

# Romatoit Artritte Hastalık Aktivitesinin Nötrofil Lenfosit Oranı ve Ortalama Trombosit Hacmi ile İlişkisi

## Relation of Disease Severity with Mean Platelet Volume and Neutrophil Lymphocyte Ratio in Rheumatoid Arthritis

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### Öz

**Amaç:** Romatoid Artrit (RA), simetrik eroziv sinovit ile karakterize, kronik sistemik inflamatuvar bir hastalıktır. Nötrofil lenfosit oranı (NLO) ve ortalama trombosit hacmi (OTH) ise inflamasyonun şiddetini belirlemek için kullanılan yeni belirteçlerdir. Biz bu çalışma ile RA'de hastalık aktivitesi ile NLO ve OTH değerleri arasındaki ilişkiyi ortaya koymayı amaçladık.

**Gereç ve Yöntemler:** Bu retrospektif çalışma Mart 2012 ile Mart 2013 arasında yapıldı. Çalışmaya toplam 156 RA hastası dahil edildi.

**Bulgular:** NLO aktif hastalık grubunda remisyon grubuna göre daha yüksekti, ancak remisyon grubu ile aktif hastalık grubu arasında anlamlı fark yoktu (p: 0.616). Düşük hastalık aktivitesi grubunda, orta derecede hastalık aktivitesi grubunda ve yüksek hastalık aktivite grubunda NLO sırasıyla  $1.98 \pm 0.71$ ,  $2.26 \pm 1.04$  ve  $3.11 \pm 2.16$  idi. Karşılaştırılan gruplar arasında istatistiksel olarak anlamlı fark mevcuttu (p: 0.030). Remisyon grubu ve aktif hastalık grubunun OTH değerleri sırasıyla  $8.54 \pm 0.78$  ve  $8.89 \pm 0.99$  fl idi ve gruplar arasında anlamlı fark yoktu (p: 0.126). Ayrıca remisyon grubu, düşük hastalık aktivite grubu, orta hastalık aktivite grubu ve yüksek hastalık aktivite grubunda OTH sırasıyla  $9.31 \pm 1.09$ ,  $8.91 \pm 0.98$ ,  $8.71 \pm 0.97$  fl idi. Daha yüksek hastalık aktivitesi olan hastalarda OTH azalmasına rağmen, gruplar arasında anlamlı fark mevcut değildi (p: 0.206).

**Sonuç:** NLO, RA hastalarında hastalık aktivitesini değerlendirmek için faydalı bir belirteçtir. Artan NLO değerleri artmış hastalık aktivitesine işaret eder. Fakat OTH değerlerinin RA hastalarında hastalık aktivite göstergesi olarak kullanılabilmesi için daha kapsamlı çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Nötrofil lenfosit Oranı, Ortalama Trombosit Hacmi, Romatoid Artrit

### Abstract

**Objective:** Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by symmetrical erosive synovitis. The neutrophil to lymphocyte ratio (NLR) and mean platelet volume (MPV) have been widely used to determine the severity of inflammation. Objectives: We aimed to investigate NLR and MPV values in RA population further assessing the relation between these indices, inflammatory markers and disease activity scores.

**Material and Methods:** The present study was performed between March 2012 and March 2013, and designed retrospectively. Total 156 patients of RA were included.

**Results:** The NLR was higher in active disease group but there was not significant difference between the remission group and active disease group (p: 0.616). Also NLR of low disease activity group, moderate disease activity group and high disease activity group were  $1.98 \pm 0.71$ ,  $2.26 \pm 1.04$ , and  $3.11 \pm 2.16$  respectively. There is significant difference between groups (p: 0.030). The MPV of remission group and active disease group were  $8.54 \pm 0.78$  fl and  $8.89 \pm 0.99$  fl, respectively and there is no significant difference between both groups (p: 0.126). Also the MPV of remission group, low disease activity group, moderate disease activity group and high disease activity group were  $9.31 \pm 1.09$  fl,  $8.91 \pm 0.98$  fl,  $8.71 \pm 0.97$  fl, respectively. Although MPV is reduced in patients with higher disease activity, it was found that there was no significant difference between the groups (p: 0.206).

**Conclusions:** NLR can be a useful marker to assess disease activity in RA patients. Increased NLR values may indicate increased disease activity. Whereas, there is a need for comprehensive studies to claim that average platelet volume as an indicator of disease severity in RA patients.

**Key Words:** Neutrophil Lymphocyte Ratio, Mean Platelet Volume, Rheumatoid Arthritis

### INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by symmetrical erosive synovitis. It can be seen in all races and ethnic groups. Rheumatoid arthritis can cause widespread and permanent sequelae and morbidity, if not treated at an early stage(1). Previous studies have shown that rheumatoid arthritis is closely related to prolonged inflammation and inflammation markers such as and C-reactive protein (CRP), sedimentation rate (2, 3).

Simple and easily available parameters such as neutrophil-lymphocyte ratio (NLR) and mean platelet volume (MPV) obtained from hemogram results are used to demonstrate the prevalence of inflammation in conditions such as cardiovascular diseases, malignancies, diabetes mellitus, hypertension and auto-inflammatory diseases (4-8). Unfortunately, studies on NLR in rheumatoid arthritis, a disease characterized by diffuse inflammation, are limited. In the studies investigating the relationship between MPV and rheumatoid arthritis, the reported results are conflicting (9,10).

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**Geliş Tarihi** : 15.01.2019

**Kabul Tarihi** : 15.04.2019

In this study, we aimed to determine the relationship between disease activity scores, which are the indications of disease activity, inflammatory parameters and inflammatory indicators such as NLR and MPV.

## MATERIAL AND METHODS

### Study Population

Between March 2012 and March 2013, 156 rheumatoid arthritis patients, admitted to Dışkapı Yıldırım Beyazıt Training and Research Hospital Internal Medicine and Rheumatology polyclinics, were retrospectively analyzed. American College of Rheumatology criteria were used for the diagnosis of rheumatoid arthritis (11). Patients with coronary artery disease, chronic renal failure, thyroid disease, hepatic insufficiency, active infection with inflammatory disease other than rheumatoid arthritis and patients with a history of trauma and/or surgery in the last 6 months were excluded from the study. The study was reviewed and approved by the Ethics committee of the Dışkapı Yıldırım Beyazıt Research and Training Hospital (decision no. 17/18 of 3 November 2014) and informed consent was obtained from patients.

All patients underwent a detailed physical examination. Disease activity score (DAS28-ESR) including 28 joints was used to determine disease activity. DAS28-ESR is a scoring system in which the patient's delicate and swollen joint count and global health score are calculated with the sedimentation value (11).

The DAS28-ESR scores below 2.6 were considered as remission, 2.6-3.2 as low disease activity, 3.21-5.1 as middle disease activity and over 5.1 values as high disease activity (12).

Blood samples were taken after 12 hours of fasting. Leukocyte, neutrophil, NLR, MPV and sedimentation were obtained by routine laboratory methods. Blood samples were taken into citrate tubes in order to avoid EDTA-induced changes in platelet volume (12). NLR and MPV were obtained by simple mathematical methods from the same hemogram.

### Statistical Analysis

SPSS statistics program (SPSS for Windows 16.0, Inc., Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to test the normal distribution of data. Spearman or Pearson correlation was used to investigate the correlation between MPV, NLR, and demographic and laboratory data. The comparison of the groups was done by t-test. Standard deviation was used to express the average.  $p < 0.05$  values were considered statistically significant.

## RESULTS

This study was performed retrospectively between March 2012 and March 2013. The study included a total of 156 patients (137 female (87.7%) and 19 male (12.2%)) with rheumatoid arthritis who met the study criteria. The mean age of the patients was  $52.15 \pm 12.35$  years (18-85

years).

Mean neutrophil, lymphocyte count and mean platelet volume were  $4.52 \pm 1.87 \cdot 10^3 / \mu\text{L}$ ,  $2.21 \pm 0.88 \cdot 10^3 / \mu\text{L}$  and  $8.84 \pm 0.96 \text{ fL}$ , respectively.

Demographic data of the patients and their classification according to <sup>1</sup>DAS28-ESR scores are summarized in Table 1 and Table 2.

A total of 135 patients (F: M = 13: 2) had active disease (DAS28-ESR $\geq$ 2.6). 38 patients (F:M = 5: 1) showed high disease activity (DAS28-ESR $>$  5.1), 82 patients (F:M = 13: 1) showed moderate disease activity (DAS28-ESR $>$  3.2 and 5.1) and 15 patients (F:M=12:1) showed low disease activity. According to DAS28-ESR scores, 21 patients (F:M = 5:2) were in remission (DAS28-ESR  $<$ 2.6).

In the remission group, NLR was  $2.30 \pm 0.30$  and in the active disease group, NLR was  $2.47 \pm 0.13$ . Although NLR was higher in the active disease group than the remission group, this difference was not statistically significant ( $p: 0.616$ ). NLR was  $1.98 \pm 0.71$ ,  $2.26 \pm 1.04$ , and  $3.11 \pm 2.16$  in patients with low disease activity, moderate disease activity and high disease activity, respectively. There was a statistically significant difference between the groups in terms of NLR ( $p: 0.030$ ).

In our study, we also investigated the relationship between disease activity and MPV in rheumatoid arthritis. In the remission group and active disease group, MPV was  $8.54 \pm 0.78 \text{ fl}$  and  $8.89 \pm 0.99 \text{ fl}$ , respectively. Although the MPV was higher in the active disease group, this difference was not significant ( $p: 0.126$ ). In patients with low disease activity, moderate disease activity and high disease activity, MPV was  $9.31 \pm 1.09 \text{ fl}$ ,  $8.91 \pm 0.98 \text{ fl}$ ,  $8.71 \pm 0.97 \text{ fl}$ , respectively. Although the MPV was higher in patients with lower disease activity, there was no significant difference between the groups ( $p: 0.206$ ).

There was a positive correlation between DAS28-ESR scores and NLR in patients with active disease ( $r: 0.306$ ,  $p: 0.001$ ), but no correlation was found between DAS28-ESR scores and MPV ( $r: -0.151$ ,  $p: 0.08$ ) (Table 3).

## DISCUSSION

In this study, we investigated the relationship between disease activity and NLR and MPV in 156 patients with rheumatoid arthritis determined by DAS28-ESR score. Our results showed that there was a positive correlation between NLR and DAS28-ESR scores in patients with active rheumatoid arthritis. It has been shown that neutrophil lymphocyte ratio, which is a simple, inexpensive and reproducible test result obtained from hemogram results, is an indicator of systemic inflammation in many diseases (13-15) and is closely related to the disease activity markers in inflammatory diseases (16-21).

Mercan et al., Fu H. et al. and Chandrashekara et al. showed that NLR was higher in patients with rheumatoid arthritis compared to patients in remission and correlated with disease activity (16,21,22). Our results are similar to these three studies. At the same time, when we classified patients according to DAS28-ESR scores, we found

Table I: Comparison of demographic and clinical variables among <sup>1</sup>DAS28-ESR groups in rheumatoid arthritis patients

	DAS28-ESR groups		P-value
	DAS28-ESR<2.6	DAS28-ESR≥2.6	
	n: 21	n: 135	
Age	50.19 ± 10.36	52.48 ± 12.64	0,31
Gender (F:M) <sup>2</sup>	5:2	13:2	
C-reactive protein, mg/L	8.26 ± 9.96	19.46 ± 29.72	0.02
Erythrocyte sedimentation rate, mm/h	22.10 ± 11.80	42.60 ± 21.40	0.01
Neutrophil to lymphocyte ratio	2.30 ± 0.30	2.47 ± 0.13	0.616
Main platelet volume, <sup>3</sup> fl	8.54 ± 0.78	8.89 ± 0.98	0.126

<sup>1</sup>DAS28-ESR: disease activity score with erythrocyte sedimentation rate, <sup>2</sup>F: female, M: Male, <sup>3</sup>fl: femtolitre

Table II: Comparison of demographic and clinical variables among DAS28-ESR groups in rheumatoid arthritis patients

<sup>1</sup> DAS28-ESR groups	P-value				
	DAS28-ESR<2.6 (Remission) n: 21	DAS28-ESR≥2.6 and ≤3.2 (Low Disease Activity) n: 15	DAS28-ESR >3.2 and ≤5.1 (Moderate Disease Activity) n: 87	DAS28-ESR>5.1 (High Disease Activity) n: 38	
Age	50.2 ± 10.36	46.69 ± 10.42	52.32 ± 12.19	54.82 ± 13.89	0.10
Gender (F:M) <sup>2</sup>	5:2	12:1	13:1	5:1	0.07
C-reactive protein, mg/L	8.26 ± 9.96	9.58 ± 10.42	14.41 ± 20.50	34.03 ± 43.72	0.01
Erythrocyte sedimentation rate, mm/h	22.10 ± 11.80	33.54 ± 21.93	37.79 ± 17.26	56.37 ± 23.63	0.01
Neutrophil to lymphocyte ratio		1.98±0.71	2.26±1.04	2.26±1.04	0.030
Main platelet volume, <sup>3</sup> fl		9.31±1.09	8.91±0.98	8.71±0.97	0.206

<sup>1</sup>DAS28-ESR: disease activity score with erythrocyte sedimentation rate, <sup>2</sup>F: female, M: Male, <sup>3</sup>fl: femtolitre

Table III: The correlation between NLR and MPV according to DAS28-ESR

	r	p
DAS28-ESR/NLR <sup>1</sup>	0.306	0.001
DAS28-ESR/MPV <sup>2</sup>	-0.151	0.080

<sup>1</sup>NLR: Neutrophil lymphocyte ratio, <sup>2</sup>MPV: Main Platelet Volume

statistically significant difference in NLR in patients with low disease activity, moderate disease activity and high disease activity. Although Chandrashekar et al reported similar results, they used DAS-CRP instead of DAS-ESR to classify patients, unlike our study.

Neutrophilia, caused when the neutrophils on the vascular wall get into the blood circulation in rheumatoid arthritis progression, and tendency to lymphopenia, due to endogenous steroids increasing in rheumatoid arthritis progression, are well known clinical conditions. We think that this mechanism is the main reason for the correlation

between NLR and rheumatoid arthritis activity.

Also in this study, we tried to reveal the relationship between MPV and patients with rheumatoid arthritis. Although we found decreased MPV in subjects with high disease activity, this difference was not statistically significant and was not correlated with disease activity. Small sample size and cross-sectional study plan may have caused this. Conflicting results of systemic inflammation and MPV were reported. In 2011, Gasparyan et al. reported that low inflammation and various risk factors resulted in decreased platelet volume (23). However, Yazıcı et al. (9) and Talukdar et al. (24) reported that disease activity and inflammatory markers correlated positively with MPV in patients with rheumatoid arthritis. Kısacık et al. reported that patients with rheumatoid arthritis had lower MPV during active disease and increased platelet volume with treatment (25). It is claimed that relatively large and active platelets are accumulated in regions such as joints where inflammation is more dense, and that there is a relatively low volume of platelets remaining, so MPV is measured low (23).

To the best of our knowledge, our study is one of the rare studies comparing disease activity classified according to DAS28-ESR scores with MPV. Although MPV was lower in patients with high disease activity, this difference was not significant. Anti-coagulation of blood samples, ambient temperature, time to analysis and drugs such as corticosteroids may have affected MPV.

Small sample size and cross-sectional study design were the limitations of our study. Moreover, since the study was conducted only in Turkish population, the results could be affected by racial differences.

As a result, according to our experience in this study; NLR is a useful marker for evaluating disease activity in RA patients. Increased NLR values indicate increased disease activity. However, more comprehensive studies are needed to be able to use MPV values as indicators of disease activity in RA patients.

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