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Research Article

The Role of Prognostic Nutritional Index in Vascular Behçet's Syndrome

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Abstract

Aim: This study aimed to evaluate the levels of the Prognostic Nutritional Index (PNI) in vascular and non-vascular subtypes of Behçet's Syndrome (BS) and its potential utility in distinguishing vascular involvement.

Material and Method: This retrospective cohort study included 386 patients diagnosed with BS based on ISG criteria. Patients were categorized into vascular (n=100) and non-vascular (n=286) involvement groups. Subgroup analyses assessed organ-specific patterns of involvement. PNI values were calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm^3). Statistical analyses were performed to compare PNI levels between subgroups. Additionally, ROC curve analysis was conducted to evaluate the discriminatory ability of PNI for detecting vascular involvement.

Results: Patients with vascular involvement exhibited significantly lower mean PNI values (51.7±6.6) compared to the non-vascular group (56.9±4.4, p<0.001). Neuro-Behçet's disease was significantly more frequent in the vascular group (19.0%) than in the non-vascular group (2.4%, p<0.001). However, among patients with Neuro-Behçet's disease without vascular disease, PNI values were found to be similar to the rest of the cohort. ROC analysis demonstrated that PNI effectively differentiated vascular involvement, with an AUC of 0.76, sensitivity of 72.7%, and specificity of 71%. The optimal cutoff value for PNI was determined to be 55.

Conclusion: PNI is a potential marker for identifying vascular involvement in BS. The significantly lower PNI values observed in patients with vascular involvement, coupled with its moderate discriminatory ability, suggest that PNI could serve as a valuable tool in clinical practice. Low PNI values are associated with impaired nutritional and immunological status, which may contribute to or result from the systemic inflammatory burden seen in vascular disease. Further multicenter, prospective studies are warranted to validate these findings.

Keywords: Behçet's syndrome, vascular involvement, prognostic nutritional index

INTRODUCTION

Behçet's Syndrome (BS) is a chronic, multisystemic inflammatory disorder characterized by diverse clinical manifestations, ranging from mucocutaneous lesions to life-threatening vascular complications (1). The pathogenesis of this complex and multifactorial disease remains incompletely understood; however, infectious, genetic, epigenetic, and immunological factors are thought to play significant roles in its development (2). BS presents heterogeneously, with recurrent oral and genital aphthae, uveitis, skin manifestations (e.g., erythema nodosum or acneiform lesions), gastrointestinal involvement, neurological symptoms, vascular disease, and arthritis (3). This variability requires accurate classification of patients for optimal management and prognostication. Among the various manifestations, vascular involvement is particularly serious, contributing significantly to morbidity and mortality and requiring specific therapeutic approaches (4). There remains a critical need to identify clinical or biochemical markers that can help distinguish between vascular and non-vascular forms of the disease.

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The Prognostic Nutritional Index (PNI), initially developed to assess nutritional and immunological status in oncology, is calculated using serum albumin levels and total lymphocyte count (5). In particular, the PNI, a tool used to assess nutritional and immunologic status in oncology (5), has recently emerged as a potential biomarker in various inflammatory and vascular disorders. In inflammatory rheumatic diseases, PNI has been found to correlate with disease activity, emphasizing that it can be used as a biomarker for disease activity assessment (6-8). BS, particularly its vascular subtype, represents a unique context where systemic inflammation and immune dysregulation play a pivotal role. In this setting, while markers of disease activity remain crucial for evaluating the systemic burden of inflammation, the PNI may provide additional insights by distinguishing vascular BS from its non-vascular subtypes, thus expanding its diagnostic relevance beyond disease activity alone.

However, despite the dual inflammatory and immunological underpinnings of BS, PNI utility in BS has not been extensively studied. Considering the importance of classification of BS according to vascular involvement for the correct clinical and therapeutic approach, the aim of this study was to evaluate the levels of the PNI in vascular and non-vascular subtypes of BS and its potential utility in distinguishing vascular involvement.

MATERIAL AND METHOD

Study Design and Population

This retrospective cohort study analyzed hospital records from patients diagnosed with BS between 2018 and 2023 using International Classification of Diseases (ICD) codes. Patients who met the International Study Group (ISG) diagnostic criteria and had available laboratory data for PNI calculation at the time of diagnosis or relapse were included (9). Demographic, clinical, and laboratory data were retrospectively extracted from the electronic medical records. Patients younger than 18 years old, those with other inflammatory diseases or malignancies, and those without laboratory data at the time of diagnosis or relaps were excluded from the study.

Out of 590 patients identified based on ICD codes, 204 were excluded according to these criteria. The final analysis included the remaining cohort with complete relevant data. Patients were categorized into two main groups: those with vascular involvement and those without. The "non-vascular organ involvement" group comprised patients with isolated mucocutaneous manifestations, uveitis, arthritis, Entero-Behçet's disease, or Neuro-Behçet's disease. Subgroup analyses were conducted within both the vascular and non-vascular groups to assess specific patterns of organ involvement.

To evaluate the role of systemic inflammation and nutritional status in BS, we utilized the PNI, calculated as 10×serum albumin (g/dL)+0.005×total lymphocyte/mm3. The primary focus was on comparing PNI values between vascular and non-vascular groups to assess differences and determine whether PNI could distinguish vascular involvement.

In addition, we investigated whether the observed differences in PNI values were driven by vascular involvement itself or by variations in specific organ involvements within the non-vascular group. This secondary analysis aimed to ensure that the predictive utility of PNI was not confounded by other patterns of organ involvement.

Finally, the discriminative capacity of PNI for vascular involvement was evaluated using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to assess the diagnostic performance of PNI in distinguishing patients with vascular involvement from those without.

The study protocol was approved by Ankara City Hospital Clinical Researches Ethics Committee (Date: 2023, Decision No: E1-23-4368).

Statistical Analyses

Statistical analyses were conducted using Jamovi Software v2.3 (10). Normality was tested using the Shapiro-Wilk test, along with assessments of skewness and kurtosis to characterize the distribution of each variable. Continuous variables were expressed as mean values with standard deviations (SD), while categorical data were summarized as absolute frequencies and percentages.

Group comparisons for PNI levels were conducted using the Student's t-test. The discriminative ability of PNI for vascular involvement was assessed via ROC curve analysis, with the area under the curve (AUC) calculated to evaluate its predictive accuracy. Optimal cutoff values for PNI were determined using Youden's Index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated for each index. All statistical analyses were performed at a significance level of $p<0.05$.

RESULTS

The study cohort consisted of 386 patients diagnosed with BS. The mean age of the cohort was 43.0±11.3 years, ranging from 19 to 76 years, with males constituting 50.0% of the population. Clinical manifestations were distributed as follows: vascular involvement (25.9%), isolated mucocutaneous involvement (37.8%), musculoskeletal symptoms (19.4%), ocular involvement (28.2%), Entero-Behçet (2.1%), and Neuro-Behçet (6.7%). Targeted treatments, including TNF inhibitors, cyclophosphamide, and IVIG, were used in 22.0% of cases. The overall mean PNI was 55.5±5.5, ranging between 31.0 and 74.5 (Table 1).

Table 1. Baseline characteristics of patients with Behçet's Syndrome	
Characteristic	**Overall (N=386)**
Age	
Mean (SD)	43.0 (11.3)
Range	19.0–76.0
Sex	
Male, n (%)	193 (50.0)
Clinical manifestations	
Vascular, n (%)	100 (25.9)
Mucocutaneous, n (%)	146 (37.8)
Musculoskeletal, n (%)	75 (19.4)
Eye involvement, n (%)	109 (28.2)
Entero-Behçet, n (%)	8 (2.1)
Neuro-Behçet, n (%)	26 (6.7)
Treatment	
Targeted therapies (e.g., TNF inhibitors, cyclophosphamide, IVIG), n (%)	85 (22.0)
Prognostic Nutritional Index (PNI)	
Mean (SD)	55.5 (5.5)
Range	31.0-74.5

Patients were stratified into vascular (N=100) and non-vascular (N=286) subgroups to evaluate differences in clinical and demographic parameters:

Patients with vascular involvement were older (Mean: 45.2±10.8) compared to the non-vascular group (Mean: 42.3±11.4) (p=0.028). A higher proportion of males was observed in the vascular group (69.0%) compared to the non-vascular group (43.4%) (p<0.001).

51% of the patients in non vascular groups had only Mucocutaneous involvement. Musculoskeletal involvement was more frequent in the non-vascular group (22.0%) compared to the vascular group (12.0%), p=0.029. No significant difference was noted in ocular or Entero-Behçet involvement between groups (p=0.749 and p=0.953, respectively). Neuro-Behçet was significantly more common in the vascular group (19.0%) compared to the non-vascular group (2.4%) (p<0.001). Targeted therapies were more commonly used in the vascular group (37.0%) compared to the non-vascular group (16.8%) (p<0.001). The mean PNI was significantly lower in the vascular group (51.7±6.6) compared to the non-vascular group (56.9±4.4) (p<0.001) (Figure 1).

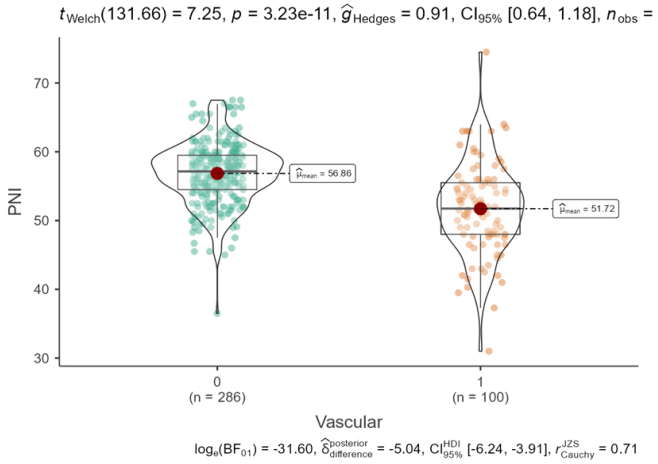

Figure 1. Distribution of Prognostic Nutritional Index (PNI) values among patients with and without vascular involvement in Behçet's Syndrome

Additionally, within the subset of patients with neurological involvement but no vascular involvement (n=7), the PNI was 59.3±7.3, which was not statistically significant from the rest (55.5±5.5, p=0.07) (Table 2).

Table 2. Comparison of characteristics between vascular and non-vascular Behçet's Syndrome groups			
Characteristic	**Non-vascular (N=286)**	**Vascular (N=100)**	**p-value**
Age			0.028
Mean (SD)	42.3 (11.4)	45.2 (10.8)	
Range	19.0 – 76.0	20.0 – 70.0	
Sex (Male), n (%)	124 (43.4)	69 (69.0)	<0.001
Isolated Mucocutaneous Involvement, n (%)	146 (51.0)	0 (0.0)	<0.001
Musculoskeletal Involvement, n (%)	63 (22.0)	12 (12.0)	0.029
Eye Involvement, n (%)	82 (28.7)	27 (27.0)	0.749
Entero-Behçet, n (%)	6 (2.1)	2 (2.0)	0.953
Neuro-Behçet, n (%)	7 (2.4)	19 (19.0)	<0.001
Treatment (e.g., TNF inhibitors, cyclophosphamide, IVIG), n (%)	48 (16.8)	37 (37.0)	<0.001
Prognostic Nutritional Index (PNI)			<0.001
Mean (SD)	56.9 (4.4)	51.7 (6.6)	
Range	36.5-67.5	31.0-74.5	
Statistical analysis was conducted using Linear Model ANOVA and Pearson's Chi-squared test			

The ROC curve analysis demonstrated that the PNI is a moderately effective tool for differentiating between vascular and non-vascular involvement in Behçet's Syndrome. The optimal cutoff value for PNI was determined to be 55, achieving an AUC of 0.76. At this threshold, the sensitivity was 72.7%, and the specificity was 87.8%, indicating moderate ability to correctly identify vascular cases (Figure 2). Additionally, the PPV was 87.8%, and the NPV was 47.7%, highlighting the stronger reliability of the test in defining vascular involvement.

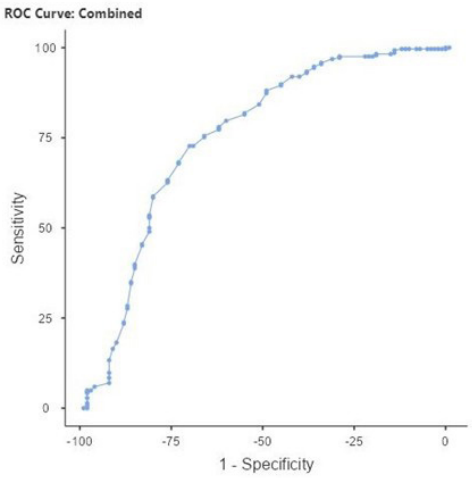

Figure 2. Receiver Operating Characteristic (ROC) curve for the use of Prognostic Nutritional Index (PNI) in distinguishing vascular from non-vascular involvement in Behçet's Syndrome. The optimal cutoff value of 55 achieved an Area Under the Curve (AUC) of 0.76, with a sensitivity of 72.7% and specificity of 71%"

DISCUSSION

This study underscores the utility of PNI as a distinguishing marker for vascular versus non-vascular involvement in BS. The observed association between low PNI values and impaired nutritional and immunological status suggests that these deficits may both drive and result from the systemic inflammatory burden characteristic of vascular disease. Importantly, our findings demonstrate that this difference in PNI values cannot be attributed solely to other organ involvements within the vascular group, such as Neuro-Behçet's disease, as evidenced by the comparable PNI values in patients with isolated neurological involvement but without vascular disease. Our study also underscores the clinical importance of vascular involvement in Behçet's Syndrome, with clear differences observed in demographic, clinical, and therapeutic parameters between vascular and non-vascular subgroups.

Vascular events develop in up to 40% of BS patients. Although vascular events can be observed at any stage of the disease, they usually develop in the early stages of the disease (11,12). The most common manifestations of vascular involvement, which mostly affect the male gender, are superficial vein thrombosis (SVT) and deep vein thrombosis (DVT), usually involving the upper or lower extremities (13,14). Vascular involvement is the main cause of morbidity and mortality (12). Early diagnosis and appropriate therapeutic intervention are critical in improving vascular BS prognosis. Regular monitoring becomes even more vital such cases. Thus, non-invasive biomarkers may play an essential role in identifying vascular involvement and facilitating timely and effective intervention.

Thrombogenesis in vascular BS results from immune-inflammatory dysfunction. In active BS, immune and inflammatory triggers cause endothelial cell damage, largely driven by activated neutrophils that congregate at these damaged sites. These neutrophils induce thrombo-inflammation, leading to platelet activation, endothelial dysfunction, and impaired fibrinolysis (14). Monocytes, the primary sources of pro-inflammatory and oxidative cytokines, further exacerbate these processes, leading to an increase in the number of monocytes and a decrease in lymphocytes (15). Systemic inflammation and abnormal immune responses then lead to significant changes in hematologic and biochemical markers.

Several studies have examined the link between these laboratory parameters and disease activity in BS. Active vascular involvement may trigger a more pronounced inflammatory response. Markers that predict immune-inflammatory response are likely to induce a more robust response in vascular involvement. However, the relationship between these markers and vascular involvement has been less extensively investigated. There are data suggesting that mean corpuscular hemoglobin concentration (MCHC) and mean platelet volume (MPV) may be predictive for vascular involvement (16-18). The Pan-Immune-Inflammation Value (PIV) has also been proposed as a predictive marker for vascular involvement in BS (19). Furthermore, studies have suggested that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with vascular BS (20,21). However, there are also articles that found no association (22). Therefore, the predictive value of these indices for vascular BS remains limited and supports the need for further investigation of inflammatory indices.

The PNI was developed as an index of nutritional status to investigate the association of the risk of postoperative complications in gastrointestinal surgery patients with baseline nutritional status (23). The index was subsequently investigated in malignancy, chronic diseases, vascular diseases and rheumatic diseases in which chronic inflammation predominates and was found to be associated with both disease activity and mortality.

Previous studies have demonstrated that PNI is associated with disease activity in conditions such as rheumatoid arthritis and systemic lupus erythematosus, indicating its role as a marker of systemic inflammation (6,8,24,25). Additionally, in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV), PNI has been identified as a useful tool at the time of diagnosis for assessing disease severity and predicting patient prognosis (7). These findings in the literature underscore the broader applicability of PNI as a marker of systemic inflammation and its potential relevance in evaluating

vascular involvement in BS. Our study adds to this growing body of evidence by highlighting PNI's utility as a differentiating index between vascular and non-vascular forms of BS.

The application of the PNI showed promising results, with a significantly lower mean PNI observed in the vascular group. ROC curve analysis further confirmed PNI as a moderately effective tool to discriminate vascular involvement with an AUC of 0.76. The PPV (87.0%) indicates that PNI may be useful in confirming vascular cases, while the moderate NPV (47.7%) highlights the need for complementary markers for ruling out vascular cases. Our study supports previous findings on the relevance of systemic inflammation markers in BS (20,21), but it uniquely highlights PNI's potential as a standalone index for vascular involvement. Unlike NLR and PLR, PNI captures both nutritional and immunological status, providing a more holistic measure of disease burden. Incorporating PNI into routine clinical practice may enhance the early detection of vascular involvement in BS, enabling timely therapeutic interventions and improved patient outcomes.

When organ involvement was compared between the groups, musculoskeletal involvement was more common in the non-vascular group, while the frequency of Entero-Behçet and uveitis was similar in both groups. In particular, Neuro-Behçet was significantly higher in the vascular group ($p<0.001$). Given that neurological involvement elicits a high inflammatory response, the question arose whether the lower PNI values observed in the vascular group could be influenced by the higher incidence of Neuro-Behçet. To address this, we specifically analyzed PNI values in the subset of patients with Neuro-Behçet but without vascular involvement and found that PNI values were higher and not significantly different from the rest of the patients ($p=0.396$). This suggests that the significantly lower PNI values observed in the vascular group cannot be attributed solely to the presence of Neuro-Behçet. The limited number of cases with isolated neuro-Behçet's syndrome in our study precludes definitive conclusions regarding the role of PNI in this subgroup. Nevertheless, our findings indicate that PNI values in neuro-Behçet's patients are comparable to those observed in the general Behçet's population and are numerically higher than those in patients with vascular involvement. Further research is required to elucidate the clinical significance of PNI in neuro-Behçet's syndrome. Thus, the reduced PNI value in the vascular group reflects a broader systemic inflammatory burden specific to vascular involvement in BS, emphasizing its utility as a marker for this particular subtype of the disease.

The study cohort was derived from a single center, which limits the generalizability of the findings. Furthermore, the cross-sectional design precludes establishing causality between PNI levels and vascular involvement. Additionally, the absence of longitudinal data and disease activity indices may limit the ability to assess the dynamic relationship between PNI levels, disease activity, and vascular involvement. Future studies with larger, multicenter cohorts and prospective designs are needed to confirm the findings and investigate the prognostic implications of PNI over time.

CONCLUSION

In conclusion, the PNI was notably lower in patients with vascular involvement, supporting its association with disease severity and systemic inflammation in BS. PNI has the potential to distinguish BS vascular involvement from non-vascular involvement. Integrating PNI into clinical practice alongside traditional clinical parameters may improve risk stratification and enhance patient follow-up outcomes by guiding personalized treatment strategies.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *The study protocol was approved by Ankara City Hospital Clinical Researches Ethics Committee (Date: 2023, Decision No: E1-23-4368).*

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