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Serum PLR and LMR in Behçet's disease

Can they show the disease activity?

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Abstract

The aim of this study is to determine platelet to lymphocyte ratio (PLR) and lymphocytes to monocytes ratio (LMR) levels in Behçet's disease (BD) and to investigate their relationships with disease activity.

Hematological and inflammatory parameters including high-sensitivity C-reactive proteins (hs-CRP), erythrocyte sedimentation rate (ESR), PLR, and LMR were examined in BD and healthy controls.

Data from 140 patients with BD (108 with active and 32 with inactive disease) and 107 controls were enrolled. PLR (153.21 ± 65.44, 106.20 ± 28.91, $P < .001$, respectively) was remarkably higher, whereas LMR (5.37 ± 5.47, 8.95 ± 5.84, $P < .001$, respectively) was significantly lower in BD than in controls. Active BD patients had significantly higher PLR (159.20 vs 131.14, $P = .037$), ESR (38.30 vs 24.55, $P = .017$), and hs-CRP (30.20 vs 17.21, $P = .027$) than those with inactive BD. However, no significant difference in LMR was found between the groups. Moreover, PLR was positively correlated with BDCAF ($r = 0.193$, $P < .05$), hs-CRP ($r = 0.402$, $P < .01$), and ESR ($r = 0.284$, $P < .01$), whereas LMR was negatively correlated with BDCAF ($r = –0.175$, $P < .05$), hs-CPR ($r = –0.263$, $P < .01$), and ESR ($r = –0.175$, $P < .05$). Additionally, both PLR and LMR were shown to be independent factors for BD by multivariate logistic regression analysis. Furthermore, a PLR level of 124.63 was determined as the best cut-off value by ROC analysis (sensitivity 64.3%, specificity 78.0%, and the area under the ROC curve 0. 753).

PLR was elevated in active BD as compared to inactive BD. PLR may be a reliable, cost-effective, and novel potential parameter to help evaluate disease activity in BD.

Abbreviations: BD = Behçet's disease, CI = confidence intervals, ESR = erythrocyte sedimentation rate, hs-CRP = high sensitive C reactive protein, LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, OR = odds ratio, PLR = platelet to lymphocyte ratio, RDW = red cell distribution width, ROC = receiver–operator curve analysis.

Keywords: Behçet's disease, lymphocyte to monocyte ratio, platelet to lymphocyte ratio

1. Introduction

Behçet's disease (BD) is a complex, inflammatory multisystem disorder characterized by recurrent attacks of oral ulcers, genital ulcers, cutaneous lesions, and inflammatory ocular findings.[1–3] Despite a worldwide distribution, BD clusters in regions that extends along the ancient "Silk Route" in which the current published estimates of the prevalence ranged from approximately 14/100,000 to 2/10,000.[4] Because of the lack of a universally recognized pathognomonic laboratory test, the diagnosis relies heavily on mucocutaneous manifestations and other clinical findings.[5] In order to diagnose and monitor disease activity in BD, many cytokines and biomarkers have been identified such as antilysozyme,[6] serum endocan,[7] serum growth differentiation factor 15 (GDF-15),[8] serum alpha 1-acid glycoprotein,[9] interleukin (IL)-8,[10] erythrocyte sedimentation rate (ESR),[11] and high-sensitivity C-reactive protein (hs-CRP).[12] However, they are not routinely used in clinical practice as they are not simple or easily derived. Limitations of these markers also include the reflection of short-term inflammatory activity and low discrimination ability with other superimposed inflammatory conditions.

Currently, the platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and similar parameters (red blood cell distribution width (RDW), mean platelet volume (MPV) and neutrophil to lymphocyte ratio (NLR)), which can be calculated from the peripheral blood easily, have been demonstrated as a new expression of the systemic inflammatory indicators that can aid in the diagnosis and assessment of disease severity in many diseases, such as ankylosing spondylitis,[13,14] rheumatoid arthritis,[15,16] systemic lupus erythematosus,[17–19] and psoriatic arthritis.[20]

Nevertheless, to our knowledge, only a few studies have investigated RDW, NLR, PLR, or MPV values in patients with BD,[21–24] none of which have evaluated the role of LMR in BD, not even the relationships between LMR, PLR levels, and disease activity in patients with BD. Therefore, to better understand these serum inflammatory parameters in BD and to gain deeper insight into the roles of LMR and PLR in BD, a retrospective study to assess PLR, LMR, MPV, NLR, and RDW all together in BD was conducted.

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2. Materials and methods

2.1. Study population

This study was performed in the First Hospital of Jilin University between February 2013 and September 2016. A total of 140 patients with BD fulfilling the inclusion criteria (male to female ratio: 46/94, mean 38.8 ± 13.2 years) and 107 healthy controls (male to female ratio: 43/64, mean 42.3 ± 15.1 years) were enrolled in the study retrospectively. BD was diagnosed according to the criteria of the International Study Group for BD.[5] The patients and healthy controls with following criteria were excluded from the study: other skin diseases, other autoimmune diseases, inflammatory or infectious diseases, allergy, any topical or systemic treatment, including colchicines, steroids, and other immune suppressor drugs within the last 6 months. Subjects with chronic diseases such as cardiovascular disorders, diabetes mellitus, or hematological, kidney, or liver diseases, hypertension, or malignant diseases were also excluded from the analysis.

The BD patients were classified as active or inactive state according to the clinical findings that at least 2 of the following features such as oral ulcers, genital ulcers, active uveitis, skin lesions, arthritis, neurological involvement, and thrombosis-thrombophlebitis were present. Severity score of BD was assessed using the simplified Behçet's Disease Current Activity Form.[2,5] This research was conducted according to the Declaration of Helsinki and was approved by the First Hospital of Jilin University Ethics Committee.

2.2. Clinical and laboratory assessments

Demographic data and medical records were recorded on a form by a researcher who was blinded to prevent bias. Blood samples were drawn from the antecubital vein of each patient between 5:00 and 6:00 AM after an overnight fasting. Age, gender, onset of symptoms, clinical features, organ involvement, ESR, LMR, PLR, RDW, MPV, NLR, and hs-CRP levels were gathered from medical records of the patients on admission.

2.3. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD). Comparisons between the groups with parametric data were done using Student's *t*-test, and with nonparametric data were done by Mann–Whitney *U* test, respectively. All the continuous variables were evaluated for normality of distribution using the Kolmogorov–Smirnov test. Categorical data were summarized as numbers and percentages and analyzed using the χ^2 test. Pearson bivariate correlation was used to evaluate the linear relationship between predictive variables. Multivariate logistic regression was also conducted to assess relationships; results are presented as odds ratios (OR) and 95% confidence intervals (CI). Furthermore, sensitivity, specificity, and the optimal cut-off values were determined using receiver operating characteristic (ROC) curves. All statistical analyses were performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL), and a 2-sided *P* value less than .05 was considered statistically significant ($P < .05$).

3. Results

3.1. Basic characteristics of the study sample

Demographic features and laboratory findings of the study population are summarized in Table 1. Our study sample comprised 140 patients with BD and 107 healthy controls. Of the patients with BD, 108 had active disease and 32 had inactive disease. There was no statistically significant difference ($P > .05$) between both the 2 groups (controls vs BD and active BD vs inactive BD) in terms of gender and age. The clinical characteristics of the BD patients are given in Table 2.

Table 1

Demographic features and laboratory findings of the participants.

	Behçet's disease (n = 140)	Controls (n = 107)	*P* value
Gender (Male/Female)	46/94	43/64	>.05
Age, y	38.8 ± 13.2	42.3 ± 15.1	.058
NLR	2.71 ± 2.19	1.79 ± 0.67	<.001
PLR	153.21 ± 65.44	106.20 ± 28.91	<.001
LMR	5.37 ± 5.47	8.95 ± 5.84	<.001
RDW, %	13.33 ± 1.32	12.76 ± 0.56	<.001
MPV, fL	10.49 ± 0.84	10.76 ± 0.83	.012
hs-CRP, mg/L	27.41 ± 28.58		
ESR, mm/1 h	35.43 ± 27.70		
Onset of symptoms, mo	63.7 ± 74.2		
Severity score	2.4 ± 1.0		

ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.
Data are presented as mean ± SD. *P* value less than .05 was considered to show a statistically significant result ($P < .05$).

3.2. PLR was increased while LMR was decreased in BD patients

When compared with healthy controls, PLR, LMR, NLR, RDW, and MPV were statistically different in patients with BD (all $P < .001$ except MPV $P < .05$; Table 1), of which PLR, RDW, and NLR were remarkably higher, whereas LMR and MPV were significantly lower in BD than in controls.

3.3. PLR was increased in active BD patients

Comparison of variables between patients with active and inactive Behçet's disease are shown in Table 3. PLR, NLR, and RDW were significantly higher in patients with active BD (159.20 ± 68.85, 2.91 ± 2.41, 13.49 ± 1.40, respectively) than in those with inactive BD (131.14 ± 44.51, $P = .037$; 2.01 ± 0.59, $P = .048$; 12.75 ± 0.73, $P = .006$, respectively), as well as ESR, hs-

Table 2

Clinical characteristics of BD patients.

Symptoms	N (%)
Headache	2 (1.4)
Mouth ulceration	140 (100)
Genital ulceration	92 (65.7)
Erythema nodosum	30 (21.4)
Skin pustules	14 (10.0)
Arthralgia	20 (14.3)
Arthritis	6 (4.3)
Nausea or vomiting or abdominal pain	8 (5.7)
Diarrhea or hematochezia	2 (1.4)
Eye involvement	6 (4.3)
Nervous system involvement	0 (0.0)
Major vessel involvement	8 (5.7)

BD = Behçet's disease.

Table 3

Comparison of variables between patients with active and inactive Behçet's disease.

Variables	Active BD (n = 108)	Inactive BD (n = 32)	P
Gender (Male/Female)	36/74	10/20	>.05
Age, years	38.9 ± 12.8	38.4 ± 14.5	.847
NLR	2.91 ± 2.41	2.01 ± 0.59	.048
PLR	159.20 ± 68.85	131.14 ± 44.51	.037
LMR	5.04 ± 5.68	6.58 ± 4.40	.175
RDW, %	13.49 ± 1.40	12.75 ± 0.73	.006
MPV, fL	10.49 ± 0.83	10.47 ± 0.88	.890
hs-CRP, mg/L	30.20 ± 30.28	17.21 ± 17.79	.027
ESR, mm/1 h	38.30 ± 29.25	24.55 ± 16.82	.017
Onset of symptoms, months	70.2 ± 76.3	40.1 ± 60.6	.049

BD = Behçet's disease, ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.
P value less than .05 was considered to show a statistically significant result ($P < .05$).

CRP, and onset of symptoms ($P = .017$, $P = .027$, and $P = .049$, respectively). No significant difference ($P > .05$) in LMR or MPV was observed in the active group compared with the inactive group (Table 3).

3.4. PLR and LMR were associated with severity score in BD

Severity score correlated positively with PLR ($r = 0.193$, $P < .05$), NLR ($r = 0.180$, $P < .05$), ESR ($r = 0.340$, $P < .01$), and hs-CRP ($r = 0.244$, $P < .01$), whereas negatively with LMR ($r = -0.175$, $P < .05$, Table 4). However, no significant correlation was observed between severity score and RDW or MPV. Meanwhile, PLR and NLR correlated positively with ESR ($r = 0.284$, $P < .01$; $r = 0.249$, $P < .01$, respectively) and hs-CRP ($r = 0.402$, $P < .01$; $r = 0.518$, $P < .01$, respectively, Table 5). LMR was negatively correlated with ESR ($r = -0.175$, $P < .05$) and hs-CRP ($r = -0.263$, $P < .01$, Table 5).

3.5. PLR and LMR were independent factors for BD by multivariate logistic analysis

Moreover, related parameters associated with Behçet's disease from controls, and with active BD from inactive BD were detected by multivariate logistic regression analysis (Table 6). Significantly higher PLR values (OR = 1.018, 95% CI = 1.008–1.028, $P = .001$; OR = 1.595, 95% CI = 1.152–2.208, $P = .005$) and lower LMR values (OR = 0.920, 95% CI = 0.851–0.994, $P = .035$; OR = 1.416, 95% CI = 1.043–1.924, $P = .026$) were seen in BD patients compared with controls, and in active BD compared with inactive BD. Both PLR and LMR were independent factors for BD found by multivariate logistic analysis. While NLR was not statistically related to Behçet's disease or active BD in multivariate logistic analysis that included MPV, RDW, PLR, and LMR.

Table 4

Correlation analyses (Pearson correlation test) between severity score and independent variables.

Severity score	r	P
Age, y	–0.113	>.05
NLR	0.180	<.05
PLR	0.193	<.05
LMR	–0.175	<.05
RDW, %	0.092	>.05
MPV, fL	0.148	>.05
hs-CRP, mg/L	0.244	<.01
ESR, mm/1 h	0.340	<.01
Onset of symptoms, mo	0.164	>.05

ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.

Table 5

Correlation analyses (Pearson correlation test) between hs-CRP, ESR, and independent variables.

	hs-CRP, mg/L		ESR, mm/1 h	
	r	P	r	P
NLR	0.518	<.01	0.249	<.01
PLR	0.402	<.01	0.284	<.01
LMR	–0.263	<.01	–0.175	<.05
RDW, %	0.147	>.05	0.136	>.05
MPV, fL	–0.055	>.05	–0.056	>.05

ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.

3.6. ROC analysis of PLR for the identification of BD

Differentiation of patients with Behçet's disease from controls using PLR was investigated with ROC analysis (Fig. 1). The optimal cut-off value of PLR was 124.63 (sensitivity 64.3%, specificity 78.0%, and area under the ROC curve (AUROC) 0.753, $P < .001$). Compared with other serum inflammatory indicators, PLR yielded a higher AUROC than NLR (0.707, $P < .001$), RDW (0.609, $P = .003$), MPV (0.418, $P = .026$), and LMR (0.180, $P < .001$). The ROC analysis of PLR, LMR, NLR, RDW, and MPV for the identification of Behçet's disease from healthy controls is shown in Fig. 1.

Table 6

Multivariate logistic regression analysis of patients with Behçet's disease versus controls, and patients with active versus inactive Behçet's disease.

Variables	OR	95% CI	P
Patients vs controls			
PLR	1.018	1.008–1.028	.001
LMR	0.920	0.851–0.994	.035
RDW	1.794	1.246–2.585	.002
NLR	1.131	0.702–1.821	.614
MPV	0.859	0.592–1.246	.424
Active vs inactive			
PLR	1.595	1.152–2.208	.005
LMR	1.416	1.043–1.924	.026
RDW	1171.668	24.769–55,425.092	.000
MPV	7.910	1.102–56.793	.040
ESR	1.231	1.084–1.397	.001
NLR	0.002	0.000–22.260	.189
hs-CRP	0.963	0.903–1.027	.256

CI = confidence intervals; ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, OR = odds ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.

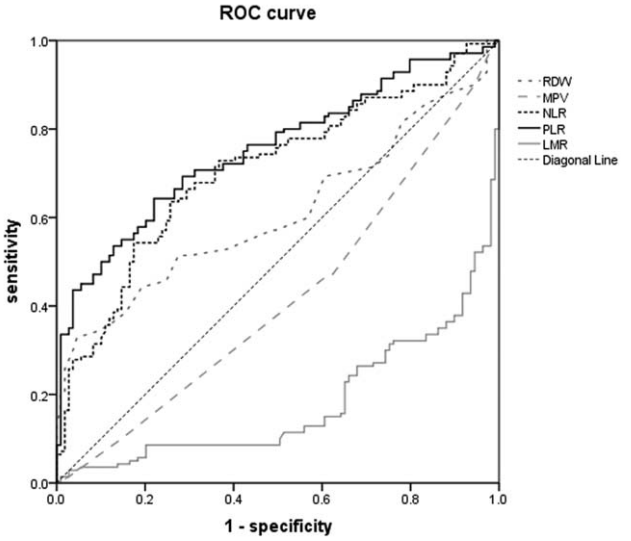

Figure 1. Receiver operating characteristic curve of PLR, LMR, NLR, RDW, and MPV for the identification of Behçet's disease from healthy controls. LMR = lymphocytes to monocytes ratio, MPV = mean platelet volume, NLR = neutrophils to lymphocytes ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.

4. Discussion

BD is a systemic inflammatory disease characterized by recurrent episodes of acute inflammation consisting mainly of neutrophil infiltration around blood vessels in affected tissues.[26] Although the exact pathogenesis of BD remains uncertain, major determinants of the genetics, various immunological abnormalities, and inflammatory changes occurring have been elucidated.[2,27–30] Inflammation is typically self-limiting in time and relapsing episodes of clinical manifestations represent a hallmark of BD,[31] and several environmental triggers may induce inflammatory episodes in genetically susceptible individuals.[32] To date, there exists no specific tool or serum marker to identify and quantify the severity of BD and the diagnosis continues to remain on clinical grounds.

As far as we know, the present study is the first to simultaneously investigate these serum inflammatory parameters (PLR, LMR, RDW, MPV, and NLR) in BD, and compare with preexisting indicators, such as ESR and hs-CRP. We enrolled 140 patients with BD and found that patients with BD were more likely to have statistically higher PLR, RDW, and NLR, whereas significantly lower LMR and MPV than controls. In addition, PLR, NLR, and RDW were significantly higher in active BD compared to inactive BD, as well as ESR and hs-CRP. Furthermore, PLR and LMR were related factors associated with BD from controls and with active BD from inactive BD by multivariate regression analysis. As a novel finding, this study had shown that PLR could be a reliable, easily derived, and noninvasive biomarker of disease activity in BD.

According to our knowledge, the only study which addressed PLR and BD was conducted by Alan et al,[23] in which the authors classified patients as mild, moderate, and severe according to disease activity. They found that PLR and NLR were significantly higher in patients with BD than in healthy controls. However, no association between the severity score of BD and PLR, NLR, and MPV was found in their research, which differed from our study that severity score of BD correlated positively with PLR and NLR, while negatively with LMR. Meanwhile, the rise in PLR and NLR levels were also linked to increasing ESR and hs-CRP. In addition, we also found a negative correlation of LMR values with these 2 inflammatory indices (ESR and hs-CRP). Although no statistically significant difference in LMR was observed between active and inactive BD, multivariate analysis found that both PLR and LMR were independent predictors for BD. Recently, increased PLR and decreased LMR have been reported to be associated with disease activity in many diseases.[33–37] But they could not show these correlations with other inflammatory marks such as hs-CRP or ESR. These serum inflammatory parameters can be considered as appropriate, confirmatory tests for hs-CRP and ESR.

In light of our findings, PLR was associated with the presence and severity of BD. Furthermore, compared with other serum inflammatory indicators, PLR yielded a higher AUROC than NLR, RDW, MPV, and LMR in differentiation of patients with Behçet's disease from healthy controls by ROC analysis. Therefore, we concluded that increased PLR was an intrinsic characteristic of BD, and it can be a new inflammatory marker which could be used to assess disease activity in patients with BD.

Previous studies have revealed that NLR was an independent predictor for BD.[23,38] In the literature, the level of NLR was elevated in active BD patients compared to inactive patients and controls.[21,23,38,39] In another study,[39] the NLR could predict the disease activity of BD and was related to endothelial dysfunction. It was also found that NLR correlated positively with hs-CRP which was in line with our study. In addition, Yuksel et al [40] showed that NLR was even associated with disease activity of ocular involvement in BD patients. Compared with the inactive BD and controls, the mean NLR level in active BD was elevated, which supported the view that neutrophils were activated in BD [26] and had an effect on the inflammatory cascade of BD and disease pathophysiology.

Moreover, there were several studies regarding MPV in BD with conflicting results. Acikgoz et al [41] revealed that MPV was significantly elevated in BD compared to controls and was even associated with an increased tendency to develop thrombosis, whereas the studies of Lee and Kim[42] and Turkcu et al [43] showed that the MPV value was decreased in BD than in controls, which was in accord with our result. In the present study, we also found that MPV did not differ between active and inactive BD and there was no significant correlation between severity score and MPV, which was in line with the recent reports.[21,23] An explanation for this discrepancy was the possibility that MPV alone was not an appropriate indicator of platelet activation in accordance with a conclusion stated by Beyan et al [44] that platelet indices such as MPV should not be used alone as direct indicators of platelet activation, as they found no correlation between platelet aggregation responses and platelet indices.

Elevated levels of various inflammatory markers have been found in BD including ESR, hs-CRP, peripheral leukocyte and platelet counts, and serum cytokines (tumor necrosis factor-α, GDF-15, IL-8, IL-17, and IL-18).[8,10,45–47] Of which, ESR and hs-CRP are often used for evaluating BD activity.[21] However, they are not specific for BD as they can be affected by various pathologic and physiologic conditions.[48] To develop new strategies for the assessment of disease severity in BD, a better understanding of the signs for systemic inflammatory status is needed. Hence, a simple, reliable, widely available, inexpensive, and reproducible laboratory biomarker such as

PLR would be a potential tool for clinical use to help identify disease activity in BD.

Limitations of the study: Of note, the present study had several potential limitations. Firstly, the data were obtained from only a single center; therefore, patient selection bias was not completely avoided. Secondly, this study was designed as a retrospective study lacking longitudinal observation. Thirdly, we did not explore the influence of treatment on these serum inflammatory parameters due to insufficient data. Further controlled studies comprising a greater number of patients are needed to validate the clinical value of PLR in BD.

5. Conclusions

Based on the results of the present study, it can be suggested that assessment of PLR in BD may provide additional information about inflammation. Also, the present study has demonstrated that there was association between PLR and disease activity in BD. This association may suggest that PLR has a significant role in BD pathogenesis and PLR may be a potential index to evaluate disease activity of BD.

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