

# Evaluation of mean platelet volume and neutrophil to lymphocyte ratio as a diagnostic indicator in patients with recurrent aphthous stomatitis

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## Abstract

**Objective:** Recurrent aphthous stomatitis (RAS) is a chronic inflammatory disease of oral mucosa characterized by recurrent painful ulcers. Despite it is a condition seen frequently, its etiology and pathogenesis are not known fully. Its etiology is reportedly idiopathic or multifactorial. Mean platelet volume (MPV) indicates thrombocytic activation, while neutrophil/lymphocyte rate (NLR) is an indicator of chronic inflammation, and both of them can be measured during routine whole blood analysis. The aim of this study is to investigate MPV and NLR values in patients with RAS and the control group.

**Methods:** A total of 39 patients with RAS and 34 control subjects were included in the study.

**Results:** When the patient and the control groups were compared, MPV, ESR, CRP and vitamin B12 values were significantly higher in the patient group while NLR, WBC, hemoglobin, neutrophil and lymphocyte values were not significantly different between both groups.

**Conclusion:** It was shown that MPV can be used as a diagnostic indicator in patients with RAS.

**Keywords:** Recurrent aphthous stomatitis, mean platelet volume, neutrophil/lymphocyte ratio.

## Özet: Rekürren aftöz stomatitli hastalarda bir tanı indikatörü olarak ortalama trombosit hacmi ve nötrofil/lenfosit oranının değerlendirilmesi

**Amaç:** Rekürren aftöz stomatit (RAS) oral mukozanın tekrarlayan, ağrılı ülserlerle karakterize, kronik inflamatuvar bir hastalıdır. Sık görülen bir durum olmasına karşın etyolojisi ve patogenezi tam olarak bilinmemektedir. Etyolojisinin idiyopatik veya multifaktöryel olduğu belirtilmektedir. Ortalama trombosit hacmi (MPV) trombosit aktivasyonunu gösteren, nötrofil lenfosit oranı (NLR) ise kronik inflamasyon göstergesi olan ve her ikisi de rutin tam kan tetkiklerinde ölçülebilen değerlerdir. Bu çalışmanın amacı RAS'lı ve kontrol grubu hastalardaki MPV ve NLR değerlerini araştırmaktır.

**Yöntem:** Bu çalışmaya 39 RAS'lı bulunan ve 34 kontrol grubu hasta dahil edildi.

**Bulgular:** Hasta ve kontrol grubu karşılaştırıldığında MPV, ESR, CRP, vitamin B12 değerlerinin hasta grubunda kontrol grubuna göre anlamlı derecede yüksek çıktı ve NLR, WBC, hemoglobin, nötrofil, lenfosit değerleri arasında her iki grup arasında anlamlı fark bulunmadı.

**Sonuç:** Ortalama trombosit hacminin, RAS'lı hastalarda tanısal bir gösterge olabileceği ortaya konuldu.

**Anahtar sözcükler:** Rekürren aftöz stomatit, ortalama trombosit hacmi, nötrofil lenfosit oranı.

Recurrent aphthous stomatitis (RAS) is an inflammatory disease of the oral mucosa characterized by painful, multiple, well-defined lesions with a necrotic center surrounded by erythematous halo, observed especially in children and adolescents.<sup>[1]</sup> The etiopathogenesis of RAS is not fully known, but is accepted as idiopathic or multifactorial. Among etiological factors genetic, immunological, hor-

monal, nutritional or hematological deficiencies and some environmental causes (trauma, stress, medications, and microorganisms) are blamed.<sup>[1-3]</sup>

Mean platelet volume (MPV) in full blood counts provides information on the size and activity of platelets and is evaluated as a marker of platelet dysfunction. Larger platelets are more active and prone to aggregation and

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thus are thought to perhaps cause endothelial dysfunction.<sup>[4]</sup> MPV correlates well with platelet function and activation and is stated to be an indicator of inflammation in chronic diseases.<sup>[5-7]</sup> Neutrophil to lymphocyte ratio (NLR), like MPV, can be determined in full blood counts. NLR is used as a marker of systemic inflammation.<sup>[8]</sup> The relationship of NLR with diseases progressing with chronic inflammation such as cardiovascular diseases, malignancy, ulcerative colitis and hepatic cirrhosis has been shown and it is stated to have prognostic importance for these diseases.<sup>[9,10]</sup>

The aim of this study is to reveal the relationship between values of MPV and NLR, used recently as indicators of inflammatory processes, in recurrent aphthous stomatitis and to investigate the correlation with some other parameters.

### Materials and Methods

Our study was completed with permission from the Clinical and Laboratory Ethics Committee of Faculty of Medicine, Abant İzzet Baysal University dated 30/04/2015 numbered 2015/22-39. All patients participating in the study were given detailed information and their written consent was obtained.

The study included a total of 73 patients who attended Dermatology and Otorhinolaryngology Clinics of İzzet Baysal Training and Research Hospital, Abant İzzet Baysal University between January 2014 and July 2015. Of these, 39 patients (13 male, 26 female) attended for at least a year, with oral aphthous ulcer complaint recurring at least 3 times per year and diagnosis of recurrent aphthous stomatitis and 34 were the patients (9 male, 25 female) of the control group.

All patients with recurrent aphthous stomatitis diagnosis were investigated for Behçet's disease. Among patients in both patient and control group, those with Behçet's disease, using medications containing iron and vitamins, with chronic diarrhea, aspirin use, diabetes mellitus, asthma, chronic obstructive pulmonary disease, peripheral and cerebral vein disease, hematological disorders, cirrhosis, portal hypertension, inflammatory bowel disease, obesity and malignancy or diseases that may cause platelet function disorders were excluded from the study. The control group comprised patients attending the Dermatology and Ear, Nose and Throat clinics of our hospital with complaints other than RAS and anemia. Exclusion criteria for the RAS group were applied to the control group.

All venous blood samples were taken between 08:00–10:00 in the morning after 12 hours starvation in EDTA blood tubes and analyses were completed within 2 hours. Blood samples of patients were measured for erythrocyte sedimentation rate, C-reactive protein (CRP), folic acid, vitamin B12 and full blood counts for white blood cells (WBC), MPV, NLR and hemoglobin (Hgb). Reference values for our laboratory are given in Table 1. Additionally in the patient group the age at first appearance of aphthous lesion, duration, and recurrence of aphthous lesion per year were recorded and history of smoking was recorded in both groups.

Statistical analyses were completed using the SPSS 16.0 program (SPSS Inc., Chicago, IL, USA). Numerical data were assessed by Kolmogorov-Smirnov test to see if they were normally distributed or not. Categorical data were expressed as frequency and percent, and numerical data were expressed as average and standard deviation. Normally distributed data were compared with Independent samples t-test and abnormally distributed data were compared with Mann Whitney-U test between control and patient group. Categorical data were compared with chi-square test between groups. The Spearman analysis was used to analyze correlation among the age at first appearance of aphthous lesion, duration, and recurrence of aphthous lesion per year in the patient group.

**Table 1.** Demographic and laboratory parameters in patients and control groups; reference values of laboratory.

	RAS (n=39)	Control (n=34)	Reference values	p value
Age	32.74±11.92	29.94±5.84	-	0.217
Mean platelet volume (MPV) (fL)	8.96±1.27	8.29±1.32	0–99.9	0.032
WBC (K/uL)	6.64±1.9	7.21±2.11	4.5–11	0.226
Neutrophil (K/uL)	4.23±1.77	4.39±1.83	1.8–7.3	0.705
Lymphocyte (K/uL)	1.89±0.46	2.05±0.69	1.1–5.1	0.244
NLR	2.12±0.65	2.26±1.02	-	0.479
Hemoglobin (Hgb) (g/dL)	13.93±1.56	13.35±2.12	11.5–17.5	0.183
Erythrocyte sedimentation rate (ESR) (mm/sa)	14 (1–37)	5.5 (1–36)	0–30	0.003*
C-reactive protein (CRP) (mg/dL)	2.2 (0.2–32.5)	0.2 (0–22)	0.01–0.5	0.000*
Vitamin B12 (pg/mL)	328 (104–1004)	287.5 (155–535)	145–914	0.033*
Folic acid (ng/mL)	8 (3–20)	5.4 (2.7–11)	3.1–19.9	0.000*

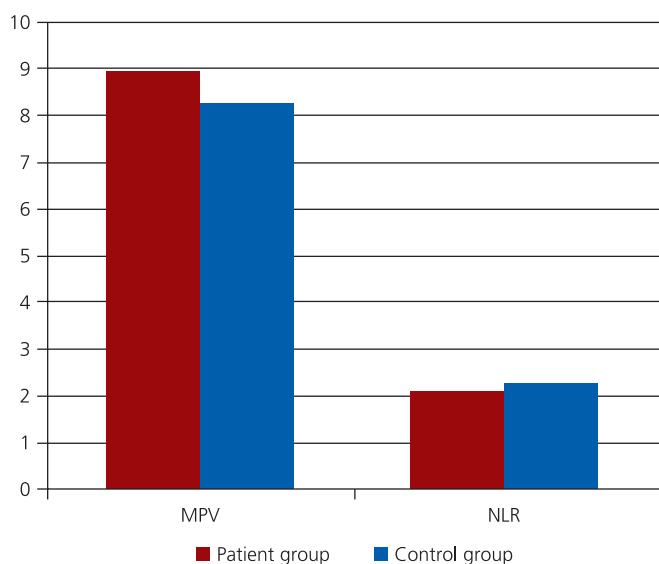
\*These values were calculated with Mann-Whitney U test and the other values were calculated with independent samples t-test.

## Results

In our study the mean age in the recurrent aphthous stomatitis group of 39 patients (13 male, 26 female) was  $32.74 \pm 11.92$  years with mean age in the control group of 34 patients (9 male, 25 female) of  $29.94 \pm 5.84$  years in a total of 73 patients. There was no statistically significant difference between the patient and control group in terms of age or sex ( $p=0.217$ ). The demographic characteristics and laboratory findings of patients are given in Table 1. According to these results, while there was a significant difference between the patient and control groups in terms of MPV, erythrocyte sedimentation rate (ESR), CRP, vitamin B12 and folic acid values, the difference in NLR, Hgb, WBC, neutrophil and lymphocyte values was not significant (Table 1). The mean values of all data with significant difference were higher in the RAS group. There were 7 patients in the patient group and 4 in the control group with a history of smoking and when examined for history of smoking the difference between the two groups was not seen to be significant ( $p=0.461$ ). The mean age at first appearance of oral aphthous lesion was calculated as  $25.28 \pm 11.97$  years. There was no correlation found between initial age of oral aphthous lesions (years), disease duration (months), and aphthous lesion incidence (number/year) and MPV and NLR values (Fig. 1).

## Discussion

Recurrent aphthous stomatitis affects 10–20% of the general population, it is more common in children and young



**Fig. 1.** Values of MPV and NLR in RAS and control group. MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio.

adults and is among the most common ulcerative mucosal diseases in the oral cavity.<sup>[11,12]</sup> Due to frequent occurrence and negative effects on the quality of life of patients, it continues to be a significant health problem. The disease has three different clinical variants described; minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers.<sup>[13]</sup> In 80–90% of RAS patients, minor aphthous ulcers are the most common clinical variant. Lesions are smaller than 1 cm, shallow ulcers that are less than 10 in number. They are common in the regions of lip mucosa, buccal mucosa and floor of the mouth. These lesions tend to heal without leaving a scar within 2 weeks. Major aphthous ulcers are more rarely observed as deep and painful ulcers larger than 1 cm. Locations are generally lips, soft palate and tonsils. Healing of ulcers may take 6 weeks and frequently leaves scars. The rarest form of herpetiform ulcers occurs as numerous small vesicular style ulcers. Ulcers are 1–2 mm in size, with a tendency to combine and form larger irregular ulcers. Generally they heal within two week without leaving a scar.<sup>[14]</sup> The etiopathogenesis of RAS is still not fully understood. However, it is thought to form due to the effect of many factors. Some researchers have proposed that RAS develops associated with an immune system function disorder. It may accompany systemic diseases such as agranulocytosis, neutropenia, inflammatory bowel disease, gluten enteropathy, B vitamin deficiencies and HIV disease and apart from these may occur with stress, trauma, iron, folic acid and B12 vitamin deficiencies.<sup>[11,12]</sup> Currently as no certain etiological factors have been found, we cannot promise curative treatment for RAS. The aim of treatment is to provide pain control, speed up healing and reduce the incidence of recurrence.<sup>[15]</sup> Biopsies taken from RAS patients have found the presence of T cells and polymorphonuclear leukocytes in lesions, leading to the consideration that these cells play a role in pathogenesis.<sup>[16]</sup> Additionally in Behçet's disease, with similar etiopathogenesis to RAS, hypersensitivity of T lymphocytes to a variety of antigens was not identified, with increased platelet and neutrophil activity was shown in blood parameters.<sup>[17–19]</sup>

Neutrophil to lymphocyte ratio has come to the agenda in recent years as an easy and practical method measured in blood that provides important information to determine diagnosis and prognosis of a variety of diseases. NLR is used as a marker of inflammation evidence in many diseases.<sup>[20]</sup> In a study by Wang et al.,<sup>[21]</sup> in patients with angiography independent of NLR, it was shown to be a predictor of mortality and cardiovascular diseases. Recently, NLR has begun to be used to measure severity of inflammation in a variety of diseases like cardiovascular diseases, malignancies and dia-

betes.<sup>[22]</sup> In a study by Demir et al.,<sup>[23]</sup> NLR was related to inflammation linked to myocardial ischemia while another study by Muhammed Suliman et al.<sup>[24]</sup> stated that NLR was an inexpensive method to show inflammation in acute coronary diseases. In our study, we did not find a significant difference between patient and control groups in terms of NLR values. The lack of significant difference in our study for this parameter, used recently to evaluate chronic inflammation evidence, may lead to the consideration that NLR cannot be shown to be a very reliable indicator of inflammation in RAS, or that it may be linked to other inflammatory processes in control group patients that we did not identify.

Mean platelet volume is a value easily evaluated in blood samples by clinicians. It correlates well to platelet function and activation and is stated to be a significant indicator of inflammation in chronic diseases.<sup>[5-7,25]</sup> The relationship between MPV and Behçet's disease was shown in a study by Acikgoz et al.<sup>[26]</sup> Immunological mechanisms play a major role in the etiopathogenesis of Behçet's and RAS diseases. Hypersensitivity of T lymphocytes to a variety of antigens plays a significant role in the pathogenesis of these diseases. Additionally, among blood parameters, Behçet's patients' platelet and neutrophil activities are shown to increase.<sup>[17-19]</sup> Evaluated as a significant marker of inflammation in chronic diseases, MPV was found to be significantly high in psoriasis patients compared to a control group with a positive relationship to psoriasis disease index score in studies by Karabudak et al.<sup>[27]</sup> and Canpolat et al.<sup>[28]</sup> on psoriasis and psoriatic arthritis patients. Unlike these studies, the study by Kisacik et al.<sup>[25]</sup> identified low MPV levels in patients with rheumatoid arthritis and ankylosing spondylitis related with high levels of inflammation. A study by Ekiz et al. on RAS and Behçet's patients showed that MPV and ESR values were significantly high in the patient group compared to the control group. They identified MPV values as an evidence of inflammation in these diseases; however, they did not find a significant difference between both diseases.<sup>[4]</sup> In our study, the MPV values were found to be high by a significant degree in the patient group compared to the control group. This supports the knowledge that MPV is an easy and cheap marker of inflammation as stated in many studies in the literature. Additionally, ESR and CRP are the acute phase reactants. CRP is thought to be an inflammatory marker and affects the development of inflammation.<sup>[29]</sup> In our study, ESR and CRP values were found to be significant higher in the RAS group compared to the control group and this supports RAS as an inflammatory process. Our study is the first to evaluate two different inflammation markers like

MPV and NLR, cheaply and easily obtained from full blood counts, together in RAS patients with a disease with chronic inflammatory characteristics. In our study, though MPV was found to be significantly high showing similar characteristics to literature studies, NLR was not found to be significant contrary to studies in the literature.

## Conclusion

Though the etiopathogenesis of RAS, common in society and negatively affecting quality of life, is not fully known, it is a chronic inflammatory disease. MPV was evaluated with the literature and shown to be a simple, easy and cheap inflammation marker for use in evaluation of these patients.

**Conflict of Interest:** No conflicts declared.

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