trial is presented in the CONSORT diagram (Figure 1).

Eligible participants were children between 3 months and 59 months, of either sex, who had >3 loose or watery stools in the past 24 hours, was expected to last <72 hours and led to hospitalization, determined by the attending physician. Written informed consent was received from a parent or guardian with assent of children less than 5 years of age or younger. Exclusion criteria were less than 3 months or >60 months of age, stool containing visible blood or mucus, chronic diarrhea (>14 days), persistent diarrhea (7-14 days), severe dehydration requiring intensive care, severe acute malnutrition (weight-for-height z-score), and major comorbidities, e.g. pneumonia, sepsis, congenital heart disease, hepatic or renal impairment, known hypersensitivity to racecadotril.

Before enrolment, the principal investigator trained all ward nurses, residents, and data collection staff in eligibility determination, randomization, and stool grading and adverse-event documentation. Standardized case report forms (CRFs), Bristol Stool Chart cards, and calibrated tools of measuring were placed at each bedside.

Each eligible child was given a unique study code. Baseline demographic data, anthropometry and hydration status (as per the WHO criteria), vitals were noted. The allocated study medication was newly reconstituted in 10 mL of potable water by the hospital pharmacist just before dosing and was administered orally at 1.5 mg/kg every eight hours (maximum 30 mg per dose) for up to five days or until discharge, whichever happened first. All participants were rehydrated per standard care based on WHO recommendations: low-osmolarity oral rehydration solution (ORS) 50-100 mL/kg during 4-6 h for mild to moderate dehydration or isotonic intravenous fluids (0.9% saline with or without 5% dextrose).

During hospitalization, the nursing staff noted the amount of stool being produced each 24 hours (from 00:00 to 23:59). Stool frequency was established as the overall count for each 24 h period during which defecation/stool passage occurred. Time to first formed stool was the number of hours from the first dose until passage of a stool of a Bristol type 3 or 4. Duration of hospital stay was calculated as the number of whole hours between the electronic admission timestamp and the signed discharge order. Dehydration status was classified as none/mild (<5% weight loss), moderate (5-9%) or severe (>10%) (The latter was not considered in this study).

Compliance was taken to be ingestion of >90% of prescribed sachets, confirmed by reconciliation of returned doses. Any new symptom, including vomiting, abdominal distention, rash, lethargy, and/or constipation that lasts for >48 hours were considered a potential adverse drug event that was evaluated by the attending physician for potential relation to the study medication. Blinding was strictly maintained - drug boxes were annotated with only study ID and dosing time, and caregivers assessors were unaware of group assignment. Any refusal, regurgitation in 15 min. or incomplete dose was entered; if so, the dose was repeated once.

The study protocol was approved by the Institutional Review Board (IRB) of Punjab Rangers Teaching Hospital, Lahore (Ref: PRTH/IRB/2023/63). Data confidentiality was guaranteed by the use of anonymized study codes and by storing all records in password-protected servers only shared by the research team. Participation was voluntary and withdrawal was not related to standard medical care. Adverse events that could cause serious harm were to be reported to the IRB within 24 hours. This over Rigorous methodology ensured standardization of enrolment, allocation concealment, intervention delivery, and outcome measurement, which could robustly echo the therapeutic benefit of racecadotril as an adjuvant to ORT in hospitalized children with acute watery diarrhea.

All statistical analyses were performed using IBM Statistics: IBM Sure Statistics 26.0. Baseline demographic and clinical characteristics: age, gender, weight, duration of diarrhea, baseline stool frequency, dehydration state, vomiting and fever were compared between the two groups in order to assure initial equivalence. Independent-sample tests of the normally distributed variables were performed using t-tests. Categorical variables were compared using the Pearson's Chi-square test. A p-value < 0.05 was used to represent significance for all tests.

RESULTS:

Table 1 demonstrates that groups were similar in terms of baseline characteristics. The mean age was approximately 18 months, 40% of both were 3-12 months and males slightly out-numbered females. There were no significant differences between the Racecadotril and Placebo groups, with similar stool frequency, as well as length of diarrhea, dehydration status, vomiting and fever.

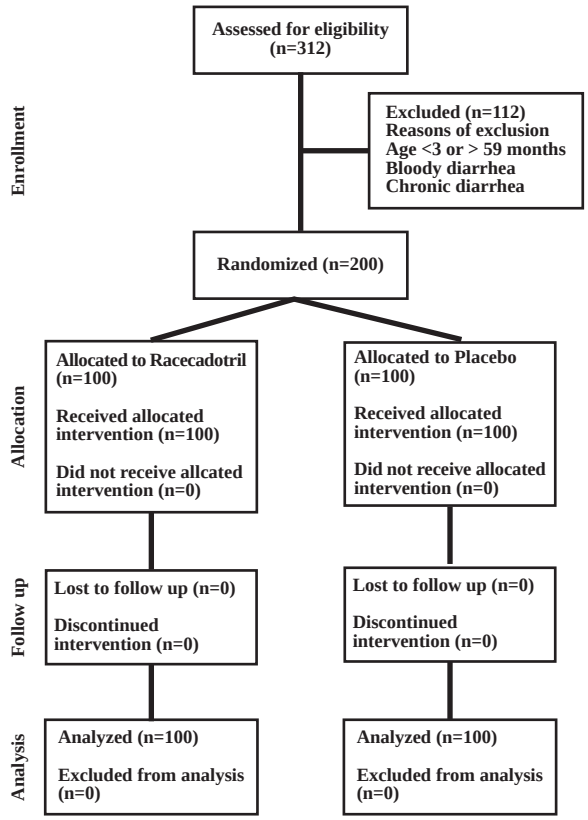
Table 2 shows the main efficacy results, which indicate a strong clinical benefit of Racecadotril compared with placebo. Stool frequency was similar at baseline and decreased faster in the Racecadotril group (3.1 ± 1.2) compared to the placebo group (4.8 ± 1.4, $p<0.001$) and remained so for the 3 days of the study. The absolute reduction in stool frequency was larger in the Racecadotril group (4.7 vs. 2.8 stools/day) and greater proportion of Racecadotril group achieved =50% reduction than placebo group (82% vs 48%, NNT = 3). Racecadotril also had a dramatic effect on the hospital stay as the treated group had an average hospital stay of 76.4 hours versus 102.8 hours in the placebo group ($p<0.001$), a mean difference of about 26 hours.

The results of safety and tolerability are summarized in table 3; Racecadotril was equally safe when compared to placebo. Adverse events occurred in 8% of Racecadotril group and in 12% of placebo group, the difference between the two groups did not reach statistical significance ($p=0.34$, RR=0.67). There were low and similar rates of specific events (persistent vomiting, abdominal distention, skin lesions, and constipation) in each group. There were no serious adverse events; and no drug-related adverse events were reported. No significant difference between groups in treatment compliance (96% from Racecadotril group and 98% from placebo group with at least 90% of treatment taken, $p=0.41$). Racecadotril had a favourable and well-tolerated safety profile overall.

Table 4 shows the result of the cost-effectiveness analysis, which revealed that Racecadotril, although it was more expensive in terms of drug cost (450 PKR vs. 50 PKR), eventually led to overall cost savings as it resulted in faster recovery and reduced hospital resource use. The reduced

length of stay in hospitals reduced the bed and nursing care cost (11,460 PKR) as compared to 15,420 PKR and consequently reduced total direct medical cost by 4,580PKR per patient. Indirect costs also were reduced with the caregivers of Racecadotril treated children missing fewer work days (3.2 vs. 4.3) with additional savings of 1,650 PKR. The cost per patient of Racecadotril was 19,730 PKR, while that of placebo was 25,960 PKR; and resulted in a saving of 6,230 PKR per patient and 623000rs saving in costs for treatment group. Therefore, Racecadotril was found to be a cost-effective strategy as it cuts down on both direct and indirect costs.

Figure 1: Consort Flow Diagram



DISCUSSION

This double blinded randomized controlled trial findings indicate that racecadotril together with conventional oral rehydration therapy (ORT) has significant clinical and economic advantages in children with acute watery diarrhea. The great reduction in the stool frequency and the time span of hospital stay and disappearance of symptoms observed in our study is in line with the increasing amount of evidence that indicates the effectiveness of racecadotril as an antisecretory agent. These results are of particular interest in the area of paediatric gastroenterology where safe and effective treatment of acute watery diarrhea is the main issue of public health, especially in the low and middle-income countries, where the disease rate is catastrophically

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Racecadotril (n=100)	Placebo (n=100)	P-value
Age (months)			
Mean ± SD	18.4 ± 12.6	17.9 ± 13.1	0.78
3-12 months, n (%)	38 (38.0%)	41 (41.0%)	0.68
13-24 months, n (%)	34 (34.0%)	32 (32.0%)	0.76
25-60 months, n (%)	28 (28.0%)	27 (27.0%)	0.88
Gender			
Male, n (%)	58 (58.0%)	56 (56.0%)	0.78
Female, n (%)	42 (42.0%)	44 (44.0%)	0.78
Weight (kg) (Mean ± SD)	10.2 ± 2.8	10.4 ± 2.9	0.62
Diarrhea Duration (hours)	36.2 ± 18.4	34.8 ± 17.9	0.58
Baseline Stool Freq. (24h)	7.8 ± 2.1	7.6 ± 2.3	0.52
Dehydration Status			
Mild, n (%)	42 (42.0%)	45 (45.0%)	0.68
Moderate, n (%)	58 (58.0%)	55 (55.0%)	0.68
Vomiting present, n (%)	64 (64.0%)	62 (62.0%)	0.77
Fever present, n (%)	48 (48.0%)	51 (51.0%)	0.68

Table 2: Primary Outcome Measures

Outcome Measure	Racecadotril (n=100)	Placebo (n=100)	Mean Diff. (95% CI)	P-value
Stool Frequency (24h)				
Day 0 (Baseline)	7.8 ± 2.1	7.6 ± 2.3	0.2 (-0.4 to 0.8)	0.52
Day 1	3.1 ± 1.2	4.8 ± 1.4	-1.7 (-2.1 to -1.3)	<0.001**
Day 2	1.8 ± 0.9	3.2 ± 1.3	-1.4 (-1.7 to -1.1)	<0.001**
Day 3	1.2 ± 0.6	2.1 ± 1.1	-0.9 (-1.2 to -0.6)	<0.001**
Reduction from Baseline				
Absolute reduction	4.7 ± 1.8	2.8 ± 1.6	1.9 (1.4 to 2.4)	<0.001**
Percentage reduction	60.3 ± 15.2%	36.8 ± 14.8%	23.5% (19.1–27.9)	<0.001**
Achieved =50% reduction	82 (82.0%)	48 (48.0%)	NNT = 3	<0.001**
Hospital Stay (hours)				
Median (IQR)	72 (60-84)	96 (84-120)	-24 (-32 to -16)	<0.001**
Mean ± SD	76.4 ± 18.2	102.8 ± 24.6	-26.4 (-32 to -20)	<0.001**

Table 3: Safety Profile and Adverse Events

Adverse Event	Racecadotril	Placebo	P-value	Risk Ratio (95% CI)
Any adverse event, n (%)	8 (8.0%)	12 (12.0%)	0.34	0.67 (0.28-1.58)
Persistent Vomiting, n (%)	3 (3.0%)	5 (5.0%)	0.48	0.60 (0.15-2.46)
Abdominal distension, n (%)	2 (2.0%)	4 (4.0%)	0.41	0.50 (0.09-2.68)
Skin rash, n (%)	1 (1.0%)	1 (1.0%)	1.00	1.00 (0.06-15.77)
Constipation (=48h), n (%)	2 (2.0%)	2 (2.0%)	1.00	1.00 (0.14-6.96)
Serious adverse events	0 (0.0%)	0 (0.0%)	-	-
Drug-related events	0 (0.0%)	0 (0.0%)	-	-
Discontinuations, n (%)	0 (0.0%)	0 (0.0%)	0.32	-
Compliance (=90%), n (%)	96 (96.0%)	98 (98.0%)	0.41	0.98 (0.93-1.03)

Table 4: Cost-Effectiveness Analysis (PKR)

Parameter	Racecadotril	Placebo	Difference
Direct Medical Costs			
Drug cost per patient	450	50	+400
Hospital bed cost (150/hr)	11,460	15,420	-3,960
Nursing care cost	2,400	3,200	-800
ORS/IV fluid cost	620	840	-220
Subtotal Direct Costs	**14,930**	**19,510**	**-4,580**
Indirect Costs			
Work days lost (Mean)	3.2	4.3	-1.1
Productivity loss (PKR)	4,800	6,450	-1,650
Total Cost Per Patient	**19,730**	**25,960**	**-6,230**
Total Savings (n=100)	-	-	**623,000**

PKR = Pakistani Rupees (1 USD ˜ 280 PKR). Racecadotril demonstrates clear cost-effectiveness through reduced hospital stay despite higher drug acquisition costs

predominant and affordable treatment options are frequently accessible. The size of the morbidity and mortality burden associated with the acute form of the gastroenteritis disease in the pediatrics sets the size of the problem as one of the most urgent ones to the healthcare systems of the developing world, and the discovery of the pharmacological agents that could allow reducing the clinical course and severity of the disease safely and meaningfully constitutes a significant challenge to both the clinical practice and the healthcare policy of the population.

Racecadotril has a therapeutic action premised on the selective inhibition of an enzyme enkephalase that breaks down the endogenous enkephalins at the intestinal mucosa. Racecadotril maintains the levels of these endogenous opioid peptides thus decreasing hypersecretion of water and electrolytes into the intestine lumen without negatively impacting the intestinal motility. This process is pharmacologically different as compared to the antimotility agents and is the basis behind the desirable safety profile that has been evidently apparent among a wide range of clinical trials in very different geographical and demographic settings. Such specificity of this enzymatic inhibition is clinically important, it is not only that unlike the agents with general effects on the gastrointestinal system, racecadotril acts specifically on the secretory activity, but also, the enteric nervous system and intestinal wall musculature associated with the action of the agent is referred to in detail. This specificity also helps to take into consideration the preservation of physiological intestinal functioning which is especially important in paediatric groups in which protracted gastrointestinal stasis poses a high clinical risk due to bacteria overgrowth, toxic build-up, and systemic dissemination of enteric pathogens.

According to Aziz et al., racecadotril was found to be reported as being similar to loperamide in reducing the length and incidence of acute infectious diarrhea among the adult population, with a better safety profile, especially in terms of no constipation and rebound effects, as described in nutrients.[19] The clinical value of preventing such adverse effects cannot be overestimated, taking into account that patients may already be in the physiologically poorly condition because of dehydration and electrolyte imbalance. This but constipation and rebound diarrhoea, which are sufficiently described (sequelae of loperamide use), inconvenient at best, but capable of contributing to the complexity of an already complicated presentation, potentially increasing hospitalization time and burden of care. Moreover, racecadotril with antisecretory therapy produced a faster rate of reduction in the number of stools and reduced length of diarrhoea than probiotic therapy in children less than two years of age with acute watery diarrhoea thus supporting the idea of better short-term effectiveness with antisecretory therapy in this most at risk group of children.[20] Such comparative advantage over probiotics is interesting given the prevailing and increasing interest in probiotic interventions in the management of diarrhoea in children; although probiotics hold mechanistic plausibility by regulating intestinal microbiome homeostasis, the urgency of the racecadotril antisecretory effect seems to have a clinically significant impact in the acute diarrhoeal treatment environment. Such findings are correlated with the current findings, in which the period of recovery in the post-racecadotril treatment group (about one day less than that in the control group) was statistically significant, which

implies that within the framework of clinical practice at the level of the personal patient of an individual patient, and, consequently, at the level of healthcare resource consumption.

Zulfiqar et al. compared the efficacy of racecadotril added to oral rehydration solution in children with acute gastroenteritis and found that oral rehydration solution with racecadotril was more effective than use of oral rehydration solution alone in reducing the number of stools and decrease in duration of diarrhoea, as well as the overall rate of clinical recovery.[21] The following findings have a significance in that they support the additive therapeutic effect of racecadotril in adjunction with ORT and reaffirm the theory that combination interventions focusing on both fluid replacement and intestinal hypersecretion may achieve better results than either one of the therapeutic approaches alone. The symbiosis of these two therapies is due to a physiologically sensible model of therapeutic action: ORT replenishes fluid and electrolytes losses, whereas racecadotril is an upstream control requiring less secretory action to be inhibited, which decreases the losses that ORT has to counter. The same was found in another study held in Pakistan by Anwer et al. in 2024 comparing racecadotril and ORT to probiotics alone, with symptoms being resolved almost 30-times faster with the former.[22] All these similar conclusions, based on a series of independent study populations, performed in diverse clinical settings, all indicate that racecadotril is a better supportive treatment modality in acute watery diarrhoea management, and point to its generality as a treatment with a generalisable, and not situation-specific, therapeutic application.

The results of a relatively low incidence of adverse events (less than 10 per 100,000-1) and none of the severe adverse reactions reported by Manfredi et al. (2025) are similar to our own safety data.14 Racecadotril has an excellent safety profile with a limited risk of constipation or abdominal stretching.[23] Tolerability data in our study are of special interest due to the fact that the population of the study was young children that drug safety is subject to the highest levels of rigour set and whose outcomes of an iatrogenic damage are most likely to be the most severe. The low rates of adverse events reported in the studies conducted in various countries and healthcare facilities consistently lend some level of external validity to the safety observations that enhance the degree of confidence in their clinical generalizability. No changes to the central nervous system which, when associated with our hypothesis that a local action of racecadotril might be responsible in the intestinal hypersecretion without any abnormal effect on motility, is in line with the pharmacological evidence that racecadotril does not cross the blood-brain barrier.[24] This property contributes further to its applicability in paediatric practice where their applicability in clinical practice among children has traditionally been constrained by the possibility of CNS-mediated side effects of the other antidiarrhoeal agents. Not only does the lack of neurological involvement separate racecadotril activity in comparison to older generations of antidiarrhoeal agent, but also it offers a mechanistic explanation of why intestinal motility is predictably preserved and no sedation or change in behaviour is reported in any paediatric cohort undergoing administration of racecadotril.

Economic analysis studies have shown that racecadotril is cost-effective in numerous health care facilities and economic conditions. In a cost-utility model based on multinational analysis, Rautenberg and colleagues demonstrated that adjunctive racecadotril showed low overall treatment costs as measured by a reduced length of hospitalisation and costs related to resource use.[25] The practical implications of the finding are of significant importance to healthcare settings with limited budget where achieving the best clinical outcomes at the least possible cost is a primary policy goal. The dependence between clinical benefit and economic worth are most directly related in the scenario of acute diarrhoeal disease wherein the main determinants of the costs of health care such as, length of hospital stays, the intensity of nursing care, and the amount of intravenous fluid and electrolyte replacement needed are all directly regulated by the rate and extent of clinical healing. Our costing study also showed that there was a major saving and an average of 6,230 PKR per patient which this figure was comparable to the southeast Asian studies that had attributed the reduced recovery to the use of the racecadotril to lower hospital expenses.[26] These savings need to be put into context in terms of generally addressing healthcare economics, where even small cash reductions per-capita can result into significant systemic savings if brought together over large numbers of patients, which may allow the redirection of resources elsewhere to address clinical need gaps. Moreover, indirect economic recovery benefits linked to a lower illness period such as the lower opportunity cost that caregivers would otherwise face by having to stay out of the labor force, constitute yet another form of economic value that costing studies focused on direct healthcare spending alone are likely to underestimate systematically.

Moreover, a review of the world networks has demonstrated that racecadotril is among the most effective and safe approaches to cure diarrhea in children. Florez et al. considered the results by finding that racecadotril could not establish a difference in clinical recovery that might be linked to a greater chance of potential adverse events than did other antidiarrhoeal agents.[27] The strength of this conclusion based on an in-depth synthesis of the evidence base present, which includes information on randomised controlled trials different types of clinical populations and geographic locations, attests to the high level of confidence in the clinical recommendations to be made based on these results. Network meta-analytic techniques are especially appropriate in answering comparative effectiveness questions that emerge in areas of therapeutic interest typified by the

availability of multiple agents, and the racecadotril positioning that persistently appears favourable in these studies, in particular, is thus of particular value. In addition, Lukasik J expressed that the advantageous use of racecadotril was particularly evident in developing and middle-income nations where bacterial diarrhoeas are more prevalent, and in which the resources to rehydrate are scarce.[28] This finding highlights the possibility that racecadotril may have a role other than as a pharmacological adjunct, but rather as a strategically relevant part of the diarrhoea management systems, in which the coinciding clinical and logistical challenges of managing acute gastroenteritis in children are greatest, and where the instances of poor management, such as severe dehydration, electrolyte imbalance, and diarrhoea-related mortality.

Limitations: However, there are some limitations to this study. Being a single center trial, the results may not be applicable to outpatient or community-based cases. Stool output was measured in terms of frequency and not total volume and therefore may not reflect reductions in fluid loss. Importantly, microbiological testing was not done which restricts pathogen-specific assessment of treatment effects. Lastly, the follow-up period was completed at discharge and late recurrences or post-discharge complications were not assessed.

CONCLUSION

Racecadotril is safe, effective and economical. It reduces the stool quantity and the hospitali stay of children with AWD promptly and irrespective of their age and dehydration condition.

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Authors Contribution:
Own Abbas: Data collection and article drafting
Ayesha Nousheen: Article drafting
Abdullah Ali: Introduction and methodology
Syed Khuzaima Arslan Bokhari: Results analysis and write-up
Shazia Naz: Results analysis
Muhammad Ali Khan: Proof-reading and final refining

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Original Article **Open Access**

Impact of Intermittent Fasting on Reproductive Markers in PCOS

Huma Habib, Fatima Lajbar, Atif Ullah, Hamasa Gul, Fazal Rahim, Miraj Ahmad

Abstract

Objective: To evaluate the effect of a six-week time-restricted feeding (TRF) regimen on anthropometric, metabolic, and reproductive hormonal parameters in women with polycystic ovary syndrome (PCOS).

Study Design and Setting: Retrospective observational study conducted at Medical Teaching Institute Bacha Khan Medical College and Mardan Medical Complex, Mardan Pakistan.

Methodology: A total of 63 women diagnosed with PCOS according to Rotterdam criteria who completed a six-week TRF dietary regimen (8-hour feeding window from 1:00 p.m. to 9:00 p.m.) were included. Anthropometric measurements and laboratory parameters were recorded before and after the intervention. Variables assessed included body mass index (BMI), waist-to-hip ratio (WHR), insulin resistance using HOMA-IR, androgen profile (free androgen index, testosterone, SHBG), gonadotropins (LH and FSH), and ovarian reserve markers (estradiol and AMH). Paired t-tests were applied and $p < 0.05$ was considered statistically significant.

Results: Significant reductions were observed in BMI, WHR, HOMA-IR, fasting insulin, and free androgen index. Total and free testosterone levels decreased, while SHBG levels increased significantly. LH levels declined and FSH levels increased, improving the LH/FSH ratio. Estradiol levels increased whereas AMH levels showed a modest decline. Clinical improvement was observed in ovulatory function (60.4%), menstrual regularity (60.9%), and hyperandrogenism (63.6%). TRF showed high adherence (82.5%) with minimal side effects.

Conclusion: Time-restricted feeding appears to be a safe and effective lifestyle intervention for improving metabolic and reproductive hormonal parameters in women with PCOS. Further randomized controlled trials with longer follow-up are required.

Keywords: Hyperandrogenism; Insulin resistance; Intermittent fasting; Polycystic ovary syndrome; Time-restricted feeding

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INTRODUCTION

"Polycystic Ovary Syndrome (PCOS) is a common and multifaceted endocrine disorder among women of reproductive ages, and it is defined by hyperandrogenemia, anovulation, and polycystic ovaries. PCOS ranks among the major ethology of menstrual irregularities, infertility, and metabolic disorders.[1] The prevalence of PCOS ranges between 6% and 21% worldwide. This variation in prevalence may be due to differences in diagnostic criteria, genetic, and environmental influences.[2] PCOS manifests with a variety of reproductive disorders, including oligo- and anovulation, hyperandrogenism, and infertility in about 70% of women with PCOS.[3] PCOS is believed to have an intricate association with various metabolic disorders, including obesity, insulin resistance (IR), hyperinsulinemia, and an increased risk of T2DM. In this way, obesity adds to the pathophysiology of PCOS by leading to insulin resistance (IR), which in turn increases the levels of androgens and thereby hyperandrogenism and impairs ovarian function.[3] This highlights the importance of lifestyle changes, particularly dietary changes, in the management of PCOS.[4]

Intermittent fasting, a promising dietary intervention for the management of metabolic and endocrine abnormalities associated with PCOS, differs from the traditional method of caloric restriction by the inclusion of a window of fasting and eating, making it a more sustainable approach for dietary control. IF has been proven to improve insulin sensitivity, support weight maintenance, and influence reproductive hormones associated with PCOS.[5] However, the pharmacologic management with metformin and clomiphene citrate primarily targets IR and ovulatory problems but is associated with side effects and low adherence rates.[6] Similarly, caloric restriction has been proven effective with regard to metabolic parameters but is difficult to sustain over a prolonged period.[7] IF is a novel approach that not only treats metabolic problems but also has the advantage of practicality and physiological compatibility with the body's natural rhythms.[5] Among the different types of IF regimens, alternate day fasting, time restricted feeding, and the 5:2 diet are the most studied. In ADF, the cycles of fasting, with restricted caloric intake, alternate with the cycles of unrestricted feeding.[8,9] ADF has been found to decrease body weight, fasting glucose, and insulin levels, all of which are important for the management of PCOS.[10] In the 5:2 diet, 2 days of the week are set for fasting, with restricted caloric intake, while on the remaining 5 days, no restrictions are placed on food intake.[11] In the 5:2 diet, only non-caloric drinks such as water and black coffee are allowed on the fasting days. This regimen is attractive because of the importance of circadian rhythms, which are known to play an important role in the regulation of metabolic and endocrine functions.[12] On the other hand, the 5:2 diet, which is a variant of the ADF, involves two days of non-consecutive fasting with reduced caloric intake (20-25% of daily caloric requirements) and regular caloric intake for the remaining five days of the week.[13] This method incorporates moderate caloric restriction with sustainability to minimize the mental pressure of constant dieting.[14] Furthermore, Ramadan fasting involves a religious fast between dawn and dusk and provides an interesting model of long-term daily fasting, providing valuable information regarding the effects of fasting on metabolism and reproductive health. IF has been recognized as a holistic and pharmacological approach for the management of PCOS. It is believed to address the key issues associated with the condition, such as insulin resistance, hyperinsulinemia, and hyperandrogenism, which may normalize hormonal balance, menstrual cycles, and ovulatory capacity. However, the effect of intermittent fasting on the reproductive parameters of women with PCOS is still unknown. Thus, the present study is designed to evaluate the effect of intermittent fasting, also called time-restricted feeding, on the hormonal profile of women with PCOS.

METHODOLOGY

Ethical approval for this retrospective observational study was obtained from Bacha Khan Medical College Ethics Review Committee (Approval No: 774/024). The study was Conducted at Medical Teaching Institute Bacha Khan Medical College, and Mardan Medical Complex. The duration of the study was from August 2024 through 30 January 2025, and the conduct was in accordance with the principles set forth in the Declaration of Helsinki regarding ethical practice in human research. Women with Polycystic Ovary Syndrome (PCOS) diagnosed according to the Rotterdam criteria (16) were retrospectively screened. They were only included if they had undergone a time-restricted feeding (TRF) dietary regimen as a first-line intervention. Subjects were excluded if they had comorbidities that would likely affect dietary consumption or hormonal balance, such as but not limited to thyroid or adrenal disease, Cushing's syndrome, sex hormone-secreting tumours, hyperprolactinemia, diabetes mellitus, and severe cardiovascular, hepatic, renal, or gastrointestinal illness. Also excluded were those diagnosed with a history of regular alcoholism or smoking.

Other exclusion criteria included individuals who were less than 18 or more than 40 years old, and those with a body mass index (BMI) outside the range of 18–30 kg/m². Participants who were on hormonal contraceptives, antiandrogens, ovulation-inducing drugs, or insulin-sensitizing drugs were also excluded. Individuals who had a history (within 3 months) of receiving antiepileptic medications, psychotropic drugs, statins, or corticosteroids were not eligible. Additionally, pregnant, lactating, or perimenopausal women were excluded. Others that were disqualified included the use of antibiotics within the last 3 weeks, having active infection, or any gastrointestinal illness at the time of assessment. After application of the eligibility criteria, 83 women were identified for evaluation. Of these, 63 women who completed the 6-week time-restricted feeding (TRF) regimen and had complete pre- and post-regimen records were included in the final analysis.

All data were analysed using IBM SPSS Statistics (Armonk, NY, USA). Statistical significance was set at a two-tailed p-value of <0.05. The Shapiro–Wilk test was used to assess normality. Continuous variables were reported as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Paired t-tests were used to compare normally distributed continuous variables before and after the TRF regimen.

RESULTS

Sixty-three women with PCOS completed the 6-week Time-Restricted Feeding (TRF) program. Statistically significant improvements in anthropometric, metabolic, and reproductive hormonal parameters were found. There was a significant reduction in body mass index (BMI) from 26.74 ± 1.34 kg/m² to 25.59 ± 1.39 kg/m² (p = 0.001), and waist-to-hip ratio (WHR) also decreased significantly from 0.88 ± 0.05

to 0.84 ± 0.04 (p = 0.001). A marked improvement in insulin sensitivity was observed, as HOMA-IR values dropped from 3.22 ± 0.55 to 2.43 ± 0.53 (p = 0.001), accompanied by a significant decline in fasting insulin levels from 18.4 ± 2.7 ìIU/mL to 14.1 ± 2.4 ìIU/mL (p = 0.001). The Free Androgen Index (FAI) significantly decreased from 10.13 ± 2.02 to 7.64 ± 1.42 (p = 0.001), indicating reduced hyperandrogenism. Total testosterone levels also showed a meaningful decline from 72.5 ± 14.2 ng/dL to 61.8 ± 12.3 ng/dL (p = 0.0015), and free testosterone levels dropped significantly from 3.8 ± 0.7 pg/mL to 2.9 ± 0.6 pg/mL (p = 0.001). In parallel, sex hormone-binding globulin (SHBG) levels increased from 31.32 ± 4.60 nmol/L to 35.11 ± 4.29 nmol/L (p = 0.001), contributing to the reduction in bioavailable androgens. Luteinizing hormone (LH) levels decreased significantly from 8.11 ± 2.24 mIU/mL to 6.32 ± 1.93 mIU/mL (p = 0.001), while follicle-stimulating hormone (FSH) levels increased from 5.69 ± 1.31 mIU/mL to 6.39 ± 1.31 mIU/mL (p = 0.0032), thereby improving the LH/FSH ratio—a key marker in PCOS diagnosis.

Estradiol (E2) levels rose significantly from 58.69 ± 10.87 pg/mL to 63.93 ± 8.95 pg/mL (p = 0.0128), indicating enhanced follicular activity. Although Anti-Müllerian Hormone (AMH) levels decreased slightly from 6.21 ± 1.27 ng/mL to 5.72 ± 1.32 ng/mL (p = 0.0265), they remained within the diagnostic spectrum of PCOS, possibly reflecting improved follicular recruitment dynamics. There were also statistically significant reductions in other hormonal parameters. Dehydroepiandrosterone sulfate (DHEAS) decreased from 195.7 ± 28.3 ìg/dL to 182.4 ± 25.6 ìg/dL (p = 0.002). Thyroid-stimulating hormone (TSH) levels declined from 2.43 ± 0.74 ìIU/mL to 2.28 ± 0.65 ìIU/mL (p = 0.041), and prolactin levels dropped from 14.6 ± 3.1 ng/mL to 13.1 ± 2.9 ng/mL (p = 0.036), potentially reflecting reduced stress and hypothalamic-pituitary axis modulation. This table presents the mean ± standard deviation (SD) values of selected clinical and laboratory parameters measured at baseline and after a 6-week time-restricted feeding (TRF) intervention (8-hour feeding window). Paired t-tests were used to compare pre- and TRF values. BMI: Body Mass Index; WHR: waist to hip ratio HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; FAI: Free Androgen Index; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; E2: Estradiol; AMH: Anti-Müllerian Hormone; SHBG: Sex Hormone-Binding Globulin. A p-value 0.001 was considered statistically significant. This table shows the number and percentage of women with improved ovulatory status, menstrual regularity, and hyperandrogenism (defined as FAI = 8) after a dietary intervention with TRF. Improvement is defined as the change from abnormal to normal, while 'No Change' indicates the persistence of abnormal values after the intervention. This bar chart illustrates the mean values of the key anthropometric, metabolic, and reproductive hormonal markers prior to and after the 6-week Time-Restricted Feeding (TRF) intervention in women with PCOS, where the sample size was 63. Parameters measured include body mass index (BMI), insulin resistance (HOMA-IR), Free Androgen Index (FAI), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), anti-Mullerian hormone (AMH), and sex hormone-binding globulin (SHBG). Values prior to the intervention are indicated by the blue bars, while the values obtained after the intervention are indicated by the teal bars, showing significant improvements in all the parameters measured, where $p < 0.05$. Table 3 shows the Pearson correlation between the change in BMI and shifts in key metabolic and hormonal markers after 6 weeks of TRF. Notable findings include a strong negative correlation between weight loss and HOMA-IR ($r = -0.62$, $p < 0.001$), indicating improved insulin sensitivity. Table 4 summarizes adherence levels and side effect profiles during the TRF intervention. High compliance and low adverse event rates suggest that TRF was both feasible and well-tolerated in this cohort.

DISCUSSION

This retrospective observational study aimed to assess the effects of a 6-week, 8-hour Time-Restricted Feeding (TRF) regimen on anthropometric, metabolic, and reproductive hormonal parameters in women with Polycystic Ovary Syndrome (PCOS). The results of this study showed that Time-Restricted Feeding can improve insulin resistance, androgen levels, gonadotropin balance, and menstrual regularity in PCOS women. Obesity among PCOS women is a common condition and usually exacerbates the metabolic abnormalities associated with PCOS, mainly through its association with insulin resistance.[6] The concomitant presence of obesity and PCOS increases the risk of cardiovascular disease, menstrual irregularities, androgen levels, hirsutism, and decreases quality of life.[5] Even small reductions in body weight, usually between 5% and 10%, have been found to have a marked effect on cardiovascular risk factors, glucose metabolism, reproductive and endocrine functions in PCOS women. Weight loss in PCOS women increases the peripheral conversion of androgens to estrogens and helps to balance the hormonal levels.[4]

In our current investigation, we observed that following a six-week 8-hour TRF regimen led to notable reductions in BMI among PCOS patients. These findings are consistent with prior research demonstrating that intermittent fasting protocols can positively influence body weight, BMI, and waist circumference.[15] However, clinical evidence specifically focusing on TRF in PCOS remains limited. For instance, Li et al. reported significant improvements in most anthropometric markers following a 6-week TRF intervention.[13] Similarly, in an animal model of PCOS, an 8-hour TRF diet over eight weeks resulted in reduced body weight and adipose tissue mass compared to ad libitum

Table 1. Changes in Anthropometric, Metabolic, and Reproductive Hormonal Parameters Before and After Time-Restricted Feeding (TRF) in Women with PCOS (n = 63)

Parameter	Baseline Mean ± SD	Post-TRF Mean ± SD	p-value
BMI	26.74 ± 1.34	25.59 ± 1.39	0.001
WHR	0.88 ± 0.05	0.84 ± 0.04	0.001
HOMA_IR	3.22± 0.55	2.43 ± 0.53	0.001
FAI	10.13 ± 2.02	7.64 ± 1.42	0.001
Insulin (ìIU/mL)	18.4±2.7	14.1±2.4	0.001
Total Testosterone (ng/dL)	72.5±14.2	61.8±12.3	0.001
Free Testosterone (pg/mL)	3.8 ± 0.7	2.9 ±0.6	0.001
LH	8.11 ± 2.24	6.32 ± 1.93	0.001
FSH	5.69 ± 1.31	6.39 ± 1.31	0.0032
E2	58.69 ± 10.87	63.93 ± 8.95	0.0128
AMH	6.21 ± 1.27	5.72 ± 1.32	0.0265
SHBG	31.32 ± 4.60	35.11 ± 4.29	0.001
DHEAS (ig/dL)	195.7 ±28.3	182.4 ± 25.6	0.002
TSH (ìIU/mL)	2.43 ± 0.74	2.28 ± 0.65	0.041
Prolactin (ng/mL)	14.6 ± 3.1	13.1 ± 2.9	0.036

Table 2. Categorical Improvements in Ovulatory Function, Menstrual Regularity, and Hyperandrogenism After TRF

Parameter	Improved (n, %)	No Change (n, %)
Ovulatory Status	29 (60.4%)	19 (39.6%)
Menstrual Regularity	28 (60.9%)	18 (39.1%)
Hyperandrogenism (FAI = 8)	35 (63.6%)	20 (36.4%)

Figure 1. Comparison of Mean Values of Clinical Parameters Before and After Time-Restricted Feeding (TRF)

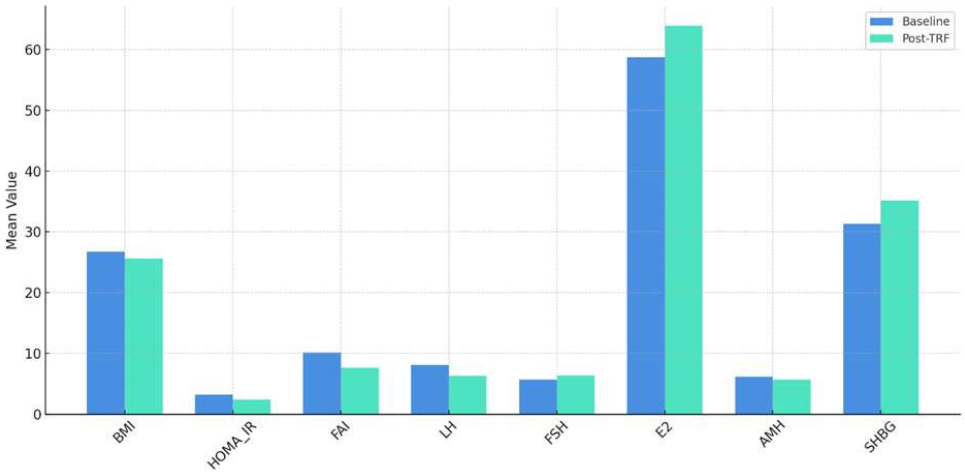

Table 3. Correlation Between ÄBMI and Changes in Hormonal and Metabolic Parameters

Parameter Change	Correlation with Ä BMI (r)	p-value
ÄHOMA_IR	0.06	0.622
ÄFAI	0.26	0.0376
ÄSHBG	0.04	0.7615
ÄLH_FSH_ratio	0.08	0.5492

Table 4. Adherence and Tolerability to TRF Regimen

Adherence Indicator	Value
Completed all 6 weeks	63/83 (75.9%)
Reported = 90% adherence to TRF	52 (82.5%)
Experienced adverse events	4 (6.3%)
Most common side effects	Headache (3.2%), Fatigue (3.1%)

feeding.[15] Other intermittent fasting strategies, such as the 5:2 diet (involving two calorie-restricted days per week), have also been shown to produce weight loss outcomes comparable to daily calorie restriction over a 6-month period in overweight young women.[16] Given the well-established connection between body composition and insulin resistance and the critical role that insulin resistance plays in the pathophysiology of PCOS our findings suggest that TRF could serve as an effective frontline intervention in the management of PCOS.

Insulin resistance (IR) is a central feature of PCOS and contributes to both its metabolic and reproductive disturbances.[17] In this study, TRF resulted in a significant reduction in HOMA-IR, aligning with previous interventional studies suggesting that intermittent fasting enhances insulin sensitivity by promoting ketogenesis, reducing oxidative stress, and modifying circadian insulin regulation.[18] This reduction in HOMA-IR levels from 3.22 to 2.43 ($p < 0.0001$) indicates an improvement in the condition and may prevent long-term risks of metabolic syndrome and type 2 diabetes. Hyperandrogenism, an essential feature of PCOS, was evaluated using the Free Androgen Index (FAI). This was found to have decreased significantly after the intervention. Insulin levels have been found to augment androgen secretion by ovarian theca cells and inhibit hepatic SHBG secretion, leading to an increase in free testosterone levels.[19] The reduction in FAI levels from 10.13 to 7.64, with a marked increase in SHBG levels, indicates hormonal rebalancing due to improved insulin levels and possible effects on hepatic SHBG secretion.[20]

The ratio of LH to FSH, which is usually high in PCOS due to increased frequency of pulsatile discharge of GnRH, was significantly reduced after TRF. This is due to decreased levels of LH and slightly increased levels of FSH, which restored homeostasis to the hypothalamic-pituitary-ovarian axis. This is important, as high levels of LH are associated with anovulation and impaired follicular development.[21] Our study is consistent with previous research that has shown that caloric restriction or intermittent fasting can modulate neuroendocrine function to improve ovulation cycles. Moreover, elevated estradiol levels and a slight decrease in AMH levels also support the idea of increased ovarian responsiveness and follicular recruitment post-TRF. AMH levels are usually elevated in women suffering from PCOS due to the presence of numerous pre-antral follicles. However, slight declines in AMH levels have been associated with better follicular dynamics and lower follicular arrest.[22] These hormonal changes were accompanied by clinical improvements in menstrual regularity and ovulation, which were achieved in over 60% of women. TRF was also associated with a significant reduction in BMI. This reduction was moderately correlated to changes in FAI ($r = 0.26$; $P = 0.0376$). Even though weight reduction was minimal, small weight losses are known to have a favorable effect on insulin and androgen levels. Notably, changes in BMI were not correlated to HOMA-IR and SHBG levels. This suggests TRF's effects on weight reduction and weight loss may not be solely responsible for its effects on metabolic parameters and may possibly include the regulation of metabolic hormones via the circadian rhythm.[23] Significantly, the TRF regimen showed good adherence rates (82.5%) and few side effects, such as fatigue and headaches. This confirms the literature that highlights the safety and tolerability of intermittent fasting regimens among women, even with hormonal imbalances.[24,25] The feasibility of the TRF regimen without the use of pharmacological agents makes it an interesting adjunct to lifestyle-based interventions for the management of PCOS. In the face of the global burden of PCOS and the limitations of pharmacological interventions, such as the side effects and poor adherence rates, the use of the TRF regimen appears to offer promise as a cost-effective and patient-centered approach to the management of PCOS, particularly in resource-scarce settings and among cultures that are resistant to pharmacological interventions. In addition, the simplicity of the dietary regimen, with an 8-hour feeding window, makes it a promising approach.

Limitations: However, some limitations have to be noted. Firstly, the non-randomized and retrospective nature of this study limits causal relationships. Secondly, the lack of control group and self-reported data on adherence might have created reporting and selection biases. Lastly, the duration of this study was only 6 weeks, and long-term effects cannot be generalized. Although the hormonal and metabolic effects of this treatment were substantial, conception and cardiovascular outcomes were not assessed. Further well-designed studies, like randomized controlled trials, with long-term follow-ups and mechanistic studies, like clock gene expression and cortisol levels, might provide further insights.

CONCLUSION

This research offers convincing proof of the benefits of a 6-week, 8-hour time-restricted feeding regimen, which has a positive impact on the metabolic and reproductive health of women living with PCOS. It was found that the regimen was effective in reducing insulin resistance, BMI, and androgens, while also facilitating the rebalancing of hormones, ovulation, and menstruation. Given the high adherence rate and lack of side effects, the TRF regimen offers promise as a non-pharmacological intervention that works in tandem with the natural rhythms of the human body, making it a suitable intervention for the management of PCOS, especially for women who are not responding to the usual treatments for the condition.

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Authors Contribution:
Huma Habib: Contributed To The Study Conception, Design, And Manuscript Drafting.
Fatima Lajbar: Participated In Data Collection, Literature Review, And Manuscript Preparation.
Atif Ullah: Assisted In Laboratory Data Interpretation And Statistical Analysis.
Hamasa Gul: Provided Clinical Supervision, Contributed To Study Design, And Critically Revised The Manuscript.
Fazal Rahim: Contributed To Data Interpretation, Clinical Correlation, And Manuscript Editing.
Miraj Ahmad: Supervised The Overall Study, Contributed To The Methodological Framework, And Served As The Corresponding Author Responsible For Final Manuscript Approval.

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Original Article **Open Access**

Pattern of Lipid Abnormalities in Newly Diagnosed Primary Hypothyroidism: A Cross-Sectional Study from Nowshera, Pakistan

Muhammad Usman, Mohammad Bilal, Tahir Hussain, Muhammad Khalid, Kalim Ullah Khan, Atif Ullah

Abstract

Objective: To evaluate the prevalence and pattern of lipid abnormalities among newly diagnosed primary hypothyroid patients presenting to a tertiary care center in Nowshera, Pakistan.

Study Design and Setting: Cross-sectional study conducted from October 2024 to May 2025 at the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera, Pakistan.

Methodology: This study was conducted over a period of six months and included 109 newly diagnosed primary hypothyroid patients aged 18–70 years, recruited through non-probability consecutive sampling. Hypothyroidism was confirmed by elevated thyroid-stimulating hormone (TSH >4.5 mIU/L) and decreased free thyroxine (free T4 <0.8 ng/dL). Fasting lipid profiles were measured, and lipid abnormalities were defined according to Adult Treatment Panel III (ATP III) criteria.

Results: Among 109 patients (mean age 38.6 ± 11.2 years; 68.8% females; mean BMI 27.8 ± 4.6 kg/m²), 86.2% had at least one lipid abnormality. The most frequent lipid abnormality was hypertriglyceridemia (59.6%), followed by low HDL-C (55.0%) and elevated LDL-C (53.2%), while hypercholesterolemia was observed in 34.9% of patients. No statistically significant differences were observed across sex, age, or BMI categories ($p > 0.05$). BMI showed a positive correlation with total cholesterol ($r = 0.30$, $p = 0.002$) and triglycerides ($r = 0.48$, $p < 0.001$), and a negative correlation with HDL-C ($r = –0.21$, $p = 0.03$).

Conclusion: Dyslipidemia is highly prevalent in newly diagnosed hypothyroid patients, with hypertriglyceridemia and low HDL-C being the most common abnormalities. These findings highlight the importance of routine lipid screening and early cardiovascular risk management in patients with hypothyroidism.

Keywords: Dyslipidemia; Hypertriglyceridemia; Hypothyroidism; Lipid profile; Low HDL-C; Pakistan

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INTRODUCTION

Hypothyroidism is characterized by an inadequate production of thyroid hormones (thyroxine [T4] and triiodothyronine [T_3]) and a compensatory elevation of thyroid-stimulating hormone (TSH), is a common endocrine disorder worldwide.[1,2] The prevalence of overt and subclinical hypothyroidism in adults has been estimated to range from about 0.5 % to 5 % and 3 % to 10 %, respectively, depending on age, sex, and iodine status of the population.[3] Thyroid hormones exert broad effects on basal metabolic rate, cardiac function, and lipid and carbohydrate metabolism.[4]

One of the well-recognized consequences of hypothyroid states is the development of dyslipidemia, often termed "secondary dyslipidemia".[5] Thyroid hormones influence nearly every step of lipid metabolism: they upregulate hepatic LDL receptor gene expression, stimulate cholesterol synthesis via HMG-CoA reductase, modulate lipoprotein lipase and hepatic lipase activities, and regulate apolipoprotein expression and reverse cholesterol transport.[6] In overt hypothyroidism, reduced LDL receptor activity and decreased lipolytic enzyme activity tend to result in elevated total cholesterol (TC), increased low-density lipoprotein cholesterol (LDL-C), and often

hypertriglyceridemia, while changes in high-density lipoprotein cholesterol (HDL-C) are more variable.[7]

Although the association between hypothyroidism and abnormal lipid profiles is well established in overt disease, data are more heterogeneous in newly diagnosed and subclinical cases, especially in different ethnic and regional populations.[8] For instance, a 2023 study by Tarboush et al. found that LDL, TG, and total cholesterol levels were significantly higher in patients with overt and subclinical hypothyroidism compared to euthyroid controls, although HDL differences were not statistically significant.[9] Some studies, however, have reported weaker or no independent association after adjustment for confounders. Regional and hospital-based studies likewise reveal varying frequencies of hypercholesterolemia, elevated LDL, low HDL, and hypertriglyceridemia in hypothyroid patients.[10,11] Characterizing the pattern and frequency of specific lipid abnormalities (i.e. hypercholesterolemia, high LDL, low HDL, hypertriglyceridemia) in newly diagnosed hypothyroid patients has both scientific and clinical importance.[12] First, early recognition of dyslipidemia in thyroid disease can guide prompt risk stratification and cardiovascular risk mitigation. Second, it informs clinicians about whether a "universal screening" approach or a more targeted lipid evaluation is warranted in hypothyroid patients. Third, knowing the prevalent lipid derangements can help tailor lipid-lowering or thyroid replacement strategies in your patient population.[13]

In view of the scarcity of data from our region and institution, this study aim to contribute to the body of knowledge by identifying the prevalence of different lipid profile abnormalities among newly presenting cases of hypothyroid patients presented to our institution. This may then serve as a basis to aid the clinician in the early intervention and management of hypothyroid patients with co-existing lipid profile abnormalities.

METHODOLOGY

This cross-sectional study was conducted in the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera, from October 2024 to May 2025. The study protocol was reviewed and approved by the Institutional Ethics Committee of Qazi Hussain Ahmad Medical Complex, Nowshera (Ref. No. 02/ERB/NMC; dated 08 October 2024). Written informed consent was obtained from all participants before enrollment. The confidentiality of participants' data was strictly maintained throughout the study. The sample size was calculated as 109 patients using the WHO sample size calculator. The calculation was based on an expected prevalence of hypercholesterolemia of 35% in hypothyroid patients[8], with 9% absolute precision and a 95% confidence level. Patients fulfilling the eligibility criteria were recruited by non-probability consecutive sampling until the sample size was reached.

Adults aged 18–70 years of either sex with *newly diagnosed primary hypothyroidism*. Newly diagnosed hypothyroidism was defined as (i) clinical symptoms suggestive of hypothyroidism (fatigue, weight gain, cold intolerance, constipation, etc.) and (ii) laboratory confirmation of elevated TSH (>4.5 mIU/L) with low free T4 (<0.8 ng/dL or <10 pmol/L), were included in the study. On the other hand patients with conditions or treatments that could affect lipid levels, including: established coronary artery disease, ischemic heart disease, diabetes mellitus, uncontrolled hypertension, pregnancy, or current use of drugs influencing thyroid or lipid metabolism (levothyroxine, amiodarone, corticosteroids, statins, or other lipid-lowering agents) were excluded from the study. After obtaining written informed consent, demographic details (age, sex, residence, education, socioeconomic status), clinical history, and anthropometric measurements (height, weight, BMI) were recorded on a structured proforma. Thyroid function tests (TSH and free T4) were performed to confirm eligibility. For the assessment of the lipid profile, 7 mL of venous blood samples were collected after an overnight fasting. These samples were analyzed in the hospital laboratory by employing standard enzymatic techniques on automated analyzers under the guidance of a consultant chemical pathologist. There were proper quality control mechanisms in place during the entire process. Definitions of abnormal lipid profiles were made in accordance with the guidelines of the Adult Treatment Panel III. An abnormal level of cholesterol in the blood was defined as levels above 240 mg/dL or 6.2 mmol/L. Similarly, abnormal levels of LDL-C were defined as =160 mg/dL or 4.1 mmol/L. Abnormal HDL-C levels were defined as those below 40 mg/dL in males and those below 50 mg/dL in females. Abnormal levels of triglycerides in the blood were defined as those between 200–499 mg/dL or 2.3–5.6 mmol/L. On the basis of the above definitions of abnormal lipid profiles, the lipid profile of each individual was classified as abnormal or normal.

IBM SPSS Statistics 25 software was used for the analysis of the collected data. For the continuous variables like age, BMI, lipid levels, the distribution of the data is checked to see whether the data is normally distributed or not. If the data is found to be normally distributed, the results will be shown in the form of mean ± SD. If the data is not normally distributed, the results will be shown in the form of median and interquartile range. Similarly, for the categorical variables like sex, the results will be shown in the form of frequencies and percentages. The primary outcome was the frequency of lipid profile abnormalities (high TC, high LDL-C, low HDL-C, high TG). Stratified analyses were performed by age group (<40 vs =40 years), sex, BMI category (normal, overweight, obese according to Asian criteria), and residential status (urban vs rural). Chi-square test (or Fisher's exact test when applicable) was used to assess associations, with $p < 0.05$ considered statistically significant. Results are

presented in tables and text.

RESULTS

A total of 109 patients with newly diagnosed primary hypothyroidism were enrolled. The mean age was 38.6 ± 11.2 years (range: 19–70 years), with 60% of participants between 30 and 50 years. Females predominated (n = 75, 68.8%), giving a female-to-male ratio of 2.2:1. The mean BMI was 27.8 ± 4.6 kg/m²; 30% were obese, 45% overweight, and 25% within the normal range according to Asian BMI criteria. Most patients resided in rural areas (55%) and 62% had attained at least secondary-level education. No statistically significant sex-based differences were observed in age or BMI ($p > 0.05$). Dyslipidemia was highly prevalent in this cohort. Overall, 94 patients (86.2%) had at least one lipid abnormality, while only 15 (13.8%) demonstrated a completely normal lipid profile. Hypertriglyceridemia was the most frequent abnormality (59.6%), followed by low HDL-C (55.0%), high LDL-C (53.2%), and hypercholesterolemia (34.9%). The mean serum lipid values were: Total cholesterol: 228 ± 46 mg/dL (64% >200 mg/dL; 35% >240 mg/dL), LDL-C: 148 ± 35 mg/dL (53.2% =160 mg/dL), HDL-C: 44 ± 11 mg/dL (42 ± 10 in men; 45 ± 11 in women); 55% below recommended cut-offs, Triglycerides: 218 ± 96 mg/dL (median 205, IQR 150–270); 15% >300 mg/dL; 2 cases >400 mg/dL. Hypertriglyceridemia was the most frequent abnormality, followed by low HDL-C, high LDL-C, and hypercholesterolemia. Among the 109 newly diagnosed hypothyroid patients, dyslipidemia was highly prevalent. Overall, 86.2% of patients demonstrated at least one lipid abnormality, while only 13.8% had a completely normal lipid profile. The most common lipid derangement was hypertriglyceridemia, which was noted in 59.6%, followed by low HDL-C levels in 55.0%, and high levels of LDL-C in 53.2%. Hypercholesterolemia was noted in 34.9% of the population. Figure 1 shows a bar chart that demonstrates the prevalence of lipid abnormalities among the population. This shows that hypertriglyceridemia and low HDL-C levels were the most common lipid abnormalities among the population. Using the continuous method of analysis, there was a significant but slight correlation between BMI and lipid levels. The percentage of dyslipidemia among the newly diagnosed hypothyroid patients was found to be 86%. The most common lipid abnormality was high triglyceride, accounting for 59.6%, followed by low HDL-C, accounting for 55.0%. High LADL-C was the third most common abnormality, accounting for 53.2%. A large percentage of the population had =2 abnormal lipid profiles. A slightly higher percentage of dyslipidemia was found among females, the elderly, and overweight/obese patients, though the results were not significant. BMI had a positive correlation with TC and TG, and negative correlation with HDL-C

Table 1. Baseline characteristics of study population (N = 109)

Variable	Value
Age (years)	38.6 ± 11.2 (range 19–70)
Age group: <30 / 30–50 / >50	20 (18.3%) / 65 (59.6%) / 24 (22.0%)
Sex (F/M)	75 (68.8%) / 34 (31.2%)
BMI (kg/m²)	27.8 ± 4.6
BMI category: Normal / Overweight / Obese	27 (24.8%) / 49 (45.0%) / 33 (30.3%)
Residence	Rural 60 (55.0%), Urban 49 (45.0%)
Socioeconomic status	Low 44 (40.4%), Middle 55 (50.5%), High 10 (9.2%)
Education = secondary	68 (62.4%)
TSH (mIU/L)	18.5 ± 9.7
TSH: 5–10 / >10	29 (26.6%) / 80 (73.4%)
Free T4 (ng/dL)	0.54 ± 0.15

Table 2. Frequency of lipid abnormalities in newly diagnosed hypothyroid patients (N = 109)

Lipid Parameter	Cut-off (ATP III)	Patients with Abnormal Level, n (%)
High total cholesterol	>240 mg/dL	38 (34.9%)
High LDL-C	=160 mg/dL	58 (53.2%)
Low HDL-C	<40 mg/dL (M), <50 mg/dL (F)	60 (55.0%)
High triglycerides	200–499 mg/dL	65 (59.6%)

Table 3. Stratified prevalence of lipid abnormalities by sex, age, and BMI

Subgroup	High TC (%)	High LDL (%)	Low HDL (%)	High TG (%)
Sex				
Male (n=34)	11 (32.4)	16 (47.1)	18 (52.9)	18 (52.9)
Female (n=75)	27 (36.0)	42 (56.0)	42 (56.0)	47 (62.7)
Age				
=40 years (n=55)	17 (30.9)	26 (47.3)	30 (54.5)	29 (52.7)
>40 years (n=54)	21 (38.9)	32 (59.3)	30 (55.6)	33 (61.1)
BMI				
<25 (n=27)	7 (25.9)	13 (48.1)	16 (59.3)	14 (51.9)
=25 (n=82)	31 (37.8)	45 (54.9)	44 (53.7)	51 (62.2)

p > 0.05 for all subgroup comparisons (Chi-square/Fisher's exact tests)

Figure 1. Prevalence of lipid abnormalities in newly diagnosed primary hypothyroid patients (N = 109).

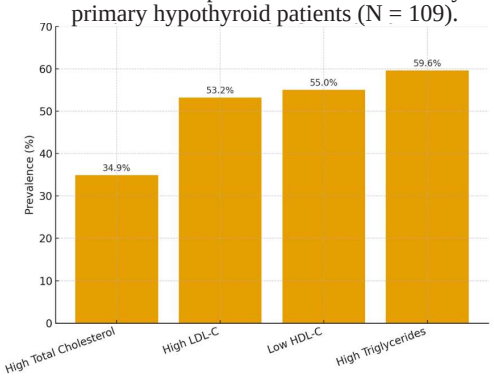

Table 4. Correlation of BMI with lipid levels

Lipid Parameter	Spearman r	p-value
Total cholesterol	+0.30	0.002
LDL-C	+0.18	0.06
HDL-C	–0.21	0.03
Triglycerides	+0.48	<0.001

DISCUSSION

In this cross-sectional study of 109 patients with newly diagnosed primary hypothyroidism, we observed a high prevalence of dyslipidemia. The most frequent lipid abnormality was hypertriglyceridemia (59.6%), followed closely by low HDL-C (55.0%) and high LDL-C (53.2%), while hypercholesterolemia was present in approximately one-third of patients (34.9%). Notably, over 86% of patients exhibited at least one lipid abnormality, highlighting the strong link between hypothyroidism and disturbed lipid metabolism.

Our findings are consistent with earlier studies reporting frequent lipid derangements in hypothyroid patients. Shams et al. described increased total cholesterol and LDL-C as classical biochemical features of overt hypothyroidism, attributable to reduced LDL receptor activity and impaired clearance of cholesterol-rich lipoproteins.[14] In our study, 53.2% of subjects were found to have high LDL levels, similar to the finding in a study done by Tarboush et al., where they found high levels of LDL in both overt and subclinical hypothyroidism.[15]

In this study, hypertriglyceridemia, the most common abnormality, was found in almost 60% of subjects.[16] Though this figure is slightly higher than in some Western studies, where hypertriglyceridemia is not a prominent abnormality, it is similar to some studies done in South Asian and Middle Eastern populations. Ethnic, dietary, and lifestyle differences may partly explain this discrepancy.[17]

In addition, low HDL-C levels were also common in our population (55%), indicating cardioprotective cholesterol levels are also decreased. Some studies have shown variable HDL levels in hypothyroidism, with mild reductions in overt hypothyroidism, whereas in subclinical hypothyroidism, these levels are less consistent.[18] It is also possible that in our study, high levels of metabolic risk factors, such as overweight and obesity, contributed to this finding.[19] The findings of the present investigation confirm the strong association between hypothyroidism and an atherogenic lipid profile with high levels of LDL-C and triglycerides and low levels of HDL-C, a lipid triad that greatly increases the risk for atherosclerosis. Of particular interest was the fact that many patients had two or more lipid abnormalities.[20]

The mechanisms behind the occurrence of dyslipidemia in hypothyroidism involve various components. Thyroid hormones control lipid metabolism. Low-density lipoprotein cholesterol (LDL-C) levels are raised due to the reduced density of the LDL receptor on the liver cell membrane. This reduces the clearance of LDL-C from the blood. As a result, total cholesterol levels are also high.[21] Triglycerides stimulate lipoprotein lipase and hepatic lipase. These enzymes

play a crucial role in the clearance of triglyceride-rich lipoproteins from the blood. Reduced levels of these enzymes in hypothyroidism result in high levels of triglycerides. Thyroid hormones control the synthesis of apolipoproteins A-I and A-II. These apolipoproteins control the levels of high-density lipoprotein cholesterol (HDL-C). Reduced levels of apoA-I result in reduced levels of HDL-C.[22]

In addition, the reduced uptake of cholesterol by the liver and reduced synthesis of bile acids, as seen in hypothyroid states, lead to reduced cholesterol catabolism. However, it is interesting to note that the lipid abnormalities seen in hypothyroidism may, in turn, contribute to the cardiovascular risk factors associated with thyroid dysfunction. For example, the elevated LDL and TG may lead to rapid atherosclerosis, endothelial dysfunction, and ischemic heart disease. In addition, the reduced HDL may weaken the body's natural defense mechanism against cholesterol deposition. Thus, the lipid-thyroid interrelationship is two-way, where hypothyroidism leads to abnormal lipid metabolism, and abnormal lipid metabolism may lead to worsening of the hypothyroid state.[23]

Our findings emphasize the need to investigate lipid profiles in patients with newly diagnosed hypothyroidism. Since >85% of the patient population presented with at least one abnormal lipid level, timely interventions can be initiated. Additionally, thyroid hormone replacement with levothyroxine has been demonstrated to significantly alter lipid levels, especially total cholesterol and LDL-C levels. However, there are reports that lipid abnormalities can persist even after the achievement of euthyroid state, especially in the context of obesity or metabolic syndrome, highlighting the need for comprehensive cardiovascular risk management.[24]

However, the study has some limitations. First of all, the study is cross-sectional in design. It only shows association rather than causality. Secondly, the study is conducted in a single center. Thirdly, the sample size is relatively small. Moreover, the study did not include a euthyroid group for comparative purposes. Finally, the study did not follow the patients for a long period to see the changes in the lipid profile of hypothyroid patients following the administration of thyroid hormone replacement therapy. Despite the aforementioned limitations of the study, the study is of significant value as it provides the baseline data of the lipid abnormalities in hypothyroid patients.

CONCLUSION

Newly presenting hypothyroid patients have a high prevalence of dyslipidemia, especially hypertriglyceridemia, low HDL-C, and high LDL-C levels. All these are mechanistically linked to decreased thyroid hormone activity on lipid metabolism and are a major contributor to cardiovascular risk in these patients. Hence, it is of utmost importance to incorporate this into the management of hypothyroidism, in addition to thyroid hormone replacement.

Furthermore, our study also emphasizes the significance of adopting a multidisciplinary approach in managing hypothyroidism, where endocrinology, cardiology, and primary care perspectives are considered in a holistic approach to managing this condition. It is also of great significance to educate patients regarding lifestyle modifications, dietary habits, and risk factors for cardiovascular disease. It is also worth considering overweight and obese patients as a high-risk subgroup, where preventive strategies could be initiated in these patients.

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Authors Contribution:
Muhammad Usman: contributed to study conception, data collection, statistical analysis, and manuscript drafting.
Mohammad Bilal: contributed to data collection, literature review, and manuscript preparation
Dr. Tahir Hussain: contributed to data collection, literature review, and manuscript preparation.
Muhammad Khalid: supervised the study, contributed to study design, interpretation of data, and critical revision of the manuscript.
Kalim Ullah Khan: assisted in data analysis and manuscript editing.
Atif Ullah: contributed to methodological support, physiological interpretation, and final manuscript review.

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Original Article **Open Access**

Comparison of Outcomes of Microscopic Versus Conventional Thyroidectomy

Laraib Abro, Arslan Liaqat, Gulnaz Arshad, Sarfraz Latif, Aqsa Yaqub, Sadaf Zafar

ABSTRACT:

Objectives: To compare the outcomes of microscopic versus conventional thyroidectomy.

Study design & settings: Randomized controlled trial from 16th December 2025 to 15th March 2026 at ENT Department at Sheikh Zayed Hospital, Lahore.

Methodology: This Randomized controlled trial (ClinicalTrials.gov Identifier: NCT07488858) involved 74 patients who underwent thyroidectomies at the age of 18 and 65 years. The patients were split into microscopic thyroidectomy (n = 37) and conventional thyroidectomy group (n = 37). EBSLN palsy, RLN palsy, transient and persistent hypocalcemia were categorical variables whereas operation time, and intraoperative blood loss were continuous. The SPSS version 26 was used to analyze the data. The independent t-test was used to compare the continuous variables and the categorical variables were compared with the chi-square test or the Fisher exact test. A p-value of =0.05 was regarded as significant.

Results: The mean time of operation of the MT group was 92.6 ± 15.4 minutes and the CT group was 78.9 ± 14.7 minutes. The intraoperative mean blood loss of the MT group was however significantly less than that of the CT group (52.3 ± 18.6 mL vs., 84.7 ± 25.1 mL). Transient RLN palsy was also seen in 5.4% of patients in the MT group, as compared to 13.5% in the CT group, and only persistent RLN palsy occurred in 2.7% patients in the CT group.

Conclusion: Even though technique was slightly slower than conventional thyroidectomy, intraoperative blood loss and postoperative complications were also reduced substantially by microscopic thyroidectomy.

Keywords: Thyroidectomy, microscopic thyroidectomy, laryngeal nerve palsy recurrent

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INTRODUCTION:

Thyroid disorders requiring surgical intervention are common, with conditions such as multi nodular goiter, thyroid malignancies, and hyperthyroidism frequently necessitating thyroidectomy.[1] The procedure, while effective, poses risks due to the intricate anatomy of the thyroid gland and its proximity to critical structures such as the recurrent laryngeal nerve (RLN), external branch of the superior laryngeal nerve (EBSLN), and parathyroid glands.[2] Such complications as RLN palsy, hypocalcemia, and hematoma may lead to serious morbidity. Hypocalcemia is reported in 20%-30% of cases and RLN injury is in 5-11 cases although bilateral RLN paralysis is an extremely rare but fatal complication that can be prevented using accurate surgical techniques, sufficient anatomy and expertise in surgeon management.[3,4]

Surgery of the thyroid has also developed greatly and it now takes different methods to increase the safety and the results. The traditional thyroidectomy (CT) is still the most commonly used, as it offers direct visualization and direct excision of the gland. Endoscopic thyroidectomy which makes use of minimal access measures has enhanced cosmetic results nevertheless has been reported to take more time to perform. Robotic-assisted thyroidectomy has also improved the accuracy, but at a cost and accessibility has been a limiting factor.[5-7] Microscopic thyroidectomy (MT), enabling the use of magnification to improve visualization, has been introduced in order to reduce complications. Research indicates that MT is better preserving RLN, EBSLN, and parathyroid glands, decreasing the levels of

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transient nerve palsies and hypocalcemia when compared to traditional methods.[8,9] it is necessary to evaluate the efficacies in the normal clinical practice.

Gautam et al.[10] compared MT and CT in 60 patients (30 per group), with a female predominance (9.1:1). Transient RLN palsy was lower in MT (3.3%) than CT (6.6%), and transient hypocalcemia was significantly lower in MT (3.3%) than CT (13.3%, $P < 0.05$). (9) Khan and Anas (2020) studied 15 patients (MT: 7, CT: 8), with mean ages of 40.3 ± 7.6 years in CT and 41.6 ± 8.3 years in MT ($P > 0.05$). Operative time was longer in MT (100.6 ± 18.4 min) than CT (75.2 ± 27.4 min, $P > 0.05$). One CT patient (12.5%) had permanent RLN palsy, while no RLN injuries occurred in MT ($P > 0.05$). No EBSLN palsy was observed. Hypocalcemia occurred in 1 CT patient (12.5%) but none in MT ($P > 0.05$).[10] Seven et al.[11] analyzed 98 patients (MT: 58, CT: 40), with similar operative times (MT: 98.6 ± 24.7 min, CT: 91.2 ± 32.4 min, $P > 0.05$) and intraoperative blood loss (MT: 95 ± 103 mL, CT: 132 ± 114 mL, $P > 0.05$). Transient RLN and EBSLN palsy occurred in 1.7% of MT and 7.5% of CT patients ($P > 0.05$). The transitory hypocalcemia rate was substantially lower in communities with complete thyroidectomy (MT: 4.1%, CT: 33.3, $P = 0.022$) than in communities without complete thyroidectomy (12.5, $P = 0.032$). Wound hematoma occurred in 1 CT patient (2.5%) but none in MT. Minor wound complications were seen in 10% of CT and 8.6% of MT patients.[11]

One of the most practiced endocrine surgical operations is thyroidectomy. However, even with the development of surgical methods, recurrent laryngeal nerve (RLN), hypocalcemia, and external branch of the superior laryngeal nerve (EBSLN) palsy are still significant issues. Optical magnification in thyroidectomy has been suggested to enhance detection of the fine anatomical structures and minimize the level of complications. Microscopic thyroidectomy remains not commonly used in local surgery practice, in which traditional thyroidectomy is conventionally used, although foreign studies have given promising outcomes. The present study aims at bridging this gap in the research, by comparing the operational time, intraoperative blood loss, and postoperative complications in microscopic versus conventional thyroidectomy in our setting.

METHODOLOGY:

After approval from institutional ethical review committee (Ref no. 02-TERC/NHRC-SZH/INT-SC/769 dated 26-6-2025), the ENT Department at Sheikh Zayed Hospital, Lahore conducted this Randomized controlled trial (ClinicalTrials.gov Identifier: NCT07488858) from 16th December 2025 to 15th March 2026. A sample size of 74 (37 in each group) is calculated by assuming the proportion of transient hypocalcemia among patient underwent microscopic thyroidectomy (4.1%) versus conventional thyroidectomy (33.3%), keeping the confidence interval of 95% and power 90%.[11] It was calculated by using online software OpenEpi.

Inclusion criteria were benign or malignant thyroid disease patients that have undergone thyroidectomy and aged between 18 and 65 years old, regardless of their gender. The inclusion criteria was patients whose vocal cords had moved normally prior to the operation as determined by the laryngoscopy and patients who were not hemodynamically unstable and did not have any significant comorbidities that would interfere with surgery or anesthesia according to the ASA classification (Class I-III). Prior history of prior thyroid surgery, evidence of lateral lymph node metastasis or local invasion on preoperative imaging (ultrasonography or computed tomograph), pre-existing hypocalcemia or parathyroid disorders, severe medical comorbidities, including uncontrolled diabetes (HbA1c > 8%), chronic kidney disease (eGFR < 30 mL/min/1.73m²), liver cirrhosis (Child-Pugh class B or C), or coagulopathy (INR > 1.5 or platelet count < 50,000/μL), were excluded from the study. Invasive thyroid carcinoma, anaplastic thyroid carcinoma, and thyroid lymphoma that demanded radical surgery were also eradicated as well as the pregnant and nursing women.

Patients were recruited based on some selection criteria in the inpatient wards and the outpatient department (OPD). It was the guidelines of the Helsinki Declaration that were adhered to when carrying out the study to ensure the safety and well-being of the participants as well as protecting their rights. Informed consent was given by each participant in writing before the recruitment and the confidentiality of patient information will be maintained at any time. Each patient was recorded in terms of age, gender, lesion type of the thyroid (multinodular goiter, Grave disease, or thyroid cancer), duration of the symptoms, and comorbidities (diabetes and hypertension). Two categories of enrolled patients were formed: Patients that have a thyroidectomy under a surgical microscope belong to Group A (Microscopic Thyroidectomy, or MT). Group B Patients who undergo Thyroidectomy (Conventional Thyroidectomy, or CT) do not use a surgical microscope.

Microscopic Thyroidectomy (MT) in Group A Despite the use of endotracheal intubation, the surgery was done under general anesthesia. A 45-cm transverse cervical incision was made along a natural line of the skin. Magnification (Magnification, Zeiss Sensera, 3x-5x) was applied to the external branch of the superior laryngeal nerve (EBSLN) and recurrent laryngeal nerve (RLN) to allow the dissection of the parathyroid glands. The ligatures were done at the superior pole of the thyroid gland and not at EBSLN. The RN was determined on the entry site to the larynx and kept in perfect condition. The parathyroid glands were distinguished, frozen or remedied in the event of the devascularization. The thyroid gland had been removed according to the intended operation (lobectomy, sub-total, or the total thyroidectomy). The wound was closed in layers

and hemodynamics was restored.

Group B - Conventional Thyroidectomy (CT) A similar method was employed except that no microscopic magnification was employed. The standard visual techniques were used to identify RN and EBSLN and the process was accomplished according to the traditional approach. The traditional methods were used to identify and preserve parathyroid glands without any further magnification. The recovery room paid close attention to patients following surgery in case of any immediate complications such as bleeding or airway obstruction. Serum calcium levels were tested 24 hours after operation to determine whether they were hypocalcaemic and indirect laryngoscopy carried out prior to discharge to determine the functioning of the vocal cords. Normal analgesic treatment was administered and supplementation with calcium or vitamin D was started in case of need. In case of a stable, patients were sent out within 48 hours and were followed after one month. In follow-up, final outcome measurements were operative time, intraoperative blood loss and laryngoscopic measure of transient or permanent RLN palsy. EBSLN palsy was determined with videostroboscopy and range of serum calcium levels were determined at 24 hours and one month after surgery to determine transient or permanent hypocalcemia. Data collection was done using data collection proforma.

All the data collected were discussed through SPSS version 26. Examples of continuous variables that were measured in mean +SD were age, the duration of operations, intraoperative blood loss, and the level of serum calcium. These variables were compared in the compartments of conventional thyroidectomy (CT) and microscopic thyroidectomy (MT) with independent t-test. Categorical variables, such as the presence of transient or persistent recurrent laryngeal nerve (RLN) palsy, external branch of the superior laryngeal nerve (EBSLN) palsy, transient and permanent hypocalcemia were represented in frequencies and percentages. The comparison of the two groups was done using either the chia-square test or the Fisher exact test depending on the expected number of cells. The post-stratification chi-square test of the effect of the confounding variables (age, gender, comorbidity, and kind of lesion) was applied after stratification of the latter. In any analysis, the p-value of less than 0.05 was considered statistically significant.

RESULTS:

The average age of the patients, who underwent microscopic thyroidectomy, was 41.3 ± 11.2 years, and that of the conventional thyroidectomy and the conventional thyroidectomy was 42.7 ± 10.5 years. The difference in the mean of ages between the two groups was not statistically significant (p = 0.58). As to gender, both groups were mainly female. The sample consisted of 11 (29.7%) and 26 (70.3%) male and female patients respectively in the MT group. The CT group had an equal amount of 13 (35.1%) men and 24 (64.9%) women. The p-value did not show any significant difference between the groups (p = 0.62). [Table I].

On the comorbid conditions, 7 (18.9%) and 9 (24.3%) of the patients in the MT and CT groups, respectively, were diabetic with 30 (81.1%) and 28 (75.7%) having no diabetes mellitus. It was established that this was not statistically significant (p = 0.54). On the same note, it was also found out that 27 (73.0%) and 25 (67.6%) patients in the normotensive and the MT and CT groups respectively were hypertensive. The group difference of the statistics was 0.47. [Table I]

In terms of the type of thyroid lesion, multinodular goiter is the most widely examined pathology in 18 (48.6%) and 16 (43.2%) participants of the MT and CT groups, respectively. The patients with the MT group had twelve (32.4%) and the CT group had fourteen (37.8) that had single thyroid nodules. Each group had seven (18.9%) patients who were diagnosed with thyroid cancer. The type of lesions in the two groups did not differ statistically (p = 0.63). [Table I].

The average operative time in the microscopic thyroidectomy group was 92.62±15.4 minutes compared to the conventional thyroidectomy group which was 78.92±14.7 minutes. The operative duration was also much more in the microscopic group of thyroidectomy (p = 0.001). (Table II).

Mean intraoperative blood loss was calculated as 52.3±18.6 mL in the group of microscopic thyroidectomy and 84.7±25.1 mL in the group of conventional thyroidectomy. This was statistically significant (p < 0.001) that showed a significant decrease in intraoperative blood loss with microscopic thyroidectomy. Table II.

There were two (5.4%) patients of the microscopic thyroidectomy group with temporary RLN palsy and five (13.5%) patients of the conventional thyroidectomy group. The difference did not turn out to be significant (p = 0.23) even though the CT group had more complications. Permanent RLN palsy was observed in one (2.7%) patient in conventional thyroidectomy and non in microscopic thyroidectomy group. The distinction was not high (p = 0.31). In Table III.

There was EBSLN palsy in one patient (2.7%) in the case of microscopic thyroidectomy and four patients (10.8%) in the conventional thyroidectomy. Although this was higher in the CT group, the incidence was statistically insignificant (p = 0.17). In Table III.

Three (8.1%) patients in the microscopic thyroidectomy group suffered temporary hypocalcemia, and seven (18.9%) patients in conventional thyroidectomy group. The statistical significance of the two groups was found not to be significant (p = 0.18). Hypocalcemia was permanent in 1 (2.7%) patient

of normal thyroidectomy and none of the patients of microscopic thyroidectomy. This was also statistically unnoticed (p = 0.31). (Table III).

Following the separation of the individuals by age, the microscopic thyroidectomy group took a significantly longer time to perform operation compared to the standard thyroidectomy group among individuals whose age range was 18 to 40 and 41 to 65 years. Similarly, both age groups had a significantly lower amount of blood during surgery following a microscopic thyroidectomy. The level of gender stratification was also of a consistent pattern, and it means that both male and female patients with microscopic thyroidectomy had a longer operating time and much fewer blood losses in comparison to the patients with conventional thyroidectomy. Microscopic thyroidectomy took a relatively long operational time than conventional thyroidectomy; however, it led to a very minimal intraoperative blood loss among the patients with diabetes mellitus. The same tendency was witnessed with non-diabetic patients. Stratified by hypertension, hypertensive and normotensive patients undergoing microscopic thyroidectomy exhibited prolonged surgery with less intraoperative blood loss than did their conventional counterparts undergoing thyroidectomy. (Table IV). In terms of type of lesion, the longest time spent on operating was with patients with thyroid carcinoma and specifically in the microscopic thyroidectomy. Regardless, the microscopic thyroidectomy group never recorded more blood loss during the surgery than the other groups which consisted of multinodular goiter, solitary thyroid nodules, and thyroid cancer.

The higher cases of RN palsy and hypocalcemia were in people who experienced conventional thyroidectomy in the groups 18-40 and 41-65 but the difference was not statistically significant. Further, gender-based stratification revealed that, females with conventional thyroidectomy had a higher probability of having RLN palsy and hypocalcemia compared with those with microscopic thyroidectomy and this was not statistically significant. In the case of the stratification of the groups in terms of the diabetes mellitus and the high blood pressure, the complication rates were found to be statistically higher in the normal thyroidectomy group. When the groups were divided, however, a major correlation was not found. Multinodular patients with thyroid cancer, solitary nodules of thyroid who underwent a regular thyroidectomy and cases with hypocalcemia were found to have high rates of RLN palsy and hypocalcemia when compared to patients with microscopic thyroidectomy. This was especially obvious in the case of thyroid cancer patients but not significantly. (Table IV)**DISCUSSION:**

In the current research, the operative time in the MT group equalized 92.6 ± 15.4 minutes, in the CT group equalized 78.9 ± 14.7 minutes. This shows that microscopic thyroidectomy took a little more time to operate. These results were also reported by Li et al. who revealed that the minimally invasive thyroidectomy procedures are likely to take longer periods to be performed than the traditional open

Table-1: Baseline Demographic and Clinical Characteristics of Patients (n = 74)

Variable	Microscopic Thyroidectomy (n=37)	Conventional Thyroidectomy (n=37)	p-value
Age (years)	41.3 ± 11.2	42.7 ± 10.5	0.58
Gender			
Male	11 (29.7%)	13 (35.1%)	0.62
Female	26 (70.3%)	24 (64.9%)	
Diabetes Mellitus			
Yes	7 (18.9%)	9 (24.3%)	0.54
No	30 (81.1%)	28 (75.7%)	
Hypertension			
Yes	10 (27.0%)	12 (32.4%)	0.47
No	27 (73.0%)	25 (67.6%)	
Type of Lesion			
Multinodular Goiter	18 (48.6%)	16 (43.2%)	0.63
Solitary Thyroid Nodule	12 (32.4%)	14 (37.8%)	
Thyroid Carcinoma	7 (18.9%)	7 (18.9%)	

Table 2: Comparison of Operative Outcomes between Groups

Variable	Microscopic Thyroidectomy (n=37) Mean ± SD	Conventional Thyroidectomy (n=37) Mean ± SD	p-value
Operativ Time (minutes)	92.6 ± 15.4	78.9 ± 14.7	0.001
Intraoperative Blood Loss (mL)	52.3 ± 18.6	84.7 ± 25.1	<0.001

Table 3: Comparison of Postoperative Complications

Complication	Microscopic Thyroidectomy (n=37)	Conventional Thyroidectomy (n=37)	p-value
Transient RLN Palsy	2 (5.4%)	5 (13.5%)	0.23
Permanent RLN Palsy	0 (0%)	1 (2.7%)	0.31
EBSLN Palsy	1 (2.7%)	4 (10.8%)	0.17
Transient Hypocalcemia	3 (8.1%)	7 (18.9%)	0.18
Permanent Hypocalcemia	0 (0%)	1 (2.7%)	0.31

Table 4: Stratification of Effect Modifiers with Respect to Operative Time, Intraoperative Blood Loss and complications (n = 74)

Effect Modifier	Category	Operative Time (min)		p-value	Blood Loss (mL)		p-value	RLN Palsy n (%)		p-value
		MT	CT		MT	CT		MT	CT	
Age (years)	18–40	90.4 ± 14.8	76.9 ± 13.9	0.002	50.6 ± 17.3	81.5 ± 23.7	<0.001	1 (5.9%)	3 (18.8%)	0.28
	41–65	94.3 ± 16.1	80.5 ± 15.2	0.004	53.8 ± 19.4	87.1 ± 26.3	<0.001	1 (5.0%)	3 (14.3%)	0.30
Gender	Male	91.8 ± 14.9	77.6 ± 13.8	0.003	51.4 ± 18.2	82.6 ± 24.5	<0.001	1 (9.1%)	2 (15.4%)	0.41
	Female	93.0 ± 15.7	79.7 ± 15.2	0.005	52.7 ± 18.9	85.6 ± 25.4	<0.001	1 (3.8%)	4 (16.7%)	0.24
Diabetes Mellitus	Yes	95.1 ± 15.8	82.3 ± 14.6	0.02	54.7 ± 19.3	88.4 ± 26.1	0.001	1 (14.3%)	2 (22.2%)	0.56
	No	91.8 ± 15.2	77.8 ± 14.5	0.001	51.8 ± 18.4	83.5 ± 24.8	<0.001	1 (3.3%)	4 (14.3%)	0.21
Hypertension	Yes	96.2 ± 16.3	83.5 ± 15.1	0.01	55.2 ± 19.8	89.7 ± 27.2	0.001	1 (10.0%)	2 (16.7%)	0.48
	No	91.3 ± 15.0	77.1 ± 14.2	0.001	51.1 ± 18.1	82.9 ± 24.6	<0.001	1 (3.7%)	4 (16.0%)	0.22
Type of Lesion	Multinodular Goiter	90.8 ± 14.6	76.5 ± 13.7	0.002	50.9 ± 17.8	80.7 ± 23.9	<0.001	1 (5.6%)	2 (12.5%)	0.30
	Solitary Nodule	93.7 ± 15.3	79.2 ± 14.8	0.003	52.8 ± 18.6	84.1 ± 25.1	<0.001	1 (8.3%)	2 (14.3%)	0.39
	Thyroid Carcinoma	97.4 ± 16.8	84.9 ± 15.9	0.02	55.6 ± 20.1	90.5 ± 27.6	0.002	0 (0%)	2 (28.6%)	0.29

Continue...

Effect Modifier	Category	Hypocalcemia n (%)		p-value
		MT	CT	
Age (years)	18–40	1 (5.9%)	3 (18.8%)	0.22
	41–65	2 (10.0%)	5 (23.8%)	0.19
Gender	Male	1 (9.1%)	2 (15.4%)	0.33
	Female	2 (7.7%)	5 (20.8%)	0.20
Diabetes Mellitus	Yes	1 (14.3%)	2 (22.2%)	0.49
	No	2 (6.7%)	5 (17.9%)	0.17
Hypertension	Yes	1 (10.0%)	3 (25.0%)	0.44
	No	2 (7.4%)	4 (16.0%)	0.19
Type of Lesion	Multinodular Goiter	1 (5.6%)	3 (18.8%)	0.26
	Solitary Nodule	1 (8.3%)	2 (14.3%)	0.31
	Thyroid Carcinoma	1 (14.3%)	3 (42.9%)	0.23

thyroidectomy because of the complexity of the dissection, and greater visualization needs.[12] Similarly, Ding et al. showed more operative times in endoscopic thyroidectomy than in conventional thyroidectomy which they put down to the accuracy needed in the identification of the anatomical structures.[13]

On the contrary, other investigations have shown reduced operating time using magnification-assisted thyroidectomy. Nagaty et al. discovered that surgical loupe would significantly cut down on the amount of time spent on the operation as nails and vessels became easy to detect.[14] Nevertheless, variations in surgeon experience, surgical technique, and case-selection could be the cause of the difference in studies.

The current research also established that the intraoperative blood loss was also very low in the microscopic thyroidectomy group (52.3 ± 18.6 mL) than in conventional thyroidectomy group (84.7 ± 25.1 mL). This finding is in line with the research carried out by Venkataramani et al., who stated that a considerable amount of blood loss was significantly reduced in patients who received loupe-assisted thyroidectomy.[15] Equally, Das et al. indicated that with improved visualization delivered by magnification, meticulous dissection and control ensues, hence minimizing intraoperative bleeding.[16]

Regarding nerve related complications, the current study demonstrated that transient RLN palsy was presented in 5.4% of the patients in the MT group and permanent RLN palsy was presented in the CT group only (2.7%). These data can be correlated with the results of Karpathiotakis et al., who had to note that better visualization during thyroid surgery leads to a substantial decrease in the risk of RLN injury.[17] Equally Haddadin et al. have found that the rates of RLN injury were highly dependent on the surgical procedure and surgeon experience.[18]

EBSLN palsy was found in 2.7% of patients in the MT and 10.8% in the CT group in the current study. This finding correlates with the research conducted by Al-Qahtani et al., who showed that magnification when performing thyroidectomy enhances the detection of the superior laryngeal nerve and minimizes the chances of damage.[19]

Hypocalcemia is still among the most common issues that follow thyroid surgery as a result of accidental damage or devascularization of the parathyroid glands. In the given research, transient hypocalcemia was observed in 8.1 behind of the patients in the MT group and 18.9% of the patients in the CT group and permanent hypocalcemia was only observed in the CT group (2.7%). Such results align with the report of Kim et al. who found lower incidence of postoperative hypocalcemia in cases of operations performed with better visualization methodology in case of thyroid surgery.[20] Surgical technique is also another determinant of postoperative hypocalcemia that was found in a meta-analysis conducted by Chen et al.[21]

The outcomes of the current research are also consistent with the data of Datta et al., who claimed that the microscopic

thyroidectomy was less related to the number of complications in comparison with the conventional thyroidectomy.[22] Likewise, systematic review by de Vries et al. also found that minimum invasive and magnifying-aided thyroid surgery methods are safe and effective options as compared to traditional thyroidectomy with equal or better complication rates.[23]

The relevance of the surgical expertise and visualization techniques has also been supported by large population-based studies. According to the report by Stopenski et al., the rate of complications was much lower in those surgeries that were carried out by special endocrine surgeons who also employed nerve monitoring and magnification methods much more frequently.[24]

Similarly, Alkaf et al. showed that risk of RLN being injured could be considerably minimized due to a careful approach and attention paid to the nerve identification during the surgical procedure.[25]

In general, the results of the current investigation indicate that microscopic thyroidectomy is beneficial in the form of minimized intraoperative blood loss and the decreased level of complications, but it might take a little bit longer to complete the surgery. Enhanced visualization during surgery is more effective in identifying and preserving vital structures like the RLN, EBSLN and parathyroid glands.

Limitations: To begin with, the sample size was smaller (n = 74). Nevertheless, since the study provided the valuable data on the comparison, a bigger sample size would have enhanced statistical power and augmented the overall generalizability of the results. The conclusions of the future studies on broader populations in numerous centers would be more significant. Second, the research was carried out in one tertiary care center and likely reduces the external validity of the findings. The result of surgical procedures can be different according to the institutional practices, the experience of the surgeon, and the resources. Thus, the results might not be entirely applicable to the results in other healthcare environments. Third, the follow-up time in this research was one month after the operation. Other complications especially the injury of nerves or hypocalcemia can recover or appear after this time. Better assessment of long-term outcomes like permanent RLN palsy and permanent hypocalcemia would be possible through a longer follow-up period.

CONCLUSION:

This study revealed that microscopic thyroidectomy was related to much less intraoperative blood loss in contrast to conventional thyroidectomy which can be explained by the fact that meticulous surgical dissection was performed under the impact of a magnifying glass and vascular structures could be more easily observed. Although, in microscopic thyroidectomy group the operative time was a little more probably because of the care and precision involved when carrying out the surgery when it was under magnification. Microscopic thyroidectomy had lower rates of transient RLN palsy, permanent RLN palsy, EBSLN palsy, transient hypocalcemia, and permanent hypocalcemia than conventional thyroidectomy with respect to postoperative complications. These differences did not have any statistical significance at all parameters but this trend was observed consistently in favour of microscopic thyroidectomy that offers greater preservation of the critical anatomical structures.

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Authors Contribution:
Laraib Abro: Conception and design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published
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Gulnaz Arshad: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published
Sarfraz Latif: Conception, acquisition of data, critical revision of the manuscript
Aqsa Yaqub: Acquisition of data, drafting and final approval of the manuscript
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Original Article **Open Access**

Evaluation of Robotic Simple Nephrectomy Outcomes Using the modified Clavien-Dindo Classification System

Sadia Laraib, Arif Ali, Ayesha Khan, Naresh Kumar Valecha, Abdul Mujeeb, Hassan Siddiqui

ABSTRACT

Objectives: To determine frequency and severity of post-op complications in patients undergoing robotic simple nephrectomy by using modified Clavien–Dindo classification.

Study Design and Setting: This longitudinal descriptive study conducted in the Department of Urological Surgery and Transplantation, Jinnah Postgraduate Medical Centre (JPMC), Karachi.

Methodology: This study was carried over a six-month (6) period. A total of 68 patients undergoing robot-assisted simple nephrectomy for benign, non-functioning kidneys were included through non-probability consecutive sampling. Sample size was calculated using OpenEpi, based on an expected postoperative complication rate of 16%, using 95% confidence and taking 5% margin of error, applying finite population correction. Postop complications occurring within 30 days or one month were graded according to the modified Clavien–Dindo classification. Data were analyzed using SPSS version 24.0. Associations were assessed using t-tests and chi-square tests, with a p-value less than <0.05 considered statistically significant.

Results: Among 68 patients, prolonged operative time was associated with increased intraoperative blood loss, higher overall complication rates, greater Clavien–Dindo grades, and the development of CKD (Chronic kidney disease) at follow-up. Higher body mass index was significantly related to prolonged hospital stay and delayed postoperative recovery. Surgical indication was also associated with increased bleeding and greater complication severity.

Conclusions: Prolonged operative time and higher body mass index were important predictors of postoperative morbidity following robot-assisted simple nephrectomy.

Keywords: Body Mass Index; Clavien–Dindo Classification; Nephrectomy; Postoperative Complications; Robotic Surgical Procedure

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INTRODUCTION

Robotic assisted nephrectomy has essentially changed and evolved how in urology surgeons approach nephrectomy, it offers minimally invasive alternative to more traditional open method. Compared to open surgery, robotic approach carries amazing clinically proven set of benefits which includes significantly reduced intraoperative blood loss, less post-operative pain, shorter hospital days, and faster than normal return to normal daily activities.[1?2] The use of robotic platforms in the operating theatre brings a lot of conveniences including 3D visualization, and effective tremor removal, each of which eventually contributes to improved operative precision and control.[3?4] These advantages eventually allow surgeons to navigate most complex anatomical dissections with confidence, with added benefits for positive peri-operative outcomes and patient overall safety.

Reported perioperative complication rates in robotic nephrectomy are 19.3% as compared to open 29.5% surgery, This reflecting a significantly lower risk is associated with the robotic approach (OR 0.53, p < 0.00001).5 In addition to these lower complication rates, robotic procedures have

positively shown to reduce average intraoperative blood loss by approximately 107 mL and effectively shorten the duration of hospital stay by nearly 2.8 days.5 These significant above mentioned findings highlight the potential of robotic surgery to decrease surgical morbidity while promoting enhanced post-op recovery.

Even though robotic nephrectomy have these advantages, It is not completely free from complications. Complications always occur with any surgical procedure, and robotic nephrectomy is no exception. Accurate and consistent complication reporting is therefore essential for evaluating surgical outcomes. We are using Clavien–Dindo classification which has become the most widely used grading system for postoperative complications.6?7 The classification categorizes complications based on the type of therapeutic intervention required, from Grade I (medical or minimal intervention or small deviations from the normal postop course not requiring significant intervention) to Grade V (death).8 By providing a structured and reproducible approach, the Clavien–Dindo system enhances transparency in surgical outcome reporting and will support evidence based evaluation of robotic nephrectomy side effects. Its use across different specialties of surgeries including urology, shows and speaks to its clinical value and broader applicability.??[1°] Multiple studies have shown to validate its reliability in both academic centers and community hospitals settings. A large multicenter study out of the United States looked at outcomes in over 886 patients who underwent robotic assisted nephrectomy. The overall complication came out to be 15.6%: intraoperative complications accounted for 2.6%, while postoperative 13%. Among the postoperative events, most of them, 77% fell under Clavien Grade I–II, meaning they were minor, remaining 23% were Grade III–IV and required either surgical, endoscopic, and/or radiological intervention. Notably, the series recorded no deaths.[11] These findings speak volume to the safety of robotic nephrectomy, but at the same time it highlights the importance of careful complication monitoring and consistent reporting.

That being said, published data specifically looking at Clavien–Dindo grading in robotic simple nephrectomy remains scarce. Most of the pre-existing literature has concentrated on robotic partial nephrectomy, radical nephrectomy, and/or nephroureterectomy, only few studies have directly addressed simple nephrectomy performed for benign, non-functioning kidneys secondary to PUJ or stone disease. Research from our department by systematically recording Clavien–Dindo Grades I–V in these patient populations would therefore contribute meaningful, institution-specific data to an otherwise sparse literature.

Such data will significantly help us identify risk factors, and benchmark our outcomes against international standards, and will help develop targeted preventive strategies. This research will help us get a better understanding of complications and their patterns and their severity would also strengthen preoperative counseling, perioperative planning, and will support more informed decision making between surgeon and patient.

METHODOLOGY:

This descriptive longitudinal study was conducted in Department of Urological Surgery and Transplantation (Ward 19), Jinnah Postgraduate Medical Centre, Karachi, over a six-month period. Before initiation of the study, we got IRB approval (No. F2.-81/2025-GENL/263/JPMC) from JPMC IRB and formally made sure all procedures conformed to the ethical principles laid down in the Declaration of Helsinki (2013 revision, which govern research involving human participants). Every patient was explained regarding the procedure and signed a written informed consent for study prior to enrollment. Each patient was explained the nature of the procedure, risks and benefits to expect, their right to withdraw at any point without any disruptions to their ongoing care, and informing them that their data that would be used will be annonymized. Enrollment ran from January 1, 2025 through June 1, 2025.

Sample size was calculated using online epidemiological tool OpenEpi, a widely used online epidemiological tool in clinical research settings. Our calculation drew on a reported postoperative complication rate of 16% from comparable tertiary care urology centres,[13?14] and we applied a 95% confidence level, a 5% margin of error, and finite population correction. Given that our institution handles roughly 100 eligible cases per year and we were collecting data over a 6-month window, this worked out to a final sample size of 68 patients.

We included patients aged 18 to 65 years male or female. All included patients had a non-functioning kidney attributable to benign causes: chronic pyelonephritis, pelviureteric junction obstruction, recurrent stone disease with significant parenchymal damage, or congenital renal dysplasia, and all were scheduled to undergo robotic simple nephrectomy.[13?14] Complete medical records with operative notes, postoperative documentation, and at least 30 days follow-up were required for inclusion. Patients were excluded if they had another surgical procedure done in the same sitting, such as contralateral renal or other abdominal surgery, as this could independently affect complication rates. Those with prior open renal surgery or transplantation were also excluded because of adhesions and altered anatomy. Patients with serious comorbidities: uncontrolled diabetes, significant cardiac disease, severe COPD, coagulopathy, or immunosuppression, were left out as these conditions affect healing and surgical risk.[15] Patients with missing records or lost to follow-up within 30 days were excluded from analysis. Data was collected prospectively using a pre-designed questionnaire made for this study, following the Declaration of Helsinki. Complications within 30 days were graded using the modified Clavien–Dindo classification.

Recorded variables included patient demographics like age, gender, BMI and past medical history; BMI was categorised according to World Health Organization (WHO) criteria: underweight (<18.5 kg/m²), normal weight (18.5–2/4.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (=30.0 kg/m²); operative details such as operative time, blood loss, conversion to open surgery and intraoperative events; and postoperative outcomes including hospital stay, time to return to daily activities, renal function at follow-up, and all complications with their Clavien–Dindo grades. Data was analysed on SPSS version 24.0. Descriptive statistics were used to summarise patient characteristics and outcomes. Continuous variables were given as mean ± SD or median with interquartile range depending on distribution. Categorical variables were reported as frequencies and percentages. Independent sample t-test was used for continuous variables and chi-square or Fisher's exact test for categorical ones, depending on expected cell counts. A p-value of less than 0.05 was considered significant, reflecting roughly a 5% chance of type I error. All tests were two-tailed. Complications were assessed at follow-up within one month of surgery and graded using the modified Clavien-Dindo system. (Table 1)

All patients had transperitoneal robot-assisted simple nephrectomy using the Da Vinci system. After general anaesthesia with endotracheal intubation, patients were placed in full lateral decubitus with the operative side up. Pressure points were padded and the table was flexed to open up the space between the costal margin and iliac crest. The pneumoperitoneum was created using a Veress needle at Palmer's point or an optical trocar (Visiport), maintaining intra-abdominal pressure somewhere between 12 and 15 mmHg throughout. Each case ran on a four-port setup. We placed the camera port lateral to the umbilicus and arranged three robotic working ports in an arc toward the upper quadrant; giving us the triangulation we needed. When the situation called for it, we dropped in an assistant port to handle suction, retraction, or clipping.

Once the robot was docked, white line of Toldt was divided and the colon was swept medially. the iliac vessels followed it upward, and carefully skeletonized it all the way to the hilum; we kept its blood supply intact right until point of division. From there, dissected the hilar vessels methodically. the renal artery and vein were ligated separately; for smaller vessels we used Hem-o-lok clips, and for larger ones we brought in vascular staplers the choice was made on case to case basis, ultimately came down to vessel size and what the operating surgeon was comfortable. Segmental or early branching vessels were handled the same way. The kidney was then freed all around by dividing lateral peritoneal attachments and working through the perirenal fat, keeping the adrenal gland in place unless there was a reason to remove it.Once the kidney was fully freed, the ureter was clipped and cut near the pelvic brim. The specimen was put in a retrieval bag and taken out through an extended assistant port incision or a Pfannenstiel incision. Haemostasis was checked after dropping the pneumoperitoneum pressure and going over the whole field. A drain was left in selectively, mainly in cases with heavy retroperitoneal dissection or any worry about lymphatic leak. Ports were taken out under vision to check for any bleeding. Fascia was closed at all sites 10 mm or larger to prevent herniation, and skin was closed with subcuticular absorbable sutures.[22]

RESULTS:

68 robotic nephrectomy cases were included in the analysis. To determine the complications in patients undergoing robot-assisted simple nephrectomy using the modified Clavien–Dindo classification. The Baseline patient and procedural characteristics were assessed using age, sex, BMI category, and indication for surgery. (Table 2) Bivariate analysis using the Pearson chi-square test and independent samples t-test revealed many statistically significant associations ($p < 0.05$). On independent samples t-test, mean operative time was significantly longer in patients who developed postoperative complications compared to those who did not (178.4 ± 28.6 min vs 138.2 ± 32.1 min; $t = 5.14$, $df = 66$, $p < 0.001$). Similarly, mean age was higher in the complication group, though this did not reach statistical significance (57.3 ± 11.8 years vs 53.9 ± 12.5 years; $t = 1.08$, $df = 66$, $p = 0.284$).

Longer operative time was strongly associated with increased intraop blood loss (÷², $p = 0.000$), higher overall postoperative complication rates (÷², $p = 0.017$), and greater complication grades as per the Clavien–Dindo classification (ordinal ÷², $p < 0.05$). On independent samples t-test, mean estimated blood loss was significantly higher among patients with operative time =180 minutes compared to those with shorter procedures (312.5 ± 84.3 mL vs 198.7 ± 61.2 mL; $t = 5.92$, $df = 66$, $p < 0.001$). Mean operative time was also significantly longer in patients who developed any postoperative complication compared to those without complications (178.4 ± 28.6 min vs 138.2 ± 32.1 min; $t = 5.14$, $df = 66$, $p < 0.001$). In addition, operative time was associated with the presence of chronic kidney disease at the last follow-up (÷², $p = 0.038$).

Higher BMI categories was significantly linked to prolonged hospital stay (÷², $p = 0.001$) and delayed return to normal activities (÷², $p = 0.001$). On independent samples t-test, obese patients had a significantly longer mean hospital stay compared to non-obese patients (5.8 ± 1.9 days vs 3.6 ± 1.2 days; $t = 5.63$, $df = 66$, $p < 0.001$). Mean time to return to daily activities was also significantly prolonged in the obese group (18.4 ± 4.7 days vs 12.1 ± 3.3 days; $t = 6.41$, $df = 66$, $p < 0.001$).

Surgical indication, as PUJ obstruction or stone disease, was associated with higher blood loss (÷², $p = 0.025$) and with more severe complication grades (÷², $p = 0.001$)

Age category was also significantly related to intraoperative

Table 1: Modified Clavien–Dindo Classification

Grade	Definition
Grade I	Minor deviation from normal postoperative course without need for pharmacological or procedural intervention
Grade II	Complications requiring pharmacological treatment, blood transfusion, or nutritional support
Grade IIIa	Complications requiring intervention without general anaesthesia
Grade IIIb	Complications requiring intervention under general anaesthesia
Grade IVa	Life-threatening complication involving single organ dysfunction requiring ICU care
Grade IVb	Multi-organ dysfunction requiring ICU care
Grade V	Death related to surgical complication

Table 2: Baseline Characteristics

Variable	**n (%)**
Age (Mean ± SD)	54.8 ± 12.3
<50 years	26 (38.2)
=50 years	42 (61.8)
Male	41 (60.3)
Female	27 (39.7)
Normal/Underweight	18 (26.5)
Overweight	31 (45.6)
Obese	19 (27.9)
PUJ obstruction/Stone	24 (35.3)
Operative time mean ± SD	145 ± 35

Table 3: Complications Based on Clavien-Dindo Classification (n = 68)

Clavien-Dindo Grade	**Number of Patients n (%)**	**Specific Complications**
Grade I	**4 (5.9%)**	
	2 (2.9%)	Ileus
	2 (2.9%)	Serous discharge in drain
Grade II	**11 (16.2%)**	
	6 (8.8%)	Fever
	3 (4.4%)	Wound Infection
	2 (2.9%)	Intra-op Hemorrhage
Grade IIIa	**3 (4.4%)**	
	2 (2.9%)	Port-site Abscess
	1 (1.5%)	Port-site Seroma
Grade IIIb	**1 (1.5%)**	
	1 (1.5%)	Bowel injury
Grade IVa	**0 (0%)**	
Grade IVb	**0 (0%)**	
Grade V	**0 (0%)**	
Total complications	**19 (27.9%)**	

Table 4 Comparison of Clavien-Dindo Complication Grades with Age Group, BMI Category, and Operative Time

Variable	**No Complications n=49**	**Complications n=19**
Age <50	20	6
Age =50	29	13
Male	30	11
Female	19	8
Normal BMI	16	2
Overweight	25	6
Obese	8	11
PUJ obstruction	18	6
Stone disease	31	13
Operative time <180 min	43	12
Operative time =180 min	6	7

blood loss (÷², $p < 0.05$). On independent samples t-test, patients aged ?50 years had a significantly higher mean estimated blood loss compared to younger patients (248.3 ± 74.1 mL vs 186.5 ± 58.9 mL; $t = 3.47$, $df = 66$, $p = 0.001$). As this was unadjusted bivariate analysis, older age should be regarded as associated with, rather than an independent predictor of, intraoperative bleeding in this cohort.

DISCUSSION

Our findings demonstrate a clinically important and statistically significant association between prolonged operative time particularly procedures lasting =180 minutes and adverse perioperative outcomes in patients undergoing robotic simple nephrectomy. Patients with longer operative times showed significantly higher postoperative complication rates ($p = 0.049$), greater intraoperative blood loss ($p = 0.000$), higher Clavien–Dindo grades, and greater CKD incidence at follow-up ($p = 0.038$). On independent samples t-test, mean operative time was significantly longer in patients who developed postoperative complications compared to those who remained complication-free (178.4 ± 28.6 vs 138.2 ± 32.1 min; $t = 5.14$, $df = 66$, $p < 0.001$), and mean estimated blood loss was significantly greater in cases lasting =180 minutes (312.5 ± 84.3 vs 198.7 ± 61.2 mL; $t = 5.92$, $df = 66$, $p < 0.001$). These associations are consistent with published robotic nephrectomy literature, where operative duration consistently emerges as an important correlate of perioperative morbidity across diverse institutional settings.[15] Prolonged operative time likely reflects underlying surgical complexity rather than mere inefficiency — many such cases involve dense adhesions, chronic inflammatory scarring, distorted tissue planes, and vascular anatomical variations such as accessory or aberrant vessels, all of which increase operative difficulty and prolong dissection. Prolonged anaesthesia and extended pneumoperitoneum exposure may further contribute to physiological stress through cardiovascular strain, reduced pulmonary compliance, and systemic inflammatory changes, thereby increasing postoperative morbidity. Importantly, prolonged operative time should not automatically be interpreted as a marker of poor surgical technique; in many complex cases it reflects deliberate, meticulous dissection in technically demanding anatomy. Distinguishing careful surgical precision from inexperience is particularly relevant when comparing outcomes across low- and high-volume centres. Although robotic surgery may require somewhat longer operative times than conventional laparoscopy owing to docking, instrument exchanges, and setup, it continues to offer advantages in visualisation, precision, and reduced tissue trauma that overall support its perioperative safety profile.

Additionally prolonged anaesthesia together with extended pneumoperitoneum exposure may also additionally contribute towards physiological stress responses through cardiovascular effects respiratory compromise reduced pulmonary compliance and systemic inflammatory changes thereby increasing postoperative morbidity delayed recovery and poorer overall postoperative outcomes in some patients. These findings broadly aligns with already existing robotic nephrectomy literature where prolonged operative duration repeatedly and consistently emerges as an important predictor of adverse perioperative outcomes across multiple different patient populations institutions healthcare systems and surgical settings worldwide. Although robotic surgery may naturally require somewhat longer operating times when compared with conventional laparoscopic surgery mainly because of robotic docking instrument exchanges setup time and learning curve related factors robotic approaches still continue to provide several advantages including reduced blood loss improved precision enhanced three dimensional visualization and comparatively much less tissue trauma when compared with open surgery and traditional operative approaches.[15] Therefore prolonged operative time should not always and necessarily be interpreted as inefficiency or lack of surgical skill because in many difficult and complicated cases it may instead represent careful slow meticulous deliberate and cautious surgical dissection in technically demanding anatomically difficult and complex patients. Distinguishing deliberate careful surgical precision from surgeon inexperience therefore becomes particularly important when comparing outcomes between low volume and high volume centres hospitals and institutions.

BMI emerged as another significant correlate of postoperative morbidity. Obese patients demonstrated higher complication rates compared to those with normal BMI ($p = 0.002$). Higher BMI categories were also significantly associated with prolonged hospital stay ($p = 0.001$) and delayed return to normal activities ($p = 0.001$). On independent samples t-test, these differences were quantitatively pronounced: obese patients had a significantly longer mean hospital stay compared to non-obese patients (5.8 ± 1.9 vs 3.6 ± 1.2 days; $t = 5.63$, $df = 66$, $p < 0.001$), and their mean time to return to daily activities was similarly prolonged (18.4 ± 4.7 vs 12.1 ± 3.3 days; $t = 6.41$, $df = 66$, $p < 0.001$). From a technical standpoint, surgery in obese patients is considerably more demanding because of thicker abdominal walls, increased difficulty with trocar placement, a restricted operative field, and more challenging tissue dissection and visualisation. These technical difficulties frequently prolong operative duration and contribute to increased perioperative burden. Beyond operative factors, obesity is associated with impaired wound healing, reduced baseline mobility, metabolic syndrome, sleep apnoea, and altered pharmacokinetics of anaesthetic medications — all of which may collectively delay postoperative recovery and increase morbidity. These findings are broadly consistent with existing literature: while most studies report no significant increase in mortality among obese patients undergoing robotic nephrectomy, prolonged operative duration, modestly increased blood loss, and longer hospital stay are consistently observed,

particularly at BMI >35 kg/m².¹6?¹7 Patients with morbid obesity often require greater perioperative resources and experience slower recovery, although long-term functional outcomes remain generally comparable when surgery is completed successfully. Robotic assistance may partially offset technical challenges through superior visualisation and instrument dexterity, but does not eliminate the physiological limitations of obesity. These findings reinforce the importance of preoperative optimisation strategies — including weight reduction, nutritional assessment, metabolic workup, and enhanced recovery protocols — specifically for obese patients undergoing robotic nephrectomy. It should be noted that all associations in this study are unadjusted bivariate findings and should not be interpreted as evidence of independent predictive relationships without multivariable confirmation.

The association between prolonged operative time and CKD at follow-up ($p = 0.038$) is a finding that deserves further investigation in larger studies. Longer procedures may involve prolonged hilar manipulation, sustained renal traction, extended pneumoperitoneum exposure, and transient reductions in renal perfusion — all of which may negatively influence postoperative renal function and long-term kidney outcomes. However, renal outcomes after unilateral nephrectomy are multifactorial and influenced by numerous variables including baseline renal reserve, diabetes, hypertension, preoperative eGFR, fluid balance, nephrotoxic medication exposure, and duration of follow-up. This association should therefore be interpreted cautiously until validated using larger multivariable analyses that adequately control for these confounding factors.

Interestingly, age and gender did not show statistically significant associations with postoperative complication occurrence in our cohort ($p = 0.671$ and $p = 1.000$ respectively). Similarly, the indication for surgery whether PUJ obstruction or stone disease did not significantly influence overall complication rates ($p = 0.814$), although it remained associated with increased blood loss and greater complication severity in subgroup analysis. Most complications observed were minor Clavien–Dindo Grade I and II events, while major complications remained relatively uncommon, and no Grade IV or Grade V complications occurred in our study population. These findings support the acceptable safety profile of robotic simple nephrectomy in carefully selected and appropriately managed patients, and are consistent with the broader literature showing that robotic renal surgery carries a low rate of serious complications in experienced hands.

Across studies published between 2020 and 2025, our findings broadly mirror reports from high-volume international centres demonstrating that operative complexity and patient-related factors such as obesity remain central determinants of perioperative outcomes following robotic nephrectomy.¹8?¹? The consistency of these associations across different healthcare systems, institutional settings, and tertiary care hospitals strengthens confidence that these relationships are clinically meaningful rather than reflecting statistical chance alone. Nonetheless, all findings in this study are based on unadjusted bivariate analysis, and multivariable confirmation is required before any variable can be designated an independent predictor of outcomes.

Limitations of the study: First and foremost one of the the biggest limitation of this study is that the analysis we ran was unadjusted and exploratory. We did no multivariable modelling, which means it can not account for confounders that may have shaped our results. Several variables were not formally controlled: preoperative kidney function such as baseline eGFR and creatinine, warm ischaemia time during dissection, and surgeon experience and its known effects on speed and complication rates. Smoking history of patients, glycaemic control in diabetic patients, and use of anticoagulation use also did not get systematically captured. Without a properly adjusted model, we cannot say with any real confidence which variables are true independent predictors and which ones are just are associated along because they may happen to correlate with something else we never controlled or measured. This was a single centre study with only 68 patients. Single centre work carries known selection bias in how our patients get chosen, how the surgeons operate, and how the complications get spotted and recorded, none of which necessarily reflects what happens elsewhere. Small numbers also hurt and effects our ability to detect effect sizes, and subgroup become unreliable, particularly for severe and uncommon complications where event counts are very low.The study had no comparison arm. No laparoscopic group, no open nephrectomy group to hold our robotic assisted nephrectomy results up against. The robotic only design only let us look closely at these complications specific to this technique, but robotic vs laparoscopic vs open like head to head data comparing approaches will be far more useful for guiding and surgical planning. We recommend that future studies tackle these shortcomings. Multivariable logistic regression or similar adjusted modelling would help locate out independent risk factors. Multicentre designs with larger sample sizes will eventually improve both generalisability and statistical reliability. Prospective randomised comparisons between surgical approaches (Open vs lap vs robotic), where feasible, would strengthen the evidence further. Follow up should be extended well past 30 days to find late complications and and to test how long lasting functional outcomes actually are. Future researches built along these lines would put findings much firmer ground and give urological robotic surgeons something more pronounced and reliable.

CONCLUSION:

In conclusion, our study showed that robotic simple nephrectomy is generally a safe and effective procedure for management of benign non-functioning kidneys, with most

complications being minor according to the modified Clavien–Dindo classification. Major complications were relatively uncommon and no mortality was observed in our study population, which overall supports the acceptable safety profile of robotic surgery in experienced hands and tertiary care settings.[20] Our findings demonstrated that prolonged operative time and higher BMI were significantly associated with increased postoperative morbidity and delayed recovery. Patients with surgeries lasting =180 minutes had higher complication rates, greater blood loss, and more difficult postoperative course. Similarly, obese patients experienced more postoperative complications, prolonged hospital stay, and slower return to normal daily activities. These findings probably reflects the increased technical difficulty and physiological stress associated with prolonged surgery and obesity. Interestingly, age, gender, and surgical indication itself did not show significant association with overall complication occurrence in our cohort. Most of the complications observed were low grade and manageable conservatively, while severe complications remained fortunately rare. Overall, our results generally aligns with current international literature suggesting that operative complexity and patient related factors are important determinants of outcomes after robotic nephrectomy. Even though our study was limited by relatively small sample size and single centre design, it still provides useful local data regarding complication patterns following robotic simple nephrectomy.

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Authors Contribution:
Sadia Laraib: Data Collection, Analysis and Interpretation, Manuscript Drafting, Conceived Original Idea
Arif Ali: Critical Revision of the Manuscript, Data Interpretation and Manuscript Drafting.
Ayesha Khan: Critical Revision of the Manuscript, Data Collection and Input on Study Design
Naresh Kumar Valecha: Critical Revision of the Manuscript, Data Collection and Input on Study Design
Abdul Mujeeb: Supervision of Study, Input on Study Design, Critical Revision of Manuscript
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Original Article **Open Access**

Comparison of Post-Operative Pain and Complications between Onlay and Sublay Mesh Repair of Incisional Hernia in Tertiary Care Hospital in Pakistan

Beenish Khan, Rabel Qureshi, Priya Bai, Mazhar Iqbal

Abstract

Objective: To assess and compare postoperative pain and complications between onlay and sublay mesh repair for incisional hernias.

Study Design and Setting: It is a Prospective Observational Study conducted at Department of Surgery, JPMC Karachi. Duration of study spanned from January to June 2025.

Methodology: 50 patients with incisional hernias either underwent onlay (Group A) or sublay (Group B) repair. Age, symptom duration, procedure duration, weight, height, and BMI were characterized using mean ± SD. Gender, ASA grade, and post-operative complication (hematoma, seroma and wound infection) were presented as frequencies and percentages. Pain was gauged using Visual analog score (VAS) at 2nd hour post-op, 24th hour, and discharge. A Chi-square test was utilized, with $p = 0.05$. A paired t-test was used to compare pre and postoperative pain score between group A and B, with $p = 0.05$.

Results: In Onlay group, incidence of wound infections were 8%, hematoma was 12%, and seroma was 16%. In sublay group, incidence of wound infections were 4%, hematoma was 8%, and seroma was 4%. In Group A, VAS was 8.2 in 2nd hour, 3.9 in 24th hour, and 1.9 at discharge. In Group B, VAS was 6.4 in 2nd hour, 3.2 in 24th hour, and 0.8 at discharge. The results were statistically significant.

Conclusion: Group B demonstrated better postoperative outcomes and lower VAS scores. Incidences of wound infection, hematoma, and seroma were lower in group B. This research contributes to valuable evidence favoring the sublay approach as more effective surgical strategy.

Keywords: Hematoma, Pain, Postoperative Complications, Surgical Mesh, Seroma, Wound Infection

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INTRODUCTION:

A frequent outcome following abdominal surgery, like laparotomies, is incisional hernia (IH), with documented occurrence rates varying between 2% and 20% depending on the patient population, risk factors and the duration of follow-up.[1] The development of an incisional hernia is usually multifactorial, resulting from a combination of patient-related and surgical factors that interfere with proper wound healing. Several important factors have been identified that weaken fascial repair after abdominal surgery. These include lifestyle-related risks such as smoking, along with medical conditions like diabetes mellitus. Smoking and diabetes impair small blood vessel circulation and reduce collagen formation, both of which are necessary for strong wound healing. In addition, conditions that raise intra-abdominal pressure for example chronic coughing in Chronic Obstructive Pulmonary Disease (COPD) or obesity place repeated strain on the healing surgical site, increasing the likelihood of hernia development.[2] Incisional hernias are treated mainly with surgery because these defects do not heal on their own. The available treatment options broadly include traditional open repair and minimally invasive techniques such as laparoscopic or robotic surgery. Regardless of the method used, current practice almost always involves placement of a synthetic mesh to repair and strengthen the weakened area of the abdominal wall. This mesh acts as a supportive framework that encourages fibrous tissue growth into it, allowing it to integrate with the patient's own tissues and thereby lowering the chances

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of the hernia coming back.[3] The success and safety of hernia repair largely depend on the specific anatomical plane where the mesh is implanted. In the sublay approach, the mesh is positioned in the retro-muscular space, situated posterior to the rectus abdominis muscle and anterior to the posterior rectus sheath, which benefits from a well-vascularized environment that promotes integration and reduces complications. Meanwhile, the onlay method entails positioning the mesh on top of the anterior fascia, beneath the subcutaneous tissue but superficial to the muscle layers, providing an accessible placement but with a higher potential for seroma or infection due to its more superficial location.[4]

Many researches indicate that utilizing the sublay technique can result in decreased occurrences of many surgical site complications.[5] Onlay repair, which entails positioning the mesh on the anterior fascia, usually involves dissecting flaps and closing the fascia beneath the mesh.[6] Sublay repair, alternatively termed retro muscular repair or simply Rives-Stoppa, involves placing mesh in retro-rectus or preperitoneal position.[7] Both of these onlay and sublay techniques are effective for repairing ventral and incisional hernias but come with certain adverse effects.[8] The assessment of postoperative discomfort and patient satisfaction is crucial in evaluating the safety and effectiveness of hernia repair treatments.[9] Schrittwieser et al in 2019 reported that onlay repair can safely address small and laterally placed incisional hernias.[10] However, Hasan et al. noted that more percentage of patients in the onlay group experienced seroma formation and wound infection.[11] There are few studies suggesting that patients undergoing sublay mesh repair experience less postoperative pain compared to those undergoing onlay repair.[12] In onlay repair, the mesh is anchored with sutures within the subcutaneous tissue, a region that is more sensitive and prone to irritation, which can contribute to increased postoperative discomfort and complications. In contrast, sublay mesh placement benefits from a more stable positioning, reducing the need for extensive suture fixation in delicate tissues. Research by Shah et al. has shown that sublay repair is associated with lower incidences of chronic postoperative pain, surgical site infections, and hernia recurrence. Nevertheless, the authors emphasized that it would be premature to declare one technique superior over the other without further rigorous, high-quality studies to substantiate these findings.[13]

Although considerable research has been conducted, there is still disagreement about which surgical approach is best for certain patient groups. This study focuses on comparing different techniques, especially onlay versus sublay repair, with respect to postoperative complications and pain levels. Since the primary aim of hernia repair extends beyond merely restoring anatomy to enhancing the patient's overall quality of life, appreciating these differences is crucial. Identifying the most effective surgical method is key to optimizing patient outcomes, ensuring their well-being and satisfaction, and providing more accurate guidance when counseling patients about surgical risks and anticipated recovery.

METHODOLOGY:

With the approval of ethics review committee (NO.F.2-81/2024-GENL/165/JPMC), this prospective observational study was conducted at the Department of Surgery, Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan. Duration of study spanned from 1st January 2025 to 30th June 2025.We included total of 50 patients, which were divided into 2 groups. Half of them underwent onlay mesh repair (Group A) and other half underwent sublay mesh repair (Group B). Inclusion criteria encompassed individuals aged 13 to 50 years of either gender, falling within ASA grade I and II, while exclusion criteria comprised those individuals with uncontrolled diabetes or hypertension, BMI exceeding 40 kg/m2, confirmed pregnancy via ultrasound, a history of intra-abdominal malignancies, or individuals who lost to follow-up. Informed consent was obtained from all patients. Patients who were diabetic (in both groups) were given medicines and were optimized preoperatively with glycated haemoglobin (HbA1c) level below 8% prior to elective repair, due to the known established association between poorly controlled diabetes and then impaired wound healing. Patients that are symptomatic or radiologically confirmed hernia defects greater than 3 cm in diameter were included, because smaller defects can be managed conservatively or where clinically appropriate and has less risk of strangulation.

Before surgery, patients underwent thorough assessments and were randomly assigned to 2 groups using a non-probability consecutive technique sampling method. We calculated the sample size using open Epi online calculator by the formula (n = [Np(1-p)]/ [($d^2/Z^2_{1-á/2}$(N-1) + p(1-p)])[2] by taking margin of error 2% and 95% confidence level. A skilled surgeon with loads of experience, proficient in sub-lay and on-lay mesh hernia repair techniques with more than 5 years of experience, performed the surgeries under G.A. Perioperative antibiotic prophylaxis with lV cefazolin was administered to all patients within 60 minutes of skin incision, in accordance with established surgical site infection (SSI) prevention guidelines. Group A (Onlay) had polypropylene mesh attached to the anterior rectus sheath using 3-0 or 2-0 polypropylene sutures, while Group B underwent a (sub-lay) approach, placing a permanent polypropylene mesh in a pre-peritoneal plane and securing it with sutures. Above the mesh redivac drains were positioned for all patients and removed once drainage decreased below 20 cc or ml/ day. Post-surgery, prophylactic antibiotics and oral analgesics were administered to all patients. Patients were being followed for 30 days or a month postoperatively. Follow-up assessments were scheduled at one week (7 days) and one month (30 days) post-discharge to evaluate for wound status, drain output where applicable, and early recurrence. Patients

were advised to return immediately if signs of wound complications developed prior to their scheduled reviews.

Data was collected using a specially crafted form and analyzed using IBM SPSS V22 statistical software. The analysis sought to compare the proportions between Group A (onlay) and Group B (sublay). Numerical factors like age, symptom duration, procedure duration, weight, height, and BMI were characterized using mean ± SD. Categorical factors such as gender, ASA grade, and post-operative complications (wound infection, hematoma, and seroma) were presented as frequencies and percentages. A Chi-square test was utilized for categorical variables, with significant threshold established at $p = 0.05$. Extended baseline chi-square analyses assessed hernia risk factors (diabetes mellitus, obesity, smoking, COPD), personal and surgical history (prior abdominal surgery, prior hernia repair, hypertension), socioeconomic status (low, middle, high income), and hernia presentation characteristics (symptomatic pain, reducibility, incidental detection). Pain was gauged using the Visual Analog Scale (VAS) at pre-operative baseline, at the 2nd hour post-op, 24th hour, and at the time of discharge from hospital, enabling direct pre-operative to post-operative pain trajectory comparison. A paired T-test was applied to compare pre and post-operative pain with p-value <0.05.

RESULTS:

The age range was 13 to 50 years. Group A (Onlay) had an average age of 34.720 ± 5.82 years, while Group B (Sublay) had an average age of 38.210 ± 7.30 years. Females constituted 56% in the Group A and 60% in the Group B. Diabetic patients made up 36% and 40% of the respective groups. Regarding ASA grading, 60% in the Group A were classified as ASA I, whereas 56% in the Group B fell into the same category. ASA II constituted 40% in the Group A and 44% in the Group B. These two groups were well-matched across all baseline parameters, with no statistically significant differences in age, sex, BMI, ASA classification, symptom duration, and prior abdominal surgical history confirming adequate comparability for outcome analysis. Chi-square test was applied. Baseline characteristic of patients are presented in Table 1. Complications such as Wound infection, seroma, and hematoma that occurred in the sublay and onlay mesh repair groups are represented in Table 2.

For the age bracket 13-30 years, neither the onlay group nor the sublay group exhibited any instances of wound infections, yielding a p-value of 1. In the 31-50 age range, 2/19 patients (11%) in onlay group and 1/20 patients (5%) in sublay group experienced wound infections, resulting in a p-value of 0.055. In the male population, both onlay and sublay groups recorded no cases of wound infections, with a p-value of 1. For females, 2/14 patients (14%) in the onlay group and 1/15 patients (6%) in the sublay group encountered wound infections, resulting in a p-value of 0.877. Among individuals with a BMI less than or equal to 25 kg/m^2, neither the onlay nor sublay group had any cases of wound infections, yielding a p-value of 1. However, for those with a BMI greater than 25 kg/m^2, 2/18 patients (11%) in onlay group and 1/18 patients (5%) in sublay group experienced wound infections, resulting in a p-value of 0.42.

In terms of hematoma, for the 13-30 age group, there was a hematoma in 1/6 patients (16%) in the onlay group and 1/5 patients (20%) in the sublay group. In the 31-50 age group, 2/19 patients (10%) in the onlay group experienced a hematoma, while none did in the sublay group, resulting in a p-value of 0.62. Among males, 1/11 patients (9%) in the onlay group had a hematoma, with none in the sublay group. For females, 1/14 patients (7%) in the onlay group and 1/15 patients (6%) in the sublay group encountered a hematoma, yielding a p-value of 0.84. Among individuals with a BMI less than or equal to 25 kg/m^2, none in the onlay group and 1/7 patients (14.3%) in the sublay group had a hematoma, with a p-value of 0.68. For those with a BMI greater than 25 kg/m^2, 3/17 patients (17%) in the onlay group and 1/18 patients (5%) in the sublay group experienced a hematoma, resulting in a p-value of 0.42.

Concerning seroma, in the 13-30 age group, 2/6 patients (33%) in the onlay group had a seroma, while none did in the sublay group, with a p-value of 0.45. In the 31-50 age group, 2/19 patients (10%) in the onlay group and 1/20 patients (5%) in the sublay group encountered a the seroma, yielding a p-value of 0.65. Among males, 2/9 patients (14.3%) in the onlay group and 1/7 patients (14.3%) in the sublay group had a seroma, resulting in a p-value of 0.21. For females, 2/16 patients (12.5%) in the onlay group had a seroma, while none did in the sublay group, with a p-value of 0.061. Among individuals with a BMI less than or equal to 25 kg/m^2, 1/4 patients (25%) in the onlay group had a seroma, with none in the sublay group and a p-value of 0.432. For those with a BMI greater than 25 kg/m^2, 3/21 patients (14%) in the onlay group and 1/20 patients (5%) in the sublay group encountered a seroma, yielding a p-value of 0.573.

Postoperative pain assessments were conducted using the Visual Analog Scale (VAS) at the 2nd, 24th hours and at discharge after surgery. Results are represented in Table 3.

The sublay group had a statistically significant reduction in early postoperative pain at 2 hours and 24 hours. Even though the difference in VAS scores at the time of discharge did not reach statistical significance ($p = 0.067$), the absolute difference will remain clinically meaningful, with sublay repair patients reporting a mean score of 0.8 compared to 1.4 in the onlay group. No patient in both group required re-intervention solely because of pain management; however, length of hospital stay exceeding three days was recorded in three patients in the onlay group versus one in the sublay group.

Table 1: Baseline Characteristics of Study Participants (n = 50)

Variable	Onlay Group (n = 25)	Sublay Group (n = 25)	p-value
Age (years), Mean ± SD	34.72 ± 5.82	38.21 ± 7.30	0.062
Age 13–30 years	6 (24%)	5 (20%)	0.74
Age 31–50 years	19 (76%)	20 (80%)	0.78
Male	11 (44%)	10 (40%)	0.78
Female	14 (56%)	15 (60%)	0.81
ASA I	15 (60%)	14 (56%)	0.78
ASA II	10 (40%)	11 (44%)	0.78
BMI (kg/m²), Mean ± SD	27.1 ± 2.9	26.4 ± 3.1	0.42
Duration of Surgery (min)	82 ± 11	88 ± 13	0.149
Symptom Duration (months)	11.2 ± 4.5	12.4 ± 5.1	0.34
Risk Factors			
Diabetes Mellitus	9 (36%)	10 (40%)	0.77
Obesity (BMI > 30)	6 (24%)	5 (20%)	0.73
Smoking	5 (20%)	4 (16%)	0.71
COPD / Chronic Cough	3 (12%)	2 (8%)	0.64
Surgical History			
Previous Abdominal Surgery	25 (100%)	25 (100%)	1.00
Prior Hernia Repair	4 (16%)	5 (20%)	0.72
Socioeconomic Status			
Low Income	14 (56%)	15 (60%)	0.79
Middle Income	8 (32%)	7 (28%)	0.74
High Income	3 (12%)	3 (12%)	1.00
Hernia Presentation			
Symptomatic (Pain / Discomfort)	22 (88%)	21 (84%)	0.69
Reducible Hernia	23 (92%)	22 (88%)	0.64
Incidentally Detected	3 (12%)	4 (16%)	0.69

Table: 2 Comparison of Post-Operative Complications

Complication	Onlay Group (n = 25)	Sublay Group (n = 25)	p-value
Wound Infection	2 (8%)	1 (4%)	0.047
Hematoma	3 (12%)	2 (8%)	0.034
Seroma	4 (16%)	1 (4%)	0.061
Overall Complication Rate	9 (36%)	4 (16%)	0.042

Table 3: Comparison of Post-Operative Pain (Vas Scores)

Time Point	Onlay Group (Mean ± SD)	Sublay Group (Mean ± SD)	p-value
2nd Hour VAS	8.2 ± 1.1	6.4 ± 1.0	0.028
24th Hour VAS	3.9 ± 0.9	3.2 ± 0.8	0.034
VAS at Discharge	1.4 ± 0.5	0.8 ± 0.4	0.067

Table 4: comparison of pre-operative vs. Post-operative pain scores

VAS Time Point	Onlay (Mean ± SD	Sublay (Mean ± SD)	p-value
Pre-operative VAS	5.6 ± 1.2	5.4 ± 1.1	0.52
VAS at 2nd Hour Post-op	8.2 ± 1.1	6.4 ± 1.0	0.028
VAS at 24th Hour Post-op	3.9 ± 0.9	3.2 ± 0.8	0.034
VAS at Discharge	1.4 ± 0.5	0.8 ± 0.4	0.067

Pre and post-operative pain score were compared between group A and Group B by applying paired T-test as presented in Table 4. Pre-operative VAS scores were comparable between both groups (Onlay: 5.6 ± 1.2 vs. Sublay: 5.4 ± 1.1; p = 0.52), confirming similar baseline pain levels. Both groups showed a statistically significant rise in VAS scores at the 2nd hour post-operatively, consistent with expected immediate post-surgical pain. The sublay group demonstrated a significantly lower peak pain score at 2 hours (6.4 vs. 8.2; p = 0.028), earlier pain trajectory decline at 24 hours (3.2 vs. 3.9; p = 0.034), and lower scores at discharge (0.8 vs. 1.4; p = 0.067). The pre-operative to discharge reduction in VAS was greater in the sublay group (-4.6 points) than the onlay group (-4.2 points), suggesting superior pain resolution with retromuscular placement.

DISCUSSION:

Complications from surgical treatments might be minor or major, early or late, but some may have an impact on the long-term result. Various surgical techniques are used for incisional hernia repair including open and laparoscopic/robotic incisional hernia repair but what varies between these approaches is the type of mesh being used and the plane in which the mesh is placed. Our study aimed for comparing pain and postoperative complications between the sublay versus onlay mesh repair techniques. Specific focus was placed on determining hematoma, seroma, wound infection, and postoperative pain levels. The onlay mesh repair is comparably easier to perform because the dissection is done down till the anterior abdominal fascia on which we secure the mesh. Since the mesh is placed more superficially, the risk of seroma formation increases and also the risk of surgical site infections. This can latter result in recurrence of incisional hernia. Potential dead space that develops after the dissection and creation of planes provides a space for seroma formation. Generally, this space is greater in the onlay hernia mesh repair, where the overlying layer is the subcutaneous fat and skin. In the sublay dissection, a space is developed between the rectus muscle and posterior rectus sheath, which is potentially a narrow space as compared to the onlay mesh repair. This provides superior strengthening, a decreased risk of seroma and eventually reduced infection rate because the mesh is placed in pre-peritoneal space. The retromuscular plane also allows wider mesh overlap beyond the hernia defect margins, a parameter recognised as a determinant of durable repair. This anatomical benefit assumes particular clinical relevance in patients with compromised tissue quality, such as those with diabetes mellitus or elevated BMI, where dependable mesh incorporation is essential for long-term outcomes. Our study also found that the rate of seroma formation was significantly higher in the onlay group as compared to the sublay group. Strong evidence is provided by the results that clear clinical advantages is offered by the sublay technique over the onlay repair. More clear evidence is provided by our research, with statistically meaningful reductions in complications after the sublay mesh repair. Wound infections occurred in 4% of the sublay patients compared to 8% in the onlay group which is a clinically important difference. This was also observed in a Systematic review by Köckerling who found that the onlay technique was linked to more postoperative complications, including wound complications and seroma, compared to the sublay mesh repair.[14]

An extensive systematic review was conducted by Holihan et al. examining how mesh location relates to clinical outcomes.[15] Significant impact on postoperative complications is determined by where the mesh sits anatomically, with clear benefits being demonstrated by placement behind the muscle. This explains why a fourfold reduction in the seroma formation was seen, with 16% after the onlay repair versus 4% with the sublay repair in our study. Reddy et al. in 2021 noted a lower recurrence rate for the sublay mesh repair compared to the onlay mesh repair, with no statistically significant differences in hematoma, seroma, infection and flap necrosis between the two techniques.[16] There was absence of statistically significant difference in individual complications in that series, despite a clear recurrence advantage for sublay repair, likely reflects the limited sample size and shorter observation period rather than true equivalence in morbidity. There is evidence by the thousands of hernia repairs from the Herniamed Registry was analyzed by Köckerling et al., showed that retromuscular mesh repair also caused sublay repair resulted in fewer complications compared to onlay placement.[17] Our data mirrors findings from an European registry, which suggests sublay repair benefits extends across geographic differences and also cultural contexts. This reproducibility strengthens confidence in our findings and also validates the approach. A thorough meta-analysis comparing onlay and sublay techniques was performed by Suwa et al.[18] Significantly lower rates of infections and seroma formation with sublay repair was identified and revealed by them. Our findings align remarkably well with their pooled data which was comprehensive. The complication rates we documented was12% hematoma with the onlay versus 8% with the sublay technique, and 16% seroma versus 4% which falls within reported ranges what other studies has shown. Patients was followed for extended periods by Bosanquet et al., and lasting benefits of retromuscular mesh placement was found by their team.[19] Consistently lower pain score was showed by the the sublay group v/s the onlay group which was 6.4 versus 8.2 at two hours, 3.2 versus 3.9 at twenty-four hours, and 0.8 versus 1.4 at discharge time. Lower pain scores result in early return to daily activities. Data from the Americas Hernia Society Quality Collaborative was analyzed by Petro et al.[20] Multiple confounding factors was accounted for by them, yet mesh position remained a significant predictor of outcomes. Benefits of the sublay repair across different patient subgroups was observed in our cohort.

Whether divided by age, gender, or BMI, the sublay approach was consistently favored across all categories what we examined.

Several noteworthy patterns were revealed by our demographic analyses which deserves attention. The majority of both groups was made up by female patients: 56% of the onlay and 60% of the sublay repair and higher complication rates was experienced by them compared to the male patients. The higher number of females is consistent with the well established occurrence of women to incisional hernias mainly following gynaecological and obstetric laparotomies, including c-section, which constitute a substantial proportion of abdominal surgeries performed in Pakistan. Among patients with BMI exceeding 25 kg/m², particularly striking differences was observed between the groups, with wound infections of 11% for the onlay mesh repair compared to 5% for the sublay mesh repair which is significant. Practical importance is held by this observation given obesity prevalence in our population and worldwide. The increased complication burden in overweight patients those who underwent onlay repair is mainly attributed to the greater subcutaneous adipose compartment, which not only enlarges the dead space beneath the mesh but it also compromises the local vascular supply, also impairing leukocyte trafficking and predisposing it to wound breakdown. The age-related patterns that emerged from the data, with no wound infections observed in younger patients in either group, while clear differences were demonstrated by the older cohort aged 31-50 years, with infection rates of 11% versus 5% which is clinically meaningful. Pain outcomes deserves detailed consideration given their importance to recovery, hospital stay and patient satisfaction. Our findings are relatively closely paralleled by those that are reported by Sevinç et al., they observed lower pain scores with the sublay repair in their study.[21] nevertheless the reduced post op pain is arguably a reliable benefit as suggested by consistency across studies from different regions. Surgical anatomy provides a solid mechanistic foundation for this distinction: onlay repair requires extensive subcutaneous dissection in order to raise skin flaps over the anterior fascia, which disrupts superficial nerves and lymphatics across a wider tissue plane. Compared to the more anatomically contained dissection needed for retromuscular placement, the resulting nociceptive and inflammatory signal is stronger. Additionally, the onlay technique's mesh fixation with transfascial sutures may directly irritate the anterior fascia's sensory nerve endings, a phenomenon that has been linked to chronic pain in some series. This is probably caused by a number of factors, including the fact that onlay repair necessitates extensive dissection, which increases tissue trauma and inflammatory response and may ultimately lead to more complications and higher pain scores.

In conclusion, significant advantages over onlay repair is demonstrated by sublay mesh repair in multiple aspects. Multiple clinically relevant areas including reduced infections, lower seroma and hematoma rates, and decreased pain is observed. The findings align with international evidence from various countries, with external validation being provided by our Pakistani cohort. From a resource allocation standpoint, the reduction in postoperative complications with sublay repair carries practical implications for healthcare systems in lower-middle-income countries, where prolonged hospital stays and reoperation for wound complications impose a disproportionate burden on already constrained surgical infrastructure. Notwithstanding the limitations inherent to a single-centre observational design, the internal consistency of our findings across multiple subgroup analyses strengthens the robustness of our conclusions. Prospective randomised trials with extended follow up remain necessary to fully characterise long-term recurrence rates and patient-reported outcome measures for both techniques.

Limitation of the study: There are few limitations of the study. The study was conducted on a relatively small number of participants, which may limit the generalizability of the findings to the wider population. As the data were collected from a single tertiary care hospital, the results may not fully represent the practices or patient outcomes in other healthcare settings. The follow-up period was limited, restricting the ability to assess long-term outcomes and complications.

CONCLUSION:

The sublay group, demonstrated significantly better postoperative outcomes and lower VAS scores compared to the onlay group. Incidence of all complications like wound infection, seroma, and hematoma were also lower in the Sublay group. Preferential use of sublay mesh repair is strongly supported by the evidence base, and priority to teaching these techniques should be given by surgical education programs in underdeveloped nations. These benefits are especially important in settings with limited resources because postoperative complications result in longer hospital stays and higher expenses. It appears that the superiority of sublay repair is not limited to a particular patient phenotype but rather represents a generalizable surgical principle, as evidenced by the consistent benefit of retromuscular placement observed across multiple subgroup analyses, including by sex, age, and BMI. To establish conclusive recurrence data and quality-of-life outcomes for both repair strategies, future multicenter randomized controlled trials with long-term follow-up are advised.

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Authors Contribution:
Beenish Khan: Data collection, Analysis and interpretation, Manuscript Drafting, Conceived original idea
Rabel Qureshi: Critical revision of the manuscript, data interpretation and manuscript drafting.
Priya Bai: Critical revision of the manuscript, data collection and input on study design
Mazhar Iqbal: Supervision of study, Input on study design, critical revision of manuscript

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Original Article **Open Access**

Frequency of Hyponatremia in Patients with Liver Cirrhosis and Its Association with Hepatic Encephalopathy

Noor Ehsan, Mahnoor Iqbal, Hateem Ahmed, Wafa Qaisar, Imran Farooka, Mahmood Nasir Malik

Abstract:

Objective: This study aims to determine the frequency of hyponatremia and to investigate its association with hepatic encephalopathy among patients with liver cirrhosis.

Study design & Settings: Descriptive cross-sectional study conducted at the Department of Medicine, Gulab Devi Teaching Hospital, Lahore.

Methodology: A non-probability consecutive sampling technique was used to enroll 140 patients with liver cirrhosis. Patients with conditions that could affect electrolyte balance or mental status were excluded. Hyponatremia was defined as serum sodium <135 mEq/L and was further categorized into mild, moderate, and severe according to admission serum sodium levels. Hepatic encephalopathy was assessed clinically using the West Haven criteria.

Results: Out of 140 patients, 58 (41.4%) had hyponatremia, including 28 (20.0%) mild, 20 (14.3%) moderate, and 10 (7.1%) severe cases. Hepatic encephalopathy was present in 90 patients (64.3%). Hepatic encephalopathy was more frequent among patients with hyponatremia than among those with normal sodium levels (82.8% vs. 51.2%; p=0.001).

Conclusion: Hyponatremia is common in patients with liver cirrhosis and has a significant association with hepatic encephalopathy. Serum sodium monitoring may help identify patients who are at increased risk of neurological complications.

Keywords: Liver cirrhosis; hyponatremia; hepatic encephalopathy

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INTRODUCTION:

Hyponatremia is a common electrolyte disorder among patients with liver cirrhosis, especially in advanced stages. Such factors as ineffective renal functioning, excessive water retention, and activity of such systems as renin-angiotensin-aldosterone system (RAAS) and vasopressin are involved in the mechanism. Cirrhosis also causes splanchnic vasodilation thereby decreasing the volume of blood and triggering the processes that increase sodium retention in kidneys and water absorption. Cirrhosis-induced systemic inflammation and portal hypertension are also known to cause hyponatremia, especially in patients with ascites.[1,2] Recent evidence associates the severity of hyponatremia with the non-functioning of the liver, especially as portal hypertension or hepatorenal syndrome in patients with cirrhosis.[3]

In addition to being a biochemical abnormality, hyponatremia is a clinically important abnormality with major implications in cirrhosis. It is closely linked to such complications like hepatic encephalopathy (HE), ascites, renal impairment, and high mortality. Hepatic encephalopathy is also a prominent complication to the quality of life and prognosis of cirrhotic patients, as it is a neuropsychiatric syndrome due to liver dysfunction and defective ammonia metabolism. New data shows that hyponatremia is an important factor that contributes to the development and course of HE. The

decreased level of sodium destabilizes osmotic balance in brain cells especially the astrocytes, resulting in cellular edema and predisposition to ammonia-induced neurotoxicity. This synergistic effect further increases cerebral edema and adds to the deterioration of the neurological functioning.[4]

Clinical trials have indicated that there is a close relationship between hyponatremia and the development and extent of hepatic encephalopathy. Lower serum sodium levels in the patients increase their chances of getting HE and also they are likely to have higher grades of the condition. In addition, hyponatremia has been part of predictors of poor outcomes in cirrhosis including high rates of hospitalization, long hospitalization, and high mortality rates. This evidence supports the value of regular monitoring of serum sodium levels in cirrhotic patients to support comprehensive disease management.[3]

Hyponatremia in liver cirrhosis is also related closely to hepatic encephalopathy (HE). Low sodium concentrations may exacerbate HE symptoms by disturbing osmoregulation in brain cells. It has been shown that in cirrhotic patients, low sodium is an important predictor of adverse outcome that may predispose them to developing hepatic encephalopathy which is associated with a poor prognosis.[4,5] Clinical evidence has suggested that hyponatremia is predictive of hepatic encephalopathy development and progression.[6]

Other than serving as a pointer to the extent of disease severity, hyponatremia in cirrhosis also influences the treatment of hepatic encephalopathy. Under extreme cases, hypertonic saline or diuretics and fluid restriction may be necessary in order to balance the salt levels. Rapid correction should be avoided because it may lead to osmotic demyelination, including central pontine myelinolysis. Recent researches have reiterated the necessity of adopting a combined approach to treating both conditions among cirrhotic patients because of their co-occurrence and complicating nature of treatment. Recent treatment interventions such as vasopressin receptor antagonists can be useful in balancing water and sodium in cirrhotic patients, and they have the potential to benefit them.[7,8]

Hyponatremia was seen in 96 (36.9%) of 261 patients with cirrhosis. HE was present in 67.7% patients. In 20.8, 23.8, 12.3 and 10.8 percent, HE grade I, grade II, grade III and grade IV were present respectively.[9] In another study, frequency of hyponatremia in patients with hepatic encephalopathy was reported to be 53.9% in 96 patients with hyponatremia. 84 patients had hepatic encephalopathy.[10]

The purpose of this study was to measure the prevalence of hyponatremia in patients with liver cirrhosis and its association with hepatic encephalopathy, in our population. The knowledge of this association might be used to define high-risk patients to be better monitored and treated at an earlier stage, which may enhance prognostic measures. The study could address a significant gap of knowledge, as it will examine the interaction between hyponatremia and hepatic encephalopathy in cirrhosis development that will guide future clinical practice and outcomes measurement.

METHODOLOGY:

This study was a descriptive cross-sectional study that took place at the Department of Medicine, Gulab Devi Teaching Hospital, Lahore, from 12 September 2025 to 11 March 2026 after institutional ethical approval. As this was a descriptive cross-sectional observational study, randomization and a control group were not applicable. The study had 140 patients with liver cirrhosis where a non-probability consecutive sampling technique was used. The sample size was determined using a 95% confidence level, an 8% margin of error and the anticipated occurrence rate of hyponatremia was 36.9% in cirrhotic patients.[10]

Patients of either sex, with a diagnosis of liver cirrhosis aged more than 12 years, were eligible to be included in the study. Clinical, biochemical, and radiological findings were used to diagnose liver cirrhosis, including a coarse echotexture and nodular hepatic surface on ultrasound, platelet less than 150,000/mm 3, AST/ALT ratio more than 1, splenomegaly (>11 cm), decreased albumin (<3.5 g/dL), and the presence of ascites. The exclusion criteria included a history of epilepsy or the use of antiepileptic medications, acute cardiac disease, renal failure, pregnancy, acute drug-induced confusion, neurological disorders (such as stroke), hypoglycemia (blood sugar levels below 70 mg/dl), hyperglycemia (blood sugar levels above 200 mg/dl), hypokalemia (serum potassium below 3.5 mEq/L), and severe hepatitis.

After approval from the hospital ethical review board, eligible patients presenting to the emergency department and outpatient department were enrolled according to the inclusion criteria. Prior to data collection, all subjects provided written informed consent. A standardized proforma was used to collect data on gender, age, place of residence, and socioeconomic status. The presence and severity of hepatic encephalopathy were determined through clinical evaluation using the West Haven criteria. These criteria classify encephalopathy from grade I to IV based on neurological observation and mental status.

During admission, blood samples were drawn and serum sodium levels were measured. Hyponatremia was considered to be a serum sodium level that is less than 135 mEq/L and it was further classified into mild (130 to 134 mEq/L) moderate (120 to 129 mEq/L) and severe (<120 mEq/L). During the first 24 hours of hospitalization, clinical evaluation and reported results provided information on HE. All the patients were treated as per the normal hospital treatment protocols and the possible confounding factors were kept to minimal by observing the rigid observance of the exclusion criteria.

The collected data were evaluated and analyzed using SPSS version 25, the Statistical Package for the Social Sciences. Qualitative variables encompassed the presence of hyponatremia, gender, and grades of hepatic encephalopathy; quantitative variables included age and serum sodium levels, presented as mean and standard deviation. The criteria used to stratify the data included age, sex, residence, socioeconomic position, presence of ascites, serum sodium level, and grades of hepatic encephalopathy. After classification, we evaluated the relationship between hyponatremia and hepatic encephalopathy using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS:

In Table I, the summary of baseline demographic and clinical characteristics of the study population is summarized to include 140 patients with liver cirrhosis. The age of the participants (mean) was 52.4 +/-11.8 years; this shows that the majority of patients were middle-aged to elderly. There was an apparent male predominance with an 88 (62.9) and 52 (37.1%), resulting in a larger prevalence of cirrhosis in males among the cohort. As far as residence is concerned, there was a slightly higher percentage of patients who lived in rural regions (55.7% versus urban regions 44.3%) which likely could be attributed to the access or disease prevalence in that location. The socioeconomic status of the patients revealed that over half of patients (54.3) were of low-income, whereas 31.4% were of middle-income, and 14.3% were of high-income group, which may indicate that liver cirrhosis is more common among the economically disadvantaged groups. Hyponatremia was clinically found in 58 patients (41.4) with 82 patients (58.6) showing normal levels of sodium. Hepatic encephalopathy (HE) occurred in 90 patients (64.3%), and 50 patients (35.7%), did not show evidence of encephalopathy. Generally, the table indicates that hyponatremia along with hepatic encephalopathy present significant burden in the study population.

Table II shows the distribution of the severity of hyponatremia among the affected patients. Among the 140 patients, 58 (41.4) were found to be hyponatremic. Of these mild hyponatremia was the most prevalent and was seen in 28 patients (20.0% of the overall sample), then moderate hyponatremia with only 20 patients (14.3%), and severe hyponatremia was observed in only 10 patients (7.1%). This distribution reflects that even though hyponatremia is a relatively common disease among cirrhotic patients, most cases lie in the range of mild to moderate diseases. Nonetheless, the occurrence of extreme hyponatremia in a group of patients is clinically important, as it can be typically linked to end-stage liver disease, and an increased amount of complications, including hepatic encephalopathy. The results highlight the significance of early diagnosis and hyponatremia grading in order to conduct suitable medical care.

Table III shows the severity of hepatic encephalopathy (HE) in the participants studied. Ninety out of 140 patients (64.3) were identified to have hepatic encephalopathy. Among these, Grade II HE was the most frequently observed (21.4%), followed by Grade I (18.6%), Grade III (14.3%), and Grade IV (10.0%). This distribution implies that a high percentage of patients came with moderate and severe forms of encephalopathy (Grades II to IV) which suggests the advanced disease status in the study population. The elevation of grade of HE also implies greater involvement of the brain and worse prognosis of patients with cirrhosis.

Table IV illustrates that there was a statistically significant relationship between hepatic encephalopathy and hyponatremia ($p = 0.001$). Of patients with hyponatremia, 48 of 58 (82.8%) developed hepatic encephalopathy with only 42 of 82 (51.2%) of patients having no hyponatremia having hepatic encephalopathy. In contrast, the percentage of patients without HE were significantly lower in the hyponatremia group (17.2%), than in the normal sodium group (48.8%). The results of the study underscore the significant association between hyponatremia and the risk of developing hepatic encephalopathy and back the claim that hyponatremia is a strong predictor of occurrence of neurological complications in liver cirrhosis.

Table V shows stratified analysis of the association between hyponatremia and hepatic encephalopathy by various demographic and clinical factors. It was found to have a statistically significant association in all the subgroups such as age ($p = 0.02$), gender ($p = 0.04$), residence ($p = 0.03$), socioeconomic status ($p = 0.05$), and presence of ascites ($p = 0.01$). The rate of combined hyponatremia and HE was more prevalent in patients above 50 years (48.3) than in younger patients. Likewise, the percentage of cases was higher among males (51.7) compared to females. The rural population and low socioeconomic status were also more frequently affected. Interestingly, the strongest correlation was noted in the presence of ascites where 69.0% patients had both hyponatremia and hepatic encephalopathy which implies that the presence of fluids and progressive disease contributes hugely to the risk of neurological problems. On the whole, this stratified review supports the fact that hyponatremia has always been linked to hepatic encephalopathy in various aspects of the patient population that qualify as clinical indicators supporting the role of hyponatremia as a clinical indicator in cirrhotic patients.

DISCUSSION:

The present analysis shows that 64.3% of the patients with liver cirrhosis presented with hepatic encephalopathy (HE) and 41.4% had hyponatremia. Both hepatic encephalopathy and hyponatremia were statistically significantly correlated, and 82.8 percent of the hepatic encephalopathy cases were found to be in hyponatremic individuals and 51.2 percent in non-hyponatremic individuals.

Table 1: Demographic Characteristics (n = 140)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	Mean ± SD	52.4 ± 11.8	—
Gender	Male	88	62.9%
	Female	52	37.1%
Residence	Rural	78	55.7%
	Urban	62	44.3%
Socioeconomic Status	Low	76	54.3%
	Middle	44	31.4%
	High	20	14.3%
Hyponatremia	Yes	58	41.4%
	No	82	58.6%
HE Present	Yes	90	64.3%
	No	50	35.7%

Table 2: Severity of Hyponatremia

Severity	Frequency (n)	Percentage (%)
Mild	28	20.0%
Moderate	20	14.3%
Severe	10	7.1%
Total	58	41.4%

Table 3: Grades of Hepatic Encephalopathy

HE Grade	Frequency (n)	Percentage (%)
Grade I	26	18.6%
Grade II	30	21.4%
Grade III	20	14.3%
Grade IV	14	10.0%
Total	90	64.3%

Table 4: Stratification of Hyponatremia with Hepatic Encephalopathy

Hyponatremia	HE Present n (%)	HE Absent n (%)	Total	p-value
Yes	48 (82.8%)	10 (17.2%)	58	**0.001**
No	42 (51.2%)	40 (48.8%)	82	
Total	90 (64.3%)	50 (35.7%)	140	

Table 5: Stratification of Hyponatremia with Hepatic Encephalopathy Across Variables

Variable	Category	Hyponatremia + HE n (%)	No Hyponatremia + HE n (%)	Total	p-value*
Age	<=50 years	20 (34.5%)	18 (22.0%)	38	**0.02**
	>50 years	28 (48.3%)	24 (29.3%)	52	
Gender	Male	30 (51.7%)	26 (31.7%)	56	**0.04**
	Female	18 (31.0%)	16 (19.5%)	34	
Residence	Rural	28 (48.3%)	24 (29.3%)	52	**0.03**
	Urban	20 (34.5%)	18 (22.0%)	38	
Socioeconomic Status	Low	30 (51.7%)	26 (31.7%)	56	**0.05**
	Middle	12 (20.7%)	10 (12.2%)	22	
	High	6 (10.3%)	6 (7.3%)	12	
Ascites	Present	40 (69.0%)	30 (36.6%)	70	**0.01**
	Absent	8 (13.8%)	12 (14.6%)	20	

The causes of hyponatremia in cirrhosis are mainly caused by failure to expel free water in the urine as a result of non-osmotic release of vasopressin, increased renin- angiotensin-aldosterone system (RAAS), and generalized vasodilation. Such pathophysiological alterations are adequately explained in the recent AASLD rather, hyponatremia is mentioned as the characteristic of severe portal hypertension and circulatory dysfunction in cirrhosis.[11] In the same regard, the recent reviews also highlight that hyponatremia is a sign of disease progression and is connected with such complications as ascites, hepatorenal syndrome, and hepatic encephalopathy.[12,13]

The rate of hyponatremia in this study (41.4%) is in line with a number of recent literature. The prevalence of 41.22% in patients with chronic liver disease in a tertiary care environment reported by Bhandari et al is virtually the same as our results.[14] Similarly, a higher prevalence of 49 percent was observed by Singh et al. with patients having cirrhosis.[15] Such differences can be explained by discrepancies in the populations of the study, the severity of liver disease, and diagnostic qualifications applied to hyponatremia.

Praharaj et al. indicated that the prevalence of hyponatremia in cirrhosis is quite not universal as the sodium threshold

applied but found that the prevalence of hyponatremia in cirrhosis with a serum sodium below 135 mmol/L, but not below 130 mmol/L, was found to be 49.4 and 21.6, respectively.[12] This underscores the significance of the operational definitions in the explanation of the prevalence rates. Our results are similar to those of the research involving the use of the definition based on the use of the 135 mmol/L that is generally accepted in clinical practice. Our findings are also supported by regional studies. In a recent Pakistani study, Azam et al. indicated hyponatremia in 36.09 percent of patients who had decompensated chronic liver disease.[16] The lower prevalence slightly than ours can be associated with the sample size, severity of the disease or the healthcare environments. In general, the prevalence among the South Asian communities is seen to be between 35-50 percent with our results falling within the expected range. The incidence of hepatic encephalopathy was 64.3 percent in our study, and it is also in line with the recent literature. According to the EASL Clinical Practice Guidelines, HE is a frequent complication of advanced cirrhosis especially in patients who have ascites and metabolic imbalances including hyponatremia.[17] The frequency of HE in our study is relatively high which could be evidence of high decompensated cirrhosis cases in our sample. Of special interest is the correlation between the hyponatremia and hepatic encephalopathy seen in this study. We discovered that 82.8% patients with HE had hyponatremia as compared to 51.2% without hyponatremia. This excellent correlation helps to confirm the hypothesis that hyponatremia leads to the occurrence and the progression of HE. The pathophysiology is based on the osmotic mismatch in the cells of the brain, which makes the astrocytes swell and become more prone to ammonia toxicity. New researches also corroborate this association. Li et al. have reported that, patients with cirrhosis and ascites with hyponatremia were at a higher risk of developing hepatic encephalopathy (56.2 vs 39.0) than without hyponatremia.[18] The absolute percentages will vary with our study but the direction of association is similar. On the same note, latest AASLD guidelines on acute-on-chronic liver failure indicate that electrolyte imbalances, such as hyponatremia, can be significant factors that lead to neuronal dysfunction among cirrhotic patients.[19] This supports the clinical significance of serum sodium monitoring as a routine examination of the patient. Rudler et al. study among critically ill patients with cirrhosis revealed that hyponatremia occurred in 22 percent of the patients with overt hepatic encephalopathy and was frequently related with other triggering factors such as infection and acute kidney disease.[20] Notably, high in-hospital mortality rate (50 percent) was also reported among these patients, which implies that hyponatremia could be a symptom of a bad prognosis and not necessarily a causative factor of hyponatremia. This could be the reason why our study showed that the percentage of HE among the hyponatremic patients was higher because our cohort was probably more advanced.

The recent treatment researches also emphasize the need to treat hyponatremia. Zaccherini et al. reported that long-term albumin therapy had a great effect on normalization of serum sodium level (45% vs 28% and increased incidences of moderate to severe hyponatremia were reduced-7). On the same note, Kulkarni et al. established that albumin infusion was linked to hyponatremia and hepatic encephalopathy outcomes that showed improved survival rates among patients with no acute-on-chronic liver failure.[21] A meta-analysis study by Zhou et al. recently verified another study revealing that albumin therapy has a significant effect on the reduction of hyponatremia in cirrhotic patients (odds ratio 0.67, 95 percent CI 0.530.85).[22] These results indicate that hyponatremia treatment can have therapeutic implications other than normalizing electrolytes, which might positively affect the neurological outcome. Moreover, recent reviews of experts emphasise the fact that hyponatremia must be viewed as an important prognostic factor in cirrhosis. Flores et al. noted that hyponatremia is a complication that is linked to high morbidity, hospitalizations, and mortality in cirrhotic patients.[23] Along with constant control and attentive correction of the sodium level, the AGA Clinical Practice Update also suggests consistent monitoring and monitoring of these complications, which can be hepatic encephalopathy and the syndrome of osmotic demyelination.[24] In general, the results of the current research are well correlated with recent literature. The incidence of observed hyponatremia is in line with the reported world and country-specific data, and its risk exposure with hepatic encephalopathy is highly supported by modern literature. The increased percentage of HE in hyponatremic patients in our study may be due to the variation in the severity of the disease, the choice of patients, or the accessibility of healthcare. The study has a number of strengths that contribute to its reliability and clinical relevance. It contains a clear purpose that aims at the frequency of hyponatremia and its relation with hepatic encephalopathy in patients with liver cirrhosis about a significant clinical problem. A descriptive cross-sectional design is suitable in establishing prevalence and finding associations. A sample of 140 patients is sufficient to enhance the validity of the results and the standardized definitions (serum sodium <135 mEq/L) and inclusion of West Haven criteria guarantee uniformity in measurements. Moreover, appropriate statistical analysis with SPSS and Chi-square further enhanced the level of scientific rigour, as statistically significant association between the two conditions was found. The stratified analysis of the demographic and clinical variables gives more detailed understanding and the fact that the study has been carried out in the environment of a real-life hospital makes it more applicable.

Limitations: The research has a number of limitations that ought to be taken into consideration when interpreting the findings. To begin with, the study, since it is not a multicenter

type, is also not conducted in the general population but in a tertiary care unit. Secondly, cross-sectional design does not allow one to reach a causal relationship between hyponatremia and hepatic encephalopathy because it is only possible to obtain associations. Thirdly, concurrent sampling could be subject to selection bias due to non-probability consecutive sampling. Also, serum sodium levels and hepatic encephalopathy were measured at a single point in 24 hours of admission, which are not always dynamic. Such possible confounding variables as infections, medications, and nutritional status were not properly managed. Lastly, the sample size is relatively small and can be associated with a lack of statistical power and accuracy of subgroup analyses.

CONCLUSION:

Hyponatremia is a frequent consequence of liver cirrhosis and is closely associated with hepatic encephalopathy, a sign of a more severe illness. Early detection and appropriate treatment of low sodium levels may be feasible in order to mitigate complications and enhance patient outcomes. The results indicate that hyponatremia is an effective marker of severe liver disease and brain conditions. Accordingly, frequent check-ups and regular check of the serum sodium levels of patients with cirrhosis can mitigate the identification of the high-risk group at an early stage, which in turn minimizes morbidity and enhances the clinical outcomes.

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Noor Ehsan: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
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Original Article **Open Access**

Effect of Maternal Anemia on Birth Weight among Newborns

Amna Younis, Iqbal Ahmad, Muhammad Irfan, Syed Usama Masood, M.I Babar

ABSTRACT:

Objectives: To evaluate the association between maternal anemia and low birth weight in newborn at SITH, Lodhran.

Study design & settings: Prospective cohort study at Department of Pediatrics nursery and gynae and obs department at Shahida Islam Teaching Hospital, Lodhran.

Materials & Methods: Pregnant women of child bearing age between 18 and 40 years with singleton pregnancies confirmed via ultrasound were included. Those who were pregnant with hemoglobinopathies, multiple pregnancies (twins, triplets, etc.), preterm pregnancy, pregnant and had such conditions as GDM, PIH, preeclampsia were excluded. Two groups of women will be divided as having been exposed and not being so. Exposed group (Anemic mothers): Hemoglobin level of less than 11 g/dL in pregnant women, as tested during their third trimester. Unexposed group (non-anemic mothers): Hemoglobin level of =11 g/dL in pregnant women, as assessed during their third trimester. The weight of babies at the time of birth was determined within 30 minutes of birth using a standard calibrated digital weighing scale, and noted in grams.

Results: Low weight of babies at birth was observed in 24(48.0%) women and was anaemic as compared to 08 (16.0%) women who were non-anaemic thus the p-value of 0.002 and relative risk of 3.00 which is noticeable and represents positive relationship of maternal anemia and low weight of babies in our study.

Conclusion: Following findings carried in the study, the likelihood of anemic women bearing low birth weight babies is greater than non-anemic women.

Keywords: Anemia, low birth weight, pregnancy.

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INTRODUCTION:

A decrease in hemoglobin concentration below 11 g/dL during pregnancy[1] is known as maternal anemia, and it is a serious public health concern worldwide, especially in low- and middle-income nations. An estimated 40% of pregnant women globally are thought to be affected, with a higher prevalence in areas like South Asia and Sub-Saharan Africa.[2] Preterm birth, low birth weight, intrauterine growth restriction, and higher perinatal morbidity and mortality® are among the negative mother and fetal outcomes linked to this syndrome.[3-6]

The clinical consequences of anemia in pregnant women are diverse and include a large number of harm to the mothers and newborns. On the maternal side, it may cause fatigue, decreased ability to work, greater weakness to infection and difficulties during childbirth. The impact is even more worrying in terms of fetal position where maternal anemia has been strongly associated with preterm birth, intrauterine growth restriction (IUGR), low birth weight (LBW) and perinatal morbidity and mortality. Of special concern among them is low birth weight as it is a leading indicator of postpartum mortality, development, and future health history. Low birth weight among infants modulate an increased risk of childhood mortality, cognitive, and developmental disorders in adulthood.[5] Maternal anemia was shown to be a substantial risk factor for low and insufficient birth weight in a study by Figueiredo et al. In this prospective cohort study conducted in Brazil, maternal anemia raised the incidence of LBW by 38%.[4]

The biological pathway between maternal anemia and low birth weight has to do mainly with the decreased blood oxygen transporting capacity. In the case where the maternal

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hemoglobin is low, the fetus and placental oxygen supply is impaired. This may cause poor fetal growth and development hence low birth weight. Moreover, placental functioning, and the transfer of nutrients may also be impacted by anemia, which will also lead to under-optimal fetal development. Iron deficiency that is the leading cause of anemia in pregnancy is also a critical factor in the development of fetal brain and general growth and hence its deficiency is very detrimental.[6]

These results were supported by a cross-sectional study conducted in central India by Verma et al. (2020), which shown that maternal anemia increased the incidence of low birth weight by a statistically significant margin (27.8%). This study further emphasized the relevance of iron supplementation, which enhanced maternal hemoglobin levels and thus reduced the prevalence of LBW.[7] Additionally, Rauf et al. (2022) found a strong correlation between LBW and maternal anemia, especially in multigravida women. The research was carried out in Pakistan and showed that 39.37 of mothers had maternal anemia with 16.62% of the children born having LBW. The results indicated that anemia and poor maternal dieting covered significant contributes an infant underweight status.[8] The rate of LBW was 29.41 when a woman is anemic and 9.04 when a woman is not anemic.[9] Though there is ample evidence across the world that maternal anemia is associated with low birth weight there is no region specific data available and issues like this are mostly underreported in a number of underdeveloped countries such as South Punjab. Local factors such as, diet, cultural beliefs, socioeconomic inequality and access to services in relation to maternal anemia can be colossal in terms of prevalence and severity of maternal anemia and its consequences. That is why, it is necessary to carry out the localized research in order to learn more about the extent of this issue among the definite populations. This study is motivated by the fact that a large amount of research has been conducted all over the world that has found a very strong relationship between maternal anemia and bad birth, especially low birth weight that is a primary cause of morbidity and mortality among newborns. But even then, given this enormous amount of international data, a significant lacuna in local studies on this subject in our south punjab is remarkable. The local context is important to understand, as the level of maternal anemia severity and impact on birth weight might be affected by the availability of healthcare, nutrition habits, as well as socioeconomic status. The proposed study aims to fill the gap by offering locally specific data that can be used to develop targeted interventions and improve maternal and neonatal health-related outcomes in our locality.

METHODOLOGY:

The ethical review committee approved (No. SIMC/ET.C./0001/24 dated 04-10-2024) this prospective cohort study, which involved 100 women and ran from 16th October 2025 to 14th January 2026. Sample size of 100 i.e. 50 exposed and 50 unexposed is estimated by WHO calculator taking significance level as 5%, power of study as 80% and percentage of low birth weight babies in anemic group as 29.41% and in non-anemic group as 9.04%.[9] Pregnant women of child bearing age between 18 and 40 years with singleton pregnancies confirmed via ultrasound were included. Pregnant women with hemoglobinopathies, multiple pregnancies (twins, triplets, etc.), preterm birth, and pregnant women with disorders such as GDM, PIH, and preeclampsia were not included.

Informed permission was obtained from all individuals before registration in the study. Women were divided into exposed and non-exposed groups. Exposed group (Anemic mothers): Hemoglobin level of < 11 g/dL in pregnant women, as tested during their third trimester. Unexposed group (non-anemic mothers): Hemoglobin level of =11 g/dL in pregnant women, as assessed during their third trimester. An elderly aged structured proforma was used to gather demographic factors like the maternal age, gestational age, parity, and socioeconomic status. The third trimester assessment of hemoglobin levels of the participants was to verify maternal anemia (hmoglobin level < 11 g/dL). Birth weight of infants was obtained after 30 minutes of delivery and the measurement weight of the infant taken in grams using a standard calibrated digital weighing scale. Other records like maternal antenatal care history, nutritional status and any complication during pregnancy were also recorded. Respondents will be monitored until delivery and the data of birth weight will be taken then. A pre-made proforma will be used to assemble all of the data. Some of the confounding variables included maternal age, the age of gestation, parity, place of residence as well as the socioeconomic status. SPSS version 25.0 was used for data analysis. The data was compiled using descriptive statistics. Continuous variables like maternal age, gestational age, BMI and birth weight were expressed as mean ± SD, while parity, antenatal care, previous h/o LBW (yes/no), place of living (rural/urban), socioeconomic status were presented as frequencies and percentages. The frequency of low birth weight newborns among anemic and non-anemic moms was compared using chi square. P value =0.05 was evaluated as significant. Relative risk was estimated to see the association between low birth weight newborns and maternal anemia and RR >1 was classified as significant. Data was further stratified by maternal age, gestational age, parity, body mass index, previous h/o LBW (yes/no), place of residence (rural/urban), socioeconomic status and post-stratification chi square was applied and P value =0.05 was evaluated as significant. Additionally, relative risk was computed.

RESULTS:

The respondents in the study were aged between 18-40 years, and the mean age was 25.49 +/-4.29 years. The mean age of women who were exposed was 26.04 ± 4.37 years

and the mean age of women who were not exposed was 25.22 ± 4.22 years. Eighty-seven (87.0) out of the patients used to be aged 18 to 30. The mean gestational age was 39.15 weeks with a range of 0.98 weeks. The mean gestation weeks of the exposed group was 39.14 +/- 0.99 and the unexposed group was 39.18 +/-0.98. The average height was 153.66 ± 10.42 cm. The average weight was 79.32 ± 7.32 kg. The average BMI for the exposed group was 25.09 ± 4.56 kg/m2, while it was 26.65 ± 4.71 kg/m2 for the unexposed group. There is a distribution of different variables as indicated in table I. Our study found that 24 (48.0%) of the women with anemia had low birth weight babies, while only 08 (16.0%) of the women without anemia had low birth weight babies. The p-value was 0.002 and the odds ratio was 3.00, which is significant and shows a positive link between maternal anemia and low birth weight in babies (Table II).

Table III shows the stratification of low birth weight (LBW) against all the possible confounding factors such as maternal age, gestational age, parity, body mass index (BMI), previous low birth weight history, residence, and socioeconomic status. This was done in an attempt to examine the consistency of the relationship between maternal anemia and low birth weight within various subgroups. Regarding maternal age, 45.24% of anemic mothers gave birth to low weight babies among women that were 18-30 year old compared to 17.78% among women who were not anemic. This was statistically significant (p = 0.010) with a relative risk (RR) of 2.54, which suggests that in this age group anemia was a significant risk factor increasing the chances of LBW. Conversely, even though a greater percentage of LBW remained in the anemic women were noted to be aged 31-40 years (62.50 vs. 0) the association was not significant (p = 0.149), probably because of smaller sample in this group. In terms of gestational age there were considerable findings of associations in both categories. With gestational age 37-39 weeks, 47.06% of blood-deficient mothers carried LBW babies as compared to 21.21% of non-deficient mothers (p = 0.037, RR = 2.22). On the same note, a high level of association was observed in 40 41 weeks group where 50.0 of the anemic mothers delivered LBW babies, in contrast to a low level of association between non-anemic mothers at 5.88 (p = 0.033, RR = 8.50). These results indicate that maternal anemia has a negative impact on birth weight even when there is gestational age.

Both groups had statistically significant results in terms of parity. Among women with parity 1–2, 41.94% of anemic mothers had LBW babies compared to 15.63% in the non-anemic group (p = 0.033, RR = 2.68). In a like manner, in women with parity 34, the incidence of LBW was found to be 57.89% in anemic mothers, 16.67 in non-anemic mothers (p = 0.027, RR = 3.47). This shows that anemia is an important risk factor of LBW irrespective of parity.

In case of body mass index (BMI), there was a significant distribution in the women with the BMI of 25 or less where 59.26 of the anemic mothers but not 14.29 of non-anemic mothers delivered LBW babies (p = 0.004, RR = 4.15). Nonetheless, the difference was not statistically significant in women with BMI >25 (p = 0.225), which implies that normal or even lower BMI with anemia is the predictor of an increased risk of LBW.

Comparing past history of LBW, it was no longer statistically significant when there was a history of it among women (p = 0.080) but the proportion was higher among anemic mothers (75.0% vs. 14.29%). Nevertheless, there was a significant association with anemia in women who had never been at risk before (p = 0.013, RR = 2.63) and this implies that anemia is a contributor to LBW in its own right.

In terms of residence, there was a very high association in urban populations where 55.17% of anemic mothers had LBW babies when compared with 14.81% of non-anemic mothers (p = 0.007, RR = 3.72). The correlation was however, not statistically important in rural populations (p = 0.141) but the trend followed was similar. Finally, at the socioeconomic level, statistically significant both the kind of association (p = 0.007, RR = 3.24) was observed in the middle socioeconomic group where the role of anemia significantly increased LBW. On the contrary, low and high socioeconomic groups showed no correlation, possibly due to the smaller sample size in these groups or it might not be associated with high variance.

DISCUSSION:

The results of this study demonstrate the strong link between maternal anemia and lower neonatal birth weight, and they are in good agreement with a large body of national and international research. In our study, low birth weight babies were observed in 24 (48.0%) anemic women compared to 8 (16.0%) anemic women. The p-value of 0.002 and odds ratio of 3.00 are significant, indicating a positive correlation between low birth weight babies and maternal anemia. Moreover, Rauf et al. (2022) noted a significant correlation between LBW and maternal anemia and multigravida women in particular. This Pakistani-based study reported a prevalence of 39.37% maternal anemia among the mothers with 16.62% of the born neonates born with LBW. The results demonstrated that underweight status of infants caused by anemia and lack of maternal nutrition was crucial. LBW was prevalent among anemia women (29.41% and non-anaemic women (9.04%).[9]

Singh et al.[10] and Kumar et al.[11] further verified these results across varied settings in India, proving maternal anemia as a substantial risk factor for intrauterine growth restriction (IUGR) and LBW. Parallel international research conducted in low-resource situations, including sub-Saharan Africa and Southeast Asia, have consistently repeated same findings.[12] For example, a comparable study by Figueiredo et al.[13] and a systematic review and meta-analysis by Rahmati et al.[14] showed strong correlations between maternal anemia

Table-1: Distribution of different variables (n=100)

		Exposed (n=50) Number (%)	**Unexposed (n=50)** Number (%)
Age (years)	**18-30**	42 (84.0%)	45 (90.0%)
	31-40	08 (16.0%)	05 (10.0%)
Gestational age (weeks)	**38-39**	34 (68.0%)	33 (66.0%)
	40-41	16 (32.0%)	17 (34.0%)
Parity	**1-2**	31 (62.0%)	32 (64.0%)
	3-4	19 (38.0%)	18 (36.0%)
BMI (kg/m^2)	**<=25**	27 (54.0%)	28 (56.0%)
	>25	23 (46.0%)	22 (44.0%)
Residence	**Rural**	21 (42.0%)	23 (46.0%)
	Urban	29 (58.0%)	27 (54.0%)
Previous h/o LBW	**Yes**	08 (16.0%)	07 (14.0%)
	No	42 (84.0%)	43 (86.0%)
Mode of delivery	**Low**	09 (18.0%)	09 (18.0%)
	Middle	25 (50.0%)	27 (54.0%)
	High	16 (32.0%)	14 (28.0%)

Table 2: Association of maternal iron deficiency anemia with low birth weight

	Exposed (n=50)		**Unexposed (n=50)**		**P-value**	**RR**
	yes	no	yes	no		
Unexposed (n=50)	24 (48.0%)	26 (52.0%)	08 (16.0%)	42 (84.0%)	**0.002**	**3.00**

Table 3: Stratification of low birth weight with respect to confounders

		Exposed (n=50)		**Unexposed (n=50)**		**P-value**	**RR**
		low birth weight		**low birth weight**			
		Yes	No	Yes	No		
Age (years)	**18-30**	19 (45.24%)	23 (54.76%)	08 (17.78%)	37 (82.22%)	0.010	2.54
	31-40	05 (62.50%)	03 (37.50%)	00 (0.0%)	05 (100.0%)	0.149	7.33
Gestational age (weeks)	**37-39**	16 (47.06%)	18 (52.94%)	07 (21.21%)	26 (78.79%)	0.037	2.22
	40-41	08 (50.0%)	08 (50.0%)	01 (5.88%)	16 (94.12%)	0.033	8.50
Parity	**1-2**	13 (41.94%)	18 (58.06%)	05 (15.63%)	27 (84.37%)	0.033	2.68
	3-4	11 (57.89%)	08 (42.11%)	03 (16.67%)	15 (83.33%)	0.027	3.47
BMI (kg/m^2)	**=25**	16 (59.26%)	11 (40.74%)	04 (14.29%)	24 (85.71%)	0.004	4.15
	>25	08 (34.78%)	15 (65.22%)	04 (18.18%)	18 (81.82%)	0.225	1.91
Previous H/o LBW	**Yes**	06 (75.0%)	02 (25.0%)	01 (14.29%)	06 (85.71%)	0.080	5.25
	No	18 (42.86%)	24 (57.14%)	07 (16.28%)	36 (83.72%)	0.013	2.63
Residence	**Rural**	08 (38.10%)	13 (61.90%)	04 (17.39%)	19 (82.61%)	0.141	2.19
	Urban	16 (55.17%)	13 (44.83%)	04 (14.81%)	23 (85.19%)	0.007	3.72
Socioeconomic status	**Low**	02 (22.22%)	07 (77.78%)	03 (33.33%)	06 (66.67%)	0.604	0.66
	Middle	15 (60.0%)	10 (40.0%)	05 (18.52%)	22 (81.48%)	0.007	3.24
	High	07 (43.75%)	09 (56.25%)	00 (0.0%)	14 (100.0%)	0.068	13.2

and unfavorable pregnancy outcomes, particularly LBW.

Kemppinen et al.[15] found that women and newborns with anemia are more likely to have serious complications such PTB, FGR, and infections after giving birth. Khezri et al. demonstrated that maternal anemia during pregnancy in Iranian women was associated with adverse pregnancy outcomes, even after controlling for confounding variables.[16] A retrospective cohort study by Biswas et al. found that anemia during pregnancy greatly increases the risk of LBW.[17] In a similar vein, Wahyuni et al.[18] discovered a substantial correlation between the prevalence of LBW newborns and anemia during pregnancy. These results align with the current body of research.

One important risk factor for childhood anemia is low birth weight (LBW), which is linked to low iron reserves at or after 37 weeks of pregnancy.[9,19] Also, babies who are born with low birth weight (LBW) are more likely to develop insulin resistance and other health problems later in life.[20] There are many things that might cause low birth weight (LBW) in children, such as the mother's age (young or old), her BMI being too low or too high, her having a chronic illness, or her having had a premature birth. Expectant women with anemia, especially in low-income nations like Pakistan, exhibit a heightened likelihood of delivering low birth weight (LBW) infants.[21]

In the current investigation, the mean age of women in exposed group was 26.04 ± 4.37 years and in unexposed group was 25.22 ± 4.22 years. Majority of the patients 87 (87.0%) were between 18 to 30 years of age. According to a study done in Muzaffarabad, the only risk factors that significantly correlated with LBW were socioeconomic demographics.[22] There is conflicting research about the association between serum ferritin levels and LBW, despite serum ferritin's correlation with other conditions such as chronic patent ductus arteriosus, sepsis, and bronchopulmonary dysplasia.[23]

By offering a thorough hospital-based study that links low birth weight to poor maternal nutrition and health inequities, Devaguru et al.[24] support these connections. All these researches highlight the importance of maternal iron status, dietary therapy and prenatal care in reducing the prevalence of low birth weight (LBW). Low birth weight (LBW) would not be prevalent in most of the populations with an all rounded approach where routine ferritin screening, better maternal nutrition, and better prenatal care services are integrated. Anemia is a preventive health problem and its treatment is likely to reduce the occurrence of the low birth weight (LBW) and even postnatal mortality among the general population. Arsyi et al.[25] propose that increased prenatal care usage has a drastic effect in reducing low birth weight newborns by four ASEAN countries. This demonstrates how crucial it is to increase access to maternity healthcare.

Lack of iron is the main cause of anemia during pregnancy in Pakistan. This is commonly linked to a poor background, lack of nutrition, and having several children. Taking iron supplements when pregnant is thought to lower the incidence of anemia and low birth weight in newborns. Research conducted in the United States has similarly elucidated this.[14]

Anemia impacts 36% of pregnant women worldwide, with around 40% of instances resulting from iron deficiency (ID).[26] The elevated incidence of low birth weight babies documented in this study may be associated with heightened levels of inbreeding resulting from frequent unions among closely related individuals of diverse ethnic backgrounds. A prospective cohort study identified low birth weight (LBW) as a significant public health issue in this area. Factors such as maternal undernutrition, iron deficiency (ID) during pregnancy negatively impacted birth weight. To enhance maternal and neonatal health, customized treatments promoting better nutrition and extensive availability of iron and folic acid supplementation are essential.[27]

A study conducted in Nigeria demonstrated that lower birth weight is a good predictor of reduced serum ferritin levels.[28] A study done in India showed that preterm babies had less iron stored than full-term babies. The main factor that affected iron levels at birth was how far along the baby was in its pregnancy. Also, a lack of iron was linked to chronic and long-term problems with brain development.[29] The elevated prevalence of LBW observed in this study and others in Pakistan may be partially attributable to insufficient iron supplementation. The percentage of people who take iron supplements for 90 days or more has gone substantially over the years, from 22% in the 2012-13 PDHS to 29% in 2017-18. However, this is still not enough to properly treat iron deficiency and its linked problems, such as LBW.[30]

These results further emphasized the imperative of improving maternal iron status through enhanced iron supplementation and nutritional therapies to reduce the incidence of low birth weight (LBW). Since many pregnant women in Pakistan are iron deficient, fixing this problem could dramatically lower the number of LBW babies and improve the health of mothers and babies.

There are minimal study constraints. Firstly, that we could not differentiate between low birth weight and preterm infants in both anemic and non-anemic populations. Future studies should therefore focus on these two different groups (Preterm and LBW) to find out their association with maternal hemoglobin and ferritin levels to help decision-makers decide what to do to best meet the interests of the mother and child.

CONCLUSION:

The outcomes of the study reveal that anaemic women are more likely to deliver babies with poor birth weights as compared to those who are not anaemic. Our proposals include the creation of community educational programs

dealing with this important issue in women of reproductive age and the training of treating doctors on the early diagnosis and treatment of maternal anemia to abate the occurrence of low birth weight babies.

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Authors Contribution:
Amna Younis: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Iqbal Ahmad: Conception, acquisition of data, critical revision of the manuscript.
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Original Article **Open Access**

Comparison of Efficacy of Mesotherapy with Tranexamic Acid versus Ascorbic Acid in the Treatment of Melasma: A Split-Face Comparative Study

Nida Khalid, Sameena Kausar, Ghazala Yasmin, Tooba Hadia, Hannah Hassan, Ammara Suleman

Abstract

Objectives: To compare the efficacy and safety of intradermal mesotherapy with tranexamic acid (TA) and ascorbic acid (AA) in patients with facial melasma.

Study Design and Setting: A quasi-experimental split-face comparative study was conducted at the Department of Dermatology, Tertiary Care Hospital, Malir Cantt, Karachi, over a period of six months after approval of the research protocol by the institutional review authority.

Methodology: Sixty patients aged 20–50 years with bilateral facial melasma were enrolled through non-probability consecutive sampling. Intradermal tranexamic acid (100 mg/mL) was administered on the right side of the face, while ascorbic acid (20%) was injected on the left side at two-week intervals for 12 weeks. Treatment response was assessed using the modified Melasma Area and Severity Index (mMASI) score at baseline and follow-up visits. Adverse effects were also recorded.

Results: Both treatment modalities showed significant reduction in mMASI scores after 12 weeks. However, the TA-treated side demonstrated a significantly greater mean reduction in mMASI score compared to the AA-treated side (73.9% ± 11.6 vs. 57.5% ± 13.2; $p<0.001$). Excellent response (=75% improvement) was observed in 56.7% of TA-treated sides compared to 30% of AA-treated sides. Adverse effects including erythema, burning sensation, and pain at injection site were mild and transient in both groups.

Conclusions: Intradermal mesotherapy with tranexamic acid was more effective than ascorbic acid in reducing the severity of melasma while maintaining a comparable safety profile. Both treatments were well tolerated; however, tranexamic acid produced faster and greater pigment reduction, particularly in patients with darker skin phototypes.

Keywords: Ascorbic Acid; Melasma; Mesotherapy; Skin Pigmentation; Tranexamic Acid

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INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder characterized by symmetrical brown to gray-brown macules and patches involving sun-exposed areas of the face, particularly the cheeks, forehead, upper lip, nose, and chin.[1] The condition predominantly affects women of reproductive age and individuals with darker skin phototypes, especially Fitzpatrick skin types III–V.[2] Melasma is highly prevalent in Asian, Middle Eastern, African, and Latin American populations because of increased ultraviolet (UV) radiation exposure and genetic susceptibility.[3] Although melasma is not associated with physical morbidity, it has a considerable psychosocial impact on affected individuals. Facial pigmentation frequently causes emotional distress, low self-esteem, social embarrassment, anxiety, and impaired quality of life because the lesions are cosmetically disfiguring and often difficult to treat effectively.[4]

The prevalence of melasma varies widely across different ethnic and geographic populations, ranging from approximately 1% in the general population to nearly 40% in high-risk populations living in tropical regions.[5] Multiple

endogenous and exogenous factors contribute to disease development. Ultraviolet radiation is considered the most important precipitating factor because it stimulates melanocyte proliferation and melanogenesis through activation of inflammatory mediators and oxidative stress pathways.[6] Hormonal influences also play an important role, as melasma commonly occurs during pregnancy and in women using oral contraceptives or hormone replacement therapy.[7] Genetic predisposition is another recognized factor, with many affected individuals reporting a positive family history of the disease.8 Additional aggravating factors include thyroid dysfunction, cosmetic products, phototoxic medications, emotional stress, and chronic sun exposure.[3]

The pathogenesis of melasma is multifactorial and remains incompletely understood. Earlier theories primarily focused on melanocyte hyperactivity; however, recent evidence suggests that several cellular and molecular mechanisms are involved in disease progression.[9] Ultraviolet radiation induces the production of reactive oxygen species and inflammatory cytokines, resulting in increased tyrosinase activity and enhanced melanin synthesis.[10] Furthermore, dermal inflammation, solar elastosis, vascular proliferation, basement membrane disruption, and increased mast cell activity have been identified as important histopathological features in melasma lesions.[11] Interactions among melanocytes, keratinocytes, fibroblasts, inflammatory mediators, and vascular endothelial growth factors also contribute to persistent pigmentation and frequent recurrence. These mechanisms explain the chronic and treatment-resistant nature of melasma.

Several treatment modalities are currently available for melasma management, including topical depigmenting agents, oral medications, chemical peels, laser therapy, and energy-based procedures. Conventional topical agents such as hydroquinone, tretinoin, azelaic acid, kojic acid, and corticosteroids remain first-line treatment options.[12] However, these therapies often require prolonged use and may provide incomplete clearance with frequent relapse. In addition, adverse effects such as erythema, irritation, post-inflammatory hyperpigmentation, contact dermatitis, and exogenous ochronosis may limit patient compliance and long-term use.[13] Laser and light-based therapies have also shown variable efficacy and may worsen pigmentation in darker skin phototypes because of increased melanocyte sensitivity and inflammatory responses.[14] Consequently, there is increasing interest in minimally invasive therapeutic approaches that provide improved efficacy with fewer adverse effects.

Mesotherapy has recently emerged as a promising treatment modality for melasma and other pigmentary disorders. It involves intradermal microinjections of active therapeutic agents directly into affected skin, thereby enhancing local drug concentration and minimizing systemic adverse effects.[9] Among the agents used in mesotherapy, tranexamic acid (TXA) has gained considerable attention because of its anti-plasmin, anti-inflammatory, and anti-angiogenic properties. Tranexamic acid inhibits plasminogen activation and suppresses ultraviolet-induced melanocyte stimulation by reducing inflammatory mediators, arachidonic acid pathways, and vascular endothelial growth factor activity involved in melanogenesis.[10] Multiple clinical studies and systematic reviews have demonstrated significant reductions in Melasma Area and Severity Index (MASI) scores following oral, topical, and intradermal administration of tranexamic acid.[11]

Ascorbic acid (vitamin C) is another therapeutic agent increasingly used in melasma management because of its antioxidant and depigmenting properties. It inhibits tyrosinase activity, neutralizes reactive oxygen species, promotes collagen synthesis, and reduces oxidative stress associated with excessive melanin production.[6] Intradermal administration of ascorbic acid through mesotherapy has shown encouraging results in improving facial pigmentation and skin texture.[14] However, comparative evidence regarding the efficacy and safety of intradermal tranexamic acid and ascorbic acid remains limited, particularly in populations with darker skin phototypes and high ultraviolet exposure. Therefore, the present study was conducted to compare the efficacy and safety of intradermal mesotherapy with tranexamic acid and ascorbic acid in patients with facial melasma using a split-face comparative design.

METHODOLOGY

This quasi-experimental split-face comparative study was conducted at the Department of Dermatology, Tertiary Care Hospital from 1-Jan-2025 to 30-Jun-2025 after approval from the Ethical Review Committee of Tertiary Care Hospital. Ethical approval was granted through the Ethical Review Committee Certificate (File No. 158/2025/Trg/ERC). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

A total of 60 patients diagnosed with melasma were recruited through non-probability consecutive sampling. The sample size was calculated using the WHO sample size calculator by considering 95% confidence level, 80% power of study, and expected difference in treatment efficacy between the two groups based on previous published studies. Adult male and female patients aged 20–50 years having bilateral facial melasma with modified Melasma Area and Severity Index (mMASI) score =5 were included in the study. Patients with known hypersensitivity to tranexamic acid or ascorbic acid, pregnancy, bleeding disorders, systemic illness, use of hormonal contraceptives, or unwillingness to participate were excluded from the study. The inclusion and exclusion criteria were adopted from previously published studies on mesotherapy for melasma. [15-18]

Demographic variables including age, gender, marital status, and occupation were recorded on a predesigned proforma.

Clinical assessment included duration and distribution of melasma, Fitzpatrick skin type, and type of melasma (epidermal, dermal, or mixed) assessed through Wood's lamp examination. Baseline and follow-up digital photographs were taken under standardized lighting conditions and fixed distance for comparison. Baseline mMASI scores were calculated separately for both sides of the face.

In the split-face design, the right side of the face received intradermal tranexamic acid (100 mg/mL), while the left side received intradermal ascorbic acid (20% solution), serving as an internal control. Prior to each procedure, topical anesthetic cream containing 10.56% lidocaine was applied for 30 minutes followed by cleansing of the treatment area. Using a 30-gauge insulin syringe, approximately 1–2 mL of the designated solution was injected intradermally into the affected malar region through multiple evenly distributed microinjections. Ice packs were applied after the procedure, and all patients were advised strict photoprotection measures including regular use of sunscreen during the study period.

Treatment sessions were performed at baseline and repeated every two weeks for a total duration of 12 weeks. Clinical improvement and adverse effects including erythema, burning sensation, pain at injection site, localized swelling, and papule formation were assessed at each follow-up visit. The mMASI score was recalculated during every assessment visit to evaluate treatment response.

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Quantitative variables such as age, duration of melasma, and mMASI scores were presented as mean ± standard deviation or median with interquartile range according to data distribution. Normality of data was assessed using the Shapiro-Wilk test. Paired sample t-test was applied to compare pre- and post-treatment mMASI scores on each side of the face, while independent sample t-test was used to compare mean differences between tranexamic acid and ascorbic acid treated sides. Qualitative variables were presented as frequencies and percentages. Chi-square test or Fisher's exact test was applied where appropriate. A p-value =0.05 was considered statistically significant.

RESULTS

Sixty patients who had bilateral melasma of the face took part in the study. The average age of the participants was 32.80055 years (21-49 years). Most of them were females (83.3%), married (70%), and Fitzpatrick IV and V skin type. The average period of melasma was 28.5 months with standard deviations of 11.2.

The baseline mMASI scores showed no statistically significant difference between the right and left face ($p > 0.05$), thus, establishing comparability of the two sides of the face of treatment before intervention. Table 1 defines the background of the 60 patients who are involved in the study. The average age was 32.8 years which indicated that melasma primarily impacted young and middle-aged adults. They consisted of a definite female preponderance (83.3) as per the established hormonal effect on melasma. The Fitzpatrick skin types IV and V were the most common type of participants, which means that the darker phototypes were prevalent in this population.

In terms of the disease features, the mean of melasma was more than two years because the disease was a chronic and persistent disorder. The most common one was epidermal melasma, then mixed and dermal. These results indicate that the population that was studied was normal to the patient who turned up at dermatology clinics in high sun exposure areas. The two treatments led to an incremental decrease in the severity of pigmentation in 12 weeks. The decrease was however more on the tranexamic acid (TA) than the ascorbic acid (AA) side

A significant percentage (=75% improvement) of respondents was reported to have a good response on the TA-treated side. This table demonstrates progressive improvement in pigmentation severity on both sides of the face during the 12-week treatment. There was no statistically significant difference between the tranexamic acid (TA) side and the ascorbic acid (AA) side at baseline, which ensures that both sides have had a similar disease severity at baseline. Both treatments showed a progressive decrease in the scores of mMASI over time, which showed clinical improvement.

Nevertheless, the decrease was always bigger on the TA-treated side with the difference becoming statistically significant starting at week 4 and only escalating at week 12. The TA side significantly reduced the mean mMASI score than the AA side by the end of the research indicating that pigment reduction with tranexamic acid mesotherapy was superior. The trend in Table 2 is graphically illustrated in this line graph. The two lines are downsloping, being an affirmation that pigmentation was enhanced in both treatments. But tranexamic acid decreases at a steeper rate and demonstrated higher and quicker rate of melasma reduction. The fact that the gap between the two lines is increasing after week 4 reflects the better efficacy of TA. Table 3 provides an excellent, moderate, and mild improvement of patient response. Over (56.7%) percent of the patients respond excellently (75 percent improvement and above) on the side treated with TA versus 30 percent on the side treated with AA. On the other hand, the responses on the AA side were more of mild character. The effect was significant enough to make the difference between the groups significant and show that tranexamic acid was the more effective one in achieving the desired clinical improvement.

Tolerance of both treatments was good. The side effects were mild and short-term., there were no side effects necessary that forced a patient to stop the therapy. There were no incidences of post-inflammatory hyperpigmentation, ulceration or any systemic side effects. Table 4 is compared

with local side effects on both treatments. The most frequent adverse events include erythema, pain and burning sensation which were mild and short lived in nature. The number of adverse effects was found to be statistically significantly higher with ascorbic acid, although no significant difference was found between the two sides. Significantly, no severe complications, scarring, or post-inflammatory hyperpigmentation was present. This shows that, both treatments were well tolerated and safe.

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

Variable	Frequency (%) / Mean ± SD
Age (years)	32.8 ± 6.4
Gender	
Male	10 (16.7%)
Female	50 (83.3%)
Marital Status	
Single	18 (30%)
Married	42 (70%)
Fitzpatrick Skin Type	
Type III	9 (15%)
Type IV	31 (51.7%)
Type V	20 (33.3%)
Type of Melasma	
Epidermal	26 (43.3%)
Dermal	11 (18.3%)
Mixed	23 (38.3%)
Duration of Melasma (months)	28.5 ± 11.2

Table 2: Comparison of Mean mMASI Scores over time

Visit	TA Side (Right) Mean ± SD	AA Side (Left) Mean ± SD	p-value*
Baseline	8.12 ± 1.44	8.05 ± 1.39	0.62
Week 4	6.21 ± 1.30	6.78 ± 1.36	0.04
Week 8	4.32 ± 1.18	5.21 ± 1.27	0.002
Week 12	2.11 ± 0.98	3.42 ± 1.12	<0.001

*Independent sample t-test comparing both sides

The **mean percentage reduction in mMASI score** at week 12 was:

- **Tranexamic acid side: 73.9% ± 11.6**
- **Ascorbic acid side: 57.5% ± 13.2**

($p < 0.001$)

Figure : Comparison of Mean mMASI Reduction Over 12 Weeks

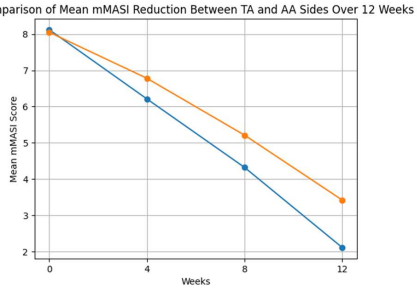

Table 3: Treatment Response at Week 12

Response Category	TA Side n (%)	AA Side n (%)	p-value
Excellent (=75%)	34 (56.7%)	18 (30.0%)	0.004
Moderate (50–74%)	19 (31.7%)	26 (43.3%)	
Mild (<50%)	7 (11.6%)	16 (26.7%)	

Table 4: Frequency of Adverse Effects

Adverse Effect	TA Side n (%)	AA Side n (%)	p-value
Erythema	9 (15%)	14 (23.3%)	0.21
Burning Sensation	7 (11.7%)	12 (20%)	0.18
Pain at Injection Site	11 (18.3%)	13 (21.7%)	0.64
Localized Swelling	6 (10%)	8 (13.3%)	0.57
Papules/Bumps	5 (8.3%)	7 (11.7%)	0.53

DISCUSSION

This split-face quasi-experimental study demonstrated that intradermal mesotherapy with tranexamic acid (TA) produced a greater reduction in mMASI scores and a higher percentage of excellent clinical response compared to ascorbic acid (AA) after 12 weeks of treatment. Both treatment modalities were well tolerated and associated with only mild and transient adverse effects.

The findings of the present study are consistent with previous studies reporting the efficacy of tranexamic acid in the management of melasma. Liao et al. reported that mesotherapy with tranexamic acid significantly reduced MASI scores and showed favorable safety outcomes in patients with melasma.[19] Similarly, Hasan et al. demonstrated superior clinical improvement with tranexamic acid compared to vitamin C-based therapy, particularly when delivered through minimally invasive techniques such as microneedling and mesotherapy.[20] The greater efficacy of TA may be attributed to its inhibitory effect on plasminogen activation, resulting in decreased melanocyte stimulation and reduced ultraviolet-induced melanogenesis. Ascorbic acid also demonstrated clinical improvement in the present study, although the response was less pronounced compared to TA. Vitamin C acts as an antioxidant and tyrosinase inhibitor, thereby interfering with melanin synthesis and reducing oxidative stress within pigmented lesions. Previous studies have shown that ascorbic acid can improve melasma severity, particularly when combined with adjunctive delivery methods or combination therapies.[21] However, its therapeutic response may be slower and less sustained than tranexamic acid in certain patient populations. The current findings are also supported by the meta-analysis conducted by Liao et al., which concluded that both tranexamic acid and vitamin C mesotherapy are effective treatment options for melasma, although tranexamic acid may provide greater clinical benefit in some cases.[22] Variations in treatment response among different studies may be related to differences in study

design, treatment duration, drug concentration, delivery technique, and patient characteristics. Regarding safety, both treatments showed good tolerability with mild and self-limiting adverse effects including erythema, burning sensation, and pain at injection sites. No cases of post-inflammatory hyperpigmentation, scarring, ulceration, or systemic adverse effects were observed. These findings are comparable with previous literature reporting favorable safety profiles of mesotherapy using tranexamic acid and ascorbic acid.[22] The present study has important clinical implications, particularly for patients with darker skin phototypes where melasma is more prevalent and difficult to manage with topical therapies alone. Intradermal tranexamic acid may serve as an effective minimally invasive therapeutic option for achieving faster and greater pigment reduction while maintaining an acceptable safety profile. Limitations: The present study had certain limitations. The sample size was relatively small, which may limit the generalizability of the findings. In addition, the duration of follow-up was limited to 12 weeks and long-term recurrence rates could not be assessed. The majority of participants were females with Fitzpatrick skin types IV and V, which may limit applicability of the results to other populations and skin phototypes. Furthermore, the split-face design may carry a possibility of local treatment interaction despite serving as an effective method for direct comparison between therapies. Future randomized controlled trials with larger sample sizes and longer follow-up periods are recommended to validate these findings and assess long-term outcomes.

Limitations: The present study had certain limitations. The sample size was relatively small, which may limit the generalizability of the findings. In addition, the follow-up duration was limited to 12 weeks; therefore, long-term efficacy and recurrence rates could not be evaluated. Most participants belonged to Fitzpatrick skin types IV and V, which may limit applicability of the findings to other skin phototypes. Further randomized controlled trials with larger sample sizes and longer follow-up periods are recommended.

CONCLUSION

Both tranexamic acid and ascorbic acid intradermal mesotherapy significantly improved melasma severity over 12 weeks of treatment. However, tranexamic acid demonstrated greater reduction in mMASI scores and a higher proportion of excellent clinical response compared to ascorbic acid. Both treatment modalities showed favorable safety profiles with only mild and transient adverse effects and no serious complications. The findings of this study suggest that intradermal tranexamic acid mesotherapy is a more effective treatment option for facial melasma, particularly in patients with darker skin phototypes, while ascorbic acid may serve as a safe alternative therapy. Further randomized controlled studies with larger sample sizes and longer follow-up durations are recommended to evaluate long-term efficacy and recurrence rates.

Authors Contribution:
Nida Khalid: Main conception of the study, manuscript writing, data collection, results and conclusion, data analysis, final approval.
Sameena Kausar: Main conception of the study, manuscript writing, final approval.
Ghazala Yasmin: Manuscript writing, data collection, data analysis, final approval.
Tooba Hadia: Data collection, results and conclusion, data analysis, final approval.
Hannah Hassan: Data collection, results and conclusion, data analysis, final approval.
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Original Article

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Comparison of Intravenous Ciprofloxacin and Intravenous Ceftriaxone in the Management of Spontaneous Bacterial Peritonitis in Cirrhosis of Liver

Hafiza Munam Akhtar, Arif Mehmood Bhatti

Abstract:

Objective: To compare the effectiveness of intravenous ciprofloxacin versus intravenous ceftriaxone in spontaneous bacterial peritonitis (SBP) treatment of patients with liver cirrhosis.

Study Design and settings: Randomized controlled trial at Nishtar Hospital Multan/department of medicine.

Methodology: 310 patients aged 25-70 years old who are liver cirrhosed, diagnosed with SBP were enrolled using nonprobability consecutive sampling. Patients were randomly allocated to two groups using lottery approach. Group A (n=155) received the intravenous ciprofloxacin (200 mg twice a day) and Group B (n=155) the intravenous ceftriaxone (1 g twice a day). Efficacy was noted after 48 hours of treatment on the basis of: fever, abdominal pains, and decrease of the neutrophil count in the ascitic fluid; and data was analyzed using SPSS version 26 and chi-square test was applied and considered significant $p<0.05$.

Findings: Both groups showed an average age of 42.8 +- 9.6 years in Group A and 43.5 +-10.1 years in Group B and an overall efficacy of 71.0% for ciprofloxacin and ceftriaxone of 79.4% respectively and the difference was statistically significant ($p=0.048$). Ceftriaxone demonstrated superiority in clinical and lab outcome particularly among patients with advanced liver disease.

Conclusion: In comparison to intravenous ciprofloxacin, intravenous ceftriaxone is more effective in treatment of spontaneous bacterial peritonitis in cirrhosis.

Keywords: Peritonitis; Liver Cirrhosis; Ciprofloxacin; Ceftriaxone; Ascites.

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INTRODUCTION:

Spontaneous bacterial peritonitis (SBP) is an illness which represents a symptom of some of the worst and most frequent infectious complication of patients with liver cirrhosis and ascites. It can be characterized as the infection of the ascitic fluid which lacks any intra-abdominal source that can be operated on. One of the major clinical problems is SBP due to its high prevalence, complex diagnosis, and morbidity linked with its dissimilar pivotal role in the morbidity and mortality of cirrhotic patients.[1] Recent epidemiological data indicate that SBP is at work in approximately 30 percent of all of the infections of patients suffering cirrhosis and nearly 5-30 percent of patients suffering ascites in hospitals.[2]

Pathogenesis of SBP is primarily linked to the intestinal lumen to mesenteric lymph nodes and its subsequent dissemination to blood and ascitic fluid. Using different factors like damaged gut barrier protein and changed intestinal microbiota, and weakened immune defenses with advanced liver disease are facilitating factors of the process.[2,3] Most commonly implicated pathogens encompass Gram-negative enteric organisms such as Escherichia coli and Klebsiella pneumoniae but in recent years, Gram-positive organisms and multidrug-resistant organisms have been on the rise at the expense of other pathogens.[3]

Low prognosis, in-hospital mortality rates of 15 to 40% and survival with a dramatic reduction of long-term survival after an episode has been associated with SBP.[2] Additionally, cirrhotic patients are prone to infections and they can die four-fold which stresses the need of an early diagnosis and early treatment intervention.[2] The repeat of SBP is also common and results in the repeat of the hospitalization and an increased healthcare-cost.[4] Therefore, effective and timely management remains an asset to improvement of clinical outcome of such patients.

Early empirical administration of antibiotics is the key to managing SBP. Third generation cephalosporins are the first-line therapy as recommended by international parameters like that of American Association of the Study

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of Liver diseases (AASLD) to treat SBP.[5] The most common ones include ceftriaxone, which has a wide spectrum of coverage, good pharmacokinetic profile, and established efficacy against most organisms that cause infections.[6] Bacteriological cure rates with cephalosporins are shown to be high, which supported their use as the routine treatment in clinical practice.[6]

But with the advent of antibiotic resistance, there has been increasing concern regarding its role in the treatment of SBP. The cumulative effects of increased prophylactic use of antibiotics, recurrent hospital hospitalizations and invasive surgical procedures have led to the emergence of multidrug-resistant organisms, which in turn could further curtail the efficacy of standard treatments.[3,7] This changing resistance trend urges the need to identify other antibiotic regimens that are effective, yet affordable.

The third-generation cephalosporins have been suggested to have their replacements by fluoroquinolones and especially ciprofloxacin. The benefits of ciprofloxacin include high oral bioavailability, wide-roughening the antimicrobial activity, and lower cost, which makes it a desirable alternative particularly in a resource-constrained environment. Recent literature has documented this similar effectiveness of ciprofloxacin versus cephalosporins in the management of SBP, and could be an alternative option in some patient groups.[8,9] Further, regimens using ciprofloxacin have been demonstrated to offer an equal clinical benefit at the possibility of decreasing the cost of treatment and hospitalization.[8]

Although these are encouraging results, the literature is still contradictory in terms of the relative effectiveness of ciprofloxacin as compared to ceftriaxone. According to some studies, cephalosporins yield better results whereas other studies show that no significant difference exists between the two modes of treatment.[9,10] Moreover, regional differences in microbial preferences and resistance to antibiotics also contribute to the problem of the choice of the best empirical treatment. Thus, local research, which would identify the most efficient interventions dependent on local people, is necessary.

SBP remains an important healthcare issue in developing countries with a high prevalence of chronic liver disease, like Pakistan. Rare resources, late presentation, and absence of standardized treatment guidelines are other causes that lead to poor outcomes. Discovering the best and most cost-effective antibiotic treatment can prove highly beneficial in enhancing patient recovery and decrease expenditures on healthcare.

In this point, the present research study aims at providing a comparison with respect to the efficacy of intravenous ciprofloxacin and intravenous ceftriaxone in the treatment of spontaneous bacterial peritonitis in liver cirrhosis patients. The study will inevitably result in valuable information on the most effective antibiotic options, evidence-based practice and help to counter the current issue of antibiotic resistance in SBP.

METHODOLOGY:

This was a randomized controlled clinical trial (ClinicalTrials.gov Identifier: NCT07552870) in the department of medicine in the Nishtar Hospital Mulitaka tertiary care teaching hospital. Institutional ethical approval of the protocol (Ref.) was obtained on 15th January 2026 until 14th April 2026, at which time the research was carried out. No. 4189/NMU dated 18-02-2026). The study utilized 310 patients with spontaneous bacterial peritonitis (SBP) diagnosed with the condition within the liver cirrhosis context with the use of a non-probability- consecutive sampling strategy.

Both males and female patients aged 25 to 70 years and known to have liver cirrhosis more than six months and met the eligibility criteria of spontaneous bacterial peritonitis. The cirrhosis was diagnosed based on ultrasonographic findings of coarse echogenicity and irregular liver margins and lab results: serum albumin less than 3.5 g/dL, serum globulin more than 3 g/dl and reverse of the albumin-globulin ratio to less than 1. The patients presenting the material symptoms of fever (temperature higher than38 o C) and abdominal pain were diagnosed with SBP and analyzed the ascitic fluid containing over 500 cells/mm3 total leukocyte count and over 250 cells/mm 3 neutrophil count. They were included in the classes A, B or C of Child-Pugh.

The study did not include patients with hemorrhagic or malignant ascites, tuberculous peritonitis, hepatocellular carcinoma, that have recently used antibiotics, known to be hypersensitive to study drugs, coagulopathy or bleeding disorder, and patients who have not given an informed consent. An informed written consent has been taken and baseline demographic information, including age, gender, residential status, duration of liver disease, comorbid conditions (diabetes mellitus, hypertension, obesity, etc) was gathered. Clinical evaluation was done and baseline tests taken, including liver function tests, serum electrolytes, coagulation profile and ultrasonic examination of the abdomen.

Randomization was performed using a lottery method with sequentially numbered, opaque sealed envelopes. The envelopes were prepared before patient recruitment by a person not involved in patient assessment or treatment. After enrollment, the next envelope in sequence was opened to allocate the patient to either Group A or Group B, ensuring allocation concealment and minimizing selection bias. Patient Group A patients received intravenous ciprofloxacin 200 mg twice daily and 1g twice daily respectively. The two treatment regimes were done over the overall duration of five days but the early response was evaluated after the 48 hours of treatment.

Ascitic fluid sampling was carried out in the aseptic conditions at the baseline and resampled after 48 hours of the antibiotic therapy beginning. The samples were forwarded to the laboratory of the hospital to measure the level of the total leukocytes count, the neutrophil count, protein as well as the glucose level in the sample. Ascitic fluid culture and antibiotic sensitivity testing were not performed or were not included in analysis. The parameters of the clinical parameters such as body temperature and abdominal pain (measured on a visual analogue scale ranging between 0 and 10) were evaluated on a regular basis. The efficacy of the treatment was evaluated, 48 hours later, on basis of falling fever (temperature normalizing), amelioration of abdominal pain and decreased neutrophil count in ascitic fluid to less than 250 cells/mm -1.

Each data were taken on a specially designed proforma without breaking the patient information in the process of recording them. In order to minimize bias on the part of the observer, the outcome assessment would be conducted by using a blinded observer who was not aware of the treatment allocation. The data obtained was inputted and analyzed with Statistical Package for Social Sciences (SPSS) version 26. Mean and standard deviation were used to present the quantitative variables (age, body mass index, laboratory values and duration of the disease) but the digital variables (gender, presence of comorbidities, Child-Pugh class and efficacy of treatment) were expressed in frequencies and percentages.

The effectiveness of the two groups was compared by chi-square test and a p-value of 0.05 or less was considered significant. The influence on treatment outcomes was identified using age, gender, obesity, duration of liver disease and Child-Pugh class which was controlled by stratification and post-stratification chi-square test.

RESULTS:

The mean age of patients in Group A was 42.8 ± 9.6 years, while in Group B it was 43.5 ± 10.1 years. There was no significant difference in the two groups with reference to age (p=0.62). Both groups were mainly comprised of male patients who constituted 72.3% of Group A and 70.3% of Group B respectively. The distribution of the patients with regards to residential status was also not sufficiently different as there were slightly more patients in urban areas in the two groups. (Table I)

Clinical characteristics like diabetes mellitus, hypertension and obesity had similar baseline clinical characteristics between the two groups. The proportions of diabetic and hypertensive individuals in Group A were 24.5 percent and 26.5 percent respectively and Group B were 29.0 percent and 31.0 percent diazepines respectively. Obesity (BMI >30 kg/m^2) was noted in 17.4% of patients in Group A and 18.7% in Group B. Neither of the two groups had a statistically significant mean body mass index as the two groups had a similar body mass index. (Table II)

Most patients of both groups were under the Child-Pugh category B and C in the case of severity of the disease. In Group A, 20.6% were in class A, 45.8% in class B, and 33.5% in class C, whereas in Group B, 18.7% were in class A, 47.7% in class B, and 33.5% in class C. This failed to be statistically significant in the difference between the two groups (p=0.81). (Table II)

Fever and abdominal pain were some of the clinical manifestations which were most predominant on presentation in both groups. In Group A and B, there was 86.5% and 88.4% fever, 82.6% and 84.5% abdominal pain among patients respectively. The mean abdominal pain score (VAS) was also the same in the two groups. (Table II)

Analysis of ascitic fluid that had not been paired revealed no big difference between the two samples. Group A and B had an average total count of cells per mm 3 of 1120 ± 240 and 1095 ± 235, respectively; there was 610 ± 260 count of neutrophils in Group A and B, respectively. (Table II)

Both groups improved, clinically and laboratory, significantly after 48 hours of treatment. But the outcomes among patients who were in the ceftriaxone group were comparatively better. The mean temperature in Group B reduced to 98.7 ± 0.6°F compared to 99.1 ± 0.8°F in Group A (p=0.01). Similarly, Group B's mean pain score dropped to 1.9 ± 1.1 from 2.3 ± 1.2 in Group A (p=0.02). Ascitic fluid neutrophil counts were substantially lower in Group B (240 ± 80 cells/mm 3) than in Group A (280 ± 90 cells/mm 3) (p=0.01). (Table III)

The percentage of patients in the ciprofloxacin and ceftriaxone groups who achieved overall treatment efficacy, which is defined as the resolution of fever, reduction of abdominal pain, and decrease of neutrophil count to less than 250 cells/mm 3 after 48 hours, was 71.0 and 79.4, respectively. Ceftriaxone demonstrated superior effectiveness, and this was statistically significant (p=0.048). (Table IV)

The stratified treatment efficacy between the ciprofloxacin and ceftriaxone is presented in Table V depending on various variables of the patients. The overall results of the study show that ceftriaxone was more effective than ciprofloxacin in the majority of subgroups. When patients were stratified by age, both age groups (patients aged =40 and patients aged >40 years) responded better to ceftriaxone but it was not statistically significant. On the same note, both male and female patients seen using ceftriaxone had a higher level of efficacy although this was no longer statistically significant. Once again, ceftriaxone demonstrated relatively superior results among patients having diabetes mellitus and hypertension but were not statistically significant. There was a borderline significant difference among patients who were not hypertensive and ceftriaxone was more effective (p=0.05). Compared to non-obese patients, ceftriaxone showed a trend of improved response even though this was

Table 1: Demographic Characteristics (n = 310)

Variable	Group A (n=155)	Group B (n=155)	p-value
Age (Mean ± SD)	42.8 ± 9.6	43.5 ± 10.1	0.62
Male	112 (72.3%)	109 (70.3%)	0.69
Female	43 (27.7%)	46 (29.7%)	
Rural	68 (43.9%)	64 (41.3%)	0.64
Urban	87 (56.1%)	91 (58.7%)	

Table 3: Post-Treatment (48 Hours)

Parameter	Group A	Group B	p-value
Temperature	99.1 ± 0.8	98.7 ± 0.6	0.01
Pain Score	2.3 ± 1.2	1.9 ± 1.1	0.02
Neutrophils	280 ± 90	240 ± 80	0.01

Table 4: Treatment Efficacy

Outcome	Group A	Group B	p-value
Effective	110 (71.0%)	123 (79.4%)	0.048
Not Effective	45 (29.0%)	32 (20.6%)	

Table 2: Baseline Clinical, Disease Severity, Presentation and Laboratory Characteristics (n=310)

Variable	Group A (Ciprofloxacin) n=155	Group B (Ceftriaxone) n=155	p-value
Comorbidities			
Diabetes Mellitus	38 (24.5%)	41 (26.5%)	0.68
Hypertension	45 (29.0%)	48 (31.0%)	0.71
Obesity (BMI >30 kg/m²)	27 (17.4%)	29 (18.7%)	0.76
BMI (Mean ± SD)	27.6 ± 4.2	28.1 ± 4.5	0.38
Child-Pugh Classification			
Class A	32 (20.6%)	29 (18.7%)	0.81
Class B	71 (45.8%)	74 (47.7%)	
Class C	52 (33.5%)	52 (33.5%)	
Clinical Presentation			
Fever (>38°C)	134 (86.5%)	137 (88.4%)	0.61
Abdominal Pain	128 (82.6%)	131 (84.5%)	0.65
Pain Score (VAS, Mean ± SD)	6.8 ± 1.5	6.9 ± 1.6	0.72
Baseline Ascitic Fluid Analysis			
Total Leukocyte Count (cells/mm³)	1120 ± 240	1095 ± 260	0.44
Neutrophil Count (cells/mm³)	610 ± 120	595 ± 135	0.39

Table 5: Stratification of Treatment Efficacy by Different Variables (n=310)

Variable	Category	Ciprofloxacin Effective n/N (%)	Ceftriaxone Effective n/N (%)	p-value
Age (years)	<=40	48/65 (73.8%)	52/63 (82.5%)	0.21
	>40	62/90 (68.9%)	71/92 (77.2%)	0.18
Gender	Male	80/112 (71.4%)	88/109 (80.7%)	0.11
	Female	30/43 (69.8%)	35/46 (76.1%)	0.48
Diabetes Mellitus	Yes	25/38 (65.8%)	30/41 (73.2%)	0.46
	No	85/117 (72.6%)	93/114 (81.6%)	0.09
Hypertension	Yes	30/45 (66.7%)	34/48 (70.8%)	0.67
	No	80/110 (72.7%)	89/107 (83.2%)	0.05
Obesity	Yes	17/27 (63.0%)	19/29 (65.5%)	0.83
	No	93/128 (72.6%)	104/126 (82.5%)	0.06
Child-Pugh Class	Class A	24/32 (75.0%)	25/29 (86.2%)	0.31
	Class B	52/71 (73.2%)	61/74 (82.4%)	0.18
	Class C	34/52 (65.3%)	37/52 (71.1%)	0.04
Disease Duration	=12 months	44/60 (73.3%)	49/58 (84.5%)	0.12
	>12 months	66/95 (69.5%)	74/97 (76.3%)	0.28

not found to have a significant value in obese patients. Ceftriaxone was more effective in all classes (Child-Pugh classification) when stratified by the severity of the disease. Interestingly, statistically significant difference was found to be in Child-Pugh class C patients (p=0.04) as ceftriaxone is more effective in patients with advanced liver diseases. On the same note, patients who had a shorter (=12 months) and longer (>12 months) period of disease exhibited better outcomes when using ceftriaxone but the differences were not significant.

DISCUSSION:

The current paper has contrasted the effectiveness of intravenous ciprofloxacin and intravenous ceftriaxone in treating SBP. We found that both antibiotics work, but ceftriaxone was much more effective than ciprofloxacin (79.4% vs. 71.0%, p=0.048). This is in line with the current pattern in the practice of SBP, with third-generation cephalosporins as first-line treatment.

The average age of the patients in the two groups studied was about 43 years in the present study, and there was no statistical significance between them. This is similar to those of recent studies in which the average age of patients with SBP was 40-50.[11,12] As an example, Sheikh et al. (2024) found an average age in the ciprofloxacin and ceftriaxone groups to be 41.71 ± 3.51 and 39.11 ± 6.21 respectively, keeping it close to our results.[11] On the same note, a multicenter observational study showed the mean age of patients was in the fourth decade of life indicating early development of complications in chronic liver disease.[12]

Male dominance that was evident in our research (around 70% in both groups) is also in line with the past literature. Other studies have documented male predominance between 65 percent to 80 percent in SBP patients, which is probably explained by the greater prevalence of chronic liver disease in males.[13,14] This similarity indicates that, our population of study qualifies to be representative of the average SBP demographic profile.

In terms of baseline comorbidities (i. e., diabetes mellitus, hypertension, obesity etc.), no significant differences were found between the two groups. The latter is corroborated by recent research that shows that comorbid conditions are prevalent among patients with cirrhosis without any significant effect on the immediate reaction to antibiotic treatment in SBP.[14,15] Similar treatment outcomes were also found within the subgroups stratified on the basis of comorbidities, implying that the effectiveness of antibiotics stays the same irrespective of other related conditions.[14]

The majority of patients in our research were in the Child-Pugh classes B and C, which indicated an advanced liver disease. The distribution is comparable to that of recent papers with most of the cases of SBP being reported in patients with decompensated cirrhosis.[16] Notably, our stratification test indicated that ceftriaxone was much more active in association with patients whose Child-Pugh class was C (p=0.04). This can be underpinned by recent evidence indicating that patients with severe liver disease might be more suitably treated with cephalosporin-based therapy as the coverage to more widespread pathogens and patterns of resistance is enhanced.[17] This presentation of SBP, which included fever and pain in the abdominal area in our study, was in agreement with the findings reported previously. It has been demonstrated that in about 70-90 percent of cases there is a fever and 60-80 percent of the patients had abdominal pain.[18] His correlation of the presentations among studies underscores the need to keep a high index of suspicion with SBP among cirrhotic patients having these symptoms. The analysis of baseline ascitic fluid in our study showed that the number of leukocytes and neutrophils was the same in the two groups demonstrating the same severity of the disease at presentation. This is in line with typical diagnostic criteria of SBP, and is in agreement with recent studies results, which show at diagnosis, mean neutrophil counts were generally above 250 cells/mm 3.[18,19]

The two groups improved significantly after a period of 48 hours of treatment in terms of clinical and laboratory results. Nevertheless, ceftriaxone reportedly showed better results regarding the decrease of temperature, pain score, and neutrophil count. The results of this study are similar to those of a randomized controlled trial which revealed quicker resolution of infection by cephalosporins than the other antibiotics.[20] Additionally, studies on response-guided therapy have underscored the need to reassess after 48 hours, and cephalosporins had higher episode rates of early response.[11] Our entire efficacy of 79.4% with ceftriaxone and of 71.0% with ciprofloxacin is comparable to the recent literature. According to Sheikh et al. (2024), ciprofloxacin and ceftriaxone were nearly equally effective, implying that these two drugs can be an option.[11] Nevertheless, other researchers have reported a marginally better efficacy of cephalosporins, the cure rates just vary between 75 and 85%.[20] Bacteriological cure of about 79%93% was also reported in a meta-analysis using third generation cephalosporin.[21] This phenomenon of relatively lower effectiveness of ciprofloxacin at the time of our study could be explained by the growth of fluoroquinolone resistance. Recent reports have indicated an increase in the number of quinolone-resistant organisms in SBP, especially in hospitalized patients.[22] With this trend, the effectiveness of ciprofloxacin is lowered and further contributes to the use of cephalosporins as first-line therapy. Ceftriaxone on the contrary is broad-spectrum against most common Gram-negative bacteria like Escherichia coli and Klebsiella pneumoniae.[23]

The other factor that should be considered is the evolving microbiological spectrum of SBP. According to recent studies, the proportion of Gram-positive infections and multidrug-resistant organisms have been reported to be increasing.[24]

This transformation can affect the physical performance of traditional antibiotics and the need to regularly analyze the local resistance trends. However, ceftriaxone is still effective in the majority of cases as it has a wide antimicrobial spectrum. Stratification analysis of our study also presented the fact that ceftriaxone was found to be more effective in most subgroups such as age, gender and comorbid conditions. These differences were not significant but the trend shows favour towards ceftriaxone. The same pattern has been observed in recent studies where treatment response rates were always greater with cephalosporins in different groups of patients.[14] This indicates that ceftriaxone can deliver more credible results with different patients. Interestingly, there was no significant difference in the duration of diseases concerning treatment response in our study. Te results were similar in patients whose disease was longer or shorter. It does so in line with recent reports that suggest that severity of liver dysfunction, as opposed to disease duration is a more significant predictor of treatment outcome in SBP.[17]

Guideline recommendations also support the superiority of ceftriaxone that was identified in our study. There is a lot of evidence-based information that implies the use of three-generation cephalosporins as the first-line treatment due to their effectiveness and good resistance.[23] Also, research has indicated that, in SBP, timely management using the right antibiotics can greatly decrease mortality ad complications.[25] Although these findings have been made, ciprofloxacin can also be used as an alternative especially in resource-limited situations. Its benefits include reduced cost and orally available property, which can boost patient adherence. Its application should however be based on local resistance patterns to achieve best results. Our research has several strengths, such as a randomized controlled design, a sufficient sample size, and an analysis of a variety of variables. Limitations: Nevertheless, there also are some limitations that are to be taken into consideration. This research design involved the use of only one center; hence, it might not be generalizable. Moreover, microbiological culture and sensitivity pattern did not undergo extensive studies, which would have given additional insights into antibiotic resistance. Also short-term assessment only at 48 hours, no recurrence/mortality follow-up, and no cost-effectiveness analysis were other limitations.

CONCLUSION:

In conclusion, spontaneous bacterial peritonitis is a serious and potentially fatal liver cirrhosis syndrome that requires prompt diagnosis and effective antibiotic therapy. Although ceftriaxone showed significantly more efficacy than ciprofloxacin after 48 hours of treatment, the current investigation found that intravenous ciprofloxacin and intravenous ceftriaxone were similarly beneficial in managing SBP. Not only did stronger resolution of clinical symptoms such as fever and abdominal pain accompany ceftriaxone but also greater decrements of neutrophil count in the ascitic fluid. In addition, it was also more effective in liver disease patients with advanced liver disease, especially in patients in Class C of the Child- Pugh classification.

Even though ciprofloxacin can still be used as an alternative particularly in resource constrained facilities, it is less effective and the emergence of increasing antibiotic resistance can restrict its usage as a first-line agent. Hence, according to the results of the current research, intravenous ceftriaxone is a treatment of choice between the two types of the empirical treatment of spontaneous bacterial peritonitis, in cirrhotic patients. Nearby diagnosis and proper choice of antibiotic are vital towards decreasing morbidity, mortality, and healthcare load in relation to SBP. It is advisable that further multicentric studies be carried out to determine long-term effects and resistance patterns, which could be utilized to consider different populations in a bid to optimize their treatment methods.

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Authors Contribution:
Hafiza Munam Akhtar: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Arif Mehmood Bhatti: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.

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Original Article **Open Access**

Effectiveness of Post-Burn Finger Contracture Release with 5-Flap Z-Plasty without Graft

Zahida Younas, Shumaila Yousaf, Bushra Akram Mughal, Urwa Tanveer Ahmad, M Behram Abbas, Saqib Shakoor

Abstract

Objective: To determine the functional outcome of the 5-flap Z-plasty technique without skin graft in terms of mean improvement in extension lag angle in the management of post-burn finger contractures.

Study Design and Setting: A prospective interventional (pre-post) study was conducted at Allied Burn and Reconstructive Surgery Centre, Allied Hospital, Faisalabad, Pakistan.

Methodology: A total of 65 patients with post-burn linear band soft tissue contracture of fingers were enrolled by consecutive sampling. Patients of both genders aged 4–40 years with supple joints, pliable surrounding skin, and moderate contractures were included. All patients underwent contracture release using a 5-flap Z-plasty without a skin graft under local or general anaesthesia.

Results: The study included 65 individuals, with a mean age of 15.75 ± 8.91 years and a male predominance (56.9%). Scald burns were the most prevalent cause (55.4%), with 52.3% involving multiple digits, including the dominant hand. The pre-operative extension lag angle of 62.46 ± 12.25° significantly reduced to 1.08 ± 2.57° post-surgery (p = 0.001). The mean improvement in extension lag was stable across subgroups, with no statistically significant differences by gender (p = 0.159) or age group (p = 0.113). The association between the finger involved and the occurrence of superficial necrosis was found to be statistically significant (p = 0.003).

Conclusion: The 5-flap Z-plasty technique without skin graft achieves significant functional improvement in post-burn finger contractures with excellent flap viability, no donor site morbidity, good colour match, and early rehabilitation.

Key Words: Burns; Cicatrix; Finger Injuries; Surgical Procedure

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INTRODUCTION

A burn injury is the coagulative destruction of the skin and its underlying tissue by thermal, chemical, electrical or mechanical energy.[1] post-burn complications range from local wound issues to systemic, life-threatening conditions resulting in long-term physiologic and psychological complications.[2]

Burn contractures are the most common postburn complication and are present in 18-50% of all burn survivors. The severity of a burn contracture depends on several factors such as, location and depth of the burn, timing of surgical or nonsurgical treatment, post-injury splinting, hand physiotherapy and scar care during the maturation process.[3]

Post-burn finger contractures represent one of the most devastating complications of thermal injury, frequently leading to physical deformity of hand, post burn web creep, restriction of range of joint motion and hence affecting the ability to perform daily activities independently and overall quality of life (QoL). Physical deformities also lead to psychiatric issues like low self-esteem and social detachment Thus, an appropriate and timely surgical intervention followed by rehabilitation from hand therapist is mainstay of treatment to prevent complete joint ankylosis.[4]

Proximal inter-phalangeal joint PIPJ flexion contractures were classified by Stern et al. into three grades. In grade I, the contracture at the PIPJ is correctable by passive flexion of the MCPJ, is considered mild. In grade II, the PIPJ flexion contracture is partially correctable with passive MCPJ flexion and is referred as moderate degree. A grade III contracture is fixed at the PIPJ regardless of the position of the MCP and is considered the severe variety.[5]

Contracture release followed by coverage with split and full thickness skin grafts has long been the mainstay of both initial and secondary burn surgeries. Full thickness skin grafts are considered more efficient than split-thickness grafts. After reconstruction Kirschner wire immobilization is mandatory to maintain full extension during the soft tissue healing process. This graft-based reconstruction imparts significant challenges including graft loss, differences in color and texture, secondary graft contraction and joint stiffness due to prolonged immobilization.[6-8]

Locoregional flaps are surgical techniques used to release scar contractures by transposing rotating, or advancing adjacent, healthy tissue into the released area. They are preferred over skin grafts because they provide good color/texture match, have less risk of secondary contraction, and grow with the patient.[9]

Z-plasty, single/multiple is a common reconstructive surgical technique used for scar revision and contracture release. It involves the transposition of two opposing triangular flaps that then changes the direction of a scar. Multiple Z-plasties breaks a long scar into series of triangular flaps (forming a "zig-zag" pattern) that are transposed. Z-plasty is an excellent option for linear bands that are surrounded by healthy tissue to restore normal contour and to provide a good color match. But there are some limitations of this technique. As the degree of contracture and surrounding tissue scarring increases the chances of flap transposition decreases due to inelastic nature of scar, also chances of flap necrosis increases due to poor blood supply of scarred tissue.[10-12]

The five-flap Z-plasty, frequently referred to as the “Jumping Man Flap”, utilizes a central Y-to-V advancement flap between two opposing Z-plasties and provide approximately 125%gain in scar length while evenly distributing tension across various tissue vectors.[12] Recent comparative evidence has confirmed its superiority in finger web contractures, with five-flap Z-Plasty yielding a significant improvement in finger abduction angles (19° ± 4°) compared to double z-plasty. Analysis of post-burn contracture release has shown that five-flap Z-plasty has mechanical effectiveness across various anatomical sites.[13]

Trapeze flap, square flap and cross finger flap are some other reconstructive options for coverage of defect after contracture release; however, each technique has its limitations and drawbacks.[14-15]

Moderate and severe degree of contractures pose a significant challenge and cannot be released with multiple z-plasty without incorporating skin graft.[5] The rationale of the present study is to address the paucity of evidence regarding the effectiveness of the 5-flap Z-plasty technique without adjunctive skin grafting in terms of mean improvement in extension lag angle, in the management of moderate-degree post-burn finger contractures. The 5-flap technique offers a compelling alternative that avoids prolonged Kirschner wire immobilization, enables early rehabilitation, and facilitates an earlier return to normal daily activities.

METHODOLOGY

A prospective interventional (pre-post) study was conducted at Allied Burn and Reconstructive Surgery Centre, Allied Hospital, Faisalabad, Pakistan, over a period of 15 August 2025 to 15 April 2026. Ethical approval was obtained from the Institutional Ethical Review Committee with Reference number 48 ERC/FMU2025-26-124, Allied Hospital, Faisalabad, and the College of Physicians and Surgeons Pakistan (CPSP) before commencement of the study. Written informed consent was obtained from all adults and parents/guardians for pediatric patients. A total of 65 patients were enrolled using consecutive sampling. Sample size was calculated using the WHO single-mean calculator, based on a population mean ± SD of 19 ± 4 degrees, a 95% confidence interval, and a margin of error of 1, yielding a minimum sample size of 65.[13]

Inclusion criteria comprised patients of both genders age ranging from 4 to 40 years with post-burn linear band type soft tissue finger contracture, pliable surrounding skin, supple joints, and moderate degree of contracture. Exclusion criteria were post-electric burn contracture, ankylosed joints, surrounding scarred skin, and previously operated cases.

Pre-operative assessment included documentation of demographics, hand dominance, duration of contracture, number of fingers involved, degree of scarring, and pre-operative extension lag angle measured using a standard goniometer. All patients underwent contracture release with 5-flap Z-plasty without skin graft under local or general anesthesia as determined by patient factors. Hemostasis was secured, and wounds were closed.

Dressing was changed on the first postoperative day to assess flap viability. Patients were discharged on 2nd postoperative day and reviewed weekly for one month, then fortnightly for three months. At each visit, wound healing, post-operative extension lag, and complications were recorded. Sutures were removed at 10–14 days. All patients were referred to a physiotherapist for physiotherapy after suture removal. Improvement in extension lag angle was calculated as the difference between pre- and post-operative values at 3 months. Data were recorded on a structured proforma.

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables (age, duration of contracture, pre- and post-operative extension lag angle,

and improvement in extension lag angle) were expressed as mean ± standard deviation. Categorical variables (gender, mode of burn, involved digits, K-wire usage) were reported as frequencies and percentages. Paired samples t-test was applied to compare pre- and post-operative extension lag angles. Effect modifiers (age group, gender, number of digits) were controlled by stratification. Post-stratification, an independent samples test was applied to assess their effect on the outcome. A p-value of =0.05 was considered statistically significant.

RESULTS

A total of 65 patients were recruited in this study. There was slight male predominance 37(56.9%) than female 28(43.1%). Pediatric patients of 4-14 years and adults of 15-40 years age groups were 33(50.8%) vs.32(49.2%,) respectively, with mean age 15.75 ± 8.91 years. The mean contracture duration was 2.98 ± 2.41 years. Dominant hand was involved in 34 (52.3%) cases. Scald burns were observed in substantial proportion (55.4%), followed by flame burns (41.5%), and contact burns (3.1%). K-wire fixation was employed in 21.5% of patients. Multiple digits were involved in comparatively higher number of patients (52.3%) than single digit (47.7%) while only 30.8% patients demonstrated superficial necrosis (Table 1). Regarding involved digits, index finger was the most common digit involved (21.5%), followed by the little finger (15.4%). Isolated thumb and ring finger involved in 4.6% of study cohort while the middle finger was involved only in 1.5% of cases. Involvement of adjacent digits such as middle and ring finger together or ring with little finger together was observed in 15.4% and 12.3% of cases respectively. However, combined involvement of three digits was observed only in 3.1% of patients (Table 2). The comparison of pre-operative and post-operative extension lag angles demonstrated a significant improvement from pre-operative extension lag angle (62.46 ± 12.25°) to post-operative extension lag angle (1.08 ± 2.57°) with mean improvement in extension lag angle of 60.82±11 with a statistically significant p-value (0.001), highlighting improved digital extension (Table 3). Female patients exhibited slightly higher mean improvement in extension lag angles (63.57 ± 10.17°) as compared to males (59.73 ±11.17°). However, this difference was not statistically significant (p = 0.159). Pediatric patients achieved slightly higher mean improvement (63.47 ± 8.96°) as compared to adults (59.22 ± 12.25°), with no statistically significant difference across age groups (p= 0.113). Patients with single affected digit demonstrated higher mean improvement of extension lag angles (62.90 ± 7.72°) in comparison to those with multiple digits involved (60.00 ± 13.02°) with difference not statistically significant p = 0.284(Table 4)

There were no cases of complete flap necrosis, only superficial flap tip necrosis was found that was managed conservatively, indicating a highly satisfactory surgical outcome. None of the patients required subsequent skin grafting and revision surgery.

DISCUSSION

Table I: Baseline demographic and clinical characteristics (n=65).

Variable	Category	n (%) / Mean ± SD
Gender	Male	37 (56.9%)
	Female	28 (43.1%)
Age (years)	Mean ± SD	15.75 ± 8.91
Age group	Pediatric (4–14 yrs)	33 (50.8%)
	Adult (15–40 yrs)	32 (49.2%)
Duration of contracture (years)	Mean ± SD	2.98 ± 2.41
Dominant hand involvement	Yes	34 (52.3%)
Mode of burn	Scald	36 (55.4%)
	Flame	27 (41.5%)
	Contact	2 (3.1%)
K-wire immobilization	Yes	14 (21.5%)
	No	51 (78.5%)
Number of involved digits	Single	31 (47.7%)
	Multiple	34 (52.3%)
Necrosis	Yes	20 (30.8%)
	No	45(69.2%)

Table 2: Distribution of involved finger(s) (n=65).

Finger(s) Involved	N	%
Thumb	3	4.6
Index	14	21.5
Middle	1	1.5
Ring	3	4.6
Little	10	15.4
Middle + Ring	10	15.4
Index + Middle	5	7.7
Ring + Little	8	12.3
Thumb + Index	6	9.2
Index + Middle + Ring	2	3.1
Thumb + Little	3	4.6
Total	65	100.0

Table 3: Pre-operative, post-operative and improvement in extension lag angle (n=65)

Variable	Mean ± SD (degrees)	CI (95%)	p-value
Pre-operative extension lag angle	62.46 ± 12.25	58.70-45.65	0.001
Post-operative extension lag angle	1.08 ± 2.57		
Mean improvement in extension lag angle	60.82±11		

Table 4: Effect of modifiers on improvement in extension lag angle (post-stratification independent samples t-test)

Variable	Category	Mean Improvement ± SD (°)	p-value
Gender	Male (n=37)	59.73 ± 11.17	0.159
	Female (n=28)	63.57 ± 10.17	
Age group	Pediatric (n=33)	63.48 ± 8.96	0.113
	Adult (n=32)	59.22 ± 12.25	
Number of digits	Single (n=31)	62.90 ± 7.72	0.284
	Multiple (n=34)	60.00 ± 13.02	

Figure 1: Pre-operative image of 23 yr/ F with post burn thumb contracture having pre-operative extension lag of 55° showing marking of 5-flap Z-plasty

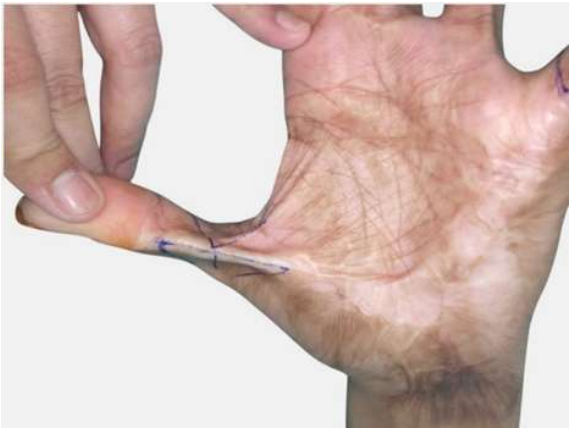


Figure 2: Immediate post-operative image demonstrating complete release with 0°post operative extension lag

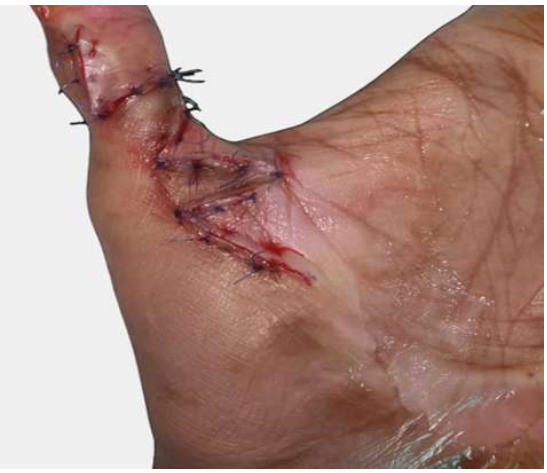
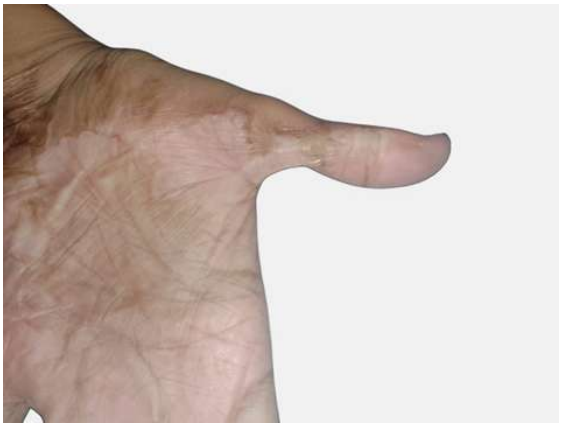


Figure 3: Post operative image demonstrating wound healing, complete contracture release having no extension lag, good color match to surrounding skin and scar characteristics.



The present study shows that five-flap Z-plasty without skin grafting is an extremely effective method of correcting post-burn finger contractures of moderate degree. In a group of 65 patients, the mean extension lag angle reduced from 62.46°±12.25 preoperatively to 1.08°±2.57 postoperatively, indicating nearly complete restoration of digital extension. This level of correction is consistent with the biomechanical basis of the five-flap technique, which includes a central Y-V advancement flap between two opposing Z-plasties to get greater longitudinal lengthening than conventional designs.[16] The lack of total flap necrosis, as well as the absence of the need for secondary skin grafting or revision surgery, lends credence to the reliability and efficacy of this reconstructive method as a stand-alone therapy option for digital burn contractures. The positive effects indicate that the treatment provides sufficient vascularity, consistent wound healing, and effective tissue repair without requiring further corrective techniques. Moreover, the removal of secondary procedures reduces patient morbidity, shortens recovery time, lowers healthcare costs, and enhances overall functional and aesthetic outcomes. The flap's persistent viability demonstrates the technical safety and resilience of the reconstructive technique for managing post-burn digital deformities and contractures. Overall, these findings support the surgical technique's function as a reliable and feasible choice for reconstructing moderate degree post burn contractures.

When compared to this study, our findings support the growing body of evidence recommending five-flap Z-plasty for post-burn contractures. Yang et al. found that five-flap Z-plasty improved abduction angle by 19° ± 4°, outperforming double Z-plasty by 12° ± 2°, and corrected web slope more effectively.[13] Our study supports these findings by confirming that when applied to finger contractures without adjunctive grafting, five-flap Z-plasty provides comparable functional restoration while avoiding donor-site complications.

The avoidance of skin grafting provides a significant advantage in digital reconstruction. Traditional contracture release has commonly relied on split-thickness or full-thickness skin graft coverage. However, graft-based techniques are associated with graft loss, color and texture mismatch, secondary contraction, and donor-site morbidity.[11] Alsaif et al. conducted a systematic review and meta-analysis and found that, while full-thickness skin graft provide better

results than split-thickness skin graft, both modalities are susceptible to suboptimal aesthetic and functional outcomes.[7]

In this study, the use of local flaps eliminated the requirement for graft harvest completely in moderate degree of finger contractures, and no patient needed secondary grafting. This is consistent with the larger shift toward flap-based reconstruction in post-burn hand surgery, as vascularized tissue not only provides superior pliability but also reduces the risk of secondary contraction when compared to graft.[16]

The present study's demographic profile revealed a slight male predominance, a mean age of 15.75 years, and scald burns as the leading etiology, which is consistent with recent epidemiological descriptions of hand and finger contractures in post-burn populations, which consistently report male predominance, high incidence in pediatric age groups, and scald burns as a common cause[17-18]. Particularly, we found no significant differences in outcomes by gender, age group, or whether single or multiple digits were involved. This indicates that five-flap Z-plasty is widely applicable in both pediatric and adult populations, as well as at varying levels of digital involvement. The finding that pediatric patients achieved marginally greater improvement than adults, although without statistical significance, is consistent with the known plasticity of pediatric tissue and the potential for stronger remodeling in younger patients.

This study's complication profile emphasizes the safety of this method. Superficial flap tip necrosis was found with no cases of complete necrosis, the results are comparable to those reported in recent large series of local flap reconstruction for burn contractures. A study reported a 10.8% overall complication rate among 243 patients undergoing local flap reconstruction for post-burn contractures of the extremities and neck, with re-contracture occurring in 3.8% and flap tip necrosis in 1.3%.[19]

When compared with loco-regional flaps, 5-flap Z plasty provides several benefits for post burn finger contractures. The keystone flap works well for wide, oval-shaped wounds but depends on healthy underlying blood vessels. In burned fingers, these vessels may be damaged, making the flap less reliable.[14] The five-flap Z-plasty is random pattern flap and can be used even in moderately scarred skin. The square flap is good for releasing contractures in the web spaces between fingers, but it is not designed for linear bands on the front (volar) surface of a finger[20]. The five-flap Z-plasty works better for linear band like contractures along the finger. The trapeze flap gives good long-term results, but it needs a broad base of healthy skin. On a burned finger, there may not be enough unscarred tissue.[15] The five-flap Z-plasty effectively utilizes lateral skin expansion around the scar, making it more practical.

Strengths of this study were found to be due to the geometry of five-flap Z-Plasty without skin grafting to release post burn moderate degree of finger contractures. Followed by another strength of this study is the generalizability is increased by encompassing both pediatric and adult patients in the present study. The standardized post-surgical rehabilitation protocol, which includes physiotherapy for all study participants after removal of sutures, ensures that the stated findings are a result of the surgical technique and not of differences in rehabilitation. Objective goniometric measurement of extension lag angles provides measurable evidence of functional recovery in patients.

Limitations: There are various limitations to this present study that require to be considered. First of all, small sample size and single center study limit the generalizability to broader segments of the population with multiple demographic and clinical characteristics of the population. The follow-up duration was limited to only 3 months after surgical procedure, which did not enable researchers to analyze the long-term functional effects, recurrence of the contracture, and long-lasting sustainability of the surgical therapy. The lack of a comparison group undergoing other surgical techniques (e.g., grafting of the skin and convention Z-plasty) limits the ability to directly compare the efficacy of the five-flap Z-plasty techniques with previous surgical procedures. Lastly, findings were assessed only by objective goniometric measurements of extension lag angle, removing reports of patient's findings measures, functional scoring systems, and quality of life (QoL) indicators that would allow more comprehensive assessment of surgical success from the perspective of the patient.

CONCLUSION

The study found that surgical release of post-burn finger flexion contractures with 5-flap Z-plasty technique yielded good functional outcomes with minimal complications. The technique restored near-complete finger extension in all patients, irrespective of gender, age, or level of digital involvement. In particular, the technique is highly effective for moderate degrees of contracture with surrounding lateral skin expansion and supple joints. These contractures are less likely to be released with multiple z-plasty without incorporating skin graft. This technique's superiority can be attributed to the use of the 5-flap Z-plasty, which provides up to 125% of length gain, compared with roughly 75% with standard Z-plasty. The high rate of flap viability and the absence of total necrosis illustrate the technique's reliability. Furthermore, the low rate of wound complications, like flap tip necrosis, all minor and managed conservatively, contributes to its safety profile. The standardized initiation of physiotherapy following suture removal on 10-14th post-operative day most certainly contributed to the positive functional outcomes. K-wiring was done only in 14(21.5%) cases for 10-14 days to break joint memory, mostly in pediatric population where compliance to external splintage was a problem. None of the examined modifiers (age, gender and number of fingers involved) had a significant impact on recovery, demonstrating consistent results across patient

groups. The surgical strategy is an effective solution for post burn moderate degree digital flexion contractures particularly in conditions where conventional Z-Plasty will not release contracture completely without incorporating graft. It also avoids prolonged immobilization with K-wiring and results in early recovery, with good color and texture match. All this leads to start of early rehabilitation by hand therapist and back to their daily life activities by patient.

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Authors Contribution:
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Bushra Akram Mughal: Introduction and Methodology.
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Original Article **Open Access**

Comparison of the Neurological Outcome of Early Vs Late Surgery for Cervical Spinal Cord Injury

Aqib Rauf, Muhammad Shahid

Abstract:

Objective: To evaluate the differences in the neurological outcome of early and late surgical intervention in cervical spinal cord injury (CSCI) patients.

Study Design & Settings: Prospective cohort study at Department of Neurosurgery, Bahawal Victoria Hospital, Bahawalpur.

Methodology: Eighty-eight patients aged between 20-60 years of age and presenting with the acute cervical spinal cord injury within the 12 hours of injury were taken. Patients were categorized into two groups according to the timing of the surgery; early surgery (less than 24 hours) and late surgery (greater than 24 hours). The assessment of neurological status was done on the basis of the American Spinal Injury Association (ASIA) preoperative and one-month postoperative. Neurological recovery was defined as the improvement of one or more by one or two ASIA grades. The analysis of the data was done using SPSS version 25.0, and the chi-square test was used to compare the results.

Findings: A statistically significant difference between the early and late surgery groups was found with 56.8% and 31.8% patients recovering neurologically respectively ($p = 0.02$). Incomplete injuries (B-D) patients showed a superior recovery in comparison to the complete injuries (ASIA grade A).

Conclusion: Timely surgery is within the first 24 hours which is linked to a significantly better neurological outcome in patients with a cervical spinal cord injury. Surgical decompression to improve functional outcomes should be given priority to improve long-term disability reduction.

Keywords: Cervical spinal, cord injury, Early surgery, Late surgery, ASIA score

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INTRODUCTION:

SCI is a serious debilitating neurological disorder that has a high morbidity, mortality, and long-term consequences on disability in the global society. According to recent epidemiological investigations, the worldwide rate of SCI has been on the increase, which can be mostly attributed to the growth of motorization, urbanization, and aging. Cervical spinal cord injury (CSCI) is the most dreadful type, which is a significant percentage of neurological losses and functional disability following the trauma. The cervical region is the area that is the most susceptible to high-energy forces and partly because of its anatomical range of mobility, it is the most frequent area of involvement in traumatic cases of SCI. Accidents like road traffic, height falls, as well as injuries during sports activities are still the leading causes in the world, however, the trend changes depending on socioeconomic and geographical environment.[1,2]

The pathophysiology of SCI is the initial mechanical insult and a secondary series of injury mechanisms, which include ischemia, inflammation, excitotoxicity, oxidative stress, and apoptosis. The mechanisms secondary should be able to intensify neuronal damage and have a major impact on neurology. Notably, this dynamic injury condition provides a period of critical therapeutic opportunity that devises, through prompt treatment, the ability to reduce additional injury and increase recovery. One of the pillars of management is surgical debridement of the spinal cord that is intended to alleviate mechanical compressibility, restore spinal height, and enhance the perfusion of the spinal cord.[3,4]

Although improved methods of surgery and critical care have emerged, the question of when to operate has been a significant issue of extensive discussion. Conventionally, delayed surgery was commonly desirable because it was believed that working on a spinal cord, which was acutely injured and edematous and likely to raise the chances of intraoperative complications, and exacerbate the neurological losses. Nevertheless, overwhelming evidence that has been building over the last decade, is questioning this conservative practice. The idea of time is spine has been coined, based

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upon the notion that early surgical decompression- often considered as the 24-hour window post-injury- can result in better neurological outcomes and less overall systemic morbidity.[5,6]

A range of recent studies have shown that early surgery offers a superior functional outcome as compared to late surgery. An example is that prospective and observational studies have demonstrated that early decompression can lead to an important increase in the neurological scores and motor recovery in short- and in the long-term follow-up. The suggested mechanisms are accelerated restoration of blood flow to the spinal cord, minimization of the ischemic tissue, and attainment of continuation of compression-associated harm. Moreover, by minimizing complications like pneumonia, deep vein thrombosis, and pressure ulcers, early surgery can help to achieve earlier mobilization and rehabilitation.[7,8] However, not every evidence has a consistent support of early intervention. According to some recent research, although early surgery can enhance neurological outcome in some patient groups - especially those with incomplete injuries - it does not necessarily correlate with a better quality of life or functional independence. Delayed surgery can compare to the same neurological outcomes in older patients or those with high comorbidity with a possible lower risk in perioperation. Moreover, some of these subpopulations, including individuals with complete spinal cord wounds, might also show minimal neurological recovery in spite of the time of surgical intervention, questioning the universality of the early intervention guidelines.[9,10]

Since this question of the clinical relevance of surgery timing and the validity of the surgery timing remains controversial, there is a need to objectively assess the neurologic outcomes of early versus late surgery. Knowing such differences can inform clinical decision-making, maximize patient care, and help to create evidence-based protocols specific to the regional healthcare systems. Consequently, this research will focus on comparing the neurological patient outcomes in early and late surgery cervical spinal cord injury with emphasis on the enhancement of the outcomes in the local community.

METHODOLOGY:

The study was carried out as a prospective cohort study from 30th January 2026 to 29th April 2026, following the permission granted by the Institutional Ethical Review Committee (Ref. No. 473/DME/QAMC Bahawalpur dated 15-10-2025) at the Department of Neurosurgery in the Bahawal Victoria Hospital. The purpose was to compare neurological outcomes in those operated upon early and late to cervical spinal cord injury (CSCI). The study had 88 patients of which 44 patients were in each group. The sample size was determined with the use of WHO sample size calculator based on the 95% confidence interval, 80% study power and the expected rates of neurological recovery of 58 and 28 percent in early surgery group and late surgery group respectively. Eligible patients who had presented during the study period were recruited by a non-probability consecutive sampling method.

Eligibility was determined on patients of both sex aged 20-60 years who had acute cervical spinal cord injury and whose injury happened within 12 hours of trauma. Employing clinical examination and magnetic resonance imaging (MRI) confirmed a diagnosis of cord edema, ligamentous disruption or soft tissue injury. Only patients with motor-incomplete injuries but with preexisting canal stenosis without fractures and dislocations were considered. The participants were not to be included in case of severe traumatic brain injury (Glasgow Coma Scale 13) or penetrating spinal injuries, non-traumatic spinal pathology, separate spinal injury, polyneuropathy, impaired consciousness or hemodynamic instability, to eliminate confounding variables to the minimum. Baseline information regarding every patient (including demographics (age and gender), anthropometrics (height and weight as well as body mass index), and clinical features (duration and mode of trauma, neurological level, and ASIA grade) was obtained with prior informed written consent. Social-economic factors like occupation and home were also documented. Patients were then categorized into two groups on basis of timing of surgery. Individuals who received surgical intervention within 24 hours of injury were classified as the early surgery group and those who had surgery after 24 hours of injury as a result of delayed presentation, delayed diagnosis, or logistical reasons were classified as the late surgery group. Consistency and minimized bias of the operator were achieved by having all surgical procedures done by consultant neurosurgeons and a minimum of three years post-fellowship to reduce bias. Anterior, posterior or a combination of both surgeries was performed, depending on the character and type of injury necessary to accomplish sufficient spinal cord decompression and stabilization. They were taken through the optimization and stabilization of all the patients before surgery.

The American Spinal Injury Association (ASIA) impairment scale was used to determine neurological performance preoperative and in the course of follow-up. The principal measure of outcome was the neurological recovery which was articulated as increase in grade of at least one on the ASIA scale. The length of the follow-ups was 4 weeks after the operation, and the patients were evaluated every two weeks with an aim to measure the neurological enhancement and identify any complication. The end of the three months follow-up was the time when the final neurological outcome was registered.

All data gathered were inputted into a preconstructed proforma and were analyzed to determine their use through the Statistical Package of the Social Sciences (SPSS) version 25.0. Continuous variables: Age, height, weight, body mass index, and time of trauma were presented as mean + SD

and categorical variables: Gender, MOI, surgical approach, ASIA grades and neurological recovery represented frequencies and percentages. The Shapiro-Wilk test was used to test the data distribution normality. Chi-square test (or Fisher exact test where valid) was employed in comparison of neurological recovery in the two groups. A p-value below 0.05 was taken as statistically significant.

Moreover, stratification was done to regulate some possible effect modifiers like age, gender, body mass index, duration and trauma mode, neurological level, pattern of injuries, and level of baseline ASIA, and surgical method. Post stratification was done to identify significant differences between the two groups using the chi-square or the Fisher exact test with a p-value of 0.05 being taken as significant. The reliability and validity of the study findings were guaranteed by using this methodological approach which reduced the potential bias and confounding factors.

RESULTS:

The average age of the early surgery was 38.5 10.2 years and that of the late surgery was 40.1 11.3 years and there was no statistical difference ($p > 0.05$) between the two groups. Most patients in the early group and in the late group were male with 72.7 percent and 68.2 percent respectively. (Table 1). Regarding clinical aspects, the mode of injury was the most frequent in both groups, i.e., road traffic accidents, followed by falls. The predominant pattern was that of having most patients with level of injuries of 4 and below with most cases being that of central cord syndrome. (Table 2). According to the groups, there was no difference in the distribution of surgical approaches (anterior, posterior and combined) and the most prevalent method was the anterior one. The baseline characteristics did not show statistically significant difference between the groups thus showing that both groups are similar before the interventions ($p > 0.05$). (Table 3). The baseline neurological status which was examined by the use of the American Spinal Injury Association (ASIA) grading system had the same distribution in both groups. There were 22.7% ASIA grade A patients, 27.3% grade B, 31.8% grade C and 18.2% grade D in the early surgery group and 27.3, 22.7, 29.5, and 20.5 in the late surgery group, respectively. (Table 4). After the three months of the follow-up time, it was found that the neurological recovery (i.e. improvement of one or more grades in ASIA scale) was more prevalent in the early surgery group than the late surgery group. Early surgery group (N=44) had 25 (56.8%) out of 44 patients (neurological recovery) and late surgery group (N=44) had 14 (31.8%) out of 44 patients (neurological recovery). This was found to be statistically significant ($p = 0.02$) which is equivalent to have an evident advantage of the early surgical intervention. (Table 5) The stratification analysis revealed that in most of the subgroups, the neurological recovery was always better with early surgery. Recovery among patients aged =40 years showed higher in the early surgery group (58.3) than the late surgery group (40.0), but statistically not significant ($p = 0.21$). In patients older than 40 years, however, early surgery was much more helpful (55.0% vs 25.0.; $p = 0.04$). Early surgery (56.3) outperformed late surgery (30.0) in male patients ($p = 0.03$) as did early intervention (58.3) compared to late (35.7), but this was not statistically significant ($p = 0.26$). In patients with BMI >25 kg/m 2 there was a significant difference in recovery with early surgery (54.5 vs 26.1 $p = 0.05$), but not with BMI 25 or less ($p = 0.16$). Road traffic accident patients improved

Table 1: Demographic Characteristics of Patients (n = 88)

Variable	Early Surgery (n=44)	Late Surgery (n=44)	p-value
Age (years, Mean ± SD)	38.5 ± 10.2	40.1 ± 11.3	0.45
Gender (Male)	32 (72.7%)	30 (68.2%)	0.64
Gender (Female)	12 (27.3%)	14 (31.8%)	
BMI (kg/m², Mean ± SD)	24.8 ± 3.2	25.3 ± 3.5	0.48
Residence (Rural)	26 (59.1%)	28 (63.6%)	0.67
Residence (Urban)	18 (40.9%)	16 (36.4%)	

Table 2: Clinical Characteristics of Injury

Variable	Early Surgery (n=44)	Late Surgery (n=44)	p-value
Mode of Injury (RTA)	25 (56.8%)	27 (61.4%)	0.66
Mode of Injury (Fall)	15 (34.1%)	14 (31.8%)	
Others	4 (9.1%)	3 (6.8%)	
Injury Level = C4	28 (63.6%)	30 (68.2%)	0.65
Injury Level > C4	16 (36.4%)	14 (31.8%)	
Central Cord Syndrome	22 (50.0%)	20 (45.5%)	0.67
Anterior Cord Syndrome	12 (27.3%)	13 (29.5%)	
Posterior Cord Syndrome	10 (22.7%)	11 (25.0%)	

Table 3: Surgical Approach Distribution

Surgical Approach	Early Surgery (n=44)	Late Surgery (n=44)	p-value
Anterior	24 (54.5%)	26 (59.1%)	0.66
Posterior	12 (27.3%)	10 (22.7%)	
Combined	8 (18.2%)	8 (18.2%)	

Table 4: Baseline ASIA Grades

ASIA Grade	Early Surgery (n=44)	Late Surgery (n=44)	p-value
A	10 (22.7%)	12 (27.3%)	0.83
B	12 (27.3%)	10 (22.7%)	
C	14 (31.8%)	13 (29.5%)	
D	8 (18.2%)	9 (20.5%)	

Table 5: Neurological Recovery

Neurological Recovery	Early Surgery (n=44)	Late Surgery (n=44)	p-value
Yes	25 (56.8%)	14 (31.8%)	0.02
No	19 (43.2%)	30 (68.2%)	

Table 6: Stratification of Neurological Recovery Between Early and Late Surgery Groups

Variable	Category	Early Surgery Recovery Yes n/N (%)	Late Surgery Recovery Yes n/N (%)	p-value
Age (years)	=40	14/24 (58.3%)	8/20 (40.0%)	0.21
	>40	11/20 (55.0%)	6/24 (25.0%)	0.04*
Gender	Male	18/32 (56.3%)	9/30 (30.0%)	0.03*
	Female	7/12 (58.3%)	5/14 (35.7%)	0.26
BMI (kg/m²)	=25	13/22 (59.1%)	8/21 (38.1%)	0.16
	>25	12/22 (54.5%)	6/23 (26.1%)	0.05*
Mode of Injury	RTA	15/25 (60.0%)	8/27 (29.6%)	0.03*
	Fall/Others	10/19 (52.6%)	6/17 (35.3%)	0.31
Neurological Level	=C4	16/28 (57.1%)	10/30 (33.3%)	0.05*
	>C4	9/16 (56.3%)	4/14 (28.6%)	0.12
Pattern of Injury	Central Cord	13/22 (59.1%)	7/20 (35.0%)	0.11
	Others	12/22 (54.5%)	7/24 (29.2%)	0.08
Surgical Approach	Anterior	15/24 (62.5%)	9/26 (34.6%)	0.04*
	Posterior/Combined	10/20 (50.0%)	5/18 (27.8%)	0.18
Baseline ASIA Grade	A	2/10 (20.0%)	1/12 (8.3%)	0.40
	B–D	23/34 (67.6%)	13/32 (40.6%)	0.03*

with early surgery (60.0 vs 29.6; p = 0.03) but there was no statistically significant difference between early and late surgery in falls or other injury (p = 0.31). On the same note, patients that had injury of level up to C4 demonstrated much better results in early surgery (57.1% vs 33.3; p = 0.05) as compared to those with the injuries beyond C4 (p = 0.12). Though there was an increased recovery when surgery occurred early in cord syndrome of the central cord (59.1% vs 35.0%), or other patterns of injuries; these were not significantly different. There was a significant difference in early intervention as patients who survived anterior surgery surgery had a much better recovery rate than those who survived the surgery through an anterior/combined surgical approach (62.5 vs 34.6, p = 0.04). Notably, patients with incomplete injuries (ASIA grade B -D) performed much better with early surgery (67.6% vs 40.6; p = 0.03) but patients with complete injuries (ASIA grade A) performed poorly in both cases and no significant difference was found (p = 0.40). (Table VI)

DISCUSSION

In the present research, it was found that there was a statistically significant difference in the neurological recovery of patients with early and late surgery, 56.8% and 31.8% respectively (p = 0.02). Such results are consistent with various other recent studies which have reported positive neurological outcomes with early surgery intervention. An example in point is a study conducted by Xiao et al. that found that the early surgical decompression showed more positive neurological outcome than delayed surgery, which indicated the idea that a timely intervention was capable of restraining secondary injury mechanisms.[11] Correspondingly, Song et al. have observed that early surgery was highly related to better neurological outcomes, especially during the short-term follow-up care.[12] Biological explanations to these findings are in the pathophysiology of spinal cord injury. Secondary damage to neurons occurs after the initial mechanical insult via mechanisms of ischemia, edema and cascades of inflammation. Early decompression will assist in the restoration of spinal cord perfusion, decrease edema, and deter continued compression, which will limit the amount of irreparable damage. Such notion receives the evidence of a work by Trung et al. that showed that early surgery within 24 hours raised the chances of neurological recovery by over three times (OR = 3.12, p = 0.006).[13] Additionally, a recent systematic review and meta-analysis found that neurological outcomes and length of stay decreased significantly with surgical decomposition in the 24 hours after surgery, and more so in the 12 hours after surgery, yet had no association with complication rate escalation.[14] These results are quite consistent with the results of the current study and they support the role of early intervention when dealing with CSCI.

Besides the overall recovery, the current study also revealed that incomplete injured patients (ASIA grades B-D) achieved a lot better outcomes as opposed to complete injured patients (ASIA grade A). This observation has been supported by other new studies which have indicated that baseline neurological state has been a robust predictor of recovery. It has been observed, for instance, that the patients who had incomplete injuries of the spine, when it was decomposed early, showed more neurological improvements than those with complete injuries.[15] On the same note, Tone et al.

established that early surgery enhanced neurological outcomes especially amongst incomplete injury patients but the outcome of complete injuries was limited.[16] Surprisingly, though the results in the early surgical case were overall better, the stratified analysis in the current study indicated that the advantage of early intervention was more evident in some subgroups, which include older adults (> 40 years), males, higher BMI and patients injured in road traffic accidents. These results indicate that though early surgery is as a rule good, patient-specificity may affect the extent of the healing. Similar is observed in other recent literature, even though the influence of demographic and injury related factors was found to alter the outcome. An example is Trung et al. who observed that higher-level lesion injury and increased cord injury were related to poor recovery in spite of early intervention.[13] Nevertheless, the benefits of early surgery have not been consistently welcomed in all studies. Recent studies have indicated that there was no significant outcome difference between early or delayed impairment of the surgical operation especially in certain groups of patients. As an example, Romijn et al did not find any significant differences between early and late decompression groups in terms of quality of life or neurological outcomes at the post discharge period of 6 and 12 months.[17] Likewise, Segi et al. performed a multicenter trial in patients of the older age on the topic and indicated that early surgery did not ensure a significantly better neurological outcome compared to late surgery, albeit the study was carried out in a safe manner.[18]

Such opposite results can be attributed to the variation in study populations, what constitutes early surgery, and outcomes measures. Comorbidities, frailty, and diminished physiological reserve in elderly patients can put a cap on the possible neurological recovery, thus weakening the beneficial effect of early intervention. Another study conducted by Marland et al. also indicated that delayed surgery could be advantageous even in some elderly individuals as it could lead to fewer complications during the perioperative phase and to fewer intensive care visits.[19]

The other one is the uncertainty in determining early and late surgery. Although the current study has assumed the use of early surgery at 24 hours, other studies have widened this to 48 or 72 hours meaning this can affect the results. According to Nori et al, a surgery conducted in the next 48 hours did not significantly show a better neurological outcome in some subgroups, which also showed the necessity to establish a standard definition of the concept of early intervention.[20]

These differences notwithstanding, the contemporary clinical practice still supports early surgical decompression. Based on more recent evidence, surgery within 24 hours of admission is correlated with a better neurological outcome and fewer complications.[21] Speed The notion of time as spine has become rather popular, with a focus on how any delay in surgical care might cause an irreversible neurological loss.[22]

The results of the current investigations also indicated that gender, BMI, mode of injury and method of surgery did not lead to relevant differences in the neurological recovery following stratification and therefore the most important outcome determinant continues to be the timing of surgery. The current literature has justified this observation by indicating that surgical timing has always been an independent predictor of recovery. Indicatively, one study carried out in 2026 indicated that early intervention showed better outcomes despite other patient-related factors.[23] Moreover, earlier surgery has been reported to minimise systemic complications, and early mobilization that is essential with regard to overall recovery. In a study by Ahmed et al. it was pointed out that early decompression is linked to a reduced level of complications and enhanced functional outcomes at one year.[24] Likewise, in a study conducted recently, early surgery was shown to decrease the time of stay and rehabilitation.[14] Nevertheless, one should take into consideration the disadvantages of the early surgical intervention. A study has shown in some cases an increase in the intraoperative blood loss and increased length of operation in the early surgery groups, however it did not correlate with the increase in complication.[25] Moreover, the logistic issues of late presentation of the patient, difficulty in accessing imaging and availability of operating rooms can also interfere with the introduction of early surgery, especially where resources are scarce as in South Asia. The current research has various strengths such as a prospective design, clear inclusion criteria, and the assessment of neurological outcomes in a standardized way with the use of the ASIA grading system. Balanced distribution of the patient population of the two categories of patients and the application of stratification to balance out the confounding factors also contribute wholly towards the reliability of the results. Nonetheless, there are some limitations to be taken into consideration. The results might be restricted by the short follow-up time (4 weeks) and the rather limited sample size. Moreover, the long-term functional outcomes and quality of life measures were not determined, which may give a better idea of the recovery.

CONCLUSION:

It was inferred that the current research found neurological outcome in case of early surgical intervention in 24 hours or later of cervical spinal cord injury showed a significant difference in the case of a positive neurological recovery. The patients with early decompression also showed an increase in a higher percent among ASIA grading indicating the significant impact of early management on salvaging neurological functions. Besides, the research results highlighted that the baseline neurological condition is a major predictor of recovery, and patients with incomplete injuries (ASIA stages B-D) demonstrated better recovery

than their counterparts with complete injuries (ASIA grade A). Finally, surgical treatment in patients with a cervical spinal cord injury in the early phase must be viewed as the treatment of choice, and health care systems should put primary focus on those strategies that will enable timely closure to limit morbidity and enhance the quality of life.

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Authors Contribution:
Aqib Rauf: Study design, conception statistical analysis, data collection
Muhammad Shahid: Literature review, proof reading

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Original Article **Open Access**

Clinical Significance of Serum C-Reactive Protein Levels in Oral Premalignancies and Oral Squamous Cell Carcinoma

Adeena Abid, Muhammad Ishaq, Nabeel Hafeez

Abstract

Objective: Assessing serum C-reactive protein (CRP) levels in healthy controls, individuals with oral premalignant disorders, and patients with oral squamous cell carcinoma (OSCC) in order to determine its potential as a screening and diagnostic biomarker.

Study Design and Setting: A cross-sectional study was carried out at PNS Shifa Hospital, Karachi over one-year period using consecutive sampling.

Methodology: Seventy-eight participants were equally divided into three groups: healthy controls (n=26), patients with oral premalignant disorders (n=26) and OSCC patients (n=26). Serum CRP levels were measured using immunoturbidimetry. Statistical analysis was carried out using one-way ANOVA, chi-square test, receiver operating characteristic (ROC) analysis, and multiple regression.

Results: The mean serum CRP level showed significantly higher levels in OSCC patients compared with premalignant and healthy groups ($p<0.001$). There was a progressively increasing trend in CRP levels from healthy controls to premalignant lesions and OSCC. ROC analysis showed acceptable discriminative ability of serum CRP in distinguishing OSCC and premalignant conditions from healthy individuals.

Conclusion: Serum CRP levels show promising ability as a diagnostic and screening tool for oral premalignant and malignant conditions with increasing levels correlating with disease progression. However larger longitudinal studies are recommended to validate these findings.

Keywords: Biomarker; C-reactive protein; CRP; Oral premalignant disorders; OPMD; Oral squamous cell carcinoma

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies affecting the head and neck region and continues to remain as a major public health concern worldwide. Global Cancer Observatory (GLOBOCAN 2020) reports that oral cancer contributes significantly to cancer-related morbidity and mortality, especially in lower and middle-class countries.[1,2] Despite advances in diagnostic techniques and treatment strategies, the overall survival rate of OSCC has not improved substantially over the past decades. This is largely due to delayed diagnosis and advanced-stage presentation. Oral potentially malignant disorders (OPMDs) including leukoplakia, oral submucous fibrosis, and oral lichen planus are some of the well-known precursors of OSCC. These lesions often precede invasive carcinoma; therefore, they provide an opportunity for early detection along with early intervention. However, predicting malignant transformation is still challenging, as clinical examination and histopathological assessment alone may not reliably identify high-risk lesions.[3] Pakistan has one of the highest burdens of oral cancer globally. This is primarily due to widespread use of smokeless tobacco, betel quid, areca nut, gutka, and naswar. These addictions play a central role in disease development as well as progression. Studies from tertiary care hospitals in Pakistan report that most patients present at an advanced stage, resulting in poor treatment outcomes and reduced overall survival rate.[4,5] This highlights the urgent need for simple, affordable, and non-invasive screening tools suitable for resource-limited healthcare settings such as in countries like Pakistan. Chronic inflammation is now widely known as a key contributor to the process of carcinogenesis. When inflammation continues to persist over time, it promotes cellular proliferation,

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genomic instability, angiogenesis, and tumor invasion.[6,7] C-reactive protein (CRP) is known as an acute-phase protein synthesized by the liver in response to inflammatory cytokines and it serves as a reliable marker of systemic inflammation. Elevated CRP levels have been known to be associated with tumor progression and advanced disease stage It has also been associated with poor prognosis in several malignancies.[8-10]

Recent studies have focused on the role of CRP in oral premalignant and malignant conditions. Raised serum and salivary CRP levels have been seen in patients with OPMDs and OSCC when compared with healthy individuals.[11-14] These findings suggest that CRP reflects the inflammatory microenvironment associated with oral carcinogenesis. However, data from Pakistani populations remain limited, and few studies have evaluated CRP levels across the full spectrum from healthy person to premalignant and carcinoma patients. In lower- and middle-class countries, such as Pakistan, access to advanced diagnostic facilities remains limited, particularly in rural and public-sector healthcare settings. Many patients present at a later stage due to lack of awareness, delayed referral, and absence of affordable screening tools. Blood-based biomarkers are particularly useful in such settings because they are minimally invasive, affordable, and can be measured even in basic laboratory facilities. Among these, systemic inflammatory biomarkers are especially relevant, as chronic inflammation has been known to play a key role in process of oral carcinogenesis. Apart from establishing key risk factors for OSCC, there is an increasing interest in identifying simple and readily available biomarkers that can aid in early detection and diagnosis. In routine clinical settings, especially where advanced diagnostic tools are not easily available, such markers may provide additional information to further support clinical judgment and improve risk stratification. A simple laboratory marker that reflects this inflammatory burden could help clinicians in early identification of individuals at higher risk and decide more quickly which patients should be referred for further assessment. Therefore, exploring the clinical utility of routinely available inflammatory markers may help bridge the gap between early suspicion and definitive diagnosis in resource-constrained environments such as Pakistan. Given the higher prevalence of oral cancer in Pakistan and the limitations associated with the existing screening approaches, this study was designed to evaluate serum CRP levels among healthy individuals, patients with oral premalignant disorders, and those diagnosed with OSCC. The objective was to evaluate the potential role of serum CRP levels as a screening and diagnostic tool and to examine its association with the progression of the disease.

METHODOLOGY

A cross-sectional study was done at the Dental Department of PNS Shifa Hospital, Karachi. Study period was of 6 months from 1st June 2025 to 1st Nov 2025. Sampling technique was non-probability consecutive sampling. Random sampling was not done. The study was reviewed and approved by the Institutional Review Board of the Ethical Committee, PNS Shifa Hospital with ERC approval number Ref# ERC/2022/DENTAL/21 dated 13 July 2022. Written informed consent was taken from all the study participants before enrollment. The study was done according to the principles of the Declaration of Helsinki. Sample size of 78 patients was calculated from WHO sample size calculator by taking standard deviation of CRP levels as 4.50, margin of error as 1 and 95% confidence interval. A total of 78 participants were included and divided equally into three groups (n = 26 each):

Group I: Healthy controls with no history of oral lesions, malignancy, or systemic inflammatory disease.

Group II: Patients diagnosed with oral premalignant disorders, including leukoplakia, oral submucous fibrosis, and oral lichen planus.

Group III: Patients with histopathologically confirmed oral squamous cell carcinoma.

Individuals aged 18 years and above were eligible for inclusion including healthy cohorts, those with OPMDs and those with OSCC. Patients with any acute or chronic infections, autoimmune disorders, systemic inflammatory diseases, cardiovascular disease, hepatic disease, or those receiving anti-inflammatory or immunosuppressive therapy were excluded to avoid confounding effects on serum CRP levels. Pregnant and lactating women were also excluded. The inclusion and exclusion criteria were based specifically on the study design. Venous blood samples were taken under aseptic conditions from all study participants. Serum was separated by centrifugation and analyzed for CRP levels using the immunoturbidimetric method in the hospital laboratory after following standard operating procedures. The assay was performed using commercially available kits according to the instructions given by the manufacturer. The lower detection limit of the CRP assay was set at 0.1 mg/L.

Data was analyzed using SPSS version 26. Quantitative data were reported as mean values with standard deviations. The Qualitative data were described using frequencies and percentages. One-way ANOVA was used to compare mean CRP levels among the three study groups. This was followed by post-hoc analysis where appropriate. The chi-square test was applied to assess the associations between categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum CRP. Multiple regression analysis was performed with serum CRP as the dependent variable and disease group, age, and gender as independent variables. A p-value of <0.05 was considered statistically significant.

RESULTS

78 participants were enrolled in the study, with 26 individuals in each group. The key demographic features of the study participants are presented in Table 1. The mean age of participants increased progressively across the three groups and was highest in Oral squamous cell carcinoma (OSCC) patients. A significant variation in age distribution was found between the groups ($p = 0.008$). A male predominance was noted in the OSCC group in comparison to the premalignant and the healthy control group. This difference was noted to be statistically significant ($p = 0.025$). Socioeconomic status also differed significantly among the groups, with a higher proportion of OSCC patients belonging to the lower socioeconomic class ($p = 0.018$). The mean serum CRP levels of the three study groups are presented in Table 2. Serum CRP levels demonstrated a clear progressive increase moving from the healthy control group to patients with oral premalignant disorders and were highest among OSCC patients. One-way analysis of variance revealed a statistically significant difference in mean CRP levels among the groups ($p < 0.001$). Post-hoc analysis showed that CRP levels in OSCC patients were significantly higher than those in both premalignant cases and healthy controls.

Subgroup analysis of oral premalignant disorders was performed to evaluate differences in serum CRP levels among various premalignant lesions (Table 3). Patients with oral submucous fibrosis showed relatively higher mean CRP levels compared to those with leukoplakia and oral lichen planus. However, the observed differences among premalignant subgroups were not statistically significant ($p > 0.05$). (Table 4) Receiver operating characteristic (ROC) curve analysis showed that serum C-reactive protein (CRP) had acceptable diagnostic accuracy in differentiating oral squamous cell carcinoma (OSCC) from healthy controls, with an AUC of 0.82 (95% CI: 0.72–0.91). At a cut-off value of 4.5 mg/L, CRP demonstrated a sensitivity of 80.8% and specificity of 76.9% (Table 5). Moderate discriminative ability was observed when OSCC was compared with oral premalignant disorders (AUC: 0.71), while CRP showed modest performance in distinguishing premalignant disorders from healthy controls (AUC: 0.69). These findings are in support of the potential role of serum CRP as an adjunctive screening biomarker when used alongside clinical assessment. In addition to the primary comparisons, variability in CRP values was observed within each study group. Although mean levels differed significantly, individual measurements showed a degree of overlap, particularly between the premalignant and malignant groups. This finding reflects the biological diversity of inflammatory responses among patients and emphasizes that CRP should be interpreted in conjunction with clinical features rather than as an isolated indicator. Overall, the results showed a noticeable difference between the groups, with higher values generally seen in the malignant cases compared to the premalignant and control groups. It is also important to note that some participants did not strictly follow the overall trend of increasing values. This is to be expected in clinical data as it usually is reflective of individual variability. In some of the cases, values were slightly higher or lower than the

Table 1. Demographic Characteristics of Study Population (n=78)

Parameter	Group I: Healthy Controls (n=26)	Group II: Oral PMDs (n=26)	Group III: OSCC (n=26)	p-value
Age (Years)				
Mean	36.2 ± 9.4	42.8 ± 10.1	54.6 ± 11.3	**0.008***
Range	(20–55)	(20–65)	38-76	
Gender, n(%)				
Male	13 (50.0%)	17 (65.4%)	22 (84.6%)	**0.025***
Female	13 (50.0%)	9 (34.6)	4 (15.4%)	
Socioeconomic Status, n (%)				
Lower	8 (30.8)	15 (57.7%)	18 (69.2%)	**0.018***
Middle	12 (46.2%)	9 (34.6%)	7 (26.9%)	
Upper	6(23.1%)	2 (7.7%)	1 (3.8%)	

Table 2: Serum CRP Levels Across Study Groups (n = 78)

CRP Levels (mg/L)	Group I: Healthy Controls	Group II: OPMDs	Group III: OSCC
N	26	26	26
Mean ± SD	5.12 ± 2.48	5.12 ± 2.48	8.87 ± 3.41
Median (IQR)	4.90 (3.4–6.8)	4.90 (3.4–6.8)	8.60 (6.2–11.4)
Range	1.2–10.9	1.2–10.9	3.3–16.8

One-way ANOVA; Post-hoc analysis (Tukey's HSD): Group III > Group II > Group I ($p < 0.001$)

Table 3. CRP Levels in Different Types of Oral Premalignant Disorders

OPMD Type	N (%)	Mean CRP ± SD (mg/L)	Median (IQR)	Range
Oral Leukoplakia	9 (34.6)	4.61 ± 2.12	4.40 (3.1–5.8)	1.2–8.9
Oral Submucous Fibrosis	10 (38.5)	5.74 ± 2.63	5.60 (3.9–7.1)	2.1–10.9
Oral Lichen Planus	7 (26.9)	4.89 ± 2.21	4.70 (3.2–6.3)	1.5–9.4

Table 4. Pairwise Comparison of CRP Levels Among OPMDs (Independent t-t

Comparison	p-value	Significance
Oral Leukoplakia vs Oral Submucous Fibrosis	0.315	Not Significant
Oral Leukoplakia vs Oral Lichen Planus	0.802	Not Significant
Oral Submucous Fibrosis vs Oral Lichen Planus	0.482	Not Significant

p-values obtained using independent t-test; p < 0.05 considered statistically significant

Table 5. ROC Analysis for CRP as Diagnostic Marker

Group Comparison	AUC (95% CI)	Cut-off Value (mg/L)	Sensitivity (%)	Specificity (%)	p-value
OSCC vs Healthy Controls	0.82 (0.72–0.91)	4.5	80.8	76.9	<0.001
OSCC vs OPMDs	0.71 (0.60–0.82)	6.3	73.1	65.4	<0.002
OPMDs vs Healthy Controls	0.69 (0.58–0.80)	3.2	69.2	64.0	<0.006

AUC = Area under the curve; OSCC = Oral squamous cell carcinoma; OPMDs = Oral Premalignant disorders. ROC analysis was done evaluate the diagnostic accuracy of serum CRP. An AUC value between 0.7 and 0.9 indicates acceptable diagnostic performance

DISCUSSION

Oral squamous cell carcinoma continues to be a major public health challenge in Pakistan due to late-stage presentation, limited screening strategies, and a high prevalence of associated risk factors. Identifying biomarkers that are both simple and widely available is therefore of clinical importance, especially for improving early detection and risk stratification. The present study evaluated serum C-reactive protein levels across healthy individuals, patients with oral premalignant disorders, and those with OSCC. It demonstrated a clear and progressive rise in CRP levels with increasing disease severity. The most notable finding of this study was the significant elevation of serum CRP levels in OSCC patients when compared with both healthy controls and patients with oral premalignant disorders. This finding was consistent with those of Metgud et al and Vankadara et al.[15,16] This observation is in support of the role of chronic systemic inflammation in process of oral carcinogenesis.[7]

CRP is a well-established acute-phase reactant produced by hepatocytes in response to inflammatory cytokines such as interleukin-6. Persistently raised CRP levels may reflect ongoing inflammatory and immune disturbances within the tumor microenvironment, which can contribute to both the development and progression of cancer.[7,8] Patients with oral premalignant disorders exhibited intermediate CRP levels, which were significantly higher than those of healthy controls but lower than those observed in patients with OSCC. This graded increase suggests that systemic inflammation may begin early in the disease process, even before malignant transformation takes place. This closely aligns with the findings of Singh et al.[11] Similar findings have been reported in previous studies, which demonstrated elevated serum and salivary CRP levels in patients with leukoplakia, oral submucous fibrosis, and oral lichen planus.[16] These findings are collectively in the support of the concept that CRP may serve as an early indicator of malignant potential. Subgroup analysis of premalignant disorders showed higher CRP levels in patients with oral submucous fibrosis compared to leukoplakia and oral lichen planus, However the differences were not found to be statistically significant. This trend may be explained by the chronic inflammatory nature of oral submucous fibrosis, which is already known to carry a higher risk of malignant transformation as discussed by Gossavi et al and Tang et al.[14,17] The lack of statistical significance may be due to the relatively small sample size within each premalignant subgroup. This is a limitation commonly encountered in single-center studies. Demographic analysis revealed a higher mean age and a marked male predominance among OSCC patients. These findings are consistent with the local and regional epidemiological data from Pakistan as explored by Saeed et al.[18] The higher prevalence of OSCC in males may be linked to greater exposure to known risk factors such as tobacco, betel quid, areca nut, and smokeless tobacco products. Additionally, a significant association between advanced stage presentation was observed as similarly reported by Memon et al.[19] This highlights the role of social determinants of health, limited access to healthcare, and delayed diagnosis in disease progression. These findings are consistent with findings of Yuktha et al.[20] Receiver operating characteristic analysis demonstrated acceptable discriminative ability of serum CRP in distinguishing OSCC patients from healthy controls, suggesting potential utility as a screening adjunct. While CRP lacks disease specificity, its low cost, wide availability, and ease of measurement make it an attractive candidate for use in resource-limited settings such as Pakistan. When used alongside clinical examination and histopathological findings, CRP may help identify individuals at higher risk who would benefit from closer follow-up and surveillance.[21,22]

The major challenge for clinicians is not just to diagnose the disease but to decide which patient is going to need urgent attention. At the time of presentation, many patients have oral lesions that appear mild or non-specific, yet they may carry significant malignant potential. This leads to an uncertainty for both the clinicians and patients, especially when access to specialized tests is limited. In such cases

serum CRP levels could provide additional context while being easily affordable and accessible. While it may not confirm malignancy, an elevated level may warrant a need for a detailed evaluation or an earlier referral.[3,8] Many oral potentially malignant disorders do not always behave uniformly. Some lesions may remain stable for years, while others may spread aggressively. Clinical appearance alone may not be sufficient enough to predict this behavior.[3] Use of a simple blood test that mirrors ongoing inflammation and tissue injury can help to identify lesions that are more active biologically. Corelating clinical examination with CRP levels could contribute to a more accurate risk assessment. These findings suggest a more structured approach of integrating laboratory markers with clinical assessment rather than simply relying on a single parameter. While individual values may vary, the overall trend helps in studying disease behavior. This combination approach may help further in enhancing clinical decision-making and support a more tailored patient management strategies in everyday practice. The actual value of serum CRP levels lies in its simplicity rather than its specificity. Although CRP alone may not replace the need of a histopathological diagnosis, it can still be considered as an adjunctive marker and may be particularly useful in settings where access to specialized testing is limited. As CRP testing is already part of routine medical practice, there is no need for additional training or equipment. In populations where there is a high prevalence of tobacco and areca nut usage, we can identify high risk patients and improve clinical decision making simply by incorporating such a readily available test into initial assessment protocols. By observing the rise in CRP levels across disease stages, we can also interpret this finding from a biological perspective. The process of Oral carcinogenesis is accompanied by ongoing tissue injury, immune system activation, and the increased release of inflammatory mediators. With the intensification of these processes there is a gradual rise in systemic makers such as CRP levels. These changes also mirror the transition from premalignant change to invasive malignancy.

Inflammation in general is not specific to cancer; however, its persistence and magnitude may reflect disease activity. Therefore, by measuring CRP levels we can get a glimpse into the broader physiological response associated with tumour progression. With careful interpretation we can use this information to get a more comprehensive assessment of patients who present with suspicious oral lesions. The observed overlap in the CRP values across the premalignant and malignant cases in this study are clinically meaningful as it indicates that CRP alone cannot be used to make clinical decisions, rather it suggests that its usage should be as a supportive adjuvant alongside clinical examination and histopathological evaluation. Patients who are presenting with borderline or moderately elevated CRP levels may benefit from closer follow-up and timely reassessment, especially when their lesions appear suspicious or seem to be progressing over time. When viewing from a healthcare system perspective, by using routinely available laboratory parameter, we are optimizing resource allocation. When it comes to settings where advanced imaging and specialist referral are limited, such as in the rural areas of Pakistan, we may be able to prioritize patients requiring urgent diagnostic workup simply with the use of readily available blood test such as serum CRP levels. By using this approach, we are not replacing definitive diagnostic procedures, rather this approach will contribute to earlier recognition of high-risk cases. When viewed together, these observations reinforce the potential value of CRP as a simple adjunctive tool that supports clinical judgment. It also enhances the overall assessment of patients with oral lesions. Study Limitations: This study has several limitations that need consideration. The small sample size that was drawn from a single center limits the generalizability of the data to broader populations. The study design was cross sectional which hinders the ability to establish a casual relationship between CRP levels and disease progression. As Serum CRP levels is a non-specific inflammatory marker it can easily be influenced by systemic factors and conditions even though efforts were made to exclude known confounders. Variability within study groups and overlap in CRP values also show that CRP should not be used alone for diagnosis. Further studies with larger sample size and conducted at multiple centers along with a longitudinal follow up are needed to better identify the usefulness of serum CRP levels.

CONCLUSION

Serum C-reactive protein levels show a progressively increasing trend from healthy individuals to patients with oral premalignant disorders and are the highest in oral squamous cell carcinoma patients. This pattern is suggestive of the role of systemic inflammation in process of oral carcinogenesis. As serum CRP levels are easily accessible and affordable, they may serve as a useful tool for screening and risk stratification in populations with a high burden of oral cancer especially in countries such as Pakistan. However, larger prospective studies are needed to establish standardized cut-off values and confirm its prognostic significance. This highlights the importance of involving simple laboratory investigations into routine dental appointments, this can lead to earlier recognition of disease and timely intervention. The findings suggest that CRP levels can play an important role as a screening and diagnostic tool for earlier detection of Oral cancer as the results show an increasing trend of Serum CRP levels as the disease progresses.

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Authors Contribution:
Adeena Abid: Conceptualization, literature review, manuscript writing, final approval study design, data collection, data analysis and interpretation
Muhammad Ishaq: Overall supervision, data interpretation, Proof reading.
Nabeel Hafeez: Initial supervision, conceptual development and study design

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Original Article **Open Access**

Diagnostic Accuracy of Magnetic Resonance Spectroscopy in Diagnosing Glioblastoma, taking Histopathology as Gold Standard

Hina Nadeem, Syed Anjum Mehdi, Iqra Siddique, Safia Nadeem

ABSTRACT

Objective: To determine the diagnostic accuracy of magnetic resonance spectroscopy (MRS) in diagnosing glioblastoma in patients with focal brain lesions, taking histopathology as the gold standard.

Study Design and Setting: Cross-sectional validation study conducted at the Department of Radiology, Madinah Teaching Hospital, Faisalabad.

Methodology: A total of 148 patients aged 20-60 years with focal brain lesions larger than 5 mm and lesion duration of more than one month were enrolled through non-probability consecutive sampling. All patients underwent proton MRS using a 1.5 Tesla MRI system with a single-voxel point-resolved spectroscopy technique. MRS diagnosis of glioblastoma was based on raised choline peak, reduced NAA/Cr ratio, raised Cho/NAA ratio, and raised Cho/Cr ratio. Post-biopsy or post-excision histopathology was used as the gold standard. Sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, likelihood ratios, and receiver operating characteristic curve analysis were calculated using SPSS version 25.0.

Results: The mean age was 42.76 +/- 10.84 years, and 92 (62.2%) patients were male. Histopathology confirmed glioblastoma in 116 (78.4%) patients. MRS showed sensitivity of 93.1%, specificity of 68.8%, positive predictive value of 91.5%, negative predictive value of 73.3%, and overall diagnostic accuracy of 87.8%.

Conclusion: MRS is a highly sensitive non-invasive adjunct to conventional MRI for preoperative assessment of suspected glioblastoma; however, histopathological confirmation remains essential because specificity and negative predictive value were moderate.

Keywords: Glioblastoma; Magnetic Resonance Spectroscopy; Histopathology; Diagnostic Accuracy; Brain Neoplasms.

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INTRODUCTION

Glioblastoma (GBM) is the most aggressive and common primary malignant tumor of the central nervous system. Despite major advancements in neuroimaging and treatment modalities, glioblastoma still has a poor prognosis because of its highly infiltrative nature, rapid progression, and resistance to therapy. Malignant brain and central nervous system tumors remain an important cause of morbidity and mortality worldwide. The World Health Organization defines glioblastoma as a grade IV astrocytic tumor characterized by marked genetic heterogeneity, necrosis, microvascular proliferation, and aggressive cellular proliferation.[1,2]

Magnetic resonance imaging (MRI) remains the preferred initial imaging modality for evaluating intracranial neoplasms because of its superior soft tissue contrast and multiplanar capability. T1-weighted, T2-weighted, contrast-enhanced, and fluid-attenuated inversion recovery (FLAIR) sequences provide useful anatomical information regarding tumor size, location, edema, hemorrhage, necrosis, and mass effect. However, conventional MRI has limited ability to accurately characterize tumor metabolism or distinguish glioblastoma from other cerebral lesions such as radiation necrosis, metastases, abscesses, and lower-grade gliomas. These limitations have encouraged the use of advanced neuroimaging techniques to improve preoperative tumor characterization and diagnostic accuracy.[3,4]

Magnetic resonance spectroscopy (MRS) is an advanced non-invasive imaging technique that evaluates tissue biochemistry by measuring metabolite concentrations within a selected voxel. Proton magnetic resonance spectroscopy

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(1H-MRS) is the most commonly used spectroscopic technique in clinical practice because of its reliable signal strength. Choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate, and lipid peaks are the main metabolites assessed on MRS. Raised choline indicates increased membrane turnover and cellular proliferation, whereas reduced NAA reflects neuronal destruction and tumor infiltration.[5,6]

Glioblastoma is typically associated with markedly increased choline peaks, reduced NAA, and altered Cho/Cr and Cho/NAA ratios. Lactate and lipid peaks are also more commonly associated with tumor necrosis and hypoxic metabolism in high-grade gliomas. Therefore, MRS may improve the ability to distinguish malignant glioma from benign lesions and non-neoplastic pathologies. Recent studies have supported the usefulness of MRS in glioma grading and in identifying highly proliferative tumor regions before biopsy or surgery.[7,8]

Advanced imaging has become increasingly important in neuro-oncology, particularly when lesions are located near eloquent brain areas or when invasive confirmation carries a higher procedural risk. MRS can assist neurosurgeons in localizing metabolically active tumor regions for targeted biopsy, thereby reducing sampling errors and improving diagnostic yield.[9]

Recent research has also highlighted the role of multiparametric MRI, especially when MRS is combined with diffusion-weighted imaging and perfusion imaging, in the assessment of glioblastoma. Combined metabolic and structural imaging has shown improved diagnostic confidence in differentiating glioblastoma from treatment-related changes and lower-grade gliomas.[10]

Although MRS has shown promising diagnostic performance internationally, local data on its diagnostic accuracy in Pakistani populations are limited. Variation in disease spectrum, imaging protocols, patient demographics, and histopathological patterns may influence diagnostic results. Therefore, this study was conducted to determine the diagnostic accuracy of MRS in diagnosing glioblastoma among patients with focal brain lesions, taking histopathology as the gold standard.

METHODOLOGY

This cross-sectional validation study was conducted in the Department of Radiology, Madinah Teaching Hospital, Faisalabad, over a period of six months, from 8 August 2025 to 7 February 2026, after approval of the study synopsis and institutional ethical review committee (Ref. No. TUF/IRB/461/2024, dated 04 November 2024). Written informed consent was obtained from all participants before enrollment, and confidentiality of patient data was maintained throughout the study.

Sample size was calculated using the WHO sample size calculator. A total of 148 patients were included by using the reported prevalence of glioblastoma (78.31%), expected MRS sensitivity, expected specificity of 94.4%, 95% confidence level, and an 8% margin of error.[7]

Patients of either gender, aged 20-60 years, with focal brain lesions greater than 5 mm in diameter and lesion duration of more than one month were included. On conventional MRI, focal lesions were assessed on T1-weighted, T2-weighted, contrast-enhanced, and FLAIR sequences. Patients with metastatic brain lesions, recurrent glioblastoma, previous brain surgery for the same lesion, contraindications to MRI, or severe comorbid conditions precluding surgery or biopsy were excluded.

Detailed demographic and clinical information, including age, gender, lesion duration, lesion size, lesion site, and residence, was recorded on a predesigned proforma. All patients underwent MRS using a 1.5 Tesla MRI system. Single-voxel point-resolved spectroscopy (PRESS) was performed. The voxel was placed within the solid component of the lesion while avoiding cystic, necrotic, hemorrhagic, and calcified areas to reduce spectral contamination. Water suppression pulses were applied before data acquisition to improve visualization of metabolite peaks and spectral quality.

MRS spectra were interpreted by an experienced radiologist with at least five years of post-fellowship experience in neuroradiology, who was blinded to histopathological findings. Glioblastoma on MRS was diagnosed on the basis of a high choline peak (>3.2 ppm), low NAA/Cr ratio (<1.6), high Cho/NAA ratio (>1.2), and high Cho/Cr ratio (>1.5). Lipid and lactate peaks were considered supportive findings for high-grade malignancy.

All patients subsequently underwent biopsy or surgical excision by the neurosurgery team as clinically indicated. Tissue specimens were sent to the institutional histopathology laboratory for definitive diagnosis. Histopathological evaluation was performed by a qualified histopathologist who was blinded to MRS findings. Glioblastoma was diagnosed on the basis of coagulative necrosis, microvascular proliferation, endothelial hyperplasia, increased mitotic activity, nuclear pleomorphism, and karyorrhectic cells. Histopathology was considered the gold standard.

As this was a cross-sectional diagnostic accuracy study, randomization and a control group were not applicable; all eligible patients underwent both the index test (MRS) and the reference standard (histopathology).

Data were entered and analyzed using SPSS version 25.0. The Shapiro-Wilk test was used to assess normality of quantitative variables. Normally distributed quantitative variables were expressed as mean +/- standard deviation, whereas non-normally distributed variables were expressed as median with interquartile range. Qualitative variables were expressed as frequencies and percentages.

Diagnostic accuracy of MRS was calculated using a 2 x 2 contingency table, with histopathology as the gold standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), overall diagnostic accuracy, positive likelihood ratio, negative likelihood ratio, and receiver operating characteristic (ROC) curve analysis were calculated. Stratification was performed for age, gender, lesion size, and lesion duration. Post-stratification chi-square test was applied where appropriate, and a p-value of <0.05 was considered statistically significant.

Table 1: Demographic and Clinical Characteristics of Patients (n = 148)

Variable	Value
Age (years), mean +/- SD	42.76 +/- 10.84
Age range (years)	20-60
Male gender	92 (62.2%)
Female gender	56 (37.8%)
Lesion duration (months), mean +/- SD	4.82 +/- 2.31
Lesion duration range (months)	1-12
Lesion size (cm), mean +/- SD	3.94 +/- 1.26
Lesion size range (cm)	1.5-7.2

RESULTS

A total of 148 patients were included in the study. The mean age was 42.76 +/- 10.84 years, with an age range of 20-60 years. Among these patients, 92 (62.2%) were male and 56 (37.8%) were female. The mean lesion duration was 4.82 +/- 2.31 months, and the mean lesion size was 3.94 +/- 1.26 cm. Demographic and clinical characteristics are shown in Table 1. On MRS, glioblastoma was diagnosed in 118 (79.7%) patients, while 30 (20.3%) patients were reported as negative. Histopathology confirmed glioblastoma in 116 (78.4%) patients and ruled it out in 32 (21.6%) patients. When MRS was compared with histopathology, 108 cases were true positive, 22 were true negative, 10 were false positive, and 8 were false negative. MRS demonstrated sensitivity of 93.1%, specificity of 68.8%, PPV of 91.5%, NPV of 73.3%, and overall diagnostic accuracy of 87.8%. ROC curve analysis showed good diagnostic performance with an area under the curve of 0.81 (95% CI: 0.73-0.89; p<0.001). After stratification for age, gender, lesion size, and lesion duration, no statistically significant difference in diagnostic accuracy was observed (p>0.05).

DISCUSSION

Glioblastoma is the most aggressive primary malignant tumor of the central nervous system and is associated with

Table 2: Diagnostic Accuracy of MRS Taking Histopathology as the Gold Standard

A. Comparison of MRS with Histopathology			
MRS finding	**Histopathology positive**	**Histopathology negative**	**Total**
Positive	108	10	118
Negative	8	22	30
Total	116	32	148
B. Diagnostic performance			
Parameter	**Formula**	**Result**	
Sensitivity	TP/(TP+FN) x 100	93.1%	
Specificity	TN/(TN+FP) x 100	68.8%	
Positive predictive value	TP/(TP+FP) x 100	91.5%	
Negative predictive value	TN/(TN+FN) x 100	73.3%	
Diagnostic accuracy	(TP+TN)/Total x 100	87.8%	
Positive likelihood ratio	Sensitivity/(1-Specificity)	2.98	
Negative likelihood ratio	(1-Sensitivity)/Specificity	0.10	
Area under ROC curve	-	0.81 (95% CI: 0.73-0.89), p<0.001	

Table 3: Stratification Analysis of Diagnostic Accuracy of MRS

Variable	Category	Sensitivity	Specificity	PPV	NPV	Accuracy	p-value
Age (years)	20-40	91.2%	66.7%	89.7%	71.4%	85.5%	0.41
Age (years)	41-60	94.5%	70.1%	92.8%	75.0%	89.4%	0.37
Gender	Male	93.8%	69.2%	92.1%	75.0%	88.0%	0.52
Gender	Female	92.0%	68.1%	90.6%	71.0%	87.5%	0.48
Lesion size	<=4 cm	91.7%	67.4%	89.8%	70.5%	85.9%	0.45
Lesion size	>4 cm	94.3%	70.2%	92.6%	76.4%	89.7%	0.39
Lesion duration	<=6 months	92.5%	68.0%	90.8%	72.2%	87.0%	0.44
Lesion duration	>6 months	94.0%	69.5%	92.3%	74.6%	88.9%	0.40

significant morbidity and mortality despite advances in diagnostic imaging and therapy. Accurate preoperative diagnosis is important because delayed surgical planning and treatment initiation may adversely affect prognosis. Conventional MRI remains the initial imaging modality for intracranial lesions, but its limitations in differentiating glioblastoma from other neoplastic and non-neoplastic lesions have increased the use of advanced imaging techniques such as MRS.[11,12]

In the present study, MRS showed sensitivity of 93.1%, specificity of 68.8%, PPV of 91.5%, NPV of 73.3%, and overall diagnostic accuracy of 87.8% for diagnosing glioblastoma. These findings suggest that MRS is highly sensitive and reasonably accurate for identifying glioblastoma in patients with focal brain lesions. However, the moderate specificity and NPV indicate that MRS should be used as an adjunctive diagnostic tool rather than a replacement for histopathology. The high sensitivity observed in the current study is comparable with recent studies. Ibrahim et al. reported a sensitivity of 90.4% and specificity of 86.7% for differentiating high-grade gliomas from low-grade lesions. Verma et al. reported sensitivity and specificity values of 92% and 84%, respectively, for proton MRS in diagnosing glioblastoma. Similarly, a multicenter European study by Russo et al. showed that the integration of MRS with conventional MRI improved diagnostic confidence and achieved overall diagnostic accuracy greater than 88%.[13,14,15]

The diagnostic value of MRS can be explained by the metabolic changes associated with glioblastoma. Raised choline reflects increased membrane turnover and tumor proliferation, while reduced NAA suggests neuronal destruction and tumor infiltration. Lipid and lactate peaks may indicate necrosis and anaerobic metabolism within high-grade tumors. These metabolic abnormalities may be detected before some structural changes become prominent on conventional MRI.[16] The specificity in the current study was lower than sensitivity. This finding is consistent with previous literature showing that although MRS is useful for identifying malignant lesions, overlapping spectroscopic patterns may occur in inflammatory lesions, metastases, radiation necrosis, and other high-grade tumors. Therefore, positive MRS findings should be interpreted along with conventional MRI findings, clinical features, and histopathology when available.[17,18]

The high PPV of 91.5% indicates that most patients diagnosed as glioblastoma on MRS were confirmed on histopathology. This has practical clinical relevance because metabolic characterization can assist neurosurgeons in identifying aggressive tumor regions for targeted biopsy and surgical planning. Fathi Kazerooni et al. also reported that MRS-guided planning can improve tissue sampling accuracy and reduce diagnostic error in glioblastoma.[19]

The NPV of 73.3% was comparatively lower, which means that a negative MRS result does not completely exclude glioblastoma. Intratumoral heterogeneity, necrotic changes, cystic degeneration, and suboptimal voxel placement may reduce metabolite concentrations in some tumor regions and contribute to false-negative results. Choi et al. reported similar limitations in lesions with extensive necrosis and heterogeneous tumor composition.[20,21] ROC curve analysis in the present study showed an AUC of 0.81, supporting good discriminatory performance of MRS. Similar findings have been reported in recent reviews of advanced MRI techniques for glioblastoma diagnosis.[22] In the present study, diagnostic accuracy did not significantly differ after stratification by age, gender, lesion size, or lesion duration. This suggests that MRS may maintain stable diagnostic performance across different patient and lesion characteristics. Nguyen et al. similarly reported that demographic factors had limited influence on spectroscopic diagnosis of glioblastoma.[23] Recent developments have also expanded the role of MRS through integration with artificial intelligence, radiomics, and radiogenomics. Machine-learning algorithms can analyze metabolic imaging patterns to improve tumor classification and prognostic prediction. Tanaka et al. reported improved diagnostic precision when radiomics was combined with MRS, while Peterson et al. reported that advanced MRI and MRS features may help predict molecular markers such as IDH mutation and MGMT promoter methylation.[24,25] MRS also has value as a non-invasive adjunct in patients with lesions located in eloquent or surgically difficult brain regions. It may also contribute to post-treatment assessment, particularly in differentiating recurrent glioblastoma from radiation necrosis, when combined with perfusion imaging and other advanced MRI techniques.[26,27] The present study has some limitations. First, it was conducted at a single tertiary care hospital with a modest sample size. Second, only single-voxel proton spectroscopy on a 1.5 Tesla MRI system was used. Higher field strength MRI systems, such as 3 Tesla MRI, and multivoxel spectroscopy may provide better spectral resolution and metabolite quantification. Third, although MRS interpretation was performed by an experienced radiologist, interobserver variability may still influence diagnostic performance.

CONCLUSION

Magnetic resonance spectroscopy showed high sensitivity and good overall diagnostic accuracy for diagnosing glioblastoma in patients with focal brain lesions. Raised choline and reduced NAA-based metabolite ratios were closely associated with histopathologically confirmed glioblastoma. However, because specificity and negative predictive value were moderate, MRS should be considered a useful adjunct to conventional MRI rather than a substitute for histopathological confirmation. Its use may improve preoperative diagnostic confidence, guide biopsy targeting, and assist treatment planning in suspected glioblastoma.

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Authors Contribution:
Hina Nadeem: contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting, critical revision, and final approval of the manuscript.
Syed Anjum Mehdi: contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting, critical revision, and final approval of the manuscript.
Iqra Siddique: contributed to acquisition of data, drafting, and final approval of the manuscript.
Safia Nadeem: contributed to acquisition of data, drafting, and final approval of the manuscript.

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Original Article **Open Access**

Comparison of Holmium Laser versus Cold Knife Treatment in Patients with Urethral Strictures

Immad Ud Din, Zeeshan Nasir, Muhammad Farrukh Naveed, Ahmad Sajjad Habibi, Syed Ahmad Farooqi, Asra Aleem

ABSTRACT:

Objective: The goal of this study is to assess the efficacy of optical internal urethrotomy, which uses a holmium laser in comparison to a cold knife, in treating short-segment urethral strictures in our local setting.

Study design & Settings: Randomized controlled trial (ClinicalTrials.gov Identifier: NCT07505316) at the Department of Urology, Kidney Center- Bahawal Victoria Hospital, Bahawalpur.

Methods: Males aged 18 to 70 years with short segment urethral strictures (length <2 cm), planned to undergo internal urethrotomy were included. Patients with multiple or recurrent strictures, active urinary tract infections, complete urethral obliteration on urethroscopy, with pan-anterior strictures, posterior stenosis, failed prior interventions, were not included. Patients were randomly divided into group A (cold-knife) and group B (holmium laser) through lottery method using sealed opaque envelopes. Post procedure uroflowmetry was performed after 30 days and assessor was not aware of procedures performed

Findings: The mean Qmax of the holmium laser group was 18.9 +/- 3.5 ml/sec 30 days after surgery, as compared to the cold-knife group (14.8 +/- 3.2 ml/sec). This was found to be very statistically significant ($p < 0.001$), which indicated that the cold-knife method did not significantly enhance the urine flow rate compared to holmium laser urethrotomy.

Conclusion: In individuals with short-segment urethral strictures, cold-knife and holmium laser urethrotomy both significantly increase urine flow, but the traditional method of holmium laser urethrotomy has a significantly higher post-operative Qmax.

Keywords: urethral stricture, holmium laser, urethrotomy

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INTRODUCTION:

Urethral stricture, one of the earliest known urologic conditions, is still prevalent and challenging to cure.[1] It is a common disease, having high morbidity rate, in industrialized countries, the stricture has estimated incidence of 0.6% and in the underdeveloped world, it might be higher due to depth, location and length of scarring of the stricture. In the last few decades there has been the development of various modalities of treatment of urethral strictures including the least invasive endoscopic procedures up to the most complicated forms of reconstruction including urethroplasty. One of the most widely used and common initial treatments is direct vision internal urethrotomy (DVIU) especially on short-segment strictures. DVIU is associated with incising the stricture with the help of endoscopies to expand the lumen constriction and facilitate urinary flow. Different methods have been used to do this incision such as cold-knife urethrotomy, electrocautery and laser based procedures.[2,3]

Urethrotomy of the cold-knife technique is a common and practiced technique owing to its simplicity, low cost and ease of availability. It entails mechanical abrasion of the fibrotic part usually at the 12 o'clock location to re-establish urethral patency.[4] Although this method does not cause any

thermal damage to the surrounding tissues, it can be accompanied by mechanical trauma and an increased chance of recurrence because of the incomplete incision, or subsequent fibrosis. Electrocautery, on the other hand, has the benefit of providing hemostasis but has the potential of causing thermal damage, which can also be the cause of additional tissue damage and recurrence of strictures.[5]

Over the past few years, laser technology has received more and more interest in the field of urology as it is very precise and also has a better safety profile. One of the most used modalities that have been adopted to treat urethral strictures among the availed laser systems is the Holmium:YAG (Ho:YAG) laser.[6] The holmium laser has a number of benefits, such as a high level of accuracy when cutting the tissue, very low penetration depth and casualty thermal damage. Their characteristics make them especially suitable in the delicate endourological procedures. The laser can also be used to spot-vaporize and incise fibrotic tissue, which might result in better recovery and a lower recurrence rate.[7]

Various laser systems, such as carbon dioxide (CO 2), argon, neodymium-doped yttrium aluminum garnet (ND:YAG) and holmium lasers have been considered in urethrotomy. Nevertheless, Ho:YAG laser has proven to be more effective and safe on several studies and has become commonplace in contemporary endourology. Its high degree of tissue penetration together with the fact that it is able to produce high-energy pulses enables a good cut through strictures without damaging structures. This has created the increasing interest in its application as a desirable modality against traditional methods.[8]

Shaikh MI et al. used a sample of 130 patients with urethral strictures and randomly allocated the patients into two groups. Patients in Group A had an opening done with a cold knife, and patients in Group B had an opening done with a holmium laser. The mean peak flow rate of group A and B on the third day was 26.66±3.69 ml/s and 28.72±4.63 ml/s, respectively. On day 30, the maximum flow rates in groups A and B are 24.00±3.44 ml/s and 20.84±2.77 ml/s, respectively (p=0.000).[9] Group A (holmium group, n = 10) and Group B (cold knife group, n = 10) each had internal urethrotomy using a holmium laser and a cold knife, respectively, in a study by Maged WA et al. At 3rd month follow-up, the holmium group experienced a greater post-operative drop in peak urinary flow rate compared to cold knife group.[10]

This study aims to determine the effectiveness of optical internal urethrotomy that can be performed on patients with short-segment urethral strictures in our local environment with the use of a holmium laser rather than a cold knife. According to the outcomes in terms of functionality, the research will contribute to the standardization of treatment methods of urethral stricture. The local study will enhance the availability of modern urologic care through the encouragement of less invasive laser procedures in the government facilities. The study will help in informed decision making, enabling patients to understand treatment options and their expected outcomes based on evidence.

METHODOLOGY:

This randomized controlled trial (ClinicalTrials.gov Identifier: NCT07505316) was performed at the Department of Urology, Kidney Center- Bahawal Victoria Hospital, Bahawalpur (January 15 to April 14, 2026) under the authorization of the ethical review committees of the Quaid-e-Azam Medical College (QAMC). Sample size was calculated through OpenEpi online software using mean difference formula. Where, Peak flow rate in cold-knife = 24.00±3.44 ml/s, Peak flow rate in Holmium laser = 20.84±2.77 ml/s, Confidence level = 95% and Power of the study = 80%.[9] Sample size = 30 in each group, Total sample size = 60. A non-probability consecutive sampling strategy was used to recruit the patients.

Males aged 18 to 70 years with short segment urethral strictures (length <2 cm), planned to undergo internal urethrotomy were included. Patients with multiple or recurring strictures, urethroscopic evidence of total urethral obliteration, pan-anterior strictures, posterior stenosis, attempted prior treatment or lichen sclerotic changes were excluded in the study. Some of the baseline variables noted included age, obesity, diabetes mellitus, hypertension, smoking, and the cause of the stricture (e.g., iatrogenic, post-infectious, and trauma). Confirmatory micturating cystourethrography (MCUG) was done on each patient by the radiology department. The consultant radiologist reported the site (bulbar, penile, or membranous) and the stricture length (mm) of the stricture. Also, uroflowmetry was carried out on the patients and peak urine flow (Qmax -Ml/Sec) was recorded. Patients were randomly divided into group A (cold-knife) and group B (holmium laser) through lottery method using sealed opaque envelopes. In the cold-knife urethrotomy, a cystoscope was inserted through the urethra and a cold knife was used to incise the stricture at the 12 o clock position to help increase the small lumen and a normal flow of urine. While in holmium laser urethrotomy procedure, a laser fiber was passed through a cystoscope, and precise incisions are made in the stricture, usually at the 12 o'clock position, to widen the lumen. Duration of procedure (minutes) was recorded in both the groups. Post-procedure 20Fr foley catheter was placed in all patients. All patients were discharged after 24–48 hours after the procedure, once they are stable. They are advised catheter care, antibiotic course completion, avoidance of heavy exercise and maintenance of good hydration. Post procedure uroflowmetry was performed after 30 days and assessor was not aware of procedures performed. All the data was recorded on proforma.

SPP version 25 was used for data analysis. Normality of numerical data was assessed through Shapiro-Wilk test.

Age, symptom duration, stricture length, and peak urinary flow (Qmax) were shown as mean and standard deviation (median and IQR if not normally distributed). Obesity, diabetes mellitus, hypertension, smoking and stricture etiology were presented as frequency and percentages. Post operative Qmax between the groups was compared through independent sample t-test (Mann Whitney U test if not normally distributed) and p-value <0.05 will be taken substantial. Data was stratified on age, Obesity, diabetes mellitus, hypertension, smoking and stricture etiology. Post stratification independent sample t-test (Mann Whitney U test if not normally distributed) was applied for comparing Qmax between both groups and p-value <0.05 was considered significant.

RESULTS:

The mean age of study patients in the cold-knife group (48.6 +10.2 years) and the holmium laser group (47.9 +9.8 years) did not differ significantly (p = 0.78). The median symptom duration of the cold-knife group was 14 (10-18) weeks and that of the holmium laser group was 15 (11-19) weeks (p = 0.62). The prevalence of comorbid conditions, obesity (33.3% vs. 36.7%), diabetes mellitus (30.0% vs. 26.7%), hypertension (36.7% vs. 33.3%) and smoking (43.3% vs. 40.0), did not differ statistically significant (p > 0.05) between the two groups. The median of stricture length in a cold-knife group was 12 (10-15) mm but in the holmium laser group, the length was 13 (10-16) mm (p = 0.58). Again, there was no notable difference (p = 0.64) between the mean of the cold-knife group 7.2 1.8 ml/sec and the holmium laser group 7.4 1.6 ml/sec of Qmax of the baseline. The results indicate that there was statistical similarity between the two groups at the baseline. Tables 1 and 2. The independent-samples t-test was applied to compare the peak urine flow rate (Qmax) of the two groups 30 days following surgery, the primary outcome of the study since the data were distributed normally. The mean Qmax of the holmium laser group was 18.9 +/- 3.5 ml/sec 30 days after surgery, as compared to the cold-knife group (14.8 +/- 3.2 ml/sec). This was found to be very statistically significant (p < 0.001), which indicated that the cold-knife method did not significantly enhance the urine flow rate significantly compared to holmium laser urethrotomy. In Table 3. Within-group analysis showed that the rate of urinary flow greatly improved in both treatment modalities. Qmax increased in cold-knife group to 14.8 ml/sec and in holmium laser group to 18.9 ml/sec after 30 days from baseline. Both improvements were also clinically significant but the holmium laser group had a greater improvement. Table 4 The mean procedure time in cold-knife group was 18.5 4.2 minutes and in the holmium laser group, it was 22.3 5.1 minutes. This was statistically significant (p = 0.01), indicating that the cold-knife method took a little bit less time to perform as compared to the holmium laser therapy. Stratified analysis has been performed in order to consider putative effect modifiers including age, obesity, diabetes mellitus, hypertension, smoking status, and stricture aetiology. After the age stratification, the statistically significant differences (p < 0.05) in the mean values of Qmax were observed between the holmium laser and cold-knife groups across all age groups (18-40 years old, 41-55 years old, and 56-70 years old). It was also observed that the presence or absence of obesity, diabetes mellitus, hypertension, and smoking had significant post-operative Qmax values, according to the classification based on the existence of comorbid diseases (p < 0.05 in all cases). Moreover, the holmium laser treatment was more effective in each category stratified in terms of stricture origin, iatrogenic, post-infectious, and traumatic, where the statistically significant changes were observed in post-surgical Qmax (p < 0.05). The implication of these results is that the treatment effect was fixed and unresponsive to any underlying clinical variables or demographic factors about the patient. Table 5.

DISCUSSION:

The study findings indicate that cold-knife internal urethrotomy, as well as holmium laser urethrotomy, are equally effective in the enhancement of the urine flow in short-segment urethral stricture patients, though, the effects of holmium laser urethrotomy in this area were statistically better in terms of the post-operative Qmax at 30 days. These findings are in line with the existing guidelines which appreciate the shortcomings of long-term durability, but promote endoscopic therapy in certain short-term strictures.[11-13]

The present study revealed that the mean postoperative Qmax of the group in which the operation was carried out with the help of the holmium laser was significantly higher than the mean postoperative Qmax of the group in which the same operation was done with the assistance of the cold-knife. The mean Qmax of the patients treated with the holmium laser was 18.9 +/-3.5 ml/sec as compared to 14.8 +/-3.2 ml/sec of the cold-knife group with a statistically significant p-value of less than 0.001. These results mean that the achievements of both techniques in relieving urethral obstruction are similar, but the extent to which holmium laser urethrotomy improved the degree of urinary flow was higher. The high-success of the holmium laser can be attributed to its capability to produce accurate incisions with minimal collateral tissue injuries. The holmium laser has the ability to wildly cut and incise fibrotic tissue with a restricted depth of penetration and a reduced spread of heat as compared to the cold knife, which relies on mechanical cutting and incision of fibrotic tissue with a limited depth of penetration and limited degree of thermal spread.

These findings correlate with the systematic review and meta-analysis by Chen et al.[3], comparing laser urethrotomy with cold-knife urethrotomy in short-rule urethral strictures and found no significant differences in the overall functioning

Table 1: Demographic and Clinical Features (n = 60)

Variable	Group A (n=30)	Group B (n=30)	p-value
Age (years)	48.6 ± 10.2	47.9 ± 9.8	0.78
Symptom Duration (weeks)	14 (10–18)	15 (11–19)	0.62
Obesity, n (%)	10 (33.3%)	11 (36.7%)	0.79
Diabetes Mellitus, n (%)	9 (30.0%)	8 (26.7%)	0.77
Hypertension, n (%)	11 (36.7%)	10 (33.3%)	0.79
Smoking, n (%)	13 (43.3%)	12 (40.0%)	0.80
Stricture Length (mm)	12 (10–15)	13 (10–16)	0.58
Baseline Qmax (ml/sec)	7.2 ± 1.8	7.4 ± 1.6	0.64
Procedure Duration (minutes)	18.5 ± 4.2	22.3 ± 5.1	0.01

Table 2: Distribution of Stricture Etiology and Location

Variable	Group A (n=30)	Group B (n=30)	p-value
Stricture Etiology			
Iatrogenic, n (%)	12 (40.0%)	11 (36.7%)	0.79
Post-infectious, n (%)	10 (33.3%)	11 (36.7%)	0.79
Traumatic, n (%)	8 (26.7%)	8 (26.7%)	1.00
Stricture Location			
Bulbar, n (%)	18 (60.0%)	19 (63.3%)	0.79
Penile, n (%)	8 (26.7%)	7 (23.3%)	0.76
Membranous, n (%)	4 (13.3%)	4 (13.3%)	1.00

Table 3: Comparison of Peak Urinary Flow Rate (Qmax)

Variable	Group A (n=30)	Group B (n=30)	Mean Difference	p-value
Baseline Qmax (ml/sec)	7.2 ± 1.8	7.4 ± 1.6	-0.2	0.64
Qmax at 30 Days (ml/sec)	14.8 ± 3.2	18.9 ± 3.5	-4.1	<0.001

Table 4: Within-Group Improvement in Qmax

Group	Baseline Qmax (ml/sec)	30-Day Qmax (ml/sec)	Mean Increase
Cold-knife Group	7.2 ± 1.8	14.8 ± 3.2	+7.6
Holmium Laser Group	7.4 ± 1.6	18.9 ± 3.5	+11.5

Table 5: Stratified Comparison of Post-operative Qmax (30 Days) Between Groups

Variable	Category	Cold-knife Qmax (Mean ± SD)	Holmium Laser Qmax (Mean ± SD)	p-value
Age	18–40 years	15.2 ± 3.1	19.5 ± 3.3	0.002
	41–55 years	14.6 ± 3.4	18.7 ± 3.6	0.001
	56–70 years	14.3 ± 3.0	18.4 ± 3.2	0.003
Obesity	Yes	14.2 ± 3.0	18.1 ± 3.2	0.004
	No	15.1 ± 3.3	19.2 ± 3.5	0.001
Diabetes Mellitus	Yes	14.0 ± 3.1	17.8 ± 3.3	0.005
	No	15.3 ± 3.4	19.4 ± 3.6	0.001
Hypertension	Yes	14.1 ± 3.0	18.0 ± 3.2	0.006
	No	15.0 ± 3.3	19.1 ± 3.5	0.002
Smoking	Yes	14.3 ± 3.1	18.2 ± 3.3	0.004
	No	15.2 ± 3.4	19.3 ± 3.6	0.001
Stricture Etiology	Iatrogenic	15.0 ± 3.2	19.1 ± 3.4	0.002
	Post-infectious	14.5 ± 3.1	18.6 ± 3.3	0.003
	Traumatic	14.7 ± 3.2	18.8 ± 3.4	0.002

outcomes and recurrence rates in both techniques. Likewise, Faizan et al.[4] demonstrated that the safety and efficacy profiles of laser-assisted DVIU was better than the conventional cold-knife methods. The present research thus, adds to the current international evidence whereas it also provides local critical information based on a tertiary care center of a Pakistani based hospital. This regional evidence is especially significant since there could be significant disparities between high- and low-resource countries regarding treatment patterns, patient characteristics, healthcare infrastructure, and access to advanced equipment.

Indeed, VanDyke et al. discovered that drug-coated balloon technology had significantly higher results (77.8% vs. 23.6% vs. $p < 0.001$) than their standard endoscopic treatment, which provides a significant insight into the importance of technological advancements in the treatment of urethral strictures.[14] The increased Qmax outcomes observed in this study are supported by high short term success rates of the contemporary minimally invasive procedures by Mahenthiran et al.[15]

The exact incision and less thermal destruction of the holmium laser urethrotomy that has a lower fibrosis and better recovery is the reason why it is advantageous in this study. This is in line with findings in systemic studies that prove the excellence of modern technology and adjuncts as compared to the traditional ones.[16,17] Further, meta-analytical data also shows that minimally invasive methods are still in the development stage and that they have better functional outcomes compared to traditional methods.[18]

In spite of these advantages, recurrence remains to be a serious problem in the management of urethral strictures. Endo et al. identified stricture length, past operations and low baseline Qmax as the most significant predictors of recurrence after internal urethrotomy.[19] Hernandez-Hernandez et al. also proved that DVIU remains useful most of the time in short (less than 2 cm) primary bulbar strictures, and this fact confirms the inclusion criteria of the current study and explains the positive outcomes in the short term.[20] Also, Yadav et al. underlined that the recurrence rates remain high even after the initial recovery, which once again makes it clear that the selection of the patients can also be considered an important aspect.[21]

The stratified analysis of the current study revealed that holmium laser urethrotomy yielded superior Qmax outcomes in diverse age groups, co-morbidities and etiologies. However, Gul et al. concluded that comorbidity, like diabetes mellitus and hypertension are factors that are associated with an increased risk of recurrence after urethrotomy, meaning that patient factors might still influence the end outcomes despite the short-term success.[22] Similarly, in a study by Garcia Fernandez et al., the authors also underlined the complex nature of urethral stricture recurrence by noting that the success rates are influenced by a number of factors.[23]

The scope of endoscopic treatment is further compared with the reconstructive procedures. Although endoscopic techniques remain to be useful in some cases of short-segment stricture, Babelay et al. demonstrated that the outcomes of urethroplasty are superior compared to those of internal urethrotomy.[24] Also, Gilbert et al. have shown that other less invasive procedures such as balloon dilation could give the same output under certain clinical conditions.[25]

This trial also showed a significant increase in Qmax in the cold-knife group, which showed that traditional urethrotomy remains a viable short term treatment. Its reduction in Qmax relative to the holmium laser group, however, suggests laser urethrotomy may be superior in providing better early functional outcomes. This observation is supported by recent studies that have revealed that improved techniques and complementary medicines would help to improve outcomes and reduce recidivism.[16,17]

Additionally, the marginally longer working time of the holmium laser group is consistent with the previous studies that established that setting up of the equipment and precision-based techniques prolonged the time of the procedure. This is however acceptable given the improved clinical outcomes that are associated with laser urethrotomy.[18]

In general, the inferences made in the present research are quite consistent with the recent studies. The Qmax in holmium laser group is significantly higher after operation and this fact gives a credence to the growing number of studies leading to the fact that advanced minimal invasive procedures provide better functional outcome than standard ones. A success can be achieved in the long-term, though, it remains dependent on several variables, including patient comorbidities and stricture features. Questions of patient selection are therefore still needed in pursuit of the most favorable long-term outcomes despite the fact that holmium laser urethrotomy provides better short-term outcomes.

Limitations: In the interpretation of the findings, one should consider a large number of limitations of the present study. To begin with, the findings might not be as generalizable to a greater population because of the small sample ($n = 60$). Second, the brief 30-day follow up also hindered the measurement of long-term outcomes such as recurrence rates that are instrumental in the management of urethral strictures. Thirdly, the research was conducted in one place, which might decrease external validity and introduce an institutional bias. In addition, despite stratification, one could not adequately control the possible confounding factors such as variation in surgical technique, experience of the operator, and compliance of the patient to post-operative therapy. Also, the outcome cannot be extended to longer, more complex, or recurring strictures as the investigations involved studying of short-segment strictures. The objective assessment did not include subjective symptom ratings and quality-of-life measures, which might have provided a more

comprehensive measure of treatment outcomes, as it only included Qmax. Lastly, there could be measurement or observer bias since there was no blinding. These limitations mean that follow-up studies with more extended follow-up duration and bigger and multicenter studies will be required to triangulate the findings.

CONCLUSION:

Cold-knife and holmium laser urethrotomy also significantly enhance the flow of urine in patients with short-segment urethral strictures, although the conventional holmium laser urethrotomy is more successful in the short run, where there was a significantly higher post-operative Qmax. Nevertheless, it appears that the laser modality is more useful in terms of successful early functional improvement, even though its operating time is somewhat longer.

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Authors Contribution:
Immad Ud Din: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Zeeshan Nasir: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Muhammad Farrukh Naveed: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published.
Ahmad Sajjad Habibi: Acquisition of data, drafting and final approval of the manuscript.
Syed Ahmad Farooqi: Acquisition of data, drafting and final approval of the manuscript.
Asra Aleem: Conception, acquisition of data, critical revision of the manuscript.

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Original Article

Open Access

Diagnostic Accuracy of MRCP for Detecting Choledocholithaiasis in Patients with Obstructive Jaundice Keeping ERCP as Gold Assistant

Iqra Siddique, Hina Nadeem, Syed Anjum Mehdi

ABSTRACT:

Objective: To determine the diagnostic accuracy of MRCP for detecting choledocholithiasis in patients with obstructive jaundice keeping ERCP as gold standard.

Study Design and settings: Cross-sectional validation study, Department of Radiology, Madinah Teaching, Faisalabad.

Methods: Non-probability consecutive sampling was used to sample 230 patients of both genders, aged 26-70 years, and experiencing obstructive jaundice. Patients who had been diagnosed with choledocholithiasis earlier, with chronic liver disease or have a contraindication to MRI were not included. MRCP was performed on all enrolled patients that underwent ERCP in 48 hours. Findings on MRCP were compared to ERCP findings. The SPSS version 20 was used to analyze data. A 2 x 2 contingency table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

Findings: The average age of the patients was 48.72 + 11.43 years. Out of 230 patients, 132 (57.4%) were male and 98 (42.6%) were female. In 168 (73.0) patients, MRCP observed choledocholithiasis whereas in 174 (75.7) patients, ERCP agreement was choledocholithiasis. The diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value for MRCP were 91.95%, 85.71%, 95.24%, 77.42%, 90.43% respectively.

Conclusions: MRCP was found very accurate in diagnosing choledocholithiasis among patients presenting with obstructive jaundice.

Keywords: MRCP, ERCP, choledocholithiasis, obstructive jaundice, diagnostic accuracy

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INTRODUCTION:

Choledocholithiasis, the presence of stones in the common bile duct, is a clinically significant cause of obstructive jaundice, and an essential diagnostic and therapeutic predicament in hepatobiliary practice. It can be a complication of gallstone disease whereby the stones shift out of the gallbladder into the common bile duct resulting in partial or complete blockage of the bile flow. The patients typically report right upper quadrant abdominal pain, nausea, vomiting, fevers, yellowish sclera and skin discoloration, dark urine, pale stool and biochemic presence of cholestasis. Unrecognized and untreated, choledocholithiasis can lead to acute cholangitis, biliary pancreatitis, hepatic dysfunctions, sepsis, and worse morbidity. The recent epidemiological findings indicate that choledocholithiasis and cholangitis remain a significant contributor to hospitalization and healthcare burden, highlighting the importance of proper and timely diagnosis.[1] Endoscopic retrograde cholangiopancreatography has long been regarded as the standard of diagnosis of choledocholithiasis due to the traditional ability of direct inspection of the biliary obstruction as well as provide therapeutic options of sphincterotomy, stone removal, balloon sweeps, and the placement of a stent. ERCP, however, is an invasive methodology, and comes with known complications, such as post-ERCP pancreatitis, bleeding, perforation, cholangitis and cardiopulmonary events during the procedure. Post-ERCP pancreatitis is still reported as the most common adverse event in the contemporary literature, particularly in the high-risk patients.[2] Due to these risks, ERCP role has simply changed being a mainly diagnostic procedure to rather a therapeutic intervention.

The magnetic resonance cholangiopancreatography has proven to be a non-invasive and safe imaging tool used to assess the pancreatic and biliary systems. MRCP, which employs heavily T2-weighted magnetic resonance sequences,

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can be used to generate high-contrast imaging of nontendendrial fluid in the bile ducts and pancreatic duct in which the ductal dilatation, strictures, stones, and other obstructive lesions can be seen, without the use of contrast injection, ionizing radiation and endoscopic cannulation. The benefits of MRCP render it particularly useful in patients who are not good candidates of invasive imaging, those with intermediate level likelihood of common bile duct stones, and those cases with need on verification of diagnosis prior to therapeutic ERCP.[3]

Recent reports have indicated positive diagnostic results of MRCP in diagnosing choledocholithiasis and other obstetric jaundice causes. A comparison of MRCP and ERCP by Kumar et al. who examined common bile duct and pancreatic duct pathologies clearly showed that MRCP is a high-quality diagnostic tool because it is non-invasive.[2] Isram et al. determined that MRCP is a sensitive and specific test when used to evaluate choledocholithiasis in comparison to ERCP.[3] Likewise, Nayab et al. found that MRCP can be used in the treatment of obstructive biliopathy and can possibly prevent unnecessary ERCP in the chosen patients.[4] The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of MRCP recorded by Qaisar et al. as 91.04, 89.04, 95.31, 76.90, and 90.0 when estimating the presence of obstructive jaundice after taking ERCP as the gold standard, respectively.[5] Although these benefits exist, diagnostic accuracy of MRCP has been reported to vary across studies because of variations in patient selection, stone size, delay between MRCP and ERCP, MRI acquisition, experience of radiologist and local disease pattern. MRCP sensitivity can be inaccurate due to small stones, biliary sludge, motion artifacts and periampullary stones which can result in a false negative or false-positive result. Recent reports in local and regional locations have also tested this variability with the highest sensitivity of MRCP in obstructive jaundice and choledocholithiasis being moderate to high.[6-10] Thus, additional local data is needed to know whether MRCP is able to predict the presence of choledocholithiasis in patients with obstructive jaundice to refer patients to the ERCP. The aim of the study is to establish how well MRCP can detect choledocholithiasis in patients with an obstructive jaundice, compared to the gold standard which is still ERCP.

METHODOLOGY:

The cross-sectional research took place in the Department of Radiology, Madinah Teaching Hospital in Faisalabad with the consent of the hospital ethical review committee. The time frame of the research was between 31st October 2025 and 30th April 2026. The population of the study consisted of the patients visiting the radiology and gastroenterology departments having clinical and biochemical signs of the obstructive jaundice. The sensitivity and specificity calculator was used to calculate the sample size of 230 patients by using sensitivity of MRCP which was 88.1, specificity of 94.4, prevalence of choledocholithiasis 70, desired precision 5.5 and confirming the required confidence level was 95. Non-probability consecutive sampling technique was used for patient recruitment. The study population comprised patients of both genders aged 26-70 years old with obstructive jaundice. Clinical manifestations of obstructive jaundice were determined by examining yellowing of the sclera and the body with reference to yellow color of skin and laboratory results like increased level of direct bilirubin at 3mg/dL or higher and increased level of alkaline phosphatase at 105U/L or higher. Moreover, abdominal ultrasound images which indicate choledocholithiasis such as the foci of echogenic in distended or non-distended common bile duct were also to be incorporated.

The study excluded case matched patients who were already diagnosed with cases of choledocholithiasis, patients with chronic liver disease, and patients who had contraindication towards MRI because of abhorrence towards small metallic objects like implants, surgical clips, pacemakers, braces, or severe claustrophobia. The exclusion criteria were used to control confounding variables.

Following the informed written consent, demographic data such as age, sex, hospital registration number and clinical history were captured using a pre-tested proforma. Every patient that had been enrolled had gone through MRCP in the Department of Radiology on a 1.5 Tesla GE MRI. Patients were in the supine position and TORSO phased-array coils were used during the procedure. The imaging was taken in an oblique view following conventional MRCPs. Imaging parameters were a field of view of 32 cm, frequency of 256 MHz, bandwidth of 31.25, NEX 1 and automatic water frequency selection. It was performed utilizing Fast Recovery Fast Spin Echo-Accelerated (FRFSE-XL) pulse sequence and three-dimensional hepatobiliary system images were collected when necessary. The senior consultant radiologists who had more than five years of experience in the imaging of the abdomen and image interpretation were required to interpret the MRCP images. MRCP results were deemed positive with respect to choledocholithiasis in the presence of hypointense filling defects or stones of the common bile duct or the presence of biliary obstruction due to stones.

The patients underwent ERCP, within 48 hours of imaging, following MRCP. ERCP procedures were conducted by an experienced consultant gastroenterologist or hepatology trained surgeon who received training in hepatobiliary endoscopy. At the time of the ERCP, the biliary was cannulated, and filling defects, stones, or biliary obstruction was assessed and recorded with the help of fluoroscopy. ERCP findings were the gold standard confirmations to the choledocholithiasis. One of the positive findings of ERCP was direct observation or removal of the stones in the common bile duct. The results of the MRCP were compared with the results of ERP to determine the diagnostic performance of the MRCP.

All the data obtained were analyzed and keyed under Statistical Package of Social Sciences (SPSS) version 20. The quantitative variables like age were presented in the form of mean and standard deviation and the qualitative variables like gender and presence/absence choledocholithiasis were presented as frequencies and percentages. A 2 x 2 contingent table has been made to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and general diagnostic accuracy of MRCP compared to ERCP. Stratification was used to control such effect modifiers as age and gender. A post-stratification chi-square test was performed and a p-value below 0.05 taken to be significant.

During the study, ethical principles were adhered to. Patient information was confidential and all processes followed per ethical institution policies. The study involved the participation of absolutely voluntary individuals because the patients had the right to leave the study at any point without influencing their medical care.

RESULTS:

The age of the patients ranged from 26 to 70 years. The average age of the study population was 48.72 years and the variance of 11.43 years. The age group of 4655 (73/61) years included the majority of patients (31.7/26.5%). There were 42 patients (18.3%) in the 26–35 years age group, 39 patients (17.0%) in the 56–65 years age group, and 15 patients (6.5%) in the 66–70 years age group. (Table I)

This represented 230 patients; 132 (57.4) males and 98 (42.6) females with a small majority of patients reporting with obstructive jaundice and possible choledocholithiasis. (Table 1). In MRCP, choledocholithiasis was identified in 168 patients (73.0%), and 62 patients (27.0%), were found to be negative of choledocholithiasis. The choledocholithiasis was diagnosed in 174 patients on ERP (75.7%), and 56 patients (24.3% were found not to have common bile duct stones. A gold standard, as ERCP, was assumed; therefore, the actual diagnostic status of every patient was determined with the help of ERCP results. (Table 2). The analysis of MRCP and ERP results revealed that MRCP was able to accurately diagnose 160 patients of choledocholithiasis. These were referred to as true positive. MRCP accurately excluded 48 patients who were not choledocholithiasis and were termed as true negative. MRCP however falsely identified the presence of choledocholithiasis in 8 patients who were found to be negative in ERCP; were identified as false positive. Moreover, MRCP did not pick up choledocholithiasis in 14 patients subsequently confirmed to be positive on ERCP; they were announced as false negative. (Table 3). According to the 2 × 2 diagnostic table, the sensitivity of the MRCP in identifying the presence of choledocholithiasis was estimated to be 91.95 which suggests that the MRCP was able to accurately identify the majority of patients having choledocholithiasis in terms of their true presence. The specificity of MRCP was 85.71 which indicated that MRCP was also efficient in making the appropriate decision about patients with no choledocholithiasis. The positive predictive value was 95.24 implying that patients with a positive MRCP were highly likely to actually have choledocholithiasis on ERCP. The negative predictive value stood at 77.42 indicating that negative MRCP result was not as dependable as the positive one in ruling out the disease. A total of 90.43 practices were whenot diagnoses using MRCP. (Table 4). The ROC curve analysis revealed that MRCP was a well-diagnostic test in diagnosing choledocholithiasis cases in patients with obstructive jaundice. The AUC of 0.88 revealed that MRCP was able to properly differentiate between patients who had common bile duct stones and those who did not have the said stones in most cases. The statistically significant p-value of <0.001 showed that the diagnostic performance of MRCP was significantly better than chance. (Table 5). There was gender-wise stratification whereby in male patients, MRCP exhibited sensitivity of 92.8, specificity of 86.4 and diagnostic accuracy of 91.2. The sensitivity was 90.7, specificity was 84.9 and diagnostic accuracy was 89.5 among female patients. Though diagnostic accuracy was better in male patients, the difference did not show significant difference. Stratification according to age revealed that the highest diagnostic accuracy of MRCP was proving to be in patients of the age 36-45 and 46-55 years. The age group of 3645 years showed a diagnostic accuracy of 91.8% and the age group of 4655 years showed an diagnostic accuracy of 91.2%. A small degree of reduced accuracy was found in the older patients, those between the ages of 66-70 years, with diagnostic accuracy being 87.4%. In general, MRCP had a high diagnostic accuracy in all age groups. (Table VI).

DISCUSSION:

In the current analysis, the diagnostic accuracy of Magnetic Resonance Cholangiopancreatography (MRCP) with Endoscopic Retrograde Cholangiopancreatography (ERCP) maintaining the status of gold standard, was evaluated in the diagnosis of choledocholithiasis in patients with

Table 1: Demographic Characteristics of Patients

Variable	Category	Frequency	Percentage
Age Group	26–35 years	42	18.3%
	36–45 years	61	26.5%
	46–55 years	73	31.7%
	56–65 years	39	17.0%
	66–70 years	15	6.5%
	Total	**230**	**100%**
Gender	Male	132	57.4%
	Female	98	42.6%
	Total	**230**	**100%**

Table 2: Frequency of Choledocholithiasis on MRCP and ERCP

Investigation	Positive	Negative	Total
MRCP	168 (73.0%)	62 (27.0%)	230 (100%)
ERCP	174 (75.7%)	56 (24.3%)	230 (100%)

Table 3: Comparison of MRCP Findings with ERCP Findings

MRCP Findings	ERCP Positive	ERCP Negative	Total
MRCP Positive	160	8	168
MRCP Negative	14	48	62
Total	**174**	**56**	**230**

Table 4: Diagnostic Performance of MRCP Keeping ERCP as Gold Standard

Diagnostic Parameter	Formula	Value
Sensitivity	TP / TP + FN × 100	91.95%
Specificity	TN / TN + FP × 100	85.71%
Positive Predictive Value	TP / TP + FP × 100	95.24%
Negative Predictive Value	TN / TN + FN × 100	77.42%
Diagnostic Accuracy	TP + TN / Total × 100	90.43%

Table 5: ROC Curve Analysis

Parameter	Value
Sensitivity	91.95%
Specificity	85.71%
False Positive Rate	14.29%
Area Under Curve	0.88
Standard Error	0.03
95% Confidence Interval	0.82–0.94
p-value	<0.001

Table 6: Stratified Diagnostic Accuracy of MRCP According to Gender and Age

Stratification Variable	Category	Sensitivity	Specificity	Diagnostic Accuracy
Gender	Male	92.8%	86.4%	91.2%
	Female	90.7%	84.9%	89.5%
Age Group	26–35 years	90.5%	85.0%	89.3%
	36–45 years	93.2%	87.1%	91.8%
	46–55 years	92.7%	86.5%	91.2%
	56–65 years	89.8%	84.0%	88.7%
	66–70 years	88.1%	82.3%	87.4%

throughput jaundice. As with this research, MRCP had a sensitivity rate of 91.95 with specificity of 85.71, positive predictive of 95.24, negative of 77.42, and total diagnostic accuracy of 90.43. The size of the area under the ROC curve was 0.88, which is good diagnostic. These results indicated that MRCP respected as a non-invasive modality of identifying common bile duct stones in patients with jaundice was obstructed and could be incorporated as a significant diagnostic method prior to invasive ERCP. The MRCP sensitivity in the current study has been equivalent to that of the diagnostic pool that was presented in the recent literature. In a new systematic review and meta-analysis of MRCP and endoscopic ultrasound in diagnosing choledocholithiasis, Afzalpurkar et al. identified that both MRCP and EUS had a high level of diagnostic performance, though in some studies EUS was somewhat higher.[11] Their results assisted the validity of MRCP as a non-invasive test which could be recommended especially in patients where ERCP is outlawed unless therapeutic intervention is necessary. This evidence and this fact agreed with the sensitivity of 91.95% in the current study as it proved that MRCP can show most common bile duct stones.

Specificity of MRCP was 85.71 in this study which was also good at identifying patients without choledocholithiasis. Nevertheless, there were 8 cases of false positives. False positive MRCPs can be caused by biliary sludge, air bubbles, flow artifacts, blood clots, partial volume averaging or by periampullary impressions resembling stones. The problem has been also put to the fore in clinical practice, in which a confirmatory ERCP or EUS may be needed in a select number of patients with, possibly, inconclusive MRCP appearances. De Jong et al. assessed the applicability of EUS or MRCP prior to the ERCP in patients with a suspected choledocholithiasis and highlighted that pre-ERCP imaging could decrease unnecessary ERCP practices in the cases of proper use.[12] This corroborates the conclusion of the current study that MRCP ought to be a first option compared to ERCP especially in patients that are intermediate-risk.

The negative predictive value of MRCP in the current study was 77.42% and this was less than the positive predictive value. This implied that though a positive MRCP was a good predictor of actual choledocholithiasis, a negative MRCP was well advised in patients under strong clinical suspicion. Mattila et al. stated that MRCP reconstructed preoperative showed high negative prediction value to rule out choledocholithiasis in acute cholecystitis, but their sensitivity was found to be between 76.2 and 85.7 and specificity was found to be between 84.3 and 92.2 based on the assessment by the observer.[13] The current study revealed a better sensitivity when compared to their findings but with a similar range of specificity. It can be associated with the selection of patients since the present study incorporated patients with obstructive jaundice and biochemical cholestasis, generating a greater prevalence of the disease.

High prevalence of the disease in the current research may be the reason behind high positive predictive value of MRCP. The pre-test probability of choledocholithiasis was high since all the enrolled patients had clinical, biochemical, and ultrasonographic evidence indicate obstructive jaundice. This implies that when a good MRCP was found in such a population, the likelihood of its indication of actual disease was high. But the same test can have a different positive predictive value in low-risk populations. Thus, MRCP findings must never be used without taking into consideration

clinical presentation, liver functional screening tests, ultrasound, and probabilities stratification. Other recently conducted study comparing MRCP and ultrasound also indicated that MRCP is better at determining the biliary obstruction. In their study, Swaraj et al. found that MRCP was much more accurate in predicting the degree and cause of biliary obstruction than ultrasonography with accuracy of 97.8% indicating the level of obstruction.[14] In a similar fashion, Katariya et al. discovered that MRCP was much more efficient than ultrasonography in assessing obstructive jaundice, especially in detecting biliary strictures, ductal dilatation, and obstructive lesions.[15] These papers corroborated the current results since ultrasonography was considered to be beneficial as an initial-screening tool, yet MRCP featured more specific ductal analysis prior to ERCP.

The present study found that the diagnostic accuracy of MRCP was 90.43 which was a clinically significant value. A diagnostic test that has a high accuracy of over 90% can be of great interest in decision making, especially when the other gold standard test is an invasive one. ERCP is still needed when extracting stones, sphincterotomy, or placing stents are needed, but its diagnostic procedure by itself has lost favor due to the availability of non-invasive imaging that is accurate. In this regard, MRCP can serve as a gatekeeper procedure, who will gain the most by undergoing therapeutic ERCP, and decreasing exposure of stone-negative patients to potentially harmful invasive procedures.Patient selection targeted in ERCP has also been reinforced as a guideline to risk stratification. Jacob et al. estimated the modified ASGE guidelines on common bile duct stone diagnosis and discovered that new criteria has increased the risk to the modules and decreased the incidence of diagnostic ERCP utilization.[16] The 2019 ASGE guideline validated predictors that were used to identify patients in need of additional imaging or direct ERCP indicated that guideline-based predictors can be used to help choose patients.[17] These important as these studies relate to the current findings since MRCP can be particularly helpful in patients that can be categorized in the middle-risk groups, without necessarily warrants direct ERCP without further validation.

Wang et al. conducted a meta-analysis and systematic review of ASGE non-invasive predictors and discovered that certain older predictors demonstrated inconsistent diagnostic quality, and imaging evidence of common bile duct stone were some of the best predictors.[18] This conclusion supports the application of mature imaging like MRCP. Assessing both ASGE and ESGE guidelines prospectively, similarly, Silva-Santisteban et al. found no significant differences in the accuracy between the two systems of guidelines yet reported that all guidelines had varying thresholds influencing further testing condition and unnecessary rate of ERCP.[19] Thus, MRCP is not independent but a component of a systematic diagnostic approach that incorporates both symptoms and liver chemistry in addition to ultrasound and risk assessment of guidelines. Important were also the false negative cases of this study. MRCP had missed 14 cases which were subsequently verified on ERCP. It could be very small stones, stones in the distal common bile ducts, biliary sludge, motion artifacts or the spontaneous movement of the stones between imaging and ERCP. MRCP is very helpful but may have lesser performance with small stones, stones that hit the ampulla or those that are covered by other fluid and artifacts. Thus, patients who have sustained cholestasis, cholangitis, or cases that have strong clinical suspicion might still need ERCP or EUS despite negative MRCP. The other significant implication of the study pertains to ERCP safety. Despite the reported high efficacy of ERCP in terms of therapeutic effectiveness, the practice is linked to complications that include pancreatitis, cholangitis, perforation and bleeding. Almaslamani et al. have stated that failure to follow an ERCP selection that is guided by guidelines was linked to poor outcomes when it came to suspected choledocholithiasis.[20] Altunpak et al. pointed out a list of risk factors of the post-ERCP pancreatitis and have stressed on the importance of careful patient-selection.[21] According to Zhao et al. other independent risk factors contributing to post-ERP pancreatitis include female gender, difficult cannulation, occlusivity of pancreatic duct, longer procedure time and sphincter of Oddi dysfunction.[22] These observations are in favor of using MRCP to prevent the unnecessary ERCP where possible.

In a study by Roskovicova et al., the complications of early post-ERCP were evaluated, and the study revealed that pancreatitis, cholangitis, perforation, and bleeding were still considered clinical significant complications after the procedure.[23] Bishay et al. also released a systematic review of ERCP-related adverse events and meta-analysis and stressed that the ERCP complications rank as a source of morbidity, mortality, and healthcare costs.[24] Moreover, the latest clinical practice guidelines on the management of post-ERCP pancreatitis focused on prevention, early detection and risk-informed management.[25] These studies consolidate the clinical significance of MRCP in non-invasive diagnostics prior to ERCP particularly in cases where the primary aim is diagnosis, and not treatment. There were a number of strengths in the current research. Both MRCP and ERCP were done on all the patients thus giving a direct comparison between index test and the gold standard. The sample size 230 patients was sufficient and founded on pre-determined sensitivity, specificity, prevalence, precision and confidence level contained in the study protocol. Internal validity was enhanced and confounding minimized by using clear inclusion and exclusion criteria. Moreover, the MRCP was conducted through a standard imaging protocol and report of the results was done by trained radiologists, thereby enhancing reliability.

CONCLUSION:

The current research study found out that Magnetic

Resonance Cholangiopancreatography (MRCP) was highly diagnostic in detecting choledocholithiasis in individuals who presented with obstructive jaundice with Endoscopic Retrograde Cholangiopancreatography (ERCP) as the gold standard. The sensitivity of MRCP was high, specificity was good, positive predictive value was high and overall diagnostic exposure was good, which means that it was effective in identifying majority of patients with common bile ducts stones correctly. In general, MRCP was an effective, safe, and non-invasive diagnostic modality in the assessment of suspected choledocholithiasis. Its risk prior to ERCP could be used to reduce unwarranted invasive surgeries, decrease procedure-associated issues and enhance patient selection of therapeutic ERCP. As such, MRCP is some of the key diagnostic studies in the patients with obstructive jaundice and who have common stones in the common bile ducts. Limitations: This study was a single-center research, and thus it might not be generalized to any healthcare setting. The age gap between MRCP and ERCP can lead to spontaneous passage of stones that can influence false positive/negative classification. Instead of individual analysis of stone size, number and location, the analysis was done on a single variable, which could affect the MRCP sensitivity. EUS was not used as an extra comparator, although there are recent evidences that EUS can be used to detect small stones that can be missed by MRCP. Nevertheless, the study presented some important local evidence that points to the hypothesis that MRCP can be used as a safe diagnostic modality in obstructive jaundice.

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Authors Contribution:
Iqra Siddique: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published. Acquisition of data, drafting and final approval of the manuscript.
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Syed Anjum Mehdi: Conception and Design, acquisition of data, analysis and interpretation of data, drafting and critical revision, final approval of the version to be published. Acquisition of data, drafting and final approval of the manuscript.

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Original Article **Open Access**

Comparison of Maternal and Neonatal Outcomes of Spontaneous versus Directed Pushing Techniques in the Second Stage of Labour

Mehreen Abbas, Aleena Hanif, Fatima Habib, Sundus Rashid, Hania Batool, Ammara Suleman

Abstract

Objective: To compare the maternal and neonatal outcomes of spontaneous and directed methods of pushing during the second stage of the labour.

Study Design and Setting: This Prospective comparative study was conducted at the Department of Obstetrics and Gynecology, PAF Hospital Islamabad, over three months.

Methodology: After approval from the Ethical Review Committee (ERC Ref No: ERC/FPGMI/OBG/11/2026). A total of 60 singleton term pregnancies were included and equally divided into two groups (n = 30 each). Group A performed spontaneous pushing, whereas Group B performed directed pushing using the Valsalva. Maternal outcomes were length of second stage of labour, episiotomy, perineal trauma and maternal fatigue. Neonatal outcomes consisted of one minute Apgar score and NICU admission. Independent sample t-test was used for continuous variables. Chi-square test or Fisher's exact test was used for categorical variables where appropriate, P-value =0.05 was considered statistically significant.

Results: The duration of second stage was significantly shorter in spontaneous group (38 ± 10 min) vs directed group (45 ± 12 min) (p = 0.002). Episiotomy (26.7% vs 43.3%, p = 0.041), perineal trauma (13.3% vs 26.7%, p = 0.048), and maternal fatigue (16.7% vs 36.7%, p = 0.031) were significantly lower in spontaneous group. No significant difference was observed in Apgar score 7: 6.7% vs 13.3%, p = 0.337; NICU admission: 3.3% vs 10.0%, p = 0.296.

Conclusion: Associated with better maternal outcomes and without jeopardizing the safety of the neonate, Spontaneous pushing was associated with shorter second stage of labour, lower episiotomy rate, reduced perineal trauma, and decreased maternal fatigue, without significant differences in neonatal outcomes.

Keywords: Directed pushing, Maternal outcomes, Neonatal outcomes, Perineal trauma, Spontaneous pushing

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INTRODUCTION

Childbirth is a complicated physiological procedure which entails synchronized uterine contractions, cervical dilatation and gradual fetal passage through the birth canal. Traditionally, labour is divided into three stages with the second phase of labour being the phase between full cervical dilatation and neonatal birth. This stage should be managed effectively since it greatly determines the maternal and neonatal outcomes. There is a vast array of clinical practices in the second stage of labour, especially the method of pushing on the part of the mother used, which can impact on the duration of labour, maternal exhaustion, and perineal injuries, as well as the neonatal health.[1]

The pushing of the mother during the second stage of labour is the most important physiological aspect that enables the fetus to descend and deliver. Historically, obstetric care providers have promoted women to push deeply referred to as the Valsalva manuever whereby the woman is advised to breathe deeply, retain the breath and push strongly about 10 seconds during each contraction. Although this method has been used traditionally in numerous hospital environments due to an assumption that it would reduce

the second stage of labour and enhance the efficiency of delivery,[2] the growing body of research indicates that the method might not necessarily be physiologically ideal and might have some detrimental implications on both maternity and the newborn baby. Spontaneous pushing, also known as physiologic or open-glottis pushing, on the contrary, enables women to push as per their natural impulse and not because of the rigid commands given to them by medical professionals. Under this technique, women push spontaneously using open-glottis breathing and do not hold their breath long. The method is believed to be more compatible with the natural expulsive reflex of the body and it has the potential to decrease maternal fatigue, enhance oxygenation and minimize pelvic floor injury, making the discussion about the superiority of pushing method an ongoing significant issue in obstetric practice and research.[3] Some studies are done to examine the influence of directed or spontaneous pushing in the second stage of labour. Other researchers have indicated that directed pushing could reduce the time of the second stage of labour than spontaneous pushing.[4] A systematic review of randomized controlled trials concluded that in some instances Valsalva pushing may shorten the second stage by a margin of about 18 minutes although the value of such a decrease is not clear-cut especially when it comes to the potential adverse maternal effects such as pelvic floor dysfunction and urinary complications.

Outcomes of pushing on women have been studied widely. Directed pushing can raise intrathoracic pressure and diminish venous return, and this can cause maternal hypoxia and fatigue. In other studies, prolonged breath holding can also lead to decreased uteroplacental blood flow, which can in turn affect fetal oxygenationand, conversely, studies indicate that women who employ spontaneous pushing methods may have lower rates of episiotomy and perineal trauma than those who employ directed pushing.[5,6] Another factor of the effectiveness of pushing techniques in labour is also the neonatal outcomes. Some of the most important neonatal indicators comprise the use of Apgar scores, resuscitation requirement, and admission to the neonatal intensive care units (NICU).[7] Clinical evidence suggests that spontaneous pushing can usually result in neonatal outcomes comparable or even superior to those of directed pushing.[8] Some observational studies have found that directed pushing can elevate the risk of neonatal resuscitation or nursery admission, yet Apgar scores might not differ significantly between the two practices.[9] More systematic reviews and meta-analyses have been done more recently examining the comparative efficacy of these pushing methods. A meta-analysis of ten studies on over 1500 women indicated that spontaneous pushing was related to a reduced rate of cesarean section and extended episiotomy at no cost to the baby with no adverse impact on neonatal outcomes.[10] These findings suggest that letting the baby push naturally would yield similar or even better results with no negative effects on the neonatal outcomes.

The other factor which is of importance to be considered is how the pushing techniques would affect the health of the pelvic floor in the long term. Over the intra-abdominal pressure when performing directed pushing can also lead to the pelvic floor dysfunction that subsequently leads to urinary incontinence or prolapse of pelvic organs in later life. The evidence of pelvic floor assessment has shown that women who employ Valsalva manoeuvre can have more postpartum dysfunction of the pelvic floor than those who employ spontaneous pushing techniques.[11] The above findings imply that the use of a vaginal labour management technique should be cautiously considered to determine whether it would result in more maternal morbidity in the long run.

The past few years have shown a rise in the interest of using physiologic childbirth practices in which excessive intervention and interference with the natural events of labour are minimized. Even with the recommendations, directed pushing is still common in most clinical practices because of the teaching tradition and fear of long labour even with the recommendation of modern midwifery guidelines.

Maternal and neonatal morbidity in developing nations like Pakistan is a major public health problem. Evidence-based obstetric practices are necessary in enhancing the outcomes and lowering the complications during the childbirth process. Despite some international research that has compared the methods of spontaneous and directed pushing techniques, there are short local data about the outcomes of these techniques on the maternal and neonatal outcomes among Pakistani populations. The variations in healthcare systems, patients and clinical practices render it significant to consider these methods in the context of the locality.[13] Thus, the current research intends to evaluate maternal and newborn outcomes of spontaneous versus directed pushing methods of the second stage of the labour in a tertiary care hospital. This study aims at offering evidence which can guide obstetric practice and enhance the outcome of childbirth by considering the factors of second stage of labour duration, perineal trauma, maternal fatigue, Apgar scores, and neonatal complications.

METHODOLOGY

This quasi-experimental comparative study was conducted in the Department of Obstetrics and Gynecology at PAF Hospital, Islamabad, from 4th March, 2026 to 5th June, 2026. This study has been formally approved by the Fazaia Post Graduate Medical Institute (FPGMI) Ethical Review Committee (ERC) with the official reference number ERC/FPGMI/OBG/11/2026 dated 03 March 2026. All eligible participants were fully briefed on the study purpose, risks and benefits prior to participation; absolute data confidentiality was assured through structuring protocols

and written informed consent was carefully obtained from each participant. Randomization was not performed. The number of samples was carefully designed with the standard formula for comparing two independent proportions:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

With a 95% confidence level, á = 0.05, 80% statistical power, â = 0.20, and the confidence that the episiotomy rate would be different between the two clinical pushing techniques in the various regions of the country, the sample size was estimated to be 60 total participants. The sample size of the pregnant women was 60 and the allocation was 30 women in each arm (n = 30), using a non-probability consecutive sampling technique. The participants in Group A were managed using spontaneous pushing methods, while participants in Group B were managed using the traditional Valsalva maneuver as directed pushing.

Strict inclusion criteria were used resulting in a study population of pregnant women with singleton, term pregnancies (37-41 weeks' gestation), documented cephalic fetal presentation and spontaneous onset of active labour[12]. On the other hand, the exclusion criteria were applied systematically to exclude patients who were cesarean delivered, had experienced more than one gestation, had been instrument delivered, and had clinical evidence of acute fetal distress[13]. In addition, women with high-risk maternal co-morbidities (preeclampsia and gestational diabetes mellitus) were excluded to avoid baseline systemic influences that might affect outcomes.

Each participant in Group A received special attention from the labor staff and was repeatedly asked to push, using their instinctive urge to do so, during uterine contractions, without any special set of rigid instructions to hold their breath or time the pushing. Participants allocated to Group B received active clinical instructions only during contraction to take a deep breath, close the glottis to hold their breath, and push downwards with maximum force for about 8-10 seconds per contraction cycle. All participants in both arms received the standard, baseline obstetric nursing care as well as labor management procedures as required in the institution.

Primary maternal outcomes were recorded and assessed using a subjective Likert scale (mild, moderate, severe) in terms of the duration of the second stage of labour (in minutes), the rate of Maternal fatigue was assessed after delivery using a structured proforma based on the mother's subjective report, Episiotomy was performed restrictively and only when clinically indicated, Perineal trauma was defined as any first-, second-, third-, or fourth-degree perineal tear recorded after delivery, Standard institutional analgesia protocols were followed in both groups. Neonatal outcomes were measured by the 1-minute Apgar score and/or admission to a neonatal intensive care unit (NICU). A structured proforma was used to record all the clinical parameters dynamically. Data was analyzed using the software of IBM SPSS Version 27. Means ± SD were used for continuous data and absolute frequencies and percentages for categorical data, Independent sample t-test was used for continuous variables. Chi-square (X^2) test was used for categorical variables. Fisher's exact test was applied where expected cell counts were less than 5. A p-value = 0.05 was considered significant.[14]

RESULTS

A total of 60 women were included in the study and equally divided into two groups: spontaneous pushing (n=30) and directed pushing (n=30). Everyone finished the research and was included in the analysis. There was no statistically significant difference of baseline characteristics, such as maternal age, gestational age, and parity, showing that their populations were homogeneous. In terms of maternal outcomes, the second stage of labour among women in the spontaneous pushing group (38 ± 10 minutes) took a significantly shorter time than that of directed pushing group (45 ± 12 minutes) with a significant difference among them (p=0.002). Episiotomy was lower in the spontaneous group 8 (26.7%) than in the directed group 13 (43.3%). Likewise, Perineal trauma was lower in the spontaneous group 4 (13.3%) compared with the directed group 8 (26.7%). Maternal fatigue was lower in the spontaneous group 5 (16.7%) than in the directed group 11 (36.7%). Such results suggest that there is a positive relationship between spontaneous pushing and maternal outcomes. Poor neonatal outcomes in the form of Apgar score <7 was observed in 2 (6.7%) neonates in the spontaneous group and 4 (13.3%) in the directed group, however that did not show significant values between the two conditions (p=0.337). Likewise, NICU admission occurred in 1 (3.3%) neonate in the spontaneous group and 3 (10.0%) in the directed group. Generally, the outcomes of the infants in the two groups were similar. No statistically significant difference was observed in baseline characteristics between the two groups ($p > 0.05$), indicating that both groups were comparable at baseline. Table 2 shows the comparison of maternal outcomes between the two groups, Women in the spontaneous pushing group experienced significantly better maternal outcomes, including shorter duration of labour, lower rates of episiotomy, reduced perineal trauma, and less maternal fatigue. Figure 1 illustrates the graphical comparison of maternal outcomes. Table 3 presents neonatal outcomes between the two groups. Figure 2 shows the graphical representation of neonatal outcomes. The Neonatal outcomes were generally comparable between the two groups, with no statistically significant differences observed ($p > 0.05$). Spontaneous pushing demonstrated a trend toward better neonatal adaptation without compromising neonatal safety.

Table 1: Baseline Characteristics of Study Participants (n=60)

Variable	Spontaneous Pushing (n=30)	Directed Pushing (n=30)	Total (n=60)	p-value
Maternal Age (years)	27.4 ± 4.2	28.1 ± 4.6	27.8 ± 4.4	0.412
Gestational Age (weeks)	38.6 ± 1.1	38.8 ± 1.0	38.7 ± 1.0	0.298
Primiparity	16 (53.3%)	17 (56.7%)	33 (55.0%)	0.721
Multiparity	14 (46.7%)	13 (43.3%)	27 (45.0%)	0.721
Booking Status (Booked)	24 (80.0%)	23 (76.7%)	47 (78.3%)	0.754
Booking Status (Unbooked)	6 (20.0%)	7 (23.3%)	13 (21.7%)	0.754
BMI (kg/m²)	26.1 ± 2.8	26.8 ± 3.1	26.4 ± 2.9	0.368
Mean Cervical Dilatation at Active Labour (cm)	5.1 ± 0.7	5.0 ± 0.8	5.0 ± 0.7	0.611

Table 2: Maternal Outcomes Comparison

Outcome	Spontaneous Pushing (n=30)	Directed Pushing (n=30)	Relative Difference	p-value
Duration of Second Stage (minutes)	38 ± 10	45 ± 12	Shorter by 7 minutes	0.002
Episiotomy	8 (26.7%)	13 (43.3%)	Reduced by 16.6%	0.041
Perineal Trauma	4 (13.3%)	8 (26.7%)	Reduced by 13.4%	0.048
Maternal Fatigue	5 (16.7%)	11 (36.7%)	Reduced by 20.0%	0.031
Prolonged Second Stage (>60 min)	2 (6.7%)	6 (13.3%)	Reduced by 13.3%	0.337
Need for Instrumental Assistance	1 (3.3%)	3 (10.0%)	Reduced by 6.7%	0.296
Postpartum Hemorrhage	1 (3.3%)	2 (6.7%)	Reduced by 3.4%	0.552

Figure 1: Maternal Outcomes Comparison

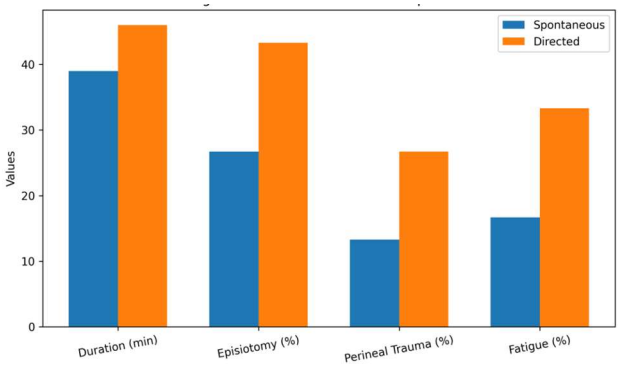

Figure 2: Neonatal Outcomes Comparison

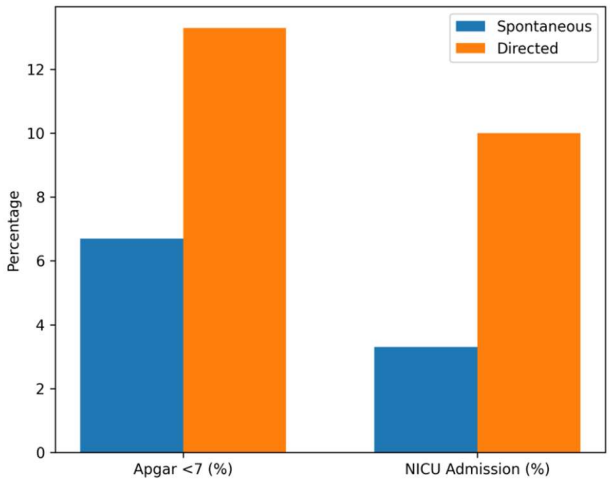

Table 3: Neonatal Outcomes Comparison

Outcome	Spontaneous Pushing (n=30)	Directed Pushing (n=30)	Relative Difference	p-value
Apgar Score <7 at 1 Minute	2 (6.7%)	4 (13.3%)	Reduced by 6.6%	0.337
NICU Admission	1 (3.3%)	3 (10.0%)	Reduced by 6.7%	0.296
Need for Neonatal Resuscitation	1 (3.3%)	3 (10.0%)	Reduced by 6.7%	0.296
Respiratory Distress	1 (3.3%)	2 (6.7%)	Reduced by 3.4%	0.552
Birth Asphyxia	0 (0.0%)	1 (3.3%)	Reduced by 3.3%	0.313
Mean Birth Weight (kg)	3.1 ± 0.4	3.0 ± 0.5	Slightly higher	0.447
Neonatal Cyanosis	0 (0.0%)	1 (3.3%)	Reduced by 3.3%	0.313

DISCUSSION

This research compared the performance of spontaneous, and directed pushing methods in the second labour stage. The results show that better maternal outcomes are linked with spontaneous pushing at a similar neonatal safety level. The duration of the second stage of labour was significantly shorter in the spontaneous pushing group. It calls the past philosophical understanding into question that directed pushing speeds up delivery.[15] Rather, the physiologic pushing can be used to increase the efficiency of uterine contractions and maternal effort coordination.[16] There was a high difference in the rates of episiotomy in the spontaneous group. Directed pushing raises the intra-abdominal pressure and causes a higher stress on perineal tissues and a higher risk of surgery. Lower rates of episiotomy prove to be clinical because it minimizes the amount of pain and complications during the postpartum stage.[17] Likewise, less common was perineal trauma with spontaneous pushing.[18] This implies that natural, but controlled pushing will decrease excessive stress on pelvic structures. Reduced occurrence of trauma results in improved post-partum recuperation and decreased long-term effects, including pelvic floor dysfunction. In spontaneous pushing maternal fatigue was much less.[19] Directed pushing has long breath-holding and hard work, which causes fatigue. On the contrary, spontaneous pushing enables women to save on energy since they go by the natural flow. [20]

There was no significant difference in neonatal outcomes such as Apgar scores and NICU admission. This shows that spontaneous pushing cannot be detrimental to fetal safety. A little improved trends of the spontaneous group further invest the safety profile of the group. These results reflect the increasing trend to physiologic practices in childbirth. The need to foster spontaneous pushing concurs with the current trends in obstetric care and is based on the comfort of the mother and less intervention[21]. The findings demonstrate that spontaneous pushing improves maternal outcomes without compromising neonatal safety. Limitation: There are some limitations in this study that must be noted. The study used a quasi-experimental comparative design, which may limit causal interpretation. The study was performed in a single tertiary care center, and the results are not necessarily generalizable to other health care settings or populations in other regions of Pakistan. Second, the number of participants was limited to 60 following the strict inclusion criteria and restricted three-month data collection window, which may limit the statistical power needed to identify subtle differences in low-incidence neonatal complications. Lastly, this study only measured immediate MNH outcomes up to the time of hospital discharge, and long-term postpartum outcomes like chronic pelvic floor dysfunction, pelvic organ prolapse, or urinary or fecal incontinence were not objectively tracked and assessed.

CONCLUSION

Spontaneous pushing was associated with shorter second stage of labour, lower episiotomy rate, reduced perineal trauma, and decreased maternal fatigue, without significant differences in neonatal outcomes. In general, spontaneous pushing is a safer and more physiologic and patient-centered method of labour management.

Conflicts of Interest: Nil

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Authors Contribution:
Mehreen Abbas: Main Conception Of Study, Manuscript Writing, Data Collection, Results, And Conclusion, Final Approval.
Aleena Hanif: Data Collection, Data Analysis, Manuscript Writing, Data Analysis.
Fatima Habib: Main Conception Of Study, Data Collection, Manuscript Writing, Data Analysis.
Sundus Rashid: Data Collection, Data Interpretation, Data Analysis.
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Medical Education - Original Article **Open Access**

Comparison of Self-efficacy of Dental house officers regarding content and Extent of Education in Rehabilitative Endodontics in Public and Private dental institutes

Kiran Fatima Mehboob Ali Bana, Farnaz Ilyas, Shama Asghar

Abstract:

Objective: To compare whether the self-efficacy score of dental house officers was associated with the extent of education content received in public & private dental institutes**.**

Study design and Setting: It was a comparative analytical study, conducted at various public and private dental colleges of Karachi from March 2022 to December 2022.

Methodology: The validated endodontic general self-efficacy scale (ESES) related to the content of endodontic education was used. Data was analyzed on SPSS version 23. The mean rank of ESES items and performance of Root Canal Treatment (RCT) was assessed through Mann-Whitney U test. P value < 0.05 was taken as statistically significant.

Result: Total of n=344 subjects were included for data analysis. A total n=88 (25.6%) were male and n=256 (74.4%) were female house officers. The mean age was 23.21+ 1.10 SD. A total n=222 (64.5%) dental house officers were from public and n=122 (35.5%) from private institutes. Novice dentists from public institutes had greater SES scores related to patient exposure (from items 1 to 7). Private institutes had better ESES related to problem-solving skills items (from 8-10). Performance in retreatment cases was greater in the public institute and influenced the mean ESES.

Conclusion: The Self Efficacy Score was greater among dental interns of public dental undergraduate institutes related to work in real patient setting and in private institute due integrated problem-solving teaching strategies. Hence, ESES score was associated with extent of education content received related to clinical experience in real patient setting and retreatment cases of endodontics in Public Institutes.

Key Words: Dental interns, Education, Endodontic, House Officers, Self-Efficacy.

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INTRODUCTION:

The transition from undergraduate training in the dental profession to becoming an independent dentist is challenging.[1] The challenges include a lack of clinical experience due to limited patient exposure or resources. Insufficient experience in root canal treatment (RCT) performance is one of the greatest challenges during undergraduate training. Novice dentists are competent enough while performing root canal treatment on anterior teeth. This is a general perception that the majority of dentists find it difficult to perform good quality RCT on posterior teeth after graduation and feel a lack of confidence and self-efficacy.[2,3] Consequently, undergraduate dental training has a great impact on independent practice, as dentists after graduation no matter if they have dealt with the problems during training.

Self-efficacy is a personal judgment of the execution of any course of action, and clinical decision-making is based upon the experience as reported by Taha NA et al in 2019.[4] Self-efficacy is defined as an emotional state of confidence and feeling competent while performing any evidence-based skill. According to Bandura 1982,[5] the criterion for self-efficacy is competence, and it has a direct positive effect on performance. In rehabilitative endodontic, this theory entails four kinds of self-efficacy sources; the first is mastery skills learnt by experience in clinical setting, the second type is during the observation which built the urge of success such as assisting endodontic treatment with peers, fellows, class mates or postgraduates, the third kind of self-efficacy is through the verbal encouragement of instructor which give belief to trainee to perform best and finally emotional state of an individual which reduces anxiety and stress to perform clinical skills. Better learning outcomes can be achieved in endodontic education through integrating

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all four sources of self-efficacy.

It is reported by Zimmerman 2000[6] that individuals having greater self-efficacy can perform more challenging tasks under stressful situations with more determination compared to individuals with low self-efficacy. It is hypothesized by Baaij et al in 2021[3] that the self-efficacy of fresh dental graduates was influenced by the clinical experience while performing RCT and self-efficacy is gradually improved from the first year till the time of graduation among those who had less confidence while entering in first year of the undergraduate program. Thereby, research by Kamali et al (2024)[7] and Baaj et al. (2024)[8] suggests that it is unrealistic to expect that all dental students possess elevated self-efficacy or feel fully confident and competent upon completion of their academic programs to commence practice autonomously.

A study by Javed MQ in 2021 revealed that 98% of 4th and 5th-year dental students are more confident during the procedure of root canal treatment on maxillary anterior teeth.[9] Therefore, the rationale was to find the self-efficacy score among novice dentists specifically performing endodontic rehabilitation procedures, particularly within the geographic region of Sindh, Pakistan. This highlights a significant challenge in assessing the self-efficacy score of dental undergraduates with respect to root canal treatment which is one of the competencies. The dental curricula prescribed by the Higher Education Commission (2013)[10] and the Pakistan Medical & Dental Council (2019) [11]articulated a comprehensive range of pre requisite competencies for dental graduates intending to engage in independent oral rehabilitation practice. In light of these considerations, this study aimed **t**o compare whether the self-efficacy score of dental house officers was associated with the extent of education content received in public & private dental institutes of Sind, Pakistan

METHODOLOGY:

This comparative analytical study was conducted at various public and private dental colleges of Karachi from March-2022 till December-2022. The ethical approval was obtained from Bahria Dental College Ref# ERC 03/2021. The administrative approval was obtained from other public and private dental institutes where data collection was carried out and target population was dental house officers, who completed their house job posting in the endodontic rehabilitation department in year 2022. Sample size was determined using the standard formula $N = Z^2 \times P(1-P) / d^2$. Assuming an unknown prevalence as 50% to ensure maximum sample size. With a 95% confidence level and 5% margin of error, the required sample size was calculated to be 384 participants. A non-probability convenience sampling technique was used to recruit dental house officers from various dental institutions in Karachi. The ESES tool is a validated tool adapted from Baaij et al (2020)[3] that assessed the content and extent of endodontic rehabilitation training received during their undergraduate dental training was distributed among dental house officers. Participants were informed that all responses would be handled anonymously, and only those who provided informed consent were included in the study.

The ESES comprised of ten items (Table 1), each rated on a 4-point Likert scale ranging from 1 = Not at all true, 2 = Hardly true, 3 = Moderately true, to 4 = Exactly true. Higher total scores indicated greater self-efficacy in endodontics. The first section of the questionnaire also collected demographic data, including age, gender, and affiliated institution.

Data analysis was performed using SPSS version 23. The Shapiro-Wilk test was performed to check the normality of data. Frequencies and percentages were computed for categorical variables. Associations between variables were examined using Fisher's exact test. Since the data did not follow a normal distribution, non-parametric tests were employed. The Mann-Whitney U test was used to compare mean ranks of ESES scores and root canal treatment (RCT) performance between public and private dental institutions. A p-value of = 0.05 was considered statistically significant.

RESULTS:

A total of n=344 questionnaires completed in all aspects from 384 distributed questionnaires; hence, the response rate was 89.58%. A total of n=88 (25.6%) were male and n=256 (74.4%) were female house officers. The mean age was 23.24+ 1.10 SD with a minimum 20 years and a maximum of 28 years. A total of n=222 (64.5%) dental house officers were from public institutes and n=122 (35.5%) were from private dental institutes.

The Mann-Whitney U test was applied to compare the mean rank of ESES among public and private institutions. The test gives a rank to the scores of the respondents from both groups, and then the mean rank was calculated for each group separately. A higher rank indicates that participants of that group have a higher SES score than the other group. In public institutes, the mean rank of (ESES score was higher in the first seven items compared to private dental institutes, and there was a statistically significant difference found in three items 1,2 and 6 at a p-value of 0.0001. It was revealed that dental house officers from public institutes had better ESES score related to patient exposure as compare to private institutes. Private institutes had better ESES related to problem solving skills as depicted from 8, 9 and 10 items of ESES and revealed statistically significant difference in items 9 and 10 at a p-value of 0.0001-table-1.

Student satisfaction with the content and extent of endodontic education was observed by the more or less teaching strategies used, as presented in (Table-2). The dental interns from private & public institutes were equally satisfied with the extent & content of endodontics delivered but a statistically

significant difference was found for a smaller number of lectures at p-value > 0.05 as depicted from table-2. Those who responded "Yes" were less satisfied, and those who responded with a "No" were more satisfied. Sessions related to clinical seminars, simulated clinical training & feedback received from peers were more conducted in private institute as presented in figure-1.

While comparing the mean rank of clinical performance of root canal treatment (RCT) and the mean of combined ESES score was measured between 10-40 was assessed with the help of mann Whitney U Test. The dental interns from private institutes had performed more number of RCT on anterior, premolars & molars as 200.47, 221.09, and 209.79 respectively as compare to public institutes with statistically significant difference at p-value of 0.0001. On the other hand, performance in retreatment cases was greater in public institute; table-3.

DISCUSSION:

To compare the endodontic self-efficacy score of dental house officers was related with extent of education content

Table-1: Mean Rank of Endodontic Self-Efficacy Score of Two Independent Cohorts of dental House Officers of Public and Private Institutes Baaij A et al[3]

Domains	Endodontic Self-Efficacy Scale (ESES)	Public N=222		Private N=122		P-Value*
		Mean	Mean rank	Mean	Mean rank	
Patient Exposure	With hard work, difficult endodontic problems can be manageable for me.	2.54	187.87	2.13	144.52	0.000
	If a patient disagrees with me, I can navigate the situation to achieve the outcome I desire.	2.72	215.07	1.53	95.04	0.000
	I find it straightforward to stay focused on my endodontic objectives and achieve my goals.	2.70	174.06	2.65	169.66	0.676
	I am confident in my ability to handle unexpected situations effectively during endodontic treatments.	2.53	175.25	2.45	167.49	0.462
	My resourcefulness enables me to manage unforeseen situations in endodontic treatments effectively.	2.44	173.50	2.41	170.68	0.789
	With the right amount of effort, I can resolve most endodontic challenges.	2.68	189.02	2.27	142.45	0.000
	I stay calm when encountering challenges in an endodontic case, trusting in my ability to cope effectively.	2.65	175.28	2.59	167.44	0.459
Problem Solving Skills	When faced with an endodontic issue, I can typically identify multiple solutions.	2.54	168.24	2.64	180.25	0.251
	If I encounter trouble during an endodontic procedure, I can usually come up with a solution.	2.68	147.71	3.25	217.61	0.000
	I am generally able to manage whatever challenges arise during endodontic treatments.	2.59	158.91	2.91	197.23	0.000

Figure-1: Student's Satisfaction with extent of Education in Public and Private Institutes.

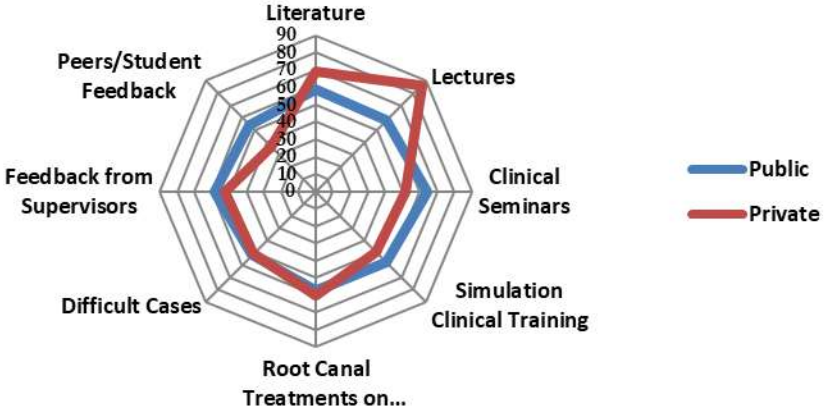

Table -2: Student satisfaction with the content and extent of Endodontic education during among public and private Institutes

I had Less		Institutes		P-Value*
		Public N=222(%)	Private N=122(%)	
Literature	Yes	91 (41)	38 (31)	0.045
	No	131(59)	84(69)	
Lectures	Yes	93(42)	16(13.3)	0.000
	No	129(58)	106(86.6)	
Clinical seminars/Tutorials	Yes	79(35.58)	59(48.3)	0.014
	No	143(64.4)	63(51.6)	
Preclinical Training	Yes	93(42)	62(50.8)	0.070
	No	129(58)	60(49.1)	
Root canal treatments on real patient setting	Yes	94(42.3)	49(40)	0.391
	No	128(57.6)	73(60)	
Difficult cases of root canal treatments on clinical setting	Yes	107 (48)	60(49.1)	0.475
	No	115(51.8)	62(50.8)	
Feedback on my performance from my supervisor.	Yes	94(42.3)	59(48.3)	0.168
	No	128(57.6)	63(51.6)	
Feedback on my performance from my peers	Yes	101(45.4)	78(64)	0.001
	No	121(54.5)	44(36)	

Grouping Variable: Public and Private institutes *Fisher's exact Test

Table-3: Mean Rank of clinical performance among Public and Private Institutes

Dependent Variables	Public N=222		Private N=122		P-Value*
	Mean	Mean rank	Mean	Mean rank	
Mean rank of SES	26.13	181.90	24.70	155.40	0.18
RCT on Anterior	2.61	157.13	3.44	200.47	0.0001
RCT on Premolars	2.05	145.80	3.92	221.09	0.0001
RCT on Molars	1.85	152.01	2.88	209.79	0.0001
Total treated teeth	6.50	150.71	10.24	212.15	0.0001
Total Number of retreatments performed	0.47	175.44	0.33	167.14	0.269

*Mann-Whitney U- Asymp. Sig. (2-tailed) Grouping Variable: two independent groups

in two different settings of public & private dental institutes was the aim of the study. Result of current study affirmed that novice dentists from public institutes had better SES related to patient exposure (from item 1 to 7) as compare to private institutes. Private institutes had better SES related to problem solving skills items as depicted from 8, 9 and 10 items of SES table-1. This result is consistent with the observation of Baaij et al 2020[3] which revealed high self-efficacy among novice dentists due to RCT performance in real patient setting. Hence in public sector there is more patient turn over, thus students experienced greater clinical experience on real clinical setting during undergraduate training. Therefore, dentists who trained in public sector are much more confident during real clinical performance as compare to their counter parts in private institutes.

According to the study conducted in 2018 in Pakistan among the house officers revealed greater confidence while performing some of the steps of RCT while less confidence was observed for placing rubber dam, management of flare ups and use of electronic apex locator comparing two dental institutes.[12] However, frequent turnover of patients in public sector and various patient centered learning strategies used to teach endodontic content such as case based learning and problem-based learning in private dental institutes has an overall impact on ESES in this study-table-2. Hansen MG et al in 2023 in pilot study observed that simulation-based learning can significantly increase pediatric dental residents' confidence levels when handling sedation-related emergencies.[13] Such findings advocate for incorporating more simulation exercises within dental curricula.

Regarding clinical performance of RCT; the dental interns from private institutes had performed more number of RCT on anterior, premolars & molars as 200.47, 221.09, and 209.79 respectively as compare to public institutes at p-

value of 0.0001 table-3 and revealed statistically significant difference. On the other hand, performance in retreatment cases was greater in public institute and has an influence on mean SES score. This is comparable from the study of Chambers D in 2012[14] and proposed that learning curve entails constant repetition of procedures to develop clinical skills is vital and ultimately improve confidence. On the contrary, Baaij et al 2020[3] reported that self-efficacy might be reduced while treating dif?cult cases (molars and retreatments). One plausible explanation could be the nature of exposure and the diversity of experiences that dental house officers experienced in public institutes are subjected to enhance self-efficacy. Public sector dental hospitals and clinics often cater larger and more varied patient population, offering a broad spectrum of real-life cases. This environment provided more hands-on experiences, which is critical to enhance self-efficacy. There are various factors which can be contribute to self-efficacy among novice dental doctors such as practical experience, hands on training, mentorship, supportive learning environment, reflective practice, continuous learning and the role of innate personality traits. Hence, provision of quality care especially as an emerging dentist is highly dependent upon the self-efficacy and confidence while performing oral rehabilitation treatment. It is vital to improve the endodontic education at undergraduate level as to enhance confidence of performing complex root canal procedures in future dentist. [15]

Furthermore, the endodontic procedure is perceived as a difficult procedure.[16] The academic and training framework in public institutions may emphasize more integrated approach to learning. This might include a stronger emphasis on practical skills training, interdisciplinary collaboration, and community engagement projects. Such experiences contribute to a well-rounded professional development, reinforcing the belief in one's capabilities; creating supportive learning environment to address short comings during clinical performance may enhance confidence and self-efficacy.[17] Additionally, the mentoring approach in public institutes might differ significantly from that in private institutions. Mentor-mentee relationships in such settings often extend beyond academic guidance, encompassing emotional support and professional networking, leading to significant competency. It's also worth considering that the selection processes and the competitive environment in public institutions might inherently attract or foster individuals with higher self-efficacy. The rigorous nature of admissions and continual evaluations could mean that only those with a strong belief in their capabilities and resilience navigate through successfully, potentially skewing the average self-efficacy levels higher.

Understanding that self-efficacy is not merely a product of integrative educational content, but also quality of experiences and nature of support systems, is pivotal.[18] By doing so, private institutions can aim to nurture dental house officers who are not only knowledgeable but also confident in their abilities to navigate the complexities of the dental profession. It is utmost important to address the limitation of the study such as assessment of support system, mentor mentee relation and feedback from peers and supervisors on effect of self-efficacy during endodontic procedures have not been studied in this study. Feedback is recognized as a critical component in enhancing trainees' confidence and performance.[19]

It is suggested that for healthcare professional such as dental professional, lifelong learning is crucial to keep them updated regarding current standards of care and to improve self-efficacy as addressed by Haug SR et al in 2021.[20] Competency based learning is vital in undergraduate dental training curriculum by incorporating hands on workshops; problem based learning, treating patients under supervision to enhance their self-efficacy and self-confidence for endodontic procedures.[21]

CONCLUSION:

Self Self-efficacy score was higher among the dental interns of public dental undergraduate institutes related to greater number of patient turnover and in private institutes due integrated problem-solving teaching strategies. Hence, ESES score was associated with the extent of education content received related to clinical experience in real patient settings and retreatment cases of endodontics in Public Institutes.

Ethics Statement: This study followed the guidelines of the Declaration of Helsinki. The ethical approval was obtained from the Institutional Review Board of Bahria University Medical and Dental College, reference # 03/2021. Informed consent was obtained from the house officers participated in the study and the rationale of the study was well explained.

Conflicts of Interest: Nil

Source of Funding: Nil

Acknowledgement: Nil

Authors Contribution:
Kiran Fatima Mehboob Ali Bana: Conception, design, analysis and/or interpretation of data.
Farnaz Ilyas: Data collection, write up
Shama Asghar: Intellectual input, data collection

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Units of Measurement:

Measurements of length, height, weight, and volume should be reported in metric units. Temperatures in degrees Celsius, Blood pressure in millimeters of mercury and all hematologic and clinical chemistry measurements in the metric system in terms of the International System of Units (SI).

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Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

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4	Medical Education	Original Structured (250)	3-10	3000-4000	20-25	4-6
		Review Unstructured (150)	3-5	3500-5000	40-60	4-6
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