European Review for Medical and Pharmacological Sciences 2024; 28: 1751-1759

Pan-immune-inflammation value could be a new marker to differentiate between vascular Behçet's disease and non-vascular Behçet's disease

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Abstract. – OBJECTIVE: Behçet's disease etiology is uncertain, and no specific diagnostic markers exist in the laboratory. This retrospective study aimed to evaluate the role of inflammatory and hematological parameters, mainly Pan-Immune-Inflammation-Value (PIV), in predicting vascular Behçet's disease (VBD).

PATIENTS AND METHODS: A total of 85 patients with VBD and 92 patients without vascular involvement (non-VBD) were included in this study. Neutrophil, monocyte, platelet, and lymphocyte subsets are all included in the PIV, a new blood-based biomarker.

RESULTS: The optimal cut-off values for the PIV were determined to be ≥261.6. White blood cell, neutrophil, monocyte, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC), red cell distribution, platelet, plateletcrit, PIV, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, sedimentation, c-reactive protein (CRP) values were significantly associated with VBD in univariate analysis. After multivariate analysis, PIV [odds ratio (OR): 2.758; 95% confidence interval (CI): 1.327-5.736; *p*=0.007] and CRP (OR: 4.029; 95% CI: 1.924-8.438; *p*<0.001) were found to be a positive predictor for VBD, while MCHC (OR: 0.722; 95% CI: 0.530-0.983; *p*=0.039) was seen as a negative predictor.

CONCLUSIONS: Based on our results, PIV, an easily accessible, cost-effective, and new composite biomarker, has a significant predictive value in VBD.

Key Words:

Vascular Behçet's disease, Non-vascular Behçet's disease, Pan-Immune-Inflammation-Value, C-reactive protein, Mean corpuscular hemoglobin concentration.

Abbreviations

PIV: Pan-Immune-Inflammation-Value, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio.

Introduction

Behçet's syndrome (BS) is a generalized systemic vasculitis affecting veins and arteries of all sizes and types[1]. Mucosa, skin, eyes, joints, arteries, veins, gastrointestinal tract, and neurological system involvement can be seen in BS. Although its etiology is uncertain, neutrophil hyperfunction, vasculitis, and inflammatory responses are the main pathogenic characteristics of the disease[2].

Vascular Behçet's disease (VBD) has been identified[1] in BS cases complicated with vascular involvement. VBD is present in up to 40% of BS patients[3]. VBD is the primary cause of mortality in BS. Even though venous thrombosis primarily affects the lower extremities, it can also affect the superior and inferior vena cava, pulmonary artery, and cardiac cavities suprahepatic vessels[4].

Inflammation of the vascular wall is the primary pathophysiology contributing to thrombosis in BS. Hematological and biochemical values are altered due to systemic inflammation and aberrant immune response[5]. Neutrophils, lymphocytes, and platelets play a significant role in systemic inflammation and thrombosis. In addition, the coagulation pathway causes a damaged blood vessel wall, which in turn contributes to thrombosis[6,7]. In addition to the number and volume of peripheral cells, changes in multiple cell count ratios, such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR), have become important predictors of the diagnosis, disease activity, severity, infectious complications, and severe organ damage in rheumatologic disorders[8,9].

The Pan-Immune-Inflammation-Value (PIV) is a novel blood-based biomarker that includes neutrophil, monocyte, platelet, and lymphocyte

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subsets[10]. Fucà et al[11], in 2020, showed that PIV performed better than previous immune-inflammatory biomarkers, such as NLR, in predicting survival outcomes in advanced colorectal cancer patients.

In clinical practice, hematological and inflammatory laboratory tests are easily accessible and cost-effective. Recent studies[5,9,12-14] investigated the relation of hematological parameters with BS and vascular involvement. Nevertheless, the predictive value of PIV in VBD has not yet been evaluated. Hence, we planned the present study to address these issues specifically.

Patients and Methods

Study Population

A total of 85 VBD patients and 92 patients without vascular involvement (non-VBD) were recruited from the Department of Rheumatology of the Faculty of Medicine in Bursa Uludag University between January 2000 and September 2022. All BD patients fulfilled the 1990 International Study Group (ISG) criteria[15] or the International Criteria for Behçet's Disease (ICBD)[16]. According to the Behçet Severity Score, all patients with VBD were in the moderate or severe group. Therefore, non-VBD patients were also chosen from moderate or severe groups. This score was calculated by assigning 1 point for each mild symptom (oral ulcers, genital ulcers, skin lesions, arthralgia, recurrent headaches, epididymitis, mild gastrointestinal symptoms, pleuritic pain, and superficial vein thrombosis), 2 points for each moderate symptom (arthritis, deep vein thrombosis in the legs, anterior uveitis, and gastrointestinal bleeding), and 3 points for each severe symptom (posterior/panuveitis, retinal vasculitis, arterial thrombosis or aneurysms, central vein thrombosis, neuro-involvement, and bowel perforation)[17]. Behçet's Severity Scores were grouped as follows: mild disease with a score <4, moderate disease with a score between 4 and 6 points, and severe disease with a score ≥7[18]. BS patients who received corticosteroid or immunosuppressive therapy and had incomplete data were excluded from the study.

Data Collection

Patient's demographic characteristics (gender, age, age of disease onset), presence of oral and/or genital aphthae, skin involvement such as erythema nodosum and folliculitis, joint involvement, neurological involvement, eye involvement, intestinal involvement, and involvement sites of patients with VBD were evaluated. Inflammatory tests [sedimentation, c-reactive protein (CRP)] and complete blood count at the time of diagnosis were recorded. Using the ratio of neutrophil, monocyte, and platelet counts to lymphocyte count, NLR, MLR, and PLR were calculated. The PIV was calculated by multiplying the neutrophil count (10^9/L) by the platelet count (10^9/L) and the monocyte count (10^9/L), and then dividing the result by the lymphocyte count (10^9/L).

Statistical Analysis

Statistical analysis was performed using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Sofware trial version 20.009 (MedCalc Sofware bv, Ostend, Belgium; available at: www.medcalc.org). The Shapiro-Wilk test was used to evaluate the normal distribution of variables. Descriptive statistics are used to present the general characteristics of patients (median, ranges, counts, and percentages). The Mann-Whitney U test for continuous variables and the Chi-squared test for categorical variables were used to compare groups. Univariate and multivariate logistic regression analyses were performed to determine the predictors of VBD. Binary logistic regression analysis was used for multivariate analysis, including the variables having a *p*-value below 0.25 in univariate analysis. The receiver operating characteristic (ROC) curve analysis was performed to identify the predictive performance of NLR, MLR, PLR, and PIV on VBD. The *p*-value <0.05 was considered statistically significant.

Results

The descriptive characteristics and clinical manifestations of the two groups are given in Table I. In the VBD group, there were 70 male participants with a mean age of 31.0±0.9 (13.1-49.5). On the other hand, 56 male participants are included in the non-VBD group with a mean age of 32.3±0.9 (12.9-56.6). While the age distribution of the groups was similar, the male gender was significantly higher in the VBD group. Oral aphthae were present in all patients. The presence of genital aphthae, uveitis, gastrointestinal involvement, epididymitis, human leukocyte antigen (HLA) B51, and

Table I. Descriptive characteristics, clinical manifestations in patient groups with vascular Behçet's disease and non-vascular Behçet's disease.

Characteristics		Vascular Behçet's disease N = 85 (48%)	Non-vascular Behçet's disease N = 92 (52%)	*p*-value
Age of Behçet's disease diagnosis	Mean ± SD (Range, years)	31.0 ± 0.9 (13.1-49.5)	32.3 ± 0.9 (12.9-56.6)	$p = 0.371$
Gender	Male	70 (82.4)	56 (60.9)	$\mathbf{p = 0.003}$
	Female	15 (17.6)	36 (39.1)	
Genital aphthae	Present	66 (77.6)	74 (80.4)	$p = 0.787$
	Absent	19 (22.4)	18 (19.6)	
Neurological involvement	Present	21 (24.7)	9 (9.8)	$\mathbf{p = 0.015}$
	Absent	64 (75.3)	83 (90.2)	
Uveitis	Present	34 (40.0)	4 (52.2)	$p = 0.105$
	Absent	51 (60.0)	88 (47.8)	
Gastrointestinal tract involvement	Present	1 (1.2)	-	$p = 0.370$
	Absent	84 (98.8)	92 (100)	
Epididymitis	Present	1 (1.2)	8 (8.6)	$p = 0.480$
	Absent	84 (98.8)	84 (91.4)	
Arthritis	Present	12 (14.1)	31 (33.7)	$\mathbf{p = 0.004}$
	Absent	73 (85.9)	61 (66.3)	
Skin involvement	Present	55 (64.7)	75 (81.5)	$\mathbf{p = 0.018}$
	Absent	30 (35.3)	17 (18.5)	
HLA B51	Present	57 (67.1)	61 (66.3)	$p = 0.915$
	Absent	28 (32.9)	31 (33.7)	
Pathergy	Present	25 (29.4)	33 (35.9)	$p = 0.694$
	Absent	60 (70.6)	59 (64.1)	

SD: Standard deviation, HLA: Human leukocyte antigen.

pathergy were similar in the two groups. Neurological involvement was significantly higher in the VBD group (p=0.015). Skin involvement and arthritis were significantly higher in the non-VBD group (p=0.018 and p=0.004, respectively). The most common site of vascular involvement was deep vein thrombosis, observed in 65.9% of the VBD group (n=56). Other sites of vascular involvement are given in Table II. While the mean CRP value was 1.6±0.2 (0.2-14.4) in the VBD group, it was found to be 0.4±0.5 (0.1-4.3) in the non-VBD group. ROC analysis values for the area under the curve, sensitivity, and specificity are presented in Table III and Figure 1. The cut-off values for PIV, NLR, PLR, and MLR were determined to be ≥261.6, ≥1.7, ≥114.8, and ≥0.25, respectively. The ROC curve analysis revealed that PIV is a significant predictor of VBD.

After univariate logistic regression analysis, 14 parameters, including white blood cell (WBC), neutrophil, monocyte, hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution (RDW), platelet (PLT), plateletcrit (PCT), PIV, NLR, PLR, sedimentation, CRP, with p<0.25 were included in the multivariate logistic regression analysis (Table IV). On multivariate analysis, MCHC [odds ratio (OR): 0.722; 95% confidence interval (CI): 0.530-0.983; p=0.039] was found as a negative predictor for VBD, while PIV (OR: 2.758; 95% CI: 1.327-5.736; p=0.007) and CRP (OR: 4.029; 95% CI: 1.924-8.438; p<0.001) were found to be positive predictors for VBD (Table IV).

Discussion

In this study, we revealed for the first time that a new inflammatory score, PIV, can be considered as one of the independent predictors for VBD, as well as other well-studied laboratory parameters such as CRP and MCHC.

VBD is generally a rare but severe condition[19]. It can affect arterial and venous vessels of any size and involves arterial aneurysms, venous thrombosis, arterial occlusions, or stenosis[20]. The majority of vascular involvement is made by venous thromboses[1]. In this study, more than half of VBD patients had venous thromboses, most common in deep veins of the lower extremities.

Table II. Involvement sites in vascular Behçet's patients.

Characteristic		Vascular Behçet's N =85 (%)
Venosus involvement		72 (84.7)
Arterial involvement		6 (7.1)
Venosus and arterial involvement		7 (8.2)
Deep vein thrombosis	Present	56 (65.9)
	Absent	29 (34.1)
Dural sinus thrombosis	Present	17 (20.0)
	Absent	68 (80.0)
Inferior vena cava thrombosis	Present	2 (2.4)
	Absent	83 (97.6)
Superior vena cava thrombosis	Present	2 (2.4)
	Absent	83 (97.6)
Superficial thrombophlebitis	Present	5 (5.9)
	Absent	80 (94.1)
Hepatic vein thrombosis	Present	2 (2.4)
	Absent	83 (97.6)
Pulmonary artery thrombosis	Present	7 (8.2)
	Absent	78 (91.8)
Pulmonary artery aneurysm	Present	3 (3.5)
	Absent	82 (96.5)
Peripheral artery disease	Present	2 (2.4)
	Absent	83 (97.6)
Portal vein thrombus	Present	3 (3.5)
	Absent	82 (96.5)
Right main iliac artery aneurysm	Present	1 (1.2)
	Absent	84 (98.8)

VBD is more common in men[21]. Similar to the available literature, the VBD presence was found to be significantly higher in the male gender in this study.

Inflammation and coagulation are two interdependent processes that are strongly related and capable of igniting one another[22,23]. However, the fundamental mechanisms of this phenomenon are still unknown. Through a variety of mechanisms, inflammation increases clotting by disturbing the balance between procoagulant and anticoagulant substances. Inflammation is defined as the activation of various types of cells, such as leukocytes, platelets, and endothelial cells, and the production of inflammatory molecules, including chemokines, cytokines, adhesion molecules, and microparticles[24]. Leukocytes, especially neutrophils, play an essential role in atherogenesis and thrombosis[25]. The majority of tissue damage is caused by neutrophils, and BS patients exhibit an inherent hyperactivation of neutrophils. The primary sources of proinflammatory and oxidative cytokines are also monocytes. Inflammatory processes typically cause a rise in monocytes and a decrease in lymphocytes[9]. Platelets are activated in BD and produce microparticles that induce a procoagulant and pro-inflammatory state, altering vascular function and promoting the course of vasculitis[26].

Table III. Receiver operating characteristic curve analyses for vascular Behçet's disease.

Curve	Cut-of value	AUC	95% CI	*p*-value	Sensitivity (%)	Specificity (%)
PIV	261.6	0.654	0.573-0.735	< 0.001	75.3	55.4
NLR	1.7	0.578	0.494-0.663	0.072	76.0	40.0
PLR	114.8	0.570	0.485-0.654	0.111	54.1	59.8
MLR	0.25	0.531	0.446-0.617	0.470	54.1	56.5

AUC: Area under the curve, CI: Confidence interval, PIV: Pan-immune-inflammation-value, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio.

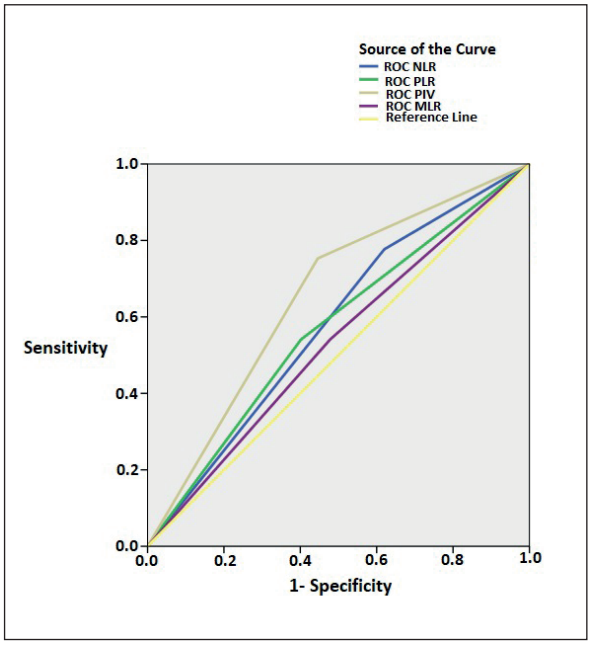

Figure 1. Receiver operating characteristic curve analysis for PIV, NLR, PLR, and MLR.

To our knowledge, few studies[27,28] have evaluated NLR and PLR in VBD despite the fact that there are numerous studies about NLR, PLR, and BS. Atherosclerosis, atherosclerotic heart disease, and severe cardiovascular issues have all been related to abnormally high platelet counts in various studies[29]. Jensvoll et al[30] reported a correlation between pre-cancer platelet count and the incidence of symptomatic venous thromboembolism in cancer patients but not in those without cancer. They also demonstrated that the synergistic effect of higher platelet and leukocyte counts resulted in a threefold increase in the risk of venous thromboembolism.

Despite the fact that our study's univariate analysis revealed statistically significant higher NLR and PLR in VBD, multivariate analysis revealed no association. In the study by Okatan et al[27], both NLR and PLR were significantly higher in patients with thrombosis, but a multivariate analysis was not performed. Erden et al[28] reported that both NLR and PLR were significantly

Table IV. Univariate and multivariate logistic regression analysis of laboratory parameters predictive for vascular Behçet's disease.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
WBC (10^9/L)	**1.171**	**1.047-1.310**	**0.006**	1.039	0.894-1.208	0.614
Neutrophil (10^9/L)	**1.178**	**1.043-1.330**	**0.008**	0.803	0.583-1.106	0.180
Lymphocyte (10^9/L)	0.892	0.616-1.291	0.544			
Monocyte (10^9/L)	**4.454**	**1.188-16.699**	**0.027**	0.666	0.077-5.132	0.630
Eosinophil (10^9/L)	0.637	0.257-1.578	0.330			
RBC (%)	0.909	0.558-1.480	0.701			
Hb (g/dL)	**0.877**	**0.727-1.059**	**0.173**	1.004	0.772-1.307	0.974
Hct (%)	0.988	0.931-1.049	0.694			
MCV (fL)	0.992	0.956-1.029	0.664			
MCH (pg)	**0.856**	**0.751-0.974**	**0.019**	0.953	0.862-1.052	0.340
MCHC (g/L)	**0.705**	**0.541-0.917**	**0.009**	**0.722**	**0.530-0.983**	**0.039**
RDW (%)	**1.175**	**1.026-1.346**	**0.020**	1.061	0.888-1.267	0.515
PLT (10^9/L)	**1.000**	**1.000-1.000**	**0.099**	1.00	1.00-1.00	0.200
MPV (fL)	1.006	0.986-1.025	0.568			
PCT (%)	**56.450**	**0.501-6,358.561**	**0.094**	29.038	0.029-291410.100	0.340
PIV	**3.791**	**1.995-7.203**	**< 0.001**	**2.758**	**1.327-5.736**	**0.007**
NLR	**2.133**	**1.101-4.133**	**0.025**	0.817	0.258-2.590	0.731
MLR	1.287	0.713-2.324	0.403			
PLR	**1.753**	**0.966-3.183**	**0.065**	1.441	0.508-4.090	0.492
Sedimentation (mm/h)	**1.028**	**1.010-1.047**	**0.003**	0.991	0.964-1.019	0.511
CRP (mg/dL)	**5.130**	**2.499-10.533**	**< 0.001**	**4.029**	**1.1924-8.438**	**< 0.001**

WBC: White blood cell, RBC: Red blood cell, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PIV: Pan-immune-inflammation-value, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, CRP: C-reactive protein, OR: Odds ratio, CI: Confidence interval.

higher in deep venous thrombosis on univariate analyses, but only PLR was found to be significantly higher in multivariate analysis.

To our knowledge, no research in the literature has yet evaluated PIV in VBD patients. Malignancies typically had higher PIV, which was linked to a poor prognosis and worse overall survival[31-33]. Murat et al[34] found that PIV has a better predictive value than PLR and NLR associated with short and long-term mortality in ST-elevation myocardial infarction. In a study conducted by Tunca and Kazan[35] in patients with IgA nephropathy, PIV was proved to be a reliable marker for predicting the response to steroids after six months. PIV was also identified to be a significant and independent risk factor of all-cause mortality in antineutrophil cytoplasmic antibody-associated vasculitis in rheumatology[36]. Erturk et al[37] found no significant difference between the PIV of patients with recurrent aphthous stomatitis and BS. In our research, multivariate analysis revealed that PIV was statistically significantly higher in VBD. There are only three factors in composite biomarkers: NLR, PLR, and MLR. Fest et al[38] showed that a novel marker, namely PIV, involving four inflammatory cell types (platelets, neutrophils, monocytes, and lymphocytes) has more predictive value than other composite biomarkers. In cancer patients, biomarkers with three or more elements have been shown to be better predictors than those that have one or two, according to previous studies[11,32,39]. PIV may have been better than other composite biomarkers in our study because it contains the four most critical components of inflammation.

In our research, CRP also had a significant predictive value for VBD in addition to PIV. CRP is an acute-phase protein of hepatic origin that elevates in response to the release of interleukin-6 by macrophages and T cells, indicating the severity of inflammation. The level of CRP is increased in diseases such as inflammation, infections, and cancers. Ridker et al[40] showed that CRP is a significant predictor of the risk of cardiovascular events in women. Yong et al[41] showed that sedimentation and CRP were higher in VBD patients than in patients with only mucocutaneous involvement, but the difference between these groups was insignificant. Despite their high sensitivity in detecting an inflammatory state, the lack of specificity of CRP in differentiating the underlying cause limits their clinical usefulness in diagnosing or assessing a specific illness[42]. Hyperexpression of acute phase reactants such as CRP, which binds to targeted antigens at the site of inflammation, and enhanced fibrinogen release from injured tissue may explain the elevated level of CRP in BD patients[43].

In this study, MCHC was significantly lower in VBD patients on multivariate analyses. In the study of Cheng et al[5], both MCH and MCHC were significantly lower in patients with vascular involvement, but the multivariate analysis was not performed. Vayá et al[44] proposed that oxidative stress in red blood cells might have a role in various disorders, including BD. Activated neutrophils cause oxidative damage to red blood cells and produce changes in structure and function, including area-to-volume ratio, membrane viscoelasticity, and internal viscosity (mean corpuscular volume and MCHC)[45]. This condition alters erythrocyte deformability, activates platelets, and leads to endothelial cell damage and hypercoagulability in BD[46,47]. These characteristics imply a possible relation between red blood cells, neutrophils, and platelets during inflammatory injury and thrombosis in BS.

Limitations

Notable limitations of our study include its presentation of the experience of a single center, its retrospective design, and the inclusion of individuals of Turkish ethnicity only. Behçet activity index could not be evaluated due to the lack of retrospective data in the activity index. Nevertheless, the Behçet Severity Score was evaluated, and since the patients with VBD fell into the moderate and severe group, the moderate and severe group in non-VBD was also included in the research.

Conclusions

Based on our results, PIV, an easily accessible, cost-effective, and new composite biomarker, seems to have a significant predictive value in VBD. However, further studies are needed to confirm our results.

Conflict of Interest
The authors declare that they have no conflict of interest.

Funding
None.

Authors' Contributions

T. Ocak designed and managed the study. T. Ocak, B. Yagız, N. Lermi, and Z.Y. Bozkurt extracted the data. T. Ocak performed the analyses and wrote the manuscript. T. Ocak, B.N. Coskun, E. Dalkılıc, and Y. Pehlivan provided comments on drafts of the manuscript. Y. Pehlivan revised the article. All authors agreed to be accountable for the work.

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Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

Our research was conducted in conformity with the Helsinki Declaration. The Clinical Research Ethics Committee of Bursa Uludag University Faculty of Medicine approved the study (approval number: 2022-18/11).

Informed Consent

Not applicable due to the retrospective design of the study.

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