ARE HEMATOLOGICAL PARAMETERS USEFUL IN THE EVALUATION OF BEHÇET'S DISEASE ?

HEMATOLOJİK PARAMETRELER, BEHÇET HASTALIĞININ DEĞERLENDİRİLMESİNDE KULLANIŞLI MIDIR ?

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ÖZET

GİRİŞ: Behçet hastalığı (BH) otoinflamatuar bir hastalıktır. Hematolojik parametreler birçok hastalıkta inflamasyon belirteci olarak araştırılmıştır. Bu çalışmanın amacı, Behçet hastalarında hemogram parametrelerini (nötrofil-lenfosit oranı, platelet-lenfosit oranı, ortalama trombosit hacmi, kırmızı kan hücresi dağılım genişliği ve trombosit dağılım genişliği) hastalık aktivitesinin bir belirteci olarak değerlendirmek ve farklı klinik bulgular ile ilişkisini tespit etmektir.

MATERYAL VE METOD: Bu tek merkezli, kesitsel çalışmaya 141 (80 erkek, 61 kadın) Behçet hastası ve 96 (51 erkek, 45 kadın) sağlıklı kontrol grubu dahil edildi. Behçet hastası ve sağlıklı kontrol gruplarında C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESR) dahil olmak üzere hematolojik ve inflamatuar parametreler incelendi. Behçet hastalarındaki hastalık aktivitesi, Behçet Hastalığı Anlık Aktivite Formu (BDCAF) kullanılarak değerlendirildi.

BULGULAR: Nötrofil-lenfosit oranı ve kırmızı kan hücresi dağılım genişliği değerleri BH grubunda sağlıklı kontrol gruplarına göre istatistiksel olarak daha yüksek bulundu. Ortalama trombosit hacmi düzeyleri BH grubunda sağlıklı kontrol gruplarına göre düşüktü. Bakılan hemogram parametreleri aktif ve inaktif hastalıkta benzerdi. Major organ tutulumu olan Behçet hastalarında Nötrofil-lenfosit oranı ve trombosit dağılım genişliği mukokutanöz gruba kıyasla istatistiksel olarak daha yüksek bulundu.

SONUÇLAR: Bu çalışma, inflamatuar göstergelerin Behçet hastalarında hastalık aktivitesi hakkında yeterli bilgi sağlayamayacağını göstermiştir. Nötrofil-lenfosit oranı ve trombosit dağılım genişliğinin ikisi de BH'da major organ tutulumu ile iyi ilişki göstermiştir. Nötrofil-lenfosit oranı üveiti olanlarda, ortalama trombosit hacmi eritema nodozumu olanlarda ve trombosit dağılım genişliği nörobehçet ve oral ülseri olan hastaları takip etmek için kullanılabilir.

Anahtar Kelimeler: *Behçet hastalığı (BD), Hematolojik parametreler, Hastalık aktivitesi*

ABSTRACT

PURPOSE: Behçet's disease (BD) is an autoinflammatory disease. Hematological indices have been investigated in many diseases as a marker of inflammation. The aim of this study was to evaluate hemogram parameters [neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), red blood cell distribution width (RDW), and platelet distribution width (PDW)] in patients with BD as a marker of disease activity and to determine associations with different clinical manifestations.

MATERIAL AND METHODS: This single-centre, cross-sectional study included 141 (80 male, 61 female) Behçet's disease (BD) patients and 96 (51 male, 45 female) healthy subjects. Hematological and inflammatory parameters including C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were examined in the BD and healthy control groups. Disease activity in the BD patients was assessed using the Behçet's Disease Current Activity Form (BDCAF).

RESULTS: The NLR and RDW levels were found to be statistically significantly higher in the BD group compared to the healthy control group. MPV levels were lower in the BD group than in the control group. The level of hemogram parameters were similar in active and inactive disease. NLR and PDW values were found to be statistically higher in the BD group with major organ involvement group compared to the mucocutaneous BD group.

CONCLUSIONS: The present study results demonstrated that inflammatory indicators may not provide enough information about disease activity in patients with BD. NLR and PDW both showed good association with major organ involvement in BD. NLR was found to be much more suitable to follow up patients with uveitis, MPV for those with erythema nodosum and PDW for neuro-Behçet and oral ulcers.

Key words: *Behçet's disease (BD), Hematological parameters, Disease activity*

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INTRODUCTION

Behçet's disease (BD) is a chronic multisystem inflammatory disease characterized by mucocutaneous and joint manifestations, recurrent thrombophlebitis/ thrombosis or deep vein thrombosis, eye and central nervous system involvement (1). Behçet's disease does not have specific laboratory findings and diagnosis is made from clinical findings. Although many studies have evaluated tests for the diagnosis and monitoring of disease activity in BD, no cytokines or biomarkers are routinely used in clinical practice.

Rheumatic inflammatory diseases cause hematological abnormalities through several immune- and non-immune-mediated mechanisms (2,3). Recent reports have concluded that the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), red blood cell distribution width (RDW), and platelet distribution width (PDW) are indicators of many diseases related with inflammatory reactions. (2,4,5)

The NLR can be calculated from the leukocyte subgroups in the complete blood count. As a consequence of lymphopenia and increased neutrophils, the NLR is increased in many inflammatory diseases (6,7). It has also been reported that NLR might have prognostic importance for some diseases (8,9).

The mean size of thrombocytes is reported in the blood count as MPV, and this can provide information about disease activity. As large platelets are more active than small ones, MPV can be used as an indicator of disease severity in many systemic inflammatory diseases (3,10). Platelet counts increase in inflammation and the P/L ratio increases. There are studies de¬monstrating that PLR can be used as a marker of systemic inflammation (11). Platelet distribution width (PDW) is a measure of the variability in platelet size, and PDW increases during platelet activation (12).

Red cell distribution width (RDW) describes red blood cell volume heterogeneity on the hemogram (13) and is known to be related with cardiovascular disease, malignancies, ulcerative colitis and autoimmune diseases (6-9).

Previous studies support the role of hemogram parameters as cheap and simple disease activity markers of endothelial activation and inflammation in many diseases. The aim of this study was to compare the levels of MPV, NLR, PLR, RDW and PDW in patients with BD and a healthy control group. Evaluations were also made of the association between disease activity and organ involvement and MPV, NLR, PLR, RDW and PDW levels.

MATERIAL AND METHODS

Patient and Controls

This cross-sectional study included 141 (80 male, 61 female) consecutive Behçet's Disease patients and 96 (51 male, 45 female) healthy control subjects who presented at the Department of Rheumatology of Ankara Numune Training and Research Hospital (Ankara, Turkey). The diagnosis of BD was made according to the International Study Group criteria. All the BD patients had no history of auto-inflammatory disease, malignancy, diabetes, infection, end-stage renal disease or hematological disorder. The control group of 96 age and gender-matched healthy subjects was selected from those who visited the Rheumatology Department for routine physical examinations. None of the control group subjects had a history of any underlying auto-immune condition, malignancy, hematological disorder or recent infection.

The study group of 141 patients with Behçet's disease, who met the inclusion criteria, were separated into two groups of active Behçet's disease and inactive Behçet's disease. The patients included in the active group had two of the following clinical findings at the time of the assessment: oral ulcers, genital ulceration, pathergy test positivity, active uveitis, papulopustular or pseudofollicular cutaneous lesions, neurological involvement and arthritis (14). Disease activity was assessed using the Behçet's Disease Clinical Activity Form (BDCAF).

Retrospective data of the clinical and laboratory characteristics of all the subjects were recorded and entered into a database. Approval for the study protocol was granted by the Institutional Review Board and Ethics Committee (Approval number: 26.06.2018 / E-18-1889) . Written informed consent was received from all the study participants.

Biochemical and Hematological Measurements

Venous blood samples were taken from the antecubital vein of patients after overnight fasting. All laboratory tests (CRP, serum glucose level, liver and kidney function tests) were analyzed in the central laboratory of the hospital. Complete blood parameters (neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet) were determined from EDTA anticoagulated tubes using an automated Coulter counter. NLR was calculated as the absolute neutrophil measurement divided by the absolute lymphocyte measurement, and PLR as the absolute platelet measurement divided by the absolute lymphocyte measurement. The Westergren method was used for ESR, and CRP was determined with the turbidimetric method. All blood samples were analysed within two hours of sampling.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS (PASW Statistics) version 18 software. Continuous variables were expressed as mean±SD, median (min-max) and categorical variables as number (n) and percentage (%). Conformity of the data to normal distribution was assessed using the Kolmogorov-

Smirnov test. The Student's t-test was used to compare the means of continuous variables and the Chi-square test was used to evaluate the differences in proportions. The Mann-Whitney U test was used for continuous variables with non-normal distribution. Numerical variables with normal distribution were compared using one-way analysis of variance (ANOVA). The comparisons of groups with data not showing normal distribution were performed with the Kruskal-Wallis test. Spearman rank correlation analysis was applied to determine the relationship between BDCAF scores, hematological and demographic parameters. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Evaluation was made of 80 (56.73%) males and 61 (43.26%) females in the BD patient group (n=141), and 51 (53.12%) males and 45 (46.87%) females in the healthy control group (n=96) ($p>0.05$). The mean age of the patients with BD and the control subjects was 36.45±8.35 years and 35.06±7.45 years, respectively. No difference was determined between the groups in terms of age and gender ($p>0.05$). From the clinical findings of BD at the time of admission, 83 (58.86%) patients were classified as active BD and 58 (41.13%) patients as inactive BD. Mucocutaneous BD was determined in 49 patients, and major organ involvement in 92. The mean duration of BD was 7 (0.08-31) years. The clinical features of the patients are given in **Table 1.**

CRP, WBC, NLR and RDW values were found to be higher in the BD group than in the healthy control group. MPV levels were lower in the BD group than in the healthy control group **(Table 2).**

CRP was statistically higher in the active BD group compared to the inactive BD group and the control group. In addition, ESR was found to be higher than that of the control group in both active and inactive BD groups, and ESR in the active BD group was higher than the inactive BD group. NLR was found to be statistically higher in the BD group compared to the healthy control group, and the NLR of the active BD and inactive BD groups were found to be similar. The PLR and PDW values were similar in all three groups **(Table 3).**

NLR and PDW were found to be statistically higher in the BD group with major organ involvement compared to the mucocutaneous BD group **(Table 4).**

Hematological indices were analyzed in respect of activity in different systems. NLR was related to eye involvement ($p<0.005$), MPV to erythema nodosum, and PDW was related to oral ulcers and neurological involvement ($p=0.006$ and $p=0.037$ respectively) **(Table 5).**

No relationship was found between hemogram parameters and disease activity. There was a positive correlation between activity and sedimentation ($r=0.227$, $p=0.016$) and CRP level ($r=0.227$, $p=0.007$).

Table 1. Sociodemographic characteristics and clinical features of patients with BD

	Numbers	Percentage (%)
Age, mean (S.D.), years	36.45±8.35	
Gender		
Male	80	56.73
Female	61	43.26
Disease duration, median (min-max), years	7 (0.08-31)	
Education		
None	3	2.1
Primary	61	43.3
Secondary	20	14.2
High school	44	31.2
University	13	9.2
Type of disease		
Major organ involvement	92	65.2
Vascular	28	19.9
Gastrointestinal	3	2.1
Neurological	9	6.4
Pulmonary	3	2.1
Cardiac	2	1.4
Eye	47	33.3
Mucocutaneous involvement	49	34.8
Disease activity		
Active	83	58.86
Inactive	58	41.13
BDCAF, means±SD	2.5 ±1.7	
Medication		
Colchicine	103	73.05
Corticosteroid	41	29.08
Azathiopurine	68	48.22
Cyclophosphamide	5	3.54
IFN	1	0.7
Anti-TNF	1	0.7
No treatment	6	4.25
Family History		
Yes	35	24.82
No	106	75.18

Table 2. Study parameters in all groups

	BD	HC	p
CRP	**7.67 ± 13.82**	**2.27 ± 2.11**	**<0.001**
ESR	11.33 ± 12.42	7.51 ± 5.78	>0.05
WBC	**8.34 ±2.90**	**7.44 ±0.17**	**0.03**
NLR	**2.66 ±1.55**	**2.23 ±1.17**	**<0.001**
PLR	130.49 ±52.85	119.78 ±45.42	>0.05
MPV	**8.62 ±1**	**9.26 ±1.18**	**<0.001**
PDW	16.45 ±1.07	16.10 ±2.13	>0.05
RDW	**14.65 ±2.29**	**13.57 ±1.28**	**<0.001**

Behcet's disease (BD), Healthy control (HC), C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC), Neutrophil lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW) and red blood cell distribution width (RDW)

Table 3. Study parameters in active and inactive groups

	Active disease	Inactive disease	p
CRP	**9.96 ± 17.2**	**4.4 ± 5.03**	**0.007**
ESR	**12.32 ± 11.11**	**9.9 ± 14.07**	**0.017**
WBC	8.62 ± 3.1	7.94 ± 2.56	>0.05
NLR	2.70 ±1.81	2.59 ±1.07	>0.05
PLR	132.43 ± 43	127.71 ±64.63	>0.05
MPV	8.54 ±0.97	8.74 ±1.03	>0.05
PDW	16.5 ±0.54	16.37 ± 1.54	>0.05
RDW	14.53 ±2.22	14.82 ± 2.40	>0.05

C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC), Neutrophil lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW) and red blood cell distribution width (RDW)

Table 4.Study parameters in organ involvement status

	Major organ involvement	Mucocutaneous	p
CRP	6.76 ± 8.58	9.38 ± 20.3	>0.05 0.200
ESR	11.42 ± 13.45	11.16 ± 10.35	>0.05 0.358
WBC	8.39 ± 2.96	8.25 ± 2.80	>0.05 0.716
NLR	**2.85 ±1.73**	**2.29 ±1.03**	**0.012**
PLR	130.90 ± 59.6	129.71 ±37.55	>0.05 0.458
MPV	8.68 ± 1.09	8.50 ±0.8	>0.05 0.470
PDW	**16.47 ± 1.07**	**16.41 ± 0.37**	**0.019**
RDW	14.86 ±2.64	14.26 ± 1.33	>0.05 0.291

C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC), Neutrophil lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW) and red blood cell distribution width (RDW)

DISCUSSION

Inflammation usually occurs through the secretion of inflammatory cytokines by macrophages and monocytes and these inflammatory molecules cause changes in the number, shape, and size of bone marrow cells and peripheral blood cells. The effects of inflammatory diseases on hematological indices are not standard (15,16).

Behçet's disease is an inflammatory disease, characterized by the activation of innate and adaptive immunity with genetic predisposition. The interaction of T lymphocytes and activated neutrophils are the main pathophysiological changes in BD. Typical BD lesions, such as pustular folliculitis, pathergy reactions, and hypopyon, have significant neutrophil infiltrations (17,18). Immune-mediated inflammatory response causes endothelial dysfunction and vasculitis which occur due to perivascular inflammation, resulting in the development of skin lesions. Lymphocytes, monocytes, and neutrophils are the major active cells of perivascular inflammation (19).

The results of this study showed that NLR, MPV and RDW were significantly higher in the BD group than in the control group. Furthermore, NLR and PDW were significantly higher in the BD patients with major organ involvement than in the mucocutaneous BD patients. NLR was higher in the patients with eye involvement. MPV was related to erythema nodosum, PDW was related to oral ulcers and higher in the patients with neuro-BD than in those without. There was no elevation of hematological indices in the active BD patients.

Neutrophils increase in inflammatory conditions and lymphocytes decrease because of the regulatory pathway. Therefore, NLR is important because it reflects inflammation. NLR has been studied in various systemic diseases including rheumatoid arthritis, systemic lupus, and others (20-22). Ozturk et al. found a higher NLR in patients with BD compared to a control group (16). In 2016, Balkarli et al. showed that NLR was higher in patients with active BD than in those with inactive BD (19). In the current study, a statistically significant increase was determined in the NLR of patients with BD compared to the healthy control group, and the NLR was seen to be similar in both active BD and inactive BD patients.

Platelets are rich in proinflammatory agents and release highly active microparticles that play a role in the development of inflammatory rheumatic diseases (22). PLR, which can be easily calculated from the peripheral blood, has been demonstrated as a new indicator of systemic inflammatory diseases and it can aid in the diagnosis and assessment of disease activity in many diseases (2,6,23). In the current study, PLR levels were found to be higher in BD patients than in the healthy control group, but not at a statistically significant level, and there was no significant difference between active and inactive patients. Yolbas et al. reported lower PLR levels in BD patients than in a healthy control group, and there was no significant difference in the PLR of patients with ocular or oral ulcer activity (6). Hammad et al investigated PLR and determined no significant difference between active and inactive groups. (24). Ying et al. found that PLR was higher in BD patients than in the control group and in active disease compared to inactive disease.

The utility of MPV as an inflammatory marker in auto-inflammatory disorders has been extensively investigated, but the results are conflicting. A retrospective study by Kisacik et al. investigated the correlation between MPV and the clinical indices of both RA and AS. The study found MPV levels to be

significantly lower in RA and AS patients compared to control peers (2). Conversely, MPV levels in SS patients were found to be higher than those of a healthy control group (25). Another study by Avci et al. found MPV levels to be significantly lower in BD than in the control group, as in the current study (26). Therefore, the clinical utility and validity of MPV has not yet been sufficiently established.

RDW has been shown to be positively correlated with inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) even after excluding anemia and reflects underlying chronic inflammation (27). Aksoy et al. found that RDW was higher in BD patients than in healthy control subjects and in active disease patients compared to inactive disease patients (28). Akturk et al. studied RDW levels in active and inactive disease groups and reported higher RDW levels in the active disease group (29). In the current study, RDW levels were determined to be higher in BD than in the control group, but there was no difference between active or inactive disease groups or organ involvement.

Platelet distribution width (PDW) is a platelet index indicating variation in platelet size and differentially diagnoses thrombocytopenia (30). PDW is used to detect fractions of larger platelets that are more active both enzymatically and metabolically. It can be said that PDW is a more specific test than MPV as it is not affected by single platelet distention caused by platelet swelling (12). Isik et al. found PDW to be a negative acute phase reactant for rheumatoid arthritis (31). Similarly, Akturk and Buyukavci found lower PDW in a fibromyalgia patient group compared to a control group (32). To the best of our knowledge, there has been no previous study of PDW in BD. The results of the current study showed similar PDW values in the BD and control groups, and in active and inactive disease patients. However, a significant difference was determined in patients with major organ involvement. Patients with oral ulcers and neuro-Behçet were observed to have high PDW levels.

There are some limitations to this study, primarily the retrospective design, so it was not possible to report clearly the treatments applied to the patients. Secondly, the data were obtained from only a single center. Thirdly,

Table 5. Study parameters in cases of different system involvements

Clinical manifestations	NLR median(range)	p	MPV Mean(±SD)	p	PDW median(range)	p
Oral ulcers						
Present (n=46)	2.26(0.8-8.6)	0.052	8.6±0.9	0.648	16.5(10.1-18.2)	**0.006**
Absent (n=95)	2.45(1-14.2)		8.6±1.1		16.7(15.3-18.5)	
Genital ulcers						
Present (n=25)	2.29(1.1-3.9)	0.80	8.6±1.1	0.944	16.5(16.1-18.1)	0.572
Absent (n=116)	2.3(0.8-14.2)		8.6±1.1		16.6(10.1-18.50)	
Papulopustular						
Present (n=31)	2.2(1-8.6)	0.39	8.5±0.8	0.399	16.6(15.6-18.1)	0.842
Absent (n=110)	2.3(0.8-14.2)		8.6±1		16.6(10.1-18.50)	
Erythema nodosum						
Present (n=32)	2.1(1-6.1)	0.4	8.7±0.9	**0.047**	16.4(13.6-18.1)	0.053
Absent (n=109)	2.3(0.8-14.2)		8.3±1		16.6(10.1-18.50)	
Joint affection						
Present (n=26)	2.2(1-4.6)	0.92	8.4±1	0.191	16.5(13.6-17)	0.767
Absent (n=115)	2.3(0.8-14.2)		8.6±0.9		16.6(10.1-18.5)	
Uveitis						
Present (n=46)	2.5(0.8-14.2)	**0.05**	8.7±1.2	0.267	16.6(15.9-18.5)	0.155
Absent (n=95)	2.1(0.9-7.6)		8.5±0.8		16.6(10.1-18.1)	
Vascular						
Present (n=28)	2.3 (1-5.8)	0.335	8.4±0.7	0.180	16.5(10.1-17.4)	0.748
Absent (n=113)	2.3(0.8-14.2)		8.6±1		16.6(15.6-18.5)	
Neuro-behcet						
Present (n=9)	2.9 (1.2-7.6)	0.39	9±1.1	0.247	16.8(16.4-18.1)	**0.037**
Absent (n=132)	2.3(0.8-14.2)		8.6±1		16.5(10.1-18.50)	

Neutrophil lymphocyte ratio (NLR), mean platelet volume (MPV) and platelet distribution width (PDW)

there was no information of nutritional status or serum folic acid, iron or vitamin B12 levels, which are known to affect hematological indices. Further controlled prospective studies are needed to validate the clinical value of hematological indices in BD.

CONCLUSION

In the light of data from previous studies, it can be suggested that assessment of NLR, MPV, RDW in BD may provide additional information about inflammation. However, the present study has demonstrated that inflammatory indicators may not provide enough information about the disease activity in patients with BD. NLR and PDW both showed a good association with major organ involvement in BD. NLR was found to be much more suitable to follow up patients with uveitis, MPV for those with erythema nodosum and PDW for patients with neuro-Behçet and oral ulcers.

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