

Original Research

Evaluation of Full Blood Count–Derived Inflammatory Indices (SII, SIRI, PIV, NLR) in Behçet’s Disease Patients and Healthy ControlsRecai Aci ^{1,*}, Adem Keskin ², Özlem Sezer ³, Taner Karakaya ³, Samet Semiz ⁴, Melek Bilgin ⁵

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Received: October 01, 2025**Accepted:** November 17, 2025**Published:** November 24, 2025**Abstract**

This study investigated three novel complete blood count–derived inflammatory biomarkers Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Pan-Immune-Inflammation Value (PIV) and their relationship with clinical features of Behçet’s Disease (BD). Established markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), were also analyzed. Seventy HLA-B51–positive BD patients and 114 HLA-B51–negative healthy controls were enrolled. Demographic, clinical, and medication data were collected. Disease activity was assessed using the Behçet’s Disease Current Activity Form (BDCAF). Hematologic indices were calculated and analyzed. Binary logistic regression and ROC analyses (with 95% confidence



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intervals) were performed to assess diagnostic value using BD diagnosis as the outcome. BD patients had significantly higher NLR ($p = 0.003$) and SII ($p = 0.001$) than controls. Both indices were independent predictors of BD diagnosis after adjusting for age, sex, and treatment status. ROC analysis showed moderate diagnostic value for NLR (AUC = 0.674, 95% CI: 0.596–0.753) and SII (AUC = 0.694, 95% CI: 0.615–0.773). No significant associations were found between BDCAF scores and inflammatory indices. NLR and SII are accessible, low-cost markers that may help distinguish BD from healthy individuals. SIRI and PIV require further validation. The study is limited by its cross-sectional design, small sample size, and predominance of inactive BD cases.

Keywords

Behçet's disease; systemic immune-inflammation index (SII); systemic inflammation response index (SIRI); pan-immune-inflammation value (PIV); neutrophil-to-lymphocyte ratio (NLR)

1. Introduction

Behçet's disease (BD) is a systemic autoinflammatory disorder characterized by recurrent attacks and mucocutaneous lesions, and it may involve the ocular, vascular, gastrointestinal, musculoskeletal, and central nervous systems [1]. The disease is global, but Japan, the Middle East, and Mediterranean nations have the highest rates of occurrence. The Turkish population shows the highest BD rate at 80–420 per 100,000 people, making Turkey the country with the highest prevalence [2]. Genetic factors are thought to play a significant role in the pathogenesis of BD. The genetic association of the disease is underscored by its increased prevalence among individuals with a family history of BD and those carrying the HLA-B51 allele [3]. The most extensively studied genetic locus in Behçet's Disease is the human leukocyte antigen (HLA) complex located on chromosome 6p21. Susceptibility to the disease has been consistently associated with polymorphisms in the HLA-B gene, particularly HLA-B51 [4]. Both the innate and adaptive immune systems are implicated in the pathogenesis of Behçet's Disease (BD). Elements of the innate immune system, such as neutrophils and monocytes, have been shown to exhibit heightened activation and produce increased levels of proinflammatory cytokines, including IL-1 β , IL-6, and TNF- α [5]. These cytokines contribute to the chronic inflammatory response observed in BD.

The leading cause of thrombosis in BD stems from vascular wall inflammation. The body shows changes in blood values due to widespread inflammation and abnormal immune reactions [6]. The blood cells, neutrophils, lymphocytes, and platelets function as key elements in the development of systemic inflammation and thrombosis. The coagulation pathway results in damage to the blood vessel wall, leading to thrombus formation [7]. The number and volume of peripheral cells, together with multiple cell count ratios, including platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR), serve as essential predictors of rheumatologic disorder diagnosis, disease activity and severity, infectious complications, and severe organ damage [8, 9].

The Pan-Immune-Inflammation Value (PIV) is a novel biomarker calculated by multiplying neutrophil, monocyte, and platelet counts and dividing the result by the lymphocyte count [10]. This

hematological index aims to reflect the overall inflammatory burden and has been validated primarily as a prognostic indicator in various malignancies. With its growing use in oncology, PIV has also been investigated in rheumatologic diseases for its potential association with disease activity [11, 12]. Fucà et al. demonstrated in their 2020 research that PIV outperformed NLR and other established immune-inflammatory markers in predicting survival in patients with advanced colorectal cancer [10].

The Systemic immune-inflammation index (SII), which combines neutrophils and platelets and is divided by lymphocytes, serves as an inflammatory marker in medical fields including oncology and rheumatology [13, 14].

The Systemic Immune Response Index (SIRI) requires the calculation of neutrophil $\times$ monocyte/lymphocyte values. The Systemic Immune-Inflammation Index (SII) and SIRI serve as reliable markers of systemic inflammation and show promise as prognostic tools across clinical scenarios, including malignancies, stroke, cardiovascular diseases, and inflammatory disorders [15].

This study aims to evaluate the relationship between clinical and laboratory findings and novel hematological biomarkers, including the Pan-Immune-Inflammation Value (PIV), Systemic Immune-Inflammation Index (SII), and Systemic Inflammation Response Index (SIRI), which are considered to reflect the level of inflammation in BD.

2. Materials and Methods

This study included 70 patients diagnosed with Behçet's disease and tested positive for HLA-B51 and 114 individuals who tested negative for HLA-B51, all of whom presented to the Department of Medical Genetics at Samsun University Training and Research Hospital. Individuals with concomitant autoimmune diseases, endocrinological disorders, tumors, active infections, liver or kidney failure, decompensated systemic diseases, or neurological disorders were excluded from the study.

The age and sex of both the patient and control groups were recorded. In the patient group, disease duration and accompanying clinical manifestations (oral aphthae, genital ulcers, uveitis, arthralgia, erythema nodosum, papulopustular lesions) were evaluated, and systemic involvement was noted. Disease activity was assessed using the Behçet's Disease Current Activity Form (BDCAF), in which a score of ≥ 2 was considered indicative of active disease. Medication use was also recorded for each BD patient, including colchicine, corticosteroids, and immunosuppressants.

Peripheral venous blood samples were collected from all participants in the morning after an overnight 8-hour fast. Complete blood count and selected biochemical parameters were analyzed. Complete blood count variables included white blood cell (WBC) count, platelet (PLT) count, neutrophil count, lymphocyte count, and monocyte count.

From these parameters, the following systemic inflammation indices were calculated using standard formulas:

- Neutrophil-to-Lymphocyte Ratio (NLR): Neutrophil count/Lymphocyte count.
- Platelet-to-Lymphocyte Ratio (PLR): Platelet count/Lymphocyte count.
- Monocyte-to-Lymphocyte Ratio (MLR): Monocyte count/Lymphocyte count.
- Systemic Immune-Inflammation Index (SII): (Platelet count $\times$ Neutrophil count)/Lymphocyte count.

- Systemic Inflammation Response Index (SIRI): (Neutrophil count × Monocyte count)/Lymphocyte count.
- Pan-Immune-Inflammation Value (PIV): (Neutrophil count × Platelet count × Monocyte count)/Lymphocyte count.

Additionally, serum levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded.

Complete blood count (CBC) analyses were performed on K₂-EDTA anticoagulated whole blood using an automated hematology analyzer (Sysmex XN-1000; Sysmex Corporation, Kobe, Japan). Erythrocyte sedimentation rate (ESR) was determined by the Westergren method, and serum C-reactive protein (CRP) levels were measured using an immunoturbidimetric assay on a Beckman Coulter analyzer (Beckman Coulter Inc., Brea, CA, USA).

Binary logistic regression and ROC analyses were performed using BD diagnosis (patient vs control) as the dependent variable. Regression models were adjusted for age, sex, and treatment status. AUC values were reported with 95% confidence intervals. Cut-off points were determined via Youden's Index. Spearman correlation was used to evaluate relationships between BDCAF scores and inflammatory indices.

Only HLA-B51-positive BD patients were included to maintain homogeneity. HLA-B51-negative BD patients were excluded to reduce phenotypic variability and ensure a genetically consistent group.

This study was approved by the Local Ethics Committee for Clinical Research at Samsun University (Approval No: GOKAEK 2024-5/2) and conducted in accordance with the principles of the Declaration of Helsinki. Written and verbal informed consent was obtained from all participants.

2.1 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 22 software (IBM Corp., Armonk, NY, USA) on a Windows operating system. Continuous variables were expressed as mean ± standard deviation. For comparisons between groups, the Independent Samples t-test was used for parametric data, while the Chi-square test was applied for categorical variables. Binary logistic regression and ROC analyses were conducted. The relationships between variables were evaluated using Spearman correlation analysis. A p-value of <0.05 was considered statistically significant in all studies.

3. Results

A total of 70 individuals who tested positive for HLA-B51, including 33 males (47.14%), were included in the patient group. The control group consisted of 114 individuals who tested negative for HLA-B51, including 47 males (41.23%). The mean age of the patient group was 25.51 ± 16.27 years, while the control group had a mean age of 25.04 ± 15.59 years. There were no statistically significant differences between the two groups in terms of gender distribution or mean age ($p = 0.432$ and $p = 0.845$, respectively).

The mean disease duration among the 69 patients with BD was 12.4 ± 9.8 years. Oral aphthae were present in 50.7% ($n = 35$), history of uveitis in 50.7% ($n = 35$), arthralgia in 2.9% ($n = 2$), erythema nodosum in 2.9% ($n = 2$), papulopustular lesions in 2.9% ($n = 2$), pulmonary involvement in 2.9% ($n = 2$), and a history of thrombophlebitis in 2.9% ($n = 2$). No patients exhibited intestinal or

neurological involvement. Clinical activity was assessed using BDCAF, with a mean score of 1.16 ± 0.23 . Most patients were in an inactive disease state. Medication use was as follows: X% on colchicine, Y% on corticosteroids, and Z% on immunosuppressants.

Laboratory findings for both groups are presented in Table 1. Among hematologic indices, NLR and SII were significantly higher in the patient group compared to controls ($p = 0.003$ and $p = 0.001$, respectively). Other indices (PLR, MLR, SIRI, PIV) did not differ significantly. Laboratory findings for both groups are presented in Table 1.

Table 1 Comparison of hematological and inflammatory parameters between Behçet's disease patients and healthy controls. Values are presented as mean $\pm$ standard deviation. Bold values indicate statistically significant differences ($p < 0.05$).

Parameter	Control (n = 114)	Patient (n = 70)	p-value
WBC ($\times 10^9/L$)	7.9 ± 2.73	8.13 ± 3.06	0.609
Neutrophil ($\times 10^9/L$)	4.46 ± 1.96	4.76 ± 2.55	0.362
Lymphocyte ($\times 10^9/L$)	2.60 ± 1.12	2.59 ± 0.97	0.952
Monocyte ($\times 10^9/L$)	0.58 ± 0.25	0.54 ± 0.18	0.339
Platelet (PLT) ($\times 10^9/L$)	298.16 ± 77.68	309.20 ± 76.90	0.349
NLR (ratio)	1.99 ± 1.33	2.68 ± 1.75	0.003
PLR (ratio)	129.73 ± 56.64	134.13 ± 57.68	0.612
MLR (ratio)	0.24 ± 0.14	0.23 ± 0.11	0.572
MPR (ratio)	0 ± 0	0 ± 0	0.155
SII ($\times 10^9/L \times$ ratio)	582.51 ± 394.50	811.12 ± 491.35	0.001
SIRI (ratio)	1.21 ± 1.38	1.18 ± 1.06	0.894
PIV (index)	362.49 ± 402.44	363.39 ± 325.30	0.987
ESR (mm/h)	21.32 ± 16.97	17.19 ± 14.94	0.097
CRP (mg/L)	6.35 ± 10.75	5.06 ± 7.69	0.381

Abbreviations: WBC: White blood cell count; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; MPR: Monocyte-to-Platelet ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; PIV: Pan-immune-inflammation value; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

To evaluate the diagnostic utility of NLR and SII for distinguishing BD patients from healthy controls, binary logistic regression analysis was performed using BD diagnosis (not HLA-B51 status) as the dependent variable. In the multivariate model adjusted for age, sex, and medication use, both NLR and SII remained independent predictors of BD ($p < 0.05$). ROC curve analysis was used to assess the discriminative ability of NLR and SII. Results are presented in Table 2 and Figure 1.

Table 2 ROC analysis of NLR and SII for predicting Behçet's disease diagnosis.

	NLR	SII
AUC (95% CI)	0.674 (0.596–0.753)	0.694 (0.615–0.773)
Cut-off	1.91	570.63
p-value	<0.001	<0.001
Sensitivity %	64.29	68.57
Specificity %	64.04	68.42
PPV (95% CI)	52.33 (41.90–62.55)	57.10 (46.00–67.60)
NPV (95% CI)	74.49 (65.05–82.08)	78.00 (68.80–85.00)

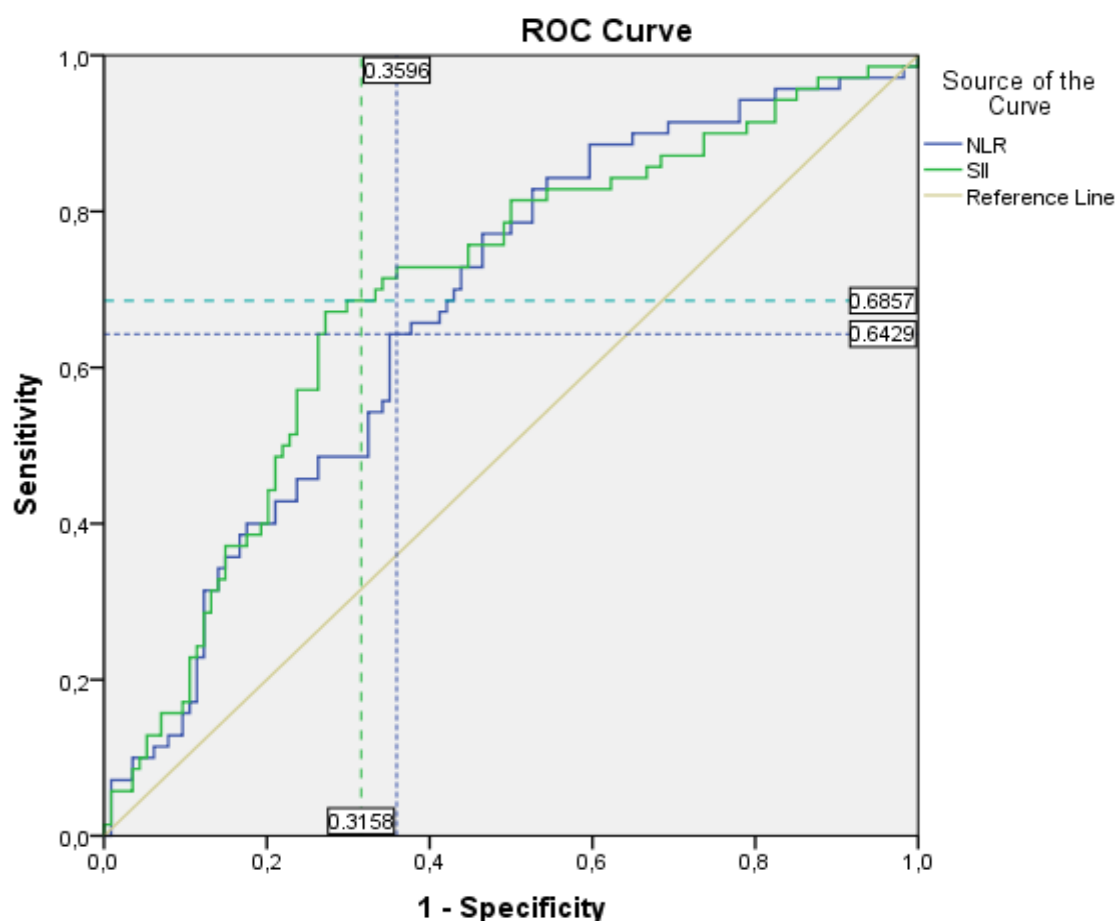


Figure 1 ROC curves for NLR and SII in predicting Behçet's disease diagnosis.

Spearman correlation analysis was performed to examine the relationship between inflammatory indices (NLR and SII) and conventional markers (CRP and ESR). Results are shown in Table 3.

Table 3 Correlation analysis of NLR and SII with ESR and CRP levels.

Group	CRP–NLR (r/p)	CRP–SII (r/p)	ESR–NLR (r/p)	ESR–SII (r/p)
Control	0.275/0.003	0.267/0.004	0.033/0.726	0.208/0.026
Patient	0.413/<0.001	0.384/0.001	0.061/0.616	0.156/0.202

Both groups showed positive correlations between NLR and SII levels, and between NLR and CRP levels. Additionally, SII levels in the control group demonstrated a positive correlation with ESR. No significant correlations were observed between ESR and either NLR or SII in the patient group.

4. Discussion

Behçet disease is a systemic vasculitis driven by complex immune dysregulation. The disease triggers an extreme activation of inflammatory pathways. Scientists have not yet identified the exact mechanisms underlying Behçet disease development. Research has identified changes in T-cell subpopulations, autoantibody production, and epigenetic modifications as factors in BD [16]. Medical professionals diagnose patients through clinical signs and symptoms, with laboratory tests and imaging methods for additional support [17].

The Complete Blood Count (CBC) indices serve as tools to detect inflammation in patients with chronic inflammatory diseases. The availability and affordability of CBC testing make it a standard tool for diagnosing and determining the severity of rheumatologic diseases [18].

The research by Alan et al. analyzed 254 BD patients through a retrospective study while using 173 healthy controls who matched the patients by age and sex. The BD patient group showed elevated white blood cell, neutrophil, and platelet counts when compared to the control group. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values were higher in BD patients than in healthy controls. The researchers divided BD patients into three groups based on disease severity and discovered that PLR and MPV values increased with more severe disease progression. The researchers studied NLR, PLR, and MPV in relation to different organ/system involvement but found no significant differences between groups. The binary forward stepwise logistic regression analysis showed that NLR independently predicted BD ($P < 0.001$; odds ratio, 2.535) [19]. Ozturk et al. demonstrated that patients with BD ($n = 65$) had elevated NLR levels compared with control subjects ($n = 62$) in a prospective study. The researchers determined that 1.29 is the NLR threshold for identifying BD [20]. Balkarli et al. conducted a retrospective study to evaluate NLR and MPV in 120 active BD patients, 66 inactive BD patients, and 79 healthy controls. The researchers found that active BD patients had elevated NLR values compared to patients with inactive BD and healthy control participants [21]. Yolbas et al. investigated the relationship between blood test results and rheumatic disease symptoms in their research. The study by Yolbas et al. revealed that BD patients with active disease presented higher NLR values than those with inactive disease. The research showed that NLR values increased in patients who had neurological symptoms and active genital ulcers [22]. Consistent with these findings, our study also demonstrated significantly higher NLR values in patients with Behçet's disease compared to healthy controls ($p = 0.003$). This result suggests that NLR may serve as a marker of inflammatory activity in Behçet's disease and indicates that this parameter, obtained from routine blood tests, could be clinically helpful in diagnosing and monitoring the disease.

The Systemic Immune-Inflammation Index (SII) served as a new complete blood count (CBC)-derived marker in this research. The SII has shown promising results in oncology practice, and medical professionals now use it as a prognostic indicator in various medical fields. The SII combines three established FBC markers of systemic inflammation, which makes it a potential tool for assessing autoimmune disease activity. Research has shown that elevated SII values are linked to increased inflammation and worse treatment outcomes [13, 23]. Evidence for the Systemic

Immune-Inflammation Index (SII) Research studies have demonstrated the clinical value of SII in BD, showing that SII levels remain elevated in patients with active BD compared to those with inactive disease and healthy controls. A major retrospective study examined peripheral inflammatory markers in BD patients and found that active BD patients showed elevated SII levels, especially when they developed cardiovascular and central nervous system complications [24, 25]. Research indicates that SII has predictive value because it shows strong connections with established inflammatory biomarkers, including CRP, ESR, NLR, and PLR. Research demonstrates that SII shows exceptional ability to distinguish between BD activity levels and identify cardiovascular disease risks in patients. The clinical utility of SII as a disease monitoring tool in healthcare settings is enhanced by its simple calculation and affordable cost, as it uses standard blood test results [25].

Research conducted in the past shows that the Systemic Immune-Inflammation Index (SII) has a proven link to vascular complications in patients with Behçet's disease. The study found that 115 out of 436 Behçet's disease patients developed vascular involvement while their SII values remained elevated at a statistically significant level ($p < 0.001$). The ROC analysis performed in this study demonstrated that SII effectively distinguished between patients with and without vascular involvement through its AUC value of 0.87 [26]. The research results match our study findings, which indicate SII functions as both a disease activity indicator and a predictive tool for severe systemic complications, including vascular involvement.

Research into the Pan-Immune-Inflammation Value (PIV) as a systemic inflammatory marker and its ability to identify different Behçet's disease (BD) clinical presentations has gained increasing attention through recent studies. A registered clinical trial evaluates PIV in BD patients through two main objectives: comparing PIV levels between patients and healthy controls of similar age and sex, and studying PIV relationships with BD symptoms and disease severity. Research shows that vascular BD patients who experience thrombotic events and endothelial damage have elevated PIV levels compared to patients with non-vascular forms of the disease [27]. Research shows that PIV is an independent risk factor for vascular complications in BD patients, as it achieves optimal diagnostic accuracy with high sensitivity and specificity. The research data showed that PIV levels were strongly linked to disease activity and vascular complications through an odds ratio of 2.758 [27].

The available evidence supports PIV as a promising biomarker for BD vascular involvement, but the results from Sjögren's syndrome and other autoimmune diseases regarding PIV discrimination have shown inconsistent findings [28].

Compared with PIV and SII, the evidence regarding the Systemic Inflammation Response Index (SIRI) in Behçet's disease is more limited. Nevertheless, the inclusion of monocyte counts alongside neutrophil and lymphocyte counts provides a strong biological rationale for its use [24]. SIRI has been shown to possess predictive and prognostic value in various inflammatory and autoimmune conditions, while its performance in Behçet's disease remains an active area of investigation. The integration of monocytes, which play a key role in chronic inflammation and immune regulation, may offer additional and unique insights into the immune dysregulation observed in Behçet's disease. Although the number of studies directly evaluating SIRI in Behçet's disease is limited, findings from related conditions suggest that SIRI may serve as a reliable biomarker reflecting both acute and chronic inflammatory processes [27]. Evidence from studies on immunological diseases further supports the notion that, similar to PIV, SIRI could contribute to a more comprehensive assessment of disease activity and potentially guide therapeutic decision-making [29]. Although

previous studies have demonstrated the predictive and prognostic value of SIRI in various inflammatory and autoimmune conditions, our study did not show a significant difference in SIRI values between patients with Behçet's disease and healthy controls ($p = 0.894$). Similarly, PIV levels did not differ significantly between the groups ($p = 0.987$). These findings suggest that further studies with larger cohorts are needed to clarify the potential role of SIRI and PIV in reflecting the inflammatory burden of BD.

5. Conclusion

In this study, complete blood count–derived inflammatory indices were evaluated to determine their utility in diagnosing Behçet's disease (BD). Among the indices studied, the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII) were significantly elevated in BD patients compared with healthy controls. Both markers demonstrated moderate diagnostic performance and correlated positively with C-reactive protein (CRP), reinforcing their association with systemic inflammation. These findings support their clinical use as cost-effective and accessible tools in the diagnostic workup and follow-up of BD.

In contrast, the systemic inflammation response index (SIRI) and pan-immune-inflammation value (PIV) did not show statistically significant differences between groups. While previous studies suggest potential utility for these indices, especially in patients with vascular involvement, our findings indicate that their routine use in general BD populations may be limited.

This study highlights the relevance of NLR and SII as inflammatory markers in BD. It encourages their further evaluation in prospective cohorts involving diverse BD subtypes, including ocular, vascular, and mucocutaneous forms.

5.1 Limitations

This study has several limitations that should be acknowledged. First, its cross-sectional design precludes causal inferences and limits the ability to evaluate the dynamics of inflammatory markers over time. Second, the sample size was relatively small, and most BD patients had low disease activity at the time of sampling. This may have reduced the sensitivity of the inflammatory indices to detect disease-related changes. Third, the study included only HLA-B51–positive BD patients, thereby enhancing genetic homogeneity but limiting generalizability to HLA-B51–negative cases. Fourth, although medication use was documented and included in multivariate analysis, drug effects on blood indices may still confound the results. Finally, the absence of subgroup analyses (e.g., vascular vs mucocutaneous BD) is another limitation.

Future studies with larger, multi-center cohorts and longitudinal follow-up are needed to clarify the diagnostic and prognostic value of NLR, SII, SIRI, and PIV in Behçet's disease and its subtypes.

Author Contributions

RA: Conceptualization, Project administration, Resources, Validation, Writing – original draft. AK: Data curation, Formal Analysis, Resources. ÖS: Conceptualization, Project administration, Resources, Validation, Writing – original draft. TK: Conceptualization, Project administration, Resources, Validation, Writing – original draft. SS: Conceptualization, Project administration, Resources, Validation, Writing – original draft. MB: Data curation, Formal Analysis, Resources.

Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

We declare that a generative AI-assisted tool was used only for language editing and grammar refinement during the preparation of this manuscript. No AI tools were used for data analysis, interpretation of results, drawing scientific conclusions, or creating original content. All scientific ideas, study design, data collection, analyses, and conclusions are the authors' own work, and the authors take full responsibility for the entire content of the manuscript.

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