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| RESEARCH ARTICLE

Systemic Immune-inflammation Index: A Potential Indicator of Disease Activity in Sjögren's Syndrome?

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| ABSTRACT
Given the autoimmune and inflammatory nature of Sjögren's Syndrome(SS), it is essential to identify reliable indicators to monitor disease progression and inform treatment strategies. This study aims to evaluate the potential of the Systemic Immune-Inflammation Index (SII) as a biomarker for assessing disease activity in SS. A prospective analysis was conducted on two groups: the first comprising 52 patients diagnosed with SS and the second a healthy control group. SII values were calculated using the following formula: platelet count multiplied by the neutrophil-to-lymphocyte ratio. The degree of disease activity was gauged according to the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) criteria. This study examines the correlations between SII and several clinical and patient-reported outcome measures, including various inflammatory markers. Compared to the control group, the SS patient cohort displayed slightly elevated SII levels ($p = 0.04$). The SII exhibited a correlation with elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), suggesting its potential as a marker of systemic inflammation. Nevertheless, the observed correlation between SII and ESSDAI scores ($r = 0.0903$) was weak and not statistically significant ($p = 0.524$). Although SII values were higher in SS patients and correlated with systemic inflammation markers, no statistically significant relationship was observed between these values and disease activity, as measured by ESSDAI.Thus, while SII may reflect systemic inflammation, its utility as a marker for disease activity in SS remains limited. Further studies are needed to elucidate its role in clinical settings.

| KEYWORDS

Systemic Immune-Inflammation Index, Sjögren's Syndrome, Disease Activity, Biomarker, Inflammation

| ARTICLE INFORMATION

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1. Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder characterized by the infiltration and damage to exocrine glands, resulting in a constellation of symptoms including sicca syndrome and xerostomia. Additionally, the disease often involves systemic symptoms like joint pain, dry skin, and multi-organ involvement. As pSS is driven by inflammatory processes, identifying appropriate biomarkers for assessing systemic inflammation is crucial for managing and predicting disease outcomes [1].

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is a detailed organ-specific scoring system used to measure the clinical activity of pSS. It was designed to monitor the disease's progression, though its effectiveness as a prognostic index is still debated [2]. A large-scale study in 2018, involving 10,500 SS patients, found that those with high ESSDAI scores had increased organ involvement, higher mortality rates, and more complications [3].

The Systemic Immune-Inflammation Index (SII) has recently been identified as a potentially valuable marker for the assessment of disease activity and prognosis in a range of autoimmune and inflammatory conditions. SII is calculated by multiplying platelet

count with the neutrophil-to-lymphocyte ratio, reflecting the extent of systemic inflammation [4]. However, its effectiveness in determining disease activity in a heterogeneous disease like pSS remains unclear. The objective of this study is to assess the correlation between SII and disease activity in patients with pSS and to compare it with other inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), ESR, and CRP, to determine the specificity of the findings.

2. Materıal And Methods

Study Design

A prospective cross-sectional analysis was employed to study a cohort of 52 patients diagnosed with primary Sjögren's syndrome according to the 2016 ACR/EULAR classification criteria. All participants had been on their treatment regimen for at least three months before the commencement of the study.

The study lasted six months, from June 2024 to January 2025. The control group consisted of 52 healthy individuals of similar age and sex who presented to the internal medicine outpatient clinic, had no history of rheumatic disease or active complaints, and underwent routine blood tests for general examination only.

Individuals with a history of malignancy, infection, immunodeficiency, hematological conditions, or other inflammatory diseases were excluded from the patient and control groups.

Data Collection and Evaluation

The data set comprised age, gender, clinical and demographic information, and erythrocyte sedimentation rate (ESR) and CRP levels for both the patient and control groups. Hemogram parameters, including neutrophil, platelet, and lymphocyte counts, were analyzed to calculate NLR, PLR, and SII values. The disease activity in the patient cohort was assessed using the ESSDAI, which evaluates 12 domains, including constitutional symptoms (fever, night sweats, weight loss), lymphadenopathy, glandular, articular, hematological, pulmonary, cutaneous, muscular, renal, CNS, peripheral nervous system, and biological domains. Each trait is rated on a scale of 0 to 3 for activity and 1 to 6 for severity. The scores are multiplied separately for each domain, and the overall activity index is calculated by summing these values. Patients were classified based on their activity levels as low (ESSDAI < 5), moderate ($5 \leq$ ESSDAI ≤ 13), or high (ESSDAI ≥ 14). The relationship between NLR, PLR, and SII values and ESSDAI was then analyzed.

Power Analysis

The power analysis was conducted utilizing the G*Power software, version 3.1. An independent t-test was used for group comparisons, with an effect size (Cohen's d) set at 0.5, an alpha level of 0.05, and a power of 0.80. A sample size of 52 participants was deemed sufficient to achieve the desired power for each group.

Statistical Analysis

Data normality was assessed using the Kolmogorov-Smirnov test. Since the data deviated significantly from a normal distribution, non-parametric tests were applied. Mann-Whitney U tests were employed to compare disease activity and clinical parameters between groups. Correlations between SII and disease activity were analyzed using Spearman's correlation coefficient. In light of the p-values being less than 0.05, a statistical significance was deemed present. All analyses were conducted using BluSky Statistics software (Version 10.3.2).

3. Results

The study included 104 participants, equally divided between the patient and control groups. There was no significant difference in the age distribution between the groups ($p = 0.502$), and the gender distribution was also comparable ($p = 0.512$). The patient group demonstrated markedly elevated levels of CRP and ESR compared to the control group ($p = 0.019$ and $p = 0.032$, respectively). Hemoglobin, neutrophil, lymphocyte, and platelet counts were similar between the two groups ($p > 0.05$). No statistically significant difference between groups was observed between SII, NLR, and PLR values (Table 1).

Table 1: *Descriptive characteristics of all participants and comparison results of groups*.

	Patient (n=52)	Control(n=52)	p
Age_median(min-max)(years)	48.0(44.0-59.0)	47.5(22.0-63.0)	0.502*
Sex _n, (%) Male Female	 13(25.0) 39(75.0)	 16(30.8) 36(69.2)	 0.512**
CRP_mean±S.D (mg/dL)	7.72±6.96	3.39±1.66	**0.019***
Sedimentation rate_mean±S.D (mm/h)	21.54±17.61	11.03±7.12	**0.032***
Hemoglobin_mean±S.D (g/dL)	13.41±1.67	13.94±1.41	0.696*
Neutrophil_mean±S.D (10^3/uL)	4.58±1.88	4.15±1.30	0.435*
Lymphocyte_mean±S.D (10^3/uL)	2.33±0.81	2.43±0.59	0.329*
Platelet_mean±S.D (10^3/uL)	267±66	257±60	0.696*
SII_mean±S.D.	580±463	461±207	0.118*
NLR_mean±S.D.	1.73±1.72	1.32±0.76	0.224*
PLR_mean±S.D.	125±47	111±35	0.172*
*Mann-Whitney U Test, ** Pearson Ki-kare, CRP:C-reactive protein, SII: Systemic immune-inflammation index, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio			

A receiver operating characteristic curve was employed to evaluate the diagnostic efficacy of CRP and ESR for predicting pSS compared to the control group. Both parameters showed statistically significant areas under the curve (Figure 1). Figure 2 illustrates the ROC analysis for SII, NLR, and PLR values. A cut-off value of 451.50 was determined for SII, with sensitivity and specificity rates of 57.7%. NLR and PLR values showed cut-off points of 1.50 and 108.00, respectively, but neither demonstrated strong discriminatory power (Table 2).

Figure 1: CRP and Sedimentation rate ROC curves for Sjögren's compared to the control group.

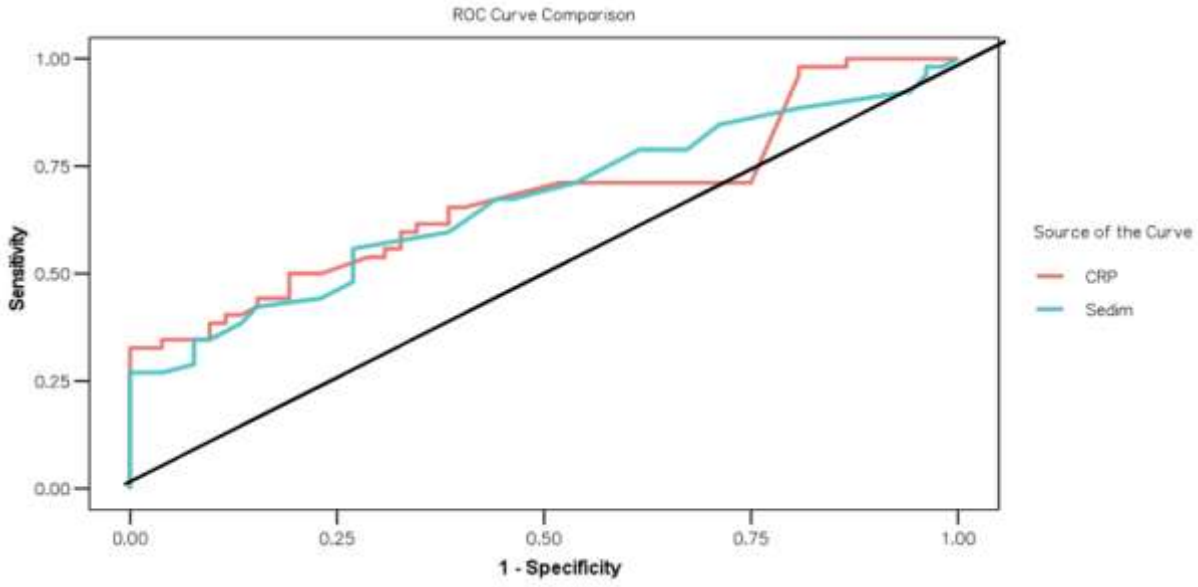

Figure 2: SII, NLR, and PLR ROC curves for Sjögren's compared to the control group.

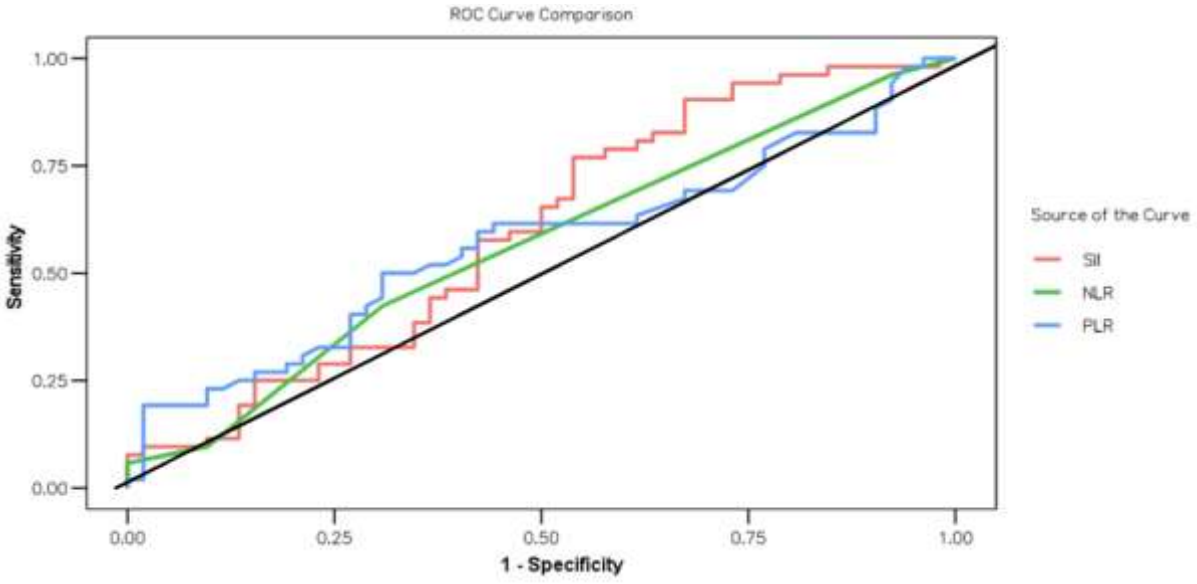

Table 2: *Evaluation of the performance of CRP, Sedimentation Rate, SII, NLR and PLR for Sjögren group (compared to control group) by ROC curve analysis*

	AUC (95.0% CI)	P	Cutoff	Sensitivity, %	Specificity, %	Z
CRP	0.673(0.568-0.778)	**<0.001**	3.27	61.5	61.5	3.49
Sedimentation Rate	0.665(0.561-0.770)	**0.001**	11.50	59.6	61.5	2.93
SII	0.597(0.486-0.707)	**0.04**	451.50	57.7	57.7	1.57
NLR	0.563(0.464-0.662)	0.10	1.50	42.3	69.2	1.53
PLR	0.566 (0.454-0.678)	0.16	108.00	59.6	57.7	1.02
CRP:C-reactive protein, SII:Systemic immune-inflammation index, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio						

Among the 52 patients with pSS, 35 had ESSDAI scores below 5, four had scores between 5 and 13, and 13 had scores above 14. Correlation analysis revealed no significant association between SII, NLR, PLR, and ESSDAI (Table 3).

Table 3: *Correlation of ESSDAI with SII, NLR and PLR*

	Correlation Coefficient (r)	p*
SII	0.0903	0.524
NLR	0.2272	0.105
PLR	-0.0372	0.793
* The Spearman correlation CRP: C-reactive protein, ESSDAI: EULAR Sjögren's syndrome disease activity index,SII: Systemic immune-inflammation index, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio		

4. Discussion

The study compared SII, NLR, and PLR values between pSS patients and a healthy control group and evaluated their effectiveness in determining disease activity. The findings indicated significantly higher CRP and ESR levels in pSS patients, whereas hemoglobin, neutrophil, lymphocyte, and platelet counts were comparable between groups.

The role of hematological parameters like NLR and PLR as biomarkers in autoimmune diseases has been explored in several studies [5-8]. While elevated NLR has been associated with poor prognosis and complications such as interstitial lung disease [9-11]. The

present study failed to reveal a statistically significant correlation between NLR, PLR, and disease activity as measured by ESSDAI ($p > 0.05$). This suggests that hematological biomarkers reflect the degree of inflammation rather than disease severity.

A recent study examined the usefulness of SII in the diagnosis of specific ILDs such as Sjogren's syndrome-associated interstitial lung disease (SjS-ILD), interstitial pneumonia with autoimmune features (IPAF), and idiopathic pulmonary fibrosis (IPF). The cut-off value of SII between IPAF and IPF in ILD patients was 576.1 with a sensitivity of 76.0% and specificity of 76.0% [12]. Similarly, in a study evaluating SII levels, NLR, and PLR in patients with dry eye disease (DED) and comparing them with control subjects, AUC values of 0.761, 0.727, and 0.653 were found in ROC analysis [13]. Our ROC analysis revealed that SII, NLR, and PLR had an average performance in distinguishing pSS patients from healthy individuals. The optimal cut-off value for SII was determined as 451.50, with sensitivity and specificity rates of 57.7% each. NLR and PLR values also showed limited discriminatory power at their respective thresholds. The results of this study indicate that while SII, NLR, and PLR may serve as general indicators of inflammation, they lack sufficient diagnostic accuracy for pSS.

Several studies have identified SII as a promising biomarker in autoimmune diseases. For example, Wu et al. reported a correlation between SII and disease activity in ankylosing spondylitis [14]. A comparable series of observations has been documented about patients presenting with Behçet's disease and psoriatic arthritis. In these instances, using SII is an efficacious method for reflecting disease activity [15-17]. In the present study, biomarkers exhibited minimal correlation with disease activity, as measured by ESSDAI, and were not statistically significant.

The present study was limited by many factors: firstly, the modest sample size; and secondly, the omission of an assessment of comorbidities such as diabetes and hypothyroidism, which have been demonstrated to impact hematological values. Furthermore, a key limitation of the study was the absence of an evaluation of the treatments received by patients diagnosed with Sjögren's disease, including steroids, rituximab, Azathioprine, MMF, and methotrexate, among others. This is because patients are in remission at the time of evaluation, irrespective of the treatment initiated. The most significant limiting factor in the study was that the diagnostic cut-off values of SII demonstrated moderate sensitivity and specificity, thus constraining its clinical applicability for pSS. Hence, larger population studies with longer follow-up periods must further confirm these findings.

5. Conclusion

In summary, the present study demonstrates that SII, NLR, and PLR, which are simple, cost-effective, and reliable markers, exhibit minimal disparities between pSS patients and other rheumatological patients. Moreover, these biomarkers demonstrate a restricted correlation with disease activity, thereby prompting deliberation on their potential for disease severity and prognosis assessment. However, the study's limitations, including the small sample size and the absence of standardized cut-off values, underscore the necessity for further research to ascertain the role of these markers. Future studies involving larger cohorts and internal validation are required to enhance our comprehension of its utility and to inform therapeutic strategies aimed at enhancing patient outcomes.

Conflict of Interest: The authors declare no conflict of interest.

Ethics: The study was carried out using the tenets outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients participating. The University Faculty of Medicine Clinical Research Ethics Committee approved the study on 11/09/2024 (decision number 62).

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