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Platelet-to-lymphocyte ratio: a superior prognostic marker for systemic lupus erythematosus compared to neutrophil-to-lymphocyte ratio and systemic immune-inflammation index

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ABSTRACT

Objective. Novel inflammatory indices are a potential substitute for traditional markers which their correlation and clinical application in different autoimmune diseases are still in question. In this study, we evaluated the association of platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) with systemic lupus erythematosus (SLE) activity.

Methods. We included 103 SLE patients in our study, compared to a matched pair of 103 healthy individuals. A blood sample was drawn to measure SII, PLR, NLR, C-reactive protein, erythrocyte sedimentation rate, autoantibodies, and complement levels. Independent sample t-test, chi-square, and Mann-Whitney U test were implemented for variables as appropriate. Linear regression was used to evaluate the factors that predict SLE activity.

Results. Our study revealed that NLR, PLR, and SII between SLE patients and the control group were significantly different. SII and NLR were correlated with renal manifestations of SLE. PLR was correlated with SLEDAI, and an independent factor of SLE activity after adjusting for multiple factors, but not NLR and SII.

Conclusion. We demonstrated that only PLR was an independent predictor of SLE activity. This may suggest that NLR and SII are more nonspecific inflammatory markers, compared to PLR being prognostic of SLE activity.

Keywords: systemic lupus erythematosus, neutrophil-to-lymphocyte ratio, SLEDAI, platelet-to-lymphocyte ratio, disease activity, systemic immune-inflammation index

List of abbreviations (in alphabetical order):

ANA – antinuclear antibodies
ALKP – alkaline phosphatase
ALT – alanine transferase
APS – anti-phospholipid syndrome
AST – aspartate transferase
BMI – body mass index
BUN – blood urea nitrogen
CBC – complete blood cell count
Cr – creatinine
CRP – C reactive protein
DMARDs – disease-modifying anti-rheumatic drugs
DVT – deep venous thrombosis
ESR – erythrocyte sedimentation rate
NLR – neutrophil-to-lymphocyte ratio
PLR – platelet-to-lymphocyte ratio
SII – systemic immune inflammation index
SLE – systemic lupus erythematosus;
SLEDAI – systemic lupus erythematosus disease activity index;
WBC – white blood cells

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INTRODUCTION

Lupus that has various clinical presentations and autoimmune nature, is a chronic with an unknown etiology. Systemic lupus erythematosus (SLE) is a type of lupus disease that presents with different levels of damage to joints, skin, kidneys, and other body organs [1].

Disease course has a remitting and relapsing nature which emphasizes the need for the evaluation of disease activity in clinical practice. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is a widely-used index for the evaluation of active SLE; however, the simplicity of its clinical use is not favorable [2]. SLEDAI is a disease activity score within the last 10 days and is calculated by the sum of the weighted score of the 24 SLE clinical and laboratory variables.

Autoimmunity in SLE results in different autoantibodies such as anti-proliferating cell nuclear antigen, anti-nuclear antibody (ANA), anti-dsDNA, and anti-phospholipid antibodies, positive Coombs test in case of hemolysis, and decreased complement levels [3,4]. Due to various pathways of organ involvement, using one hematological test for measuring SLE activity seems to be unattainable. Still, a simple, affordable, easily-available test to measure disease activity is in need.

Complete blood cell count (CBC) with differential is a routine blood test and its use in different inflammatory states is well-established. However, there are still ongoing studies on different CBC-derived markers in autoimmune diseases [5]. Blood cell lineages play different roles in inflammatory states but establishing the exact role of each cell type is challenging; therefore, most of the blood-derived inflammatory markers are nonspecific [6,7].

Thrombocytopenia is a prevalent abnormal CBC result in SLE patients which is suggested to be due to antibodies against platelets and increased destruction in the spleen. Low platelet count is related to disease activity, neurological manifestations, nephritis, and arthritis [6]. Platelet-to-lymphocyte ratio (PLR) has been evaluated in SLE patients, among other autoimmune and chronic diseases [8]. Neutrophil-to-lymphocyte ratio (NLR) is another novel inflammatory marker that has been explored in infections, cancers, and chronic diseases. Also, NLR was found to be higher in SLE, RA, Behcet's disease, and systemic sclerosis patients than in healthy individuals in some studies [2,8,9]. Systemic immune-inflammation index (SII) is another blood-derived marker that is calculated by neutrophil count × platelets/lymphocyte count. SII, as an inflammatory marker has been assessed in sepsis, chronic diseases, and inflammatory diseases [10-14]. However, to the best of our knowledge, SII has been evaluated in only two studies in SLE patients and only one of them showed considerable results regarding the association between SLE and SII [15,16]. In this paper, we aimed to look over PLR, NLR, and SII in SLE patients compared to the healthy individuals.

METHODS

Study design

This is a case-control study that was approved by our institution's ethics review board. Written informed consent of all participants was obtained. The sample size was calculated as 206 patients which were included in the study and grouped into two, 103 patients with SLE and 103 healthy individuals. All the participants were White with Iranian ethnicity. The study was conducted on 20- to 65-year-old patients who visited the rheumatology clinic of our hospital from March 2020 to 2021. Exclusion criteria were history of other rheumatological diseases, coagulopathy and lymphoproliferative diseases, diseases and consumption of drugs that have established effect on blood cell counts, heart failure, liver diseases, renal diseases, recent infection, and malignancy. SLE was diagnosed based on the American College of Rheumatology criteria.

Data collection and study outcome

Demographic characteristics and medical and drug histories were obtained from patients through personal interviews, questionnaires, and medical records. A blood sample was drawn from patients to examine laboratory variables and all laboratory analyses were performed within 2 hours of sample collection. The variables included complete blood cell count (CBC) and differential of white blood cells (WBC), quantitative erythrocyte sedimentation rate (ESR), qualitative C-reactive protein (CRP), AST, ALT, ALKP, ANA, anti-ds-DNA, urea, creatinine, blood urea nitrogen (BUN), 24-hour urinary protein, C3, C4, and CH50 using standard methods.

NLR, PLR, and SII were calculated for all the participants as follows:

SII = platelets × neutrophil / lymphocyte count

PLR = platelets / lymphocyte count

NLR = neutrophil / lymphocyte count

SLEDAI was calculated by the sum of the score of the presented variables which are presented in parentheses: Psychosis (8), Recent onset seizure (8), Organic brain syndrome (8), New onset sensory or motor neuropathy (8), Visual disturbance (8), New onset stroke (8), Lupus headache (8), Myositis (4), Vasculitis (4), Arthritis (4), Heme-granular or RBC urinary casts (4), Proteinuria (4), Hematuria (4), Pyuria (4), Inflammatory-type rash (2), Alopecia (2), Oral or nasal mucosal ulcers (2), Pericarditis (2), Pleurisy (2), Low complement (2), High DNA binding (2), Temperature

more than 100.4 °F (38°C) (1), Platelets less than 100 x 109 per Liter (1), and WBC less than 3 × 109 per liter (1).

Inactive SLE was considered in patients with a score of less than 4, while active SLE was considered in patients with a score of 4 and more [17,18].

Statistical analyses

Data analysis was performed using SPSS version 22 (SPSS, Chicago, IL). Quantitative and qualitative variables were expressed as means ± SD and frequency with percentages, respectively. Kolmogorov-Smirnov test was used for assessing normal distribution of variables. T-test, chi-square, and Pearson correlation tests were used for the analysis of data. There was no missing data in this study. Linear Regression Model with multiple variables was performed for predicting SLEDAI with collinearity statistics. P-value <0.05 was considered statistically significant in all of the tests.

RESULTS

The mean of SLEDAI in our SLE patients was 8.80 ± 6.89. Most of our participants in both groups were male. The demographic, laboratory, and clinical descriptive of both SLE patients and healthy individuals are presented in Table 1. NLR, PLR, SII, lymphocyte count, and Alkp were significantly different between the two groups (Table 1); however, when SLE patients were divided into two groups of active (SLEDAI ≥ 4) and inactive disease (SLEDAI < 4), the means of only SII, C3, and C4 were statistically different and the means of NLR and PLR were not significantly different between the two groups (Table 2).

Further, we divided different clinical manifestations of SLE into five groups of renal, musculoskeletal, mucocutaneous, neuropsychiatric, and serositis. We evaluated the correlation between each group with SII, NLR, and PLR. Our results revealed that SII and NLR are correlated with renal manifestations of SLE (r = 0.196, p = 0.047 and r = 0.217, p = 0.028, respectively) (Table 3).

In SLE patients, NLR was correlated with ESR (r = 0.388, p <0.001). PLR was correlated with SLEDAI (r = 0.233, p = 0.018) and CRP (r = 0.222, p = 0.024). Moreover, SII was correlated with CRP and ESR (r = 0.212, p = 0.031, r = 0.328, p = 0.001, respectively). SLEDAI demonstrated no significant correlation with either NLR or SII (Table 4).

Linear regression model with implementation of smoking, SII, NLR, PLR, ALKP, ESR, C3, C4, CH50 demonstrated that PLR (p-value = 0.038) along with C3 (p-value = 0.000), CH50 (p-value = 0.005), anti-dsDNA (p-value = 0.027), and ESR (p-value = 0.042) are independent risk factors of active SLE (Table 5).

TABLE 1. Demographic, laboratory, and clinical descriptive of our studied groups

Variable	Case (n=103)	Control (n=103)	p-value
Demographic			
Age, years, mean ± SD	45.68 ± 10.91	43.50 ± 12.89	0.191
BMI, kg/m²	24.99 ± 3.05	25.68 ± 3.63	0.142
Gender, n (%)			
Male	92	90	0.664
Female	11	13	
Family history, n (%)	8 (7.8)	-	-
History of chronic diseases, n (%)			
Hypertension	27 (26.2)	15 (14.6)	0.516
Diabetes mellitus	10 (9.7)	9 (8.7)	0.810
Dyslipidemia	28 (27.2)	19 (18.4)	0.135
Laboratory parameters			
NLR	1.99 ± 1.17	1.47 ± 0.50	< 0.0001
PLR	131.89 ± 72.83	97.78 ± 35.02	< 0.0001
AST (U/L)	23.39 ± 9.56	21.99 ± 6.02	0.211
ALT (U/L)	24.67 ± 14.65	22.25 ± 8.11	0.114
Alkp	110.82 ± 34.07	137.73 ± 54.95	< 0.0001
Cr (µmol/L)	0.98 ± 0.66	0.94 ± 0.16	0.601
Lymphocyte count	2001.32 ± 843.54	2582.31 ± 744.69	<0.0001
C3 (mg/l)	89.48 ± 9.68	-	-
C4 (mg/l)	11.21 ± 1.94	-	-
ESR (mm/h)	24.84 ± 19.78	-	-
CH50	108.74 ± 12.10	-	-
CRP, (mg/L) (median, IQR)	48 (46.6)	-	-
Negative	33 (32)	-	
+1	18 (17.5)	-	
+2	4 (3.9)	-	
+3			
ANA	88 (85.4)	-	-
Lupus activity			
SLEDAI	8.80 ± 6.89	-	-
SII (10^9/L), mean ± SD	453.51 ± 358.27	350.26 ± 158.07	0.008
Corticosteroid use, n (%)			
Yes	62 (60.2%)	0	-
No	41 (39.8%)	103 (100%)	
DMARD use, n (%)			
Yes	91 (88.3%)	0	-
No	12 (11.7%)	103 (100%)	

Variable	Case (n=103)	Control (n=103)	p-value
SLE clinical features, n (%)			
Rash	78 (75.7)	-	
Alopecia	66 (64.1)	-	
Arthritis	39 (37.9)	-	
Low complement levels	36 (35)	-	
Osteoporosis	35 (34)	-	
Oral ulcer	32 (31.1)	-	
Proteinuria	16 (15.5)	-	
Organic brain syndromes	11 (10.7)		
Hematuria	9 (8.7)	-	
Nephritis	9 (8.7)	-	
Myositis	9 (8.7)	-	
Seizure	8 (7.8)	-	
APS	8 (7.8)	-	
DVT	6 (5.8)	-	
Pleurisy	5 (4.9)	-	
Pyuria	5 (4.9)	-	
Lupus headache	3 (2.9)	-	
Abortion	3 (2.9)	-	
Fever	2 (1.9)	-	
Vasculitis	2 (1.9)	-	
Visual disturbance	1 (1)	-	
Cerebrovascular accident	1 (1)	-	

Abbreviations: ANA, anti-nuclear antibody; ALKP, alkaline phosphatase; ALT, alanine transferase; APS, anti-phospholipid syndrome; AST, aspartate transferase; BMI, body mass index; Cr, creatinine; CRP, C reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; DVT, deep venous thrombosis; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index

TABLE 2. Comparison of inflammatory markers and complement markers between SLE patients with inactive and active disease

Variable	SLE activity		
	SLEDAI < 4 (n=24)	SLEDAI ≥ 4 (n=79)	p-value
NLR, mean ± SD	1.75 ± 0.65	2.06 ± 1.27	0.112
PLR, mean ± SD	119.34 ± 42.74	135.70 ± 79.59	0.196
SII, mean ± SD	370.52 ± 166.68	478.73 ± 396.10	0.050
C3, mean ± SD	94.79 ± 1.02	87.86 ± 10.53	0.002
C4, mean ± SD	12.00 ± 0.00	10.97 ± 2.16	0.022
CH50, mean ± SD	109.17 ± 4.08	108.61 ± 13.66	0.750

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index

TABLE 3. Correlation between clinical manifestations of systemic lupus erythematosus in SLEDAI and inflammatory markers

Variable	SII	PLR	NLR
Renal	r= 0.196, p= 0.047	r= 0.150, p= 0.132	r= 0.217, p= 0.028
Musculoskeletal	r= 0.041, p= 0.681	r= 0.179, p= 0.071	r= 0.006, p= 0.955
Serositis	r= -0.008, p= 0.936	r= -0.087, p= 0.384	r= 0.036, p= 0.719
Neuropsychiatric	r= -0.037, p= 0.708	r= 0.036, p= 0.715	r= -0.077, p= 0.438
Mucocutaneous	r= 0.128, p= 0.197	r= 0.165, p= 0.095	r= 0.126, p= 0.205

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SLEDAI, systemic lupus erythematosus disease activity index

TABLE 4. Correlation between inflammatory markers in systemic lupus erythematosus patients

	NLR	PLR	SII	Lymphopenia
ESR	r= 0.388, p= 0.000	r= 0.143, p= 0.151	r= 0.328, p= 0.001	r= -0.023, p= 0.816
SLEDAI	r= 0.130, p= 0.190	r= 0.233, p= 0.018	r= 0.150, p= 0.130	r= -0.131, p= 0.186
CRP	r= 0.152, p= 0.126	r= 0.222, p= 0.024	r= 0.212, p= 0.031	r= -0.051, p= 0.607

Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index

DISCUSSION

Systemic inflammation in rheumatologic diseases results in anemia, thrombocytosis, neutrophilia, monocytosis, and lymphopenia. The changes in circulating blood cells can be prognostic in different inflammatory diseases [16]. NLR, PLR, and SII are novel inflammatory markers that have been well-discussed in different inflammatory diseases and malignancies including inflammatory bowel diseases, hepatocellular carcinoma, cervical cancer, ovarian cancer, urinary system cancers, and thyroid cancers [19-24]. Also, NLR and PLR have been associated with chronic diseases such as Hashimoto's disease, type 2 DM, and liver fibrosis [25-28]. These markers have been assessed in different rheumatologic diseases.

Studies showed that NLR is higher in SLE patients compared to healthy individuals [9]. Soliman et al. and Qin et al. revealed the correlation of NLR with CRP, ESR, and SLEDAI and the correlation of PLR with SLEDAI in both studies [29,30]. Peirovy et al. showed that SLEDAI is associated with PLR and NLR as well [31]. These results are compatible with our results that showed NLR and PLR had a significant difference between the two groups of SLE patients and healthy individuals. Although our results revealed

TABLE 5. Multiple Linear Regression Model of SLEDAI

Model[a]		Unstandardized Coefficients		Standardized Coefficients	t	Sig	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	43.462	10.463		4.154	0.000		
	ALKP	-0.003	0.018	-0.014	-0.162	0.872	0.844	1.185
	NLR	-0.642	0.977	-0.109	-0.658	0.512	0.240	4.174
	PLR	0.025	0.012	0.263	2.108	0.038	0.420	2.380
	SII	-2.038E-6	0.000	-0.106	-0.539	0.591	0.169	5.016
	C3	-0.293	0.081	-0.412	-3.628	0.000	0.508	1.969
	C4	-0.233	0.382	-0.065	-0.609	0.544	0.568	1.760
	CH50	-0.148	0.052	-0.259	-2.852	0.005	0.792	1.262
	Smoking	3.498	2.467	0.120	1.418	0.160	0.922	1.085
	Anti-dsDNA	2.623	1.165	0.190	2.252	0.027	0.917	1.090
	ESR	0.067	0.033	0.193	2.066	0.042	0.747	1.339

a. Dependent Variable: SLEDAI

Abbreviations: Alkp, alkaline phosphatase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index

that PLR was correlated with and an independent risk factor for SLEDAI, we failed to find a significant correlation between NLR and SII with SLEDAI.

In a study by Taha et al., they evaluated blood-derived markers in SLE, RA, and AS patients in comparison with healthy individuals. They found that PLR and SII had a significantly higher amounts in RA and AS patients, and NLR and PLR were significantly higher in SLE patients than in the controls; however, there were no significant differences in NLR in RA and AS patients and only PLR was correlated with SLEDAI-2k, ESR, and CRP. Taha et al. revealed that NLR was not significantly different between active and inactive SLE patients. They suggested that NLR is useful in SLE diagnosis but not in the prognosis [16]. In a study by Oehadian et al., NLR didn't show any difference between mild and moderate SLE [32]. In our study, we divided SLE patients into two groups of active and inactive SLE based on SLEDAI with the cut-off of 4 and evaluated the mean of PLR, NLR, and SII. The results indicated that only the mean of SII was significantly different between active and inactive SLE groups.

Previous studies demonstrated that NLR was significantly higher in lupus nephritis [29,30]. In a study by Suszek et al., NLR had higher amounts in patients with mucocutaneous manifestations [1]. In our study, we revealed that NLR and SII were correlated with only renal manifestations; this is one of the strengths of our study that SII was not previously assessed to this extent in SLE patients.

SII implements neutrophil, lymphocyte, and platelet counts. Higher SII was associated with ischemic stroke severity, higher risk of coronary artery diseases, adverse neonatal outcomes in preterm premature rupture of membranes of pregnant women, and malignancies [33-35]. SII is mostly evaluated in other autoimmune diseases rather than SLE. Satis et al. demonstrated that in RA patients, SII is not only significantly higher in comparison to healthy individuals, but also it is higher in patients with active RA than those in remission [10]. In our study, SII was not only significantly different between the SLE and control groups, but also between active and inactive SLE groups; however, it was not correlated with SLEDAI.

Using linear regression, we revealed that after adjusting for multiple factors, PLR with other well-known markers such as C3, CH50, ESR, and anti-dsDNA were independent prognostic factors of SLE activity.

In a recent study by Ozdemir et al., they evaluated NLR, PLR, and SII in patients with lupus nephritis and showed that only NLR is significantly higher in lupus nephritis. However, we demonstrated that SII, along with NLR, is associated with renal manifestations of SLE [15]. We also evaluated these three markers with different manifestations of SLE but only renal manifestations were associated with NLR and SII. This encourages more multi-center studies with more participants to be performed in order to establish SII role in SLE patients.

The limitations to this study are as follows: first, this is a case-control study which has the limitations of the nature of the study design. Second, one blood sample was drawn from the patients and evaluated; this does not reflect the dynamics of the blood-derived parameters. However, we assessed the clinical manifestations and other variables when the blood sample was drawn in order to moderate this limitation. Finally, there may be some variations in the blood cell count in different months of the year due to changes in the weather. This may have some effects on our results, which was unavoidable.

CONCLUSIONS

PLR, NLR, and SII are emerging inflammatory markers that demonstrated good results in SLE activity. However, in this study, we revealed that PLR was a better marker correlated with SLE activity. More studies are suggested to assess the role of SII in SLE with consideration of numerous confounding factors.

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