

Which is Best for Predicting Uveitis in Behçet's Syndrome: Systemic Immune Inflammatory Index, Mean Platelet Volume, Platelet/Lymphocyte Ratio, or Neutrophil/Lymphocyte Ratio?

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ABSTRACT

Objective: Behçet's Syndrome (BS) is a multisystemic disease characterized by oral and genital ulcers, which can cause vasculitis that can affect all size of the vessels. We aimed to investigate the power of predicting uveitis of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) and a new parameter, the systemic inflammatory immune index (SII).

Methods: Two hundred four patients with BS were enrolled at Kayseri City Education and Research Hospital, whose follow-up continued from July 2018-September 2020. Thirty-three patients were excluded because of history of cancer, colchicine use, arthritis at the time of diagnosis and complete blood count parameters being excessively higher or lower than the limit values. Of the remaining 171 patients, 35 uveitis patients' NLR, PLR, MPV and SII at the time of uveitis were compared with the results of patients without uveitis.

Results: The sensitivity of NLR in predicting uveitis was calculated as 74.3% and specificity was 64.7%. The sensitivity and specificity of SII, in predicting uveitis, were 62.9% and 65.4%, respectively. The area under the ROC curve for NLR was 0.684 and ($P = 0.001$). In addition, the area under the curve for SII was 0.662 ($P = 0.003$). Again for PLR and MPV, the area under the ROC curve was found as 0.566 and 0.428, respectively ($P = 0.188$ and 0.230, respectively).

Conclusion: There is no specific test that can precisely predict BS and its complications. . These findings suggest that NLR is a better marker than SII, MPV and PLR in predicting anterior uveitis in patients with BS.

Keywords: Behçet's syndrome, uveitis, systemic immune inflammatory index, mean platelet volume, platelet /lymphocyte ratio, neutrophil/lymphocyte ratio

INTRODUCTION

Behçet's syndrome (BS) is a multisystemic disease characterized by oral and genital ulcers, vasculitis, which can be affect any size of vessels, arthritis, especially in the lower extremity, eye involvement, and both vascular and parenchymal damages in the central nervous system.¹ Although it causes quite a variety of morbidity, the etiopathogenesis of the disease has not been clearly elucidated yet.² Although the most distinctive form of involvement in the eye is nongranulomatous posterior uveitis; anterior, intermediate uveitis, and optic neuropathy can also occur. There are characteristic vascular involvements such as thrombosis in lower extremity veins and pulmonary arterial aneurysm.³ Although the pathergy test can be used as an auxiliary test in BS, there is no test that can be used as a gold standard in diagnosis. In addition, there are still no markers that can

predict joint, intestinal, central nervous system, eye, and vascular involvements.

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and mean platelet volume (MPV) have been studied in many diseases, especially in cancers and atherosclerotic conditions, in which inflammation is blamed in the etiology.⁴⁻⁶ In addition, the systemic immune inflammatory (SII) index, which has been a popular marker for the last few years, has also been studied as a marker in predicting diagnosis and prognosis in many diseases, especially cancers.⁷⁻⁹

In this study, we aimed to investigate whether SII, NLR, PLO, and MPV predict eye involvement in BS, especially in the form of uveitis, and to examine the sensitivity and specificity of

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these parameters and investigate their superiority to each other.

METHODS

Patient Selection

Two hundred and four BS patients, whose follow-up and treatment were continued in the rheumatology and ophthalmology outpatient clinics between July 1, 2018 and September 1, 2020 at Kayseri City Education and Research Hospital, were included in the study. The diagnosis of uveitis/iridocyclitis of the patients was made by the ophthalmologists in the uvea clinic, which is the ophthalmology subunit of the same hospital (uveitis group). Patients known to have BS and who did not have any uveitis/iridocyclitis during routine rheumatology and ophthalmology examinations were included as the control group.

SII was calculated as neutrophil \times platelet/lymphocyte in complete blood count. In people who had uveitis, the complete blood counts at the time of the relevant attack were taken as basis, while the blood counts in the control group were based on the blood counts of the patients in their first outpatient clinic visits. Patients who exceeded some of the following limits in the complete blood count of the patients were excluded from the study: platelet count 150,000–400,000 mm^{-3} , leukocyte count 4,000–10,000 mm^{-3} , neutrophil count 2,000–7,000 mm^{-3} , lymphocyte 1,300–3,500 mm^{-3} , and hemoglobin 11–16 g dL^{-1} . Patients with neurobehçet and pulmonary aneurysmatic changes, articular, intestinal, vascular, or ocular involvements were excluded in the first outpatient clinic examination. Among the patients with other autoimmune diseases (familial Mediterranean fever, ankylosing spondylitis, rheumatoid arthritis, Hashimoto's thyroiditis, etc.), who used colchicine, steroids, and other immunosuppressive treatments within 3 months before their outpatient clinic visit, and those with solid or hematological malignancies were also excluded. One of the 204 BS patients had a history of breast cancer, eight of them had started using colchicine, which was previously started by the family doctor or internal medicine specialist, and seven of them had articular involvement at the time of diagnosis. Also, 16 patients with values higher or lower than the above limit values in complete blood counts were also excluded. Since a total of 33 patients were excluded, analyzes were made on 171 patients.

Demographic data of the patients, C-reactive protein (CRP) and erythrocyte sedimentation rates, MPV, NLR, PLR, and SII were

compared, and the sensitivity and specificity data of the relevant data were analyzed.

Consent was obtained from the patients in accordance with the Declaration of Helsinki for participation. This study was approved by the Turkish Republic Ministry of Health, Kayseri City Education and Research Hospital Ethics Committee on November 5, 2020 (study number 43)

Statistical Analysis

Percentages and total percentages are used for the frequencies. Demographic tables were created for these rates. Kolmogorov–Smirnov test was used to check the normal distribution of the data. To compare the groups of continuous data without normally distributed, the Mann–Whitney U test was used. Student t test was used for normally distributed continuous data. Regression models were created to determine whether NLR, PLR, MPV, and SII; age; CRP; sedimentation; and gender were associated with uveitis/iridocyclitis. Correlation tables were made for variables. Receiver-operating characteristics (ROC) curves were drawn, and the area under the curves (AUC) were calculated. In the prediction of uveitis/iridocyclitis, NLR, PLR, MPV, and SII sensitivity and specificity values were chosen to correspond to the best relevant Youden index value calculated as follows: Youden index = sensitivity + specificity – 1. All *P* values were given bivalent. It was performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM SPSS Corp.; Armonk, NY, USA). Probability values $<.05$ were considered as significant.

RESULTS

Seventy eight of 171 (45.6%) patients who participated in our study were male, and the mean age of the patients was 39.3 ± 10.9 years. Thirty-five of 171 (20.5%) patients had involvement in the form of uveitis/iridocyclitis. In the uveitis group, the number of men was 26/35 (74.3%), while the number of women was 9/35 (25.7%) ($P < .001$). The mean age of the uveitis group was 39.2 ± 12.0 , while the mean age of the control group was 39.4 ± 10.7 ($P = .947$). The demographic and clinical data of the patients are summarized in [Table 1](#).

NLR median value of patients in the uveitis group was 2.46 (2.04–2.93), while it was 1.85 (1.45–2.55) in the control group ($P = .001$). The SII median value of the patients in the uveitis group was 640,656.72 mm^{-3} (483,750.00–865,000.00), while it was 487,529.83 mm^{-3} (380,343.75–665,720.69) in the control group ($P = .003$). The PLR median value of the uveitis group was 123.92 (102.69–158.24), while the PLR median value of the control group was 116.46 (92.65–147.70) ($P = .230$). Mean MPV values were 9.00 ± 1.40 and 9.44 ± 1.37 in the uveitis and control groups, respectively ($P = .098$). The sensitivity and specificity for predicting uveitis for the 2.120 cut off value of the NLR were calculated as 74.3% and 64.7%, respectively (likelihood ratio = 2.105). The sensitivity and specificity for predicting uveitis for the cut off value of 563,569.70 of SII, which is another statistical difference between the two groups, were determined to be 62.9% and 65.4%, respectively (likelihood ratio = 1.819). Relevant NLR, SII, PLR, and MPV values in both groups, the power of these values in predicting uveitis, sensitivity/specificity

Main Points

- NLR is found to be a good predictor of uveitis in patients with BS.
- Another effective predictor of uveitis in BS is SII.
- NLR predicts uveitis with a sensitivity of 74.3% and a specificity of 64.7%.
- Although the NLR and SII seem to be a good predictor of uveitis, it should be kept in mind that the diagnosis of uveitis is mainly by an appropriate eye examination performed by experienced specialists.

Table 1. The Demographic and Clinical Data of the Uveitis Group and Control Group

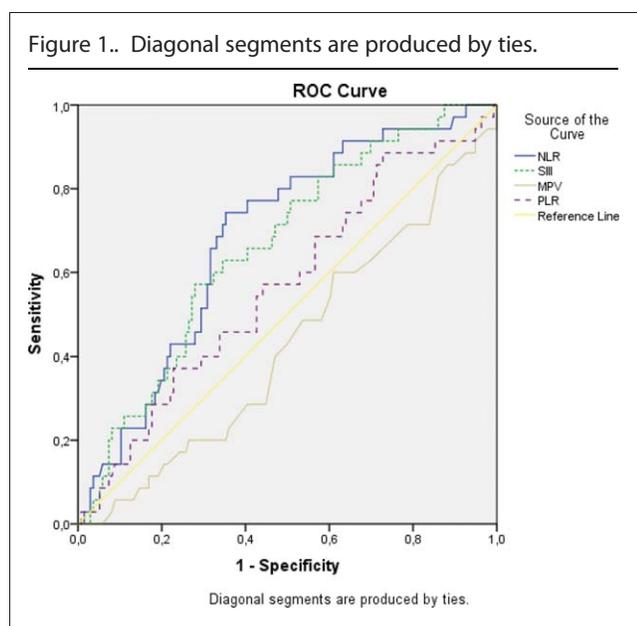
	Uveitis Group (n = 35)	Control Group (n = 136)	P value
Age (years), mean ± SD	39.2 ± 12.0	39.4 ± 10.7	.947
Men, no. (%)	26 (74.3)	9 (25.7)	<.001
BMI (kg m ⁻²), median ± SEM	26.52 ± 4.26	26.84 ± 4.13	.965
Smoking, no (%)	20 (57.14)	72 (52.94)	.657
CRP (mg dL ⁻¹), median ± SEM	11.89 ± 34.21	5.82 ± 12.56	.094
ESR (mm), median ± SEM	12.26 ± 14.82	13.62 ± 13.00	.593

Abbreviations: SD, standard deviation; No, number; BMI, body mass index; SEM, standard error of the mean; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2. The Sensitivity, Specicity, Likelihood Ratios, Positive Predictive Values, and Negative Predictive Values of NLR, SII, MPV, and PLR for Predicting Uveitis

	Uveitis Group (n = 35)	Control Group (n = 136)	P Value	Cut Off Value	Sensitivity (%)	Specificity (%)	Likelihood Ratio	PPV (%)	NPV (%)
NLR, median ± SEM	2.46 ± 0.14	1.85 ± 0.07	0.001	2.120	74.3	64.7	2.105	35.1	90.7
SII (mm ⁻³), median ± SEM	640,656.72 ± 39,028.69	487,529.83 ± 23,218.25	0.003	563569.70	62.9	65.4	1.819	31.9	87.3
PLR, median ± SEM	123.92 ± 7.64	116.46 ± 3.65	0.230	121.140	57.1	55.9	1.295	25.0	83.5
MPV (fL), mean ± SD	9.00 ± 1.40	9.44 ± 1.37	0.098	8.850	60.0	39.0	0.983	20.2	79.1

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; SEM, standard error of the mean; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; MPV, mean platelet volume; fL, fL femtolitre; SD, standard deviation.



criteria, likelihood ratios, positive predictive values, and negative predictive values are summarized in Table 2.

Area under the ROC curve was 0.684 for NLR (95% confidence interval (CI), 0.591 to 0.776; *P* = .001). In addition, the AUC for SII was 0.662 (95% CI, 0.567 to 0.757; *P* = .003). Also, the area under the ROC curve for PLR and MPV was calculated and found to be 0.566 and 0.428, respectively (95% CI, 0.460 to 0.672 and 0.324 to 0.532; *P* values .188 and .230, respectively) (Figure 1).

When the correlation of uveitis and related variables was examined, it was found to be significant as gender (*R*: 0.292, *P* < .001), NLR (*R*: 0.257, *P* : .001), and SII (*R*: 0.227, *P* : .003). The relationship between the uveitis and gender was the strongest, while the second strongest relationship was in the NLR (Table 3).

DISCUSSION

The most important finding of our study is that NLR is the best predictor of eye involvement in the form of uveitis from MPV,

Table 3. Correlation of Uveitis and Related Variables

	Gender	Age	BMI	CRP	ESR	NLR	SII	PLR	MPV
r value	0.292	-0.014	0.014	-0.010	-0.076	0.257	0.227	0.092	-0.101
P value	<.001	.853	.857	.894	.320	.001	.003	.231	.188

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index; PLR, platelet to lymphocyte ratio; MPV, mean platelet volume.

NLR, PLR, and SII in BS, and NLR predicts uveitis with a sensitivity of 74.3% and a specificity of 64.7%. Our other important finding is that SII predicts uveitis with a 62.9% sensitivity and 65.4% specificity, although not as much as NLR. However, it has been observed that MPV and PLR have very limited predictive power of predicting uveitis. Although the aim of this study is to compare the power of predicting uveitis of NLR, SII, PLR, and MPV, it was also seen that one of the most important risk factor for uveitis is male gender, in line with the literature.¹⁰ In a study in which Tugal-Tutkun et al.¹¹ analyzed 880 patients, it was observed that men were exposed to uveitis more frequently, had earlier ages of onset, and had a more severe and bilateral involvement rate. We see that hematological parameters such as NLR, MPV, SII, and PLR are frequently studied, especially in cancerous diseases. NLR is the most studied parameter among the parameters counted.^{12–14} According to a study by Soyulu et al.,¹⁵ NLR was found to be associated with clinical and angiographic risk scores in non-ST segment elevated acute coronary syndromes (NSTE-ACS). In the related study, it has been shown that low NLR can be a good predictor for low in-hospital mortality and simple coronary anatomy in NSTE-ACS patients.

MPV is advocated by Atas et al.¹⁶ as a simple measure for indirectly showing platelet activity and thrombotic potential. In this study, it has been shown that MPV and also erythema nodosum are independent risk factors for vascular thrombosis in BS. However, there are studies showing the opposite of this argument. In a study by Balkarlı et al.¹⁷ active BS patients were compared with inactive BS and healthy controls, and it was observed that MPV was similar in all three groups. Another finding of the study is that NLR was found higher in the active patient group compared to inactive patients and healthy controls. In our study, in parallel with the study of Balkarlı et al., we determined that although MPV is not sufficient in predicting uveitis, NLR is the most sensitive and specific parameter among the parameters examined. Although there are some studies involving NLR, SII, MPV, and PLR for BS and related complications, their comparison with each other has not been clearly examined, and a study analyzing a relatively new data such as SII in uveitis patients in BS could not be found in the literature.

The etiopathogenesis of BS is still unclear, but previous studies have shown that vasovazorum inflammation and endothelial cell activation dominated by neutrophils are the cause of vascular damage.¹⁸ Indeed, neutrophils have been shown to be hyperactive in BS patients, possibly with an additive effect related to HLAB51, and are the main cells that infiltrate not only

oral and genital ulcers or erythema nodosum but also other areas such as the eye, central nervous system, and vascular wall.¹⁹ After the neutrophils are activated in BS, there is a serious production of reactive oxygen molecules during nicotinamide adenine dinucleotide phosphate-H (NADPH)-mediated oxidative explosion, and the fibrinogen structure is changed due to inflammation. Finally, it has been revealed that fibrinogen, whose structure has changed, often causes thrombus formation that is tightly adhered to the vessel wall and is resistant to plasmin. It is known that neutrophils are accused of being the blood element that pulls the trigger by a mechanism called neutrophil extracellular trapping at the beginning of all these events.²⁰ In the light of these data, it is not surprising that NLR, which is the ratio of activated and relatively increased neutrophils to lymphocytes, has higher sensitivity and specificity in predicting uveitis in our study. In addition, the positive predictive value and negative predictive value of NLR were found higher than other parameters examined. The low positive predictive values in the NLR and other parameters in our study are striking. We think that the reason for this is the low number of uveitis cases in BS. Because, as it is known, the positive predictive value is a data obtained by dividing *uveitis + BS* patients, in which the tested parameter is positive, from *all BS* patients, in whom the tested parameter is positive, it is known that PPV is obtained by dividing the true positives by the number of true positives and false positives in the classical formulation ($a/a + c$). In other words, when the number of *uveitis + BS* patients is low, the positive predictive value is expected to be low. Conversely, the low number of *uveitis + BS* patients caused the negative predictive value data to be relatively high.²¹ In summary, the low number of cases with uveitis among BS patients was the most important limitation of us. Another limitation of us was only study the involvement in the form of uveitis and not to include other involvements such as retinal vein occlusion and macular edema.

SII, a new inflammatory index, has been tried to be used as a prognostic marker especially for malignancies and inflammatory conditions. According to the results of an analysis by Lolli et al.,²² it has been shown that SII can be used as an early and easily accessible prognostic marker in metastatic castration-resistant prostate cancer. In addition, it has been shown that SII can be used as a marker in idiopathic sudden hearing loss, which includes inflammatory components and is pulse steroid therapy frequently used for the treatment, and can provide meaningful information in prognosis.²³ In a idiopathic sudden hearing loss study by Ulu et al., SII was also compared with NLR and PLR, and

in the ROC curve analysis, it was observed that the highest value as in the AUC was in NLR. In parallel with this, in our study, we found NLR as the best predictor for uveitis in BS patients.

CONCLUSION

There is no specific test to fully describe and predict BS and its associated complications. NLR was found to be a better marker than SII, MPV, and PLR in predicting uveitis in patients with BS. Although these data have been shown to predict uveitis with an average sensitivity and specificity, it should be kept in mind that the diagnosis of uveitis is mainly an appropriate eye examination performed by experienced specialists.

Ethics Committee Approval: Ethical committee approval was received from the Turkish Republic Ministry of Health Kayseri City Education and Research Hospital Ethics Committee (study number 43, November 5, 2020).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K.; Design - S.K.; Data Collection and/or Processing - S.K., H.E.; Literature Search - S.K., H.E.; Writing Manuscript - S.K., H.E.; Critical Review - S.K., H.E.

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