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Assessing clinical activity in Behçet's disease: relationship between BDCAF score and inflammatory markers

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Abstract

Objective: This study aims to evaluate the correlation between the Behçet Disease Current Activity Form (BDCAF) score, which assesses disease activity in Behçet's disease (BD), and inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), red blood cell distribution width (RDW), mean platelet volume (MPV), and monocyte/high-density lipoprotein (HDL) ratio (MHR), as well as to compare these parameters between BD patients and a healthy control group.

Methods: This case-control study included 55 BD patients and 35 healthy controls. Disease activity was determined using BDCAF scores. Laboratory parameters including ESR, CRP, NLR, PLR, MLR, RDW, MPV, and the monocyte/HDL ratio (MHR) were evaluated in both groups.

Results: No correlation was found between the BDCAF score and ESR, CRP, NLR, PLR, MLR, MHR, RDW and MPV ($p = 0.747$, $p = 0.741$, $p = 0.52$, $p = 0.232$, $p = 0.815$, $p = 0.605$, $p = 0.340$, $p = 0.886$, respectively). ESR, CRP, MLR, and MHR were significantly higher in the BD group compared to the healthy control group, and these values had the power to distinguish the BD group from the healthy control group ($p < 0.05$, $p = 0.003$, $p < 0.05$, $p < 0.05$).

Conclusion: Since the evaluated inflammatory markers did not correlate with the BDCAF score, these parameters are insufficient to assess disease activation in BD on their own. On the other hand, although MLR and MHR were not significant for disease activation, they serve as strong markers to differentiate BD from healthy controls. These findings should be supported by further contemporary studies.

Keywords: Behçet's disease, inflammatory markers, monocyte-to-HDL ratio, monocyte-to-lymphocyte ratio, Behçet's disease current activity form.

INTRODUCTION

Behçet's disease (BD) is defined as a systemic vasculitis affecting multiple vascular territories and causes acute inflammation attacks depending on the disease course (1). Defining disease activity in BD has proven difficult due to its fluctuating course, lack of laboratory tests reflecting disease severity, and the existence of only a few validated forms of BD activity assessment. An English language questionnaire to assess BD activity, namely the Behçet's Disease Current Activity Form (BDCAF), was first created in 1999 (2,3). This form was updated in 2006 and has become the most widely used tool to assess disease activity in BD (3).

There is no specific laboratory marker for BD activity. However, laboratory abnormalities may be observed in some

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patients. Several studies have noted that serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are significantly higher in patients with BD compared to the general population. However, the decisive role of these parameters in the diagnosis and evaluation of BD has not yet been established (4). This situation has paved the way for the search for new markers to define disease activity. In the literature, studies have been conducted on the capacity of parameters such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), red blood cell distribution width (RDW), mean platelet volume (MPV), and monocyte/high-density lipoprotein (HDL) ratio (MHR) to detect inflammation in various inflammatory conditions (5,6).

This study aimed to investigate inflammation markers such as ESR, CRP, NLR, PLR, MLR, RDW, MPV, and MHR in patients with BD compared to healthy controls and to examine the relationship between these inflammation markers and the BDCAF score, the most commonly used activity scale in BD.

METHOD

This study is a single-center, case-control study conducted with 55 patients diagnosed with BD using the International BD Study Group criteria and 35 healthy controls (7). The study was approved by the Non-Interventional Clinical Research Ethics Committee of Çukurova University (Date/Number: 23.02.2024/141).

Patients diagnosed with BD admitted to the Rheumatology clinic between February 2024 and April 2024 were included in this study. Patients under 18 years of age, patients with active infection, obesity, malignancy, chronic liver disease, diabetes mellitus, hypertension, hematologic diseases, other rheumatologic or inflammatory disease, pregnancy and dialysis patients were excluded.

Demographic data of all participants including age, sex, ESR, CRP, NLR, PLR, MLR, RDW, MPV and MHR values were recorded. NLR was calculated as hemogram neutrophil count divided by lymphocyte count, PLR as hemogram platelet count divided by lymphocyte count, MLR as monocyte count divided by lymphocyte count, and monocyte to HDL as monocyte count divided by HDL concentration. ESR: 0-15 mm/h for men under 50 years of age; ESR: 0-20 mm/h for women; ESR: 0-20 mm/h for men over 50 years of age; ESR: 0-30 mm/h for women; CRP: 0-5 mg/L, RDW: 11.8-13.4%, MPV: 6.5-11.6 fL re considered normal laboratory values.

BD activity was assessed using the BDCAF score. The Turkish BDCAF form used in this study was translated and assessed in terms of reliability by Hamuryudan et al.(8). The BDCAF assessment was based on clinical findings related to Behçet's disease that occurred in the last four weeks before the examination date. Twelve clinical items were evaluated in the form: headache, oral ulcer, genital ulcer, erythema nodosum, pustular lesion, arthralgia, arthritis, gastrointestinal symptoms, gastrointestinal bleeding, ocular involvement, central nervous system involvement, and large vessel involvement. Each item was recorded as present/absent; present findings were scored as one, absent findings as 0. The total BDCAF score was obtained by summing the 12 items and ranged from 0 to 12; higher scores indicated higher disease activity.

Statistical Analysis

Statistical studies were conducted utilizing SPSS for Windows version 25.0 software (Armonk, NY: IBM Corp.). The normality of the variables was assessed using analytical methods, including the Kolmogorov-Smirnov and Shapiro-Wilk tests. A p-value exceeding 0.05 in the Kolmogorov-Smirnov test suggests that the data conforms to a normal distribution. In the absence of a discernible normal distribution, the Mann-Whitney U test was employed to compare patient and control groups. Mean values were utilized. The receiver operating characteristic (ROC) curve was employed to evaluate the area under the curve (AUC), sensitivity, specificity, and threshold values. The Spearman correlation test was employed for correlation evaluation, with the correlation coefficient denoted as rho. Correlation coefficient <0.25 indicates no or a very weak relationship; 0.25-0.5 signifies a weak to moderate relationship; 0.5-0.75 denotes a strong relationship; and >0.75 represents a very strong relationship (9). Statistically, p-value<0.05 was deemed significant.

RESULTS

The study included 55 BD patients (56.3% female; mean age: 40.2±11) and 35 age-sex-matched healthy controls (57% female; mean age: 37.8±8.1). There was no statistically significant difference in the age and sex distribution of the patient and healthy control groups (p=0.494, and p=0.214, respectively).

Demographic data (age, sex) and clinical characteristics (disease duration, smoking status, and BDCAF scores) of patients with BD are given in Table 1. The mean BDCAF score of the Behçet's disease group was 1.89±1.6. The distribution of BDCAF-related clinical manifestations is presented in Table 1, with oral ulcers being the most frequent manifestation (92.7%), followed by papulopustular lesions (67.3%) and genital ulcers (65.5%).

Patients were further stratified according to BDCAF thresholds (0-2, 3, and >3) to evaluate the distribution of organ involvement across different levels of disease activity (Table

2). Ocular involvement was the most frequent manifestation across all activity groups and remained relatively stable (60.0%, 62.5%, and 60.0%, respectively). In contrast, vascular involvement showed an increasing trend with higher disease activity, rising from 36.7% in patients with BDCAF=0-2 to 60.0% in those with BDCAF >3. Musculoskeletal involvement demonstrated a relatively consistent distribution across activity levels (33.3%, 31.2%, and 30.0%, respectively). Neurological and gastrointestinal involvement were infrequent and did not show a clear pattern across BDCAF strata.

Table 1. Characteristics of patients with Behcet's disease

Variable	Behçet's disease patients (n=55)
Age, years, mean ± SD	40.2 ± 11
Female sex, n (%)	31 (56.3)
Disease duration, years, mean ± SD	11 ± 6
Smoking, n (%)	21 (38.0)
BDCAF score, mean ± SD	1.89 ± 1.6
Pathergy positivity, n (%)	13 (23.6)
BDCAF-related clinical findings during the preceding 4 weeks	
BDCAF item	**n (%)**
Oral ulcer	51 (92.7)
Genital ulcer	36 (65.5)
Erythema nodosum	27 (49.1)
Papulopustular lesion	13 (23.6)
Arthralgia / painful joints /Arthritis	18 (32.7)
Gastrointestinal symptoms	2 (3.6)
Ocular involvement	29 (52.7)
Central nervous system involvement	4 (7.3)
Large vessel involvement	28 (50.9)

BDCAF: Behçet's disease current activity form, SD: standard deviation

Table 2. Distribution of organ involvement according to BDCAF thresholds

Organ involvement	BDCAF=0-2 (n=30)	BDCAF=3 (n=15)	BDCAF >3 (n=10)
Ocular	18 (60.0%)	10 (62.5%)	6 (60.0%)
Vascular	11 (36.7%)	6 (37.5%)	6 (60.0%)
Neurological	1 (3.3%)	1 (6.2%)	0 (0%)
Gastrointestinal	2 (6.7%)	0 (0%)	0 (0%)
Musculoskeletal	10 (33.3%)	5 (31.2%)	3 (30.0%)

BDCAF: Behçet's disease current activity form

Among the 55 patients, 44 (80%) were receiving colchicine therapy. Azathioprine was used in 14 patients (25.5%), infliximab in patients (18.2%), adalimumab in six patients (10.9%), and methotrexate in four patients (7.3%). Combination therapy was present in 22 patients, most commonly colchicine plus azathioprine (n=9) and colchicine plus infliximab (n=6).

Comparative evaluation of ESR, CRP, NLR, PLR, MLR, RDW, and MPV results of BD and healthy control groups are given in Table 3.

Subgroup analyses were performed to evaluate inflammatory markers according to different patterns of organ involvement. Patients with musculoskeletal involvement had significantly higher ESR and CRP levels compared to those without musculoskeletal involvement (p=0.025 and p=0.013, respectively) (Table 4).

Table 3. Evaluation of laboratory parameters between groups

	Behçet Disease (n=55) Mean±SD	Healthy Control (n=35) Mean±SD	P-value
ESR	14±10	7±3.2	<0.05
CRP	5.2±5.1	3.09±3	0.003
NLR	2.5±1.4	2.5±1.6	0.753
PLR	162±154	119±35	0.066
MLR	0.31±0.15	0.19±0.16	<0.05
RDW	14.3±1.5	14.2±2.1	0.365
MPV	10.4±1.3	10.39±1.6	0.977
MHR	0.157±0.12	0.016±0.018	<0.05

CRP: C-Reactive Protein, ESR: Erythrocyte sedimentation rate, MHR: Monocyte to HDL ratio, MLR: Monocyte lymphocyte ratio, MPV: Mean platelet volume NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, RDW: Red cell distribution width.

Table 4. Inflammatory markers according to musculoskeletal involvement in Behçet's disease

Parameter	MSK (+) (n=18)	MSK (–) (n=37)	p-value
ESR (mm/h)	17.7 ± 10.5	12.8 ± 9.6	**0.025**
CRP (mg/L)	6.82 ± 5.3	4.13 ± 4.8	**0.013**

MSK: Musculoskeletal involvement, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein; data are presented as mean ± SD; comparisons were performed using the Mann–Whitney U test.

In contrast, no statistically significant differences were observed across any other patterns of organ involvement including ESR, CRP, NLR, PLR, and MLR, in patients with oral ulcers, genital ulcers, papulopustular lesions, erythema nodosum, vascular involvement, ocular involvement, or gastrointestinal involvement compared to those without these manifestations (p>0.05 for all comparisons).

The correlation of the BDCAF score, which used to evaluate disease activation in the BD group, with ESR, CRP, NLR, PLR, MLR, RDW, and MPV values was evaluated and given in Table 5.

The power to distinguish the patient group from the healthy group was evaluated by performing ROC analysis between the laboratory values of the BD and healthy control

groups. The results are presented in Table 6. It was found that NLR, PLR, RDW, and MPV did not have significant power (p=0.743, p=0.066, p=0.365, p=0.977, respectively). The ROC curve is shown in Figure 1.

Table 5. Correlation analysis results between BDCAF and laboratory parameters

		BDCAF
ESR	**rho**	**0.044**
	p	0.747
CRP	rho	0.046
	p	0.741
NLR	rho	-0.089
	p	0.52
PLR	rho	-0.164
	p	0.232
MLR	rho	0.032
	p	0.815
RDW	rho	0.120
	p	0.340
MPV	rho	0.078
	p	0.886
MHR	rho	0.058
	p	0.605

BDCAF: Behcet's Disease Current Activity Form, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, MHR: Monocyte to HDL ratio, MLR: Monocyte lymphocyte ratio, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, RDW: Red cell distribution width.

Table 6. ROC analysis results of laboratory parameters of Behçet's disease group and healthy control group

	ESR	CRP	MLR	MHR
Cut-off	8.5	2.9	0.24	0.05
Sensitivity, %	63	57	69	91
Specificity	64	65	69	95
AUC (95% CI)	0.753 (0.658-0.849)	0.677 (0.567-0.786)	0.673 (0.559-0.788)	0.993 (0.983-1)
p-value	**<0.01**	**0.03**	**0.04**	**<0.01**

AUC: Area under the curve, CI: Confidence interval, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, MHR: Monocyte to HDL ratio, MLR: Monocyte lymphocyte ratio.

DISCUSSION

In this study, inflammation markers in patients with BD were compared with healthy controls and the relationship between BDCAF scores and the power of the evaluated parameters to indicate disease activity was investigated. According to our results, no correlation was found between ESR, CRP, NLR, PLR, MLR, RDW, MPV, MHR and the BDCAF scores. Based on this, the laboratory parameters are insufficient to evaluate disease activation on their own. However, among these parameters; ESR, CRP, MLR and MHR were found to be significantly higher in the BD group compared to the healthy control group and the power to distinguish the BD group from the healthy control group was shown according to the ROC analysis results.

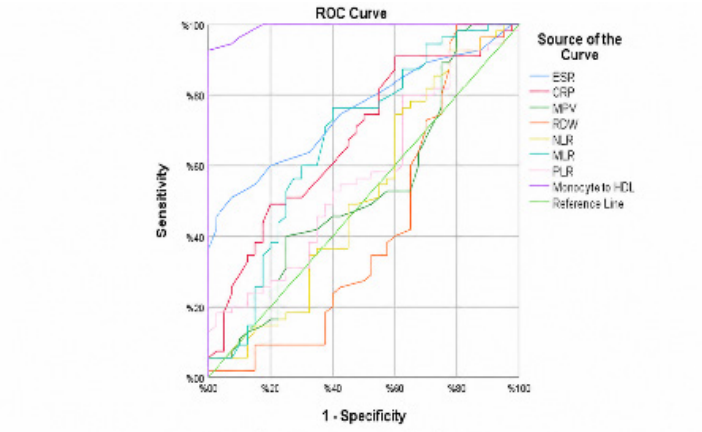


Figure 1. ROC curve of inflammation markers in differentiating Behçet's patients and healthy control group

Although BDCAF is a clinical disease activity measure, the absence of a correlation between BDCAF and inflammatory markers suggests that systemic laboratory inflammation does not necessarily parallel clinically recorded disease activity in Behçet's disease. This may be related to the heterogeneous and episodic nature of BD, the predominance of mucocutaneous manifestations, treatment effects, and the relatively low mean BDCAF score in the present cohort. Therefore, inflammatory markers may help distinguish BD patients from healthy individuals but should not be used as stand-alone indicators of current BD activity.

Another important point that may explain the lack of correlation between BDCAF scores and inflammatory markers is the relatively low disease activity in the present cohort. The mean BDCAF score was 1.89 ± 1.6, indicating that most patients had mild or clinically inactive disease at the time of assessment. This restricted distribution of BDCAF scores may have limited the ability to detect significant correlations between clinical activity and laboratory-based inflammatory markers. In other words, the absence of a correlation should not necessarily be interpreted as evidence that these markers are unrelated to disease activity in all Behçet's disease populations. Rather, it may reflect a floor effect related to low clinical activity, treatment-controlled disease, and the limited number of patients with high BDCAF scores. Therefore, future studies enrolling larger numbers of patients with moderate-to-high disease activity and longitudinal BDCAF assessments are needed to clarify the relationship between inflammatory markers and disease activation better.

A review of the literature reveals that several studies have evaluated laboratory parameters in BD. The first of these studies was conducted by Alan et al. in 2015 and investigated the relationship between the NLR, PLR and MPV and the presence and severity of BD. In their study, the NLR and PLR were reported to be significantly higher in the BD group compared to the healthy control group, while MPV was similar. NLR was found to be an independent risk factor for the presence of BD (10). ESR, CRP, MLR and MHR values were found to be significantly higher in the BD group compared to the healthy control group.

Hammad and colleagues investigated the relationship between the BDCAF score and NLR and PLR values (11). In their study, NLR and PLR were found to be correlated with BDCAF scores, with NLR showing a stronger correlation. In contrast, this study was not observe a significant correlation between NLR or PLR and BDCAF scores in our cohort. This discrepancy may be explained by several factors. Firstly, the sample size differed between the studies (23 vs. 55 patients), which have influenced the statistical power. Secondly, Hammad et al. classified patients according to clinical involvement patterns, demonstrating that NLR was associated with mucocutaneous involvement, while both NLR and PLR were linked to joint and gastrointestinal involvement. In line with this approach, this study performed additional subgroup analyses according to organ involvement. However, this study observed that inflammatory markers were significantly elevated only in patients with musculoskeletal involvement, while no significant differences were detected across other clinical manifestations. These findings suggest that the relationship between inflammatory markers and disease activity in Behçet's disease may depend on specific clinical phenotypes rather than reflecting a uniform systemic process.

In the present study, stratification of patients according to the BDCAF thresholds provided additional insight into the relationship between disease activity and organ involvement. While ocular involvement remained relatively consistent across different activity levels, vascular involvement appeared to be more frequent in patients with higher BDCAF scores. This finding may suggest that vascular manifestations are associated with increased systemic inflammatory burden in Behçet's disease. Although the number of patients with neurological and gastrointestinal involvement was limited, thereby precluding definitive conclusions, our results highlight the potential value of BDCAF-based stratification in identifying clinically relevant patterns of organ involvement.

In the present study, subgroup analyses according to organ involvement revealed that ESR and CRP levels were significantly higher in patients with musculoskeletal involvement, whereas no significant differences were observed across other clinical manifestations, including mucocutaneous, ocular, vascular, and gastrointestinal involvement. These findings suggest that systemic inflammatory markers may reflect disease activity more accurately in patients with musculoskeletal involvement, possibly due to a higher systemic inflammatory burden associated with articular manifestations. In contrast, mucocutaneous and certain organ-specific manifestations may not be accompanied by a comparable systemic inflammatory response, which could partly explain the lack of correlation between the BDCAF scores and the inflammatory markers observed in the overall cohort. These results highlight the heterogeneity of Behçet's disease and indicate that the utility of inflammatory markers in assessing disease activity may vary depending on the clinical phenotype. These findings further support the concept that inflammatory markers in Behçet's disease should be interpreted in the context of clinical phenotype rather than as universal indicators of disease activity.

In a study conducted by Shadmanfar et al. in 2021, Behçet's disease patients were evaluated for disease activity using the Iranian Behçet Disease Dynamic Activity Measurement (IBDDAM) score. The study found that NLR and PLR values were significantly higher in active Behçet disease patients compared to inactive ones (12). Additionally, it was noted that NLR showed a mild correlation with the IBDDAM score and had a significant relationship with ocular involvement. Our study differs from their research in that patients were not divided into active and inactive groups, and laboratory parameters were compared with a healthy control group. Instead, the patients in this study were categorized based on their involvement patterns, similar to those in the previously mentioned study by Hammad et al. (11) Given that Behçet's disease has a wide clinical spectrum, we believe that including patients with different involvement patterns in statistical analyses may yield different results.

Demirbaş et al. evaluated the anti-inflammatory efficacy of colchicine based on MHR, NLR, and MLR levels. In their study, patients with Behçet's disease were divided into three subgroups according to their disease activity status using the Krause's Behçet Clinical Severity Scoring System and followed for three months (13). It was demonstrated that there was a significant relationship between disease activity and the MHR, and that MHR, along with NLR and MLR, could be used to assess the anti-inflammatory efficacy of colchicine. In this study, however, no correlation was found between MHR and disease activity. While disease activity in this study was assessed using the BDCAF score, Demirbaş and colleagues used the Krause and Behçet Clinical Severity Scoring System. We believe that the difference in the results regarding the relationship between MHR and disease activity stems from the

use of different activity scoring systems.

Limitations of the Study

When considering the limitations of our study, it can be noted that it is single-centered, and the scores such as the Krause's Behçet Clinical Severity Scoring System and the IBDDAM were not concurrently evaluated with the BDCAF score as done in other studies. Although patients were not prospectively designed as phenotype-defined subgroups, we performed post-hoc subgroup analyses according to organ involvement. However, several involvement categories (especially neurological and gastrointestinal) included very small numbers of patients, limiting the statistical power. In addition, treatment regimens were heterogeneous, and medication-specific subgroup analyses could not be reliably performed. Another limitation is that the overall BDCAF score of the cohort was relatively low, which may have created a restricted range of disease activity and reduced the likelihood of detecting significant correlations between BDCAF score and the inflammatory markers.

CONCLUSION

In this study, the ESR, CRP, MLR, and MHR were significantly higher in patients with Behçet's disease than in healthy controls. However, none of the evaluated inflammatory markers showed a significant correlation with the BDCAF scores. These findings suggest that although some laboratory parameters may help distinguish patients with Behçet's disease from healthy individuals, they do not appear to reliably reflect current clinical disease activity as assessed by the BDCAF in this cohort. Therefore, a BDCAF-based clinical assessment remains essential when evaluating disease activity. Further longitudinal studies including larger cohorts and patients with a wider range of disease activity are needed to clarify the role of inflammatory markers in monitoring BD activity.

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