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Inflammation-based biomarkers for the prediction of nephritis in systemic lupus erythematosus

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Abstract

Background/Aim: Inflammation is a crucial component in the pathophysiology of systemic lupus erythematosus (SLE) nephritis. Immune-based scores, such as the neutrophil-lymphocyte and the platelet-lymphocyte ratios (NLR and PLR, respectively) have been suggested as predictors of inflammation and prognosis in SLE. This study aimed to investigate the value of the systemic immune-inflammation index (SII), inflammatory prognostic index (IPI), and systemic inflammatory response index (SIRI) in SLE and lupus nephritis (LN).

Methods: This case-control study consisted of 108 newly diagnosed SLE patients (separated into two subgroups, which included 34 patients with biopsy-proven LN and 74 without nephritis) and 108 age- and gender-matched healthy controls who presented to our outpatient clinic between October 2015 and June 2020. Patients with malignancy, lymphoproliferative and hematologic disorders, active infection, and autoimmune diseases other than SLE were excluded. Inflammation-based biomarkers were calculated at the first presentation of the disease and before any medication was administered. SII was calculated as Neutrophil/Lymphocyte x Platelet, SIRI as Neutrophil x Monocyte/Lymphocyte, and IPI as CRP x NLR/serum albumin. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was used to measure disease activity. The capability of SII, SIRI, NLR, PLR, and IPI to distinguish between SLE patients with or without nephritis was assessed using receiver operating characteristic (ROC) curves. Correlations of inflammation-based scores (SII, SIRI, IPI, NLR) with disease activity and laboratory data of SLE patients were analyzed.

Results: SII, SIRI, and IPI were significantly higher in SLE patients than in healthy controls ($P=0.003$, $P=0.019$, and $P<0.001$, respectively) and also significantly higher in patients with nephritis than in those without ($P<0.001$, $P=0.009$, and $P=0.007$, respectively). The area under the curve (AUC) for SII, SIRI, and IPI in terms of differentiating SLE patients with or without nephritis was 0.748, 0.690, and 0.663, respectively. The cut-off value of SII, SIRI, and IPI to predict LN was 552.25 (sensitivity: 64.7%; specificity: 64.9%; $P<0.001$), 1.08 (sensitivity: 61.8%; specificity: 62.2%; $P=0.002$), and 4.48 (sensitivity: 61.8%; specificity, 62.2%; $P=0.007$), respectively.

Conclusion: SII, SIRI, and IPI may be valuable and promising inflammation-based biomarkers in SLE and for the presence of nephritis in SLE patients. SII was found to be the most reliable predictor of SLE among the inflammation-based biomarkers in our study.

Keywords: lupus nephritis, inflammation, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a complex multisystem, autoimmune disease involving almost all organs [1]. The impact of inflammation on disease pathogenesis and prognosis is well-established [2]. Lupus nephritis (LN) is a leading cause of mortality and morbidity. Despite immunosuppressive treatments, approximately 40% of patients develop renal failure [3]. Thus, prompt identification and early treatment of LN are essential. The need for biomarkers to enable a rapid and easy assessment of inflammatory status in renal involvement in SLE patients exists. Many serum markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complements, and anti-double-stranded DNA (anti-dsDNA), are used to assess the inflammatory status, organ damage, and disease activity of SLE [4]. However, these markers can be costly to use during follow-up and can be influenced by some conditions, such as infections and hypergammaglobulinemia [5,6]. Furthermore, clinical and serological variety in addition to diversity may affect the correct interpretation of disease activity and inflammation.

Neutrophil, lymphocyte, monocyte, and platelet counts are routinely performed during clinical evaluations and follow-ups. Numerous studies have shown the role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio (NLR and PLR, respectively) in determining inflammation and prognosis in rheumatic diseases and malignancies [7, 8]. Recent studies have identified NLR and PLR as valuable biomarkers in the assessment of inflammation and disease activity in SLE [7].

The systemic immune-inflammation index (SII) is a combination of platelet count and NLR. SII was recently developed by Hu et al. [9] as a novel inflammation marker to evaluate the predictive value in hepatocellular carcinoma (HCC) and has been widely studied in many malignancies [10]. It has been reported that SII could provide better information than NLR and PLR about systemic inflammation in cancer patients [9]. The Systemic Inflammatory Response Index (SIRI) and the Inflammatory Prognostic Index (IPI) are two other inflammatory biomarkers that have been shown to be valuable in predicting the prognosis of various types of malignancy. [11,12]. In addition to NLR, CRP, and albumin are used to calculate IPI and monocyte count for SIRI.

Limited evidence in the literature evaluating the association between inflammation-based biomarkers such as SII, SIRI, and renal involvement in SLE patients is available. Also, the association between IPI and SLE has not been previously reported. Therefore, the goal of the study was to evaluate the value of the SII, SIRI, and IPI for predicting the presence of nephritis in SLE patients.

Materials and methods

Study design

This case-control study included 108 SLE patients (34 with biopsy-proven lupus nephritis and 74 without nephritis) and gender and age-matched 108 healthy control (HC) groups who applied to our outpatient clinic between October 2015 and June 2020. SLE patients had been newly diagnosed in our center and did not yet receive treatment. Inflammation-based biomarkers are calculated at the first presentation of the disease and before any medication. Patients with malignancy, lymphoproliferative and hematological disorders, active infection, and autoimmune diseases other than SLE were excluded. The flow diagram of included SLE patients and controls is shown in Figure 1. The study was approved by the Research Ethics Committee of Mersin University (2020/591). The study was conducted in compliance with the Declaration of Helsinki.

Figure 1: Flow diagram of included Systemic Lupus Erythematosus (SLE) patients and controls
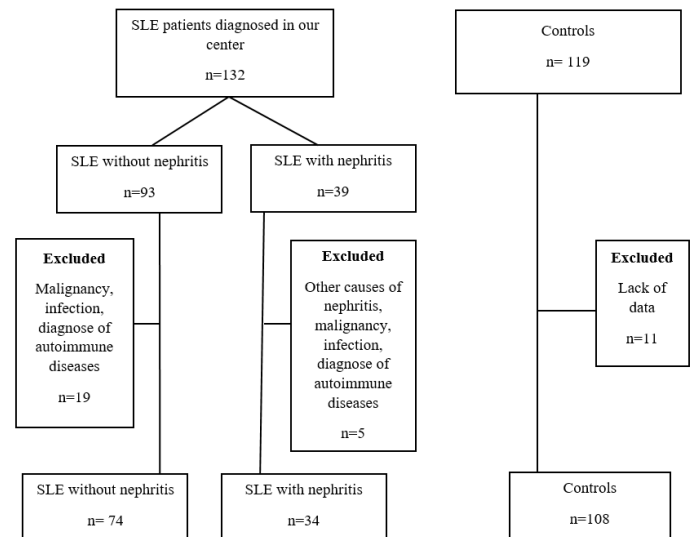
Participant selection

G*power 3.1 was used to calculate the sample size (Franz Faul, University of Kiel, Germany). With a Type I error of 0.05 and an 80% confidence interval, a sample size of at least 29 was required.

All SLE patients' diagnoses were based on the established 2012 Systemic Lupus International Collaborating Clinics Classification (SLICC) criteria [13]. Patients with LN were those who had the diagnosis confirmed by a biopsy.

The healthy control group consisted of healthcare providers who applied to the general internal medicine outpatient clinic for regular periodic checkups and had no known diseases.

Data collection

All subjects' demographic characteristics and clinical and laboratory data were obtained from the medical records. Information was obtained from the patients before treatment, including glucocorticoids: (1) white blood cell count, (2) lymphocyte, neutrophil, and platelet count, (3) ESR, (4) CRP, (5) complement C3 and C4, (6) creatinine, and (7) albumin. Autoantibodies, including anti-dsDNA, anti-nuclear, anti-Smith, and anti-SS-A/anti-SS-B, were recorded.

Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [14].

Calculations of systemic inflammation-related indices

SII was calculated as Neutrophil/Lymphocyte x Platelet, SIRI as Neutrophil x Monocyte/Lymphocyte, NLR as Neutrophil/Lymphocyte, IPI as CRP × NLR/serum Albumin, and PLR as Platelet/Lymphocyte.

Statistical analysis

Statistical analyses were performed using IBM SPSS 18.0 (SPSS Inc., Chicago, USA). The demographic and laboratory data are given as means and standard deviations. The

distribution of the variables was tested with the Kolmogorov–Smirnov test. Student's t-test was used to analyze the difference between the two groups if it's normally distributed. Otherwise, the Mann–Whitney U test was used. The variables' correlation was assessed using Spearman's correlation for non-normal and Pearson's correlation for normal distribution. Receiver operating characteristics (ROC) were used to evaluate the ability of SII, SIRI, NLR, PLR, and IPI to differentiate between SLE patients with nephritis or without nephritis. $P<0.05$ was considered statistically significant.

Results

Demographic data and laboratory findings are shown in Table 1. In both groups, 99 patients were female (91.6%), and nine were male (8.3%). The mean age of SLE patients was 37.33 (12.45) years. No significant differences in gender and age between the groups were found ($P>0.05$). Symptom duration was 8.91 (11.92) months. Biopsy-proven LN was present in 34 (31.5%) patients. All patients were separated into three groups: (1) control, (2) SLE without nephritis, and (3) SLE with nephritis. Neutrophil, lymphocyte, leucocyte, monocyte, platelet counts were lower in SLE patients compared to healthy controls ($P<0.001$ for all). NLR and PLR were higher in SLE patients than in healthy controls ($P<0.001$ for all). SII, IPI, and SIRI were also higher in SLE patients than in healthy controls (685.18 [561.82] versus 512.74 [197.37]; $P=0.003$, 11.04 (20.33) versus 1.30 [1.48]; $P<0.001$, 1.30 [1.19] versus 1.00 [0.48]; $P=0.019$, respectively) as shown in Table 1.

Table 1: Demographic and laboratory parameters of patients and healthy controls.

	Healthy control (n=108) Mean (SD)	SLE (n=108) Mean (SD)	P-value
Age (years)	39.59 (12.00)	37.33 (12.45)	0.176
ESR (mm/hour)	12.16 (8.55)	40.94 (28.24)	<0.001
CRP (mg/L)	3.39 (3.52)	13.29 (26.47)	<0.001
Leukocytes (×10³/mm³)	7.434 (1.69)	5.491 (2.21)	<0.001
Neutrophils (×10³/mm³)	4.357 (1.31)	3.545 (1.69)	<0.001
Lymphocytes (×10³/mm³)	2.35 (0.53)	1.379 (0.82)	<0.001
Platelets (×10³/mm³)	268.93 (57.61)	222.49 (97.17)	<0.001
Monocyte (×10³/mm³)	0.521 (0.151)	0.402 (0.156)	<0.001
NLR	1.90 (0.60)	3.23 (2.51)	<0.001
PLR	119.11 (32.55)	201.59 (135.13)	<0.001
SII	512.74 (197.37)	685.18 (561.82)	0.003
SIRI	1.00 (0.48)	1.30 (1.19)	0.019
IPI	1.30 (1.48)	11.04 (20.33)	<0.001
Creatinine (mg/dL)	0.61 (0.11)	0.75 (0.37)	<0.001
Albumin (g/dL)	43.3 (3.2)	36.11 (8.82)	<0.001
Proteinuria (mg/day)		1240.24 (2339.24)	
SLEDAI-2K		9.70 (8.51)	
C3 (mg/dL)		74.87 (36.32)	
C4 (mg/dL)		14.24 (9.02)	
		n, %	
ANA		104, 96.3%	
Anti-SS-A/Anti-SS-B		34, 31.5%	
Anti-Smith		24, 22.2%	
Anti-dsDNA		51, 47.2%	
Nephritis		34, 31.5%	

ANA: Anti-Nuclear Antibody, CRP: C-Reactive Protein, dsDNA: Anti-Double Stranded Antibodies, ESR: Erythrocyte Sedimentation Rate, IPI: Inflammatory prognostic index, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet to-Lymphocyte Ratio, SD: Standard Deviation, SII: Systemic Immune-Inflammation Index, SLE: Systemic Lupus Erythematosus, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SIRI: Systemic inflammation response index

SII, SIRI, IPI, NLR, and PLR values were significantly higher in SLE patients with nephritis than those without nephritis ($P<0.001$, $P=0.009$, $P=0.007$, $P=0.014$, and $P=0.002$, respectively). ESR, CRP, SLEDAI-2K, and C3 and 4 levels were not statistically different between the SLE patients without nephritis and LN ($P>0.05$ for all) as shown in Table 2.

Table 2: Differences between inflammatory biomarkers and disease activity in patients with lupus nephritis and without nephritis.

	SLE with nephritis (n=34) Mean (SD)	SLE without nephritis (n=74) Mean (SD)	P-value
ESR (mm/hour)	39.67 (31.85)	41.52 (26.63)	0.753
CRP (mg/L)	12.50 (17.14)	13.65 (29.90)	0.836
NLR	4.36 (3.55)	2.71 (1.64)	0.014
PLR	258.82 (154.47)	175.29 (117.27)	0.002
SII	1009.0 (730.39)	536.40 (387.58)	<0.001
SIRI	1.74 (1.46)	1.10 (0.98)	0.009
IPI	19.54 (30.58)	7.13 (11.58)	0.007
SLEDAI-2K	10.82 (9.83)	9.18 (7.85)	0.357
C3 (mg/dL)	74.16 (44.03)	75.19 (32.51)	0.891
C4 (mg/dL)	14.93 (10.52)	13.92 (8.30)	0.593

CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, IPI: Inflammatory prognostic index, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet to-Lymphocyte Ratio, SD: Standard Deviation, SII: Systemic Immune-Inflammation Index, SLE: Systemic Lupus Erythematosus, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SIRI: Systemic inflammation response index

SII was not correlated with SLEDAI-2K, complement levels, creatinine, proteinuria, ESR, or CRP levels in SLE patients ($P>0.05$ for all). SIRI was correlated with C3, C4 and serum creatinine levels ($r=0.236$; $P=0.014$, $r=0.268$; $P=0.005$, $r=0.195$; and $P=0.043$, respectively). NLR only correlated with serum creatinine ($r=0.215$; $P=0.025$). IPI was positively correlated with SLEDAI-2K, ESR, CRP, serum creatinine, and proteinuria ($r=0.209$; $P=0.030$, $r=0.530$; $P<0.001$, $r=0.625$; $P<0.001$, $r=0.264$; $P=0.006$, and $r=0.345$; $P<0.001$, respectively) as shown in Table 3.

Table 3: Correlations of inflammation-based scores (SII, SIRI, IPI, NLR) with disease activity and laboratory data of SLE patients.

	SII r	SII P-value	SIRI r	SIRI P-value	IPI r	IPI P-value	NLR r	NLR P-value
SLEDAI-2K	0.086	0.375	-0.004	0.970	0.209	0.030	0.012	0.906
C3	0.058	0.554	0.236	0.014	0.108	0.264	0.186	0.054
C4	0.041	0.671	0.268	0.005	0.082	0.399	0.175	0.070
ESR	0.139	0.151	-0.072	0.459	0.530	<0.001	0.047	0.631
CRP	-0.088	0.363	-0.149	0.123	0.625	<0.001	-0.118	0.223
Creatinine (mg/L)	0.182	0.059	0.195	0.043	0.264	0.006	0.215	0.025
Proteinuria (mg/day)	0.085	0.384	0.111	0.252	0.345	<0.001	0.094	0.332

CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, IPI: Inflammatory prognostic index, NLR: Neutrophil-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SIRI: Systemic inflammation response index

The area under the curve (AUC) for SII in terms of differentiating SLE patients with or without nephritis was 0.748. The cutoff SII value was 555.26 sensitivity, 64.7% specificity 64.9%, and 95% confidence interval (CI) 0.651–0.845 ($P<0.001$). However, the AUCs for NLR, PLR, SIRI, and IPI were <0.7. AUC for NLR in terms of differentiating SLE patients with or without nephritis was 0.665 (95% CI: 0.547–0.784; $P=0.006$), and the cutoff NLR value was 2.64 (sensitivity: 64.7%,specificity: 64.9%). AUC for PLR was 0.687 (95% CI: 0.579–0.796; $P=0.002$), and the cutoff PLR value was 182.73 (sensitivity: 64.7%,specificity: 63.5%). AUC for SIRI was 0.690 (95% CI: 0.584–0.797; $P=0.002$), and the cutoff SIRI value was 1.08 (sensitivity: 61.8%, specificity: 62.2%). AUC for IPI was 0.663 (95% CI 0.550–0.776; $P=0.007$), and the cutoff IPI value was 4.48 (sensitivity: 61.8%, specificity: 62.2%) as shown in Figure 2.

Figure 2: Receiver operating characteristics analysis of SII, NLR, and PLR for differentiating SLE patients with nephritis from SLE patients without nephritis.

Diagonal segments are produced by ties.
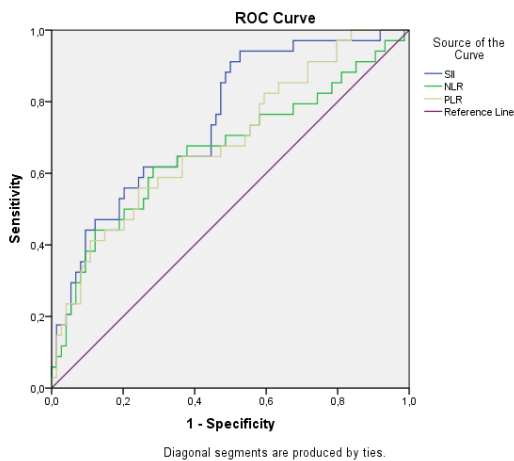
Discussion

The need for biomarkers that can facilitate a fast and easy assessment of ongoing inflammation in SLE is present. NLR and PLR were found to be increased in SLE patients and might be a relevant indicator of inflammation and disease activity [15]. However, the role of SII, SIRI, IPI, which are composite indices, is not entirely clear.

This study was conducted to assess the clinical value of SII, SIRI, and IPI in evaluating SLE and LN. Our results show that SII, SIRI, and IPI were higher in SLE patients than in controls, and they were also higher in SLE with nephritis than without. This finding indicates that SII, SIRI, and IPI may be easy-to-use, widely available, and inexpensive inflammation markers for SLE and LN.

SLE is characterized by enhanced autoantibody generation, leukocyte recruitment, immune complex deposition, and complement activation, all of which result in acute and chronic inflammation and tissue damage [16]. The interactions between neutrophils, dendritic cells, interferon alpha (IFN)-alpha, and autoantibodies are essential events in SLE pathogenesis, which initiates and maintains chronic inflammation [17]. Systemic inflammation can induce neutrophilia and lymphopenia in the peripheral blood and correlates with the severity of inflammation [18]. Neutrophils and platelets play an active role in both systemic and local inflammatory responses [19, 20]. Based on this process, many hematological indices, including the NLR, PLR, and mean platelet value (MPV), have been reported as potential biomarkers of systemic inflammation in various rheumatic disorders in recent years [7, 21].

Qin et al.'s [22] studies show that NLR, MPV, and PLR were higher in SLE patients and correlated with acute phase reactants and disease activity. Wu et al. [15] reported that NLR and PLR were higher in SLE compared to controls and also positively correlated with SLEDAI scores. Additionally, NLR was higher in patients with nephritis. Similarly, Yu et al. [23] reported a positive correlation between NLR and ESR, CRP, and SLEDAI-2K in a study that included 201 healthy controls and 212 SLE patients. However, they emphasized that NLR did not correlate with complement levels, possibly due to different inflammatory markers involved in distinct biological processes. NLR was higher in SLE than in healthy controls according to a meta-analysis of 14 article that included SLE (1,781 patients) and healthy controls (1,330). Furthermore, NLR indicates active disease and renal involvement [24].

SLEDAI-2K is a weighted index developed for evaluating SLE-related disease activity [14]. Although this index includes thrombocytopenia and leukopenia, the index does not include lymphopenia. However, lymphopenia is the most common white blood count abnormality among patients with SLE [10]. Furthermore, SLEDAI-2K assesses the disease manifestations as absent or present rather than according to their severity, so it may not be capable of detecting the degree of disease activity or inflammation with adequate sensitivity [25].

As a consequence of immunological responses, LN is characterized by immune complex deposition, autoantibody generation, and infiltration of inflammatory cells [16]. Aggressive and rapid treatment is essential to achieve remission and prevent renal damage. It has been shown that platelets mediate neutrophil-induced glomerular injury and immune complex nephritis [26]. Li et al. [27] reported that NLR is independently associated with SLE and may reflect renal involvement. Similarly, Ayna et al. [28] reported that NLR and MPV could be predictors of LN. In our study, we found that the SII, SIRI, and IPI indices may reflect renal involvement.

A recent study reported that SII was significantly higher in SLE patients, whereas NLR was performed better as a biomarker than SII [29]. However, in our study, SII was the most reliable index among SIRI, NLR, PLR, and IPI indices. In line with our findings, no association between SLEDAI-2K and SII in that study was described. Our findings revealed only a weak correlation between SLEDAI and IPI, but no correlation between other indices and SLEDAI was found.

Our study showed that SII, IPI, and SIRI might predict LN. SII, SIRI, and IPI (which require only whole blood counts, CRP, and serum albumin) and may be promising inflammation biomarkers for the diagnosis of LN and follow-up due to their low cost and practical use. Furthermore, to our knowledge, this study is the first one to evaluate the usefulness of IPI as a marker for SLE and LN.

Limitations

A small sample size and the study's retrospective design are the main limitations of our study. Biomarkers are only based on a single measurement of whole blood count and biochemistry at the time of disease onset. Another limitation is that the study was conducted in a single center. This study is a retrospective study in which data was extracted and entered manually. The measurement of peripheral blood cells with an automated counter may also have caused the measurement error. Bias in patient selection is another possibility. The fact that our study was conducted at a tertiary care center to which more severely ill patients are referred may have resulted in patient selection bias.

Conclusion

In conclusion, SII, SIRI, and IPI may be valuable inflammation biomarkers in SLE nephritis, and they may serve as indicators of nephritis in SLE patients. SII seems to be the most reliable predictor of LN among the inflammation-based biomarkers (SIRI, IPI, NLR, PLR) in our study. SII, SIRI, and IPI can be used to determine patients' renal involvement or exacerbation of renal disease in conjunction with other

inflammatory markers. They may help clinicians identify subgroups of patients who are at risk of high nephritis relapses of or predict treatment response.

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