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Original Article

Use of prognostic nutritional index in the evaluation of disease activity in patients with Behçet's disease

Nuh Ataş[1], Hakan Babaoğlu[1], Ertuğrul Demirel[2], Bülent Çelik[3], Reyhan Bilici Salman[1], Hasan Satış[1], Hazan Karadeniz[1], Aslıhan Avanoğlu Güler[1], Seminur Haznedaroğlu[1], Berna Göker[1], Abdurrahman Tufan[1], Mehmet Akif Öztürk[1]

Abstract

Objective: Behçet's disease (BD) is a chronic, multisystem disorder that can cause severe morbidity and mortality. Monitoring tools that measure disease activity are required for effective management of BD. We aimed to investigate the association of prognostic nutritional index (PNI) with disease activity in BD.

Methods: In this cross-sectional study, we enrolled 88 adult patients with BD and 51 healthy controls. The patients were divided into patients with active and inactive BD according to their disease activities. PNI was calculated using the following formula: 10×serum albumin (g/dL)+0.005×peripheral lymphocyte count (per mm3). To evaluate BD activity, the Behçet Disease Current Activity Form was used. The relations of BD activity with PNI, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, erythrocyte sedimentation rate, and C-reactive protein were investigated. A receiver operator characteristic curve analysis was used to define the optimum cutoff value of PNI for active BD.

Results: A total of 48 patients were classified as having active BD and 40 as having inactive BD. Patients with active BD had lower mean PNI than patients with inactive BD and healthy controls (51.8±4.2, 57.4±2.9, and 56.6±3.6, respectively; p<0.001). In multivariate analysis, PNI was the only independent predictor of BD activity (odds ratio, -0.687; 95% confidence interval 0.548-0.861; p=0.001). The optimum cutoff of PNI for active BD was 55.35 with 79.2% sensitivity and 77.75% specificity.

Conclusion: PNI was significantly associated with BD activity. PNI may be a useful tool for the assessment of disease activity in BD.

Keywords: Behçet's disease, prognostic nutritional index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

ORCID iDs of the authors:
N.A. 0000-0001-5880-4974;
H.B. 0000-0002-3728-0259;
E.D. 0000-0002-6510-4893;
B.Ç. 0000-0002-0481-4808;
R.B.S. 0000-0002-2523-1695;
H.S. 0000-0002-7605-1301;
H.K. 0000-0003-4665-3421;
A.A.G. 0000-0001-9866-9797;
S.H. 0000-0003-3929-6884;
B.G. 0000-0001-9242-0907;
A.T. 0000-0001-6244-9362;
M.A.Ö. 0000-0001-7203-3934.

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[1] Division of Rheumatology, Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey
[2] Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey
[3] Department of Statistics, Gazi University School of Science, Ankara, Turkey

Address for Correspondence:
Nuh Ataş; Division of Rheumatology, Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey

E-mail: nuhatas2008@gmail.com

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Introduction

Behçet's disease (BD) is a chronic, relapsing/remitting, multisystem disorder characterized by recurrent oral aphthous ulcers and systemic manifestations, such as gastrointestinal, neurologic, ocular, and vascular diseases (1). Although BD has a worldwide distribution, its prevalence is higher in the Mediterranean, Middle East, and East Asia populations who live around the ancient Silk Road. BD is more common in men and it affects them more seriously. The most widely used classification criteria are the International Study Group (ISG) and the International Criteria for Behçet's Disease, which are based on the clinical manifestations of BD (2, 3). Mucocutaneous manifestations decrease the health-related quality of life, whereas major organ involvement may result in severe morbidity/mortality. Treatment of BD depends on the organ involvement and disease severity. Improvement in health-related quality of life, maintenance of disease remission, and prevention of organ damage are the main treatment goals. Measurement of disease activity is an important part of management of BD, similar to any other rheumatic disease.

There is no specific test to assess disease activity in BD. The Behçet Disease Current Activity Form (BDCAF) is the most widely used tool to measure disease activity in BD (4). However, it is completely based on the clinical manifestations. To evaluate disease activity, several laboratory tests have been studied. Among these tests, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were positively correlated with BDCAF in one study (5). However, the correlation was found only with the arthritis and erythema components of BDCAF. In addition, normal ESR and CRP levels may be observed during an active disease in some cases (6). The mean platelet volume, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were other studied measurements for the evaluation of disease activity in BD (7, 8). Although these

measurements are useful in some cases, they require more controlled studies. Hence, laboratory markers that measure disease activity will facilitate the management and follow-up of patients with BD.

The prognostic nutritional index (PNI) is a predictor of perioperative complications in patients undergoing cancer surgery (9). PNI is also related with the immune-nutritional status of patients and calculated from the serum albumin level and total lymphocyte count (10). Recently, PNI was evaluated in patients with systemic lupus erythematosus and antineutrophil cytoplasmic antibodies-associated vasculitis. In these studies, PNI was associated with disease activity and severity (11-13). To the best of our knowledge, there is no study that has evaluated the relation between PNI with BD activity. Therefore, we aimed to investigate the association of PNI with BD activity.

Methods

Patients and study design

In this cross-sectional study, 88 adult patients with BD who visited the outpatient rheumatology clinic and 51 age- and sex-matched healthy controls who consisted of patient accompanists without any systemic disease were included. The diagnosis of BD was made according to the ISG criteria (2). Patients with severe systemic diseases, other rheumatic diseases, treatment with >7.5 mg prednisolone, any acute or chronic infections, pregnancy, heart failure, and conditions that may affect the level of albumin and lymphocytes, such as hematologic and hepatic diseases, were excluded from the study. Demographic characteristics, duration of disease, body mass index (BMI), and clinical manifestations (mucocutaneous, eye, musculoskeletal, neurologic, and vascular) were recorded.

Evaluation of disease activity, PNI, and laboratory data

BDCAF was used for the assessment of disease activity. BDCAF evaluates clinical features in the last 4 weeks and has the following 12 components: headache; oral ulcer; erythema; genital ulcer; arthritis; arthralgia; nausea/vomiting/abdominal pain; frank blood per rectum; diarrhea; and new symptoms in eye, vascular, and nervous systems. Each component is scored as absent (0) or present (1). The final BDCAF score is calculated by adding the positive components and the maximum score is 12. The Turkish validation of BDCAF was performed (14). A BDCAF patient index score ≥2 was defined as active BD, whereas a score <2 was defined as inactive BD (15). The study participants were further divided into 3 groups: patients with active disease, patients with inactive disease, and healthy controls.

On the same day of evaluation of patients and healthy controls, laboratory analyses [including the neutrophil, lymphocyte, and platelet counts, ESR, CRP, serum albumin, blood urea nitrogen, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] were performed. PNI was calculated using the following formula: 10×serum albumin (g/dL)+0.005×peripheral lymphocyte count (per mm^3) (10). By calculating the ratio of the absolute neutrophil count to the absolute lymphocyte count and the ratio of platelet count to lymphocyte count, NLR and PLR were obtained, respectively. This study was approved by the Ethical Committee of Gazi University (Approval Date: July 26, 2019; Approval Number: 2019-247) and conducted in accordance with the Helsinki Declaration of 1975. Informed consent was obtained from all the participants included in the study.

Statistical analysis

All the statistical analyses were performed using Statistical Package for Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA). Continuous variables were presented as mean with

Table 1. Baseline characteristics of patients with Behçet disease.

	Patients with BD (n=88)
Demographic data	
Age (years)	36.9±11.1
No. of males	55 (62.5)
BMI (kg/m^2)	26.0±4.2
Smoker	31 (35.2)
Disease duration (years)	8.6±7.8
Clinical manifestation	
Oral ulcer	88 (100)
Genital ulcer	59 (67)
Skin involvement	48 (54.5)
Arthritis	20 (22.7)
Uveitis	46 (52.3)
Vascular involvement	24 (27.3)
Neuro-Behçet	14 (15.9)
Current medication, n (%)	
Colchicine	52 (59.1)
Azathioprine	35 (39.8)
Cyclosporin A	7 (8)
Corticosteroids	28 (31.8)
Interferon α	7 (8)
Infliximab	13 (14.8)
Adalimumab	6 (6.8)

Values are presented as number (%), unless stated.

BD: Behçet's disease; BMI: body mass index.

Main Points

- The current lack of specific tests to assess disease activity makes the management of BD difficult.
- PNI was significantly associated with disease activity in patients with BD.
- PNI is a cheap and easily available index that can be used for the assessment of disease activity in BD.

Table 2. Baseline clinical and laboratory features of patients with active/inactive Behçet disease and healthy controls.

	Active BD (n=48)	Inactive BD (n=40)	Healthy controls (n=51)	p
Demographic data				
Age (years)	36.8±10.2	37.1±12.3	39.0±12.6	0.587
Males, n (%)	27 (56.3)	28 (70.0)	26 (51.8)	0.177
BMI (kg/m^2)	25.7±4.5	26.4±3.8	26.2±4.6	0.743
Disease duration (years)	7 (7)	7 (8.8)		0.813
Current medication, n				
Colchicine	28	24		0.874
Conventional immunosuppressants	29	22		0.608
Biological immunosuppressants	11	8		0.741
Laboratory data				
BUN, mg/dL	13 (6)	14 (5)	13 (5)	0.124
Creatinine, mg/dL	0.7±0.1	0.7±0.1	0.7±0.1	0.600
AST, IU/L	20 (9)	19 (6)	20 (7)	0.338
ALT, IU/L	18 (14)	16.5 (15)	17 (14)	0.900
Albumin, g/dL	4.2 (0.3)	4.6 (0.2)	4.5 (0.2)	<0.001*
Neutrophil, µ/L	5548.1±1454.2	4673.3±1328.5	4175.3±1228.6	<0.001*
Plt x10^3, µ/L	272.5 (116.8)	268.5 (62.8)	247 (87)	0.439
Lymphocytes, µ/L	1,930 (493)	2,240 (603)	2,170 (710)	0.001†
ESR, mm/h	17.5 (17)	9 (9)		0.010
CRP, mg/L	7 (11.8)	3.3 (2.9)		0.001
PNI	51.8±4.2	57.4±2.9	56.6±3.6	<0.001*
NLR	2.7 (0.8)	1.9 (0.8)	1.9 (0.9)	<0.001*
PLR	138.5 (49.4)	118.9 (43.9)	127.7 (57.2)	0.016†
Hemoglobin, g/dL	13.9 (2.3)	14.2 (2.7)	14.7 (2.5)	0.190
Disease activity				
BDCAF	3 (2)	1 (1)		<0.001

Values are presented as n (%) or median (interquartile range). p<0.05 was considered statistically significant.
Conventional immunosuppressants include azathioprine, cyclosporin A, corticosteroids, and interferon α. Biological immunosuppressants include infliximab and adalimumab.
*The statistically significant difference is between the active BD group and other 2 groups, while there is no statistical significant difference between the inactive BD group and healthy controls.
†Statistically significant difference is between patients with active and inactive BD. Healthy controls have no statistically significant difference with patients with active and inactive BD.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; BD: Behçet's disease; BDCAF: Behçet Disease Current Activity Form; BUN: blood urea nitrogen; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Plt: platelet; PNI: prognostic nutritional index.

standard deviation or median with interquartile range, and categorical variables were presented as frequencies and percentages. Normality distribution of the continuous variables was determined using the Kolmogorov-Smirnov test/Shapiro-Wilk test. Comparison of numerical variables of the groups was performed using one-way analysis of variance with post hoc Bonferroni correction, if normally distributed. For non-normally distributed data, comparisons were made using Kruskal-Wallis test and Mann-Whitney U test for post hoc analyses. Correlation coefficients were calculated using the Spearman's rank test. First, we assessed the relationship between each variable and BD activity. The variables with significant association with BD activity and without a high correlation (r<0.7) between each other were then entered into the multiple logistic regression analysis to determine the independent predictors of disease activity. The determinants of PNI were not separately included in the model. The optimum cutoff value of PNI that differentiates active and inactive BD was calculated using a receiver operator characteristic (ROC) curve analysis. A p-value of <0.05 was considered statistically significant for all analyses.

Results

Mean age of patients at inclusion was 36.9±11.1 years, and 55 patients (62.5%) were men. The median disease duration was 7 years. The frequencies of clinical manifestations of the patients were as follows: oral ulcers 100% (n=88), genital ulcers 67% (n=59), skin involvement 54.5% (n=48), uveitis 52.3% (n=46), vascular involvement 27.3% (n=24), arthritis 22.7% (n=20), neuro-Behçet 15.9% (n=14), and no gastrointestinal involvement. The demographic and clinical characteristics of patients with BD are provided in Table 1.

Among 88 patients, 48 (54.5%) had active BD, and 40 (45.5%) had inactive BD. A total of 51 participants were included in the healthy control group. There were no statistically significant differences between the 3 groups in terms of age, sex, BMI, and treatment features (p>0.05, Table 2). The median BDCAF score was 3 in the active BD group and 1 in the inactive BD group (p<0.001). The mean PNI was significantly lower in the active BD group than in the inactive BD and healthy control groups, 51.8±4.2, 57.4±2.9, and 56.6±3.6, respectively (p<0.001). The mean PNI was similar between inactive BD and healthy control groups. Creatinine, ALT, and AST levels were similar between the 3 groups. ESR (p=0.010) and CRP (p=0.001) levels were higher in the active BD group. NLR was significantly higher in the active BD group. There was no difference in PLR between the active BD and healthy control groups, whereas PLR in the active BD group was higher than that in the inactive BD group (Table 2).

In Spearman's correlation analysis, BDCAF was correlated with ESR, CRP, NLR, PLR, and PNI [(r=0.332, p=0.002), (r=0.351, p=0.001), (r=0.503, p<0.001), (r=0.332, p=0.002), and (r=-0.680, p≤0.001), respectively]. Although ESR, CRP, NLR, PLR, and PNI were associated with BDCAF in univariate analysis, only PNI was significantly associated with BD activity [odds ratio, -0.687; 95% confidence interval (95% CI) 0.548-0.861; p=0.001] in multivariate analysis

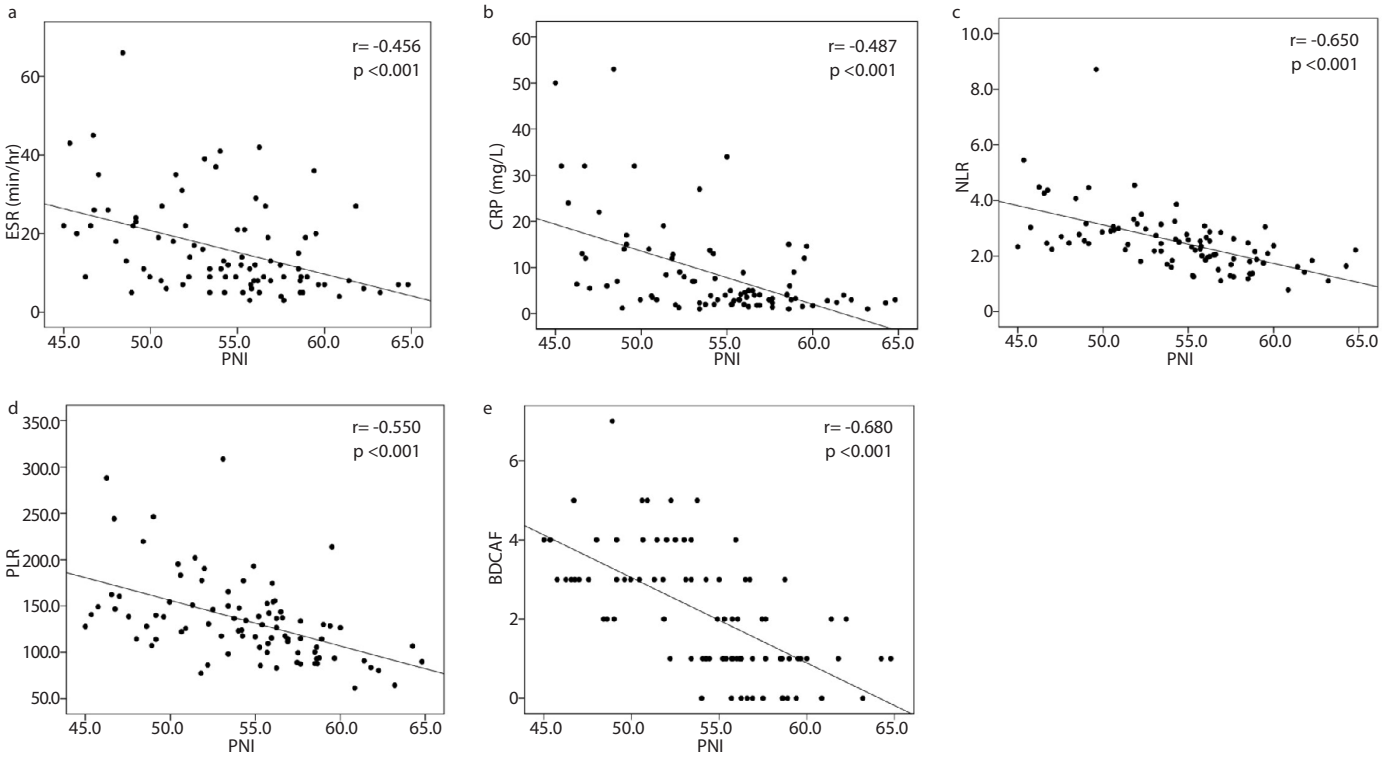

Figure 1. a-e. ESR (a), CRP (b), NLR (c), PLR (d), and BDCAF (e) were moderately correlated with PNI.
BDCAF: Behçet Disease Current Activity Form; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.

Table 3. Laboratory variables associated with Behçet disease activity.

	Univariate analysis			Multivariable analysis		
Variables	OR	95% CI	p	OR	95% CI	p
ESR	1.057	1.011-1.104	0.015	1.006	0.948-1.068	0.841
CRP	1.140	1.042-1.248	0.005	1.038	0.938-1.147	0.471
PNI	0.643	0.531-0.778	<0.001	0.687	0.548-0.861	0.001
NLR	4.338	2.014-9.342	<0.001	1.490	0.544-4.082	0.438
PLR	1.018	1.005-1.031	0.006	0.997	0.981-1.014	0.748

p<0.05 was considered statistically significant.
CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.

(Table 3). PNI was moderately correlated with BDCAF (r=-0.680, p≤0.001), NLR (r=-0.650, p<0.001), PLR (r=-0.550, p<0.001), CRP (r=-0.487, p<0.001), and ESR (r=-0.456, p<0.606) (Figure 1). From the ROC analysis, the optimum PNI cutoff for patients with active BD was 55.35 with 79.2% sensitivity and 77.75% specificity (area under the curve=0.865, 95% CI 0.789-0.942, p<0.001) (Figure 2).

Discussion

In this study, we evaluated the association of PNI with BD activity. In addition to PNI, we also evaluated NLR, PLR, ESR, and CRP that have been investigated in many studies. We observed a significant association of PNI with disease activity. To date, no marker has been accepted as a specific tool to identify and estimate BD activity. Hence, identification of a new marker associated with BD activity will facilitate follow-up and management of patients with BD.

Although PNI was first used to predict the complications in patients undergoing gastrointestinal surgery, it was also used for predicting the prognosis of many other chronic inflammatory diseases and nonoperable malignancies (16-18). However, because PNI is a temporal measure that is affected by many factors, it may be more valuable in the evaluation of the disease at the time of measurement rather than predicting the long-term results. Recently, the association of PNI with disease activity was observed in many rheumatic diseases (11-13). To our knowledge, this was the first study that evaluated the relation of PNI with disease activity in patients with BD. ESR, CRP, NLR, and PLR were significantly higher and PNI was significantly lower in the active BD group. All these parameters had an association with BD activity in the univariate analysis, but among them only PNI had a significant association with BDCAF in the multivariate analysis. Spearman's analysis also found the highest correlation between PNI and BDCAF.

Hypoalbuminemia in active BD may be present because of several conditions, such as malnutrition and systemic inflammation. The synthesis of albumin mostly depends on the nutritional intake (19). Painful oral aphthous ulcers, malaise during active disease, and cognitive dysfunction in neuro-Behçet disease may result in lower nutritional intake and malnutrition-related hypoalbuminemia. Although there was no patient with alimentary involvement in our study, hypoalbuminemia is a possible finding owing to malabsorption and protein loss in patients with BD and active gastrointestinal involvement. Systemic inflammation may be another cause of hypoalbuminemia. Albumin is a negative acute phase reactant that decreases with inflammation. The rate of albumin synthesis is mainly controlled by mRNA concentration (20).

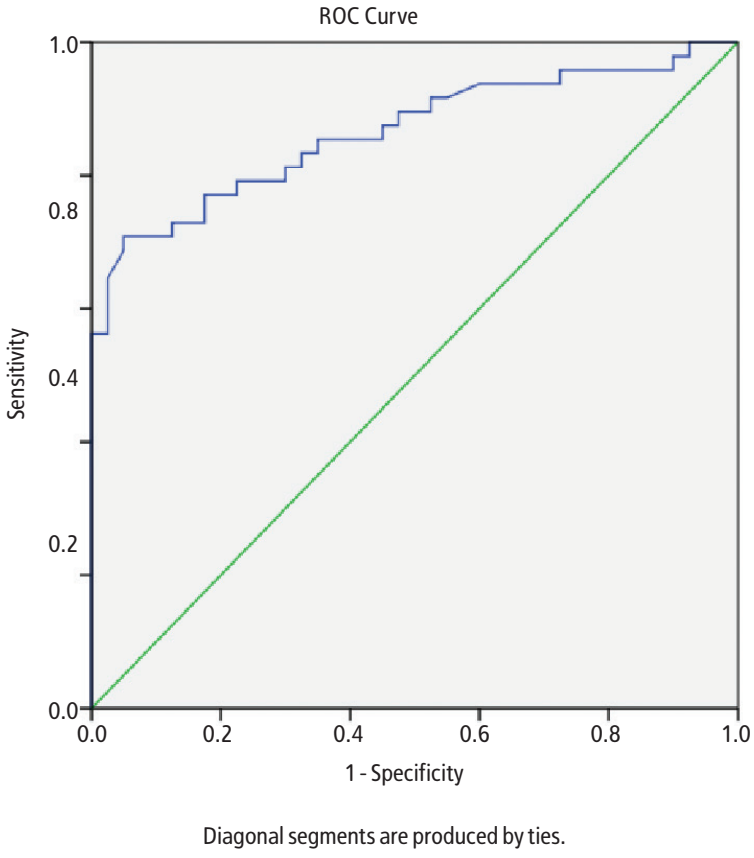

Figure 2. Receiving operating characteristic curve of prognostic nutritional index to predict active Behçet's disease.

Inflammation increases the gene transcription rate for positive acute phase reactants; however, it decreases the synthesis of albumin by reducing the albumin mRNA concentration (21). This inflammation-induced hypoalbuminemia is mainly mediated by interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (22-24). IL-6 and TNF-α levels are elevated in patients with active BD (25, 26). Hypoalbuminemia in active BD may be related with these cytokines. Another mechanism of inflammation-induced hypoalbuminemia other than decreased synthesis of albumin is increased catabolism of albumin in inflammation (27).

Although not statistically significant, the lymphocyte count, the other component of PNI, was lower in patients with active BD. The neutrophil count was significantly higher in the active BD group. Neutrophils are essential components of the innate immune system. Many proinflammatory and/or inflammatory cytokines are produced because of the chronic inflammatory nature of BD, and the recruitment and activation of neutrophils are regulated by these cytokines (28, 29). The activated neutrophils may be involved in the process of tissue damage in BD. The inflammatory state in the active disease may result in the dysregulation of apoptosis of the lymphocytes, and, consequently, a decrease in lymphocyte production may be observed (30). There are several studies that observed the significant association of NLR with BD activity (31, 32). In contrast, although NLR was higher in patients with active BD, in multivariate analysis, there was no association with disease activity in our study.

The association of BD activity with ESR and CRP, which are commonly used tests in the clinical practice, has been investigated in many studies. The results of these studies were incompatible with each other (5, 33, 34). PLR is another investigated parameter for BD activity (8, 35). In our study, PLR, CRP, and ESR were not associated with BD activity.

There are some limitations to our study. First, there was no patient with an alimentary involvement in our cohort. Second, temporary changes in follow-up could not be assessed owing to the measurement of all calculated values at a single time. Third, the prognostic role of PNI in BD was indefinite because of the cross-sectional nature of our study. To evaluate the effect of changes in treatment and other clinical features of BD on PNI, prospective and longitudinal studies with serial measurements should be performed.

In conclusion, PNI was associated with disease activity in BD. PNI is a cheap and easily available index derived from routine hemogram and biochemical tests. In addition to BDCAF, PNI may be a convenient tool for the assessment of disease activity in BD.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of Gazi University (Approval Date: July 26, 2019; Approval Number: 2019-247).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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