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RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

The Clinical İmportance of Complete Blood Count Parameters in Tuberculosis as Biomarkers

Tam Kan Sayımındaki Parametrelerin Tüberkülozda Biyobelirteç Olarak Klinik Önemi

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ABSTRACT

Objective: The neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), platelet distribution width (PDW), and mean platelet volume (MPV) are little known in the pulmonary medicine area. The aim of our study was to determine the effect and clinical importance of these new markers in tuberculosis (TB) in comparison with well-known inflammation markers.

Material and Methods: Patients with bacteriologic evidence for pulmonary TB who were admitted to our hospital for 1 year period as inpatients and 43 controls were included into the study. We compared NLR, RDW, MPV, and PDW from complete blood counts of our patients with other routine and commonly-used inflammation markers.

Results: The study comprised 112 patients with TB and 43 control patients. The distribution of sex between groups and the mean ages of participants were similar (p=0.48 and p=0.63). With the exception of PDW, NLR, RDW, MPV, total leukocytes (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) was found statistically different between the control and TB groups; p=0.29 for PDW, p<0.05 for the rest. In patients with bilateral infiltrates (n=67) on chest X-ray, NLR (7.25 vs. 4.47) and RDW (17.7% vs. 16.4%) were significantly higher (p<0.001 for both parameters). NLR and RDW made discrimination between TB and controls (AUC=0.930, p<0.001 and AUC=0.859, p<0.001, respectively). NLR correlated well with CRP and ESR, and RDW correlated with CRP.

Conclusion: This study showed that NLR and RDW, as recent markers in pulmonary medicine, were correlated with common inflammation markers such as CRP and ESR, and helped to predict TB diagnosis and radiologically-advanced disease.

Keywords: Blood cell count, inflammation, tuberculosis.

ÖZ

Amaç: Nötrofil/lenfosit oranı (NLR), kırmızı hücre dağılım genişliği (RDW), trombosit dağılım genişliği (PDW) ve ortalama trombosit hacmi (MPV) göğüs hastalıkları alanında çok az bilinmektedir. Çalışmanın amacı, bu yeni belirteçlerin tüberkülozdaki etkisini ve klinik önemini iyi bilinen inflamasyon belirteçleriyle karşılaştırmalı olarak belirlemektir.

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Gereç ve Yöntemler: Bir yıllık sürede, hastanemizde bakteriyolojik olarak kanıtlanmış akciğer tüberkülozu tanısıyla yatmış hastalar ve 43 kontrol grubu çalışmaya dahil edildi. Hastalarımızın tam kan sayımlarından NLR, RDW, MPV, PDW'yi diğer rutin ve yaygın olarak kullanılan inflamasyon belirteçleriyle karşılaştırdık.

Bulgular: Çalışmaya 112 tüberküloz hastası ve 43 kontrol hastası dahil edildi. Gruplar arası cinsiyet dağılımı ve katılımcıların yaş ortalamaları benzerdi (p=0,48 ve p=0,63). Kontrol ve tüberküloz grupları arasında PDW haricinde, NLR, RDW, MPV, total lökositler (WBC), C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESH) istatistiksel olarak farklı bulundu (PDW için p=0,29, geri kalanı için p<0,05). Akciğer grafisinde bilateral infiltrat olan hastalarda (n=67) NLR (7,25 ve 4,47) ve RDW (%17,7 ve %16,4) anlamlı olarak daha yüksekti (p<0,001). NLR ve RDW, tüberküloz ve kontroller arasında ayrım yaptı (sırasıyla AUC=0,930, p<0,001 ve AUC=0,859, p<0,001). NLR, CRP ve ESH ile RDW ise CRP ile iyi korelasyon gösterdi.

Sonuç: Bu çalışma, göğüs hastalıkları alanında yeni belirteçler olan NLR ve RDW'nin, CRP ve ESH gibi yaygın inflamasyon belirteçleri ile korele olduğunu ve tüberküloz tanısını ve radyolojik olarak ilerlemiş hastalığı öngörmede yardımcı olduğunu gösterdi.

Anahtar kelimeler: İnflamasyon, kan hücresi sayımı, tüberküloz.

INTRODUCTION

In recent years, new inflammation markers have been studied besides well-known markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, fibrinogen, and leukocyte count.[1] Increasing numbers of studies have investigated the potential effects of leukocyte subgroups on the inflammatory process of chronic diseases such as chronic renal failure, cardiovascular diseases, osteoporosis, and Alzheimer's disease.[2–4]

The neutrophil to lymphocyte ratio (NLR) is a new and practical inflammation marker that can be calculated easily from a complete blood count. In the literature, the investigation on possible effects of NLR is ongoing. There are studies suggesting its relationship with survival and prognosis in cancer types such as colorectal cancer, hematologic malignancy, ovarian malignancy, prostate cancer, lung cancer, and malignant mesothelioma.[5–11] As another marker, mean platelet volume (MPV) has been shown to reflect an inverse relationship with inflammatory disease activity.[12] In some other studies, MPV, platelet distribution width (PDW), and red cell distribution width (RDW) were studied in tuberculosis (TB) and found to be important complete blood count parameters.[13–17]

There are limited data on the use of NLR, PDW, RDW, and MPV as inflammation markers in the area of pulmonary medicine. Accordingly, the aim of our study was to evaluate the value and importance of these parameters in patients with TB.

MATERIAL AND METHODS

One hundred and twelve patients who were hospitalized in our clinic because of pulmonary TB (new cases) for 1 year-period were enrolled in the study. Data were collected retrospectively from our hospital records. In our study, patients were determined as having TB through positive sputum smears for acid fast bacilli (AFB) and/or positive cultures for Mycobacterium TB. Exclusion criteria were known hematologic diseases; active malignancy; acute coronary syndrome; acute bacterial diseases other than TB (having symptoms of any infection healed with antibiotics); chronic inflammatory disease (connective tissue disorder, inflammatory bowel disease); active systemic steroid use; history of chemotherapy or radiotherapy in the past 4 weeks; and miliary and/or multidrug resistant TB. Forty-three asymptomatic patients who were admitted to the internal medicine out-patient clinic for routine health control were included as the control group. Patients who had infectious, inflammatory, and malignant pathologies were excluded from the study.

To determine the characteristics of the patients, we recorded age, sex, prevalence of lesions in chest X-ray, the presence of cavity in chest X-ray, and anti-TB drug resistance patterns.

We recorded complete blood counts, albumin, ESR, and the patients' CRP values in venous blood samples before anti-TB treatment. Analyses were performed using an Abbott Cell-Dyne 3700 System (Abbott Diagnostics, Santa Clara, CA, USA) for complete blood count and a Beckman Coulter AU 2700 plus (Olympus, Tokyo, Japan) was used for biochemical analysis. For ESR, Eriline AR analyzer (Linear Chemicals, Barcelona, Spain) was used. The total leukocyte, neutrophil, lymphocyte counts, PDW, RDW, and MPV in complete blood count of the patients were recorded. NLR was calculated by dividing the number of neutrophils by lymphocyte count.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (IBM SPSS Statistics Data Editor) was used for statistical analysis of the data. All variables were tested for normality of distribution using the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation. Categorical variables are presented as total number and percentage. Differences between the groups were assessed using independent t-test or Mann–Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. We performed Spearman's correlation analysis in order to evaluate correlations of inflammation markers. In order to determine a cutoff value of NLR, PDW, RDW, and MPV to discriminate TB, we used receiver operating characteristics (ROC) analysis. P<0.05 was considered statistically significant. Ethical approval for the study was obtained from our institutional review board in accordance with the Helsinki recommendations (Approval number: 2015/5 date: 13.01.2015).

RESULTS

Among the 112 patients with TB, 48.2% (n=54) were men and 51.8% (n=58) were women. For the 43 controls, there were 41.9% (n=18) men and 58.1% (n=25) women. The distribution of sex be-

Table 1: Inflammation markers of the patients with tuberculosis and controls

Laboratory parameters	Tuberculosis group (n=112) Mean±SD (min-max)*	Control group (n=43) Mean±SD (min-max)	p
WBC count ($10^3/\mu L$)	10411±3425 (3660–18800)	7152±1398 (4400–11800)	**<0.001**
Neutrophil count ($10^3/\mu L$)	7778±3093 (1890–16600)	3992±1108 (2350–7950)	**<0.001**
Lymphocyte count ($10^3/\mu L$)	1619±774 (295–4400)	2446±604 (1190±4200)	**<0.001**
NLR	6.14±4.35 (0.94–24.6)	1.73±0.69 (0.88–3.94)	**<0.001**
PDW (fL)	17.42±1.26 (12.8–24.5)	17.17±1.17 (14.6–20.5)	0.29
RDW (%)	17.23±2.08 (14.3–26.6)	14.42±1.89 (11.1–19.6)	**<0.001**
MPV (fL)	7.41±1.25 (5.24–13.5)	8.36±1.13 (6.63–11.7)	**<0.001**
ESR (mm/hr)	66.98±25.4 (2–120)	18.08±10.97 (2–42)	**<0.001**
CRP (mg/L)	97.69±71.65 (2–398)	2.49±2.49 (0.12–12.81)	**<0.001**
Albumin (g/dL)	3.22±0.61 (1.9–4.5)	4.62±0.27 (4.1–5.2)	**<0.001**

Significant p values were given as bold. *: Mean±Standard deviation (minimum-maximum), WBC: White blood cell, NLR: Neutrophil lymphocyte ratio, PDW: Platelet distribution width, RDW: Red cell distribution width, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.

Table 2: Results of ROC analysis of inflammation markers to discriminate patients with tuberculosis from controls

İnflammation markers	Sensitivitiy (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	p
CRP (cut-off=5.9mg/L)	97	92	97.2	92.3	95.9	0.988	**<0.001**
ESR (cut-off=35.5mm/h)	92	92	96.1	82.9	91.6	0.946	**<0.001**
NLR (cut-off=2.16)	91	77	91.1	76.7	87.1	0.930	**<0.001**
RDW (cut-off=15.15%)	88	72	89.1	70.4	83.8	0.859	**<0.001**

Significant p values were given as bold. ROC: Receiver operating characteristics, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio, RDW: Red cell distribution width.

tween groups was similar (p=0.48). The mean age of the participants was 43±20 years in the TB group and 44±14 years in the control group (p=0.63).

The total leukocyte count (WBC), absolute neutrophil and lymphocyte counts, NLR, PDW, RDW, MPV, CRP, ESR, and albumin were evaluated as markers of inflammation in the TB and control group. With the exception of PDW, all inflammation markers were found statistically different between the control and TB groups (p=0.29 for PDW, for the rest p<0.05). The p values, mean, minimum and maximum values of the inflammation markers relative to the study groups are detailed in Table 1. We made ROC analysis to determine cut-off values of different inflammation markers to discriminate TB from controls. For NLR, a cut-off value of 2.16 made this discrimination with 91% sensitivity, 77% specificity, and 87.1% accuracy (AUC=0.930, p<0.001). For RDW, a cutoff value of 15.15 made this discrimination with 88% sensitivity, 72% specificity, and 83.8% accuracy (AUC=0.859, p<0.001). Details are given in Table 2 and the ROC curve analysis is given in Figure 1. We found no statistically significant cutoff value for MPV and PDW.

We analyzed subgroups of TB patients and compared them for the levels of acute phase reactants. Details are given in Table 3. When we looked at smear positivity, 17% (n=19) of the patients with TB included in the study were negative for sputum smear (AFB) and 83% of the patients were positive for AFB (n=93). In patients with smear-positive sputum for AFB, NLR (6.54 vs. 4.16), CRP (105.70 mg/L vs. 54.82 mg/-L), and ESR (69.46 mm/h vs. 51.0 mm/h) were significantly higher compared with patients who were smear-negative (culture positive) (p=0.002, p=0.001, and p=0.024, respectively). We found no relationship between smear positivity and the other inflammation markers. We also found no relationship with NLR, PDW, RDW, and MPV levels and the duration of smear conversion to negative for the patients with sputum smear-positive for AFB at the beginning (p=0.86, p=0.81, p=0.28, and p=0.12, respectively).

According to the evaluation of the patients' posteroanterior (PA) chest radiographs, there were cavitary lesions in 62.5% (n=70) of the patients, and 59.8% (n=67) had bilateral pulmonary infiltrates in chest X-ray. With the exception of albumin, there was no significant relationship between markers of inflammation and having cavitary pulmonary TB. Albumin values were found significantly lower in cavitary patients with TB compared with those with non-cavitary disease (p=0.037) (Table 3). In patients with bilateral infiltrates on chest X-ray, NLR (7.25 vs. 4.48), and RDW (17.78% vs. 16.42%) were significantly higher (for both parameters p<0.001). Similarly, ESR (73.13 mm/h vs. 55.76 mm/h) and CRP (117.25 mg/L vs. 68.14 mg/L) were significantly higher in patients with bilateral disease (p=0.003, and p<0.001). In contrast, albumin and the absolute lymphocyte count

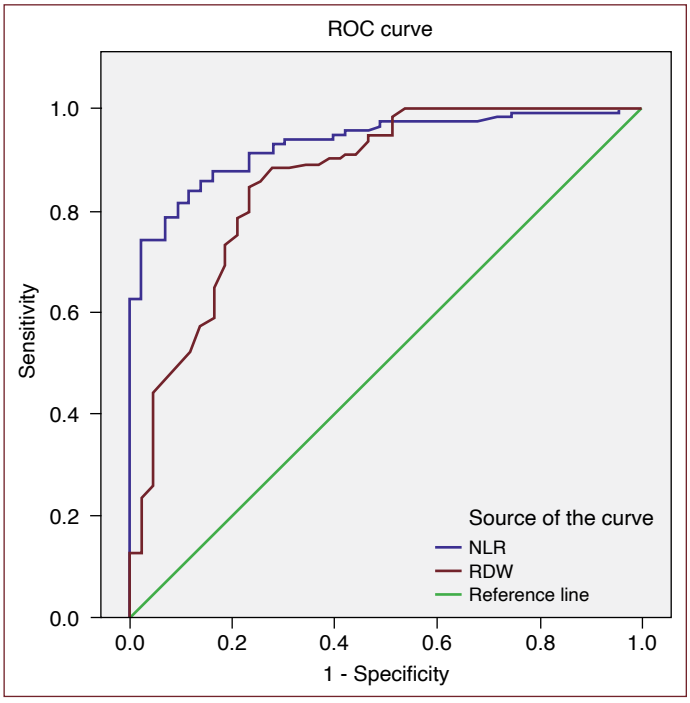

Figure 1: ROC analysis showing NLR and RDW to discriminate patients with tuberculosis from controls (p<0.001, AUC=0.930 and p<0.001, AUC=0.859, respectively).

ROC: Receiver operating characteristic, NLR: Neutrophil lymphocyte ratio, RDW: Red cell distribution width, AUC: Area under the curve.

were significantly lower in patients with bilateral disease compared with unilateral TB on chest X-ray (p<0.001 and p<0.001, respectively).

We observed no significant relationship between the presence of any major drug resistance and NLR, PDW, RDW, and MPV (p=0.41, p=0.58, p=0.66, and p=0.69, respectively). Other markers of inflammation were also not associated with the presence of major drug resistance (p>0.05).

As expected, NLR showed a positive correlation with WBC and absolute neutrophil count in the TB group (p<0.001, r=0.378, and p<0.001, r=0.603). In addition, NLR had a negative correlation with lymphocyte counts and albumin values (p<0.001, r=–0.780, and p<0.001, r=–0.447). CRP and ESR, as the most commonly used markers of inflammation in daily practice, also showed a positive correlation with NLR (p<0.001, r=0.475 and p=0.041, r=0.226) (Fig. 2). There was also a positive correlation between RDW and CRP (p=0.02, r=0.232) and a negative correlation between RDW and albumin (p<0.001, r=–0.394) in the TB group; there were no other correlations between MPV and PDW and the rest of the inflammation markers.

DISCUSSION

TB is endemic in our country and is a major public health problem. TB can mimic many other diseases and can cause difficulties in the differential diagnosis. New markers for early diagnosis are being investigated because TB is an infectious disease. The aim of this study was to investigate the role and clinical importance of complete blood count parameters such as NLR, PDW, MPV, and RDW in TB in comparison with other well-known markers.

The increase in total leukocyte and neutrophil counts is accompanied by a decrease in the number of lymphocytes, especially in bacterial infections. In this way, NLR can be expected to increase in this group of diseases.[18] Therefore, NLR may be a stronger predictor than leukocytosis, neutrophilia, and lymphopenia. De Jager et al.[19] showed that NLR and lymphocytopenia were stronger markers for bacteremia in the emergency department than CRP, WBC, and neutrophil count. Neutrophils and macrophages which are responsible for phagocytosis are the first-stage actors of immune response in TB infection.[20] Usually, infection and inflammation are brought under control at the end of this first contact of bacteria with the host.[21] However, in some cases, the inflammatory response is inconclusive and causes unrestricted destruction of the infection focus. Thus, tuberculous granuloma occurs.[22] Here, neutrophils phagocytize M. TB from infected macrophages.[23] In previous studies, it has been shown that neutrophil levels are higher in active TB cases, TB with cavity, and TB with extensive lung involvement. Based on these, it was understood that neutrophil count was correlated with bacillus burden and disease prognosis.[24,25]

In our study, we observed a strong correlation between NLR and other inflammatory markers in patients with TB. NLR is also a powerful test to discriminate patients with TB from healthy controls using cutoff 2.16. WBC, CRP, and ESR are routinely used markers of inflammation. In addition to these markers, NLR has emerged as an inflammation marker that can be easily calculated and used in daily practice. In some other studies, MPV, PDW, and RDW were studied in TB and found to be important complete blood count parameters in TB.[13–17]

NLR is being studied in different areas of medicine and has been shown to contribute to the prognosis and survival in malignancies and cardiovascular diseases.[3,5–11] In a recent study on the role of NLR in the course of chronic diseases, NLR and other markers of inflammation were higher in the group of patients with lung cancer and chronic obstructive pulmonary disease (COPD) compared with healthy volunteers or patients who had COPD without malignancy.[26] Günay et al.[27] showed that NLR was higher in active and stable patients with COPD than in healthy volunteers. Similar to our study, NLR was also found to correlate with CRP in Günay et al.'s[27] study. Other studies have shown that pleural NLR might also help in the diagnosis of TB pleurisy.[28] The role of NLR in the differential diagnosis of pulmonary TB and sarcoidosis was evaluated in a study consisted of 51 patients with TB, and 40 with sarcoidosis.[29] In this study, NLR was found to be supportive in differentiation of TB and sarcoidosis.[29] Huang et al.[13] enrolled 68 patients with active Crohn's disease (CD), 35 with intestinal TB, and 22 controls. The authors reported that RDW was more successful than CRP and ESR to differentiate intestinal TB and controls.[13] Similarly, in our study, NLR and RDW were found significant markers to predict TB as ESR and CRP. For PDW and MPV, we could not show such a relationship.

The differential diagnosis of TB and community-acquired pneumonia (CAP) is difficult in the early stages of TB.[30] The reasons for this may be the nonspecific radiologic findings of the early stages of TB and/or the difficulties in showing AFB in sputum. This is a common situation in countries where there is high incidence of TB. Yoon and colleagues' study[31] focused on this issue. They found that NLR was the strongest marker to distinguish CAP and TB. This was followed by absolute neutrophil count, leukocyte count, CRP, and lymphocyte count. In their study, the NLR was significantly lower in pa-

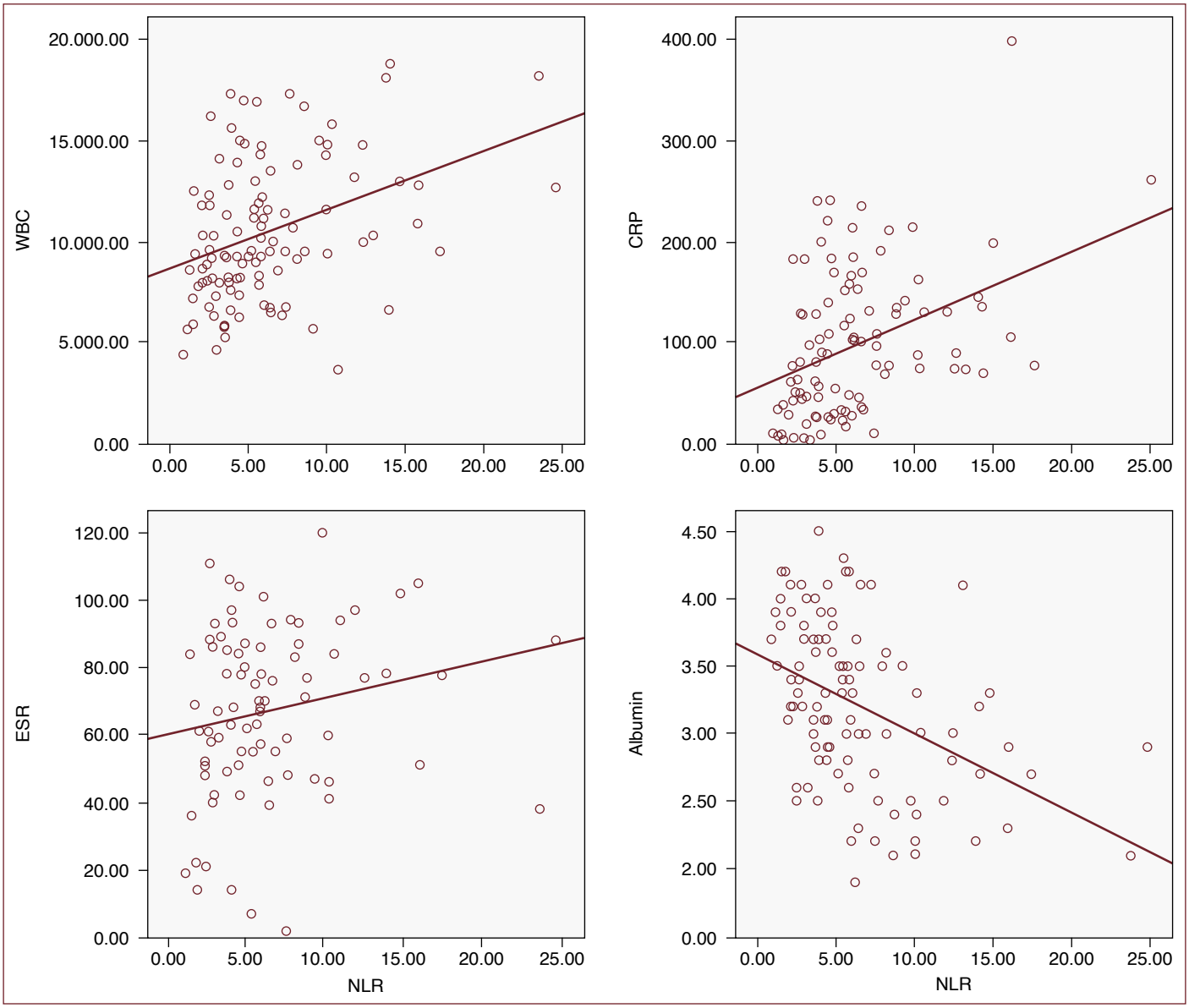

Figure 2: The correlation of NLR with WBC, CRP, ESR and albumin. There was a negative correlation with albumin, and positive correlations with WBC, CRP, and ESR.

WBC: Total leukocyte count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio.

tients with TB (3.67±2.12) compared with patients with pneumonia (14.64±9.72), also lymphocytosis was higher in TB group compared with pneumonia group.[31] The higher NLR in pneumonia may be due to the more prominent elevation of neutrophils in pneumonia than in TB and higher lymphocytosis in TB. In addition, their NLR in TB group was lower our NLR in TB group (6.14±4.35). That might be due to different extent of TB or disease severity in these studies. However, in Yoon et al.'s[31] study, there were no details explaining disease severity in their TB group to compare with ours. Tozkoparan et al.'s[15] study consisted of 82 patients with TB and 87 non-TB controls. PDW and MPV values were higher in the TB group. For the patients with pneumonia in the control group, PDW and MPV were found to be significantly lower than in the TB group.[15] Another study enrolled 100 patients with TB, 50 with CAP, and 28 healthy controls. They revealed that PDW was higher in the TB group compared with controls, but they could not show a difference between PDW levels of the TB and CAP groups.[16]

In our study, patients with TB with bilateral infiltration on chest radiograph showed significantly higher NLR (7.25 vs. 4.47) and RDW (17.7% vs. 16.4%) levels than in patients with unilateral disease. Therefore, we may say that NLR and RDW were correlated with the radiologic extent of the disease such as ESR and CRP did. Similarly, Abakay et al.[14] showed that NLR (4.7 vs. 3.1) and RDW (17.7% vs. 15.7%) were higher in advanced TB compared with milder forms. According to Tozkoparan et al.'s[15] study, PDW and MPV also correlated with the radiologic extent of TB, but this correlation was weaker

Table 3: Comparison of acute phase levels according to different tuberculosis subgroups

Tbc subgroups (n=112)	NLR		RDW		CRP		ESR		Alb	
	Mean±SD	p	Mean±SD	p	Mean±SD	p	Mean±SD	p	Mean±SD	p
ARB (+) (n=93)	6.54±4.54	**0.002**	17.25±2.08	0.850	105.70±72.36	**0.001**	69.46±25.07	**0.024**	3.18±0.61	0.102
ARB (–) (n=19)	4.16±2.49		17.15±2.18		54.82±50.68		51.00±22.49		3.43±0.57	
Unilateral infiltration (n=45)	4.48±3.06	**<0.001**	16.42±1.46	**<0.001**	68.14±77.29	**<0.001**	55.76±29.07	**0.003**	3.57±0.57	**<0.001**
Bilateral infiltration (n=67)	7.25±4.73		17.78±2.27		117.25±60.73		73.13±21.01		3.00±0.54	
Cavitary tbc (n=70)	5.99±4.46	0.640	17.45±2.21	0.143	102.79±63.15	0.337	69.28±22.71	0.310	3.13±0.60	**0.037**
Non-cavitary tbc (n=42)	6.39±4.19		16.86±1.82		89.02±84.34		63.41±29.15		3.38±0.61	
Any major drug resistance[a] (n=22)	7.06±6.22	0.410	17.26±2.09	0.664	91.70±79.12	0.658	56.50±29.48	0.091	3.34±0.69	0.387
No major drug resistance (n=79)	5.90±3.53		17.04±2.05		99.69±66.58		68.05±23.39		3.21±0.59	

Significant p values are given as bold. [a]: Drug resistance has missing data on 11 patients. Tbc: Tuberculosis, NLR: Neutrophil lymphocyte ratio, RDW: Red cell distribution width, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, Alb: Albümin, ARB: Acid resistant bacilli, SD: Standard deviation.

than ESR. There are also studies showing no relationship between the radiologic extent of TB and MPV and PDW.[16] In our study, there were also no such relationship for MPV and PDW.

In conclusion, few studies have investigated the use of PDW, MPV, RDW, and especially NLR, in the field of pulmonary medicine. Our study showed a good correlation of NRL and RDW with inflammation markers used in routine practice in TB disease. These parameters were also helpful to predict the presence of TB and correlated well with the radiologic extent of TB. There were no relationship with these new markers and ARB conversion duration or drug resistance test results. With further publications that elucidate the role of NLR and RDW in the differential diagnosis and prediction of mortality of different pulmonary diseases, we may start to use them in daily practice.

Disclosures

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