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Role of the Monocyte-to-Lymphocyte Ratio as a Biomarker for Pulmonary Tuberculosis

Akciğer Tüberkülozunda Biyomarker Olarak Monosit-Lenfosit Oranının Rolü

Swadha Kovilvenni Narayanan, Ruchee Khanna, Gaurvi Piplani, Riya Shirish Shenvi Kuncolienkar

Kasturba Medical College, Manipal Academy of Higher Education, Department of Pathology, Manipal, India

Abstract

Introduction: Pulmonary tuberculosis (PTB) is a major global health concern, and rapid and reliable diagnosis in endemic areas is crucial. The monocyte-to-lymphocyte ratio (MLR) represents the relationship between absolute monocyte and lymphocyte counts, and recent studies suggest that an elevated MLR is a promising diagnostic and prognostic biomarker for PTB. It provides insight into the immune response to chronic infection, making it a potential biomarker. This study aimed to evaluate changes in the MLR in patients with active PTB before and after treatment completion.

Materials and Methods: This retrospective study was conducted in the Department of Pathology at Kasturba Medical College, Manipal Academy of Higher Education, Manipal in Karnataka over a 4-year period. The study included 136 patients diagnosed with PTB and 150 healthy controls. The MLR was assessed in patients with PTB before and after treatment completion and compared with that in healthy controls. Data were analyzed using appropriate statistical methods.

Results: Patients with PTB had significantly higher MLR values than the control group ($p < 0.05$). The MLR also significantly decreased following treatment in patients with PTB ($p < 0.0001$), suggesting a significant treatment effect. Receiver operating characteristic analysis showed that an MLR cut-off value of 0.38 yielded a sensitivity of 76.47% and a specificity of 94.67% for detecting active PTB.

Conclusion: This study confirms that the MLR is a valuable biomarker for PTB. It effectively distinguishes patients with PTB from healthy controls and may be useful for monitoring treatment response. The established cut-off value of 0.38 demonstrated moderate sensitivity and high specificity, indicating that the MLR may be a reliable tool for assessing disease progression and treatment efficacy in PTB.

Keywords: Biomarker, tuberculosis, monocytes, predictive, ratio, pulmonary

Öz

Giriş: Akciğer tüberkülozu (PTB) küresel bir sağlık sorunudur ve endemik bölgelerde hızlı ve güvenilir tanı çok önemlidir. Monosit-lenfosit oranı (MLR), mutlak monosit ve lenfosit sayımları arasındaki ilişkiyi temsil eder ve son çalışmalar, yüksek MLR'nin PTB için umut vadeden bir tanıl ve prognostik biyomarker olduğunu göstermektedir. Kronik enfeksiyona karşı bağışıklık yanıtına dair bilgi sağlar ve bu da onu potansiyel bir biyomarker haline getirir. Bu çalışma, aktif PTB'li hastalarda tedavi tamamlanmadan önce ve sonra MLR'deki değişiklikleri değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Bu retrospektif çalışma, Karnataka'da bir üçüncü basamak sağlık kuruluşunun Patoloji Bölümü'nde 4 yıllık bir süre boyunca yürütülmüştür. Çalışmaya, tüberküloz tanısı konmuş 136 hasta ve 150 sağlıklı kontrol dahil edildi. Monosit-lenfosit oranı (MLR) değerleri, tüberkülozlu hastalarda tedavi öncesi ve sonrası değerlendirildi ve sağlıklı kontrol grubuyla karşılaştırıldı. Veriler uygun istatistiksel yöntemler kullanılarak analiz edildi.

Bulgular: Tüberkülozlu hastaların MLR değerleri kontrol grubuna göre anlamlı derecede daha yüksekti ($p < 0,05$). MLR ayrıca, tüberkülozlu hastalarda tedavi sonrası anlamlı derecede azaldı ($p < 0,0001$), bu da önemli bir tedavi etkisine işaret etmektedir. Alıcı işletim karakteristik analizi, 0,38'lik bir MLR eşik değerinin, aktif tüberküloz tespit etmede %76,47 duyarlılık ve %94,67 özgüllük sağladığını gösterdi.



Address for Correspondence/Yazışma Adresi: Assoc. Prof. Ruchee Khanna, MD, Kasturba Medical College, Manipal Academy of Higher Education, Department of Pathology, Manipal, India

E-mail: ruchee.khanna@manipal.edu **ORCID ID:** orcid.org/0000-0002-4308-2961

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Sonuç: Bu çalışma, MLR'nin tüberküloz için değerli bir biyobelirteç olduğunu doğrulamaktadır. Tüberkülozlu hastaları sağlıklı kontrol grubundan etkili bir şekilde ayırt eder ve tedavi yanıtının izlenmesinde faydalı olabilir. Belirlenen 0,38 eşik değeri, orta düzeyde duyarlılık ve yüksek özgüllük göstermiş olup, MLR'nin PTB'de hastalık ilerlemesini ve tedavi etkinliğini değerlendirmek için güvenilir bir araç olabileceğini göstermektedir.

Anahtar Kelimeler: Biyobelirteç, tüberküloz, monositler, prediktif, oran, akciğer

Introduction

Tuberculosis (TB) is an infection caused by the bacterium *Mycobacterium tuberculosis*, with the lungs being the most commonly affected organ, accounting for 79%-87% of all cases^[1]. Pulmonary TB (PTB) is one of the leading causes of death worldwide. According to the World Health Organization Global Tuberculosis Report 2024, the estimated TB incidence rate in 2023 was 134 per 100,000 population, representing a 0.2% increase compared with 2022. Five countries accounted for 56% of the global total of TB cases, with India being the largest contributor, accounting for 26%. The TB-affected population comprised 55% men, 33% women, and 12% children and young adults^[2]. Hematological manifestations of TB infection can provide insights into its pathogenesis. Lymphocytes and monocytes play important roles in the induction of the immune response, and their levels in the peripheral blood may reflect the host immune response^[3]. Some studies have suggested that the ratio of monocytes to lymphocytes in peripheral blood correlates with the extent of TB^[4]. Other studies have found that an increased monocyte-to-lymphocyte ratio (MLR) is associated with active TB and is affected by antitubercular treatment^[5,6]. This study aimed to evaluate changes in the MLR in patients with PTB before and after anti-TB treatment and compare the values with those of healthy controls to establish a significant cut-off value for this biomarker.

Materials and Methods

Study Population

A retrospective study was conducted Kasturba Medical College, Manipal Academy of Higher Education in Manipal, Karnataka, between January 2021 and December 2024. All newly diagnosed patients with PTB who had positive sputum acid-fast bacilli or GeneXpert (Cepheid, Sunnyvale, CA, USA) results, were aged >18 years, and had complete post-treatment follow-up records were included in the study. Pediatric cases; cases of extrapulmonary TB; patients with other comorbidities, such as hepatitis B, hepatitis C, or human immunodeficiency virus (HIV), or other known underlying systemic conditions; and patients who were lost to follow-up after treatment were excluded. Healthy controls were recruited from the routine health checkup center of the hospital and comprised individuals with no prior history of TB, no current active TB

or related symptoms, and no known comorbidities. Controls were aged >18 years and were recruited during the same study period. Written informed consent was not obtained because no patient-identifiable data were included in the study. The study was conducted after obtaining ethical clearance from the Kasturba Medical College and Kasturba Hospital Institutional Research Ethics Committee on May 28, 2025 (protocol number: IEC2: 165/2025).

Data Collection

Complete blood counts (CBCs) of peripheral blood samples were performed by Kasturba Medical College, Manipal Academy of Higher Education, Manipal hematology laboratory using five-part differential automated hematology analyzers [SYSMEX (Sysmex Corporation, Kobe, Japan) and DxH 900 (Beckman Coulter, Brea, CA, USA)]. CBC testing was subject to strict quality assurance procedures in the laboratory, which was accredited by the National Accreditation Board for Testing and Calibration Laboratories and operated in accordance with ISO standards. Absolute monocyte and lymphocyte counts were retrieved from the CBC reports of the selected patients. The MLR for each patient was calculated before initiation of and after completion of the treatment regimen. Treatment completion was defined as completion of the standard 6-months antitubercular regimen with clinical and microbiological resolution. Post-treatment blood parameters were obtained from the available laboratory reports following review of the patients' medical records. All data were obtained from the hospital's medical records.

Statistical Analysis

All quantitative data were described using the mean, median, and interquartile range (IQR). A non-parametric Wilcoxon signed-rank test was used to compare MLR values before and after treatment in patients with PTB. The Mann-Whitney U test was used to compare age and MLR values between patients and controls. A p value <0.05 was considered statistically significant. The Wilcoxon signed-rank test was used to compare absolute monocyte and lymphocyte counts before and after treatment completion. Categorical variables, including sex, were compared between groups using Pearson's chi-square test. Additionally, multivariable logistic regression analysis was performed to evaluate the MLR as an independent predictor of active PTB after adjustment for sex, with the odds ratio (OR) scaled to a 0.1-unit increase in the MLR. Furthermore,

receiver operating characteristic (ROC) curve and Youden index analyses were performed to establish the cut-off value for the MLR in patients with TB. The MLR value corresponding to the maximum area under the curve in the ROC analysis was selected as the cut-off value, and its sensitivity and specificity were calculated. All statistical analyses were performed using RStudio software for Windows.

Results

A total of 136 newly diagnosed patients with PTB and 150 healthy controls were included in the study. The median age was 54 years (range, 19-87 years) among the patients and 53 years (range, 23-89 years) among the healthy controls. Of the 136 patients, 101 (74%) were males and 35 (26%) were females. Among the 150 controls, 84 (56%) were males and 66 (44%) were females. Because the data were not normally distributed, the Mann-Whitney U test was performed, and no statistically significant difference in age distribution was identified between the PTB and control groups ($p = 0.3997$). Pearson's chi-square test revealed a statistically significant difference in sex distribution between the two groups ($p = 0.0019$). To account for this demographic imbalance, multivariable logistic regression analysis was performed. MLR remained an independent and statistically significant predictor of active PTB after adjustment for sex [adjusted OR: 4.05 per 0.1-unit increase, 95% confidence interval (CI): 2.79-5.87, $p < 0.001$], indicating that each 0.1-unit increase in MLR was associated with an approximately 4-fold increase in the odds of being a patient with PTB. Sex was not significantly associated with PTB status after adjustment (adjusted OR: 0.58, 95% CI: 0.27-1.26, $p = 0.169$).

Peripheral white blood cell (WBC) counts in patients with PTB before and after treatment were evaluated to assess changes in WBC subpopulations. The total leukocyte count decreased significantly after treatment completion, with median values of 8.8 (IQR: 6.67-11.1) and 6.9 (IQR: 5.7-9.0), respectively. Similarly, the absolute monocyte count showed a statistically significant decrease following treatment ($p < 0.001$), from a median value of 0.75 (IQR: 0.59-1.03) to 0.60 (IQR: 0.48-0.79). In contrast, the absolute lymphocyte count showed a statistically significant increase after treatment ($p < 0.001$), from a median

value of 1.34 (IQR: 0.90-1.87) to 1.90 (IQR: 1.39-2.38). The post-treatment values for all parameters studied were similar to those of the healthy controls (Table 1).

The MLR was calculated from the absolute monocyte and lymphocyte counts of patients with PTB before treatment and after completion of treatment. The median MLR before treatment was 0.580 (IQR: 0.39-0.90), whereas the median MLR after treatment was 0.331 (IQR: 0.24-0.50), representing a significant decrease following treatment. The Wilcoxon signed-rank test demonstrated a significant decrease in MLR following treatment ($p < 0.0001$), suggesting that treatment significantly influenced MLR levels (Figure 1).

Data were also obtained from a separate group of healthy controls, and the MLR was calculated from their absolute monocyte and lymphocyte counts. The Mann-Whitney U test was used for statistical analysis. The median MLR among healthy controls was 0.222 (IQR: 0.18-0.27). The MLR of healthy controls was compared with that of patients with PTB before treatment, and the MLR values were significantly higher in patients with PTB than in controls ($p < 0.05$) (Figure 2). A summary of the median MLR values in patients with PTB and healthy controls is presented in Table 2.

To use the MLR as a biomarker for PTB, an appropriate cut-off value must be established. ROC curve analysis was

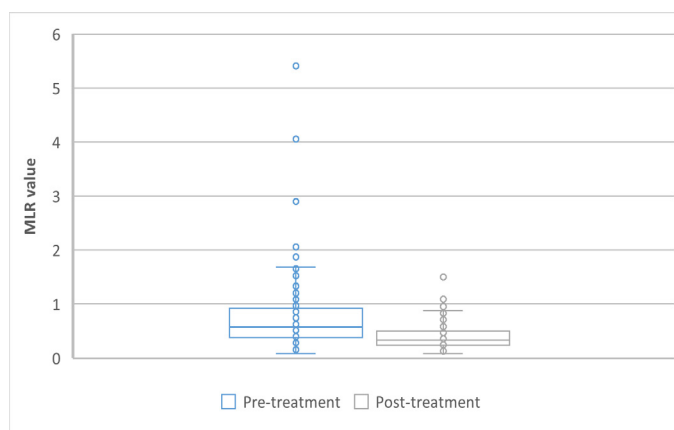


Figure 1. This is a boxplot image depicting that the median monocyte-to-lymphocyte ratio (MLR) value is higher in PTB patients prior treatment and the reduction in the median MLR post-treatment. PTB, pulmonary tuberculosis.

Table 1. The median total leucocyte count, absolute monocyte counts, and absolute lymphocyte counts in pulmonary tuberculosis patient's pre-treatment and post-treatment as compared to healthy controls. The IQR is given within the brackets.

Parameters	Pre-treatment values of PTB patients	Post-treatment values of PTB patients	Healthy controls
Total leucocyte count ($n \times 10^3/\mu\text{L}$)	8.8 (6.67-11.1)	6.9 (5.7-9)	6.95 (5.7-8.3)
Absolute monocyte count ($n \times 10^3/\mu\text{L}$)	0.75 (0.59-1.03)	0.6 (0.48-0.79)	0.5 (0.42-0.62)
Absolute lymphocyte count ($n \times 10^3/\mu\text{L}$)	1.34 (0.9-1.87)	1.9 (1.39-2.38)	2.23 (1.88-2.66)

IQR, interquartile range; PTB, pulmonary tuberculosis.

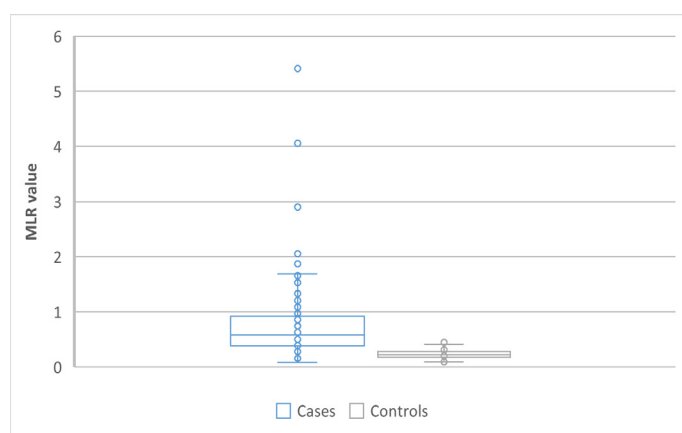


Figure 2. This is a boxplot image depicting that the median monocyte-to-lymphocyte ratio (MLR) value is higher in PTB patients' in comparison to the median MLR in healthy controls which is significantly lower. PTB, pulmonary tuberculosis.

Table 2. Summary showing statistical results of MLR values.

Group	Median MLR	Interquartile range
PTB patients-pre treatment	0.580	0.39 -0.90
PTB patients-post treatment	0.331	0.24-0.50
Healthy controls	0.222	0.18-0.27

MLR, monocyte-to-lymphocyte ratio; PTB, pulmonary tuberculosis.

performed to evaluate the MLR against GeneXpert results, which served as the reference standard and were positive for patients with PTB and negative for healthy controls. The ROC analysis demonstrated that the MLR was a strong predictor of GeneXpert status. At an optimal threshold of 0.3816, the MLR had a sensitivity of 76.47% and specificity of 94.67%, with a Youden index of 0.7114. This optimal threshold was used as the decision boundary, with an MLR >0.3816 indicating a higher likelihood of PTB. In our study population, the negative predictive value of the established MLR cut-off was 99.98%, suggesting that the MLR cut-off may be effective for ruling out TB and could therefore serve as a useful screening tool (Figure 3).

Discussion

PTB remains a global health challenge, particularly in endemic regions where rapid and reliable diagnostic tools are essential. The MLR has increasingly been recognized as a clinically relevant biomarker in TB, representing the balance between innate and adaptive immune responses. An elevated MLR in PTB has been attributed to concurrent monocytosis and lymphopenia, with the latter arising primarily from CD4+ T-cell depletion secondary to chronic immune activation. The shift toward monocyte-driven inflammation is characteristic of active TB^[7,8].

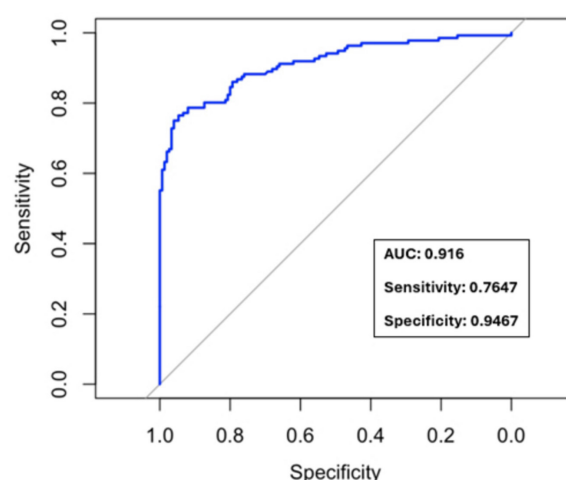


Figure 3. ROC curve analysis, blue line shows the performance of the monocyte to lymphocyte ratio. The curve is significantly above the diagonal, indicating that the ratio has strong predictive power in distinguishing between positive and negative cases. A steeper ascent early in the curve suggests that high sensitivity is achieved even at low false positive rates. ROC, receiver operating characteristic; AUC, area under the curve.

A total of 136 newly diagnosed patients with PTB were included in the study, and 150 individuals were included as controls. Of the 136 patients, 101 (74%) were males and 35 (26%) were females. The median age of patients with PTB was 54 years, which was comparable to that reported in the study by Wang et al.^[5], in which the median age was 55 years.

The total leukocyte count was elevated before treatment in patients with PTB and showed a significant decrease following treatment. The absolute lymphocyte count increased significantly, whereas the absolute monocyte count decreased significantly following treatment. These findings were comparable to those reported by Wang et al.^[6] The decrease in absolute monocyte and leukocyte counts following treatment was consistent with the findings of Okeke et al.^[9]; however, their study also reported a mild decrease in the absolute lymphocyte count following treatment. In a study evaluating various blood parameters in patients with active PTB, Ngahane et al.^[10] reported that monocytosis and lymphopenia were the most common hematological abnormalities. Monocytosis in PTB is considered important and may be attributed to the release of chemoattractants following the engulfment of bacilli by macrophages, resulting in increased monocyte production when some organisms overcome host defense mechanisms. However, lymphocyte counts may vary, either increasing or decreasing, and generally normalize following treatment. Peripheral lymphopenia in PTB may be mechanistically explained by the redistribution of lymphocytes toward the site of infection. The variability in lymphocyte counts reported

across different studies highlights the complex and dynamic nature of the immune response in TB^[9,11-13].

Monocytosis is a recognized feature of PTB, whereas lymphocytes contribute to infection containment and mycobacterial clearance. Given this immunological interplay, the MLR has been studied as a prognostic marker in PTB, including its potential to predict the risk of active TB in adults, infants, postpartum women, and individuals with HIV infection. An increased MLR in PTB may indicate disease severity and serve as an indicator of treatment effectiveness^[9,11]. Naranbhai et al.^[14] first established the predictive role of the MLR in patients with PTB for the early detection of disease in 3- to 4-month-old children. In our study, the median MLR was significantly higher in patients with PTB (0.58) than in healthy controls (0.22). The MLR value observed in our study (0.58) was comparable to that reported by La Manna et al.^[15], who compared the MLR, absolute monocyte count, and monocytic CD64 expression as biomarkers for discriminating between TB stages. The MLR values reported by La Manna et al.^[15] and Choudhary et al.^[16], which were 0.50 and 0.48, respectively, were consistent with the value obtained in the present study (0.58). The higher MLR in patients with TB than in controls was consistent with findings from studies by Wang et al.^[5], Ngahane et al.^[10], and Liana et al.^[17], who investigated the MLR in patients with active PTB and assessed its diagnostic value. Van Ginderdeuren et al.^[18] reported a considerably lower MLR value of 0.22, which could be attributed to their study population, which included HIV-positive individuals (Table 3).

The increase in MLR observed in PTB reflects underlying immune dysregulation involving type I and type II interferons, which promote monocyte production while reducing lymphocyte counts through apoptosis and sequestration. The increased number of monocytes, accompanied by alterations in their transcriptional and functional profiles, may lead to an impaired antimycobacterial response. Treatment of PTB

reduces inflammation and interferon signaling, allowing monocyte function to normalize and resulting in a decline in the MLR. Thus, the MLR may serve as a dynamic marker of disease activity and treatment response^[19,20]. In the present study, the median MLR was 0.58 before treatment and 0.33 after treatment. A significant decrease in the MLR was observed following treatment for TB. These findings were consistent with those of studies comparing the MLR before and after treatment completion in various populations of patients with PTB, including those with PTB. Iqbal et al.^[11] concluded that the MLR could be considered a prognostic marker in TB and may also be useful for monitoring the response to therapy. Wang et al.^[5] analyzed changes in the MLR before and after treatment completion and found that the elevated MLR decreased with therapy and was correlated with treatment effectiveness and phase. Wang et al.^[6] also investigated the role of the MLR in monitoring TB therapy and reported a decrease in the MLR following treatment, in addition to significant differences in the MLR across different age groups, sexes, and types of TB. Okeke et al.^[9] investigated the impact of TB infection and treatment on the MLR and neutrophil-to-lymphocyte ratio and similarly reported a decrease in the MLR among patients undergoing anti-TB treatment (Table 4).

Using ROC curve analysis, an MLR cut-off value of 0.3816 was established. Patients were more likely to have PTB if the MLR was >0.38. At this threshold, the sensitivity was 76.47% and the specificity was 94.67%, with a Youden index of 0.7114. Notably, the negative predictive value was remarkably high (99.98%), supporting the potential utility of the MLR as a non-invasive biomarker for PTB screening in adults. However, because this was a retrospective case-control study, the extremely high negative predictive value may have been partially influenced by the study design and patient selection. Therefore, this finding should be interpreted cautiously when considering its application to general population screening.

When compared with previous studies, our findings were generally consistent. Choudhary et al.^[16] reported that an MLR cut-off value >0.378 demonstrated good overall diagnostic utility for PTB in their cohort of HIV-infected Kenyan children,

Table 3. The median MLR value of different studies comparing active TB cases and healthy controls.

Studies	MLR in cases	MLR in controls	P value
Wang et al. ^[5]	0.36	0.16	<0.001
La Manna et al. ^[15]	0.50	0.18	<0.0001
Fayed et al. ^[19]	0.46	0.15	0.0001
Ngahane et al. ^[10]	0.39	0.19	<0.001
Liana et al. ^[17]	0.97	0.57	<0.0001
Choudhary et al. ^[16]	0.48	0.23	<0.01
Van Ginderdeuren et al. ^[18]	0.22	0.34	N/A
Present study	0.58	0.22	<0.05

MLR, monocyte-to-lymphocyte ratio; TB, tuberculosis; N/A, not applicable.

Table 4. The median MLR values by different studies done on TB patients before treatment and after anti-tuberculosis treatment.

Studies	MLR before treatment	MLR after treatment	p value
Iqbal et al. ^[11]	0.24	0.19	0.006
Wang et al. ^[5]	0.47	0.22	< 0.001
Wang et al. ^[6]	0.45	0.32	< 0.001
Okeke et al. ^[9]	0.11	0.08	<0.05
Present study	0.58	0.33	<0.0001

MLR, monocyte-to-lymphocyte ratio; TB, tuberculosis.

in contrast to the adults with PTB without comorbidities included in our cohort. Despite differences in the study populations, the MLR cut-off values established in both studies were comparable.

La Manna et al.^[15] established a lower MLR cut-off value of 0.28 when comparing patients with PTB and healthy controls. They reported a higher sensitivity (91.04%) and comparable specificity (93.55%). This difference may be attributed to heterogeneity in the study population, which included patients with latent, active, and treated TB, as well as a relatively small healthy control group. The study also proposed a revised MLR threshold of 0.34 for distinguishing active PTB from TB after treatment, with a sensitivity of 77.61% and specificity of 77.42%, respectively. This threshold more closely aligns with our findings and supports the relevance of the MLR in distinguishing active PTB.

Liana et al.^[17] reported an MLR cut-off value of 0.476 in culture-positive TB cases, with higher sensitivity (95.1%), lower specificity (70%), and a comparable negative predictive value (95.45%). The differences in cut-off values and diagnostic performance may be attributed to their inclusion of a broader age range and their comparison of patients with chronic cough with and without TB.

Buttle et al.^[21] investigated the prognostic significance of the MLR and reported sex-specific MLR cut-off values for a heterogeneous study population. The study established the optimal diagnostic points based on ROC analysis, with MLR cut-off values of 0.375 in males and 0.33 in females for sputum-positive contacts and patients with active PTB. The minimal difference between the cut-off values established in our study and those reported in their study may be attributed to the inclusion of diverse groups, including PTB contacts, patients initially suspected of having PTB, and HIV-positive individuals.

In our study, an MLR cut-off value of 0.3816 was established, which was consistent with the thresholds reported in similar previous studies. This value aligns with the cut-off threshold proposed by Wang et al.^[5], as it is above the 25th percentile (0.24), and is comparable to those reported by Choudhary et al.^[16] and Buttle et al.^[21], further supporting its potential clinical relevance in PTB. Although MLR values may vary across studies because of differences in population characteristics and study design, our study primarily focused on confirmed cases of active PTB without comorbid conditions or extrapulmonary manifestations, providing a relatively uniform cohort and potentially a more specific MLR threshold. Our threshold remained within the range reported in the literature and demonstrated strong diagnostic utility.

Study Limitations

This retrospective, single-center study had a modest sample size, with many cases excluded because of loss to follow-up. The exclusion of patients with comorbidities may limit the generalizability of the findings. Sex-based variation in the MLR was not assessed. Additionally, because this study relied on CBC parameters, external factors, such as corticosteroid use or the presence of non-active underlying inflammatory conditions that may influence blood cell counts, could not be completely controlled for. Furthermore, there was a statistically significant difference in sex distribution between the study groups, reflecting the epidemiological predominance of males among patients with PTB. Multivariable analysis confirmed that sex did not independently influence the predictive value of the MLR. Nevertheless, future prospective studies with sex-matched cohorts are warranted. Larger, prospective, multicenter studies are needed to validate MLR cut-off values across diverse populations, assess changes in MLR over time in patients with PTB, and evaluate its predictive value for treatment success or failure.

Conclusion

Our study reinforces and builds upon previous research supporting the diagnostic and prognostic value of the MLR in PTB. The established cut-off value of 0.38 demonstrated high specificity and a strong negative predictive value, highlighting its potential utility for screening and early detection of PTB, particularly in TB-endemic areas where rapid and cost-effective diagnostic tools are crucial. Although cut-off values may vary across studies, our findings are consistent with the existing literature and demonstrate strong diagnostic utility. Further validation through multicenter studies is warranted.

Ethics

Ethics Committee Approval: The study was conducted after obtaining ethical clearance from the Kasturba Medical College and Kasturba Hospital Institutional Research Ethics Committee on May 28, 2025 (protocol number: IEC2: 165/2025).

Informed Consent: Written informed consent was not obtained because no patient-identifiable data were included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.K., G.P., Concept: R.K., G.P., Design: R.K., Data Collection or Processing: S.K.N., R.S.S.K. Analysis or Interpretation: S.K.N., R.S.S.K., Literature Search: S.K.N., G.P., Writing: S.K.N., R.K., G.P., R.S.S.K.

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

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