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Use of Red Blood Cell Distribution Width, Platelet Distribution Width, and Mean Platelet Volume Values as Diagnostic Markers in Patients with Recurrent Aphthous Stomatitis

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BACKGROUND/AIMS
To evaluate the use of red blood cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) as diagnostic markers in patients with recurrent aphthous stomatitis (RAS).

MATERIAL and METHODS
The retrospective case-control study included a patient group of 51 RAS patients a control group of 51 age- and gender-matched healthy individuals. RAS and control groups were determined as two groups. Complete blood counts were registered from patients' medical records. RDW, MPV, PDW, NLR, and PLR were recorded for each subject and were compared between the two groups.

RESULTS
Mean RDW was 15.66±2.03 in the RAS group and 14.86±1.44 in the control group (p=0.026). Mean PDW was 15.44±2.86 in the RAS group and 14.42±1.69 in the control group (p=0.032). Mean MPV was 8.82±0.87 in the RAS group and 8.42±0.56 in the control group (p=0.007). Mean NLR was 1.94±0.74 in the RAS group and 1.80±0.80 in the control group (p=0.374). Mean PLR was 119.49±36.58 in the RAS group and 121.98±32.96 in the control group (p=0.718). Only RDW, PDW, and MPV values were significantly higher in the RAS group compared to the control group.

CONCLUSION
The results indicated that both NLR and PLR cannot be considered as valuable parameters for routine diagnosis and in the prediction of prognosis in RAS patients. Increased RDW, PDW, and MPV values could have a diagnostic value in RAS patients. Accordingly, it is wise to consider that inflammation, thrombosis and acute hypoxic ischemia should be prioritized in the etiology of RAS.

Keywords: Erythrocyte, lymphocyte, mean platelet volume, neutrophil, recurrent aphthous stomatitis

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is an inflammatory disease that develops most frequently on the buccal mucosa and less frequently on the undersurface of the tongue and floor of the mouth, characterized by recurrent episodes of solitary, painful, and round or ovoid ulcers with a necrotic center surrounded by erythematous halo (1). RAS occurs in the absence of systemic diseases and typically heals within 7-10 days without scarring (2). With a prevalence ranging between 0.9-78% across countries, RAS affects almost 20% of the general population (1). RAS is the most common disease of the oral mucosa and is associated with chronic inflammation and endothelial dysfunction (1, 2), and is mostly seen children and adolescents (3).

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are peripheral blood markers of systemic inflammation, calculated simply from complete blood count (CBC) test. Additionally, mean platelet volume (MPV), red blood cell distribution width (RDW), and platelet distribution width (PDW) are also calculated from CBC test. PDW assesses variability in platelet size, changes with platelet activation, and indicates the heterogeneity in platelet morphology (4). MPV is a platelet function index used for the determination of platelet size, which directly reflects platelet function

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and activity and indirectly reflects platelet production and stimulation. Platelets play a key role in immune and/or inflammatory events (5). RDW reflects variability in red blood cell size and plays a role in the detection of false-negative mean corpuscular volume results in the assessment of morphological alterations in erythrocytes (6).

The present study aims at evaluating the use of CBC parameters including RDW, PDW, MPV, NLR, and PLR as diagnostic markers in patients with RAS. Additionally, the present study, to our knowledge, is the first of its kind to evaluate the effects of all these five parameters in RAS through a holistic approach. With this study, we aim to compare the RAS patients in the world with the conditions of such patients in our region. In RAS, it is aimed to take necessary measures in line with the underlying causes and to plan the treatments for these reasons.

MATERIAL AND METHODS

The retrospective case-control study included a RAS group of 51 patients that presented to Ear-Nose-Throat (ENT) department between October 2018 and May 2019 with at least three episodes of active RAS within the previous one year and a control group of 51 age- and gender-matched healthy volunteers. This study was accepted by Scientific Research Ethic Board. It was performed in accordance with the Helsinki Declaration.

A detailed ENT examination was performed in each patient and the patients' CBC results were retrieved from their medical records.

CBC test was performed in all subjects using a hematology analyzer (Sysmex XE-2100; Sysmex, Kobe, Japan), and the parameters including white blood count (WBC), absolute neutrophil, lymphocyte, and platelet counts, RDW, MPV, and PDW were recorded for each subject. NLR and PLR were calculated as follows: NLR=absolute neutrophil count/absolute lymphocyte count; PLR=absolute platelet count/absolute lymphocyte count.

Inclusion criteria included a history of RAS for at least two years, a diagnosis of minor or major RAS, and no history of smoking. Exclusion criteria were as follows: a known diagnosis of cardiovascular and endocrine diseases, metabolic syndrome, Behçet's disease, recurrent herpetic ulcers, malignancies, acute and chronic inflammatory diseases, vertigo, tinnitus, obesity, facial palsy, platelet and neutrophil disorders, a history of drug or alcohol abuse, and a history of drug use including steroids, oral contraceptives, aspirin, iron supplementation drugs, vitamins, and immunosuppressive drugs.

Main Points:

- NLR and PLR cannot be considered as valuable parameters for routine diagnosis and in the prediction of prognosis in RAS patients.
- Increased RDW, PDW, and MPV values could have a diagnostic value in RAS patients.
- Inflammation, thrombosis and acute hypoxic ischemia should be prioritized in the etiology of RAS.

Statistical Analysis

Data were examined using IBM Statistical Package for the Social Sciences Standard Concurrent User V 25 (IBM Corp., Armonk, NY, USA). Descriptives were expressed as frequencies, mean, and standard deviation (SD). The two groups were compared by Independent-samples t-test for parametric data. Categorical variables were evaluated using Chi-square test. The two groups were compared regarding RDW, PDW, MPV, NLR, and PLR values. P value of <0.05 was considered significant.

RESULTS

The patient group comprised 29 (56.9%) women and 22 (43.1%) men with a mean age of 44.35±15.43 years. The control group comprised 26 (51.0%) women and 25 (49.0%) men with a mean age of 46.58±17.62 years. No significant difference was found between the two groups with regard to age and gender (p>0.05) (Table 1).

Mean RDW was 15.66±2.03% in the RAS group and 14.86±1.44% in the control group (p=0.026). Mean PDW was 15.44±2.86% in the RAS group and 14.42±1.69% in the control group (p=0.032). Mean MPV was 8.82±0.87 fL in the RAS group and 8.42±0.56 fL in the control group (p=0.007). Mean NLR was 1.94±0.74 in the

TABLE I. Distribution of demographic and complete blood count values between recurrent aphthous stomatitis (RAS) and control groups (Independent sample test and chi-square test were applied between groups)

Variable	RAS Group (n=51) Mean±SD	Control Group (n=51) Mean±SD	p
Age	44.35±15.43	46.58±17.62	0.497
Gender			
Female	29 (56.9%)	26 (51%)	
Male	22 (43.1%)	25 (49%)	0.556
White Blood Cell (WBC) Count	6.96±1.99 $10^3/mm^3$	6.65±1.83 $10^3/mm^3$	0.419
Absolute Neutrophil Count	4.10±1.47 $10^3/mm^3$	3.78±1.43 $10^3/mm^3$	0.268
Absolute Lymphocyte Count	2.21±0.71 $10^3/mm^3$	2.19±0.59 $10^3/mm^3$	0.846
Absolute Platelet Count	246.92±59.36 $10^3/mm^3$	255.75±56.43 $10^3/mm^3$	0.444
Neutrophil to lymphocyte r atio (NLR)	1.94±0.74	1.80±0.80	0.374
Platelet to lymphocyte ratio (PLR)	119.49±36.58	121.98±32.96	0.718
Mean platelet volume (MPV)	8.82±0.87 fL	8.42±0.56 fL	0.007*
Red cell distribution width (RDW)	15.66±2.03%	14.86±1.44%	0.026*
Platelet distribution width (PDW)	15.44±2.86%	14.42±1.69%	0.032*

SD: Standard Deviation
* Statistically significant

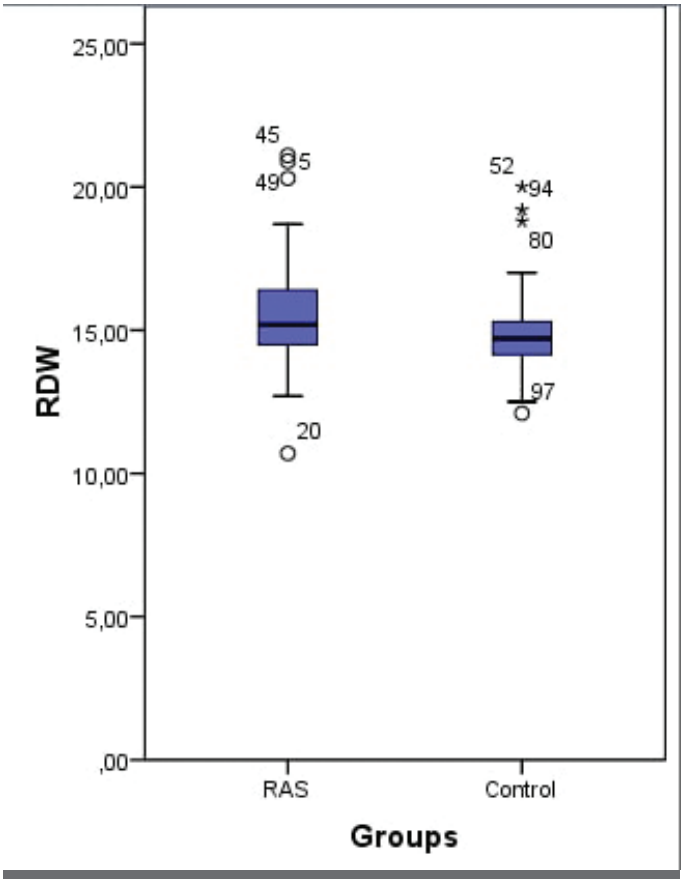

FIGURE 1. Distribution of red blood cell distribution width (RDW) values between RAS and control groups

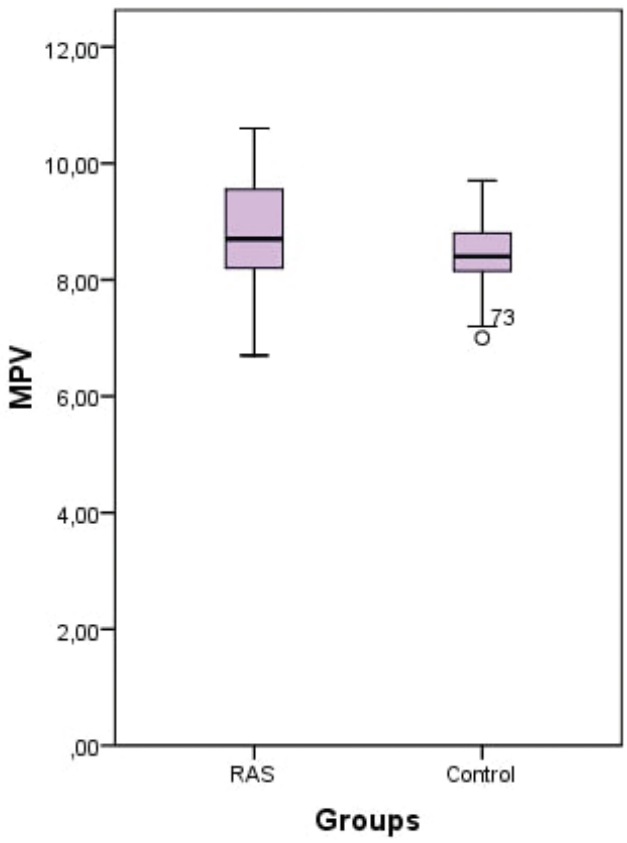

FIGURE 3. Distribution of mean platelet volume (MPV) values between RAS and control groups

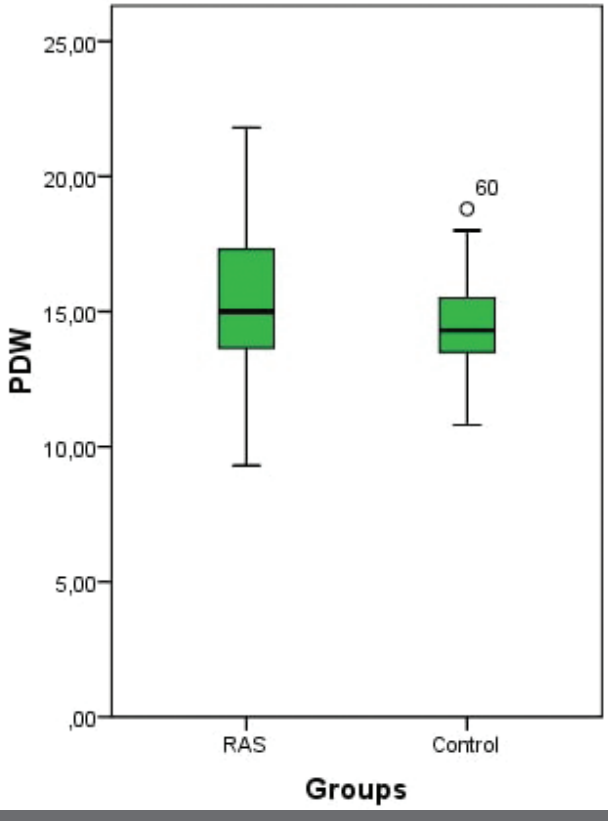

FIGURE 2. Distribution of platelet distribution width (PDW) values between RAS and control groups

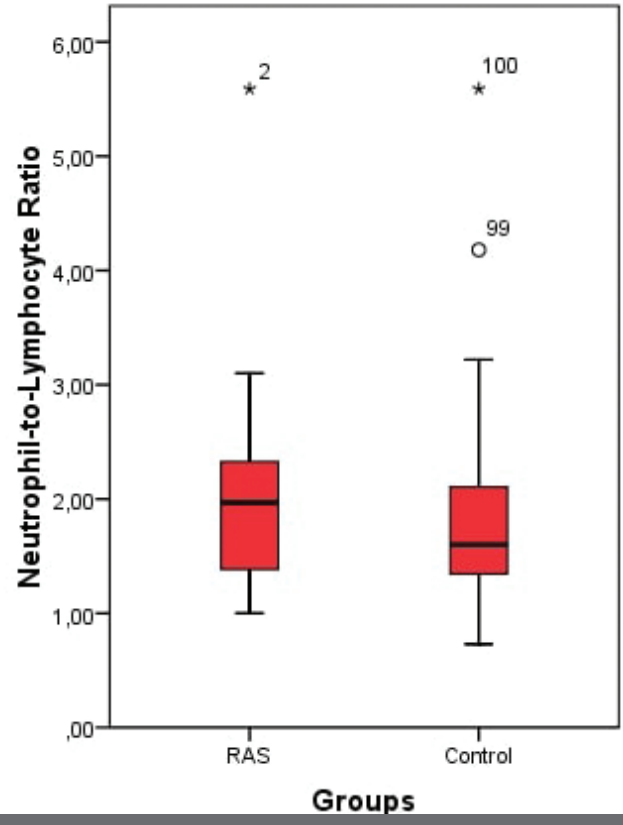

FIGURE 4. Distribution of neutrophil-to-lymphocyte ratio (NLR) values between RAS and control groups

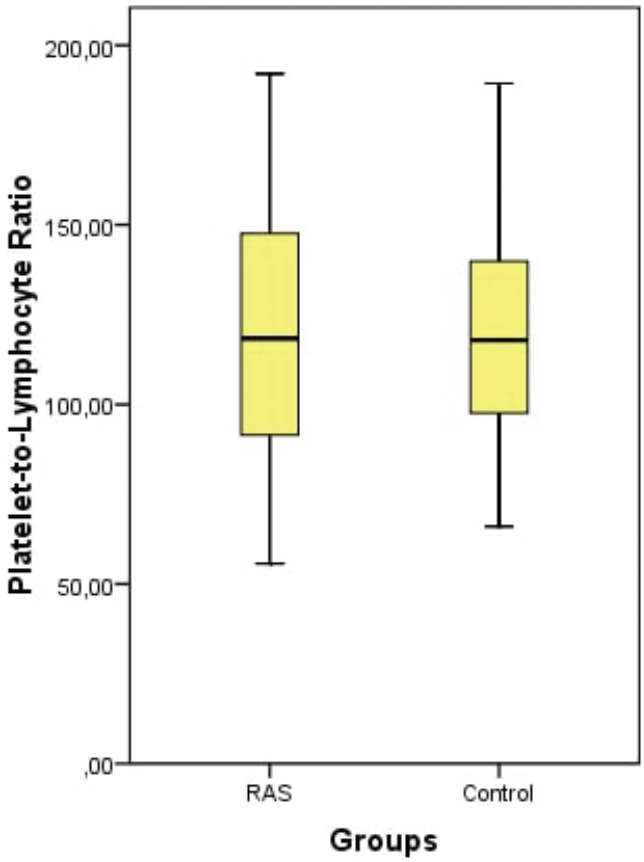

FIGURE 5. Distribution of platelet-to-lymphocyte ratio (PLR) values between RAS and control groups

RAS group and 1.80±0.80 in the control group (p=0.374). Mean PLR was 119.49±36.58 in the RAS group and 121.98±32.96 in the control group (p=0.718). The RDW, PDW, and MPV values were significantly higher in the RAS group compared to the control group (Figure 1, 2, and 3). Although NLR was significantly higher in the RAS group compared to the control group, no significant difference similar to that of PLR was found (Figure 4 and 5). On the other hand, no significant difference was found between the RAS and control groups with regard to WBC and neutrophil, lymphocyte, and platelet count (p>0.05) (Table 1).

DISCUSSION

The exact etiology and pathogenesis of RAS remains unknown although it has been attributed to chronic inflammation. The formation of RAS is multifactorial. These are positive family history, smoking cessation, immune system disorder, excessive food sensitivity, genetic, allergic, microbial factors, immunosuppressive drugs and psychological stress (1, 7). The etiology of RAS is largely unknown and racial/ethnic differences may help explain disparities in RAS presentation. The differential diagnosis of RAS includes PFAPA (Periodic fever - aphthous stomatitis-pharyngitis - adenopathy) syndrome, Behçet's disease, Crohn's disease, celiac disease, acquired immunodeficiency syndrome (AIDS), nutrition disorders, and immune and neutrophil disorders. Moreover, numerous other factors have been blamed in the formation of RAS, including relevant family history (genetic predisposition), food hypersensitivity, cessation of smoking, psychological stress, vascular abnormalities, oxidative stress, endocrine disorders, mechanical trauma, viral and bacterial infections, vitamin and mineral deficiencies, immune system disorders, and anxiety (1, 2).

RAS is typically diagnosed by family history and physical examination. However, there are no hematological or biochemical inflammatory markers used for the diagnosis of RAS. Typical histological findings of RAS include vascular dilatation, inflammatory cell infiltrate, and epithelial ulceration. RAS is classified into three types based on clinical manifestation – minor, major, and herpetiform. Of these, the minor type is the most common form detected in 80-90% of all cases, in which the lesion size is often <5 mm (8).

Both NLR and PLR are new biomarkers of subclinical inflammation that have emerged as popular markers in the determination of the severity of inflammation and the diagnosis and prognosis of various diseases (9, 10). In RAS patients, the increased production of proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-2, and IL-12 and the decreased production of antiinflammatory cytokines such as IL-10 implicate the role of inflammation in RAS (11). Additionally, NLR is a valuable diagnostic tool in the prediction of long-term mortality and poor prognosis in various malignant diseases (12).

Increased NLR has been reported in numerous clinical conditions including vascular pathologies such as ischemic cerebrovascular events and acute coronary syndrome, as well as inflammatory diseases including head and neck squamous cell carcinoma (HNSCC), sudden hearing loss, peripheral facial palsy, vertigo, ulcerative colitis, and appendicitis (12-18). Acartürk et al. (19) used NLR as an inflammatory marker for the assessment of the severity inflammatory bowel disease and found a significant correlation between NLR and disease severity. Seçkin et al. (20) evaluated CBC parameters in a total of 60 RAS patients both before and three months after the colchicine treatment and found a significant decrease in NLR, WBC, and RDW values while they found no significant change in the MPV, PLR, and hemoglobin values. Similarly, Terzi et al. (21) evaluated a cohort of 80 RAS patients and found significantly increased NLR values, which confirmed the role of inflammation in the pathogenesis of RAS. However, the authors found no significant difference with regard to PLR values between the patient and control groups.

PLR is a novel marker that reflects chronic inflammation and has been associated with atherosclerosis and peripheral arterial occlusive disease (POAD) (22). Additionally, there are some studies suggesting that PLR is a better marker than NLR in patients with soft tissue carcinomas and end-stage renal disease (23, 24). In our study, however, both NLR and PLR established no significant difference between the RAS and control groups.

MPV is an inexpensive and practical inflammatory marker of chronic diseases. Increased MPV values reflect increased platelet activation (*i.e.* platelet dysfunction), which, in turn, may aggravate inflammation. MPV has been shown to increase in various conditions including cardiovascular and cerebrovascular diseases, atherosclerosis, venous/arterial thrombosis, and thromboembolism (5). In ENT practice, increased MPV values have been reported particularly in patients with hypoxic conditions, idiopathic sudden hearing loss, and subjective tinnitus, and MPV has been shown to be a significant marker (25, 26). In

a similar way to our study, a study by Şereflican et al. suggested that MPV could be a diagnostic marker in RAS patients (3). Another study found a significant relationship between increased MPV values and Behçet's disease with thrombotic tendency while no significant relationship was established between NLR and the disease (27). Similarly, Ekiz et al. (28) found significantly increased MPV values in patients with RAS and Behçet's disease compared to healthy controls. Moreover, the authors proposed that increased MPV values can be indicative of inflammation, as was revealed in our study.

RDW is a potential marker of acute hypoxemia which can increase in anemia, hematological diseases, and myelodysplastic syndromes and may lead to peripheral microvascular diseases (29). Felker et al. (30) postulated that RDW could be an ischemic marker in the prediction of coronary artery disease and cardiac failure. Based on these notions, the present study investigated the ischemic relationship between RDW and RAS. The results indicated that RDW was significantly increased in RAS patients compared to healthy controls, thus supporting the existence of an ischemic relationship between RDW and RAS.

Ischemic and hypoxic tissues stimulate the production of reticulated platelets from bone marrow, thereby promoting platelet production, and ultimately leading to increased PDW values. The increased PDW values, in turn, may trigger thrombosis (4).

According to our knowledge, literature reviews indicate that there have never been study reporting on a relationship between RDW and PDW in RAS patients. The present study revealed that PDW was significantly increased in RAS patients. The limitations of study can be counted meticulous selection of patients and control subjects based on the exclusion criteria of the study, small sample size, and heterogeneity of the RAS group.

The results indicated that both NLR and PLR cannot be considered as valuable parameters for routine diagnosis and in the prediction of prognosis in RAS patients, and that the use of these parameters as inflammatory markers remains controversial. Nonetheless, it was revealed that increased RDW, PDW, and MPV values could have a diagnostic value in RAS patients. Accordingly, it is wise to consider that inflammation, thrombosis and acute hypoxic ischemia should be prioritized in the etiology of RAS. Future studies with larger patient series and long-term follow-ups are needed to substantiate our findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Nevsehir Hacı Bektaş Veli University Scientific Research Ethics Committee (26.04.2019/2019.06.62).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Author has no conflict of interest to declare.

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