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ORIGINAL ARTICLE

The relation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume with the presence and severity of Behçet's syndrome

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Abstract Behçet's syndrome (BS) is associated with chronic inflammation and endothelial dysfunction. Although there have been extensive investigations on neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) in many diseases, their roles in BS is unclear. The purpose of the present study was to evaluate NLR, PLR, and MPV levels in BS patients and explore their clinical significance. The study included 254 patients with BS and 173 healthy individuals. Age, sex, age of onset, duration of disease, smoking, Behçet activity score, total white blood counts, neutrophil, platelet, and T lymphocyte counts of the patients were recorded. White blood cell (WBC), neutrophil, platelet, NLR, and PLR were significantly higher in patients with BS when compared with healthy controls (all $p < 0.001$). Lymphocyte counts and MPVs of the BS group were not statistically different from healthy controls (all $p > 0.05$). In the BS group, PLR and MPV were significantly different among the three severity groups ($p = 0.037$ and $p = 0.016$, respectively). We showed that any laboratory markers were not associated with joint, eye, central nervous system, large vessel, or gastrointestinal involvement in BS. NLR was shown to be an independent factor for BS by multivariate analysis. We suggest that NLR can be considered to be a diagnostic criterion of BS given the support of the findings from larger prospective studies.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Behçet's syndrome (BS) is an inflammatory vasculitis characterized by mucocutaneous and joint manifestations, recurrent thrombophlebitis/thrombosis or deep vein thrombosis, and eye and central nervous system involvement [1]. BS is classified among vasculitides of unknown etiology and pathogenesis. BS is associated with chronic inflammation and endothelial dysfunction [2]. Laboratory tests are not useful and diagnosis is based upon clinical manifestations. Blood parameters such as neutrophils and platelet activities are increased in BS [2,3].

High neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values indicate increased inflammation [4—7]. NLR and PLR in peripheral blood are easy systemic inflammatory responses. NLR possesses diagnostic value in certain pathologies characterized by systemic or local inflammatory response such as diabetes mellitus, coronary artery disease, ulcerative colitis, and inflammatory arthritis [8,9]. PLR is a new biomarker indicating inflammation [10]. PLR is associated with bad prognosis in patients, with a key role in atherosclerosis and atherothrombosis in peripheral arterial occlusive disease patients [2]. Furthermore, PLR is thought to be a more sensitive marker and also assumed to be a prognostic factor in many malignancies [11]. Mean platelet volume (MPV) is another marker that shows platelet count and activity. The MPV has been shown to be associated with inflammation and inflammation severity [12].

According to the literature, there are only a few studies examining the relationship between NLR, MPV, and BS. But there is no study examining the relationship between PLR and BS. In this study, we aimed to compare the levels of MPV, NLR, and PLR in patients with BS and healthy controls. Also, we evaluated the association between disease activity and MPV, NLR, and PLR as well as other laboratory parameters.

Methods

Study population

The study was conducted retrospectively in the Dermatology and Venereology Department of Akdeniz University, Antalya, Turkey. The data were extracted from medical records of patients between January 2014 and December 2014. The study included 254 patients with BS. BS was based on the criteria of the International Study Group for Behçet's Syndrome (ICBS) [13]. The study included 173 non-BS patients diagnosed with pruritus in the dermatology outpatient clinic. These patients were age- and sex-matched to the cases. They did not have any dermatologic or systemic disorder. First, laboratory test results of the patients at first diagnosis with BS were recorded during the examination of the medical records of the patients. The patients were not taking any medication when the laboratory tests were performed. Through making phone calls and examination of the medical records of the patients, it was determined that: 52 patients did not take any treatment because of remission or other causes; 69 patients only used colchicine; and the remaining 133 patients took single, binary, or triple combined immunosuppressant treatment. Age, sex, age of onset, duration of disease, follow-up time, smoking, Behçet activity score, total white blood counts, neutrophil, platelet, T lymphocyte counts, and human leukocyte antigen (HLA)-B51 positivity of the patients were recorded.

Patients and control participants who had other skin diseases, inflammatory or infectious diseases, diabetes mellitus, or cardiovascular, liver, or kidney diseases were excluded from the study. Patients with BS who received colchium, azothiopurin, steroids, and other immune suppressor drugs during the previous 6 months were also excluded.

Measurements

Total white blood cell (WBC) count, neutrophil, and lymphocyte differentials were determined using an automated blood cell counter (Siemens Advia 2120 analyzer, Erlangen, Germany). Complete blood counts were measured by the method of laser-based flow cytometric impedance (BN2 Siemens). Severity score was calculated as the sum of one point for each of the mild symptoms (oral aphtosis, genital ulcer, erythema nodosum, papulopustular lesions, folliculitis, leucocytoclastic vasculitis, arthralgia, recurrent headaches, epididymitis, chronic diarrhea, chronic recurrent abdominal pain, colic, pleuritic pain, and superficial vein thrombosis). They received 2 points for each moderate symptom (arthritis, deep vein thrombosis of the legs, anterior uveitis, and gastrointestinal bleeding), and 3 points for each severe disease manifestation (posterior/pan uveitis, retinal vasculitis, arterial thrombosis or aneurysms, major vein thrombosis, neuro-Behçet, and bowel perforation). Categorization of the severity of the disease was not done according to the total score. The patient was categorized in the severe group, even if the patient experienced the severe manifestations of the disease once in their lifetime. If there were no severe findings, whereas one of the moderate manifestations was detected at a time, the patient was categorized in the moderate group. Lastly, the patients who did not have moderate or severe manifestations of the disease and had BS with only mild manifestations were considered in the mild group (Figure 1) [14]. Total scoring was only used in the correlation analysis. Scoring of the disease and blood sampling were not done simultaneously. For the blood counts, first blood test results of the patients when they had been just diagnosed with BS (e.g., 10 year old hematologic test results of the patient) were considered. But for the disease severity scale, every symptom/attack that the patient had experienced throughout his/her life was taken into consideration. The patients that were on any drugs during the blood sampling were left out of the study.

Statistical analysis

Analyses were performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean $\pm$ standard deviation (SD). Differences in the continuous variables between groups were determined by

Mild (each one 1 point)	Oral aphtosis, genital ulcer, typical skin lesions (erytema nodosum, papulopustular lesions, folliculitis leucocytoclastic vasculitis), arthralgia, recurrent headaches, epididymitis, mild gastrointestinal symptoms (chronic diarrhea, chronic recurrent abdominal pain, colic), pleuritic pain, superficial vein thrombosis.
Moderate (each one 2 points)	Arthritis, deep vein thrombosis of the legs, anterior uveitis, gastrointestinal bleeding,
Severe (each one 3 points)	Posterior/pan uveitis, retinal vasculitis, arterial thrombosis or aneurysm, large vein (vena cava, hepatic) thrombosis, neuro-Behçet, bowel perforation.

Figure1. Krause's assessment of Behçet's syndrome activity (Krause, 1999).

Student *t* test or the Mann–Whitney *U* test, for variables with or without normal distribution, respectively. To test the normal distribution, the Kolmogorov–Smirnov test was used. Categorical variables were summarized as percentages and compared with the χ^2 test. Because all continuous variables are non-normal, the Spearman correlation coefficient was computed to examine the association between two continuous variables. Because some variables are non-normal and some variables are normal the Kruskal–Wallis test and one way analysis of variance test were used to compare the three severity groups. Logistic regression analysis was also conducted to assess relationships; results are presented as odds ratios (OR) and 95% confidence intervals. Input variables of binary logistic regression were NLR, PLR, and sex. Statistical significance was defined as $p < 0.05$.

Results

Our study sample comprised 254 patients with BS and 173 healthy controls. Age and sex were similar between the groups. The comparisons among the healthy and patients groups of demographic features and laboratory findings are shown in Table 1. WBC, neutrophil, platelet, NLR, and PLR were statistically significant in patients with BS when compared with healthy controls (all $p < 0.001$; Table 1). One hundred and twenty of them were in the mild group, 66 of them in the moderate group and 68 of them were in the severe group. In the BS group, PLR and MPV were significantly different among the three severity groups. ($p = 0.037$ and $p = 0.016$, respectively; Table 2). There were no statistically significant differences between PLR and MPV of the severe and moderate groups and the moderate and mild groups. PLR and MPV of the severe group were significantly higher than the PLR and MPV of the mild group ($p = 0.032$, $p = 0.015$, respectively; independent-samples Mann–Whitney *U* test). Otherwise we showed that NLR, PLR, and MPV were not associated with joint, eye, central nervous system, large vessel, or gastrointestinal involvement in BS ($p > 0.05$; Table 3). According to Krause's scoring system, the mean severity scores of the patients with BS were detected as 5.28 ± 0.13. There were no correlation between the severity score of BS and the laboratory parameters ($p > 0.05$). Multivariate analysis found that NLR was an independent predictor for BS ($p < 0.001$, OR = 2.535; Table 4).

Discussion

The marked findings of the present study were that NLR, PLR, WBC, neutrophils, and platelets were different in the

Table 1 The demographic and laboratory characteristics of the patients with Behçet's syndrome and control groups.

	Behçet's syndrome ($n = 254$)	Control ($n = 173$)	*p*
Age (y)	42.83 ± 10.49	41.06 ± 12.31	0.150
Male/female	140/114	99/74	0.667
WBC	8.48 ± 1.72	6.69 ± 1.51	< 0.001
Neutrophil (10^3/mL)	5.72 ± 1.74	3.80 ± 1.20	< 0.001
Lymphocyte (10^3/mL)	2.01 ± 0.64	2.17 ± 0.91	0.125
Platelet (10^3/mL)	287.36 ± 70.89	253.61 ± 67.37	< 0.001
NLR	3.37 ± 2.74	1.95 ± 1.21	< 0.001
PLR	157.69 ± 73.59	127.75 ± 46.02	< 0.001
MPV	8.69 ± 1.03	8.70 ± 0.99	0.305

Data are presented as mean ± standard deviation.
MPV = mean platelet volume; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; WBC = white blood cell.

Table 2 Demographic and clinical characteristics of different severity groups in patients with Behçet's syndrome.

	Mild disease (n = 120)	Moderate disease (n = 66)	Severe disease (n = 68)	p
Age (y)	42.90 ± 9.94	44.62 ± 12.27	40.99 ± 9.30	0.689
Male/female	57/63	36/30	47/21	0.016
Follow up time (y)	5.51 ± 3.38	6.68 ± 3.32	6.13 ± 3.59	0.067
Duration of disease (y)	6.94 ± 5.92	8.91 ± 5.99	8.51 ± 5.81	0.006
Family history (+)	18/102	10/56	8/60	0.801
Current smokers	19/101	14/52	44/24	< 0.001
HLA B51 (+)	20/100	21/45	34/34	< 0.001
Hematuria (+)	19/101	10/56	16/52	0.339
Proteinuria (+)	9/111	3/63	6/62	NA[a]
WBC	8.45 ± 1.68	8.38 ± 1.67	8.63 ± 2.33	0.590
Neutrophils (10^3/mL)	5.65 ± 1.64	5.64 ± 1.89	5.92 ± 0.21	0.051
Lymphocytes (10^3/mL)	2.06 ± 0.54	2.00 ± 0.63	1.99 ± 0.68	0.080
Platelets (10^3/mL)	287.34 ± 68.65	281.66 ± 62.65	292.94 ± 82.06	0.205
NLR	3.03 ± 1.07	3.50 ± 1.12	3.82 ± 1.41	0.150
PLR	150.28 ± 71.74	156.61 ± 69.23	171.82 ± 79.75	0.037
MPV	8.59 ± 0.96	8.61 ± 1.10	8.92 ± 0.13	0.016

Data are presented as mean ± standard deviation.
MPV = mean platelet volume; NA = not applicable; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; WBC = white blood cell.
[a] Two cells (33.3%) have an expected count < 5. The minimum expected count is 4.68.

patients of BS and healthy controls. In addition, PLR and MPV were significantly higher in patients with severe BS compared with mild BS. We showed that NLR was an associated factor for the presence of BS.

Some studies claimed that NLR is a new biomarker which indicates the presence of inflammation in literature. Various studies have demonstrated the correlation between NLR and the severity of some systemic inflammatory diseases as well as coronary artery disease [4]. In the literature, Balta et al. [15] showed that the NLR, C-reactive protein (CRP), and the WBC levels were higher in patients with BS than controls. In addition, NLR was higher in patients with active BS than in those with inactive BS. Öztürk et al. [16] investigated the correlation between NLR and inflammatory activity in BS. They showed that NLR levels were significantly higher in active patients with BS than in inactive patients. Similarly, different studies demonstrated NLR as a useful marker for indicating the presence and

Table 3 Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume values in cases of different system involvements.

		NLR	PLR	MPV
Joint involvement	+	3.30 ± 2.82	155.34 ± 66.91	8.62 ± 0.99
	−	3.48 ± 2.62	161.28 ± 84.06	8.81 ± 1.10
	p	0.205	0.646	0.250
Eye involvement	+	3.81 ± 3.70	166.27 ± 83.11	8.79 ± 1.06
	−	3.11 ± 1.97	152.60 ± 67.23	8.63 ± 1.02
	p	0.241	0.225	0.078
CNS involvement	+	3.69 ± 2.01	155.40 ± 45.85	8.57 ± 1.45
	−	3.35 ± 2.76	157.78 ± 74.57	8.69 ± 1.02
	p	0.250	0.537	0.765
GIS involvement	+	3.49 ± 1.53	165.16 ± 59.64	8.75 ± 1.16
	−	3.36 ± 2.76	157.51 ± 73.99	8.69 ± 1.03
	p	0.454	0.621	0.518
Arterial/venous involvement	+	2.73 ± 1.86	100.73 ± 40.98	8.75 ± 1.34
	−	3.37 ± 2.75	158.02 ± 73.79	8.69 ± 1.04
	p	0.750	0.153	0.911
Thrombo phlebitis	+	3.44 ± 1.52	153.39 ± 52.74	8.75 ± 1.23
	−	3.36 ± 2.85	158.03 ± 73.75	8.68 ± 1.03
	p	0.165	0.751	0.591

Data are presented as mean ± standard deviation.
CNS = central nervous system; GIS = gastrointestinal system; MPV = mean platelet volume; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio.

Table 4 Binary forward stepwise logistic regression analysis of variables related to Behçet's Syndrome.

			95% CI			
	p	OR	Lower	Upper	Nagelkerk R^2	Cox–Snell R^2
NLR	<0.001	2.535	1.878	3.301		
PLR	0.323	0.998	0.992	1.003		
MPV	0.315	0.898	0.729	1.109	0.219	0.162

CI = confidence interval; MPV = mean platelet volume; NLR = neutrophil/lymphocyte ratio; OR = odds ratio; PLR = platelet/lymphocyte ratio.

prognosis of inflammatory diseases and malignancies [8,18]. Also in our study, only NLR was detected as an independent decisive factor among the laboratory parameters in BS according to the multivariate analysis. Based on this data, we believe that NLR can be a useful laboratory parameter in the diagnosis of BS. Similarly to the literature, we found that the mean NLR values of the patient group were significantly higher than the mean NLR values of the control group.

PLR is a novel biomarker which can demonstrate the presence and severity of inflammation [10]. Kokcu et al. [17] reported that the NLR, platelet count, and the PLR increased with the increasing stage of ovarian cancer. Also, they claimed that the PLR was an independent prognostic factor related to the stage of epithelial ovarian cancer. Racz et al. [18] showed that high PLR was associated with reduced recurrence-free survival in patients with gastrointestinal stromal tumors. Similarly, Azab et al. [7] reported the presence of a correlation between increased PLR and long-term mortality in patients presented with non-ST segment elevation myocardial infarction. In another study, increased PLRs were found to be associated with non-dipper state in hypertensive patients [19]. This is the first study that showed the association between PLR and a novel marker of the presence and severity of BS.

MPV has been widely used as a new marker of inflammation. Ekiz et al. [20] showed that the patients with BS and recurrent aphtous stomatitis had significantly higher MPV and erythrocyte sedimentation rate levels compared with controls. Similarly, Yazici et al. [21] found that MPV was significantly higher in patients with ankylosing spondyloarthritis and rheumatoid arthritis, and MPV reflected the activity of both diseases. Nevertheless, we did not find a significant difference in MPV levels among the patients with BS and healthy controls. Kisacik et al. [22] showed that high grade inflammation was associated with a decrease in MPV levels in the other chronic inflammatory diseases such as rheumatoid arthritis and ankylosing spondyloarthritis. Similar to this study, Açıkgöz et al. [23] demonstrated that any difference between MPV levels and disease activity was not found. On the contrary, we found a significant difference in MPV levels of different BS severity groups. Platelets are essential in hemostasis and the formation of both arterial [24] and venous thrombosis [25]. Platelet count is also a marker of host systemic inflammation [10]. The platelet count can be determined by both inherited and environmental factors [26]. In different studies, abnormal increases in platelet counts have been associated with the development of atherosclerosis, atherosclerotic heart disease, and major cardiovascular events [27]. Jensvoll et al. [28] claimed that precancer platelet count was associated with risk of symptomatic venous thromboembolism in cancer patients, but not in cancer-free individuals. Also, they showed that the combination of platelet and leukocyte counts in the upper quintiles had a synergistic effect and yielded a threefold increased risk of venous thromboembolism.

Neutrophils are actively involved in systemic and local inflammatory responses by releasing proinflammatory elements [9]. Significant roles of leukocytes and particularly neutrophils in atherogenesis and atherothrombosis are already recognized [29]. Neutrophils are the main agents responsible for tissue damage and have an intrinsic hyperactivation in BS patients [29]. Our study demonstrates that the platelet, neutrophil, and leukocyte counts are higher in patients with BS compared to healthy controls. Otherwise, we found that leukocyte and platelet counts were not associated with venous and arterial thrombosis or other systems involvement.

There are some limitations of our study. First, this is a retrospective study. Because this study was not a cohort study, the findings did not offer convincing evidence to demonstrate that PLR and MPV might be helpful as a biomarker to "predict" the severity of BS. Second, we used spot NLR, PLR, and MPV values for our analysis, rather than follow-up values. Because this study was retrospective, we couldn't use Behçet's Syndrome Current Activity Form (BSCAF) for assessing disease activity. Third, we did not perform an analysis of the prognostic value of NLR, PLR, and MPV in BS.

In light of our findings, NLR and PLR might be associated with the presence and severity of BS. We suggest that NLR can be considered to be a diagnostic criterion of Behçet's syndrome given the support of the findings from larger prospective studies.

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