

Journal of
Basic & Clinical
Medical Sciences

Volume 4 | Issue 2 | 2025

JOURNAL OF BASIC & CLINICAL MEDICAL SCIENCES CONTENTS

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An official journal of the
Academy for the
Advancement of Science
Education & Research
(A.A.S.E.R.) published by
Logixs Journals

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Journal of Basic & Clinical Medical Sciences is published by Logixs Journals on behalf of the Academy for the Advancement of Science, Education & Research (A.A.S.E.R.).

eISSN: 2959-9210

pISSN: 2959-9202

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Editorial Office: 125-A, AEHS, Kheyaban-e-Jinnah Road, Lahore - 54600, Pakistan

Publisher Address: 51-A, AEHS, Kheyaban-e-Jinnah Road, Lahore - 54600, Pakistan

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Volume 4 | Issue 2 | 2025

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Original Article

Surgical fixation versus conservative management for rib fractures caused by blunt chest trauma: a comparative study

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Citation: Majeed FA, Raza A, Mazhar R, Ullah F, Asghar AR, Chatta S. Surgical fixation versus conservative management for rib fractures caused by blunt chest trauma: a comparative study. *J Basic Clin Med Sci.* 2025;4(2):55-64.

Received: 09 July 2025**Revised:** 04 September 2025**Accepted:** 07 September 2025**Published:** 15 October 2025

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Abstract

Rib fractures are a frequent consequence of blunt chest trauma and are associated with significant morbidity and mortality, particularly in cases of flail chest or multiple displaced fractures. While conservative management remains the traditional approach, surgical stabilization of rib fractures (SSRFs) has gained increasing attention for its potential to improve outcomes. This prospective comparative cohort study, conducted between April 2018 and August 2023, compared the effectiveness of SSRF with that of nonoperative management. A total of 114 patients with respiratory compromise from unstable rib fractures were enrolled, 57 of whom underwent SSRF via custom-made titanium plates and screws (Group A) and 57 of whom received conservative treatment (Group B). Baseline demographics and associated injuries were comparable between the groups, although flail chest was more common in the surgical cohort (40.4% vs. 19.3%, $p = 0.012$). By discharge, patients in the SSRF group reported significantly lower pain scores (3.6 vs. 7.5, $p < 0.001$) and demonstrated superior pulmonary function at follow-up (FEV₁ at 3 months: 2.84 ± 0.40 L vs. 2.06 ± 0.36 L, $p < 0.001$). Oxygen dependence was shorter in the surgical group (2.5 ± 0.7 vs. 5.1 ± 0.8 days, $p < 0.001$), and fewer patients required ventilatory support (12.3% vs. 29.8%, $p = 0.022$). Among ventilated patients, 50% in the SSRF group were weaned within 3 days, whereas none were weaned in the conservative group ($p < 0.001$). The length of hospital stay was nearly halved with surgery (4.4 ± 1.5 vs. 9.4 ± 2.3 days, $p < 0.001$). Mortality was lower in the surgical group (5.3% vs. 15.8%), although this difference was not statistically significant ($p = 0.062$). Importantly, return-to-work rates at one month were markedly higher following SSRF (62.96% vs. 12.50%, $p < 0.001$). Compared with conservative management, SSRF offers significant benefits in terms of pain control, respiratory recovery, and functional outcomes. These findings support broader adoption of SSRF, particularly in patients with flail chest or multiple displaced rib fractures, and highlight the feasibility of custom-made implants in resource-limited settings.

Keywords

Rib fractures; Fracture fixation, internal; Thoracic injuries; Conservative treatment; Treatment outcome

1. Introduction

Thoracic trauma frequently leads to rib fractures, which are often accompanied by damage to the pleura, intrathoracic vessels, and pulmonary parenchyma. These injuries can lead to serious complications, such as pulmonary contusions, hemothorax, pneumothorax, and diaphragmatic trauma. When rib fractures are accompanied by a flail chest

segment, the risk of respiratory compromise significantly increases, often necessitating ventilatory support and contributing to higher morbidity and mortality rates [1,2,3,4].

Compared with isolated and multiple nonflail rib fractures, flail chest fractures are associated with poorer outcomes because of their increased occurrence of respiratory insufficiency and concurrent injuries [5,6]. Traditionally, rib fractures are managed conservatively with respiratory support, analgesia, and physiotherapy. Although surgical stabilization of rib fractures (SSRFs)—historically referred to as surgical fixation—was first described in the early 20th century, it remained uncommon until recent advances in surgical techniques, implant technology, and thoracic surgical expertise.

Several recent studies have compared SSRF with conservative approaches in the management of rib fractures, particularly those presenting with flail chest [6]. These studies consistently demonstrated that, compared with nonoperative treatment, SSRF significantly reduces the duration of mechanical ventilation, ICU and hospital stays, incidence of pneumonia, and need for tracheostomy [7,8].

Despite these benefits, surgical intervention is still underutilized in many centers because of variability in clinical guidelines, the limited availability of surgical expertise, and concerns about operative risks. Consequently, real-world data comparing the two approaches in different trauma populations are crucial for optimizing patient selection and outcomes. Therefore, this research aimed to evaluate the clinical outcomes of SSRF compared with those of conservative management in patients with flail chest fractures or multiple displaced rib fractures. We hypothesized that operative fixation, when applied under appropriate indications and performed by experienced surgeons, would yield superior short- and medium-term outcomes and inform best practices in rib fracture management.

2. Methodology

2.1. Study design and setting

This prospective, comparative cohort study was conducted at the Department of Thoracic Surgery, Combined Military Hospital (CMH), Rawalpindi, between April 2018 and August 2024.

2.2. Selection criteria

Patients aged ≥ 16 years who presented with respiratory compromise due to painful, unstable rib fractures refractory to analgesia were considered for inclusion. Eligible cases included individuals with flail chest, multiple (≥ 4) severely displaced rib fractures, or thoracic injuries requiring thoracotomy. Patients were excluded if they had severe head or spinal injuries; polytrauma with multiorgan failure (MOF); acute respiratory distress syndrome (ARDS); empyema; or significant systemic diseases such as advanced cardiac, hepatic, or renal dysfunction.

2.3. Sample size

The sample size was based on Liu et al. [9], who reported mean ICU stays of 4.02 ± 1.41 days after surgery versus 5.06 ± 1.80 days with conservative care. Using these values, with a pooled standard deviation of 1.615, a two-tailed α of 0.05, and 80% power, the minimum required sample size was estimated to be 38 patients per group via the online sample size calculator ClinCalc [10]. To strengthen the analysis and allow for detailed subgroup comparisons, a total of 57 patients were enrolled per group.

2.4. Study groups and interventions

A total of 114 patients meeting the criteria were enrolled via convenience sampling and divided into two equal groups. Group A (n = 57) underwent SSRF via titanium locking plates (1.9 mm thickness, 10 mm width) and 3.5 mm locking screws. All procedures were performed by experienced thoracic surgeons under general anesthesia. Group B (n = 57) received conservative treatment consisting of multimodal analgesia (oral, intravenous, or epidural), oxygen therapy, nebulization, and chest physiotherapy.

2.5. Follow-up and outcome measures

A three-month follow-up was completed for all patients, with assessments at 1, 2, and 3 months post-treatment. The outcomes evaluated included pain severity via the VAS, pulmonary function measured via spirometry (FEV1), and radiographic assessment of rib healing. Additional parameters included hospital and ICU stay duration, oxygen dependence, need for ventilatory support and duration of weaning, incidence of pulmonary infection, mortality, and return-to-work status. Associated injuries such as hemothorax, pneumothorax, flail chest, clavicle fractures, and diaphragmatic injury were also documented.

2.6. Ethical approval

The study was approved by the Institutional Review Board of the CMH, Rawalpindi (No. 815). All participants provided written informed consent.

2.7. Statistical analysis

Statistical analysis was performed using IBM SPSS version 26. The data were analyzed as the means with standard deviations, frequencies, and percentages. Group comparisons were conducted with the Mann-Whitney U test, chi-square test, and Fisher's exact test. A p value < 0.05 was considered statistically significant.

3. Results

Table 1 shows the baseline demographic and injury-related characteristics of the patients in both groups. The distributions of sex, hemothorax, pneumothorax, bilateral rib fractures, clavicle fractures, and diaphragmatic injuries were statistically comparable between the groups ($p > 0.05$ for all). However, flail chest was significantly more common in the SSRF group, affecting 40.4% of patients, whereas it affected 19.3% of patients in the conservative group ($p = 0.012$). While hemothorax and pneumothorax were slightly more common in the SSRF group (91.2% and 89.5%, respectively), these differences were not statistically significant. Diaphragmatic injury was observed only in the SSRF group (3.5%) but occurred rarely overall.

Table 1. Baseline demographic and injury-related characteristics of patients undergoing surgical fixation versus conservative management (N = 114).

Variables		Group A: Surgical (n = 57)	Group B: Conservative (n = 57)	p Value
		Frequency (%)	Frequency (%)	
Sex	Male	39 (68.4)	33 (57.9)	0.244
	Female	18 (31.6)	24 (42.1)	
Hemothorax		52 (91.2)	46 (80.7)	0.106
Pneumothorax		51 (89.5)	53 (93.0)	0.508

Variables	Group A: Surgical (n = 57)	Group B: Conservative (n = 57)	p Value
	Frequency (%)	Frequency (%)	
Bilateral rib fracture	8 (14.0)	9 (15.8)	0.793
Flail chest	23 (40.4)	11 (19.3)	0.012 **
Clavicle fracture	9 (15.8)	7 (12.3)	0.590
Diaphragmatic injury	2 (3.5)	0 (0.0)	0.496

* Data were analyzed via the chi-square test and Fisher's exact test. ** Significance at $p < 0.05$.

Table 2 compares the clinical outcomes between the two groups across pain scores, lung function (FEV1), and oxygen dependence. The initial pain scores at admission were similar ($p = 0.416$), indicating comparable baseline discomfort. By discharge, however, patients who underwent SSRF reported significantly lower pain scores, averaging 3.6 vs. 7.5 in the conservative group ($p < 0.001$). In addition, the analgesic requirements differed: patients in the SSRF group were managed with on-demand oral or epidural analgesia, whereas those in the conservative group required continuous multimodal analgesia for approximately three days. Pulmonary function, as measured by FEV1, was consistently greater in the SSRF group than in the control group at all follow-up intervals. At three months, the mean FEV1 reached 2.84 L in the SSRF group compared with 2.06 L in the conservative group, reflecting a 38% greater volume ($p < 0.001$). The need for supplemental oxygen was also significantly lower among surgically treated patients, who required support for an average of 2.5 days versus over 5 days in the conservative group ($p < 0.001$), demonstrating faster respiratory recovery.

Table 2. Comparison of clinical outcomes between the surgical and conservative groups in terms of pain score, FEV1, and oxygen dependence (N = 114).

Variables	Group A: Surgical (n = 57)	Group B: Conservative (n = 57)	p Value
	Mean $\pm$ SD	Mean $\pm$ SD	
Pain Score at admission	8.544 $\pm$ 0.569	8.632 $\pm$ 0.522	0.416
Pain score at discharge	3.579 $\pm$ 1.209	7.526 $\pm$ 1.754	< 0.001 **
FEV1 at 1 month (L)	2.062 $\pm$ 0.137	1.534 $\pm$ 0.310	< 0.001 **
FEV1 at 2 months (L)	2.597 $\pm$ 0.440	1.859 $\pm$ 0.317	< 0.001 **
FEV1 at 3 months (L)	2.838 $\pm$ 0.400	2.056 $\pm$ 0.358	< 0.001 **
Oxygen dependence (in days)	2.509 $\pm$ 0.710	5.140 $\pm$ 0.833	< 0.001 **

* Data were analyzed via the Mann-Whitney U test. ** Significance at $p < 0.05$.

Table 3 highlights significant differences in ventilatory needs and hospital course. Ventilatory support was required in 12.3% of the SSRF patients compared with 29.8% in the conservative group ($p = 0.022$). Among ventilated patients, half of those in the SSRF group were weaned within 3 days, whereas no patient in the conservative group achieved early weaning. The majority of conservatively managed patients (70.6%) required prolonged ventilation beyond 5 days ($p < 0.001$). The mean hospital stay was markedly shorter in the SSRF group (4.4 $\pm$ 1.5 days) than in the conservative group (9.4 $\pm$ 2.3 days) ($p < 0.001$). Although mortality was lower in the SSRF group (5.3% vs. 15.8%), this difference did not reach statistical significance ($p = 0.062$).

Table 3. Comparison of ventilation support, weaning duration, hospital stay, and mortality across study groups.

Variables		Group A: Surgical	Group B: Conservative	p Value
		Frequency (%)	Frequency (%)	
Ventilatory support		7 (12.3)	17 (29.8)	0.022 ***
Weaning from ventilator	Weaning < 3 days	4 (50.00)	0 (0.0)	< 0.001 ***
	Weaning 3–5 days	4 (50.00)	5 (29.4)	
	Weaning > 5 days	0 (0.0)	12 (70.6)	
Mean hospital stay (days $\pm$ SD)		4.421 $\pm$ 1.499	9.421 $\pm$ 2.322	< 0.001 ***
Mortality		3 (5.3)	9 (15.8)	0.062

* Data were analyzed via the chi-square test, Fisher's exact test, or the Mann-Whitney U test. ** Duration of weaning categorized by intervals. *** Significance at $p < 0.05$.

Table 4 shows the return-to-work outcomes across the follow-up intervals. A significantly greater proportion of SSRF patients had resumed work by one month (62.96% vs. 12.50%, $p < 0.001$). At two months, the return-to-work rates increased in both groups (27.78% in the SSRF group vs. 41.67% in the conservative group). By three months, 100% of the SSRF patients had resumed work, whereas 77.09% had resumed work in the conservative group, indicating faster and more complete functional recovery with surgical management.

Table 4. Number of patients who resumed occupational activities at follow-up intervals.

Variables		Group A: Surgical	Group B: Conservative	p Value
		(n = 54)	(n = 48)	
		Frequency (%)	Frequency (%)	
Return to work status	At 1 month	34 (62.96)	6 (12.50)	< 0.001 ***
	At 2 months	15 (27.78)	20 (41.67)	
	At 3 months	5 (9.26)	11 (22.92)	

* Return-to-work frequencies were calculated among surviving patients and compared via the chi-square test.

** At 3 months, 11 patients (22.92%) in Group B had not returned to work. *** Significance at $p < 0.05$.

Preoperative imaging (Figure 1) provided detailed 3D CT reconstructions of rib fractures, assisting in surgical planning. Intraoperative photographs (Figure 2) illustrate the exposure, reduction, and fixation of fractures with titanium plates and screws, demonstrating the technical feasibility of SSRF. Postoperative radiographs (Figure 3) confirmed satisfactory alignment and secure fixation, which was consistent with the improved clinical outcomes observed in the SSRF group.

**Figure 1.** Three-dimensional computed tomography (CT) reconstruction of the thoracic cage demonstrating multiple displaced rib fractures predominantly involving the left lateral and posterolateral ribs. This scan was used preoperatively for fracture assessment and surgical planning.

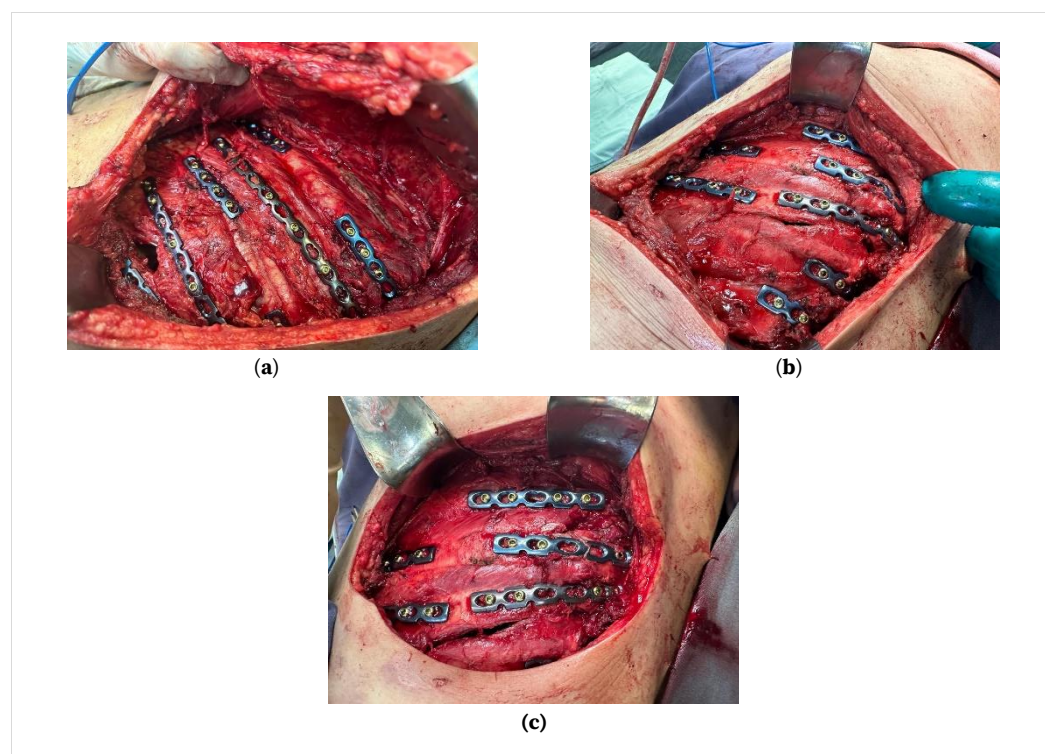


Figure 2. Intraoperative images showing surgical rib fixation via titanium locking plates and screws. (a) Exposure of multiple displaced rib fractures prior to fixation. (b) Alignment and plating of fractured segments. (c) Final view after complete fixation and stabilization of the ribs.



Figure 3. Postoperative chest X-ray image showing stable alignment of the ribs with visible titanium plates on the right side of the thoracic cage, confirming successful surgical fixation.

4. Discussion

This study demonstrated that the SSRF offers meaningful clinical benefits over non-operative management in adult patients with multiple rib fractures following blunt chest trauma. Patients in the surgical group experienced significantly shorter hospital stays, reduced oxygen dependence, and improved pulmonary function recovery. These findings support the growing body of evidence favoring operative fixation in carefully selected patients with unstable chest wall injuries [11,12].

The observed benefits are attributed primarily to biomechanical stabilization of the thoracic cage, which improves pulmonary mechanics, reduces paradoxical chest movement, and enhances pain control, as evidenced by our lower discharge VAS scores (3.6

vs. 7.5). Similar improvements in pain relief with surgical fixation have been reported by Majeed et al., who reported a significant reduction in postoperative pain compared with conservative management (VAS 3.6 vs. 5.5, $p = 0.032$) [13]. This enhanced stabilization facilitates improved pulmonary hygiene, earlier ambulation, and accelerated respiratory recovery, as reflected in our superior FEV₁ values at 1, 2, and 3 months post-injury. These outcomes are consistent with prior evidence demonstrating the role of SSRF in optimizing pulmonary function recovery [14,15].

In addition, the surgical cohort in our study required significantly less ventilatory support, was weaned earlier, and demonstrated a trend toward lower in-hospital mortality than did the nonoperative cohort. These results align with those of the meta-analysis by Leinicke et al., which revealed that, compared with conservative management, surgical stabilization reduced the duration of ventilator use by an average of 4.5 days; shortened the ICU stay by 3.4 days and hospital stay by 5 days; and significantly lowered the risks of pneumonia, tracheostomy, and mortality [16].

However, our results contrast with those of Meyer et al., who, in a randomized controlled trial of severe chest wall injury without clinical flail chest, reported a significantly longer hospital stay in surgically managed patients (median 9 days) than in those treated conservatively (median 6 days) [17]. While some studies have similarly reported longer ICU or hospital stays among surgically treated patients, these findings are often attributable to differences in baseline injury severity. In particular, a greater proportion of flail chest cases in the operative groups—as observed in our cohort (23 vs. 11 cases)—likely contributed to the increased resource utilization in those studies [18].

Another important factor is patient selection bias inherent in nonrandomized studies, where patients with more severe injuries are frequently allocated to surgical intervention. This may partly explain the variability in reported outcomes across the literature and emphasize the importance of context-specific interpretation of results [19].

In the context of low-resource settings, the adoption of custom-made, low-cost rib fixation implants has been associated with favorable clinical outcomes and a significantly faster return to work [19,20]. In our study, all surgically treated patients had resumed employment by three months, compared with only 77.09% in the conservative group. These results highlight not only the clinical benefits of SSRF but also its potential long-term economic and functional advantages, particularly in resource-limited healthcare settings [19].

Our findings also align with several recent meta-analyses, including a comprehensive review in 2022, which concluded that SSRF reduces mortality, pneumonia, and duration of mechanical ventilation—particularly in patients with flail chests [19,20]. These analyses also emphasize the importance of early surgical intervention, with Sawyer et al. demonstrating that procedures performed within 72 hours were associated with significantly improved outcomes, including shorter hospital and ICU stays, lower pneumonia rates, and fewer deaths [21].

Finally, beyond short-term recovery, surgical fixation restores thoracic symmetry, corrects deformities, and prevents nonunion—factors that are crucial for preserving long-term pulmonary function and optimizing physical recovery [22,23]. While some reports suggest comparable pain outcomes between operative and nonoperative groups [24,25], our data indicate a superior quality of recovery with surgical intervention, as evidenced by lower discharge VAS scores and improved pulmonary function over follow-up. These discrepancies are likely explained by patient selection bias in nonrandomized studies [26].

As this was a single-center study, our results may not be generalizable to other public or private institutions with different patient populations, socioeconomic back-

grounds, or levels of surgical expertise. Variability in operative technique and implant selection could also influence outcomes, and nonuniform follow-up durations may have limited the accuracy of assessing chronic pain, nonunion, or long-term functional recovery [27]. Although efforts have been made to control for confounding factors, such as the uneven distribution of flail chest cases, selection bias remains an inherent limitation. While propensity score matching and careful statistical adjustment can reduce this effect, they cannot substitute for the rigor of randomized controlled trials. In addition, excluding deceased patients from functional outcomes such as return-to-work may introduce survivor bias, potentially overestimating recovery in the conservative group, where mortality was higher. The reliance on scheduled follow-up rather than real-time monitoring may also have introduced recall or reporting bias in outcomes such as return-to-work or pain scores. Future research should therefore focus on large, multicenter RCTs to validate the benefits of rib fixation in both flail and nonflail fracture patterns, complemented by rigorous cost-effectiveness analyses to better define the economic implications of surgical stabilization. Additionally, the development of standardized treatment protocols—including clear indications, optimal timing of fixation, implant choice, and postoperative rehabilitation—will help reduce variability in practice. Finally, incorporating patient-reported outcomes, such as pain, quality of life, and return-to-work measures, will provide a more holistic evaluation of treatment success and its impact on long-term recovery [28].

5. Conclusions

Compared with conservative management, SSRF in appropriately selected patients with flail chest fractures or multiple displaced rib fractures demonstrated clear clinical benefits in this study. Operative fixation resulted in significantly better pain control, improved pulmonary function recovery, shorter hospital stays, earlier return to work, and reduced ventilatory support requirements. Although a trend toward lower mortality was observed in the surgical group, this difference did not reach statistical significance. The successful use of custom-made, low-cost implants further highlights the feasibility and value of SSRF in resource-limited settings. Conservative treatment remains an appropriate option for nondisplaced injuries or patients who are unfit for surgery and who are provided with optimal analgesia and pulmonary care.

Author contributions: Conceptualization, FAM; methodology, FAM, AR, and ARA; software, AR, FU, and ARA; validation, FAM, and RM; formal analysis, FAM, AR, RM, ARA, and SC; investigation, FU; resources, RM, and SC; data curation, FAM, and FU; writing—original draft preparation, FAM; writing—review and editing, AR, RM, FU, ARA, and SC; visualization, SC; supervision, FAM; project administration, FAM. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: The study was approved by the Institutional Review Board of the CMH, Rawalpindi (No. 815).

Consent to participate: Not applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Ahmed Raza, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

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Original Article

Delays in the referral, diagnosis, and treatment of tuberculosis patients in a community pharmacy network in Pakistan

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Citation: Ullah W, Almansour H, Saini B, Fatima R, Gondal SA, Sohaib AU, et al. Delays in the referral, diagnosis, and treatment of tuberculosis patients in a community pharmacy network in Pakistan. *J Basic Clin Med Sci*. 2025;4(2):65-76.

Received: 15 November 2025

Revised: 16 December 2025

Accepted: 18 December 2025

Published: 20 December 2025

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Abstract

Timely diagnosis and treatment delays among tuberculosis (TB) patients remain among the major challenges for controlling and eradicating the disease globally. Delayed health-seeking behavior among TB patients may either contribute to undetected and untreated TB cases or lead to poor treatment outcomes when patients are eventually diagnosed. Managing these delayed TB consultations becomes even more challenging in lower-middle-income countries (such as Pakistan), where TB incidence and transmission rates are high, but limited evidence is available on patient and health system delays in seeking and initiating TB treatment. This study aimed to assess the time delays of patients attending pharmacies managed by TB referral initiatives in Pakistan. A case detection approach utilizing a public-private-mix (PPM) partnership was developed and fully protocolized for use; this approach involved participation in pharmacies to assess and provide a formal written referral to patients presenting with symptoms indicative of TB. Ranges of pharmacy referral implementation delay as well as diagnostic and treatment delay of TB patients were defined. Among the 500 pharmacies trained in PPM partnerships, 427 (85%) were active in providing referrals. The median pharmacy referral implementation delay was found to be 46 days. Among the 547 TB cases identified through the community pharmacy-referral network, the median diagnostic delay and treatment delay were found to be 4 days and 1 day, respectively. Time delays among TB patients diagnosed through the community pharmacy referral network in Pakistan were relatively low for diagnosis and treatment; however, delays related to the implementation of pharmacy referrals were at times longer than those reported in local, regional, and global settings.

Keywords

Delay in tuberculosis diagnosis, Health-seeking behavior, Pharmaceutical public health, Pharmacy services, Physician-pharmacist collaborative care, Public-private partnership

1. Introduction

A major impediment in the effective control and eradication of tuberculosis (TB) is the delay in the diagnosis and initiation of effective treatment for patients with TB [1]. D-

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delays in patients' help seeking, diagnosis confirmation and treatment initiation impact TB control even in settings where there are active case detection strategies and cure rates are high [2,3]. A clear consequence of time lags between developing TB disease and being screened or being screened and referred for treatment initiation is the higher risk of community transmission, along with other sequelae such as increased morbidity or even mortality for those infected with TB disease (active cases) [4,5].

An active TB patient may release up to 3,000 *Mycobacterium* TB organisms as infectious aerosols while coughing or talking for just 5 minutes, which are highly pathogenic, and even exposure to a single organism can cause the disease [6]. An exposure of five hours or more to the bacterial nuclei within such infectious droplets was reported as a risk factor for infection with TB in one study [7]. The case for minimizing the delay between disease onset and treatment is further supported by findings that indicate that the possibility of death from TB is relatively high in TB patients who have delayed TB diagnosis [8]. The mortality rate of nontreatment in active cases has been reported to be as high as 50% [9].

These data clearly highlight that delayed consultation, diagnosis, and treatment of TB may lead to undetected and untreated patients who will have the ability to infect and cause TB within their social/occupational network to many others, resulting in increased infection and TB disease load for health systems and imposing personal burdens such as income loss for individual patients [10,11]. It is therefore imperative to identify and address the reasons for consultation, diagnostic and treatment delays to prevent the unnecessary burden of infection transmission and active disease incidence [12].

Community pharmacies have been reported to often serve as consultation and referral points for presumptive TB patients who prefer to self-medicate and thus delay medically supported TB case investigation processes [13,14,15,16,17,18]. While unprofessional TB-related practices in pharmacies, such as supplying medications (e.g., antimicrobials), have the potential to do harm, harnessing the accessibility of pharmacies for assessment and triage in presumed TB case presentation is an effective model that leverages the privately funded infrastructure of pharmacies for public health benefit. With adequate training, procedural support and collaboration with publicly funded medical facilities, pharmacists in community pharmacies can facilitate accelerated TB case detection and early inclusion of patients in treatment programs [19].

Indeed, community pharmacy-based TB case detection, referral and follow-up of referred presumptive cases has been a strategy used in many countries, but evidence of the impact of this model in the Pakistani healthcare system has only recently been demonstrated [20,21]. In this Pakistan-based community pharmacy–public system triage model, 500 pharmacies across 3 districts participated and contributed to 9% of all new TB cases identified through private venues in the project time frame, thus demonstrating the positive impact of the ability of the pharmacy to progress presumptive TB cases through to receive guideline concordant TB care from trained general practitioners (GPs) [20]. However, it was clear that even in this Boosted model, time lags were possible in the actions required by the presumptive TB cases assessed in pharmacies, the assessing pharmacy/pharmacists and the GP clinic and linked laboratory testing facility. Delays in this public–private–mix (PPM)-Boosted model could be caused by a) pharmacies (in counseling, referring to and facilitating follow-up of a presumptive case identified in the pharmacy), b) the presumptive TB patient (in receiving the pharmacist's referral and actioning a visit to the referred GP clinic), and c) GPs and Labs (during TB case diagnosis after a presumptive case presentation and anti-TB treatment initiation).

To increase the efficiency of such PPM-Boosted models, analyzing and addressing sources of delay across the patient trajectory, i.e., progressing a TB presumptive patient

initially presenting at a pharmacy to a confirmed diagnosis through treatment initiation (see Figure 1), would be important for establishing efficient community pharmacy PPM-Boosted models for TB case detection in Pakistan. Additionally, understanding the particular weak spots (those where most delays in forward movements are occurring) in this trajectory would, in a quality improvement approach, help in refining strategies to make the PPM-Boosted models more time efficient. In Pakistan, this research is critical, as the incidence, prevalence, and transmission of TB are high; 200,000 active TB cases are ‘missed’ annually, yet research on patient and health system delays in seeking and initiating TB treatment in Pakistan is scarce [21]. Therefore, this study aims to assess the time delays across the linear trajectory from presumptive TB patients who are presenting at community pharmacies and who are participating in the PPM-Boosted program (pharmacy referral network) through diagnosis and treatment initiation in GP clinics.

2. Methods

The detailed methods adopted to test the impact of the PPM-Boosted model have been described previously [20] but are summarized below as they form the context for the current study.

2.1. Study setting

As mentioned in the introduction, the PPM-Boosted model project was conducted within 500 community pharmacies from January to December 2017. These pharmacies were located in Gujrat (n = 50), Lahore (n = 350), and Sheikhupura (n = 100), districts of Punjab, Pakistan. These private pharmacies were mapped, recruited, trained and implemented with the PPM-Boosted model. The details of these processes have been published previously [20]. Notably, pharmacies had to complete two sets of training, initial onsite training (Training-1) and comprehensive collective training at a district’s central location (Training-2); ideally, the protocols stipulated that referrals should occur after both training sessions had been completed by a pharmacy.

2.2. Study design and subjects

It was an implementation trial in which a case detection approach was developed and protocolized fully for use by participating pharmacies in assessing and providing a formal written referral to patients presenting with symptoms indicative of TB [20].

2.3. Data collection

Data were collected from the participating pharmacies by 10 cluster facilitators (1 facilitator per 50 pharmacies and associated GP clinics/labs within a 5–10 km radius of pharmacies in each cluster) during planned weekly visits to the participating pharmacies. For each patient assessed and referred, the completion of the referral slip also autogenerated two copies; a pink copy meant to be retained by the referring pharmacy, and a yellow copy was handed to the referred TB patient. At weekly visits, the cluster facilitators collected the original referral slip, and later, each ‘pharmacy-referred case’ was followed up on the basis of a patient identification code to retrieve diagnostic and treatment initiation forms (and dates) in each district. The cluster facilitators were also encouraged to diarize the key findings of their weekly follow-up telephone calls and conversations with case patients right from the point of referral provision until treatment initiation. This process allowed further consolidation of time lapse data confirmed by dates recorded on the referral slip and notification of diagnosis and treatment initiation.

2.4. Study participants

This study included all presumptive TB patients who completed the whole cycle within the PPM-Boosted model between January 2017 and December 2017, i.e., who presented at a trained participating pharmacy, who received a referral from the pharmacy staff, who visited a GP clinic, and who underwent diagnosis as well as treatment initiation by a GP. Presumptive patients who did not receive any referrals from the pharmacy staff were excluded from these analyses.

2.5. Range of time delays for study participants

The time delays were defined across the linear trajectory from presumptive TB patients presenting at community pharmacies who participated in the PPM-Boosted program (pharmacy referral network) through diagnosis and treatment initiation in GP clinics.

2.5.1. Pharmacy referral implementation delay

The average duration of time lapses between pharmacies being trained and referring their first case to the participating local GP clinic (time elapsed between Points A and B in Figure 1).

2.5.2. Diagnostic delay

The average duration of time lapses between a pharmacy-referred case presenting at their GP clinic and the date of confirmed diagnosis (time between points B and C in Figure 1).

2.5.3. Treatment delay

The average duration of time lapses between the confirmed diagnosis of TB and the initiation of treatment at the GP clinic (time between points C and D in Figure 1).

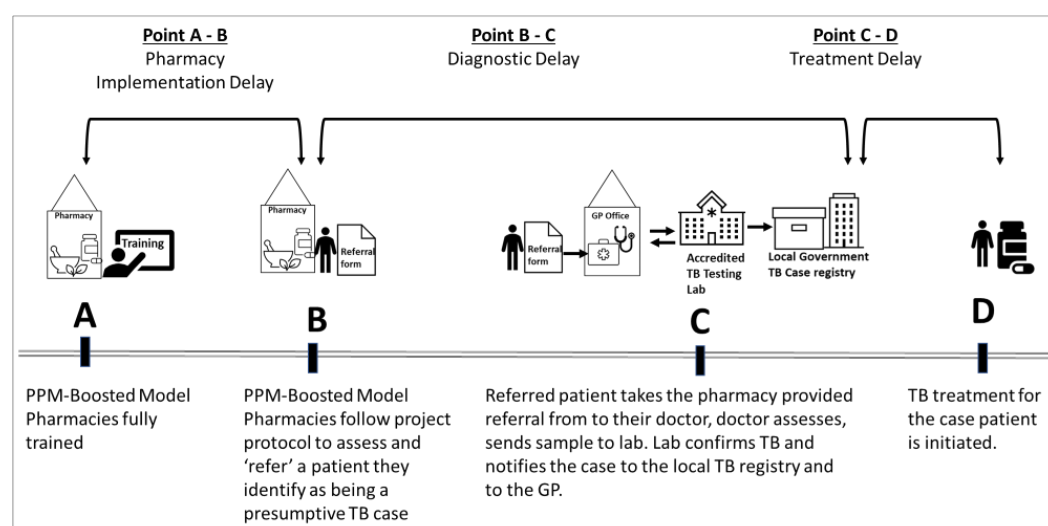


Figure 1. Trajectory of time lapses associated with the PPM.

2.6. Ethical approval

This study was conducted after ethical approval was obtained from the Institutional Review Board (IRB) Ethics Committee, Common Unit, National Tuberculosis Control Pro-

gram, Ministry of National Services, Regulations and Coordination, Islamabad, Pakistan (No. IRB-CMU-2019-06).

2.7. Data analysis

The collected data were entered into Excel (Microsoft Excel 2017 edition). The data were cleaned, verified for accuracy, and analyzed descriptively for the study period. Dia-rized findings reported by cluster facilitators were collated and carefully examined for any key data that could elucidate any patient, pharmacy or other barriers related to referral provision, uptake, diagnosis or treatment initiation.

3. Results

Out of 500 pharmacies trained in the PPM Boosted model, 427 (85%) pharmacies were active in providing (a total of 3025) referrals to GP clinics from January to December 2017, and a total of 547 patients were confirmed as new TB patients among referrals, as reported earlier [20].

3.1. Pharmacy referral implementation delay

In terms of the actively participating (427) pharmacies, 16% commenced referring to presumptive patients before they had completed the comprehensive training session. These referral data were not included in the analyses; as per the protocol, the completion of comprehensive training (Training-2) was considered a cutoff point for documenting the referral implementation delay. With respect to postcomprehensive training, approximately 25% of the pharmacies started referring to presumptive TB cases within a median of 13 (range: 1–30) days, and 18% of the pharmacies started referrals after a median delay of 45 (range: 31–60) days. Overall, the median delay in pharmacy referral implementation within the PPM-Boosted model was 46 days (range: 1–270 days). The distribution of delays in pharmacy referral implementation for the entire group of pharmacies in operational districts in terms of days of delay is shown in Figure 2.

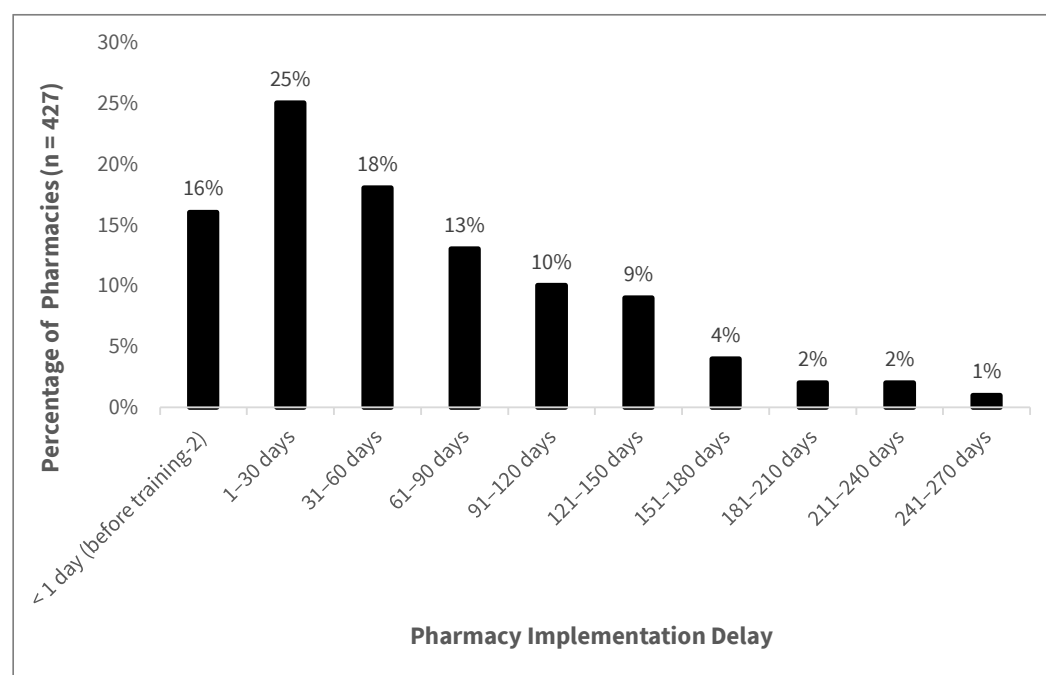


Figure 2. Proportion of pharmacies in different ranges of referral delay in the operational districts.

3.2. Diagnostic delay

Diagnostic delay data were categorized into nine groups for ease of analysis (Figure 3). Among 547 notified TB cases that stemmed through the community pharmacy referral network, the overall median diagnostic delay for diagnosed TB patients was found to be 4 (range: < 1–32 days). The diagnostic delay ranged from less than 1 day to as long as 29–32 days. Approximately 43% of the TB patients had a median diagnostic delay of 3 (range: 1–4) days, followed by 22% with a median delay of 6 (range: 5–8) days. Additionally, 11% of TB patients were diagnosed at GP clinics either on the same day of presentation or within 8–12 days of their referral from community pharmacies. The distribution of diagnostic delays for the entire group of notified TB patients in the PPM-Boosted model is depicted as days in Figure 3.

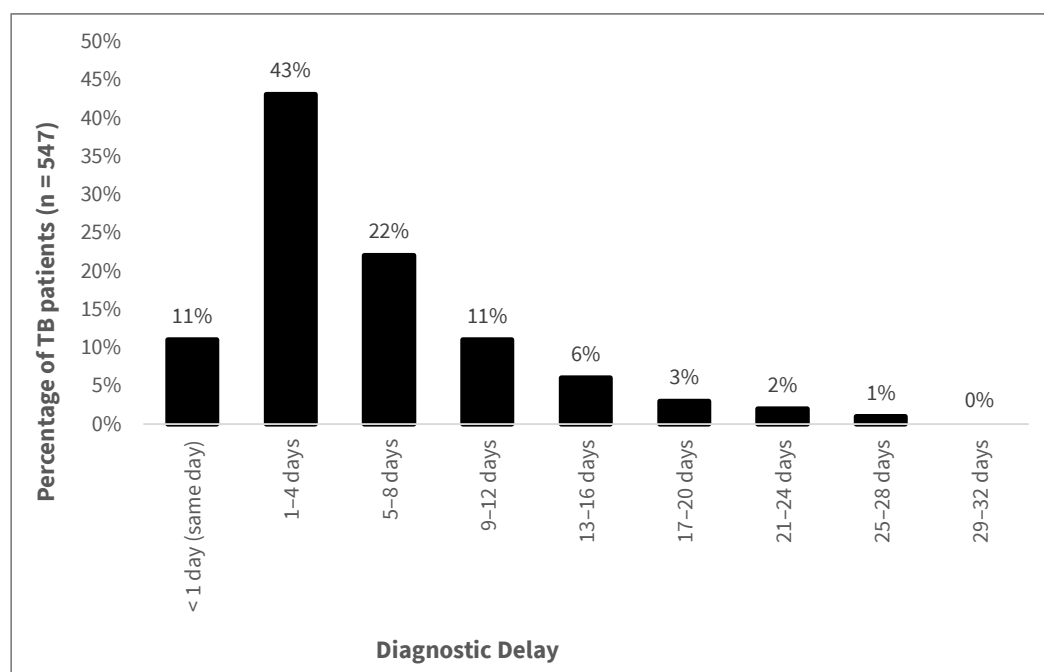


Figure 3. Proportion of TB patients in different ranges of diagnostic delays in operational districts.

3.3. Treatment delay

Anti-TB treatment for diagnosed TB patients was mostly (82%) initiated after a delay of one day from their date of case registration, while the longest treatment delay was > 2 days. Moreover, 16% of the diagnosed TB patients received their prescribed TB treatment on the same day as their diagnosis at GP clinics. The median treatment delay was just 1 (range < 1 to > 2) day. The quantile distribution of treatment delay for the entire group of diagnosed TB patients in the PPM-Boosted model in terms of days of delay is shown in Figure 4.

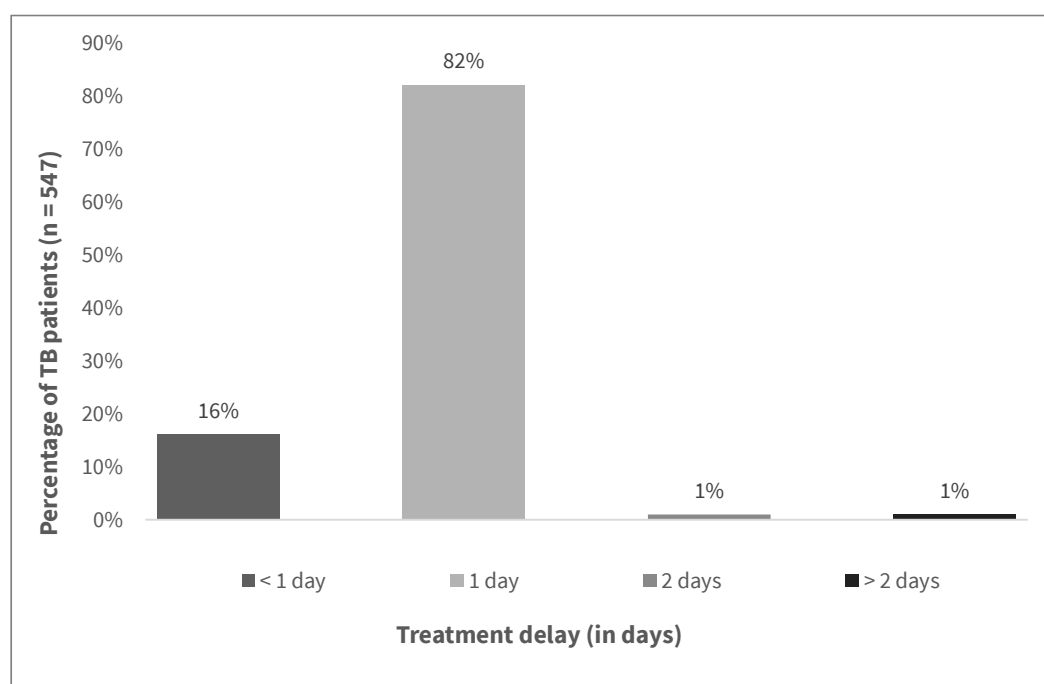


Figure 4. Proportion of TB patients in different ranges of treatment delay in operational districts.

4. Discussion

This is the first large-scale project to pragmatically estimate the time delay between patient symptom recognition and treatment initiation in TB patients who present at community pharmacies; this project is attached to a PPM-Boosted model for TB case detection in the Pakistani health care system. While most PPM models for TB case detection explore the contribution of ‘case numbers’, few explore the time sensitivity in looping presumptive TB case patients into established health system pathways for diagnosis and treatment, which we assessed during this study. Our analysis revealed significant delays at the pharmacy end of the PPM-Boosted model, which includes pharmacies, even though such a model can contribute to case detection rates. In this project, the delay in the implementation of pharmacy referrals constituted the main delay in TB case detection, diagnosis, and treatment initiation. Given that community pharmacists significantly contributed to the detection of missing TB cases, exploring methods to enhance the adoption and implementation of established PPM-Boosted protocols more widely is needed.

A positive observation regarding the provision of referrals to pharmacies for presumptive TB cases presenting in community pharmacies was that a majority of the pharmacists were ‘prompt’ in implementing the assessment and triaging patients via the referral; 43% of the actively participating pharmacies started referring presumptive TB patients to GP clinics during the first two months of participation (i.e., referral delay of 1 day to 60 days) after their comprehensive training), which may be denoted as the ‘early adopters’ of this role on the basis of Rogers’ Model of the diffusion of innovations [22]. Usually, only a handful of players in an innovation are ‘early adopters’; hence, this reasonable level of initial uptake may suggest the overall readiness of the pharmacy community in Pakistan to contribute to infectious disease control. Motivational strategies in future versions of this PPM-Boosted model could involve showcasing these early adopters as ‘role models’ for other pharmacists participating in the project. Michie’s work on implementation research suggests that enablement and training are key motivational strategies for enabling practice behavior change [23].

An analysis of the delay in pharmacies initiating referral provision provides additional insight from data collected within the PPM Boosted model, which has not been commonly established in other research studies examining the potential of community pharmacy referral networks for TB case detection, e.g., in countries such as Vietnam [17], Bolivia [16], Cambodia [13], the Dominican Republic [18], and a previous pilot-scale project in Pakistan [24]. A few similar projects have attempted to document this referral implementation lag; for example, in India, researchers reported an implementation lag of 30 days (median) [14], which is lower than that in our project [i.e., an implementation lag of 46 days (median)]. Indian pharmacies in that project had several facilitators that may have prompted patient consent for assessment and referral; e.g., these pharmacies had the ability to refer the patient being assessed directly for a chest radiograph (CXR) or to a linked GP irrespective of the CXR result or to a private laboratory of their choice [14]. In our project, consenting to a case presenting with TB symptoms relied on verbal patient counseling rather than proactively being able to perform a diagnostic process. Being referred for a ‘test’ can psychologically enhance perceptions about the seriousness of symptoms and prompt patients to follow through with recommended actions. In our study, the reasons for the delay in referral implementation reported by cluster facilitators after pharmacy and patient follow-up included low patient perceived symptom severity or a preference for self-medication on a previous physician’s prescription initially. Similar findings have been reported in other studies [14,25]. Pharmacy training perhaps should have included strategic risk communication skills.

In our data, we were unable to pinpoint delays attributed to the patient. For example, patients who may have not actioned their provided referrals quickly or even refused a referral when offered this for the first time at the pharmacy and only consented when counseled repeatedly. Our data were obtained only from referral slip dates at the pharmacy and the appearance of a referred patient tracked to a GP clinic and registered as diagnosed. According to studies that have assessed patient delay in initial TB consultation with a medical practitioner after referral from venues other than private pharmacies, patient factors clearly contribute to the time taken for TB diagnosis and treatment. For example, median patient delays of 30 days in Thailand [26], 32 days in Nepal [27], 35 days in Ethiopia [28], 58 days in China [29], 59 days in Ghana [30], and 61 days in the Peruvian Amazon [31] have been reported.

Finally, a general note in countering this patient delay during the pharmacy referral implementation lag would be to suggest that increased awareness of the roles of pharmacies in public health programs needs to be better highlighted to the public in countries where community pharmacies are still perceived to be mere ‘medicine outlets’ rather than trusted members of the health care profession. Studies report major gaps between public expectations and actual experience at Pakistani pharmacies. In a survey of 385 members of the public, only half expected pharmacists to be medication experts [30]. Given this situation, it is not surprising that some delay in referring patients may have been due to patient mistrust of what the pharmacists were proposing. Local area advertising highlighting what the pharmacists were doing, supported by other prominent medical professionals, may have prompted patients to consent to receive a referral.

The mean diagnostic delay for TB patients identified through the PPM-Boosted model was 4 days. This four-day period was a normally established mechanism after the referral provision in Greenstar Social marketing (GSM, i.e., the implementing organization) operated PPM facilities during the study period. This normal period included a patient visit from the pharmacy to the GP check-up on a pharmacy referral slip, receiving a TB diagnostic test-free voucher and providing an on-the-spot sample to the PPM laboratory (Day 1), a patient providing an empty stomach sputum sample (i.e., the second) to

the PPM laboratory the next morning (Day 2), receiving sample results from the laboratory after 24 hours (Day 3), and finally revisiting the GP clinic for final diagnosis (Day 4). Given that the project implementation team developed processes to facilitate speedy diagnostics, the efficiency of the diagnostic process once patients entered the medical system is not surprising. This four-day diagnostic delay was substantially lower than the median diagnostic delay of 29 days previously reported in China and Taiwan [32] and 60 days in Pakistan [33]. These two studies with longer diagnostic delays mainly involved initial or direct contact of TB patients with a GP clinic where training around complete diagnostic procedures may not have been provided to the patients. The lower delays in diagnosis in our PPM-Boosted model might be attributed to pharmacy staff counseling at the time of referral provision and their careful selection of the referred GP clinic (from the GSM directory) lying either within a five-kilometer radius of the pharmacy or close to the referral's home address, as well as providing additional information (opening and closing times) about TB facilities (GP clinics and labs) to patients. Working around patient preference and counseling are processes that have been shown to predict referral uptake in both high-income [34] and low-income countries [35,36].

Once diagnosed, all patients (i.e., 547 patients) commenced their TB treatment in the PPM Boosted model, and no case of pretreatment loss to follow-up was recorded. In total, the treatment of 98% of the TB patients was initiated either on the day of diagnosis or the day after diagnosis at the GP clinic, with a median treatment delay of 1 day after their date of registration. These findings are substantially better than those of previous private TB health care facilities in Pakistan, where an analysis of TB treatment in 8 Pakistani districts (four districts in each of the Punjab and Sindh provinces of Pakistan) indicated that only 66% of smear-positive patients initiated TB treatment either on the same day or 1 day after diagnosis, with a median treatment delay of seven days and a 5% loss to follow-up of diagnosed TB patients in the pretreatment phase [37]. The main reasons for the lower proportion of TB patients who received treatment initiation (66% vs 98%) and longer median treatment delay (7 days vs 1 day) in this study than in our study were pretreatment loss-to-follow-up of the diagnosed patients and the lack of a mechanism for tracking such TB patients [37]. These two factors in the aforementioned study seem to be largely resolved in the PPM-Boosted model.

A key strength of our study is the inclusion of all categories (pulmonary and extrapulmonary cases) of TB patients contributing to the TB infectious pool at different levels, which has remained a limitation in previous studies examining delays in TB referral, diagnosis, and treatment [11]. However, this study has several limitations. The time interval between symptom appearance in patients and the patient visit at their pharmacy (patient delay) could not be calculated. Additionally, we were unable to determine the delay incurred between referral by the pharmacy and the patient's actual attendance at the GP clinic. Both these data are of key importance in understanding how future TB case detection and treatment models could hasten patient entry into treatment pathways. Unlike the total delay for TB patients receiving treatment reported in the literature [17], the time delays assessed in our study (pharmacy referral implementation, diagnosis, and treatment) were not all patient centered. The pharmacy referral implementation delay calculation was based on the number of pharmacies engaged and referrals made to TB clinics, from which a median delay per pharmacy was derived. The diagnostic and treatment delay calculations focused on diagnosed TB patients among the overall referrals.

5. Conclusions

Patients referred to GP clinics through trained community pharmacies under the PPM-Boosted model contributed to TB case detection and treatment initiation. The time

delays for diagnostic confirmation and treatment initiation among TB patients diagnosed through this model in Pakistan were relatively short, whereas the median delay in the implementation of pharmacy referrals was relatively long. The short diagnostic and treatment delays observed in this study may reflect the structured referral pathway within the PPM-Boosted model and the coordination between pharmacies, GP clinics, and laboratories. However, the longer median pharmacy referral implementation delay suggests variation in the timing of referral uptake following training. A more comprehensive assessment of delays could be achieved by separately evaluating patient delays and pharmacy-level delays. Additionally, strengthening pharmacy-based TB assessment capacity may further increase referral efficiency beyond the reliance on verbal counseling alone.

6. Recommendations

Implementing TB screening services at pharmacies or enabling direct referral from pharmacies to laboratories may facilitate the filtering of presumptive TB patients presenting at pharmacies before referral to GP clinics, which could also assist timely patient consent for referral and potentially reduce the median delay in pharmacy referral implementation (currently 46 days). Additionally, prescreening at referring pharmacies may further increase the proportion of confirmed TB cases among referrals in Pakistan (approximately one in five referrals from community pharmacies were diagnosed as active TB at the GP clinic) [20].

Given the passive TB case-finding approach (i.e., patient-initiated pathway for TB investigation) adopted in our study, reducing pharmacy referral implementation delay (including both patient- and pharmacy-related delays) may require a transition toward a more active or enhanced TB case-finding strategy, which could involve systematic screening and clinical evaluation of persons outside traditional health facility settings, similar to approaches implemented in other settings such as China [2].

It may also be valuable to conduct in-depth qualitative research with patients and pharmacists who participated in the PPM-Boosted model to better understand the contextual factors contributing to delays in referral implementation.

Supplementary materials: The following supporting information can be accessed through the embedded link: [Supplementary Table S1](#), Key definitions of community pharmacies referral network.

Author contributions: Conceptualization, WU, BS, RF, SAG, and GMK; methodology, WU, HA, BS, RF, AUS, MIK, and GMK; software, WU, HA, AUS, and MIK; validation, WU, HA, AUS, and MIK; formal analysis, WU, HA, AUS, and MIK; investigation, WU, HA, and SAG; resources, WU, and GMK; data curation, WU, HA, AUS, and MIK; writing—original draft preparation, WU, HA, BS, RF, SAG, AUS, MIK, and GMK; writing—review and editing, WU, AUS, and MIK; visualization, WU, HA, and SAG; supervision, WU, and GMK; project administration, WU, and GMK. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: This study obtained ethical approval from the Institutional Review Board (IRB) Ethics Committee, Common Unit, National Tuberculosis Control Program, Ministry of National Services, Regulations and Coordination, Islamabad, Pakistan (No. IRB-CMU-2019-06).

Consent to participate: Not applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Waseem Ullah, upon reasonable request.

Acknowledgments: We appreciate the efforts of Khalid Farough (General Manager, Program, TB Project, GSM), Amjed Abbas (Regional Coordinator, GSM), Naseem Ullah (Project Officer, GSM),

Syed Azadar Gillani (Project Manager, GSM), Syed Ghulam Haider (Monitoring & Evaluation Manager, GSM), and Sobia Faisal (Technical Manager, GSM) for their continuous support throughout the implementation of this project.

Conflicts of interest: The authors declare no conflicts of interest.

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Original Article

Effectiveness of folic acid supplementation in children under five years of age with acute watery diarrhea: a randomized placebo-controlled trial

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Citation: Jamil R, Pracha HS, Jamil H, Shabbir S, Paracha UA. Effectiveness of folic acid supplementation in children under five years of age with acute watery diarrhea: a randomized placebo-controlled trial. *J Basic Clin Med Sci*. 2025;4(2):77-84.

Received: 01 September 2025

Revised: 07 December 2025

Accepted: 19 December 2025

Published: 22 December 2025

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Abstract

Diarrhea is caused by bacteria, viruses, or parasites, a major contributor to morbidity and mortality in children below 5 years of age. This randomized placebo-controlled trial evaluated effectiveness of folic acid supplementation for acute watery diarrhea (AWD) in children below 5 years of age. The study was conducted at the Department of Pediatric Medicine, Mayo Hospital, Lahore, and enrolled and randomized 324 pediatric patients in a 1:1 ratio to two groups. Children in Group A were given folic acid for 5 days while children in Group B were administered distilled water as a placebo for the same period. Clinical proformas were used to record and monitor the frequency of loose stools and stool consistency across both groups, on daily basis. Results of the study revealed that, compared with placebo group, folic acid supplementation did not significantly decrease frequency of loose stools, improve stool consistency, or shorten the duration of diarrhea. The average change in the number of loose stools from presentation to day 5 was similar in both groups [Group A: median = 7 (IQR = 4) versus Group B: Median = 7 (IQR = 4); $p = 0.704$]. The average duration of diarrhea was not significantly different between Group A [median = 4 (IQR = 2)] and Group B [median = 5 (IQR = 3)] ($p = 0.530$). The maximum duration of diarrhea was 11 days in Group A and 10 days in Group B. The study concluded that folic acid supplementation in AWD was not effective in reducing the frequency of loose stools, improving stool consistency, or decreasing the duration of illness among children under 5 years of age. Future studies should explore additional adjunctive therapies to help reduce diarrhea-related complications and mortality.

Keywords

Acute watery diarrhea; Child, preschool; Diarrhea; Dietary supplements; Folic acid; Randomized controlled trial

1. Introduction

Diarrhea is an intestinal disease caused by bacteria, viruses, or parasites, with viruses being the most common etiologic agents in children [1]. In children under the age of 5 years, diarrhea remains a major cause of morbidity as well as mortality. Every year, diarrheal disease accounts for more than 801,000 child deaths around the globe and is associated with growth retardation in 10 to 80% of affected children [2]. High incidence of diarrhea is due to a unsafe water supply, a lack of breastfeeding, and delayed seeking of medical care [3]. Currently, management of acute watery diarrhea (AWD) mainly relies on oral rehydration therapy (ORS). It not only corrects the patient's hydration status but is also safe, cost effective, easily available, and a major life-saving remedy. However, in underdeveloped and developing countries, appropriate rehydration therapy is often not given owing to a lack of caregiver education and a limited understanding of the prep-

aration and administration of fluids, leading to a greater number of deaths from diarrhea and dehydration [4]. Furthermore, rehydration therapies do not significantly affect disease duration, resulting in increased parental concern regarding the course of disease, which may lead to the inappropriate use of antibiotics and/or alternative medications for rapid recovery [5].

Any drug that would reduce the frequency of loose stools or disease duration would be a useful addition to ORS, for example, zinc [6,7]. Moreover, a variety of drugs, including probiotics, dioctahedral *smectite*, racecadotril, and oral immunoglobulins of bovine origin, have been studied for their role in reducing the duration of diarrhea [8,9]. However, none of these are routinely recommended because of their potential side effects, high cost, or poor palatability. Folic acid is a synthetically produced form of vitamin B9 [10]. Amino acid metabolism, as well as the synthesis and repair of DNA and RNA, depends on the adequate presence of folic acid [11]. Diarrhea may result in potential damage to the intestinal mucosal lining; therefore, folic acid has been studied as an adjuvant therapy because of its role in DNA synthesis, especially in rapidly regenerating cells.

Previous scientific evidence regarding role of folic acid in acute diarrhea has reported inconsistent findings. Multiple studies have reported that folic acid supplementation was linked with reduction in duration as well as severity of diarrheal episodes, whereas other studies failed to observe any significant therapeutic advantage of supplementation [12,13,14]. These conflicting results limit the current scientific evidence base and leave clinical utility of folic acid in management of acute diarrhea uncertain. Furthermore, few similar studies have been conducted in South Asian populations, where disease burden, nutritional status, and environmental factors may influence treatment outcomes.

Folic acid is an inexpensive, easily available, and generally safe micronutrient with a favorable tolerability profile in children and adults [15]. Though its biologically active metabolite, L-methylfolate, is often preferred because it bypasses metabolic activation and can be directly consumed in cellular processes, and it is most accessible form in many resource-limited settings. However, targeted, safe, and cost-effective pharmacological interventions capable of reducing stool frequency, improving stool consistency, or shortening the duration of acute diarrheal illness are lacking. Therefore, evaluating the therapeutic efficacy of folic acid in children with acute diarrhea is warranted, given its proposed role in intestinal mucosal repair, cellular regeneration, and immune modulation. Therefore, our study assessed effectiveness of folic acid supplementation in children under the age of five years with AWD by determining its effects on stool frequency, stool consistency, and illness duration compared with those of a placebo.

2. Methods

2.1. Study design, duration and setting

This randomized placebo-controlled trial was conducted between November 2020 and August 2021 in the Department of Paediatrics Medicine at Mayo Hospital, Lahore, Pakistan.

2.2. Sample size calculation

The sample size was calculated to detect a difference of 23.8 hours in the average length of diarrhea between groups (expected means 123.6 ± 32.90 versus 147.4 ± 33.06 hours) [16]. Using a two-sided two-sample test with $\alpha = 0.05$ and 90% power, the pooled variance formula yielded 41 participants per group (82 total). Allowing for 10% attrition, the recruitment target was set at 46 per group (92 total). Calculations were verified using OpenEPI (two-means module) and G*Power software. Although the minimum required

sample size was 92 participants, all eligible participants who presented during the study period were enrolled, resulting in a final sample of 324 children.

2.3. Study population and sampling technique

Of the 358 children assessed for eligibility, 324 eligible participants were enrolled consecutively and subsequently randomized using a simple randomization method. Children aged 2 months to 5 years of either gender presenting with AWD, defined as the passage of ≥ 3 loose stools/day, and with a duration of diarrhea of less than 7 days, were eligible for enrollment. Severely malnourished children; those with bloody or chronic diarrhea; patients who had received folic acid within the preceding two weeks; and those with comorbid conditions such as pneumonia, sepsis, and meningitis were excluded from the study.

2.4. Ethical considerations

Formal ethical clearance and institutional approval for this investigation were granted by Advanced Studies and Research Board (ASRB) and Institutional Review Board (IRB) of King Edward Medical University, Lahore (No. 321/RC/KEMU). The study was also registered with ClinicalTrials.gov (Identifier: NCT04782037). Written informed consent was obtained from parents as well as guardians of all eligible pediatric patients before enrollment. No personal identifiers were recorded to maintain confidentiality, and the data was used only for research purposes.

2.5. Randomization and allocation

Participants were randomized using the lottery method, and group allocation was concealed until enrollment to minimize selection bias. Eligible patients were randomly allocated to either folic acid group or placebo group following a single-blind design in which participants as well as their parents or guardians were unaware of assigned intervention. A CONSORT flow diagram summarizing participant screening, randomization, allocation, follow-up, and analysis is provided in [Supplementary Figure S1](#).

2.6. Intervention and study procedures

A baseline assessment including demographic and clinical parameters was performed for all enrolled patients. Participants in Group A received oral folic acid, with children aged < 1 year receiving 3 drops daily and those aged ≥ 1 year receiving 5 drops daily for five days, whereas participants in Group B received an equal volume of placebo preparation (distilled water) according to age category. All patients received standard treatment, including breastfeeding support, nutritional counseling, zinc sulfate supplementation, and oral rehydration therapy, in accordance with World Health Organization (WHO) guidelines.

2.7. Outcome assessment and follow-up

Clinical outcomes were assessed daily using a predesigned proforma and included stool frequency, consistency according to WHO grading, and duration of diarrhea. Patients showing clinical improvement were discharged and followed daily through hospital visits or telephone communication for completion of outcome data over a five-day period.

2.8. Statistical analysis

The data were analyzed using SPSS version 26.0. On the basis of the results of the normality test, continuous variables were tabulated as medians (IQRs) and compared between groups using the Mann–Whitney U test, whereas, categorical variables, including stool consistency grades, are tabulated as frequencies and percentages and were compared using the chi-square test. A two-sided p value < 0.05 indicated statistical significance.

3. Results

The study population included 202 (62.35%) males and 122 (37.65%) females. Group A included 100 (61.73%) males and 62 (38.27%) females, whereas Group B included 102 (62.96%) males and 60 (37.04%) females. Table 1 shows that the median ages of patients in the folic acid (Group A) and placebo (Group B) groups were 14 (20.20) months and 15 (18.50) months, respectively. Similarly, the median weights of patients are presented in Table 1.

Table 1. Comparisons of age and weight across treatment groups.

Variables	Treatment Groups		p Value
	Group A	Group B	
	Median (IQR)	Median (IQR)	
Age (months)	14.00 (20.20)	15.00 (18.50)	0.417
Weight (kg)	9.00 (7.00)	9.85 (5.00)	0.426

Table 2 depicts that the median number of loose stools tended to decrease in both groups from presentation to day 5. No statistically significant differences in stool consistency grades were observed between the groups on days I–V.

Table 2. Comparison of the number of loose stools on days 1–5 between the study groups.

Number of Loose Stool	Treatment Groups		p Value
	Group A	Group B	
	Median (IQR)	Median (IQR)	
On day 1	6.00 (3.00)	6.00 (4.00)	0.236
On day 2	3.50 (2.00)	3.00 (1.00)	0.084
On day 3	2.00 (1.00)	2.00 (1.00)	0.121
On day 4	2.00 (1.00)	2.00 (1.00)	0.144
On day 5	1.00 (1.00)	1.00 (1.00)	0.540

Table 3 presents the distribution of stool consistency grades among children receiving folic acid and placebo during the five-day follow-up period. Both groups demonstrated progressive improvement in stool consistency over time; however, no statistically significant differences were observed between the treatment groups at any follow-up day ($p > 0.05$), suggesting that folic acid supplementation had no significant effect on stool consistency.

Table 3. Comparison of stool consistency grades on days I–V between the study groups.

Days	Grade of Stools	Treatment Groups		χ^2	<i>p</i> Value
		Group A (n = 162)	Group B (n = 162)		
		Frequency (%)	Frequency (%)		
Day 1	II	1 (0.62)	1 (0.62)	6.178	0.103
	III	3 (18.52)	45 (27.78)		
	IV	7 (43.21)	73 (45.06)		
	V	61 (37.65)	43 (26.54)		
Day 2	I	1 (0.62)	0 (0.00)	7.397	0.116
	II	18 (11.11)	22 (13.58)		
	III	76 (46.91)	92 (56.79)		
	IV	53 (32.72)	42 (25.93)		
	V	14 (8.64)	6 (3.70)		
Day 3	I	3 (1.85)	9 (5.56)	8.146	0.086
	II	60 (37.04)	63 (38.89)		
	III	70 (43.21)	75 (46.30)		
	IV	27 (16.67)	13 (8.02)		
	V	2 (1.23)	2 (1.23)		
Day 4	I	29 (17.90)	23 (14.20)	6.158	0.104
	II	87 (53.70)	104 (64.20)		
	III	38 (23.46)	33 (20.37)		
	IV	8 (4.94)	2 (1.23)		
Day 5	I	54 (33.33)	58 (35.80)	4.608	0.203
	II	92 (56.79)	97 (59.88)		
	III	14 (8.64)	7 (4.32)		
	IV	2 (1.23)	0 (0.00)		

The maximum duration of diarrhea was 11 days in Group A and 10 days in Group B. In Group A, 53 (32.71%) patients had a diarrhea duration exceeding 5 days, whereas in Group B, 49 (30.25%) had a duration of diarrhea of 4.00 (2.00) days and 5.00 (3.00) days, respectively, with no significant difference between the groups ($p = 0.530$).

4. Discussion

This randomized placebo-controlled trial revealed that folic acid supplementation did not significantly reduce stool frequency, improve stool consistency, or shorten the duration of AWD in children under five years of age. Both groups showed gradual clinical improvement from day 1 to day 5, but the pattern of recovery was comparable between the folic acid group and the placebo group. The average length of diarrhea was slightly lower in the folic acid group; however, this difference was not statistically significant.

Childhood diarrhea is a major global health problem despite declines in mortality due to this disease. Recent global studies have shown a high burden of diarrhea among children under the age of five years, especially in low- and middle-income regions [17]. Rahmat et al. highlighted persistent diarrhea-related morbidity among Pakistani children and linked it to unsafe water consumption, poor water sanitation, and health system-related challenges [2]. Another case-control study from Pakistan revealed that breastfeeding, maternal age, paternal education, and household income were the primary factors associated with childhood diarrhea [18].

Recent scientific literature emphasizes the assessment of dehydration among patients, the administration of oral rehydration solution, continued feeding, and the selec-

tive use of adjunct therapies as the key components of diarrhea management [19,20]. Florez et al. reported that several interventions have been clinically assessed for a reduction in diarrhea duration, but only zinc and supportive care have proven to be more effective, while many other adjunct therapies are supported by low-certainty evidence [19]. Similarly, Leung et al. reported that viral gastroenteritis is generally managed supportively and that most children improve over time with adequate hydration and oral feeding [20]. A 2024 systematic review and meta-analysis of 38 randomized controlled trials revealed that zinc supplementation increased recovery at the last follow-up and reduced diarrhea duration by approximately 13 hours in children with acute diarrhea, although vomiting was more frequent in zinc-treated children [21].

Minaz et al. reported that probiotics were associated with a clinical cure and a shorter duration of diarrhea [22]. Collinson et al. reported no clear benefit in low-risk-of-bias analyses and highlighted heterogeneity and publication bias [23]. In contrast, Yang et al. and Huang et al. reported reductions in diarrhea duration and stool frequency with probiotics or supportive care but also highlighted variability across formulations and study settings [24,25]. The ESPGHAN 2020 update stated that despite many trials, high-quality evidence for benefit was limited, and recommendations for several strains were weak [26]. The 2023 ESPGHAN position paper again emphasized that probiotic effects are strain-specific and that products without documented benefit should be discouraged [27]. Recent randomized and meta-analytic evidence for selected probiotics has reported that some interventions can be effective under specific conditions. Rerksupphol et al. reported that *Lactobacillus reuteri* (DSM 17938) shortened diarrhea duration in Thai children with acute gastroenteritis in an outpatient setting [28]. McFarland and Li reported that *Saccharomyces boulardii* (CNCM I-745) reduced duration of pediatric acute gastroenteritis [29]. These findings contrast with those of the present study and suggest that interventions targeting gut microbiota, inflammation, or pathogen-related mechanisms may influence diarrheal outcomes through mechanisms different from those proposed for folic acid. Recent folate literature highlights differences in the bioavailability, metabolism, and clinical interpretation of different folate forms [13]. Maruvada et al. reported that the clinical effects of folate depend on baseline folate status, dose, metabolic context, and interactions with vitamin B12 status [12].

Racecadotril provides another useful comparison. It has a direct antisecretory mechanism, yet a 2019 Cochrane review concluded that racecadotril appears safe but offers little benefit for acute diarrhea in children under five years of age, and current evidence does not support its routine use outside placebo-controlled trials [30]. This supports conclusion that even mechanism-based adjunctive therapies may fail to provide meaningful clinical benefit in routine pediatric diarrhea care and that not all low-cost adjuncts improve clinically relevant outcomes when standard care is already provided.

Our study targeted children under the age of five years with a large sample size. Furthermore, the study considered multiple clinical outcomes related to diarrhea management, which adds to the strengths of the study. However, the single site design of this study may limit the generalizability of the findings. Stool frequency and consistency were partly based on caregiver reporting, which may introduce recall or observation bias. Baseline folate, vitamin B12, zinc, and nutritional biomarkers were not measured. Stool volume, dehydration episodes, the need for intravenous fluids, and recurrence after follow-up were also not assessed.

5. Conclusions

It is concluded that folic acid supplementation in AWD was not effective at reducing the frequency of loose stools, improving the grades of diarrhea or decreasing the overall

duration of illness among children under 5 years of age. Future studies should explore additional adjunctive therapies that may help reduce diarrhea-related complications and mortality among children.

Supplementary materials: The following supporting information can be accessed through the embedded link: [Supplementary Figure S1](#). CONSORT flow chart for recruitment of participants, allocation, and follow-up.

Author contributions: Conceptualization, RJ, HSP, HJ, SS, and UAP; methodology, RJ, HSP, HJ, SS, and UAP; software, RJ, HJ, and SS; validation, RJ, HJ, and SS; formal analysis, RJ, HJ, and SS; investigation, RF, HJ, and SS; resources, RF, HSP, and SS; data curation, HJ, and UAP; writing—original draft preparation, RJ, HJ, SS, and UAP; writing—review and editing, HSP; visualization, HJ, and UAP; supervision, HJ; project administration, RJ, HJ, and SS. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement and consent to participate: Formal ethical clearance and institutional approval for this investigation were granted by Advanced Studies and Research Board (ASRB) and Institutional Review Board (IRB) of King Edward Medical University, Lahore (No. 321/RC/KEMU). The study was also registered with ClinicalTrials.gov (Identifier: NCT04782037). Written informed consent was obtained from parents as well as guardians of all eligible pediatric patients before enrollment.

Consent to publication: Not applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Hafiza Saima Pracha, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

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Original Article

Depressive symptoms among working women and homemakers in an urban community of Pakistan: a community-based comparative study

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Citation: Khan ZH. Depressive symptoms among working women and homemakers in an urban community of Pakistan: a community-based comparative study. *J Basic Clin Med Sci*. 2025;4(2):85-94.

Received: 14 August 2025

Revised: 16 December 2025

Accepted: 21 December 2025

Published: 23 December 2025

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Abstract

Depression is a public health problem affecting both males and females and is contributed by multiple social, demographic, and economic factors. However, scientific evidence comparing depressive symptoms among working women and homemakers in Pakistan remains limited. This community-based comparative study compared the proportion of depressive symptoms among working women and homemakers and determined their associations with sociodemographic characteristics. The study included 350 women aged 20–60 years residing in Hirabad, Hyderabad, Sindh, Pakistan, comprising 175 working women and 175 homemakers, and were selected using stratified random sampling. Data were collected using a structured questionnaire, and the Center for Epidemiologic Studies Depression Scale (CES-D) score and depressive symptoms were defined as a CES-D score > 23. The results showed that 137 (39.1%) participants had depressive symptoms, and the proportion of depressive symptoms was greater among homemakers than working women (42.9% vs. 35.4%); however, the difference was not statistically significant ($\chi^2 = 2.027$, $df = 1$, $p = 0.155$). Depressive symptoms were significantly associated with age ($p = 0.030$), marital status ($p = 0.014$), educational attainment ($p = 0.010$), and socioeconomic status ($p = 0.005$), whereas no significant associations were observed with employment status or area of residence ($p > 0.05$). The study concluded that depressive symptoms were common among both working women and homemakers. Although a nonsignificant higher proportion of depressive symptoms was observed among homemakers. Sociodemographic factors, rather than employment status, were significantly associated with depressive symptoms in this study population.

Keywords

Depression; Working women; Homemakers; Center for Epidemiologic Studies Depression Scale; Depressive symptoms; Pakistan

1. Introduction

Depression is a major public health problem and a common mental disorder contributing significantly to impaired functioning, disability, reduced quality of life (QoL), and increased risk of suicidal tendencies among patients. According to the World Health Organization (WHO), approximately 332 million people are living with depression globally, with women affecting depression approximately 1.5 times more frequently than men do [1]. The burden of major depressive disorder (MDD) increased substantially during and after the COVID-19 pandemic [2]. Depression is characterized and influenced by biological, psychological, and social factors, including but not limited to gender roles, socioeconomic disadvantage, employment conditions, and access to healthcare [3]. Compared with their counterparts, women experience a greater burden of depression be-

cause of the combined influence of biological, reproductive, psychological, and social factors [4]. Recent scientific evidence has highlighted that proportion of depressive disorders among women of reproductive age increased considerably between the years 2019 and 2021 [5].

Compared with men, women are required frequently to balance paid employment, unpaid domestic work, childcare, family responsibilities, and social expectations, which may affect mental health differently among women according to their employment status [6,7]. Moreover, employment may also affect mental health of a woman through both protective and adverse mechanisms; for example, paid work may provide financial security, social interaction, and greater autonomy to a woman, thus improving her psychological well-being [8]. However, employment may also expose a woman to occupational stress, workplace discrimination, job insecurity, long working hours, and work–family conflict, resulting in depressive symptoms [9,10]. Therefore, relationship between employment and depression depends not only on employment status but also on the nature of work, working conditions, working hours, family support, socioeconomic position, and cultural context [11].

Household work among nonworking women is unpaid, repetitive, mostly unappreciated and usually receives limited social recognition despite of its importance in daily operations. Furthermore, financial dependence, reduced autonomy, limited socialization, and continuous domestic responsibilities among nonworking women may contribute to psychological suffering [12]. Literature has reported burnout, loneliness, anxiety, and depressive symptoms among homemakers, emphasizing unpaid domestic work, the family environment and recognition as important determinants of women's mental health [13,14]. Some scientific studies have reported greater depression among homemakers, whereas others have reported greater psychological discomfort among working women, with variations in education, demographic characteristics, and social roles, suggesting that employment alone does not protect against psychological morbidity [6,7,15,16].

Employment opportunities for women and domestic responsibilities in low- and middle-income countries (LMICs) are influenced by the level of education, household income, family structure, marital relationships, and prevailing gender norms and societal values [17]. Similarly, in Pakistan, depression among women is linked to socioeconomic disadvantage, lower educational attainment, marital stress, reduced decision-making authority, domestic violence, and limited access to mental healthcare [18,19]. Studies during the COVID-19 pandemic period have also reported notable levels of depression, anxiety, and stress among the Pakistani population, especially females [20,21]. Despite increasing interest in women's mental health, evidence in Pakistan remains limited, and most available studies have focused on students, pregnant women, healthcare workers, clinical populations, or online surveys [19,20,21,22]. Such population groups are not true representatives of community settings for screening depressive symptoms [23]. Therefore, this study compared depressive symptoms among working women and homemakers in an urban community in Pakistan by assessing the proportion of depressive symptoms, and examining the association between sociodemographic factors and depressive symptoms. These findings may contribute to a better understanding of women's mental health and support evidence-based community mental health planning.

2. Methods

2.1. Study design and setting

This community-based comparative study was conducted in Hirabad, one of the oldest residential localities of Hyderabad, Sindh, Pakistan. Hyderabad is the second-largest

city in the province and comprises a heterogeneous urban population with diverse ethnic, educational, occupational, and socioeconomic backgrounds. Data were collected over a three-month period from November 2024 to January 2025. The study was designed to compare the proportion of depressive symptoms between working women and homemakers residing in the study area.

2.2. Study population

The study population included adult women from different socioeconomic backgrounds and who were eligible for study and included both working women employed outside their homes and homemakers who were engaged primarily in domestic responsibilities. Working women from different occupational categories, including teachers, healthcare professionals, bankers, beauticians, office employees, and other salaried workers from both the public and private sectors, were made part of the study. The homemakers were categorized as women who performed household responsibilities without paid employment outside the home.

2.3. Participant selection

Women aged between 20 and 60 years who had been residing in the study area for more than one year were included. Working women employed in private or public organizations from Basic Pay Scale (BPS) 1 to BPS 18 levels were included in the employed group, whereas women exclusively engaged in household work constituted the homemaker group. However, the study did not include women who refused participation consent for the study or who had cognitive impairments in understanding and responding to the study questions.

2.4. Sample size determination

The sample size was calculated using a two-sample comparison of proportions formula for a comparative study design. The anticipated depression among working women (3.9%) and nonworking women (17.6%). Using these proportions ($p_1 = 0.039$, $p_2 = 0.176$), a two-sided significance level α of 0.05 and 90% power ($Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 1.282$), the standard two-sample proportion formula yields a required sample of 106 participants per group (212 total) to detect the observed difference [24]. Allowing for an anticipated 10% nonresponse (refusal or incomplete participation) and to further increase the strength of the study, the sample was inflated to 175 per group (350 total). This calculation follows the approach used in comparable community studies of depression among working and nonworking women [24].

2.5. Sampling procedure

A stratified random sampling approach was adopted. Initially, the study population was divided into two predefined strata according to employment status: working women and homemakers. Participants were afterwards recruited from different geographical strata within the study area until required sample size was achieved for each study group. Equal representation of both strata was maintained throughout the process of recruitment to allow a direct comparison of depressive symptoms between targeted two groups. To limit biasness in selection of participants, identical inclusion and exclusion criteria was applied to both groups, and recruitment of participants was conducted using a standardized approach across all selected areas. Although potential confounding variables such as age, educational status, and socioeconomic status were not matched at the design

stage, these variables were collected and analyzed as sociodemographic covariates during the statistical analysis.

2.6. Study variables

The primary variable was employment status, categorized as working women or homemakers, and the primary outcome was depressive symptoms among selected groups of women, measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [25]. Sociodemographic variables included age, area of residence, marital status, educational attainment, and socioeconomic status. All sociodemographic variables were analyzed in a bivariate analysis to assess their association with depression. No matching or multivariable adjustment was performed in the study design and analysis.

2.7. Outcome assessment

Depressive symptoms were assessed using the CES-D, a standardized screening instrument developed for epidemiological research [26]. The CES-D consists of 20 items assessing depressive symptoms experienced during the preceding week. Each item on the scale is scored on a four-point Likert scale ranging from 0 to 3, yielding a total score between 0 and 60. Consistent with the original study protocol, a CES-D score greater than 23 was used to identify women with depressive symptoms on the basis of the recommendation by Radloff and Locke [26]. The CES-D has demonstrated good psychometric performance in community populations, with reported internal consistency coefficients ranging from 0.85 in the general population to approximately 0.90 among psychiatric patients [3]. The CES-D is a widely validated instrument and has been used in studies conducted in Pakistani populations. We employed the CES-D as an interviewer-administered tool during face-to-face interviews. Although the CES-D was originally in English, it was translated and explained in Urdu during administration by trained data collectors to ensure participant comprehension, and responses were recorded accordingly. The internal consistency reliability in our study population was assessed using Cronbach's alpha, $\alpha = 0.81$, which indicates acceptable scale reliability in our study sample.

2.8. Data collection

Data were collected using a structured tool for the study which consisted of two sections. First section of the study tool recorded sociodemographic characteristics of the participants, whereas the second section of the study tool included CES-D questionnaire. Prior to data collection, the study tool was pretested among approximately 5% of the target population to gauge its clarity, sequence, and comprehensibility, and feedback received during pilot phase was incorporated before data collection from the targeted populations was commenced, however, participants of pilot phase were not included in final analysis of data.

Participants were approached either at their residences or workplaces after confirming eligibility, and written informed consent was obtained from each participant. Face-to-face interviews were conducted, with each participant, in a private setting to maintain confidentiality. Sociodemographic questions were completed before CES-D tool was administered to facilitate participant engagement. Standard scoring procedures described in the CES-D manual were followed throughout the data collection process.

2.9. Data quality assurance

Several measures were adopted to maintain quality of data for the purpose of the study, and includes pretesting and standardization of tool before field implementation;

data collection by principal investigator using a uniform procedure to minimize interviewer variation; recruitment of participants throughout different periods of the day to maximize participation from both working women and homemakers. Furthermore, completed questionnaires were reviewed immediately after each interview to determine any incomplete responses or inconsistencies before data entry into software.

2.10. Statistical analysis

The data were entered into Microsoft Excel 365 and then exported to IBM SPSS version 25.0 for statistical analysis; descriptive statistics were used to summarize participant characteristics.

Depression was defined as a binary outcome based on the CES-D scale, with a cutoff score of ≥ 23 highlighting depressive symptoms present in respondent and score < 23 highlighting absence of depressive symptoms. Associations between depression and sociodemographic variables were assessed using Pearson's chi-square test. All tests were two-sided, and a p value ≤ 0.05 was considered to indicate statistical significance. Therefore, findings from sociodemographic analyses should be interpreted as unadjusted associations rather than independent effects.

2.11. Ethical considerations

The Research Ethics Committee of Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan granted ethical approval for the study (LUMHS/REC/271), before the initiation of data collection. Participation in the study was entirely voluntary, and written informed consent was obtained from all participants before enrollment. Participants were informed about the objectives of the study, confidentiality of the collected information, and their right to decline participation or withdraw at any stage without consequences. Personal identifiers were removed before analysis to maintain anonymity.

3. Results

3.1. Sociodemographic characteristics

Table 1 presents sociodemographic characteristics of study participants, showing that highest proportion of participants was observed in the younger age category of 20–30 years, with 50.9% among working women and 32.6% among homemakers. Most participants in both groups were from urban areas (78.9% and 82.3%, respectively). More than half of the working women were married (50.9%), while a greater percentage of homemakers were married (78.3%). A relatively greater proportion of working women were single (38.9%) than homemakers (12.0%). The largest proportion of working women were graduates (40.0%), whereas among homemakers, the highest proportion had matriculation-level education (25.7%). Postgraduate education was more common among working women (28.6%) than among homemakers (6.3%). Most participants in both groups belonged to the middle class (46.3% of working women and 58.3% of homemakers), while a smaller proportion belonged to the upper socioeconomic category, particularly among homemakers (2.9%).

Table 1. Sociodemographic characteristics of study participants according to employment status.

Characteristic		Working Women (n=175)	Homemakers (n=175)
		Frequency (%)	Frequency (%)
Age	20–30 years	89 (50.9)	57 (32.6)
	31–40 years	37 (21.1)	54 (30.9)
	41–50 years	37 (21.1)	38 (21.7)
	51–60 years	12 (6.9)	26 (14.9)
Area of residence	Urban	138 (78.9)	144 (82.3)
	Rural	37 (21.1)	31 (17.7)
Marital status	Single	68 (38.9)	21 (12.0)
	Married	89 (50.9)	137 (78.3)
	Divorced	5 (2.9)	1 (0.6)
	Widowed	13 (7.4)	16 (9.1)
Education	Illiterate	13 (7.4)	21 (12.0)
	Primary	7 (4.0)	35 (20.0)
	Matriculation	14 (8.0)	45 (25.7)
	Intermediate	21 (12.0)	30 (17.1)
	Graduate	70 (40.0)	33 (18.9)
	Postgraduate	50 (28.6)	11 (6.3)
Socioeconomic status	Lower	47 (26.9)	68 (38.9)
	Middle	81 (46.3)	102 (58.3)
	Upper	47 (26.9)	5 (2.9)

3.2. Proportion of depressive symptoms

Among 350 participants, 137 (39.1%) met the CES-D criteria for depression, including 62 of 175 working women (35.4%) and 75 of 175 homemakers (42.9%).

3.3. Associations between depression and selected sociodemographic variables

Bivariate analysis showed that depression was observed to be significantly associated with age ($\chi^2 = 8.912$, $df = 3$, $p = 0.030$), marital status ($\chi^2 = 10.552$, $df = 3$, $p = 0.014$), education attainment ($\chi^2 = 15.065$, $df = 5$, $p = 0.010$), and socioeconomic status ($\chi^2 = 10.697$, $df = 2$, $p = 0.005$). No statistically significant association was observed between depression status and employment status ($\chi^2 = 2.027$, $df = 1$, $p = 0.155$) or area of residence ($\chi^2 = 3.122$, $df = 1$, $p = 0.077$).

Table 2. Bivariate association between depression status (CES-D ≥ 23) and selected sociodemographic variables among study participants (N = 350).

Variables		Depression Status (CES-D ≥ 23)		Chi-Square Value	Degree of Freedom (df)	p Value
		Depression n (%)	No Depression n (%)			
Employment status	Working women	62 (35.4)	113 (64.6)	2.027	1	0.155
	Homemakers	75 (42.9)	100 (57.1)			
Participant's age	20–30 years	52 (35.6)	94 (64.4)	8.912	3	0.030
	31–40 years	44 (48.4)	47 (51.6)			
	41–50 years	22 (29.3)	53 (70.7)			
	51–60 years	19 (50.0)	19 (50.0)			
Area of residence	Urban	104 (36.9)	178 (63.1)	3.122	1	0.077
	Rural	33 (48.5)	35 (51.5)			

Variables		Depression Status (CES-D $\geq$ 23)		Chi-Square Value	Degree of Freedom (df)	p Value
		Depression	No Depression			
		n (%)	n (%)			
Marital status	Single	28 (31.5)	61 (68.5)	10.552	3	0.014
	Married	87 (38.5)	139 (61.5)			
	Divorced	4 (66.7)	2 (33.3)			
	Widowed	18 (62.1)	11 (37.9)			
Education	Illiterate	21 (61.8)	13 (38.2)	15.065	5	0.010
	Primary	18 (42.9)	24 (57.1)			
	Matriculation	26 (44.1)	33 (55.9)			
	Intermediate	22 (43.1)	29 (56.9)			
	Graduate	35 (34.0)	68 (66.0)			
	Postgraduate	15 (24.6)	46 (75.4)			
Socioeconomic status	Lower	52 (45.2)	63 (54.8)	10.697	2	0.005
	Middle	75 (41.0)	108 (59.0)			
	Upper	10 (19.2)	42 (80.8)			

Notes: The chi-square test of independence was applied. Depression was defined as a CES-D score $\geq$ 23 (depressed) and $<$ 23 (not depressed). All analyses were bivariate, and no adjustment for confounding was performed.

4. Discussion

This community-based comparative study assessed depression among working women and homemakers residing in an urban community in Pakistan. The findings showed that depression was common in both groups, with a higher proportion among homemakers than among working women. In contrast, depression was significantly associated with age, marital status, educational attainment, occupation, and socioeconomic status. These findings highlight presences of depressive symptoms among homemakers and the employment status alone is not a significant determinant of depression among women.

Lack of significant association among employment status and depression among women is consistent with previous scientific studies which have highlighted complex nature of relationship between work status of women and mental health. A systematic review from Turkey reported varying levels of depressive symptoms among employed and unemployed women, as per level of education, demographic characteristics, and social role rather only than employment status [15]. Similarly, among homemakers, psychological discomfort is related to perceived stress, loneliness, the family environment, and burnout [27]. Depression was more frequently observed among homemakers than among employed women, although not statistically significant. Unpaid domestic work is usually supplemented by financial dependence, limited autonomy, social isolation, and continuous caregiving responsibilities, all adversely affecting mental health of a homemaker [12]. Similarly, a Bangladeshi study reported lower mental health help-seeking behavior and practices among homemakers as compared to employed women [28]. Paid employment should also not be regarded as inherently protective; employment may provide some income, social interaction, and independence, and it may also expose women to occupational stress, long working hours, job insecurity, and work-family balance [8,9,10]. Studies from Saudi Arabia and India have reported substantial levels of depression and anxiety among employed women despite active workforce participation [6,7].

Age, marital status, education, occupation, and socioeconomic status were significantly associated with depression in the current study. Similar findings have been reported from Bangladesh, Pakistan, China, and Nepal, indicating that depression among

women is associated with socioeconomic disadvantage, educational attainment, marital circumstances, and household conditions and living environment [18,29,30,31,32,33]. Education and socioeconomic status may affect mental health through health literacy, financial resources, autonomy, and access to healthcare, whereas occupation may reflect differences in job demands, working conditions and workplace competition [6,34,35].

Our study findings show that depression among women is affected by broader social and economic determinants. The Lancet-World Psychiatric Association Commission highlighted that depression is strongly affected by social hardships and requires interventions beyond clinical care for its complete cure [3]. Similarly, scientific evidence from Pakistan have also highlighted considerable burden of mental health issues among women and contribution of socioeconomic disadvantage as a key factor contributing to poor mental health [18,19,36].

The study has several strengths, including but not limited to the equal representation of working women and homemakers, use of a standardized depression screening instrument, and assessment of multiple sociodemographic variables. However, this comparative study rule out causal inference; study was limited only to a single urban community, and depression was determined by using a screening tool rather than a diagnostic interview. Moreover, wide age range may have introduced variability in depressive symptoms; however, age was included in the analysis as a sociodemographic factor. Future studies should include larger representative samples, multivariable analyses, and direct estimations of work-related stress, domestic workload, social support mechanism, and autonomy among women to develop better understanding of determinants of depression among women.

5. Conclusions

Depression was common among both working women and homemakers, with a higher proportion of depressive symptoms observed among homemakers compared to working women; however, this difference was not statistically significant. Age, level of education, marital status, and socioeconomic status were significantly associated with depressive symptoms, whereas employment status and area of residence were not statistically significant determinants. These findings imply that depressive symptoms among women in this population are more likely to be affected by sociodemographic factors than only by employment status.

Author contributions: The author herself wrote and revised the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement and consent to participate: Ethical approval for this study was obtained from the Research Ethics Committee of the Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan (LUMHS/REC/271). Written informed consent was obtained from all participants prior to data collection.

Consent to publication: Not applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Zara Husaain Khan, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The author declares no conflicts of interest.

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Original Article

Socioeconomic and clinical determinants of the cost of illness in breast cancer: an analytical study

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Citation: Khan UA, Mahmood HZ, Rana MO, Gondal KM, Khaliq IH, Aslam SF. Socioeconomic and clinical determinants of the cost of illness in breast cancer: an analytical study. *J Basic Clin Med Sci*. 2025;4(2):95-105.

Received: 22 June 2025

Revised: 18 November 2025

Accepted: 26 December 2025

Published: 28 December 2025

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.



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Abstract

Breast cancer poses a significant economic burden on affected households, especially in low- and middle-income countries where healthcare services rely mainly on out-of-pocket expenditures. This analytical study determined the associations between the socioeconomic and clinical characteristics of breast cancer patients and different elements of the cost of illness (COI). The study included 200 women with breast cancer receiving healthcare services at two public tertiary care hospitals in Lahore, Pakistan. Demographic, clinical, and household cost data were collected from patients through face-to-face interviews using a pretested questionnaire. COI was categorized into direct medical, direct nonmedical, indirect nonmedical, and overall costs according to the World Health Organization framework. Our study results highlighted that the mean age of the patients was 43.87 ± 9.67 years; most were married (84.5%), were housewives (73.0%), and had stage III breast cancer (54.0%). Direct medical costs differed significantly according to patient education, the education level of the husband, and monthly household income (all, $p < 0.05$). Direct nonmedical costs differed significantly by patient age, location, and marital status, whereas indirect nonmedical costs differed by patient age and prediagnosis occupation (all, $p < 0.05$). The overall COI was significantly associated with patient age, level of education, level of education of the husband, and monthly household income (all, $p = 0.05$). Multivariable analysis showed that the level of education of the husband ($p = 0.022$), location ($p = 0.022$), self-employment ($p = 0.011$), employment status ($p = 0.049$), stage II breast cancer ($p = 0.013$), and family history of breast cancer ($p = 0.047$) were independently associated with the overall cost of disease. The study concluded that the household economic burden of patients with breast cancer varies according to their socioeconomic and clinical characteristics, with multiple factors affecting individual cost elements and the overall cost of disease treatment.

Keywords

Breast neoplasms; Health care costs; Cost of illness; Noncommunicable diseases; Demography; Socioeconomic factors; Developing countries

1. Introduction

Breast cancer is the most frequently diagnosed cancer among all types of cancers in women and is a leading cause of cancer death globally [1]. In 2022, an estimated 2.29 million new breast cancer cases were recorded worldwide. In the recent past, Africa has recorded the highest mortality-to-incidence ratio among all continents, at 0.51, reflecting

limited access to early detection and treatment compared with higher-income regions worldwide. On the basis of the available data, projections highlight that the number of global breast cancer cases could exceed 6 million by the year 2050, with the steepest increase expected in Asia, where the number of cases may increase to approximately 2 million, followed by Africa, where the number of cases may reach 1.1 million, indicating regions with the greatest future burden of disease, a zone that is even least equipped to absorb it [2].

Within the Asian continent, Pakistan has the highest burden of breast cancer in the region [3]. National data from the country show that breast cancer accounted for 34,066 new cases, and in recent years, it has been both the most frequently diagnosed as well as the primary cause of cancer death among Pakistani women [4]. Lifetime risk estimates for Pakistan reveal that one in every nine women in the country will develop breast cancer at some point in her life, and the age-standardized incidence rate in the country, approximately 110 per 100,000 women, is significantly higher than that in neighboring countries of the region. Hospital-based data from Karachi revealed that the number of diagnosed cases nearly doubled between the years 2004–2005 and 2014–2015, with projections showing a further increase in cases in the years 2024–2025 [5]. Studies from two major cities in Pakistan, Lahore and Faisalabad, have reported an increasing incidence of disease, with the majority of women presenting with disease at stage III or later and the majority of patients diagnosed at forty years of age [6]. Pakistan still lacks a nationwide, completely functional cancer registry, which makes it difficult to track the true prevalence of the disease in the country and plan future healthcare delivery services accordingly [7].

The cost of breast cancer to patients and their families extends well beyond the clinical care of disease [8]. The healthcare delivery system of Pakistan is usually based on out-of-pocket payments, with public spending on healthcare remaining low and healthcare insurance coverage being minimal for most households in the country [9]. Another study reported that a patient in Pakistan on average spends 1093.13 USD on the treatment of breast cancer [10]. In low- and middle-income countries (LMICs), cancer patients and their caregivers are estimated to spend as much as 42% of their annual household income on out-of-pocket costs related to the treatment of disease, compared with approximately 16% in high-income countries [11]. These costs usually push households to borrow money, sale assets, or reduce spending on food and education, and in some stances, they also lead to delay or discontinuation in treatment, which worsens survival outcomes and deepens household poverty [12].

Although the clinical burden of breast cancer in Pakistan is well documented, far less is known about how the financial burden on households varies according to patients' demographic and clinical profiles or which specific factors lead a household into a higher-cost category of morbidity. Without this concrete evidence, it is difficult for healthcare service policy makers in the country to determine which patients are most financially vulnerable and to design targeted support, such as subsidized treatment programs, transport assistance, or income-protection schemes, for those who need it most. Therefore, this study examined the differences in demographic and clinical characteristics of breast cancer patients across different household cost categories of breast cancer morbidity. This study also identified factors associated with the overall cost burden of breast cancer morbidity.

2. Methods

2.1. Study design

This analytical study was conducted between August and December 2015.

2.2. Ethical considerations

The study was approved by the Institutional Review Board (IRB) of King Edward Medical University/Mayo Hospital Lahore (No. 348/RC/KEMU).

2.3. Study setting

The study was conducted in the second-most populous city of Pakistan, which has a population of 11,126,285 people [13]. The data were collected from two major public tertiary care hospitals providing complete breast cancer care: Mayo Hospital and Jinnah Hospital. The patients were recruited from the oncology, surgery, chemotherapy, and radiotherapy departments.

2.4. Patient recruitment

One physician and one researcher identified 200 patients who met selection criteria. Before data collection, patients were informed about the study purpose, IRB approval, the benefits and risks of the study as well as provisions to uphold confidentiality. All the patients then provided written informed consent.

Our study included females aged 18 years or older with clinically diagnosed primary malignant breast cancer who had been under treatment for at least 3 months but not more than 2 years and who were able to communicate English, Urdu, Saraiki, or Punjabi [14,15]. Those who were not able to provide informed consent were excluded from the study.

2.5. Sample size and sampling technique

A purposive sampling technique was used to identify 200 breast cancer patients. During the study period, 115 (57.5%) patients were selected from Mayo Hospital, and 85 (42.5%) were selected from Jinnah Hospital.

2.6. Questionnaire development

The multidisciplinary team of authors developed a questionnaire that was further pretested with 10 breast cancer patients receiving cancer care at one of the study sites, i.e., Jinnah Hospital to assess question presentation, ease of understanding, acceptability, as well as facial validity. The study instrument needed few modifications prior to the collection of data.

2.7. Baseline characteristics

Eleven survey questions were used to assess baseline characteristics of the breast cancer patients. They were asked about their age, marital status (unmarried, married, widowed, separated), education level (number of years at school), education level (if married), geographical location (urban, rural), monthly household income, household size, number of children, employment status of the prediagnosis of breast cancer (house lady, employed, self-employed), stage of breast cancer, and family history of breast cancer.

The income was later converted into United States dollars (US\$) using the average exchange rate of 2015, when US\$ 1 was equal to PKR 102.77.

2.8. The overall cost of illness (COI)

The survey also collected information concerning COI borne by the families of breast cancer patients. Three cost categories were calculated by following the framework

suggested by the WHO [16,17,18]. Each of the cost categories had various elements, as defined below:

- Direct medical costs included payments for diagnostic procedures, treatment, follow-up appointments with clinicians, spending on prescriptions, hospital inpatient expenses as well as outpatient expenses etc.
- Direct nonmedical costs were the costs borne by the patients and families during the diagnosis period and throughout treatment. These costs were not directly related to medical care but represent nontreatment-related out-of-pocket expenses, such as travel from home to health facilities and vice versa, as well as lodging and food expenses, etc.
- Indirect nonmedical costs were related to losses in income owing to morbidity in terms of time off work and decreased income of patients and patient attendants. In addition, this cost category included expenses incurred on additional educational services (for example, tuition services) to children, paid home help taken, and any other cost incurred due to breast cancer morbidity.

Finally, the overall COI was derived by summing the totals of the three cost categories in PKR and later converted into US\$.

2.9. Data collection

The principal investigator (PI) is multilingual; he or she conducted face-to-face interviews in a private room and answered any of the participants' questions. On average, the interviews lasted between 30 and 40 minutes in respondent's desired language.

2.10. Data analysis

The data thus collected were entered into Microsoft Excel and analyzed using SPSS 25.0 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics were used as the primary analytical approach. The Shapiro–Wilk test was rendered to assess data normality. Based on this, the Mann-Whitney U test and Kruskal–Wallis H test, along with post hoc analysis, were applied to assess differences between two groups of variables (i.e., marital status, patient location, and family history of breast cancer) across cost categories. These tests were also used to evaluate differences among more than two groups of sociodemographic and clinical attributes (i.e., patient age, patient education, spouse's education, monthly household income, stages of breast cancer, etc.) across cost categories. Post hoc analysis compared all pairwise group differences with adjusted *p* values to control the overall the Type I error rate at 5%.

We also employed a multiple regression model in order to predict the values of an outcome variable (i.e., COI) from different predictor variables (i.e., socioeconomic and medical characteristics).

3. Results

The average age of the breast cancer patients was 43.87 ± 9.67 years, and their average number of years of education at school was 4.64 ± 5.23 (Table 1). Most of the patients were married (84.50%), and on average, their spouses had 7.51 ± 5.08 years of education at school. The median number of people living in a house was 7 (interquartile range [IQR], 5), and the median number of children in each family was 4 (IQR, 2). The median monthly household income was PKR 16,000 (IQR, PKR 19,750). Among the 200 breast cancer patients, the majority had stage III (108) cancer, followed by stage IV (56) and stage II (36) cancer. Moreover, 40 (20%) patients had a family history of breast cancer.

Table 1. Demographic/clinical characteristics of the respondents.

Variable		Frequency (%)	Mean $\pm$ SD	Median (IQR)
Patients' age (years)		-	43.87 $\pm$ 9.67	45.00 (14.00)
Patients' education (years)		-	4.64 $\pm$ 5.23	2.00 (10.00)
Husbands' education (years)		-	7.51 $\pm$ 5.08	8.00 (7.00)
Household size (in number)		-	7.93 $\pm$ 3.74	7.00 (5.00)
Number of children of the patient		-	3.83 $\pm$ 1.85	4.00 (2.00)
Monthly households' income (US\$)		-	23,552.34 $\pm$ 20,548.43	16,000.00 (19,750.00)
Marital status	Unmarried	3 (1.50)	-	-
	Married	169 (84.50)	-	-
	Widowed	25 (12.50)	-	-
	Separated	3 (1.50)	-	-
Patient geographical location	Urban	95 (47.50)	-	-
	Rural	105 (52.50)	-	-
Employment Status (prediagnosis of breast cancer)	Employed	35 (17.50)	-	-
	Self-Employed	19 (9.50)	-	-
	House lady	146 (73.00)	-	-
Stage of breast cancer	Stage II	36 (18.00)	-	-
	Stage III	108 (54.00)	-	-
	Stage IV	56 (28.00)	-	-
Breast cancer family history		40 (20.00)	-	-

Table 2 delineates that direct medical costs varied significantly among breast cancer patients with different levels of education ($p = 0.001$). The median direct medical costs were lower among patients with no formal education (US\$ 717.60) and high school or below (US\$ 813.14) than among those with a college degree or above (US\$ 2,113.42). These differences were statistically significant ($p = 0.001$), as corroborated by post hoc analysis using adjusted p values (not depicted in the table). Similarly, direct medical costs varied significantly among patients whose spouses had different levels of education ($p = 0.001$). Post hoc analysis showed that direct medical costs were significantly lower ($p = 0.001$) among patients whose spouses had no formal education (US\$ 563.21) and who had completed high school or less (US\$ 784.56) than among those whose spouses had completed a college degree or above (US\$ 1,717.11). Furthermore, direct medical costs were significantly lower ($p = 0.001$) among patients whose monthly household income was $\leq$ PKR 15,000 (US\$ 531.69) than among all the other income groups, i.e., 15,001 to 25,000 (US\$ 892.19), 25,000 to 40,000 (US\$ 903.89), and $\geq$ 40,001 (US\$ 1,488.81).

Direct nonmedical costs varied significantly among patients by age ($p = 0.014$). Post hoc analysis accentuated that this difference was statistically significant ($p = 0.020$) between the age groups of 40 to 49 years (US\$ 291.91) and $\geq$ 50 years (US\$ 163.96). Direct nonmedical costs also differed significantly ($p = 0.001$) between breast cancer patients in urban areas (US\$ 108.98) and those in rural areas (US\$ 350.29). Additionally, compared with unmarried, widowed or separated patients (US\$ 155.68), married patients had high direct nonmedical costs (US\$ 256.39), and the results were statistically significant ($p = 0.004$). Table 2 further shows that indirect nonmedical costs were significantly affected by patient age ($p = 0.002$). The results of the post hoc test corroborated the significant differences between the age groups < 40 years and ≥ 50 years ($p = 0.002$). Moreover, the indirect nonmedical costs were strongly affected by the patient's occupation immediately before her breast cancer diagnosis ($p = 0.001$). It was learnt by the post hoc analysis that

the indirect nonmedical costs reported by self-employed and employed patients were significantly greater than those reported by home lady patients ($p = 0.001$).

Finally, Table 2 presents the differences in the overall COI borne by breast cancer patients by varying socioeconomic and medical gradients. The COI was significantly affected by patient age ($p = 0.047$), but the post hoc analysis revealed that none of the values fell below our criterion of $p < 0.05$. Although the comparisons between < 40 years and ≥ 50 years were fairly close ($p = 0.063$), it might be useful to understand the significant differences between the two age groups. COI was also strongly influenced by patient education ($p = 0.001$), patients' spouses' education ($p = 0.001$), and monthly household income ($p = 0.001$). Besides, the post hoc analysis corroborated that patients who belonged to low-income families, i.e., those whose PKR was $\leq 15,000$, had a lower COI that was significantly different only from that of patients who belonged to high-income families, i.e., those whose PKR was $\geq 40,001$ ($p = 0.001$).

Table 2. Differences in the cost of illness of breast cancer morbidity by patient demographic/medical characteristics (N = 200).

Demographic Characteristics	n	DMC in US\$ Median (IQR)	p Value	DNMC in US\$ Median (IQR)	p Value	INMC in US\$ Median (IQR)	p Value	COI in US\$ Median (IQR)	p Value
Patient age (years)									
< 40	65	878.15 (943.07)	0.144	239.37 (310.10)	0.014 *	102.17 (536.14)	0.002 *	1524.30 (1461.30)	0.047 *
40–49	67	857.32 (1380.17)		291.91 (428.13)		100.71 (245.20)		1404.93 (1634.98)	
≥ 50	68	669.75 (1057.77)		163.96 (300.67)		0.00 (153.25)		1055.86 (1633.26)	
Locality of patient									
Rural	105	740.31 (824.14)	0.054	350.29 (337.35)	0.001 *	93.41 (244.23)	0.295	1356.14 (1138.03)	0.632
Urban	95	878.15 (1746.45)		108.98 (270.02)		43.79 (350.29)		1409.19 (2677.63)	
Marital status									
Married	169	802.05 (1209.60)	0.063	256.39 (342.51)	0.004 *	72.98 (238.39)	0.112	1404.93 (1554.81)	0.106
Unmarried/widowed/separated	31	506.58 (671.08)		136.22 (189.74)		210.17 (674.64)		972.65 (1358.91)	
Patient education									
No formal education	100	717.60 (1052.46)	0.001 *	288.02 (431.78)	0.521	87.57 (252.50)	0.865	1388.16 (1697.68)	0.001 *
High School or less	73	813.14 (998.87)		209.20 (302.13)		29.19 (223.80)		1238.36 (1275.78)	
College graduate or greater	27	2113.42 (3558.40)		155.68 (360.02)		58.38 (278.29)		2764.40 (3235.06)	
Patient's husband education									
No formal education	44	563.21 (608.89)	0.001 *	238.88 (435.92)	0.367	87.57 (332.05)	0.361	1139.35 (1056.39)	0.001 *
High School or less	86	784.56 (1020.21)		288.02 (316.23)		71.52 (216.01)		1389.89 (1468.54)	
College graduate or greater	44	1717.11 (2605.72)		177.43 (349.07)		28.22 (226.23)		2157.40 (2995.40)	
Patient occupation before breast cancer diagnosis									
Self-employed	19	798.91 (1259.49)	0.522	241.31 (406.73)	0.372	245.20 (739.50)	0.001 *	1924.21 (2308.92)	0.064
Employed	35	773.12 (1072.72)		196.55 (288.99)		554.63 (843.13)		1795.79 (1345.55)	
House lady	146	776.27 (1065.64)		233.53 (354.91)		17.51 (128.93)		1234.17 (1359.63)	
Monthly household income (PKR)									
≤ 15,000	96	531.69 (747.91)	0.001 *	259.56 (285.10)	0.475	91.22 (291.91)	0.329	1127.62 (1268.47)	0.001 *
15,001 to 25,000	42	892.19 (1161.56)		183.90 (508.46)		35.68 (138.66)		1359.43 (1534.44)	
25,001 to 40 ,000	33	903.89 (1476.26)		108.98 (405.75)		145.95 (491.38)		1544.74 (2029.45)	
≥ 40,001	29	1488.81 (2064.71)		195.58 (337.64)		50.60 (221.85)		2102.50 (2557.33)	
Stages of breast cancer									
Stage II	36	826.95 (1294.18)	0.329	196.07 (267.34)	0.375	9.73 (153.25)	0.191	1234.17 (1493.82)	0.251
Stage III	108	717.60 (979.13)		206.77 (370.97)		77.84 (288.99)		1276.26 (1523.33)	

Demographic Characteristics	n	DMC in US\$	p Value	DNMC in US\$	p Value	INMC in US\$	p Value	COI in US\$	p Value
		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
Stage IV	56	739.34 (1248.91)		262.23 (331.32)		92.44 (430.57)		1763.45 (1684.11)	
Family history of breast cancer									
Positive family history	40	909.42 (1632.40)	0.517	183.90 (309.42)	0.226	61.79 (336.64)	0.968	1333.92 (1544.79)	0.732
No family history	160	761.19 (1044.97)		233.53 (345.18)		82.71 (279.75)		1374.21 (1446.06)	

* Significance level = p value < 0.05. ** DMC = Direct medical costs; DNMC = Direct nonmedical cost; INMC = Indirect nonmedical cost; and COI = Cost of illness. *** In 2015, the average value of the official exchange rate was US\$ 1 = PKR 102.77.

Table 3 shows positive relationships between outcome variable and most of the dependent variables, except for patient age, patient location and monthly household income, whose values were negative. Table 3 also indicates that a one-year increase in education caused an approximately 0.277-fold increase in the total COI. As per the observation and result of the regression analysis, patients' spouse education positively affect the COI. A negative relationship between the locality of the patient and the COI was identified, indicating that patients located in urban areas contributed less to the total COI than those living in rural areas did. The COI was high among breast cancer patients who were self-employed and employed by 0.279 and 0.206, respectively, compared with that of the house lady. More patients with stage II cancer than with stage III cancer were diagnosed with stage II cancer, with an increase in the overall COI of 0.228. The results further showed that patients with a positive family history tend to increase the COI by 0.171.

Table 3. Multiple linear regression for the cost of illness of breast cancer morbidity.

Independent Variables		Standardized Coefficients (B)	p Value
Patient age		-0.111	0.318
Patient education		0.003	0.977
Patient husband's education		0.277	0.022 ****
Locality of patient		-0.250	0.022 ****
Patient occupation (base: house lady)	Patient occupation as self-employed	0.279	0.011 ****
	Patient occupation as employed	0.206	0.049 ****
Monthly household income		-0.002	0.987
Stages of breast cancer (base: Stage III)	Breast cancer stage II	0.276	0.013 ****
	Breast cancer stage IV	0.036	0.735
Family history of breast cancer		0.215	0.047 ****

* Dependent Variable: Patient's overall cost of illness (US\$). ** $F = 3.530$. *** $R^2 = 0.342$. **** Sig = 0.001.

4. Discussion

Our study findings show that the economic burden of breast cancer is not uniformly distributed across patients but varies according to demographic, socioeconomic, and disease-related characteristics. Distinctive patterns were observed across individual components of cost, revealing that direct medical, direct nonmedical, and indirect costs are affected by different patient attributes. Furthermore, multivariable analysis identified several independent determinants of the overall COI, indicating that both sociodemographic factors and patients' clinical profiles contribute to the financial burden experienced by cancer-affected households.

The association of higher direct medical and overall costs of treatment with patient age or husband's education is consistent with reviews of financial toxicity reports concerning the influence of education, household income, employment, insurance, and treatment setting on economic strain, although the direction of the association may vary

across health systems depending on public subsidies, private-sector use, and insurance coverage [19,20,21,22]. The current study reported that patients from higher-income backgrounds have greater direct medical and overall costs, which does not imply lower hardship among poorer households; rather, they may underscore constrained spending, delayed care, incomplete treatment, or reliance on public-sector healthcare services among low-income families. Similar apprehension has been observed in LMICs, where lower expenditure may reflect unmet healthcare needs rather than protection from financial harm [23,24,25].

The higher direct nonmedical cost among rural patients with breast cancer is in line with the scientific literature showing that transport, food, lodging, and attendant costs contribute to a major share of the hidden cost of cancer care [26,27,28]. Patients residing in rural settings often have to make repeated visits to tertiary care hospitals, at times away from household responsibilities, and increase their dependence on attendants, making it difficult for patients to seek healthcare services. In China, India, Iran, and other LMICs, nonmedical and indirect costs contribute significantly to catastrophic expenditures among patients with breast cancer and other types of cancer from different socioeconomic backgrounds [11,26,27,28,29].

The findings of the current study, in which employed and self-employed women had higher indirect costs than housewives did, are supported by the breast cancer survivorship literature, which has correlated financial toxicity with work disruption, job retention problems, reduced income, and treatment-related loss of productivity among working patients [30,31,32,33]. The findings of the current study also highlight that indirect cost is not limited to the patient's own work; attendant time, child education support, paid domestic help, and household reorganization can also transfer disease burden to the family economy, which is relevant in settings where paid and unpaid female labor are both vital to household operations and functioning [34,35]. Furthermore, studies have reported that younger and middle-aged patients may face greater financial burdens because of work, childcare, debt, and family responsibilities [36,37,38]. However, older patients may spend less because of lower treatment intensity, dependency on family decision-making, or lower access to advanced care.

The findings of the study also highlighted stage II disease as a significant predictor of overall cost compared with stage III disease, whereas stage IV disease was not independently significant. The higher adjusted cost among stage II patients may reflect more active curative-intent pathways, surgery, chemotherapy, diagnostics, and follow-up for cancer treatment. On the other hand, the lower observed expenditure in advanced disease can be attributed to patients not being able to afford complete treatment and not seeking healthcare, being present late, or receiving mainly palliative care only. Recent studies on cancer-related out-of-pocket spending have reported that stage and treatment pathway affect cost, but this relationship is not always linear in low-resource settings [39,40].

The current study has several strengths, including but not limited to a detailed assessment of direct medical, direct nonmedical, indirect nonmedical, and overall costs of breast cancer by using a standardized cost-of-illness framework and an evaluation of both socioeconomic and clinical determinants through multivariable analysis in breast cancer patients recruited from two major public tertiary care hospitals. However, certain limitations should be acknowledged, including that the study design may cause inference, purposive sampling from two public hospitals in a single city may limit the generalizability of the findings, and cost estimates were based on patient-reported information, making them susceptible to recall bias.

5. Conclusions

This study concluded that the household cost burden of breast cancer in Pakistan is affected by both socioeconomic and clinical factors. Education, household income, occupation, place of residence, disease stage, and family history contributed to variations in economic burden, highlighting that the financial burden of disease treatment extends beyond treatment expenditures alone. Further multicenter prospective studies are needed to determine the long-term economic outcomes and impact of breast cancer among patients and to promulgate evidence-based policies for equitable cancer care in Pakistan.

Author contributions: Conceptualization, UAK, HZM, KMG, and IHK; methodology, HZM, MOR, and IHK; software, IHK, and SFA; validation, HZM, KMG, and MOR; formal analysis, HZM, and IHK; investigation, KMG, and IHK; resources, HZM, KMG, and IHK; data curation, IHK; writing—original draft preparation, UAK, MOR, IHK, and SFA; writing—review and editing, HZM, and KMG; visualization, IHK, and SFA; supervision, HZM, and KMG; project administration, UAK, and IHK. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from public, commercial, or not-for-profit funding agencies.

Ethics statement and consent to participate: The study was approved by the Institutional Review Board (IRB) of King Edward Medical University/Mayo Hospital Lahore (No. 348/RC/KEMU). All the patients then provided written informed consent.

Consent to publication: Not applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Hafiz Zahid Mahmood, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

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Letter to the Editor

Low use of annual influenza vaccination in Pakistan among patients with heart failure and COPD

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Citation: Khan H. Low use of annual influenza vaccination in Pakistan among patients with heart failure and COPD. J Basic Clin Med Sci. 2025;4(2):106-107.

Received: 05 December 2025

Revised: 26 December 2025

Accepted: 29 December 2025

Published: 31 December 2025

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.



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Extract

Influenza vaccination is usually recommended as a clinical protocol for heart failure (HF) and chronic obstructive pulmonary disease (COPD) patients, primarily because they are at increased risk of infection, prolonged hospitalization, and death. However, despite international guidelines for annual immunization, vaccine coverage in Pakistan is unsatisfactory. International scientific evidence has reported that influenza vaccination is effective at reducing exacerbation, hospital admissions, and mortality among HF and COPD patients. However, in Pakistan, low influenza vaccine coverage is a result of limited vaccine awareness among patients as well as healthcare providers, vaccine hesitancy, patients' financial constraints, and the absence of structured influenza vaccination programs by the government for such groups, all of which contribute to increases in preventable morbidity and mortality and add pressure on the healthcare delivery system of the country. Improving vaccination coverage would require a coordinated and intersectoral approach across the country.

Keywords

Vaccination; Community Healthcare; Heart Failure; Preventive Medicine; Chronic Obstructive Pulmonary Disease; Influenza; Pakistan

Dear Editor,

Influenza vaccination is among the fundamentals of preventive medical care, especially for patients with chronic diseases such as heart failure (HF) and chronic obstructive pulmonary disease (COPD), who are at increased risk of intensive complications of influenza, hospitalization, and death. Despite global directives regarding the importance of annual influenza vaccinations in such vulnerable populations, the rate of influenza vaccine uptake is very low in Pakistan [1].

Scientific studies across the globe have validated the use of influenza vaccination in HF and COPD patients to improve exacerbations, hospitalization, and mortality [2,3]. However, recent scientific studies have shown that the prevalence of influenza vaccination among these high-risk groups is significantly inadequate in low- to middle-income countries such as Pakistan. A lack of awareness among patients as well as healthcare providers, vaccination hesitancy, cost barriers, and a lack of structured vaccination programs are major contributors to inadequate vaccination coverage [4]. This disparity in preventive healthcare services has grave health implications for society, as the burden of already strained healthcare facilities in Pakistan and the failure to prevent seasonal influenza infections among such a high-risk population are associated with the failure to improve health outcomes and to decrease healthcare expenditures [5].

Interventions at multiple levels in the healthcare system are essential and are needed to improve the situation, including but not limited to training healthcare professionals to prescribe influenza vaccination to HF and COPD patients. Misinformation and misconception regarding influenza vaccination may be countered through increasing awareness among people and patients and highlighting the advantages of the use of an influenza vaccine to make it more acceptable for treatment. In addition, the vaccine initiatives funded by the government play an effective role in disease management and infection prevention.

In conclusion, the coverage of influenza vaccination among heart failure and COPD patients is a serious public health issue in Pakistan, and there is an urgent need to increase the awareness, acceptance and coverage of the influenza vaccine to safeguard high-risk population groups and improve public health indicators.

Author contributions: The author herself wrote and revised the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement and consent to participate: Not applicable.

Consent to publication: Not applicable.

Data availability: Not applicable.

Acknowledgments: None.

Conflicts of interest: The author declares no conflicts of interest.

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