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Diagnostic Contribution of Hematological Parameters in Patients with Lung İnvolvement in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a prevalent autoimmune condition, with lung involvement being its most frequent extra-articular manifestation. This study aims to investigate the contribution of hematological parameters to diagnosing lung involvement in patients with RA. Individuals with RA were divided into two groups according to lung involvement in thorax computed tomography. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil, lymphocyte, monocyte, platelet, neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR) and systemic immune-inflammatory index (SII) were evaluated in all patients. Twenty-nine of the seventy-five RA patients were found to have lung involvement, and lung involvement was not observed in forty-six patients. CRP, ESR, and neutrophils were high in patients with lung involvement and a statistically notable distinction was observed. Lymphocyte count was low in patients with lung involvement and was statistically significant. NLR, NMR, and SII rates were high in patients with lung involvement and were statistically significant. It is observed that hematological parameters contribute to diagnosing RA lung involvement.

Keywords: Hematological tests, Lung inflammation, Rheumatoid arthritis

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Introduction

Rheumatoid arthritis(RA) is a systemic inflammatory disorder characterized by chronic polyarthritis that causes irreversible destruction and deformities in the joint synovium and can also lead to skin, eye, heart, and lung involvement (McInnes & Schett, 2011; Smolen et al., 2016). The most frequent non-joint manifestation is associated with the lungs, affecting around 50-60% of individuals diagnosed with RA (Wilsher et al., 2012; Kim et al., 2009). Clinically RA; presents with interstitial lung disease (ILD) or rheumatoid nodules with parenchymal involvement, with pleural inflammation and effusion as a result of pleural involvement, with constrictive or follicular bronchiolitis and bronchiectasis involving the airways, and with vasculitis or pulmonary hypertension in the pulmonary vascular structures. RA-ILD is a significant cause of morbidity and mortality and its prognosis is heterogeneous. The pathogenesis of RA-ILD is quite complex. It is thought to occur due to oxidative stress by stimulating autoimmunity and fibrotic pathways in a genetically susceptible host (Shaw et al., 2015; Scott et al., 2019). This process may result in lung fibrosis(Scott et al., 2019). RA accompanied by ILD presents a serious pulmonary complication, adversely affecting the overall prognosis. Approximately 10% of RA patients develop ILD(Zhang et al., 2017; Ha et al., 2018). RA-ILD most commonly presents as usual interstitial pneumonia (OIP)(Dawson et al., 2001; Duarte et al., 2019). The presence and severity of lung involvement are the main factors to be considered in the treatment decision. A significant decrease in survival was observed when comparing RA patients with and without ILD; This shows the need to improve diagnostic methods (Hyldgaard et al. 2017).

While lung parenchymal findings remain stable in some patients with RA-ILD, increased progressive fibrosis results in poor prognosis in some patients. Previous studies have used some parameters in patients with RA-ILD, including low forced vital capacity, and low carbon monoxide diffusion capacity. However, these parameters may be misleading in the evaluation due to variability between clinicians or inadequate respiratory procedures. For this reason, more objective markers are needed. In routine clinical practice, the measurement of mononuclear cells in peripheral blood is used as easy, non-invasive objective markers (Hozumi et al., 2013; Dawson et al., 2002; Solomon et al., 2016). RA pathophysiology involves a significant contribution from inflammation. Therefore, inflammatory markers are high in the active phase of RA and correlate with the level of disease activity. (Prete et al., 2011). Evaluating inflammatory processes in RA with reliable parameters is significant for determining long-term results. For this reason, the most commonly used markers include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, since these two markers reflect short-term inflammatory activity, their distinguishing feature from other inflammatory factors is low (Norton et al., 2013).

Recently, hematological parameters like the ratio of neutrophils to lymphocytes (NLR), the ratio of monocytes to lymphocytes (MLR), and the systemic immune inflammation index (SSI) have started to be employed as indicators of systemic inflammation. Studies have indicated a noteworthy elevation in NLR among individuals with RA compared to those in the healthy control cohorts (Chandrashekara et al., 2017).

This study aims to evaluate the relationship of NLR, MLR, and SSI parameters with lung involvement in RA patients.

Material and Methods

This study is a retrospective cross-sectional study and approval was received from the local ethics committee (decision no: 2023-12/34).

Patients who applied to our hospital between January 2014 and March 2023 and were diagnosed with RA by the guidelines were included in this study (Alunno et al., 2017). The medical records of 85 registered patients diagnosed with RA between the ages of 26 and 80 were examined retrospectively. Firstly, the patient's demographic data such as age and gender, and thorax computed tomography (CT) and complete blood count (CBC) values performed on the same date were examined. Ten patients who did not have CBC and thorax CT of the same date, whose image quality was poor, and whose laboratory data were not available were excluded from the study. CRP, ESR (mm/h), neutrophil count (109/L), lymphocyte count (109/L), monocyte count (109/L), and platelet count (109/L) were obtained and NLR, MLR, and SII values were calculated. SII value was calculated with the formula platelet count X monocyte/lymphocyte. CRP value 0-5 mg/L, ESR 0-30 mm/h, neutrophil count 2-7.15 109/L, lymphocyte count 1.16-3.18 109/L, monocyte count 0.29-0.71 109/L was considered normal within reference ranges. Lung parenchyma was evaluated on thorax CT images by an experienced radiologist. Patients were divided into 2 groups according to lung involvement. Lung involvement was evaluated according to CT findings. Lung involvement was classified as a rheumatoid nodule, bronchiectasis, NSIP, OIP, LIP (lymphoid interstitial pneumonia), follicular bronchiolitis, interstitial fibrosis, and ground glass (Figure 1).

The data from the study were analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0. The normality of the variables was assessed using Kolmogorov-Smirnov test. For continuous variables that followed a normal distribution, the mean ± standard deviation (SD) was reported, while for non-normally distributed variables, the median and minimum-maximum values were provided. Categorical data were presented in terms of frequency and percentage. To compare normally distributed continuous variables, the independent sample t-test was used, and the Mann-Whitney U test was employed for non-normally distributed continuous variables. The significance level for statistical tests was set at 0.05.

Results

Out of the 75 patients with RA in this study, 81.3% were female (n = 61), and 18.7% were male (n = 14), indicating a predominance of female participants. The average age of the patients was 59.52 ± 11.78, with an age range of 26 to 80. The patients were divided into two groups based on the presence or absence of lung parenchymal involvement. A total of 29 patients had lung involvement, while 46 did not. Among the 29 patients with lung involvement, 79.31% (n = 23) were female, and 20.68% (n = 6) were male. The average age of patients with lung involvement was 62.03 ± 10.97, compared to 58.91 ± 11.88 for those without lung involvement.

C-reactive protein, ESR, and neutrophil counts were found to be higher in patients with lung disease detected on thorax CT compared to those without lung involvement, while the lymphocyte count was found to be lower. These results were statistically significant ($p<0.05$). However, although monocyte and platelet counts were high in patients with lung involvement, no statistically significant difference was detected ($p>0.05$). NLR, MLR, and SII are high in patients with lung involvement and are statistically significant ($p<0.05$). Laboratory information regarding lung involvement is shown in Table 1.

Lung involvement was detected in 29 of 75 patients in the study population. 24.13% (n=7) of the patients had NSIP, 20.68% (n=6) had rheumatoid nodüle, 17.24% (n=5) had ground glass, 10.34% (n=3) had bronchiectasis, 10.34% (n=3) had OIP, 10.34%(n=3) had interstitial fibrosis, 3.44%(n=1) had LIP, 3.44%(n=1) follicular bronchiolitis were observed. The frequency of lung involvement patterns detected on computed tomography is shown in Figure 2.

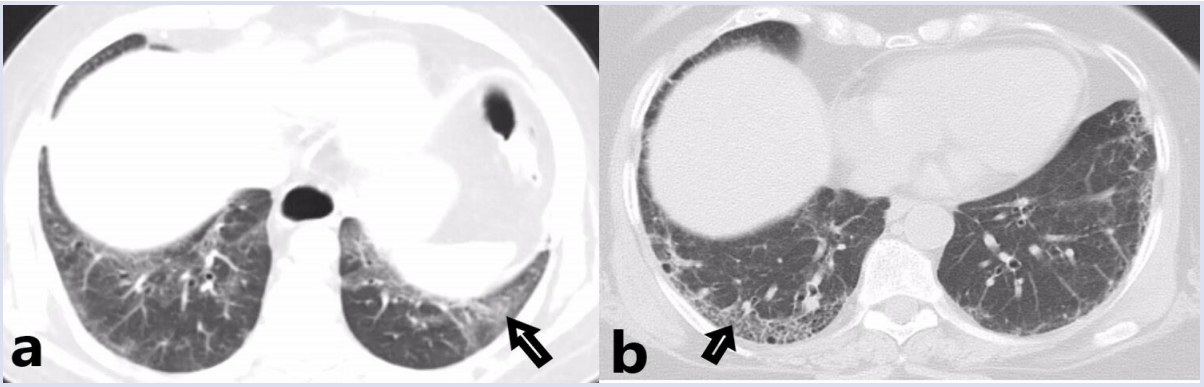

Figure 1. (a)OIP in RA, OIP pattern consists of peripheral basilar dominant reticular abnormalities, honeycombing (arrow), traction bronchiectasis, (b) NSIP in RA. The NSIP consists of reticulation and ground glass(arrow) with little or no architectural distortion

Table 1. Hematological parameters according to lung involvement in rheumatoid arthritis patients

	Lung involvement (+)(n:29)	Lung involvement (-)(n:46)	p
CRP, mg/L median (min-max)	9.6(0.63-142.0)	4.89(0.15-202.3)	**P=0.033***
ESR, mm/h median (min-max)	30(1-124)	16(1-108)	**P=0.018** *
Neutrophil count(10^9/L) median (min-max)	5.53(1.93-13.45)	3.28(0.56-10.71)	**P=0.001***
Lymphocyte count(10^9/L) median (min-max)	1.67(0.55-2.78)	1.95(0.90-5.58)	**P=0.042***
Monocyte count(10^9/L) median (min-max)	0.59(0.22-1.82)	0.50(0.24-1.34)	P=0.125
Platelet count(10^9/L)(mean ± SD)	281.51± 74.75	252.46± 73.16	P=0.584
NLR median (min-max)	2.89(0.96-17.02)	1.84(0.42-5.17)	**P=0.0001***
MLR median (min-max)	0.34(0.2-2.30)	0.28(0.14-0.65)	**P=0.007***
SII median (min-max)	807.38(238.42-6965.51)	404.44(97.92-2167.87)	**P=0.0001***

CRP C- Reactive protein, ESR Erythrocyte sedimentation rate, NLR Neutrophil/lymphocyte ratio, MLR Monocyte/ lymphocyte ratio, SII Systemic immune-inflammatory index

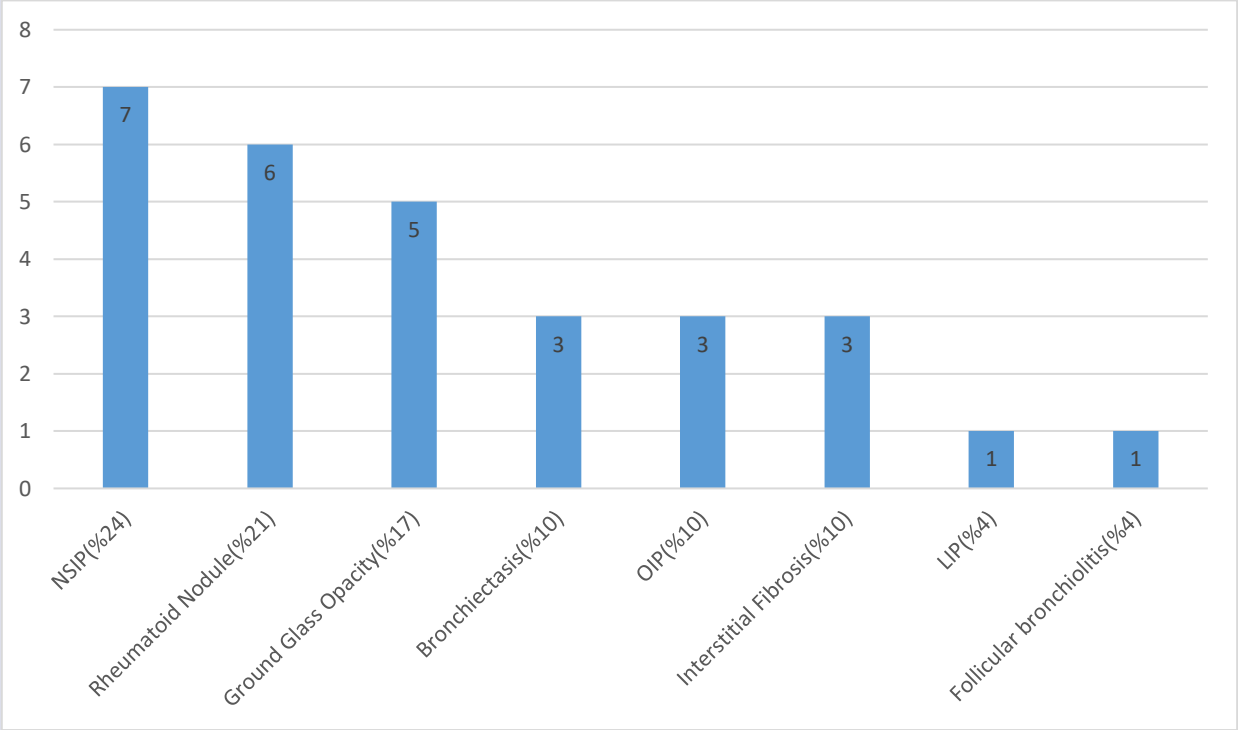

Figure 2. Frequency of lung involvement patterns detected on computed tomography in RA patients evaluated in our study.

Discussion

This study evaluated the relationship between hematological inflammatory markers and lung involvement in RA patients. In RA patients, ILD is one of the most common lung diseases and the second most common cause of mortality after lung cancer and secondary infection. Although lung clinical findings occur in approximately 10% of patients, it has a subclinical course in 30% (Doyle et al., 2018). In patients diagnosed with RA, ILD is detected in 10% throughout the disease, and 34% of patients are diagnosed with RA and ILD simultaneously. The most frequently detected interstitial lung patterns in RA patients in the literature and our study are NSIP and OIP. Although OIP is detected more frequently in the literature, NSIP was found more frequently in our study. Rheumatoid nodules are very specific to RA disease and are seen in 24% of patients. On CT, rheumatoid lung nodules have nodular or lobulated contours, range from a few millimeters to a few centimeters in size, are often peripherally located, and are predominant in the middle-upper lobes. Patients are usually asymptomatic. Similarly, in our study, rheumatoid nodules were detected in 21% of the patients (Kristen Demoruelle et al.,2018).

Hematological markers are very inexpensive, widely used, and can be evaluated in every patient. While ESR and CRP serve as reliable markers for systemic inflammation, they might not accurately mirror localized and subclinical inflammatory processes. Therefore, more sensitive tools are needed to assess persistent inflammation, especially in RA. In this study, inflammatory parameters such as CRP, ESR, neutrophil count, NLR, MLR, and SII were found to be higher in patients with lung involvement than in those without lung involvement. The results were statistically significant.

The neutrophil/lymphocyte ratio encompasses two defense mechanism components. Neutrophils assume a

primary role in the defense system, responsible for generating lytic enzymes, free oxygen radicals, and cytokines. In patients with RA, lymphopenia in peripheral blood occurs as a result of increased lymphocyte apoptosis and heightened inflammation in the joints, causing them to accumulate in those regions. Peripheral lymphopenia and a gradual increase in the number of neutrophils have been frequently noted with the progression of RA(Chandrashekara et al., 2017). The results of our study also support this mechanism. The high difference detected in NLR suggests that this marker is guiding for lung involvement.

Reactive thrombocytosis occurs in conditions where cytokine and thrombopoietin production increases, such as cancer and inflammatory diseases. Platelets; have an important role in active inflammatory processes such as cytokine production and immune system regulation (Uslu et al., 2015). Neutrophils, lymphocytes, and platelets differ in the inflammatory process. Differences in inflammatory markers may occur as a result of lifestyle habits such as smoking and other inflammatory conditions (Chandrashekara et al., 2017). For this reason, the use of inflammatory markers such as NLR and MLR is emerging. SII was found to be high in patients with chronic inflammation in joints and other tissues (Kelesoglu Dincer Sezer, 2022). SII is a usable marker in RA patients. In this study, SII values were found to be higher and more significant in RA patients with lung involvement. As a result, we think that SII can be used in the early diagnosis of RA patients with lung involvement.

Computed tomography chest imaging provides valuable information on ILD, including the pattern and extent of the disease, the evaluation of disease progression over time, and the evaluation of extra-parenchymal abnormalities (Salaffi et al., 2019). In this study, routine hematological markers that can be used in all healthcare institutions, including primary care, were investigated for RA patients with lung involvement determined by CT. We believe that in cases where hematological markers such as NLR, MLR, and SII are elevated, suspicion of RA lung involvement should prompt referral for CT.

This study has certain inherent limitations. First of all, our study is retrospective. Concomitant medication use, smoking, and other medical conditions may affect the values of hematological markers. These factors could not be excluded in this study. At the same time, our study has many strengths. As far as we know, there are not many studies on this subject in the literature, and when compared to other studies, consistent results have been obtained. A notable advantage of this study is its rarity in addressing this specific subject. We believe that conducting prospective studies with larger populations will make significant contributions to the literature.

As a result, it seems that hematological parameters contribute to the diagnosis of lung involvement in RA. We believe that patients with elevated hematological parameters such as NLR, MLR, and SII during routine checks should be evaluated with CT.

Sources of Financial Assistance

None.

Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity interested in this manuscript's subject matter.

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