

# Correlation of Clinical Signs and Symptoms of Behçet's Disease With Platelet to Lymphocyte Ratio (PLR) and Neutrophil to Lymphocyte Ratio (NLR)

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## Original Research

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# Abstract

## Background

Behçet's disease (BD) is a chronic disorder that involves multiple organs and is pathologically considered as a form of vasculitis. The current study aims to assess the metric properties of platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) in assessing BD disease activity.

## Methods

Three-hundred-nineteen patients with BD were enrolled in this cross-sectional study. Demographic and epidemiological data, including IBDDAM, time since the onset, and medication and manifestation history was recorded. Complete blood counts (CBC), NLR, and PLR were assessed by analyzing blood samples. On the last visit, patients were assessed for active manifestations of disease. IBDDAM and ocular IBDAAM scores were calculated for activity of disease in each patient.

## Results

Both PLR and NLR were higher in patients with active BD (Man-Whitney U test,  $P$ -value $<0.05$ ). Patients with active ocular manifestation had significantly higher NLR and PLR (Man-Whitney U test,  $P$ -value $<0.05$ ). These ratios, however, were not associated with other active BD manifestations. A value of NLR  $>2.58$  had 46% sensitivity and 85% specificity for the diagnosis of active ocular manifestations (AUC: 0.690). NLR had a significant though weak positive correlation with IBDDAM (Spearman's rho = 0.162;  $p$ -value  $<0.05$ ) and ocular IBDDAM (Spearman's rho = 0.159;  $p$ -value  $<0.05$ ).

## Conclusion

Active Behçet's presented with higher NLR and PLR ratios; however, there was only a modest correlation between NLR and BD activity (IBDDAM score). Also NLR and PLR have significant relationship with ocular features of BD patients.

## Introduction

Behçet's disease (BD) is a chronic disorder that involves multiple organs and is pathologically considered as a form of vasculitis, with specific clinical signs and symptoms, making it easily distinguishable since it can affect all small, medium and large vessels (1). Despite the clinical nature of BD's diagnosis, several other methods have also been utilized to evaluate the disease (2, 3). Applicability of a number of immunochemical techniques for BD's diagnosis and follow-up have been explored, yet, these techniques are highly dependent on the disease activity in clinical practice (4-7). Thus, the search for specific markers for the diagnosis and evaluation of the disease is still ongoing.

In fact, failure of self-tolerance of the innate immune system results in to the cascade of autoimmunity and leads to lasting signs and symptoms. BD, in particular, is caused mostly as a result of the unleashing of the innate immune system resulting in endothelial dysfunction and not characterized by the development of autoantibodies (8).

This results in the build-up of inflammatory and immune cells in the body during the disease flare-ups. A notable predictive role has been suggested for platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in rheumatologic diseases with predominant neutrophilic inflammation, including BD (9, 10). NLR, which is the ratio of absolute neutrophil count to lymphocyte count, has been investigated in a number of diseases, such as malignancies, familial Mediterranean fever, cardiovascular disease, and rheumatologic disorders (11, 12). Recent studies point at NLR as an inexpensive and highly accessible biomarker of endothelial activity in disorders with inflammatory characteristics (13).

Furthermore, the accumulation of pro-inflammatory agents can result in a series of manifestations in patients with rheumatologic disorders, a process in which platelets also have inflammatory roles (14). This, in turn, might give platelets a considerable diagnostic value for the evaluation of inflammatory and chronic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (15-18). In the current literature, platelets have been found to be associated with the progression of radiological findings in RA patients (9).

Utilizing NLR and PLR to evaluate BD activity has been discussed in several studies (19-22); however, a certain relationship between NLR and PLR indices and BD activity remained unclear. Besides, neither PLR nor NLR has been assessed in BD activity using Iranian Behçet's Disease Dynamic Activity Measurement (IBDDAM). This study aims to assess the metric properties of NLR and PLR in assessing BD's activity.

## Materials And Methods

### Study design

In a cross-sectional study, BD patients were included and assessed. The study protocol was approved under the supervision of Tehran University of Medical Sciences' Research and Ethics Committee, and implemented according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (23).

### Setting

Data of BD patients from Shariati Hospital (Tehran University of Medical Sciences, Tehran, Iran) between January 2017, and January 2018, obtained after informed consent. Demographic and clinical information was collected using a designated questionnaire, which included but was not limited to the current medications (such as colchicine, prednisolone, cytotoxic agents, and disease-modifying anti-rheumatic drugs [DMARDs]), the onset of the disease, and the patients' IBDDAM score (24). The IBDDAM scores obtained for this study was based on active manifestations at the time of last two visit and did not affect the clinical decision-making and treatment of the patients. Patients were examined by an expert rheumatologist in two sessions and were scored using IBDDAM, accordingly.

### Participants

Patients diagnosed with BD by an expert rheumatologist (based on the criteria of International Study Group for Behçet's Disease (25) were deemed eligible for this study, regardless of their current disease status, which might have been inactive or active at the time of enrollment. Patients with malignancies, current infections, other autoimmune diseases, and endocrine diseases were excluded from the study. Also, azathioprine, cyclophosphamide and cyclosporine affect bone marrow and cause leukopenia, but in order to not face with these problem, we didn't include the patients with excessive changes in CBC and leukopenia.

### Definition of Active BD and active Ocular BD

Based on evaluation of active manifestations of the BD at the time of last two visits we labeled patients as active/inactive BD. In this study, patients with at least one active manifestation of BD were considered as active BD patients.

At the time of study on last visit, the overall score of IBDDAM was calculated. The IBDAAM score is a numeric measure for disease activity. Because of the importance of active ocular manifestations in disease activity, apart from total IBDDAM, an Ocular IBDDAM score was also defined for each patients.. The IBDAAM score contains clinical manifestations including (26):

1. Oral aphthosis: one point for every 5 aphthous lesions.
2. Genital aphthosis: one point for each lesion.
3. Skin lesions: Pseudofolliculitis, one point for every 10 lesions; Erythema nodosum, one point for every 5 lesions.
4. Ocular lesions: Anterior uveitis, 1 to 4 points are given for flare, hypopion, cell and keratic precipitate; Posterior uveitis, 1 to 4 points are given for cell, snow ball, and snow banking and the total is multiplied by two (gravity indices to adjust the value of the inflammatory index); Retinal vasculitis, 1 to 4 points are given for the edema of disc, macular edema, retinal edema, periphlebitis, periarteritis, and papillitis. The total is multiplied by three (gravity indices to adjust the value of the inflammatory index). For the visual acuity, the observed number is subtracted from 10 and the remaining is multiplied by 2 (gravity index). As an example, a visual acuity of 6/10 will give  $(10-6) \times 2 = 8$ . The calculation is made separately for each eye.
5. Joints: Arthralgia, 1 point regardless of the number of involved joints. Monoarthritis, 2 points. Polyarthritis, 3 points.
6. CNS: Isolated cephalgia, 1 point; Mild involvement, 3 points; Moderate to severe involvement, 6 points.
7. Vessel thrombosis: Superficial phlebitis, 1 point; Deep vein thrombosis, 2 points for each vein; large vessel thrombosis, 6 points for each vessel.
8. Gastrointestinal tract: Mild manifestations (chronic diarrhea, rectal bleeding, abdominal pain). 3 points. Moderate to severe manifestations, 6 points.
9. Epididymitis: 2 points.
10. Positive pathergy test: 1 point.

Duration of lesions: if a lesion does not heal in one month, the same point is given for one additional month. The calculation of duration does not take in account sequels of post organ activities. Therefore, a CNS attack that produced a sequel will not receive any additional points for the following months unless the inflammatory attack recurs.

Blood samples were collected during the first session and were consequently analyzed to determine the complete blood count (CBC), blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), aspartate transaminase (AST), NLR, PLR, erythrocyte sedimentation rate (ESR), and c-reactive protein (CRP). Laboratory tests were performed twice with a month interval in between, and the average was reported.

## **Bias**

The risk of bias for the study was minimized by associating the clinician's judgment directly to the criteria (27) and IBDDAM, and limiting the tests to an exclusive laboratory, the Shariati Hospital's.

## **Statistical methods**

Continuous variables are presented in median and interquartile range or mean  $\pm$  standard deviation (SD), and categorical data are presented in percentage and frequency. Continuous and parametric data were compared between groups using Student's t-test with Mann-Whitney U test being used for variables without normal and standardized distribution and comparing the nonparametric data. Categorical data were analyzed using the  $\chi^2$  test. Pearson bivariate correlation was used to evaluate the linear relationship between predictive variables. The sensitivity, specificity, and the optimal cut-off values were determined using receiver operating characteristic (ROC) curves. Youden's J statistics were utilized to evaluate the performance of our dichotomous diagnostic test. Analyses were

performed using SPSS Statistics for Windows version 24.0 (IBM Corporation, Armonk, NY, USA) and MedCalc Windows version 19.0. A p-value of less than 0.05 was considered statistically significant.

## Results

### Participants and descriptive data

Three hundred nineteen patients with BD participated in this study with mean age of  $43.56 \pm 12.0$  years. One hundred and forty-two participants (44.5%) were female. Time since the onset of the disease was between 1 to 40 years ( $12.02 \pm 8.58$  years). Medications used by the patients are Colchicine 157(49.2%), Azathioprine 123(38.3%), Methotrexate 97(30.4%), Cyclosporine 10(3.1%), Infliximab 3(0.6%), Levamisole 2(0.6%) and Tofacitinib 2(0.6%). The mean PLR and NLR in the study population are reported as  $128.79 \pm 103.35$  and  $2.34 \pm 1.88$  respectively. The laboratory findings indicate that mean for all parameters except for CRP were within normal ranges. Fifty patients (15.6%) had CRP 1+ or higher (Table 1).

### Are NLR and PLR different based on history of manifestations?

The history of each BD manifestation in patients is shown in Table 2. Using Man-Whitney U test, NLR and PLR were compared between patients with or without history of different manifestations. The results show that patients with a history of ocular manifestations had significantly higher NLR (Mann-Whitney U test, P-value<0.05). No substantial difference was observed regarding NLR or PLR in patients with history of other BD manifestations.

### Are NLR and PLR related to active manifestations of BD?

Active manifestations of Behçet's disease at the time of last visit are showed in Table 3.

A total of 161 patients (50.5%) were suffering from at least one active complication of BD (Active BD). Both PLR and NLR were significantly higher in patients with active BD compared with the ones with inactive BD (Man-Whitney U test, p-value<0.05). Moreover, both PLR and NLR were significantly higher in patients with active ocular manifestations compared with the ones without ocular manifestations (Man-Whitney U test, P-value<0.05). No significant difference in NLR or PLR was found in patients with or without other active manifestations.

### NLR and PLR correlated with disease activity

The results show that, PLR and NLR correlated significantly (Spearman's rho: 0.552, p-value<0.001). Moreover, NLR significantly correlated with IBDAAM (rho: 0.162, p-value<0.05) and ocular IBDAAM score (rho: 0.159, p-value<0.05). We found no significant correlation between PLR and IBDAAM or ocular IBDAAM score.

### NLR and PLR receiver operating curve for active BD and active ocular manifestations

A ROC analysis (Table 4) was performed to determine the optimal value of NLR and PLR for the incidence of active BD (Figure 1) or active ocular manifestations (Figure 2). Using Youden index for optimal cut-off point, A value of PLR > 130 (39.75% sensitivity and 75.32% specificity, AUC: 0.573) and NLR > 2.58 (38.51% sensitivity, 87.34% specificity, AUC: 0.657) are considered optimal for classification of patients with Active BD.

Moreover, A PLR > 117.97 (53.21% sensitivity, 64.29% specificity, AUC: 0.589) and NLR > 2.58 (46.79% sensitivity, 85.24% specificity, AUC: 0.690) are optimal for classification of patients with active ocular manifestations.

## Discussion

The present study aimed to evaluate the applicability of PLR and NLR as biomarkers for the assessment of BD activity while using IBDDAM to score the disease status in each patient, carefully. Among Laboratory results CRP found to be higher in the participants than the laboratory normal range. Oral aphthae were the most common manifestation in the history of the disease, followed by ophthalmic manifestations and genital ulcers. While, active ocular manifestations, followed by active oral aphthae were the most common active manifestations of the disease at the time of last visit. Based on the history of manifestations, only NLR was significantly higher in patients with history of ocular manifestations. Moreover, NLR and PLR were both higher than normal in patients with active BD and active ocular manifestations. Our results indicate that only NLR correlated with overall disease activity (IBDAAM) and ocular activity (ocular IBDAAM).

ROC analysis determined the optimal cut-off value of PLR and NLR in classification of active/inactive BD and also classification of patients based on presence of active ocular manifestations. Results were significant, while only NLR showed a barely acceptable diagnostic ability (AUC: 0.690) for diagnosis of active ocular manifestations.

Several methods have recently been developed to evaluate systemic inflammation in patients; yet, additional specific and sensitive markers are still in demand. NLR has been receiving considerable attention as a new marker for inflammation, with several studies reporting high predictive and diagnostic value in cases of systemic inflammation (15, 20, 28-31).

White blood cells and platelets play a substantial role in the development of inflammation and inflammatory diseases (32); as a result, elevated levels of these parameters are expected in such diseases (33).

Recent studies illustrated that NLR as an independent prognostic factor in several chronic diseases and their manifestations, such as hyperlipidemia, cardiovascular and coronary artery diseases, atherosclerosis, inflammatory bowel disease, and arthritis (15, 20, 28-31).

BD, on the other hand, is defined as a form of inflammatory vasculitis that encompasses several organs and has a wide variety of clinical presentations, including mucocutaneous manifestations, recurrent deep vein thromboses, genital, ophthalmic, and gastrointestinal involvement, in all of which inflammatory processes have prominent roles and related biomarkers appear in higher levels in affected individuals as a result of chronic inflammation and endothelial dysfunction (34-37).

Utilizing WBC count to determine disease activity in BD patients was first discussed by Alan et al. (19) who categorized patients into three groups using NLR and PLR as a system of severity classification (Mild, Moderate and Severe disease). They reported higher NLR and PLR in patients with a currently active state of the disease in comparison with patients with an inactive disease state or healthy individuals. They, however, failed to find an association between the severity of the disease using BD Activity score criteria, PLR, and NLR.

On the contrary, Jiang et al. (38) measured the BD activity score using the simplified Behçet's Disease Current Activity Form (BDCAF) and demonstrated acceptable diagnostic value for PLR with a cut-off value of 124.63. PLR was elevated in active BD as compared to inactive BD. It may be a reliable, cost-effective, and novel potential parameter to help evaluate disease activity in BD.

Our study yielded results similar to the one done by Alan et al. (19), as we did observe a significant increase in PLR and NLR, and were able to find a cut-off point for determining the disease activity status; yet, these values did not have adequate sensitivity for BD. In line with the previous studies, PLR and NLR lack strong correlation with IBDDAM scores, which prevented us from using them to predict the severity of disease activity.

To the best of our knowledge, this is the first study to evaluate the applicability of NLR and PLR for the assessment of BD activity and its clinical presentations with reference to IBDDAM scores of the patients. Avci et al. (39) had previously found NLR to have a stronger correlation with the development of anterior uveitis in comparison with PLR in an attempt to evaluate the efficacy of NLR and PLR for the diagnosis of BD. Another study by Erden et al. (39) demonstrated an increased risk of deep vein thrombosis in BD patients with higher NLR and PLR.

Considering the results of our study and the previous studies in the field, we recommend further investigation of PLR and NLR and their relationship with various manifestations of the disease separately, since specific associations between NLR and PLR and activity of BD seem to be existent but are not yet examined enough to be applicable for diagnostic purposes.

Since the study was a single-center cross-sectional work, the available data was limited. The duration of the treatment in each patient could have altered PLR and NLR which needs to be investigated in future studies. Despite these limitations, we were able to find a positive correlation between NLR and the activity of the disease as measured by IBDDAM. However, active BD manifestations (except for ocular) were found not to be associated with PLR and NLR, even though these ratios were higher in BD patients compared to normal laboratory ranges. Considering IBDDAM and the conventional physical examinations, laboratory tests, clinical settings, and statistical analyses, the study protocol could easily be applied to the other circumstances of BD.

## Conclusion

Active Behçet's presented with higher NLR and PLR ratios; however, there was only a modest correlation between NLR and BD activity, with reference to IBDDAM. Also NLR and PLR have significant relationship with ocular features of BD patients.

## Abbreviations

ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under the curve; BD, Behçet's disease; BUN, blood urea nitrogen; CBC, complete blood count; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; IBDDAM, Iranian Behçet's Disease Dynamic Activity Measurement; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; SD, standard deviation; WBC, white blood cell

## Declarations

### Ethics approval and consent to participate

The Ethics Committee of Tehran University of Medical Sciences approved the study protocol, and all patients provided informed consent before participating.

### Consent for publication

Not applicable

### Availability of data and material

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request

### Competing interests

The authors declare that they have no competing interests

## Funding

None declared

## Author contributions

SS, MM, FD, FS, MA, TF, and HK conceived and planned the experiments. SS, MM, FD, and ZRM carried out the physical examinations. SS, MM, and ZRM planned and carried out the laboratory tests. FD, FS, TF, HK, MA, and SM contributed to the analysis of the results. SS, MM, TF, HK, HM, KS, MA, ZRM, FD, SM, and JB contributed to the interpretation of the results. MM, HM, KS, SM, and JB, took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript, and were in complete agreement to publish the work.

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## Tables

**Table 1. Mean values of laboratory tests in patients with Behçet's disease (regardless of disease activity)**

Laboratory test (normal range)	Mean ± SD	
WBC (4-10 × 10 <sup>9</sup> /L)	7.66 ± 2.72	
PMN (40-60% of total WBC)	60.50 ± 11.07	
Lymphocyte (20-40% of total WBC)	32.42 ± 10.13	
Hb (12-17 g/L)	14.22 ± 1.61	
MCV (80-100 fL)	88.01 ± 7.21	
Platelet (150-400 × 10 <sup>9</sup> /L)	256.12 ± 66.64	
RDW (11.5-14.5%)	13.96 ± 1.36	
MPV (7.5-12 fL)	10.43 ± 2.26	
ESR (0-30 mm/hr)	12.82 ± 12.05	
CRP, n (%)	Negative	269 (84.33%)
	1+	24 (7.52%)
	2+	19 (5.96%)
	3+	5 (1.57%)
	4+	2 (0.63%)
BUN (8-21 mg/dL)	14.48 ± 5.46	
Creatinine (0.8-1.3 mg/dL)	0.94 ± 0.18	
AST (5-30 U/L)	22.14 ± 9.74	
ALT (5-30 U/L)	27.40 ± 19.40	
PLR	128.79 ± 103.35	
NLR	2.34 ± 1.88	
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; MCV, mean corpuscular volume; MPV, mean platelet volume; N, number; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PMN, polymorphonuclears; RDW, red blood cell distribution width; WBC, white blood cells		

**Table 2. Comparison between platelet to lymphocyte ratio and neutrophil to lymphocyte ratio according to history of Behçet disease manifestations**

History of manifestations		Platelet to lymphocyte ratio (PLR)				P-value	Neutrophil to lymphocyte ratio (NLR)			P-value
		N(%)	Mean Rank	Sum of Ranks	U		Mean Rank	Sum of Ranks	U	
Oral aphthae	No	4(1.3)	171.75	667	583	0.798	149.25	597	587	0.815
	Yes	315(98.7)	159.85	50353			160.14	50443		
Genital aphthae	No	137(42.9)	162.38	22246	12141	0.689	162.06	22202	12185	0.729
	Yes	182(57.1)	158.21	28794			158.45	28838		
Dermal	No	236(74)	161.42	38096	9458	0.642	161.90	38207	9346	0.536
	Yes	83(26)	155.95	12944			154.61	12832		
Ocular	No	68(21.3)	156.15	10618	8272	0.698	138.04	9386	7040	0.027*
	Yes	251(78.7)	161.04	40422			165.95	41653		
Central nervous system	No	316(99.1)	159.36	50358	272	0.204	159.39	50366	280	0.222
	Yes	3(0.9)	227.33	682			224.67	674		
Vascular	No	294(92.2)	158.72	46665	3300	0.397	159.80	46981	3616	0.894
	Yes	25(7.8)	175	4375			162.36	4059		
Gastrointestinal	No	305(95.7)	161.76	49338	1597	0.111	161.04	49116	1819	0.349
	Yes	14(4.3)	121.57	1702			137.43	1924		

\*Statistically significant (Man-Whitney U test, P-value<0.05)

Table 3. Comparison between platelet to lymphocyte ratio and neutrophil to lymphocyte ratio according to active manifestations of BD

Active manifestaions		Platelet to lymphocyte ratio (PLR)				P-value	Neutrophil to lymphocyte ratio (NLR)			P-value
		N (%)	Mean Rank	Sum of Ranks	U		Mean Rank	Sum of Ranks	U	
Oral aphthae	No	260 (81.6)	159.56	41484	7554	0.857	160.25	41664	7605	0.920
	Yes	59 (18.4)	161.96	9555			158.91	9375		
Genital aphthae	No	310 (97.2)	161.64	50109	886	0.062	160.91	49881	1114	0.303
	Yes	9 (2.8)	103.44	931			128.78	1159		
Skin lesion	No	315 (98.8)	159.85	50352	582	0.793	159.40	50212	442	0.305
	Yes	4 (1.2)	172	688			207	828		
Pathergy	No	200 (62.7)	164.08	32816	11084	0.306	160.87	32173	11727	0.828
	Yes	119 (37.3)	153.14	18224			158.55	18867		
Ocular	No	210 (65.9)	150.31	31565	9410	0.009*	139.27	29247	7092	0.0001*
	Yes	109 (34.1)	178.67	19474			199.93	21792		
Vascular	No	316 (99.1)	159.84	50510	424	0.753	159.26	50326	240	0.141
	Yes	3 (0.9)	176.67	530			238	714		
Arthritis	No	316 (99.1)	160.12	50599	435	0.806	160.19	50621	413	0.701
	Yes	3 (0.9)	147	441			139.67	419		
Active BD	No	158 (49.5)	148.29	23430	10869	0.025*	134.79	21297	8736	0.0001*
	Yes	161 (50.5)	171.49	27610			184.74	29743		

\*Statistically significant (Man-Whitney U test, P-value<0.05)

**Table 4. Receiver operating curve analysis to determine the optimal value of NLR and PLR for the incidence of active BD or active ocular manifestations of BD**

Test Result Variable(s)	Optimal Cut-off	Sensitivity	Specificity	Area	SE	P value	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
<b>Active BD</b>								
PLR	>130.00	39.75	75.32	0.573	.032	<0.05	0.510	0.636
NLR	>2.58	38.51	87.34	0.657	.030	<0.05	0.597	0.716
<b>Active ocular manifestation</b>								
PLR	>117.97	53.21	64.29	0.589	.035	<0.05	0.521	0.657
NLR	>2.58	46.79	85.24	0.690	.032	<0.05	0.628	0.753
The test result variable(s): NLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.								

## Figures

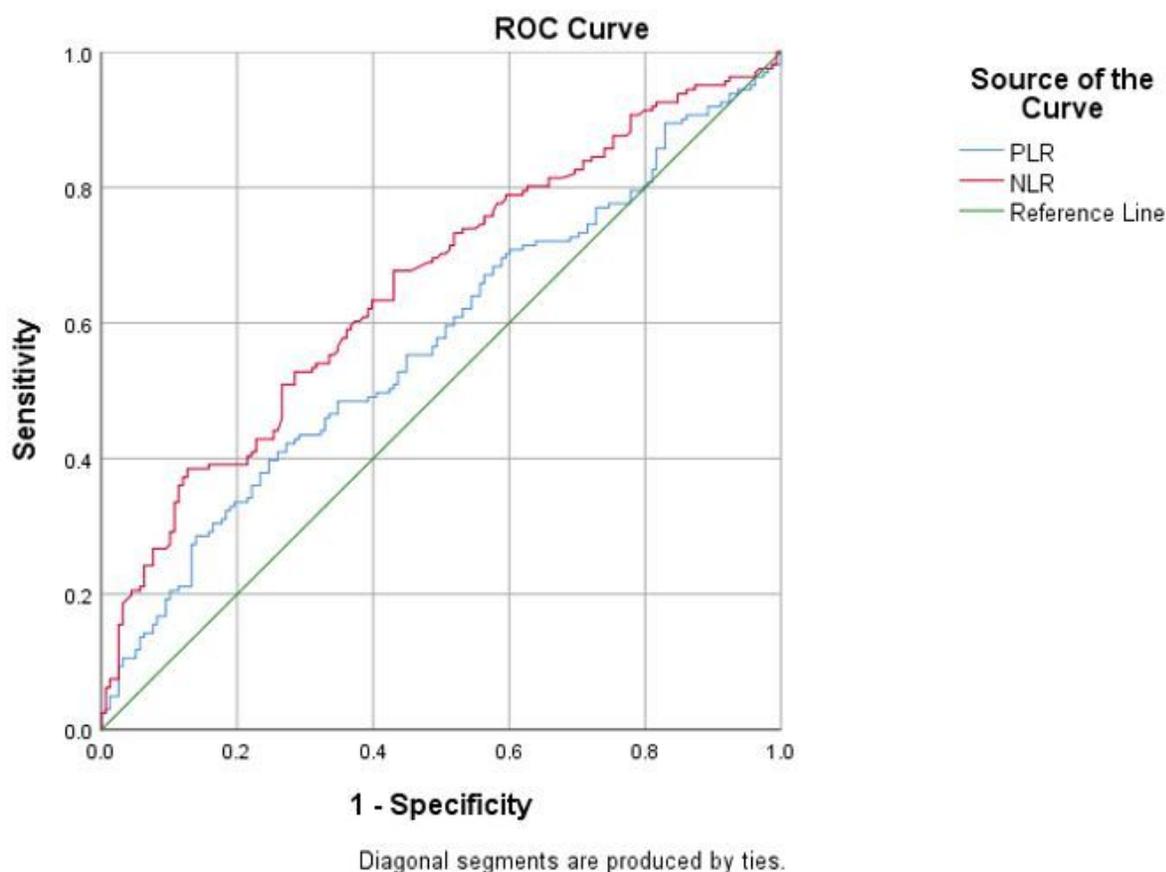
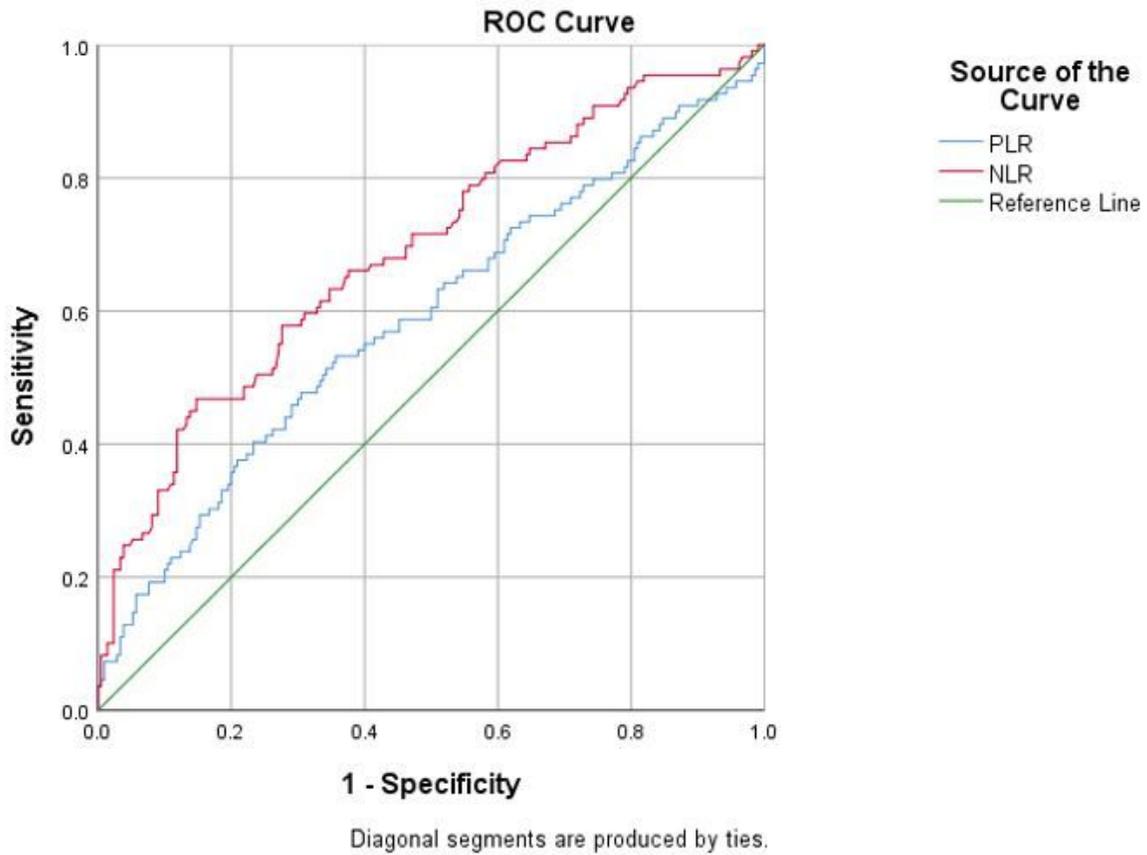


Figure 1

Receiver operating curve (ROC) of platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) in patients with active BD



**Figure 2**

Receiver operating curve (ROC) of platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) in patients with active ocular manifestations of BD