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Original Article RHEUMATOLOGY

A potential biomarker of disease activity in systemic lupus erythematosus, systemic immune-inflammation index

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ABSTRACT

OBJECTIVE: Biomarkers using routine laboratory tests accurately presenting systemic lupus erythematosus (SLE) disease activity may have important practical values in clinical settings. The primary purpose of this study was to investigate neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII; neutrophil X platelet/lymphocyte) as potential biomarkers of disease activity in cases with SLE.

METHODS: In this case-control observational study, cases with SLE and demographically similar healthy controls were included. For clinical evaluation demographic features, disease duration and drugs were recorded. SLE clinical disease activity was assessed with SLEDAI scores. For laboratory assessments; erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and C3-C4 levels and anti-dsDNA positivity were recorded. Based on the simultaneous complete blood count (CBC) of the participants NLR, PLR and SII were calculated. The correlation between clinical and laboratory data was analyzed.

RESULTS: 68 cases with SLE (64 women, 8 men) and 69 controls (65 women, 4 men) were included in this investigation. The demographic features of the cases and controls were similar. ESR, CRP, NLR, PLR and SII scores were statistically higher in cases with SLE than controls ($p<0.000$). Statistically significant positive correlations between SLEDAI and NLR, PLR and SII scores were demonstrated ($p=0.01$, $r=0.505$; 0.414; 0.698, respectively). We determined a cut-off value of SII as 681,3 presenting 77% sensitivity and 76% specificity to discriminate no-mild disease activity and moderate-higher SLE disease activity status. The SII cut-off value was determined as 681,3 presenting 77% sensitivity and 76% specificity ($p<0.000$, and AUC=0.930).

CONCLUSION: CBC indices were shown to be higher in cases with SLE than healthy controls in our study. By presenting a strong correlation with disease activity and discriminating ability of disease status, SII might serve as a biomarker supporting clinical evaluation in SLE.

Keywords: Biomarker; disease activity; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; systemic immune-inflammation index; systemic lupus erythematosus.

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Systemic lupus erythematosus (SLE) is a multisystem disease which has a broad range of manifestations with a clinical course presenting remissions and relapses [1]. In the management of SLE, the evaluation of its activity is of utmost importance. The validated SLE disease activity instruments mainly rely on assessing the involvement of the various organs and on some limited laboratory data [2]. The clinical assessment maintains its essential role in the evaluation of SLE activity since a really satisfactory solution has not yet been established in spite of many po-

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tential biomarkers investigated. Biomarkers using routine laboratory tests accurately presenting SLE disease activity may have important practical values in clinical settings.

In recent years, estimation of inflammation based on complete blood count (CBC), as a practical, unexpansive and routine test, has become a useful method. Various subparameter combinations of CBC have been investigated as cellular immune inflammation markers. The indices combining CBC cell types participate in the inflammatory process including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII; neutrophil X platelet/lymphocyte) have emerged as new markers of disease-related inflammation. These parameters have been shown to be associated with poor outcomes, especially in several malignancies and have been limitedly investigated in some inflammatory diseases such as Behcet's Disease (BD), Ankylosing Spondylitis (AS), psoriasis-psoriatic arthritis [3–7]. However, there is no previous study evaluating the possible relationship between these indices and disease activity in SLE.

The primary purpose of this investigation was to investigate NLR, PLR and SII as potential biomarkers of disease activity in cases with SLE.

Highlight key points

- The indices combining CBC cell types participate in the inflammatory process including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII; neutrophil X platelet/lymphocyte) were found to be higher in patients with SLE than healthy controls.
- SII presented a strong correlation with SLE disease activity with a cut-off value of 681,3 discriminating no-mild disease activity and moderate-higher SLE disease activity status (with 77% sensitivity and 76% specifity).
- By presenting strong correlation with disease activity and discriminating ability of disease status, SII might serve as a biomarker supporting clinical evaluation in SLE.

MATERIAL AND METHODS

Study Design and Population

Our investigation was designed as a case-control observational study which was performed in Ataturk University School of Medicine Rheumatology clinic between December 2021 and April 2022 in accordance with the Declaration of Helsinki principles. Its protocol was approved by the Ataturk University Ethics Committee (no: 07/41, 04.11.2021) and an informed consent was obtained from all the participants. After calculating the sample size as 64 with 90% power and 95% reliability, 70 consecutive cases with SLE fulfilling the 2019 EULAR/ACR classification criteria and 67 healthy controls were included [7, 8].

Our inclusion criteria were being older than 18 years old, cases who met current SLE classification criteria for patient group and demographically similar healthy participants without known diseases for control group. Our exclusion criteria were existence of pregnancy or lactation, any other inflammatory or autoimmune diseases, infectious diseases, hematological disorders (as well as cytopenia due to SLE) and malignancies.

Evaluations

Demographic features (age, gender), disease duration (months) and current drugs for SLE were recorded.

In order to perform the evaluation of SLE clinical disease activity SLEDAI scores were recorded as recommended [9]. SLEDAI index includes 24 weighted objective clinical and laboratory variables and it measures disease activity within the last 10 days. Its range can be between 0 to 105 presenting the following categories; no activity (SLEDAI=0), mild activity (SLEDAI=1–5), moderate activity (SLEDAI=6–10), high activity (SLEDAI=11–19), very high activity (SLEDAI ≥20) [10].

For laboratory assessments; erythrocyte sedimentation rate (ESR; mm/h) and C-reactive protein (CRP; mg/L) levels were measured by using standard laboratory methods. Also, anti-dsDNA positivity (IFA) and C3-C4 levels (g/L) were recorded. Based on the simultaneous CBC of the participants NLR, PLR and SII were calculated [11].

Statistical Analysis

Our results were analyzed statistically using SPSS for Windows 22.0 software (SPSS Inc., Chicago, IL, USA). Means and standard deviations (SD) were used for the evaluation of normal distribution. The categorical variables were presented with numbers and percentages. The student t-tests were performed to compare the mean values between the groups and chi-squared test was used to compare categorical variables. Correlation analysis was performed by Spearman test determining the rho coefficient and level of significance. The weak, moderate and strong correlations referred to r=0.3–0.5, r=0.3–0.5 and r=0.5–1.0, respectively [11]. $P<0.05$ was considered statistically significant.

Table 1. The comparison of the demographic features, disease durations, ESR, CRP, NLR, PLR and SII values of the participants

	Cases with SLE (n=68)	Controls (n=69)	p
Age (years)			NS
Mean±SD	38.90±11.86	36.18±13.27	
Min/Max	19/66	18/66	
Gender, n			NS
Female	64	65	
Male	4	4	
Disease duration (years)			
Mean±SD	5.16±5.04		
Min/Max	0/24		
Medications, n (%)			
Glucocorticoids	34 (50)		
Hydroxychloroquine	65 (95)		
Immunosuppressive drugs (methotrexate, azathioprine, cyclophosphamide, leflunomide, mycophenolate mofetil)	27 (39)		
Biologics (rituximab)	1 (1)		
Low dose salicylate	10 (15)		
Ramipril	4 (6)		
SLEDAI			
Mean±SD	3.61±2.30		
Min/Max	0/10		
Disease activity, n			
No (SLEDAI=0)	3		
Mild (SLEDAI=1–5)	52		
Moderate (SLEDAI=6–10)	13		
High (SLEDAI=11–19)	0		
Very high (SLEDAI ≥20)	0		
C3	1.76±1.04		
C4	0.21±0.10		
Anti-dsDNA			
Negative	55		
Positive	12		
ESR (mm/h) Mean±SD	**16.73±11.47**	**6.37±4.00**	**0.000**
CRP (mg/L) Mean±SD	**6.85±5.15**	**1.98±1.66**	**0.000**
NLR	**2.29±0.88**	**1.45±0.40**	**0.000**
PLR	**150.21±85.87**	**108.19±28.49**	**0.000**
SII (10^3/mm^3) Mean±SD	**606.92±336.54**	**390.43±131.61**	**0.000**

SLEDAI: SLE disease activity index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII; Systemic immune-inflammation index; SD: Standard deviation; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; C3: Complemant 3; C4: Complemant 4; NS: Not significant.

RESULTS

68 cases with SLE (64 women, 8 men) and 69 controls (65 women, 4 men) were included in this investigation. The demographic characteristics of the cases and controls were similar. The mean±SD of ESR, CRP, NLR, PLR and SII were statistically higher in cases with SLE than controls (p<0.000). The demographic characteristics, disease durations, ESR, CRP, NLR, PLR and SII values of the participants were shown in Table 1.

Table 2. The correlations between clinical disease activity, laboratory parameters and NLR, PLR and SII

Cases with SLE (n=68)	NLR	PLR	SII
SLEDAI			
P	0.01	0.01	0.01
r	0.498	0.414	0.698
ESR			
p	0.01	0.01	0.01
r	0.401	0.363	0.383
CRP			
p	0.01	0.01	0.01
r	0.276	0.159	0.266
C3	NS	NS	NS
C4	NS	NS	NS

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII; Systemic immune-inflammation index; SLEDAI: SLE disease activity index; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; C3: Complemant 3; C4: Complemant 4; NS: Not significant.

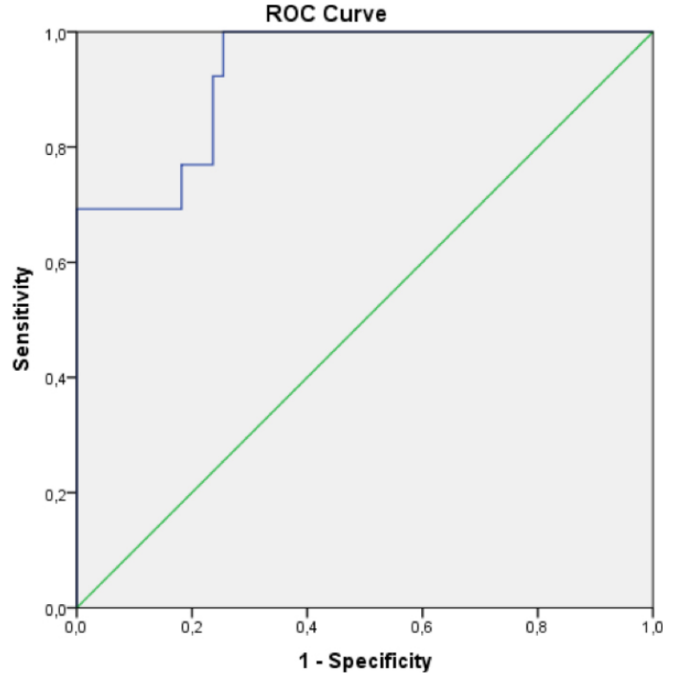

Figure 1. Receiver operating characteristic (ROC) curve analysis for assessing the performance of the Systemic immune-inflammation index in determining SLE disease activity (SLEDAI).

The correlations between NLR, PLR, SII and disease activity parameters were also investigated. Statistically significant positive correlations between SLEDAI and NLR, PLR and SII scores were demonstrated (p=0.01, r=0.505; 0.414; 0.698, respectively). Also, weak positive correlations were determined between ESR-CRP levels and these parameters. However, we found no significant correlation between C3-C4 levels and NLR, PLR and SII. Data are shown in Table 2.

In terms of anti-dsDNA positivity, there was no difference in NLR, PLR and SII scores between patients who are anti-dsDNA positive and those who are negative.

Since we demonstrated a significant strong correlation between SLEDAI and SII we performed a ROC analysis to define cut-off SII values to discriminate no-mild and moderate-higher SLE disease activity status (the SII cut-off value for SLEDAI≤5 and SLEDAI>6). The SII cut-off value was determined as 681,3 presenting 77% sensitivity and 76% specificity (p<0.000 and AUC=0.930) (Fig. 1).

DISCUSSION

In this study, it was aimed to evaluate NLR, PLR and SII as potential biomarkers of disease activity in cases with SLE. Our results demonstrated that these parameters were significantly higher in cases with SLE than healthy participants. Although no correlation was determined between these parameters and serum C3-C4 levels, there were weak-moderate correlations between these parameters and ESR-CRP levels and between SLEDAI and NLR-PLR. Furthermore, SII presented a strong correlation with SLEDAI with a cut-off value of 681,3 discriminating no-mild disease activity and moderate-higher SLE disease activity status (with 77% sensitivity and 76% specificity).

The evaluation of disease activity in SLE is a task for clinicians in daily practice and it is also required for clinical research. Over the past 2 decades, many indices have been suggested to measure objectively SLE disease activity mainly based on assessing the involvement of the various organs and some limited laboratory data [2, 10]. Potential biomarkers supporting these clinical indices will contribute to the physician in the evaluation of the SLE disease activity.

Various subparameter combinations of CBC have been used as prognostic markers in various diseases for years [6]. In recent years, they emerged as new markers of disease-related inflammation, especially in oncology [3]. Among CBC subparameter combinations, SII has gained remarkable popularity as an immune inflamma-

tion marker since it integrates the kinetics of three cell populations (neutrophil X platelet/lymphocyte) into one single parameter [12]. In clinical settings, it has been studied mainly in malignancies as an inflammation-based prognostic marker [3]. It has also been studied in some inflammatory diseases such as psoriasis presenting higher SII in these patients [5, 6]. In rheumatology practice, SII was investigated limitedly and in these studies, SII was shown to be significantly higher in cases than controls with a positive correlation with disease activity in some diseases such as AS, PsA and BD [4, 5, 7]. In our study, SII was higher in cases with SLE than controls and in addition to moderate correlations between disease activity and other two parameters, our results demonstrated a statistically strong correlation between SII and SLEDAI. It also presented an ability in discriminating no-mild disease activity and moderate-higher SLE disease activity.

Among other CBC indices showing moderate correlations, SII appeared to be a more informative parameter by presenting a strong correlation with disease activity in SLE. SII, as a simple, practical and cost-effective tool, seemed to be a supporting biomarker of the disease activity in our study. However, CBC parameters may be affected by several factors such as infections, anemia and thrombocytopenia [7, 13]. SII might have some advantages since it includes three parameters of CBC. By including the count of platelets which take part in crucial immune-mediated processes such as playing important roles in coagulation, fibrinolysis, tissue regeneration, angiogenesis and producing inflammatory cytokines, it might reflect more accurate information about both acute and chronic inflammation [6, 14, 15]. Keeping these limitations of SII in mind, it seemed to appear as a practical informative tool reflecting disease activity in SLE.

The absence of cases with high or very high disease activity was the main limitation of our study. Being the first study showing a strong correlation between SII and SLEDAI and its discriminating ability can be considered as the main strengths of the present study.

Conclusion

In conclusion; CBC indices were found to be higher in patients with SLE than healthy controls in our study. By presenting a strong correlation with disease activity and discriminating ability of disease status, SII might serve as a biomarker supporting clinical evaluation in SLE.

Ethics Committee Approval: The Ataturk University Clinical Research Ethics Committee granted approval for this study (date: 04.11.2021, number: 07/41).

Authorship Contributions: Concept – MRA; Design – MAM; Supervision – MAM; Materials – MRA; Data collection and/or processing – MRA; Analysis and/or interpretation – MAM; Literature review – MAM; Writing – MAM; Critical review – MAM.

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