Associations of Acute Phase Reactants with Disease Activity and Radiological Involvement in Pulmonary Tuberculosis

Akciğer Tüberkülozunda Akut Faz Reaktanlarının Hastalık Yaygınlığı ile İlişkisi

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ABSTRACT

Background: Smear microscopy is widely used in diagnosing tuberculosis (TB), but its sensitivity may be limited in cases with low bacillary load or extrapulmonary involvement. This has led to growing interest in laboratory biomarkers that reflect disease activity. The immune response to *Mycobacterium tuberculosis* stimulates the release of inflammatory cytokines, triggering an acute-phase reaction. This study aimed to evaluate the associations of acute-phase reactants-including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and mean platelet volume (MPV)-with bacillary load, radiological involvement, and hospital stay in pulmonary TB patients.

Materials and Methods: This retrospective study included 137 patients diagnosed with pulmonary TB. They were grouped as smear-positive or smear-negative, and culture-positive. Data on demographics, laboratory results (CRP, ESR, MPV), chest radiography, bacillary load, culture results, and length of hospital stay were analyzed. Radiological involvement was categorized as minimal, moderate, or extensive

Results: The cohort was 69% male with a median age of 42 years. Smear positivity was found in 71% and culture positivity in 74% of cases. Radiological assessments showed minimal (47%), moderate (41%), and extensive (12%) involvement. CRP levels were significantly higher in smear-positive patients (p<0.001) and increased with more extensive radiological involvement (p=0.02). These patients also had longer hospital stays (p=0.001). No significant associations were found between MPV or ESR and bacillary load or radiological extent (p>0.05).

Conclusion: CRP is a sensitive marker of inflammatory activity in pulmonary TB, correlating with both bacillary burden and radiological spread. It may be useful for evaluating disease severity and treatment response. MPV and ESR, however, appear to have limited clinical relevance in this context.

Keywords: C-reactive protein, erythrocyte sedimentation rate, pulmonary tuberculosis, mean platelet volume, inflammation

ÖZ

Amaç: Tüberküloz (TB) tanısında kullanılan yayma mikroskopisi, basil yoğunluğunun düşük olduğu veya ekstrapulmoner tutulumun bulunduğu olgularda yetersiz kalabilmektedir. Bu nedenle hastalık aktivitesini değerlendirmeye yönelik laboratuvar belirteçlerine olan ilgi artmıştır. Bu çalışmada, akciğer TB'li hastalarda akut faz reaktanlarından C-reaktif protein (CRP), eritrosit sedimantasyon hızı (ESH) ve ortalama trombosit hacmi (MPV) düzeylerinin; basil yoğunluğu, radyolojik tutulum ve hastanede yatış süresi ile olan ilişkileri araştırılmıştır.

Gereç ve Yöntemler: Retrospektif olarak tasarlanan bu çalışmaya, akciğer TB'si tanısı almış 137 hasta dahil edilmiştir. Olgular yayma pozitif (ARB pozitif) ve yayma negatif-kültür pozitif olmak üzere iki gruba ayrılmıştır. CRP, ESH, MPV düzeyleri, radyolojik tutulum (minimal, orta, ileri), basil yoğunluğu ve hastanede yatış süreleri değerlendirilmiştir.

ÖZ

Bulgular: Katılımcıların %69'u erkek, yaş ortancası 42 (25-56) yıldır. Yayma pozitiflik oranı %71, kültür pozitiflik oranı %74 olarak bulunmuştur. Radyolojik olarak %47 minimal, %41 orta, %12 ileri düzey tutulum mevcuttur. Yayma pozitif hastalarda CRP düzeyleri anlamlı şekilde daha yüksektir (p<0,001) ve bu hastalarda hastanede yatış süresi de daha uzundur (p=0,001). Radyolojik tutulum arttıkça CRP düzeylerinde de anlamlı artış saptanmıştır (p=0,02). MPV ve ESH düzeyleri ile basil yoğunluğu veya radyolojik tutulum arasında anlamlı ilişki gözlenmemiştir.

Sonuç: CRP düzeyi, TB hastalarında hastalık yaygınlığını ve enflamatuvar aktiviteyi yansıtan duyarlı bir biyobelirteç olarak öne çıkmaktadır. Buna karşılık MPV ve ESH'nin sınırlı prediktif değeri olduğu görülmüştür.

Anahtar Kelimeler: C-reaktif protein, eritrosit sedimantasyon hızı, akciğer tüberkülozu, ortalama trombosit hacmi, enflamasyon

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a significant global public health concern, particularly in developing countries. Early diagnosis and effective monitoring are crucial for controlling the disease and improving patient outcomes. Acute phase reactants (APRs) such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and mean platelet volume (MPV), a hematological parameter, have been investigated as potential biomarkers for the diagnosis and prognosis of TB (1-3).

CRP is an acute phase protein whose levels increase in response to various inflammatory conditions. Previous studies have demonstrated significantly elevated CRP levels in patients with active pulmonary TB compared to healthy individuals. Furthermore, CRP levels have been shown to correlate with disease severity and radiological involvement, suggesting that CRP may serve as a valuable marker for evaluating TB activity and monitoring treatment response (1,4). Similarly, elevated ESR levels have been observed in patients with active pulmonary TB, with significant correlation to radiological extent. Therefore, ESR may also be considered an indicator of disease severity and a useful parameter for assessing treatment efficacy (1).

MPV reflects the average size of platelets and is considered a marker of platelet activation and production rate. Although inflammatory states may influence MPV levels, findings on its association with TB are inconsistent. Some studies have reported decreased MPV levels in active TB, suggesting a reduction during systemic inflammation, while others have found no significant difference between TB patients and healthy controls (5). These discrepancies may be attributed to differences in study populations, disease severity, and methodological variations.

Evaluating APRs such as CRP, ESR, and MPV in TB patients has important clinical implications. Increases in CRP and ESR may support early detection of active TB, especially in cases with non-specific or absent clinical symptoms. Moreover, monitoring these biomarkers during treatment can provide insight into disease progression and therapeutic response. A decrease in CRP and ESR levels may indicate effective treatment and disease regression, whereas persistently elevated levels may suggest treatment failure or the presence of complications (5,6).

In this study, we aimed to investigate the relationship between the APRs CRP, ESR, and MPV and radiological involvement, bacillary load, and length of hospital stay in patients with pulmonary TB.

Materials and Methods

This retrospective cohort study included 137 patients diagnosed with pulmonary TB who received inpatient treatment in the TB ward. Patients were classified into two groups: smear-positive (Group 1) and smear-negative but culture-positive (Group 2). Patients with chronic obstructive pulmonary disease, asthma, bronchiectasis, human immunodeficiency virus (HIV) infection, or other inflammatory conditions (e.g., connective tissue diseases, inflammatory bowel diseases, acute or chronic infections, endocrinological, hematological, hepatic, or renal disorders, peripheral vascular disease, hypertension, or diabetes mellitus) were excluded, as these conditions could potentially influence MPV. In addition, patients who had returned from treatment failure; had interrupted and later resumed treatment, were referred from other centers; had chronic forms of the disease; had received anti-TB treatment for more than one week; or had missing data for complete blood count, CRP, ESR, sputum and culture results, or chest radiography, were also excluded from the study.

Data were obtained by reviewing electronic medical records and patient files. Patients were included if they were either smear-positive for acid-fast bacilli (AFB) or smear-negative but culture-positive, and had received anti-TB treatment. Demographic data (age and sex), laboratory parameters (complete blood count, ESR), chest X-ray findings, bacteriological test results, and duration of hospitalization were recorded. All laboratory parameters, including complete blood count, CRP, ESR, and MPV, were measured at baseline, prior to the initiation of anti-TB

therapy, to ensure that the recorded values reflected the patients' pretreatment status without the influence of anti-TB medications. Smear-positive patients were compared with those diagnosed based on culture positivity, despite a negative smear.

Chest Radiograph Assessment

Chest X-rays were classified as minimal, moderate, or advanced involvement based on radiological scoring (7).

• Minimal lesions included non-cavitated, mildly to moderately dense lesions, limited to one lung or both lungs but not exceeding one lung volume, and not extending beyond the second chondrosternal junction and the level of the fourth or fifth thoracic vertebra.

• Moderate lesions could be unilateral or bilateral, involving an entire lung with mild-to-moderate density or bilateral involvement of similar volume. If cavitation had been present, its diameter did not exceed 4 cm.

• Advanced lesions indicated more extensive and confluent involvement beyond the criteria for moderate lesions.

Additionally, radiological findings such as infiltration, consolidation, cavitation, nodules, lymphadenopathy, and pleural effusion were recorded.

Bacteriological Examination

Sputum samples were examined using the Ziehl-Neelsen staining method for direct smear microscopy and reported as AFB positive or negative. Smear results were semi-quantitatively graded based on bacillary count:

• Negative: No bacilli in 300 fields
• +: 1-9 bacilli in 100 fields
• ++: 1-9 bacilli in 10 fields
• +++: 1-9 bacilli in 1 field
• ++++: ≥10 bacilli in 1 field (8)

Sputum samples were also cultured and reported as either positive or negative.

CRP levels were measured nephelometrically using CardioPhase hsCRP (Siemens Healthcare Diagnostics Inc., Newark, DE, USA) on a Siemens BN II analyzer. The reference range was 0-5 mg/L, and the threshold for bacterial infections was 40 mg/L. Complete blood counts were analyzed using a Beckman Coulter analyzer (Tokyo, Japan), and ESR was measured using the Alifax analyzer (Italy).

The study was approved by the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Scientific Research Ethics Committee (approval number: 2024/397, dated: 26.12.2024), in accordance with the principles of the Declaration of Helsinki. As this was a retrospective study, informed consent was not obtained; however, patient confidentiality was strictly maintained.

Statistical Analysis

Statistical analyses were performed using SPSS version 24. The distribution of variables was assessed using analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Non-normally distributed variables were expressed as medians and interquartile ranges (IQRs). Since the duration of hospitalization and biochemical parameters did not follow a normal distribution, they were compared between groups using the Kruskal-Wallis test, and pairwise comparisons were conducted with the Mann-Whitney U test, applying Bonferroni correction. Spearman correlation coefficients were used to assess relationships between pairs of variables where at least one variable was non-normally distributed or ordinal. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 137 patients diagnosed with TB were included in the study. Among them, 69% were male, and the median age was 42 years. The proportion of patients with a history of smoking was 54%. The median length of hospital stay was 23 days (IQR: 8-30).

AFB smear positivity was observed in 71% of patients, and culture positivity was observed in 74%. Based on chest radiograph scoring, 47% of the patients had minimal, 41% moderate, and 12% advanced pulmonary involvement. The most common radiographic findings were infiltration (44%), cavitation (24%), and pleural effusion (21%). Demographic and clinical characteristics of the study population are summarized in Table 1.

Age, sex distribution, and smoking status were similar between smear-positive and culture-positive groups (p>0.05 for all comparisons; p=0.81 for smoking). The median length of hospital stay was significantly longer in the smear-positive group (21 days, IQR: 12-33) compared to the culture-positive group (10 days, IQR: 5-19) (p=0.001).

Leukocyte count, platelet count, MPV, and ESR levels were also similar between the two groups (p=0.25, p=0.91, p=0.34, and p=0.06, respectively). In contrast, CRP levels were significantly higher in smear-positive patients [median: 50 mg/L (IQR: 24-89)] than in culture-positive patients [median: 16 mg/L (IQR: 5-52)] (p<0.001) (Table 2).

Acute Phase Reactants According to Radiological Involvement

CRP levels were significantly higher in patients with moderate and advanced radiological involvement

Table 1. Demographic and clinical characteristics of the cases (n=137)

Case group, n (%) AFB positive Culture positive	97 (71) 40 (29)
Sex, male, n (%)	94 (69)
Age, years, median (25-75)	42 (25-56)
Smoking status, n (%) Non-smoker Smoker	63 (46) 74 (54)
Length of stay, days, median (25-75)	23 (8-30)
Chest X-ray score, n (%) Minimal Moderate Advanced	64 (47) 56 (41) 17 (12)
Chest X-ray lesion, n (%) Infiltration Consolidation Cavity Nodule Lymphadenopathy Pleural effusion	60 (44) 6 (4) 33 (24) 5 (4) 4 (3) 29 (21)
AFB, n (%) Negative + ++ +++ ++++	73 (53) 38 (28) 12 (9) 8 (6) 6 (4)
Culture, n (%) Negative Positive	36 (26) 101 (74)
Resistance, n (%) None H E S H + S H + R + S H + Z + S	126 (92) 3 (2.2) 1 (0.7) 2 (1.5) 2 (1.5) 2 (1.5) 1 (0.7)

AFB: Acid-fast bacilli, H: Isoniazid, E: Ethambutol, S: Streptomycin, R: Rifampicin, Z: Pyrazinamide

Table 2. Comparison of clinical and laboratory parameters in accordance to AFB and culture positivity

	AFB positive, n=97	Culture positive, n=40	p-value
Sex, male, n (%)	**67 (71)**	**27 (29)**	**0.85**
Age, years, median (25-75)	40 (24-61)	36 (26-54)	0.82
Smoking status, n (%) Non-smoker Smoker	44 (70) 53 (72)	19 (30) 21 (28)	0.81
Length of stay, age, median (25-75)	21 (12-33)	10 (5-19)	**0.001**
Chest X-ray score, n (%) Minimal Moderate Advanced	44 (69) 40 (71) 13 (76)	20 (31) 16 (29) 4 (24)	0.81
Chest X-ray lesion, n (%) Infiltration Consolidation Cavity Nodule Lymphadenopathy Pleural effusion	38 (63) 5 (83) 27 (82) 2 (40) 2 (50) 23 (79)	22 (37) 1 (17) 6 (18) 3 (60) 2 (50) 6 (21)	0.14
Leukocyte, median (25-75)	8.420 (7.000-11.000)	7.680 (6.500-9.900)	0.25
Platelet, median (25-75)	306 (240-384)	287 (240-385)	0.91
MPV, mean ± SD	8.1±0.9	8.2±0.9	0.34
ESR, median (25-75)	80 (50-105)	50 (30-110)	0.06
CRP, median (25-75)	50 (24-89)	16 (5-52)	**<0.001**

AFB: Acid-fast bacilli, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, SD: Standard deviation

compared to those with minimal findings (p=0.02 for both comparisons). MPV and ESR levels were similar across all radiological groups (p>0.05) (Table 3).

Discussion

TB is a disease that requires both clinical and laboratory-supported evaluations throughout the diagnostic and therapeutic process. In recent years, the role of APRs in assessing the presence and extent of active disease has been increasingly explored. In our study, higher CRP levels were observed in patients with positive smears and greater radiological involvement, reflecting increased inflammatory activity. Likewise, CRP levels showed a stepwise increase

in accordance with the progression of radiological severity from minimal to advanced disease.

The observed parallel between increased radiological extent and elevated CRP levels supports the potential role of CRP as an indirect marker of disease activity. Kagujje et al. (4) similarly reported that CRP demonstrated high sensitivity in TB diagnosis and had 100% negative predictive value for ruling out active TB among HIV-positive individuals with CD4 counts ≥350.

Regarding MPV levels, no significant differences were observed across groups in terms of radiological extent or bacillary burden. This is consistent with previous reports suggesting that MPV has limited value as a negative APR in TB. For example, Gunluoglu et al. (6) concluded that MPV is not a reliable marker of inflammation in active pulmonary TB and does not reflect disease severity. Similarly, Yildiz et al. (9) emphasized the limited utility of MPV as a marker of inflammatory activity in *Mycobacterium tuberculosis*

Table 3. Relationship between chest X-ray severity and CRP, MPV, ESR						
	Minimal, n=64	Moderate, n=56	Advanced, n=17	Minimal-moderate, p	Minimal-advanced, p	Moderate-advanced, p
CRP, mg/L, median (25-75)	14 (7-52)	48 (22-79)	54 (35-82)	0.02	0.02	0.43
MPV, fl, median (25-75)	7.95 (7.6-8.7)	7.8 (7.6-7.9)	7.9 (7.6-7.9)	0.32	0.38	0.50
ESR, mm/s, median (25-75)	80 (30-120)	75 (50-110)	90 (40-125)	0.88	0.90	0.90
Comparisons were performed using the Kruskal-Wallis test and Bonferroni-adjusted Mann-Whitney U tests for pairwise comparisons. CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MPV: Mean platelet volume						

infection. These findings collectively suggest that MPV may not be suitable as a standalone marker for diagnosis or assessment of disease activity in chronic infections such as TB. Gunluoglu et al. (6) reported that although MPV levels were lower in TB patients than in healthy controls, the difference was limited, and MPV did not correlate with disease extent. Additionally, no significant correlations were observed between MPV and inflammatory markers such as CRP or ESR in their study. These findings are in line with our results, indicating that MPV does not serve as a determinant of TB activity.

Although ESR levels were higher in smear-positive patients (80 mm/h vs. 50 mm/h), the difference did not reach statistical significance (p=0.06). This may be attributed to the non-specific nature of ESR and its susceptibility to various confounding factors. Nevertheless, the trend toward increased ESR in patients with advanced lesions suggests that it may still have clinical relevance during follow-up.

No significant relationship was found between hospitalization duration and APRs. This supports the notion that length of hospital stay is influenced not only by clinical severity but also by various factors such as socioeconomic status, access to healthcare, and comorbidities. In addition, our analysis focused on hospitalization length rather than the total duration of anti-TB therapy. The study was not designed to assess treatment completion time beyond discharge. Further studies specifically addressing this issue are warranted to clarify whether elevated baseline CRP levels are associated with prolonged treatment courses in pulmonary TB.

A significant increase in CRP levels was observed with increasing radiological involvement. While CRP levels were notably lower in patients with minimal disease, they were significantly higher in those with moderate or advanced disease. This finding further supports the role of CRP as a surrogate indicator of inflammatory activity and, by extension, disease burden. Radiological involvement in our study was classified according to the system proposed by Falk et al. (7), which divides pulmonary TB into minimal, moderate, and advanced disease. This classification has long been used in clinical practice and research, providing consistency and comparability with earlier studies. However, more contemporary scoring systems have been proposed in recent years, which allow a more quantitative and detailed assessment of pulmonary involvement (7,8). While we used the Falk classification to maintain methodological consistency, future studies may benefit from incorporating these newer approaches to further refine radiological evaluation in TB.

In contrast, MPV and ESR levels did not differ significantly across radiological subgroups. This aligns with previous findings highlighting the limited ability of MPV to reflect inflammatory status in TB (10,11). The lack of association between ESR and radiological extent may be explained by its non-specific nature and its susceptibility to systemic and chronic influences. Although several studies have reported elevated ESR values in TB patients; one study found high ESR levels in 98% of TB cases (12)-its non-specific profile limits its utility as a sole indicator of disease extent.

Overall, our findings suggest that among the evaluated APRs, CRP stands out as the most informative and reliable biomarker in pulmonary TB. Its association with both bacillary burden and radiological extent highlights its potential role not only in reflecting inflammatory activity but also in evaluating disease progression and treatment response. In contrast, MPV and ESR appeared to have limited value in this setting, showing no clear relationship with disease severity or extent. Therefore, CRP may be considered a useful tool for monitoring inflammatory status and guiding clinical follow-up in patients with pulmonary TB.

Conclusion

In conclusion, CRP was the only APR that consistently reflected disease severity in pulmonary TB, showing clear associations with both bacillary burden and radiological extent. MPV and ESR did not demonstrate meaningful

clinical value. Overall, CRP appears to be the most useful biomarker for assessing inflammation and supporting clinical follow-up in pulmonary TB.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Scientific Research Ethics Committee (approval number: 2024/397, dated: 26.12.2024), in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.U.B., M.Y., E.A., Design: E.U.B., M.Y., E.T., E.A., Data Collection or Processing: E.U.B., P.S., S.G., Analysis or Interpretation: E.U.B., M.Y., Literature Search: E.U.B., P.S., A.Y., S.G., Writing: E.U.B., M.Y., E.T., S.G., E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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