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Cost-Effective Monitoring of MDR-TB Treatment: A Comparative Assessment of C-Reactive Protein and Erythrocyte Sedimentation Rate in a High-Burden Setting

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ABSTRACT

Background: Monitoring treatment response in multidrug-resistant tuberculosis (MDR-TB) presents significant challenges, especially in resource-limited settings. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are cost-effective, widely accessible inflammatory markers that may provide complementary information during treatment.

Objective: To compare the effectiveness and potential cost implications of serial CRP and ESR measurements for monitoring treatment response among patients with MDR-TB during the initial three months of therapy.

Methodology: A prospective prognostic cohort study was conducted in Peshawar from January 2024 to June 2025. Patients with confirmed MDR-TB were monitored for three months, with monthly clinical assessments, sputum examinations, and measurements of CRP and ESR. Treatment response was determined by sputum conversion. Changes in biomarkers were analyzed using repeated-measures ANOVA, and factors associated with unfavorable outcomes were evaluated using logistic regression.

Results: Of the 102 enrolled patients, 92 completed follow-up and were included in the final analysis. The mean age was 37.2 ± 13.8 years, with 52.2% male. Sputum conversion occurred in 65 patients (70.6%). Mean CRP levels decreased from 30.8 ± 27.4 mg/dL at baseline to 19.8 ± 18.6, 12.4 ± 12.9, and 9.6 ± 10.2 mg/dL at months 1, 2, and 3, respectively ($P < 0.001$). ESR values declined from 52.6 ± 31.8 to 40.2 ± 28.5, 29.8 ± 24.6, and 24.4 ± 22.1 mm/h ($P < 0.001$). CRP improved in 81.0% of patients, while ESR improved in 79.0%.

Conclusion: Serial measurements of CRP and ESR demonstrated significant declines during MDR-TB treatment and may serve as valuable complementary markers of treatment response. ESR may be especially practical in resource-limited settings; however, formal cost-effectiveness studies are warranted.

Keywords: MDR-TB; C-Reactive Protein; ESR; Peshawar

Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least rifampicin and isoniazid, is linked to prolonged treatment duration, increased complexity, higher risk of treatment failure, and greater mortality compared to drug-susceptible TB.[1] The ongoing burden of MDR-TB is especially pronounced in countries such as Pakistan, where persistent TB transmission and drug resistance pose significant public health challenges. Recent global estimates identify Pakistan as a major contributor to the worldwide TB burden, underscoring the urgent need for effective and practical strategies to improve treatment monitoring and outcomes.[2]

Significant changes in MDR-TB treatment have occurred in recent years, including the adoption of shorter and all-oral regimens. Although these advances have improved the likelihood of successful outcomes, patients still require intensive clinical, microbiological, and laboratory monitoring. Sputum smear microscopy and culture remain essential for assessing microbiological response, particularly sputum conversion. However, factors such as turnaround time, laboratory infrastructure, sample quality, and limited access to culture facilities constrain these methods. As a result, there is increasing recognition of the need for additional, simple, inexpensive, and reproducible markers to inform treatment response.[3]

Inflammatory biomarkers can provide valuable complementary information during anti-TB treatment, as active tuberculosis induces a substantial systemic inflammatory response.[3] C-reactive protein, an acute-phase protein synthesized primarily by the liver in response to inflammatory cytokines, increases significantly during active infection and declines rapidly when inflammation is controlled. This dynamic profile suggests that CRP may serve as a useful marker for monitoring changes in disease activity during treatment. In contrast, ESR is a well-established and inexpensive marker of systemic inflammation. Although ESR is widely available and simple to perform, it is influenced by various physiological and pathological factors and typically changes more slowly than CRP.[4] These differences in biological kinetics may influence the utility of CRP and ESR for monitoring patients undergoing MDR-TB treatment.

Despite its lower specificity and slower response to changes in inflammation, ESR remains appealing in resource-limited settings because of its simplicity, broad availability, and minimal laboratory requirements. Recent research in tuberculosis demonstrates that ESR can change during treatment and may serve as a valuable marker of clinical response. For instance, a study evaluating host biomarkers in spinal TB compared changes in candidate biomarkers with ESR over 12 months, emphasizing ESR's continued role as a conventional reference marker for treatment monitoring.[5]

The economic aspect of laboratory monitoring is a critical consideration in MDR-TB care. Patients frequently require repeated investigations over extended periods, resulting in substantial cumulative costs for individuals, treatment programs, and health-care systems.[6] In resource-limited settings, the most clinically valuable monitoring strategy may not be the most analytically advanced test, but rather the one that provides sufficient information at an acceptable cost. Therefore, comparisons between CRP and ESR should consider not only their capacity to reflect treatment response but also their affordability and feasibility for repeated use.[7] This issue is particularly relevant in high-burden settings such as Pakistan, where MDR-TB services must balance increasing laboratory demands with limited health-care resources.

Studies from Pakistan indicate that early sputum culture conversion is associated with improved subsequent outcomes.[8,9] However, there is limited local research directly evaluating inexpensive inflammatory markers as serial monitoring tools among MDR-TB patients, particularly in high-burden treatment centers such as those in Khyber Pakhtunkhwa. Routinely available inflammatory markers can complement microbiological monitoring during MDR-TB treatment. Comparing CRP and ESR may determine whether the more commonly used, potentially more resource-intensive CRP measurement provides meaningful additional information over the inexpensive ESR test. Such evidence would be particularly valuable for treatment centers that must conduct repeated laboratory testing within constrained budgets.

This study was conducted with the aims to address this gap by prospectively evaluating serial CRP and ESR measurements in patients undergoing MDR-TB treatment at the Programmatic Management of Drug-Resistant Tuberculosis Unit of Lady Reading Hospital and Khyber Medical College, Peshawar. The research examines changes in both biomarkers during treatment and investigates their association with sputum conversion, while also considering the costs of repeated testing.

Objective

To compare the effectiveness and potential cost implications of serial CRP and ESR measurements for monitoring treatment response among patients with MDR-TB during the first three months of therapy.

Methodology

This prospective prognostic cohort study was conducted at the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) Unit of Lady Reading Hospital (LRH) and Khyber Medical College (KMC), Peshawar. Lady Reading Hospital serves as a tertiary care referral center with a specialized PMDT unit that manages drug-resistant

tuberculosis cases from Khyber Pakhtunkhwa province and neighboring regions. This study was conducted from January 2024 to June 2025, with patient recruitment taking place between January and March 2025. Each participant was followed for three months, and the final follow-up was completed by June 2025.

All newly diagnosed and previously treated patients with confirmed multidrug-resistant tuberculosis (MDR-TB) registered at the PMDT-LRH during the study period were included. MDR-TB was defined as resistance to at least both isoniazid and rifampicin. Inclusion criteria comprised patients with confirmed MDR-TB, aged 18 years or older, who provided informed consent. Exclusion criteria were atypical mycobacterial infection, negative sputum smears, pregnancy, and refusal to participate.

The sample size was determined using the single-proportion formula for a prognostic cohort study. The anticipated proportion of unfavorable treatment outcomes (25.7%) was based on a previous retrospective study at the same PMDT Unit, Lady Reading Hospital, which reported a treatment success rate of 74.3% among MDR-TB patients. Applying the formula $n = Z^2 \times P \times (1-P) / d^2$, with a 95% confidence level ($Z = 1.96$) and an absolute precision of 9%, the calculated sample size was 90.8, rounded to 91 participants. To accommodate an expected 10% loss to follow-up, incomplete serial CRP/ESR measurements, treatment interruption, or other attrition during the three-month follow-up, the sample size was adjusted to 101.1. The final target sample size was therefore set at 102 patients with confirmed MDR-TB.[10,11]

For the purposes of the study, a comprehensive medical history was collected from each patient. This included demographic data (age, gender, weight, residence, occupation), smoking status, previous tuberculosis treatment history, duration of illness, prior anti-TB treatment, and comorbidities such as diabetes mellitus, liver disease, or ischemic heart disease. A detailed clinical examination, comprising both general physical and focused chest assessments, was conducted by the attending physician. Baseline chest radiography was performed to document radiological findings, including the presence and extent of lung cavitation (unilateral or bilateral) and lesion distribution (unilateral or bilateral involvement).

Sputum samples were collected from all patients to diagnose and confirm multidrug-resistant tuberculosis (MDR-TB). The GeneXpert MTB/RIF automated molecular platform was utilized to detect Mycobacterium tuberculosis (MTB) and rifampicin resistance (RRD) by targeting mutations in the rpoB gene. This assay was conducted directly on raw sputum samples, providing results within 2 to 3 hours. GeneXpert testing was carried out at the GeneXpert laboratory at PMDT-LRH. Sputum from all RRD cases was subsequently sent to the Provincial Reference Laboratory, Hayatabad Medical Complex, Peshawar, for culture and drug susceptibility testing. Sputum culture was performed on solid Lowenstein-Jensen (LJ) medium, with results available within 4 to 8 weeks. Drug susceptibility testing (DST) was conducted using the standard agar proportion method on enriched Middlebrook 7H10 medium for both first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin) and second-line drugs (ofloxacin, ethionamide, amikacin, capreomycin, and kanamycin).

Blood samples were collected from all enrolled MDR-TB patients and transported to the Hematology Laboratory at Khyber Medical College, Peshawar, following standard laboratory procedures. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured for all patients at monthly intervals during the three-month follow-up period. Quantitative high-sensitivity CRP was assessed using a digital immunochemical assay capable of quantifying CRP in whole blood, serum, and plasma. The instrument included an operational and calculating unit as well as a reader pen for signal detection. CRP levels were reported in milligrams per deciliter (mg/dL).

Erythrocyte sedimentation rate (ESR) was measured using the Westergren tube method, which indirectly assesses the degree of inflammation in the body. This method determines the rate at which erythrocytes sediment in a tall, thin tube of blood over one hour. Results were reported in millimeters per hour (mm/h). To minimize confounding, patients with active inflammatory illnesses other than tuberculosis were excluded at the time of each assessment.

The direct laboratory costs of serial CRP and ESR testing were assessed as part of the cost implications of biomarker-based monitoring. Each patient underwent seven measurements of both CRP and ESR during the first three months of follow-up. The cost of a single CRP test was PKR 1,900, whereas the cost of a single ESR test was PKR 900. Accordingly, the total laboratory monitoring cost per patient was calculated as PKR 13,300 for CRP and PKR 6,300 for ESR. The absolute and percentage differences in laboratory costs were calculated. The analysis was limited to direct laboratory testing costs.

At PMDT LRH, all enrolled multidrug-resistant tuberculosis (MDR-TB) patients commenced a standardized treatment regimen in accordance with National TB Control Programme guidelines. Drug dosages were adjusted based on each patient's body weight and clinical condition. The empiric regimen was maintained until drug susceptibility testing (DST) results became available (median time: 54 days; range: 22–98 days). Following confirmation of resistance patterns through DST, patients requiring changes were transitioned to individualized treatment regimens tailored to their DST profiles.

All enrolled patients were monitored monthly for three months. During each visit, clinical symptoms (cough, expectoration, hemoptysis, fever, night sweats, weight loss) and adverse drug reactions were assessed. Treatment adherence was evaluated using direct observation of therapy (DOT), and patient counseling was

conducted. Sputum samples were collected at each follow-up for smear microscopy to assess sputum conversion status. Serial C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were measured monthly for each patient until sputum conversion or completion of the three-month follow-up.

The primary outcome was sputum conversion, defined as two consecutive negative sputum smears collected at least 30 days apart, or the absence of conversion by the end of the three-month follow-up. Secondary outcomes included the temporal patterns of CRP and ESR levels and their correlation with sputum conversion status.

All collected data were initially entered into the Electronic Nominal Recording and Reporting system, a datasheet specifically designed for data collection in DR-TB patients. Subsequently, the data were transferred to SPSS version 26 for analysis. Continuous variables, including age, CRP levels, ESR levels, and weight, were summarized as mean ± standard deviation (SD). Categorical variables, such as gender, residence, smoking status, comorbidities, radiological findings, drug resistance patterns, and treatment outcomes, were presented as frequencies and percentages.

Serial changes in CRP and ESR levels over the three-month period were compared using repeated measures analysis of variance (ANOVA). Paired t-tests assessed differences in CRP and ESR levels before and after sputum conversion. Differences in proportions between patient subgroups were evaluated using Pearson's chi-square test. The Mann-Whitney U-test was applied for comparisons of continuous variables between groups. Univariate analysis identified factors associated with unfavorable treatment outcomes. Variables with a P-value less than 0.25 in univariate analysis were included in multivariate logistic regression to determine independent predictors of poor outcomes. Multivariate logistic regression was conducted using the backward elimination method with Wald statistical criteria. All tests were two-sided, and a P-value less than 0.05 was considered statistically significant.

Approval for the study was obtained from the Institutional Research Board of Lady Reading Hospital, Peshawar (serial number 0102/24/lrh). Written informed consent was secured from all participants prior to enrollment.

Results

This prognostic cohort study enrolled 102 patients with confirmed MDR-TB at PMDT-LRH and Khyber Medical College in Peshawar between January 2024 and June 2025. All participants were monitored for three months, concluding in June 2025. Ninety-two patients (90.2%) completed follow-up. Ten patients (9.8%) were excluded from the final analysis due to loss to follow-up, incomplete CRP/ESR measurements, or treatment discontinuation. There were 48 (52.2%) were males and 44 (47.8%) females (Figure 1).

The mean age was 37.2 years (SD 13.8; range 15–72). Smokers accounted for 47.8% (44 patients), while 52.2% (48 patients) were non-smokers. Most participants were

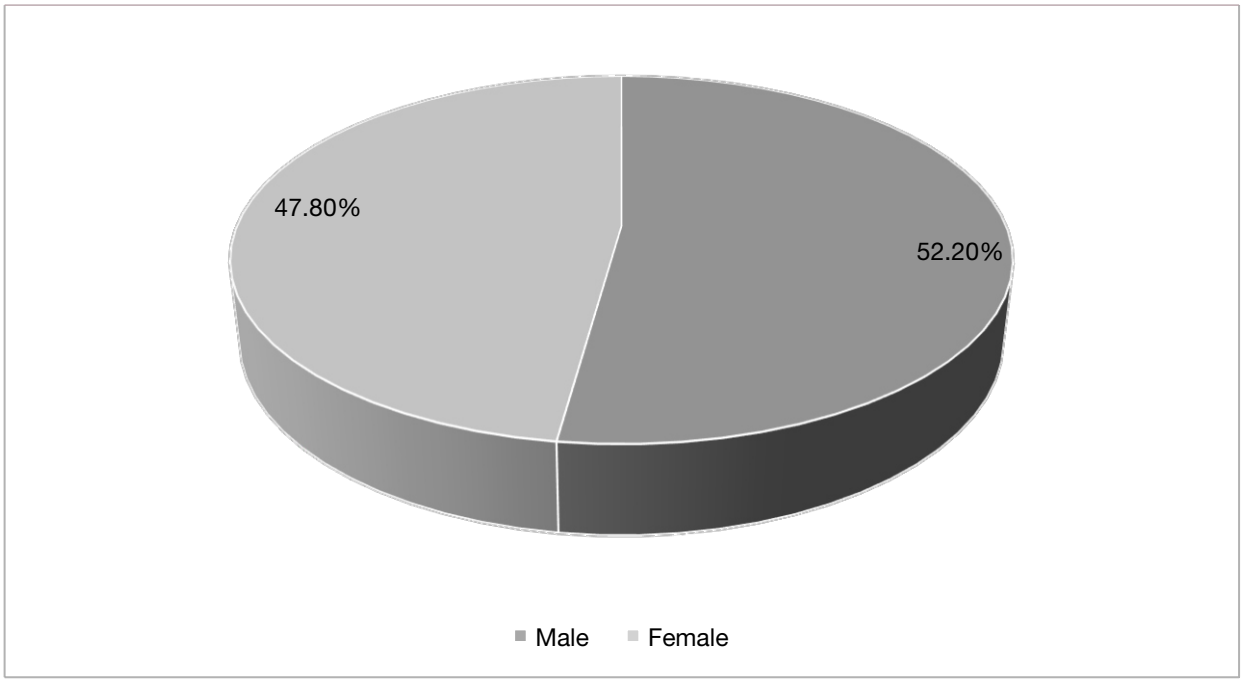

Figure 1. Gender based distribution of study cases

Table 1. Baseline Sociodemographic Characteristics of MDR-TB Patients (N = 92)

Characteristic	Category	n (%)
Age (years)	Mean ± SD	37.2 ± 13.8
	15–44 years	68 (73.9)
	≥45 years	24 (26.1)
Weight (Kg)	Mean ± SD	42 (20-76)
	<40	28 (30.5)
	40-60	59 (64.1)
	>60	5 (5.4)
Smoking Status	Smoker	44 (47.8)
	Non-smoker	48 (52.2)
Occupation	Unemployed	57 (62.0)
	Employed/Shopkeeper/Farmer	35 (38.0)
Residence	Urban	40 (43.5)
	Rural	52 (56.5)
Comorbidities	Present	20 (21.7)
	Diabetes Mellitus	10 (10.9)
	Liver Disease	6 (6.5)
	Ischemic Heart Disease	4 (4.3)

unemployed (62.0%, 57 patients). A majority lived in rural areas (56.5%, 52 patients), with the remainder in urban areas (43.5%, 40 patients) (Table 1).

All patients exhibited cough, expectoration, and constitutional symptoms, including fever, night sweats, and weight loss. Hemoptysis occurred in 40.2% (n = 37) of cases. Radiological assessment indicated that 57.6% (n = 53) had unilateral lesions, whereas 42.4% (n = 39) had bilateral lesions. Baseline lung cavitation was present in 36.9% (n = 34) of patients, with 10.9% (n = 10) demonstrating unilateral cavitation and 26.1% (n = 24) exhibiting bilateral cavitation. A total of 82.6% (n = 76) of patients had a documented history of prior anti-tuberculosis treatment. Of these, 32.6% (n = 30) experienced Category I treatment failure, 39.1% (n = 36) had Category II treatment failure, and 10.9% (n = 10) experienced relapse. Newly diagnosed cases accounted for 17.4% (n = 16) (Table 2).

All strains showed resistance to both isoniazid and rifampicin. Additionally, 70 (76.1%) isolates showed resistance to pyrazinamide, 56 (60.9%) to ethambutol, 39 (42.4%) to streptomycin, and 42 (45.6%) to Fluroquinolone. Resistance to at least one second-line drug was observed in 50 (54.3%) of patients. The most common second-line drug resistance was to ofloxacin, observed in 43 (46.7%) of patients, followed by resistance to ethionamide 5 (5.4%), amikacin (3.3%), capreomycin (2.2%), and kanamycin (2.2%) (Figure 2).

After enrollment all patients started on standardized MDR-TB regimen with dosages adjusted according to body weight in accordance with National TB Control Programme guidelines. Following availability of drug

Table 2. Baseline Clinical and Disease Characteristics of MDR-TB Patients (N = 92)

Characteristic	Category	n (%)
Symptoms	Cough	78 (84.8)
	Expectoration	67 (72.8)
	Hemoptysis	37 (40.2)
Radiological Findings	Unilateral Lesions	53 (57.6)
	Bilateral Lesions	39 (42.4)
Lung Cavitation	No Cavitation	58 (63.1)
	Unilateral Cavitation	10 (10.9)
	Bilateral Cavitation	24 (26.1)
Previous TB Treatment	New Case	16 (17.4)
	Relapse	10 (10.9)
	Category I Failure	30 (32.6)
	Category II Failure	36 (39.1)

susceptibility testing results (median time: 54 days; range: 22–98 days), 61 patients (66.3%) required modification of their regimen, whereas 31 patients (33.7%) continued the initial empiric regimen.

Among the 92 patients who completed the three-month follow-up period, 64 patients (69.6%) achieved sputum conversion (negative sputum smear and culture) during the follow-up period, while remaining 28 (29.4%) had unfavorable outcomes. Among those who converted, 35 (38.0%) converted after the second month of treatment, and an additional 24 (26.6%) patients converted during the third month. Among the 35 patient, 13 (37.1%) interrupted their treatment, 5 (14.3%) died after their 3rd month treatment and remaining 17 (48.6%) still continuous their treatment with positive culture (Figure 3).

At treatment initiation, the mean CRP level was 30.8 ± 27.4 mg/dL, and the mean ESR was 52.6 ± 31.8 mm/h. Both markers were substantially elevated relative to normal reference ranges, indicating active inflammatory disease in patients with multidrug-resistant tuberculosis (MDR-TB). CRP and ESR were measured monthly for each patient until sputum conversion or completion of the six-month follow-up. Both markers exhibited a progressive and statistically significant decline ($P < 0.001$)

Table 3. Serial Changes in CRP and ESR Levels During Treatment

Time Point	CRP (mg/dL) Mean ± SD	ESR (mm/h) Mean ± SD
Baseline	30.8 ± 27.4	52.6 ± 31.8
Month 1	19.8 ± 18.6	40.2 ± 28.5
Month 2	12.4 ± 12.9	29.8 ± 24.6
Month 3	9.6 ± 10.2	24.4 ± 22.1
P-value	< 0.001	< 0.001

Table 4. Comparison of CRP and ESR Before and After Sputum Conversion

Biomarker	Before Conversion (Mean ± SD)	After Conversion (Mean ± SD)	P-value*
CRP (mg/dL)	30.8 ± 27.4	13.2 ± 11.8	< 0.001
ESR (mm/h)	52.6 ± 31.8	31.4 ± 22.6	< 0.001

throughout the treatment period. Error bars indicate standard deviation (Figure 4).

The mean CRP level decreased from 30.8 ± 27.4 mg/dL at baseline to 19.8 ± 18.6 mg/dL at month 1, 12.4 ± 12.9 mg/dL at month 2, and 9.6 ± 10.2 mg/dL at month 3 among patients who continued follow-up. This reduction in CRP levels was statistically significant (P < 0.001, repeated measures ANOVA). Similarly, the mean ESR decreased from 52.6 ± 31.8 mm/h at baseline to 40.2 ± 28.5 mm/h at month 1, 29.8 ± 24.6 mm/h at month 2, and 24.4 ± 22.1 mm/h at month 3. This reduction was also statistically significant (P < 0.001) (Table 4).

To further assess the effectiveness of these biomarkers in monitoring treatment response, CRP and ESR levels were compared at baseline (prior to treatment initiation) and at the time of sputum conversion. Among the 64 patients who achieved sputum conversion, the mean CRP level decreased significantly from 30.8 ± 27.4 mg/dL at baseline to 13.2 ± 11.8 mg/dL at sputum conversion (P < 0.001, paired t-test). Similarly, the mean ESR declined significantly from 52.6 ± 31.8 mm/h at baseline to 31.4 ± 22.6 mm/h at sputum conversion (P < 0.001) (Table 5).

Figure 5 illustrates the comparison of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels before and after sputum conversion. Both biomarkers demonstrated a significant reduction following conversion compared to baseline (P < 0.001).

Among the 92 patients, both CRP and ESR demonstrated improvement (defined as a reduction in biomarker levels). CRP improvement showed in 81 (88.0%), and ESR in 79 (85.9%) cases. No improvement showed in CRP in 11 (12.0%) cases and in ESR, 13 (14.1%) cases showed no improvement (Table 6).

The direct laboratory cost of CRP testing was PKR 1,900 per test compared with PKR 900 per ESR test. As seven measurements of each biomarker were performed per patient, the corresponding monitoring costs were PKR 13,300 per patient for CRP and PKR 6,300 per patient for ESR. Thus, ESR monitoring resulted in a saving of PKR 7,000 per patient, representing a 52.6% lower laboratory cost compared with serial CRP monitoring.

Univariate analysis identified several factors significantly

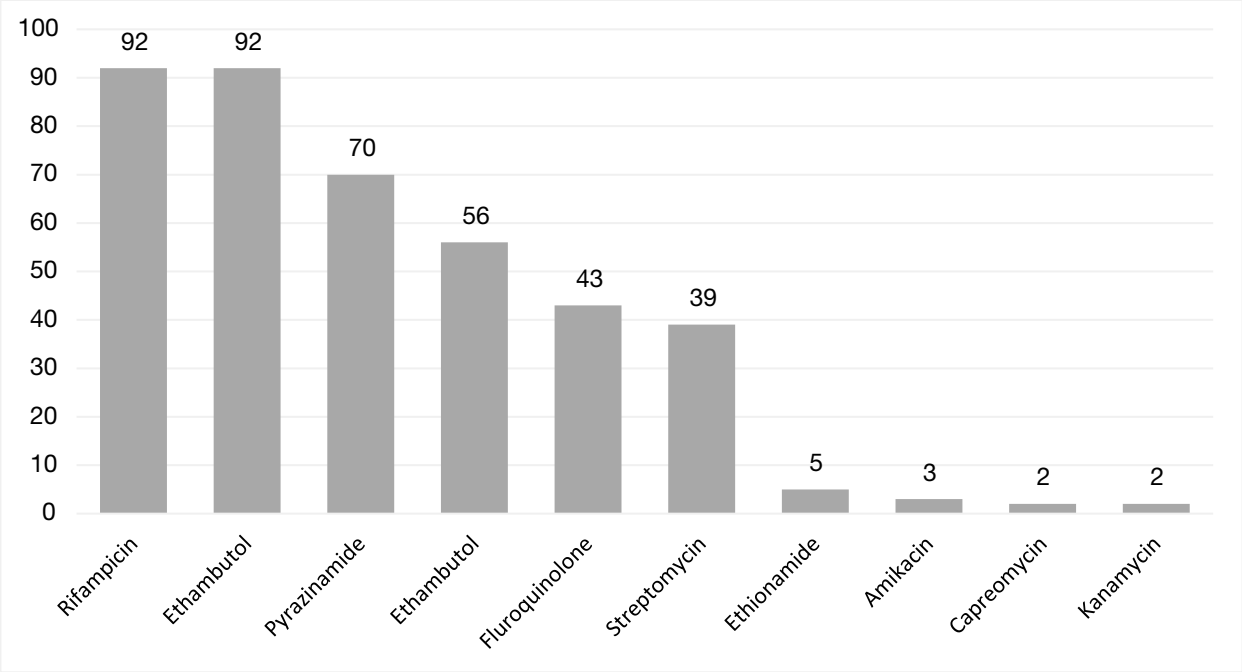

Figure 2. Drug Sensitivity pattern of the study cases

Table 6. Comparative Monitoring Capability of CRP and ESR

Biomarker	Improvement (n)	No Improvement (n)	Percentage Improvement
CRP	81	11	88.0%
ESR	79	13	85.9%

associated with unfavorable treatment outcomes, defined as treatment failure or death. These factors included age of 45 years or older (P = 0.004), rural residence (P = 0.02), baseline lung cavitation (P = 0.001), resistance to second-line drugs (P = 0.002), and resistance to ofloxacin (P = 0.008). In contrast, gender (P = 0.31), smoking status (P = 0.18), and the presence of comorbidities (P = 0.22) were not significantly associated with unfavorable outcomes (Table 7).

Discussion

This prospective cohort study assessed the utility of serial C-reactive protein and erythrocyte sedimentation rate measurements for monitoring treatment response in patients with multidrug-resistant tuberculosis. Both inflammatory markers were markedly elevated at the start of treatment and declined steadily over the course of therapy. Specifically, CRP decreased from 30.8 ± 27.4 mg/dL at baseline to 19.8 ± 18.6 mg/dL at month 1, 12.4 ± 12.9 mg/dL at month 2, and 9.6 ± 10.2 mg/dL at month 3. ESR declined from 52.6 ± 31.8 mm/h at baseline to 40.2 ± 28.5 mm/h at month 1, 29.8 ± 24.6 mm/h at month 2, and 24.4 ± 22.1 mm/h at month 3. Both trends were statistically significant (P < 0.001). These results indicate that routinely available inflammatory markers may serve as valuable complementary indicators of treatment response in MDR-TB.

Among the patients in this study, 64 (69.6%) achieved sputum conversion during follow-up, whereas 28 (30.4%) experienced unfavorable outcomes. This conversion rate highlights persistent challenges in the management of drug-resistant tuberculosis in Pakistan. A multicentre study involving 701 MDR-TB patients in Pakistan reported mean sputum culture conversion times of 2.0 months for the shorter regimen and 2.7 months for the longer regimen, with corresponding treatment success rates of 83.7% and 73.2%.[1] The lower conversion proportion observed in the present study may be attributable to differences in patient selection, disease severity, prior treatment history, and patterns of drug resistance. Notably, a substantial proportion of patients

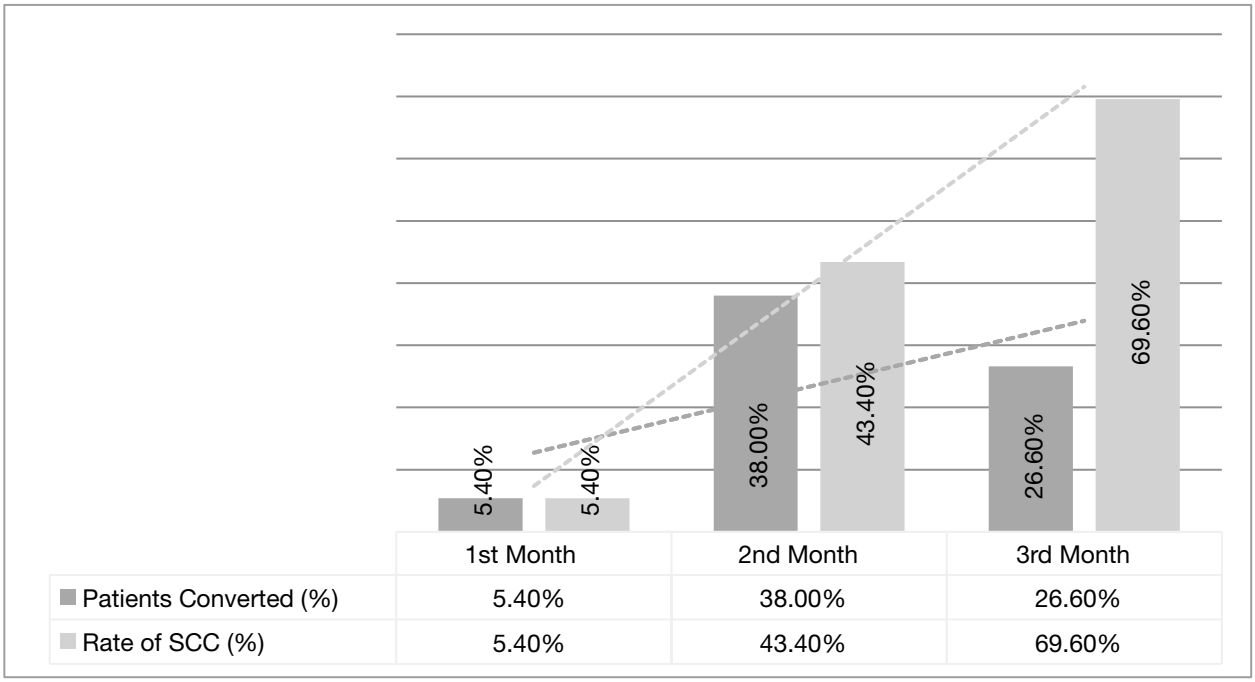

Figure 3. Monthly sputum culture conversion and its rate over time

Table 7. Factors Associated with Unfavorable Treatment Outcomes

Factor	Unfavorable Outcomes (n=28)	Favorable Outcomes (n=64)	Odds Ratio (95% CI)	P-value
Age ≥ 45 years	5 (62.5%)	19 (22.6%)	4.28 (1.52-12.06)	0.004
Rural Residence	6 (75.0%)	46 (54.8%)	4.96 (1.22-20.18)	0.02
Lung Cavitation	7 (87.5%)	27 (32.1%)	8.63 (2.44-30.52)	0.001
SLD Resistance	6 (75.0%)	44 (52.4%)	6.52 (1.88-22.61)	0.002
Fluoroquinolone Resistance	5 (62.5%)	38 (45.2%)	5.29 (1.62-17.28)	0.008

had experienced prior treatment failure, which may have contributed to delayed microbiological response.

Other Pakistani studies have also demonstrated the importance of early sputum conversions in MDR-TB patients. Abubakar et al., in a nationwide study of extensively drug-resistant tuberculosis, found that sputum culture conversion within the first two months of treatment was associated with a reduced risk of mortality.[2] Similarly, the multicentre study by Wahid et al. reported significantly earlier sputum culture conversion among patients treated with shorter MDR-TB regimens.[12] These findings support the use of sputum conversion as a key microbiological reference for interpreting changes in inflammatory biomarkers.

A key finding of this study was the significant elevation of both CRP and ESR before treatment. The mean baseline CRP was 30.8 ± 27.4 mg/dL, and the mean ESR was 52.6 ± 31.8 mm/h. These elevated baseline inflammatory markers are biologically plausible, as Musteikien et al. reported similar findings in patients with active pulmonary TB, identifying significantly elevated CRP levels and showing that baseline CRP correlated with the extent of radiological lung destruction.[13] Their study further showed a significant decrease in CRP after the first month of treatment. Therefore, the elevated baseline CRP observed in this MDR-TB cohort aligns with existing evidence that CRP serves as a marker of inflammatory disease activity.

The magnitude of CRP reduction observed in the patient cohort was particularly notable. CRP levels decreased by about one-third in the first month and continued to decline through the second and third months. This progressive reduction aligns with findings from several prospective studies. Azam et al. demonstrated that blood CRP decreased in parallel with sputum bacillary load during anti-tuberculosis therapy, with a significant correlation between CRP reduction and resolution of bacillary burden.[14] These findings are relevant to the present study, as they suggest that declining CRP may indicate microbiological improvement rather than nonspecific clinical recovery. Similarly, Mvumbi et al. reported a significant reduction in CRP after four weeks of anti-tuberculosis treatment among patients with pulmonary tuberculosis, supporting CRP as a potential early marker of treatment response.[15]

The progressive decline in CRP observed in the present study agrees with findings from Kivrane et al., who evaluated serial serum CRP after initiating anti-tuberculosis therapy. Their results showed that patients generally had reduced CRP during treatment and examined whether early CRP patterns could identify individuals with delayed sputum culture conversion.[5] Although their study did not demonstrate a statistically significant predictive effect of early CRP values on culture conversion, the overall decline in CRP supports its utility as a marker of changing inflammatory status. This distinction shows that a biomarker may reflect treatment-associated inflammation but lacks sufficient specificity to predict the final microbiological outcome independently.

The erythrocyte sedimentation rate decreased from 52.6 mm/h at baseline to 24.4 mm/h by month 3, indicating substantial improvement. Afzal et al. recently reported that a reduction in ESR after three months was significantly associated with clinical improvement in Pakistani tuberculosis patients ($P < 0.001$).16 Both studies, conducted in Pakistan, support the use of ESR as an inexpensive marker for patient follow-up.[16] However, Afzal et al. studied patients with pulmonary tuberculosis (PTB), whereas the present study focused on multidrug-resistant tuberculosis (MDR-TB), a population with greater treatment complexity.

The simultaneous decline of CRP and ESR in this cohort matches findings from a Spanish longitudinal study, where both markers significantly reduced during TB treatment follow-up. Romero-Tamarit et al. also found that baseline clinical severity predicted delayed sputum conversion, emphasizing the need to interpret inflammatory markers alongside clinical and micro-biological data.[17] In our 64-patient cohort, mean CRP dropped from 30.8 to 13.2 mg/dL and ESR from 52.6 to 31.4 mm/h, both statistically significant ($P < 0.001$). These results support using serial inflammatory marker

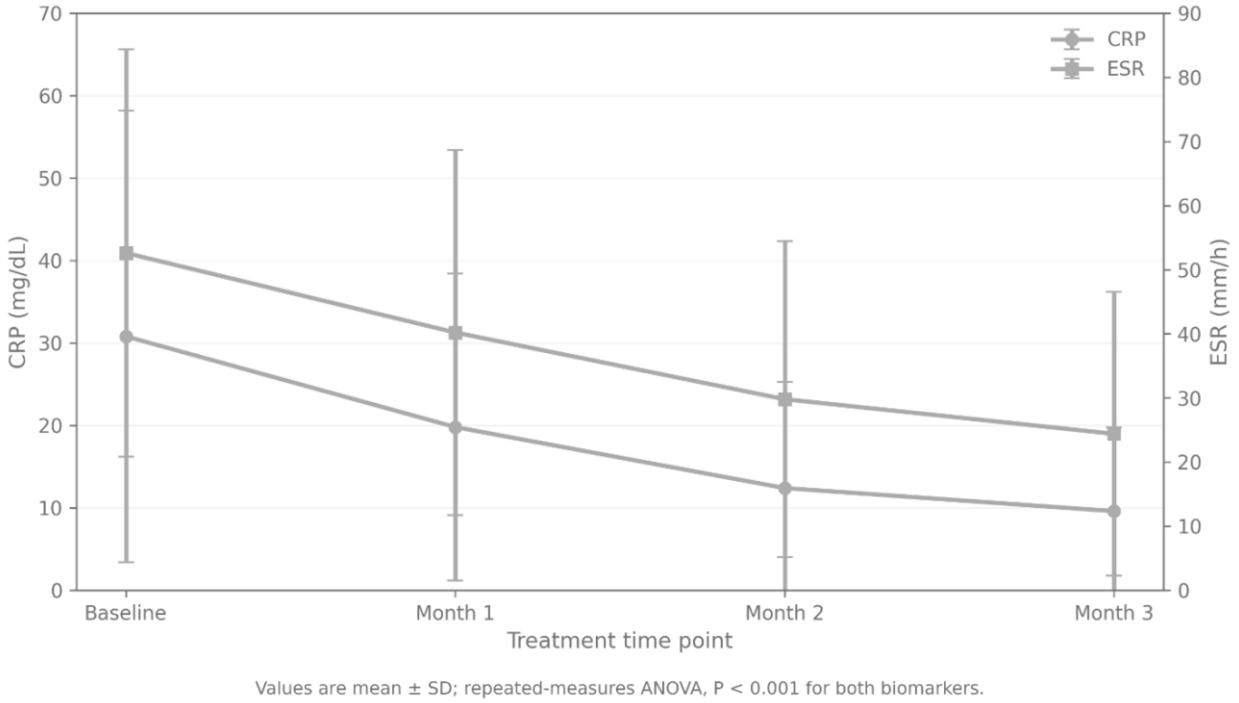

Figure 4. Serial Changes in CRP and ESR Levels During Treatment

measurements to monitor microbiological response. Azam et al. similarly observed that declining CRP tracked reductions in sputum bacillary load, showing CRP and microbiological measures are complementary during treatment.[14]

These findings should not be interpreted as evidence that CRP or ESR can replace sputum microbiological monitoring. The systematic review and meta-analysis by Zimmer et al. highlighted the ongoing need for biomarkers that can complement sputum smear and culture, given the limitations of these reference methods, such as delayed results and challenges in obtaining suitable specimens.[18] Notably, that review reported that CRP consistently declined during the early weeks of treatment, but also identified substantial heterogeneity among studies and the lack of a validated biomarker cutoff for routine treatment monitoring. Consequently, the most appropriate role for CRP and ESR is likely to be as complementary tools rather than substitutes.

Comparing CRP and ESR is clinically significant in this study. CRP improved in 81 of 92 patients (88.0%), and ESR improved in 79 (85.9%). Both biomarkers classified outcomes identically, so neither showed a practical advantage. This matches Khalil et al., who also found significant decreases in both CRP and ESR during MDR-TB treatment and after sputum conversion, concluding both are equally effective for monitoring. The concordance is notable, especially given the larger size of the present cohort.[11] The similar performance of CRP and ESR has important implications for MDR-TB programs in resource-limited settings. CRP provides a rapid, quantitative measure of inflammation, while ESR is inexpensive, accessible, and requires minimal equipment. Since ESR performed as well as CRP, it remains valuable in areas with limited CRP testing. This is especially relevant in Pakistan, where laboratory resources vary widely. Afzal et al. also found ESR linked to clinical improvement and highlighted its cost-effectiveness for integration into patient management.[16]

C-reactive protein may offer an advantage when early detection of changes is clinically important, as it responds more rapidly to changes in inflammatory activity than ESR. Longitudinal studies support this, reporting measurable reductions in CRP soon after treatment initiation.[5,13,15] However, the present study did not demonstrate the superiority of CRP over ESR. Consequently, these findings alone do not support replacing ESR with CRP. Selection between CRP and ESR should instead be guided by laboratory availability, cost, turnaround time, and each patient's specific clinical context.

Several clinical and disease-related factors were identified as being associated with unfavorable outcomes. Age ≥45 years was significantly associated with unfavorable MDR-TB treatment outcomes (OR 4.28), consistent with previous studies from Pakistan that emphasize the need for enhanced monitoring of older patients due to elevated risks and greater treatment challenges.[12,2] The consistency of these findings suggests that older MDR-TB patients may require more intensive

clinical monitoring because of increased disease severity, comorbidities, reduced physiological reserve, and potentially lower treatment tolerance.

Rural residence was also significantly associated with unfavorable outcomes (odds ratio 4.96, 95% CI: 1.22–20.18; P = 0.02). This association is particularly relevant in Peshawar and its surrounding areas, where patients frequently travel long distances to access specialized Programmatic Management of Drug-resistant Tuberculosis services. Although comparative studies have not consistently evaluated rural residence as an independent predictor, multiple studies have emphasized that treatment adherence, access to care, and patient support are critical determinants of treatment success.[9] These findings underscore the importance of adherence and the need for increased attention to patients residing far from treatment centers. The results suggest that laboratory monitoring alone is insufficient to address barriers to treatment access or interruptions in care.

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Gender, smoking status, and comorbidities were not significantly associated with unfavorable outcomes in this study. This finding contrasts with some reports from other MDR-TB cohorts, where demographic and clinical characteristics have demonstrated variable associations with outcomes. These discrepancies may be attributable to differences in sample size, treatment regimens, outcome definitions, disease severity, or underlying population characteristics. The lack of significant associations in this cohort should not be interpreted as evidence that these factors lack clinical relevance. Instead, the relatively small number of unfavorable outcomes may have limited the statistical power to detect moderate associations.

The economic impact of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) monitoring requires

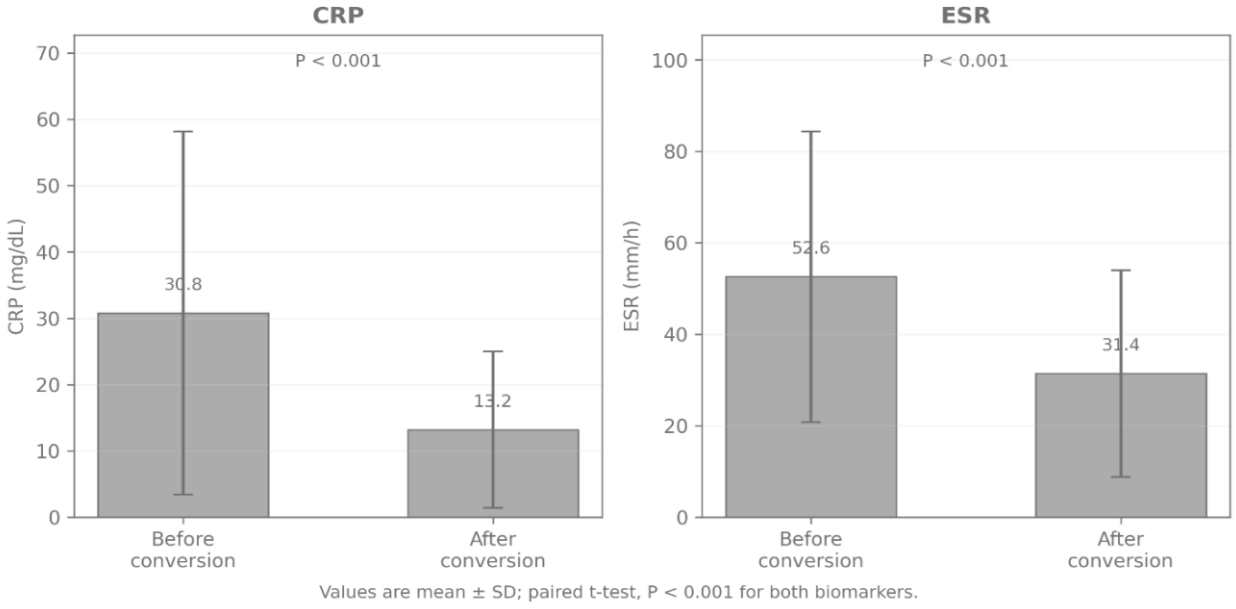

Figure 5. CRP and ESR Before and After Sputum Conversion

further investigation. Although this study compared monitoring approaches and associated costs, the results emphasized clinical outcomes rather than cost data. While ESR appears economically advantageous because of its low cost and widespread availability, its cost-effectiveness relative to CRP remains uncertain. Future research should incorporate test costs, personnel expenses, transportation, turnaround time, and costs associated with delayed recognition of treatment failure to accurately assess cost-effectiveness.

This study's results indicate that serial measurements of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) provide complementary information during multidrug-resistant tuberculosis (MDR-TB) treatment. Both biomarkers demonstrated significant reductions throughout therapy, including at the point of sputum conversion. The comparable rates of improvement suggest that ESR, although less specific, retains value in resource-limited MDR-TB programs. Nevertheless, neither biomarker should replace standard sputum microscopy, culture, or drug-susceptibility testing. Serial inflammatory markers are most effective as supplementary tools to assess whether the inflammatory response aligns with expected treatment progress and to identify patients who may require closer monitoring. The prospective evaluation conducted in high-burden Peshawar contributes locally relevant evidence for resource-sensitive monitoring strategies. The observation that ESR performed similarly to CRP is particularly significant in settings where repeated CRP testing is not feasible. However, larger multicentre studies with standardized thresholds and extended follow-up periods are necessary before these biomarkers can be adopted as surrogate endpoints for MDR-TB treatment response.

Strengths

The strengths of this study include its emphasis on clinically relevant risk factors for unfavorable outcomes in multidrug-resistant tuberculosis in a real-world context, its rigorous statistical analysis, and its direct comparison with previous national research. By identifying key patient characteristics linked to poor outcomes, the study offers practical guidance for improving management and support strategies in comparable populations.

Limitations

This single-center study presents several limitations, including a small sample size, short follow-up period, and potential bias resulting from loss to follow-up or incomplete data. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are nonspecific markers that can be affected by other inflammatory conditions, which complicates interpretation. The selection criteria may have excluded certain patient groups, and external validation was not conducted. The limited number of unfavorable outcomes reduced statistical power. Additionally, biomarker and microbiological changes did not always coincide, which restricts the ability to draw definitive conclusions regarding predictive value.

Conclusion

This prospective cohort study shows that both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) declined significantly and progressively during treatment for multidrug-resistant tuberculosis (MDR-TB), with marked reductions observed at the time of sputum conversion. CRP improved in 81.0% of patients, while ESR improved in 79.0%, indicating that both markers have comparable utility for monitoring treatment response. These results suggest that serial measurements of CRP and ESR can serve as practical, straightforward, and complementary indicators of changes in inflammatory activity during MDR-TB therapy, particularly in resource-limited settings. Nevertheless, neither biomarker should replace microbiological monitoring, such as sputum examination and culture. Factors including older age, rural residence, baseline lung cavitation, second-line drug resistance, and fluoroquinolone resistance were associated with unfavorable outcomes. These factors may help identify patients who require closer follow-up. ESR may provide a practical and cost-effective monitoring option where access to CRP testing is limited. Further large-scale, multicentre studies with formal cost-effectiveness analyses are necessary to determine the most appropriate biomarker-based monitoring strategy for MDR-TB.

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