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Original Article

# C-Reactive Protein Lymphocyte Ratio in the Diagnosis of Pulmonary Tuberculosis

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## ABSTRACT

***Background*** Tuberculosis (TB) is still a severe problem in underdeveloped and developing countries. Diagnostic tests are unavailable in every health institution, and TB culture can take up to 45 days. Therefore, there is a need for cheaper, faster, and easily accessible diagnostic methods that can guide the diagnosis. This study aimed to determine whether red blood cell distribution width (RDW), C-reactive protein (CRP)-lymphocyte ratio (CLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) can be used as biomarkers in the diagnosis of pulmonary TB in patients with no comorbidities.

***Material and Methods*** Files of microbiologically confirmed 122 patients with pulmonary TB and 153 patients in whom pulmonary TB was excluded were retrospectively reviewed. Out of them, patients with comorbidities were excluded from the study. Eighty-one patients with TB and 100 controls were included in the study.

***Results*** The lymphocyte, eosinophil, and LMR levels remained significantly lower in the TB group, while neutrophil, monocyte, RDW, platelet, and PLR levels were higher in the same group.

***Conclusion*** In those patients suspicious of pulmonary TB, higher levels of RDW, PLR, and CLR, whereas lower levels of eosinophil, PDW, and LMR may predict the diagnosis of pulmonary TB in previously healthy individuals.

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## Introduction

Tuberculosis (TB) is an infectious disease that is a significant public health problem transmitted via aerosols. A definitive diagnosis of pulmonary TB is put bacteriologically; in some cases, histopathology can make the diagnosis. But in both cases, usually, the diagnosis is delayed and, in some patients, leads to the progress and transmission of the disease. In the light of developing science, the fight against infectious diseases has gained momentum with new treatment methods and vaccinations. Although TB poses a lesser risk for the western world, it is still a severe problem in underdeveloped and developing countries. The acid-fast bacillus (AFB) tests used to diagnose the disease are not available in every health institution, and the result of the TB culture can take up to 45 days. Therefore, there is a need for cheaper and easily accessible diagnostic methods that can guide physicians in the diagnosis phase. The biomarkers of inflammation that are derived from the peripheral blood and hemogram parameters such as white blood cell (WBC) count, red blood cell distribution width (RDW), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) have been used as independent predictors of the prognosis of systematic inflammatory diseases.[1,2] In a previous study, high platelet distribution width (PDW) levels have been associated with COVID-19 mortality.[3] All parameters mentioned above are studied by routine complete blood count tests that clinicians might overlook. The physician's primary difficulty is translating the recommended guidelines into clinical practice. There is a need for tests that help physicians diagnose and give information about which patients should have an anti-TB treatment. This study aimed to investigate laboratory-based differences between the patients with microbiologically confirmed pulmonary TB and controls those proven not to have and to determine whether RDW, C-reactive protein (CRP)-lymphocyte ratio (CLR), NLR, PLR and lymphocyte monocyte ratio (LMR) can be used as biomarkers in the early diagnosis of pulmonary TB.

## Material and Methods

Data on patients admitted to a tertiary city hospital in Turkey between January 2021 and October 2021 with complaints compatible with pulmonary TB were retrospectively investigated. We retrospectively reviewed files of microbiologically confirmed 122 patients with pulmonary TB and 153 patients in whom pulmonary TB was excluded. Patients with comorbid diseases (such as malignancy, chronic kidney disease, immunosuppressive diseases, diabetes mellitus, and hypertension) were excluded from both groups. Out of reviewed files, 81 patients with microbiologically confirmed pulmonary TB and 100 controls were included in the study. All laboratory parameters belong to the first admission before treatment, including anti-TB therapy. The NLR, PLR and CLR were obtained by dividing neutrophil, platelet, and CRP levels by lymphocyte count. LMR, lymphocyte-eosinophil ratio (LER), and platelet-neutrophil ratio (PNR) values were obtained by dividing lymphocyte levels by monocyte, eosinophil, and neutrophil levels, respectively. CRP-neutrophil ratio (CNR) and CLR were obtained by dividing CRP levels by neutrophil and lymphocyte levels, respectively. The ethical committee approval was obtained from a tertiary city hospital Clinical Research Ethical Committee (Ethics Committee Approval No: 2021-24/6).

*Statistical Analysis*

All statistical analyses were carried out using SPSS 25.0 software. The Kolmogorov-Smirnov test was performed to examine the normality of the data. Continuous variables were given as mean±standard deviation and median values (interquartile range %25-%75), while the categorical variables were presented as frequency and percentage. The independent groups were compared to the Student's t-test for parametric assumptions and Mann Whitney U test for nonparametric hypotheses. The ROC analysis was performed to determine the optimal cut-off values for predicting the TB. The Youden index values were used to identify the optimal cut-off values. In addition, a p-value less than 0.05 was set as the statistical significance level. Spearman's correlation coefficient (p) was used to analyze associations between investigated parameters. In all instances, p values <0.05 were taken to indicate statistical significance.

## Results

The mean age was determined to be 51.6±20.7 years in the TB group and 43.9±11.2 years in the control group (*Table 1*), with the TB group having a significantly greater mean age (p<0.03). The gender distribution in the control group was 32% women and 68% men, while it was 28.4% (n: 23) women and 71.6% (n: 58) men in the TB group.

The levels of lymphocyte, eosinophil, mean platelet volume (MPV), PDW, LMR, LER, and PNR remained significantly lower in the TB group. In contrast, the WBC, neutrophil, monocyte, basophil, RDW, platelet, CRP, NLR, PLR, CNR, and CLR levels were higher in the same group. The ROC analysis calculated optimal cut-off values for RDW, NLR, PLR, CNR, CLR (*Figure 1*) and lymphocyte, eosinophil, PDW, LMR, and PNR (*Figure 2*).

When TB group compared to controls the areas under the curve (AUC) of RDW, NLR, PLR, CNR, CLR, lymphocyte, eosinophil, PDW, LMR, and PNR were found as 0.93, 0.88, 0.89, 0.94, 0.96, 0.84, 0.70, 0.65, 0.87 and 0.61

**Table 1.** Demographic data and laboratory findings of patients with pulmonary tuberculosis and controls*.

| Parameters | Controls (n: 100) | Pulmonary TB (n: 81) | P-value |
|---|---|---|---|
| Age (years) | 43.9±11.2 | 51.6±20.7 | 0.030 |
| Number of females | 32 (32%) | 23 (28.39%) | 0.600 |
| WBC | 8.6 (4.6-24) | 9.2 (3-35) | 0.035 |
| Neutrophil | 4.9 (0.65-19) | 6.8 (2-32) | 0.001 |
| Lymphocyte | 2.5 (0.69-11.5) | 1.37 (0.07-4.04) | 0.001 |
| Monocyte | 0.68±0.24 | 0.88±0.5 | 0.003 |
| Eosinophil | 0.15 (0.01-0.63) | 0.08 (0.01-1.2) | 0.001 |
| Basophils | 0.04 (0.01-0.4) | 0.05 (0-0.29) | 0.005 |
| RDW | 13(11.5-46.2) | 42.6 (32-75) | 0.001 |
| Platelet | 279.7±67.5 | 334.5±132 | 0.001 |
| MPV | 10.1±0.87 | 9.7±0.8 | 0.008 |
| PDW | 11.5±1.7 | 10.6±1.7 | 0.001 |
| CRP | 1.5 (0.2-98) | 90.7 (1.7-386) | 0.001 |
| NLR | 1.89 (0.16-13.16) | 5.06 (1.2-234) | 0.001 |
| PLR | 114.9 (30.8-345.7) | 260.5 (24-1742) | 0.001 |
| LMR | 4.09 (0.22-12.3) | 1.6 (0.1-5.5) | 0.001 |
| LER | 17.2 (0.22-287) | 16.7 (0.28-218) | 0.001 |
| CNR | 0.34 (0.04-14.4) | 10.8 (0.3-43.6) | 0.001 |
| CLR | 0.66 (0.08-59.2) | 70 (0.87-1831) | 0.001 |
| PNR | 55.4 (12.8-615.3) | 48.4 (1.2-109.9) | 0.010 |

*p<0.05, statistically significant.
WBC: white blood count, RDW: red blood cell distribution width, MPV: mean platelet volume, PDW: platelet distribution width, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, LER: lymphocyte-eosinophil ratio, CNR: CRP-neutrophil ratio, CLR: CRP-lymphocyte ratio, PNR: platelet-neutrophil ratio.

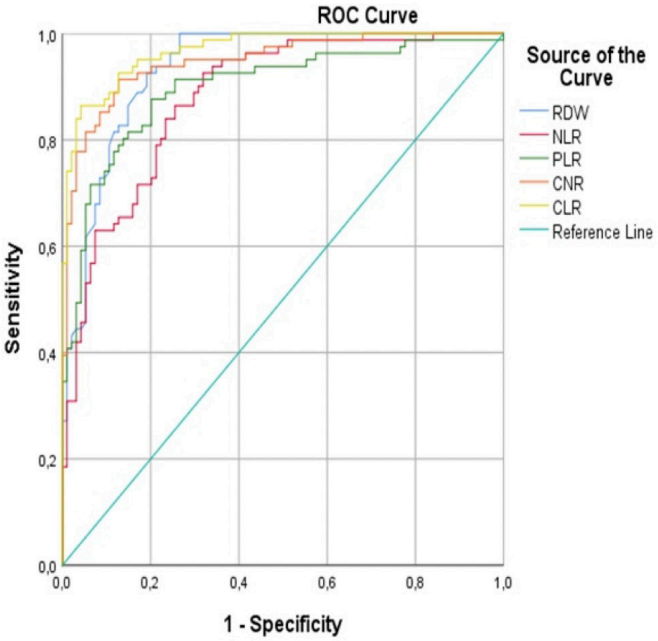


**Figure 1.** ROC curves comparing the prediction of pulmonary tuberculosis. Variables for RDW: red blood cell distribution width, NLR: neutrophil-lymphocyte ratio, PLR: platelet lymphocyte ratio, CNR: C-reactive protein (CRP)-neutrophil ratio, CLR: CRP-lymphocyte ratio.

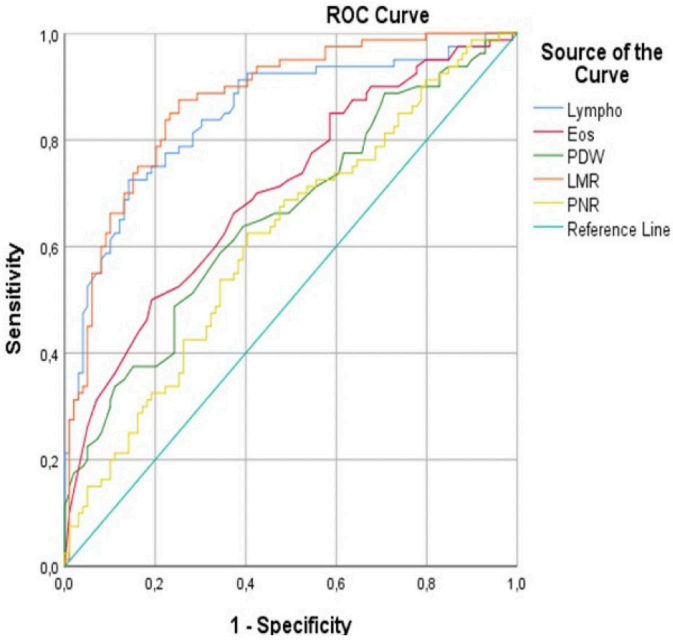


**Figure 2.** ROC curves comparing the prediction of pulmonary tuberculosis.
*p<0.05 statistically significant. Variables for Lymph: lymphocyte, Eos: eosinophil, PDW: platelet distribution width, LMR: lymphocyte monocyte ratio, PNR: platelet neutrophil ratio.

**Table 2.** ROC analysis of patients with pulmonary tuberculosis and controls*.

| Variable | AUC | Cut-off | Sensitivity (%) | Specificity (%) | P-value |
|---|---|---|---|---|---|
| RDW | 0.934 | 37.7 | 86 | 85 | 0.001 |
| NLR | 0.880 | 3.26 | 79 | 78 | 0.001 |
| PLR | 0.898 | 167 | 82 | 82 | 0.001 |
| CNR | 0.948 | 2.9 | 88 | 87 | 0.001 |
| CLR | 0.968 | 8.5 | 88 | 87 | 0.001 |
| Lymph | 0.847 | 1.84 | 77 | 77 | 0.001 |
| Eos | 0.702 | 0.11 | 66 | 62 | 0.001 |
| PDW | 0.657 | 11.1 | 63 | 60 | 0.001 |
| LMR | 0.871 | 2.5 | 80 | 79 | 0.001 |
| PNR | 0.613 | 52.3 | 60 | 59 | 0.009 |

*p<0.05 statistically significant.
AUC: area under the ROC curve, RDW: red blood cell distribution width, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, CNR: C-reactive protein (CRP)-neutrophil ratio, CLR: CRP-lymphocyte ratio, Lymph: lymphocyte, Eos: eosinophil, PDW: platelet distribution width, LMR: lymphocyte-monocyte ratio, PNR: platelet-neutrophil ratio.

**Table 3.** Spearman correlations between laboratory findings of patients with pulmonary TB and healthy controls.

| | | Age | Lymph | RDW | PLT | MPV | CRP | NLR | PLR | PDW | CNR | CLR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | r | 1 | -0.354 | 0.449 | 0.040 | -0.099 | 0.429 | 0.339 | 0.369 | -0.138 | 0.416 | 0.447 |
| | p | | 0.001 | 0.001 | 0.59 | 0.18 | 0.001 | 0.001 | 0.001 | 0.06 | 0.001 | 0.001 |
| Lymph | r | -0.3 | 1 | -0.48 | -0.06 | 0.20 | -0.60 | -0.81 | -0.88 | 0.30 | -0.60 | -0.74 |
| | p | 0.001 | | 0.001 | 0.41 | 0.006 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |
| RDW | r | 0.44 | -0.48 | 1 | 0.25 | -0.09 | 0.58 | 0.53 | 0.56 | -0.19 | 0.56 | 0.61 |
| | p | 0.001 | 0.001 | | 0.001 | 0.205 | 0.001 | 0.001 | 0.001 | 0.009 | 0.001 | 0.001 |
| PLT | r | 0.040 | -0.061 | 0.252 | 1 | -0.409 | 0.257 | 0.224 | 0.458 | -0.395 | 0.186 | 0.227 |
| | p | 0.594 | 0.413 | 0.001 | | 0.001 | 0.001 | 0.002 | 0.001 | 0.001 | 0.014 | 0.002 |
| MPV | r | -0.099 | 0.205 | -0.095 | -0.409 | 1 | -0.189 | -0.254 | -0.342 | 0.919 | -0.163 | -0.200 |
| | p | 0.188 | 0.006 | 0.205 | 0.001 | | 0.013 | 0.001 | 0.001 | 0.001 | 0.033 | 0.008 |
| CRP | r | 0.42 | -0.60 | 0.58 | 0.25 | -0.18 | 1 | 0.72 | 0.65 | -0.29 | 0.95 | 0.96 |
| | p | 0.001 | 0.001 | 0.001 | 0.001 | 0.013 | | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |
| NLR | r | 0.33 | -0.81 | 0.53 | 0.22 | -0.25 | 0.72 | 1 | 0.8 | -0.3 | 0.58 | 0.8 |
| | p | 0.001 | 0.001 | 0.001 | 0.002 | 0.001 | 0.001 | | 0.001 | 0.001 | 0.001 | 0.001 |
| PLR | r | 0.36 | -0.88 | 0.56 | 0.45 | -0.34 | 0.65 | 0.8 | 1 | -0.42 | 0.62 | 0.76 |
| | p | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | | 0.001 | 0.001 | 0.001 |
| PDW | r | -0.13 | 0.3 | -0.19 | -0.39 | 0.9 | -0.29 | -0.3 | -0.4 | 1 | -0.29 | -0.31 |
| | p | 0.065 | 0.001 | 0.009 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | | 0.001 | 0.001 |
| CNR | r | 0.41 | -0.6 | 0.56 | 0.18 | -0.16 | 0.95 | 0.58 | 0.62 | -0.29 | 1 | 0.9 |
| | p | 0.001 | 0.000 | 0.001 | 0.014 | 0.033 | 0.001 | 0.001 | 0.001 | 0.001 | | 0.001 |
| CLR | r | 0.44 | -0.74 | 0.61 | 0.22 | -0.2 | 0.96 | 0.8 | 0.76 | -0.3 | 0.93 | 1 |
| | p | 0.001 | 0.001 | 0.001 | 0.002 | 0.008 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | |

Lymph: lymphocyte, RDW: red blood cell distribution width, PLT: platelet, MPV: mean platelet volume, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, PDW: platelet distribution width, CNR: CRP-neutrophil ratio, CLR: CRP-lymphocyte ratio.

(*Table 2*). The correlation analysis was carried out to explore the correlation between laboratory parameters. A positive correlation was observed between age and RDW, CNR, CLR, RDW and PLR, MPV and PDW, CRP, and CLR. In contrast, a negative correlation was detected between age and lymphocyte levels, lymphocyte and RDW, NLR, and CLR (*Table 3*).

## Discussion

Despite the developing science, there are still no tests that make a rapid diagnosis of TB at the first admission. Hemogram parameters are inexpensive, easily accessible, and have fast results. RDW is the variation coefficient which is a simple test with low cost. Previously high levels of RDW have been associated with the severity and prognosis of community-acquired pneumonia.[4]

In a study, Henry et al. found a progressive increase of RDW with advancing COVID-19 severity.[5] But data about TB is minimal. In the present study, the TB group had higher RDW levels with an AUC of 0.93 alongside 86% sensitivity and 85% specificities. RDW levels had a positive correlation with CRP levels. High RDW values may be associated with infection and inflammation derived from *Mycobacterium tuberculosis*. In light of the present study results, RDW might be a valuable parameter in predicting pulmonary TB.

Researchers have investigated the usefulness of some ratios in the diagnosis and prognosis of many inflammatory conditions in recent years. These are neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratio. The NLR is easily calculated from the WBC of routine complete blood count, not introducing additional cost or workload to the laboratory or the clinician. In the pandemic of our time, high NLR was reported in patients who tested positive for SARS-CoV-2 compared to controls.[6] Iliaz et al.[7] have demonstrated NLR of patients with TB was higher than those with sarcoidosis. High levels of NLR helped diagnose TB among HIV-infected individuals.[8] In the present study, NLR levels were higher in the TB group with an AUC of 0.88 (79% sensitivity and 78% specificities), and also had a positive correlation with RDW and a strongly negative correlation with lymphocyte levels. PLR was reported to help identify TB infection in chronic obstructive pulmonary disease patients and predict sepsis mortality.[9,10] According to the results of the present study, patients with pulmonary TB had a higher PLR than controls. AUC was 0.89 with an 82% sensitivity and specificity. PLR was positively correlated with CRP (r=0.65) and negatively with lymphocyte levels (r=–0.88).

CRP is a biomarker that increases in many inflammatory and infectious conditions. High levels have been associated with a need for mechanical ventilation and a poor prognosis in patients with COVID-19.[11] Serum CRP levels are reported to be high in the human immunodeficiency virus (HIV) infected individuals.[12] As CRP is elevated in many other inflammatory and infectious diseases, it is not specific for diagnosing TB. In this study, we hypothesized that the ratio of this vital marker to neutrophil and lymphocyte values might guide the diagnosis of TB. When the results were analyzed, it was found that CNR and CLR were both significantly higher in the TB group. On ROC analysis CNR and CLR had AUC of 0.95 and 0.96, respectively (both 88% sensitivity and 87% specificities). To our knowledge, no previous studies investigated the diagnostic value of NLR, PLR, CNR, and CLR in pre-TB healthy individuals. The results of our study suggest that these parameters, which are inexpensive, easily accessible, and result quickly, may guide the diagnosis of TB.

After the pandemic of COVID-19, investigations on monocyte cells increased, and a preeminent role for monocyte-macrophage activation in the development of immunopathology of COVID-19 patients was reported.[13] Other studies pointed to morphological and inflammation-related phenotypic changes in peripheral blood monocytes in patients with COVID-19.[14] In the present study, monocyte levels were higher in the TB group. Kos et al.[15] reported a reduced rate of activated monocytes in a study mainly observed in patients with severe COVID-19. TB and COVID-19 may affect the lungs, but they are distinct diseases and may affect cells differently. The present study investigated if LMR could help physicians diagnose previously healthy patients with pulmonary TB. According to the current study results, LMR remained lower in the TB group and had an AUC of 0.87 (80% sensitivity and 79% specificity).

Studies have shown that platelets have essential roles in the immune system.[16] But there are few studies about changes in platelet levels and platelet indices, including MPV and PDW in pulmonary TB. MPV is a helpful index of platelet activation, which has been reported to be a marker to determine the disease activity in TB patients.[17] In the present study, PDW and MPV levels remained lower in the TB group. Xu et al.[18] have demonstrated that MPV might be a good clinical laboratory marker in distinguishing patients with TB and diabetes mellitus (DM) from those without DM. PDW is a direct measure of the variation of platelet size and a marker of platelet activation, which may be affected in many inflammatory and infectious conditions. In the present study, platelet levels of patients with TB were significantly higher, suggesting that thrombocytes may have a role in the fight against TB.

## Limitations

This study has limitations since we included healthy individuals in both groups; this study does not provide information about TB patients with comorbid diseases. The present study investigated the diagnostic value of the parameters mentioned above and did not provide post-treatment status or prognosis information.

## Conclusions

In conclusion, in those patients suspicious of pulmonary TB, higher CRP, PLR, CNR, and CLR levels, whereas low PDW, LMR, LER, and PNR may predict the diagnosis of pulmonary TB.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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### *Ethical Approval*

For this study, approval was obtained local ethics committee.

### *Authors' Contribution*

Study Conception: IK; Literature Review: IK, YTG; Data Collection and/or Processing: IK; Statistical Analysis and/or Data Interpretation: IK, YTG; Manuscript preparing: IK, YTG.

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