

The importance of red cell distribution width and neutrophil-lymphocyte ratio as a new biomarker in rheumatoid arthritis

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ABSTRACT

Objective. Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects the joints. Various biomarkers have been used for the prognosis and clinical follow-up. There are few studies that have investigated whether or not neutrophil-lymphocyte ratio (NLR) and red cell distribution width (RDW) are good indicators of systemic inflammation. The present study aims to explore the prognostic value of RDW and NLR in rheumatoid arthritis (RA) as a new inflammatory marker. **Methods.** RA patients (n = 124) who presented to the Rheumatology outpatient clinic in our hospital between March 2015 and May 2015 were included in this study retrospectively. As a first group, 47 clinically active RA patients who had high acute phase proteins were included. In the second group, 73 clinically in-remission RA patients who had normal acute phase proteins were included. Fifty-five healthy volunteers constituted the control group. **Results.** The mean RDW was found to be 15.2 ± 2.9 in the active group; 14.6 ± 2 in the inactive group and 13.4 ± 1.4 in the control group ($p < 0.01$). The mean NLR was found to be 3.7 ± 2.2 in the active group; 3.7 ± 1.6 in the inactive group and 3.2 ± 0.9 in the control group ($p = 0.190$). There were statistically significant differences between the RDW values of the active-period RA patients with the control group ($p < 0.01$). There was statistically significant difference between RDW values of active RA and inactive RA patients ($p < 0.01$). The NLR results between the RA group and the control group ($p = 0.700$); the active RA group, and the inactive RA group ($p = 0.169$) were similar. There was not statistically difference between the NLR values of active RA patients with the control group ($p = 0.360$). There was statistically difference between the NLR values of inactive RA patients with the control group ($p = 0.047$). **Conclusion.** RDW was found higher in all RA group than control, additionally was also higher in active RA group than remission group. NLR values of remission group was higher than control.

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Introduction

Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that primarily affects the joints. It typically results in warm, inflated, and painful joints [1]. The course of disease in RA is variable. Various biomarkers have been used for the prognosis and clinical follow-up [1, 2].

Red cell distribution width (RDW) is a measurement that shows heterogeneity of erythrocyte volume, a condition also known as anisocytosis. RDW has been shown in recent studies to be increased in inflammatory as well as in arteriosclerotic cardiac diseases [2].

The neutrophil to lymphocyte ratio (NLR) is usually calculated by dividing the number of neutrophils into the number of lymphocytes in peripheral blood samples; it can sometimes be obtained from infiltrated tissue cells such as tumor tissue [3, 4]. This ratio has been used as a subclinical inflammation marker for many diseases. RDW and NLR are one of the important total blood cell count parameters [1-4].

Sometimes, markers such acute phase proteins, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are insufficient to show disease activity. Acute phase proteins are insufficient to indicate a systemic inflammatory response, because they increase only as an indirect result of local inflammatory processes. In addition, ESR and CRP values can be affected by a recent infection and therefore are nonspecific for prediction of the inflammation [5-8].

However, there are few studies that have investigated whether or not NLR and RDW are good indicators of systemic inflammation. The present study aims to explore the prognostic value of RDW and NLR in RA as a new inflammatory marker.

Methods

RA patients (n = 124) who attempt to the Rheumatology outpatient clinic of our hospital between March 2015 and May 2015 were included in this study. As a first group, 47 clinically active RA patients who had high acute phase proteins were included. In the second group, 73 clinically in-remission RA patients who had normal acute phase proteins were included. Fifty-five healthy volunteers constituted the control group.

Diagnosis of RA was done according to the 2010 American College of Rheumatology (ACR)/ The European League Against Rheumatism (EULAR) classification criteria. Inclusion criteria were RA diagnosis without any infection, any other systemic inflammatory disease, trauma history, bleeding and malignancy. Biochemical, hematological, and inflammatory parameters were measured. Clinical anamnesis and complete blood parameters and derivatives, RDW and NLR values, rheumatoid factor (RF, 0-20), CRP (0-4.9 mg/L), ESR (0-20 mm/h) were obtained from the hospital data in all groups. Laboratory parameters CRP > 15 mg/L, ESR > 28 mm/h values were accepted as high inflammation together with clinical signs.

The study approved by the local ethics committee and was adhered to the principles of Helsinki declaration.

Statistical Analysis

The SPSS 16 version was used for data analysis. Descriptive data were presented as mean \pm standard deviation and median scores. The coherence of variables to normal distribution (normality) was analyzed using the Kolmogorov–Smirnov test. One-way Anova and student t tests were used to analyze normally distributed data and Kruskal Wallis test was used to compare abnormal distributed data among groups. A P value of <0.05 was considered statistically significant.

Results

Descriptive characteristics of the groups were shown in Table 1. The mean age of RA patients in the active period was 53.5 ± 13.7 years; the mean age of RA patients in the inactive period of the disease was 48.7 ± 13.61 years; the mean age of the control group was 48.3 ± 13.81 years ($p = 0.027$).

The mean RDW was found to be 15.2 ± 2.9 in the active group; 14.6 ± 2 in the inactive group and 13.4 ± 1.4 in the control group ($p < 0.01$). The mean NLR was found to be 3.7 ± 2.2 in the active group; 3.7 ± 1.6 in the inactive group and 3.2 ± 0.9 in the control group ($p = 0.190$).

There were statistically significant differences between the RDW values of the active-period RA patients with the control group ($p < 0.01$) (Figure 1)

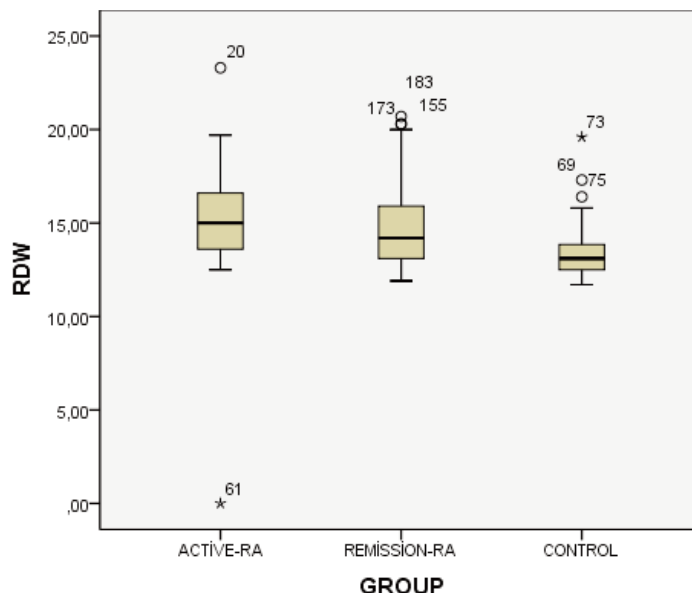


Figure 1. Boxplot of red cell distribution width (RDW) values among the groups.

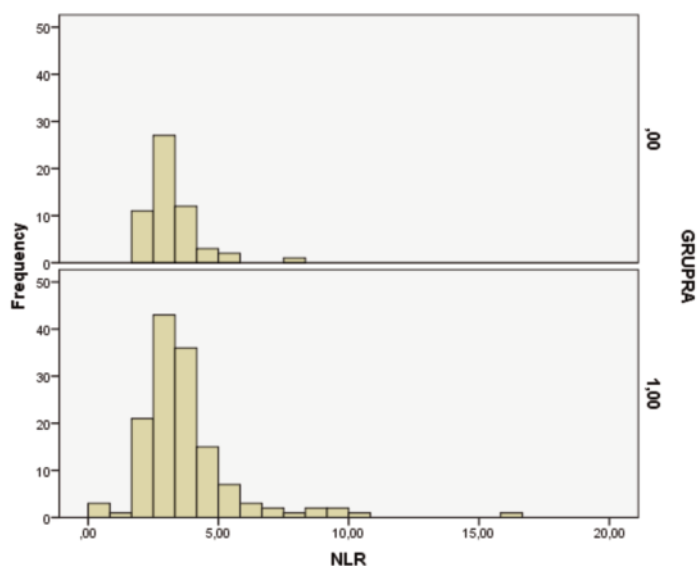


Figure 2. Histogram of neutrophil-lymphocyte Ratio (NLR) values between rheumatoid arthritis (number 1) and control (number 0) groups.

Table 1. Characteristics of demographic and laboratory data

	Active RA (n = 47)	Inactive RA (n = 73)	Control (n = 55)	p value
Age (year)	53.5 ± 13.7	48.7 ± 13.61	48.3 ± 13.81	0.027
Gender (M/F)	9/52	13/64	13/43	0.47
Sedimentation (mm/h)	49.51 ± 13.4	20.00 ± 9.30	17.38 ± 9.05	< 0.01
CRP (mg/dL)	2.22 ± 2.9	0.52 ± 0.28	0.39 ± 0.22	0.02
Leukocyte (×10 ³)	7.68 ± 1.7	7.75 ± 2.42	7.45 ± 1.93	0.370
Erythrocyte (×10 ³)	4.73 ± 0.4	4.8 ± 0.40	4.92 ± 0.47	0.270
Thrombocyte (K/mm ³)	297.0 ± 65.0	268.8 ± 49.4	263.49 ± 53.80	0.110
Hemoglobin (gr/dL)	13.06 ± 1.26	13.55 ± 1.12	14.06 ± 1.70	< 0.01
Lymphocyte (×10 ³)	2.16 ± 0.67	2.3 ± 0.89	2.34 ± 0.64	0.570
Monocyte (×10 ³)	0.67 ± 0.23	0.62 ± 0.21	0.52 ± 0.19	0.870
Basophil (×10 ³)	0.05 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.080
Eosinophil (×10 ³)	0.14 ± 0.09	0.18 ± 0.13	0.17 ± 0.11	0.370
RDW (%)	15.2 ± 2.9	14.6 ± 2	13.4 ± 1.4	< 0.01
NLR (%)	3.7 ± 2.2	3.7 ± 1.6	3.2 ± 0.9	0.190

Data are shown as mean ± standard deviation. CRP = C- reactive protein (CRP), NLR = neutrophil-lymphocyte ratio, RA = rheumatoid arthritis, RDW = red cell distribution width

Table 2. Comparisons of RF presence with RDW/NLR

	RF negative RA (n = 60)	RF positive RA (n = 64)
RDW		$p = 0.041$
NLR		$p = 0.260$

NLR = neutrophil-lymphocyte ratio, RA = rheumatoid arthritis
RF = rheumatoid factor, RDW = red cell distribution width

(Table 1). There was statistically significant difference between RDW values of active RA and inactive RA patients ($p < 0.01$).

The NLR results between the RA group and the control group ($p = 0.700$); the active RA group, and the inactive RA group ($p = 0.169$) were similar. There was not statistically difference between the NLR values of active RA patients with the control group ($p = 0.360$). There was statistically difference between the NLR values of inactive RA patients with the control group ($p = 0.047$).

When we divide our RA patients into two groups on the bases of RF-positive and RF-negative, statistically difference was found in RDW values between the groups ($p = 0.041$) (Table 2) (Figure 2).

Discussion

RA is a chronic autoimmune disease that is characterized by widespread synovitis results in joint damage and erosion in the articular cartilage and marginal bone [1]. RA pathophysiology shares the common cascades with atherosclerosis, including endothelial dysfunction related to the underlying chronic inflammation [5].

At the onset of the disease, many patients are negative for the rheumatoid factor (RF), but 85% of the patients will show positivity in the course of disease. High RF levels indicate destructive joint disease. In recent years, many laboratory tests specific to disease monitoring have been developed in RA [9].

RDW is a quantitative measurement that shows the volume heterogeneity of red blood cells and RDW has been used in differential diagnosis of anemia. Many studies have shown that RDW, also called anisocytosis, increases during systemic inflammation or the cardiometabolic effect [6, 7]. In addition to differential diagnosis of anemia, recent evidence shows that anisocytosis is an important indication for cancer, cardiovascular disease, venous thromboembolism, diabetes, community-acquired pneumonia, chronic obstructive pulmonary disease,

kidney and liver failure, and other acute and chronic illness [10, 11].

It is a well-known fact that red blood cell life is approximately 120 days, and rapid changes in RDW values are more powerful for predicting chronic inflammation in RA patients with acute infections as compared with ESR and CRP levels. Many studies have found RDW to be positively correlated with CRP and ESR [12-14].

In the study by Baynes *et al.* [15], which evaluated hematological parameters of 265 RA patients, measurements of iron-related RDW of RA patients were studied. In all study groups, a slight decrease in hemoglobin and mean corpuscular volume (MCV) values were found to be related to an increase in RDW, ESR, and platelet levels. In another study by Hassan *et al.* [16], RDW level was found to be a useful parameter to show inflammation and high risk of progress. A high level of RDW also had a strong and independent correlation with ESR and CRP in systemic lupus erythematosus [17, 18], Sjögren syndrome [19], systemic sclerosis [20], and familial mediterranean fever [21] patients in recent studies. RDW has also been found to be related to cardiovascular disease in various diseases [22].

High numbers of neutrophils are mostly associated with poor prognosis and an increased mortality rate. In recent years, studies that addressed the relation between inflammation and neutrophils subtypes have shown an increasing trend. It has been reported that the NLR value increases in response to activity in various inflammatory diseases [22-26]. However, the clinical importance of these values for evaluating RA progression remains unclear. In the study by Mercan *et al.* [23], NLR was shown to be an inexpensive and easily measurable method for evaluating the disease activity in patients with RA and AS. According to the study by Fu *et al.* [24], the NLR is found positively correlated with ESR, CRP, and disease activity score (DAS 28) values in RA patients. Uslu *et al.* [25] have reported that NLR and the platelet-lymphocyte ratio (PLR) values showed a positive correlation in RA patients. Another study by Tekeoglu *et al.* [26] also showed that mean platelet volume (MPV) and NLR values change according to activity level of the disease.

The NLR has also been used as a marker for various systemic autoimmune diseases such as ankylosing spondylitis [27], familial mediterranean fever [21, 28], Behçet syndrome [29], Sjögren syndrome [19], systemic lupus erythematosus [30],

and psoriasis [31]. In recent years, complete blood parameters and derivatives are guiding us in showing the severity of diseases especially in inflammatory rheumatic diseases [32-34].

In this study, statistically significant differences of RDW values among the three groups have led us to think that the RDW might be positively related to inflammation and also to ESR and CRP values. ESR and CRP values were used to separate the two groups of RA patients. Those two parameters sometimes are not able to diagnose active disease, in half of active RA patients these parameters may be found normal. They are also affected by the infection. On the other hand, RDW values of both RA groups were found higher compared with those of the control group. This indicates that RDW can be used as an inflammation marker, both in diagnosis and clinical follow-up.

When RA patients were separated into two groups as RF positive and negative, it was observed that the RDW value was higher in positive group. According to that result, we can conclude that RDW might be used as a biomarker for determining the severity of the disease.

We compared the values of NLR among all three groups. We only found a statistically difference between the NLR values of remission period-RA patients with control group. In the light of this result, we may say that NLR may show chronic inflammation. We should also conclude that there could be other factors that affect NLR. In elderly patients who are in an active period of the disease may be seen as normal in laboratory and it may have affected the results of the study. Additionally, NLR was not found to be related with the RF. In young patients at an early stage of the disease, the positivity of RF is 15%, which is independent of disease progression; it becomes positive over time. These younger patients could have affected the results of the study.

The Limitations of the Study

One of the limitation of our study is having a small sample size due to low prevalence of the disease. Additionally as it is a retrospective study, we could not calculate DAS 28 score because most of the patients' visual analogous score (VAS), number of tender and swollen joints and duration of morning stiffness were not found in the hospital data. In most of RA patients chronic anemia is observed over time. But we didn't consider the hemoglobin, vitamin B12, and folic acid values that may affect the RDW values.

Conclusions

According to our study; RDW was found higher in all RA group than control, additionally was also higher in active RA group than remission group. NLR values of remission-RA group was found higher than control. Biomarkers that measures the activity of RA disease is a rapidly growing field in recent years. RDW and NLR biomarkers might contribute as a potential marker to detect diagnosis and disease activity in RA patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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