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Can the Systemic Immune Inflammation Index (SII) Indicate Disease Activity in Patients with Rheumatoid Arthritis?

Sistemik İmmün İnflamasyon İndeksi (Sİİ) Romatoid Artritli Hastalarda Hastalık Aktivitesini Gösterebilir mi?

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Abstract

Objective: This study aimed to investigate the clinical utility of the systemic immune-inflammation index (SII) as a potential marker for disease activity in patients with rheumatoid arthritis (RA).

Materials and Methods: A total of 104 RA patients aged between 18 and 65 years, along with 69 healthy controls, were included. RA patients were categorised into two subgroups based on the Disease Activity Score-28-Erythrocyte Sedimentation Rate (DAS-28-ESR): remission (DAS-28-ESR <2.6, n=51) and active disease (DAS-28-ESR >2.6, n=53). Associations between SII and conventional inflammatory markers as well as clinical disease activity indices were examined. Receiver operating characteristic analysis was conducted to assess the diagnostic performance of SII in distinguishing active RA.

Results: SII levels were significantly elevated in both the overall RA group and particularly in the active RA subgroup ($p<0.001$). SII showed strong positive correlations with C-reactive protein ($r_s=0.627$, $p<0.001$), ESR ($r_s=0.383$, $p<0.001$), DAS-28-ESR ($r_s=0.775$, $p<0.001$), the simplified disease activity index ($r_s=0.796$, $p<0.001$), and the clinical disease activity index ($r_s=0.798$, $p<0.001$). The most effective SII threshold for identifying active RA was 479.36×10^9/L, with an area under the curve of 0.968 (95% confidence interval: 0.914-0.993), yielding a sensitivity of 92.45% and specificity of 86.27%.

Conclusion: SII appears to be a valuable, accessible marker for assessing disease activity in patients with rheumatoid arthritis.

Keywords: Erythrocyte sedimentation rate, rheumatoid arthritis, systemic immune-inflammation index

Öz

Amaç: Bu çalışmada, sistemik immün enflamasyon indeksinin (SII), romatoid artrit (RA) hastalarında hastalık aktivitesini değerlendirmedeki yararlılığı araştırıldı.

Gereç ve Yöntem: Çalışmaya yaşları 18-65 arasında değişen 104 RA hastası ile 69 sağlıklı gönüllü dahil edildi. RA hastaları, hastalık aktivite skoru-28 (DAS-28-ESR skoru) <2,6 olan remisyon grubuna (n=51) ve >2,6 olan aktif RA grubuna (n=53) olmak üzere ikiye ayrıldı. SII ile enflamatuvar belirteçler ve hastalık aktivite indeksleri arasındaki ilişkiler analiz edildi. RA hastalık aktivitesinin değerlendirilmesinde SII'nın tanısal gücünü belirlemek amacıyla alıcı çalışma karakteristik eğrisi analizi uygulandı.

Bulgular: SII düzeyleri, hem genel RA grubunda hem de aktif hastalık grubunda anlamlı olarak yüksekti ($p<0,001$). SII; C-reaktif protein ($r_s=0,627$, $p<0,001$), ESR ($r_s=0,383$, $p<0,001$), DAS28-ESR ($r_s=0,775$, $p<0,001$), simplifiye hastalık aktivite indeksi ($r_s=0,796$, $p<0,001$) ve klinik hastalık aktivite indeksi ($r_s=0,798$, $p<0,001$) ile pozitif yönde anlamlı korelasyon gösterdi. RA hastalık aktivitesini belirlemede SII için en uygun eşik değerin $479,36\times10^9$/L olduğu belirlendi (eğri altında kalan alan: 0,968; %95 güven aralığı: 0,914-0,993; duyarlılık: %92,45; özgüllük: %86,27).

Sonuç: SII, romatoid artritli hastalarda hastalık aktivitesini değerlendirmek için değerli ve erişilebilir bir belirteç gibi görünmektedir.

Anahtar kelimeler: Eritrosit sedimentasyon hızı, romatoid artrit, sistemik immün-enflamasyon indeksi

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Introduction

Patients with rheumatoid arthritis (RA) experience limits in their physical function and everyday activities as well as a loss of their ability to work due to the advancement of joint destruction (1). Extra-articular involvement such as rheumatoid nodules, vasculitis, cardiovascular disease, pulmonary disease, neurological disease, gastrointestinal disease, renal disease and hematological diseases can be seen in the course of RA. Although it can occur at any age, it is most common in women in the third to fifth decade of life (2,3). Its prevalence is expressed as approximately 5 in every 1000 adults worldwide (1).

In addition to the existing acute phase reactants routinely used to assess the extent of inflammation in RA, studies have also been conducted on markers calculated from complete blood count (CBC) results, such as platelet (PLT)-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) (4-9). While there are studies demonstrating an association between disease activity in RA and NLR and PLR (5,9), there are also studies reporting insignificant results (6,8).

The indices for assessing disease activity in RA are recognised and routinely used (10-12). Systemic Immune Inflammation index (SII) is derived by multiplying the PLT and neutrophil counts and then dividing the result by the lymphocyte count (13). It was evaluated in subjects with malignancies, depression in diabetic patients, hypertension, aphthous stomatitis, psoriasis, hidradenitis suppurativa, interstitial lung disease, non-infectious uveitis and ulcerative colitis (14-24). Studies have investigated its potential as an innovative biomarker for the evaluate of disease activity in various rheumatologic diseases such as ankylosing spondylitis, Behçet's disease, Adult Still's disease (AOSD) and antineutrophil cytoplasmic antibody-associated vasculitis (25-29).

The relationship between RA activity and SII has not been sufficiently investigated in the literature (30-32). A CBC is ordered at every routine examination of patients with RA. The SII, which is calculated based on the parameters of the CBC, can reduce costs if it indicates disease activity without the need for an additional inflammatory marker. Based on this information, we wanted to evaluate the benefits of SII in RA.

Materials and Methods

The study population consisted of patients who had received treatment at the Outpatient Clinic for Physical Therapy and Rehabilitation at Bursa Uludağ University (ethical approval date: February 23, 2022, protocol code: 2022-4/24). In accordance with the classification criteria (33), 104 patients with ages between 18 and 65 years who had been diagnosed with RA were enrolled in the study. Patients with comorbidities were excluded. The control group consisted of 69 healthy volunteers. Those included in the study were interviewed face-to-face during their application to the outpatient clinic. Data was collected on the participants' age, gender, level of education, occupation, disease duration, current treatments and laboratory findings. NLR, PLR and SII values were calculated using the CBC results. The values of the clinical disease activity index (CDAI), the disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR), and the simplified disease activity index (SDAI) were calculated to assess disease activity. Patients with a DAS28-ESR <2.6 were categorized in the remission group, whereas those with DAS28-ESR > of 2.6 were classified in the active disease group (10).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY). Quantitative data were presented as mean ± standard deviation or as median (minimum–maximum), depending on distribution characteristics. The normality of continuous variables was assessed using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Categorical variables were reported as frequencies and percentages (n, %). Comparisons between groups were carried out using the chi-square test for categorical variables, and either the independent samples t-test or the Mann-Whitney U test for continuous variables, depending on the distribution. Correlation analysis was performed to assess the relationships between SII and C-reactive protein (CRP), ESR, NLR, PLR, DAS28-ESR, SDAI, and CDAI, and the Spearman correlation coefficient was calculated. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values for SII, ESR, CRP, NLR, and PLR. A p-value of less than 0.05 was considered statistically significant.

Sample size estimation was based on data from a prior study on the same subject (30). Power analysis was conducted at a 99% confidence level, with an effect size of 0.84 and a Type I error rate of 5%. This analysis indicated that a minimum of 17 participants per group was necessary.

Results

The RA group was not statistically different from the healthy volunteers in terms of demographics (p>0.05). SII, neutrophil count, NLR, and PLR values were significantly elevated in the RA group compared to healthy controls, whereas lymphocyte levels were reduced. No statistically significant difference was observed between the groups regarding PLT counts (p=0.067) (Table 1).

RA patients in remission were compared to those with active disease to evaluate group differences. No differences were found with regard to gender, age, disease duration, occupation, educational level, drug use and lymphocyte count (p>0.05). SII, neutrophil, PLT, CRP, ESR, NLR, PLR, DAS28, SDAI and CDAI values were higher in the active RA group when compared with the RA patients in remission (p<0.05) (Tables 2 and 3). Figure 1 shows the flow chart for both the healthy control group and the patients with RA.

A positive correlation was observed between SII and CRP levels. (Figure 2a), ESR (Figure 2b), DAS28-ESR (Figure 2c), SDAI (Figure 2d), and CDAI (Figure 2e) variables. Correlations of SII with CRP, ESR, DAS-28, SDAI, and CDAI in RA patients are shown in Figure 2.

Table 1. Clinical, laboratory and demographic parameters of healthy controls and RA

	RA (n=104)	Control (n=69)	p
Age (year)	53 (20-68)	54 (18-64)	0.808[m]
Gender, n (%)			
Female	79 (76)	51 (73.9)	0.760[χ2]
Male	25 (24)	18 (26.1)	
Level of education, n (%)			
Uneducated	2 (1.9)		
Primary education	66 (63.5)		
High school	23 (22.1)		
University	13 (12.5)		
Job, n (%)			
Housewife	56 (53.8)		
Retired	18 (17.3)		
Employee	17 (16.3)		
Officer	8 (7.7)		
Freelancer	5 (4.8)		
Medications, n (%)			
NSAIDs	4 (2.8)		
bDMARDs	22 (15.6)		
csDMARDs	86 (60.0)		
JAK inhibitors (tofacitinib, baricitinib)	9 (6.3)		
Glucocorticoids	22 (15.6)		
Neutrophils (×10⁹/L)	4.32 (1.93, 8.16)	3.73 (2.11, 6.67)	**<0.001[m]**
Lymphocytes (×10⁹/L)	2.20 (± SD: 0.58)	2.64 (± SD: 0.57)	**<0.00[t]**
PLT (×10⁹/L)	259.40 (9.00, 572.00)	237 (135.00, 339.00)	0.067[m]
NLR	1.97 (1.03, 5.22)	1.43 (0.79, 2.23)	**<0.001[m]**
PLR	119.46 (11.61, 303.80)	96.70 (39.82, 160.31)	**<0.001[m]**
SII (×10⁹/L)	500.32 (186.44, 1938.28)	355.16 (167.65, 532.23)	**<0.001[m]**

bDMARDs: Biological disease-modifying anti-rheumatic drugs, csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, JAK inhibitors: Janus kinase inhibitors, [m]: Mann-Whitney U test, NLR: Neutrophil-to-lymphocyte ratio, NSAIDs: Non-steroidal anti inflammatory drugs, PLR: Platelet-to-lymphocyte ratio, PLT: Platelet, RA: Rheumatoid arthritis, SD: Standard deviation, SII: Systemic Immune-Inflammation Index, [t]: Independent samples t-test, [χ2]: Chi-square test

Table 2. Comparisons of clinical data and demographics between the remission group and of patients with RA

	Active RA (n=53)	Remission RA (n=51)	p
Age (year)	57 (32-68)	52 (20-65)	0.251[m]
Gender, n (%)			
Female	39 (73.6)	40 (78.4)	0.563[χ2]
Male	14 (26.4)	11 (21.6)	
Disease duration (year)	10 (1-38)	11 (1-40)	0.386[m]
Level of education, n (%)			
Uneducated	2 (3.8)	0 (0.0)	0.528[f]
Primary education	34 (64.2)	32 (62.7)	
High school	12 (22.6)	11 (21.6)	
University	5 (9.4)	8 (15.7)	

Table 2. Continued

	Active RA (n=53)	Remission RA (n=51)	p
Job, n (%)			
Housewife	31 (58.5)	25 (49.0)	0.648[f]
Retired	8 (15.1)	10 (19.6)	
Employee	9 (17.0)	8 (15.7)	
Officer	4 (7.5)	4 (7.8)	
Freelancer	1 (1.9)	4 (7.8)	
Medications, n (%)			
NSAIDs	3 (3.8)	1 (1.6)	0.350[f]
bDMARDs	11 (13.8)	11 (17.5)	
csDMARDs	43 (53.8)	43 (68.3)	
JAK-inhibitors (tofacitinib, baricitinib)	7 (8.8)	2 (3.2)	
Glucocorticoids	16 (20)	6 (9.5)	

bDMARDs: Biological disease-modifying anti-rheumatic drugs, csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, [f]: Fisher's exact test, JAK inhibitors: Janus kinase inhibitors, [m]: Mann-Whitney U test, NSAIDs: Non-steroidal anti inflammatory drugs, RA: Rheumatoid arthritis, χ^2: Chi-square test

Table 3. Comparisons of laboratory parameters between the remission group and of active group patients with RA

	Active RA (n=53)	Remission RA (n=51)	p
Neutrophils ($\times10^9$/L)	5.39 (± SD: 1.37)	3.58 (± SD: 0.79)	**<0.001[t]**
Lymphocytes ($\times10^9$/L)	2.10 (± SD: 0.59)	2.29 (± SD: 0.56)	0.089[t]
PLT ($\times10^9$/L)	287.00 (178.30, 572.00)	236.00 (145.00, 361.00)	**<0.001[m]**
NLR	2.45 (1.31, 5.22)	1.50 (1.03, 2.60)	**<0.001[m]**
PLR	135.93 (82.42, 303.80)	106.07 (56.10, 201.42)	**<0.001[m]**
SII ($\times10^9$/L)	670.75 (436.60, 1938.28)	370.74 (186.44, 571.26)	**<0.001[m]**
CRP (mg/L)	11.40 (2.00, 162.20)	2.00 (2.00, 9.50)	**<0.001[m]**
ESR (mm/h)	25 (2, 73)	9 (2, 27)	**<0.001[m]**
DAS28-ESR	4.90 (2.70, 6.70)	2.00 (1.10, 2.50)	**<0.001[m]**
SDAI	25.20 (4.30, 79.00)	4.30 (2.10, 10.80)	**<0.001[m]**
CDAI	24.00 (4.00, 40.00)	4.00 (2.00, 10.00)	**<0.001[m]**

CDAI: Clinical disease activity index, CRP: C-reactive protein, csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs, DAS28-ESR: Disease activity score 28-erythrocyte sedimentation rate, ESR: Erythrocyte sedimentation rate, [m]: Mann-Whitney U test, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PLT: Platelet, RA: Rheumatoid arthritis, SDAI: Simplified disease activity index, SD: Standard deviation, SII: Systemic immune inflammation index, [t]: Independent samples t-test

Areas under the ROC curve (AUC) can be listed as; 0.968 for SII (Figure 3) [95% confidence interval (CI): 0.914-0.993], 0.898 for NLR (Figure 3) (95% CI: 0.823-0.948), 0.784 for PLR (Figure 3) (95% CI: 0.692-0.859), 0.864 for CRP (Figure 3) (95% CI: 0.783-0.923) and 0.765 for ESR (Figure 3) (95% CI: 0.672-0.843). It was determined that SII and NLR variables were better in determining disease activity than CRP and ESR. For the SII to evaluate disease activity, the ideal cut-off point was 479.36 ($\times10^9$/L) (sensitivity: 92.45%, specificity: 86.27%). ROC curve analyzes are shown in Figure 3.

Discussion

In the present study, RA patients exhibited elevated levels of SII, neutrophils, NLR, and PLR compared to healthy controls, while lymphocyte counts were notably reduced in the RA group. SII, neutrophil, PLT, CRP, ESR, NLR, PLR, DAS28, SDAI and CDAI values were elevated in the active disease group. A strong positive association was identified between SII and the variables CRP, ESR, DAS28-ESR, SDAI, and CDAI. It was determined that SII and NLR variables were better in determining disease activity than CRP and ESR with an effect size of 0.84.

ESR, CRP, DAS-28, SDAI and CDAI are valid laboratory and clinical variables used in determining RA disease activity. Recently, studies have been conducted on NLR, PLR and SII values calculated with CBC parameters, which is an easily accessible and inexpensive method routinely requested at every control of patients to determine RA disease activity (5-9,30-32).

Neutrophils, lymphocytes and PLTs have an important role in inflammation. Neutrophils play a role by activating antigen-presenting cells and producing pro-oxidant mediators and lytic enzymes (9). Although it is controversial in some sources whether PLTs play a pro-inflammatory or anti-inflammatory role in the pathogenesis of RA (9), they have recently been reported to be active in exacerbating and maintaining inflammation (7).

While elevated PLT levels are difficult to detect in the joints of patients with inactive RA, numerous PLT-specific proteins can be identified in the synovial fluid and serum of those with active disease. Furthermore, during active RA, increased T-cell infiltration into the synovium leads to a relative depletion of T-cells in the peripheral blood, which is reflected as a decreased lymphocyte count in CBC measurements.

Consequently, patients with RA in the active phase should expect an increase in neutrophil and PLT counts, while lymphocyte counts should decrease (7). In our study, neutrophil and PLT counts were significantly higher in the active RA group compared to the remission group. The lymphocyte counts decreased, although the difference observed did not reach statistical significance.

Our study showed that active RA patients had higher values than the remission group when the NLR and PLR variables were taken into account. The RA group also had higher values than the healthy controls. Since NLR and PLR are variables calculated by a formula including neutrophils, lymphocytes, and PLT, it can be predicted that they can reflect the active RA disease.

According to Jin et al. (5), the RA group had higher NLR and PLR values than the other groups with rheumatic diseases and the healthy control groups. In their ROC curve analysis (AUC: 0.831, cut-off point: 2.13, sensitivity: 76.7%, specificity: 75.9%) they pretended to demonstrate the effectiveness of NLR in evaluating the disease activation, although it is less valuable than CRP, but more valuable than ESR. Consistent with the present results,

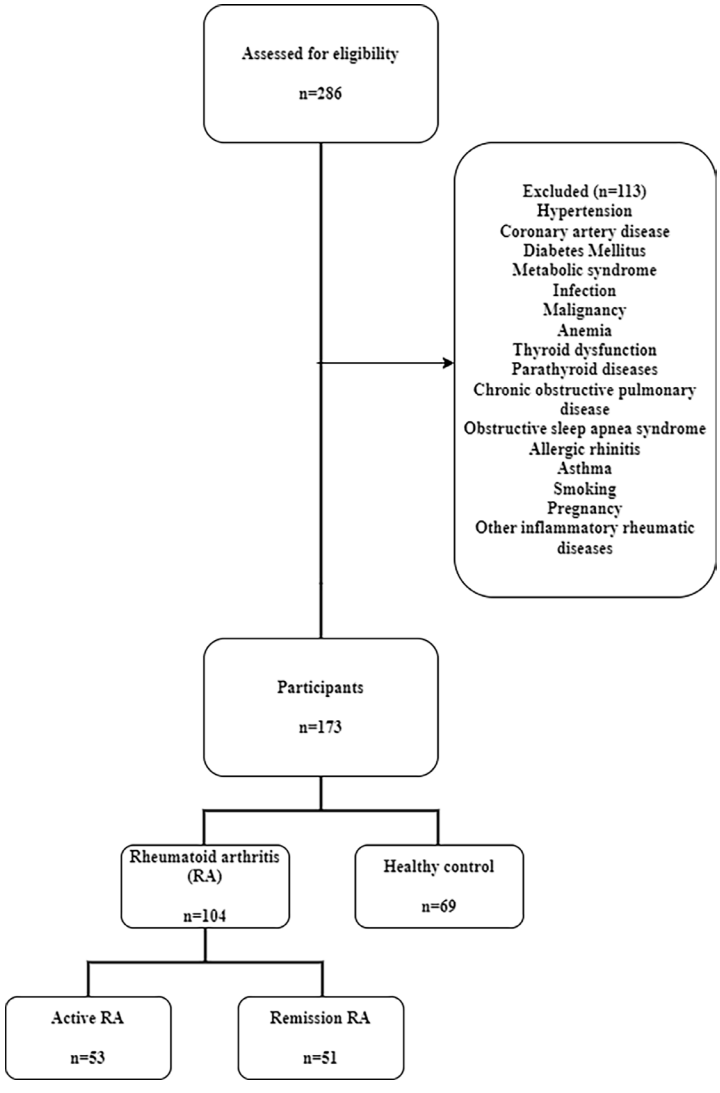

Figure 1. Flow chart
RA: Rheumatoid arthritis

both NLR and PLR values were high in our study. In the ROC curve analysis (AUC: 0.898, cut-off point: 2.08, sensitivity: 77.36%, specificity: 90.20%), the efficiency of NLR in determining RA disease activity was better than ESR and CRP. According to Chen et al. (7), patients with RA showed increased NLR and PLR values compared to controls. Analysis of the ROC curve showed that the cut-off value for PLR was 171.92 (AUC=0.676, sensitivity=61.28%, specificity=81.68%). A significant correlation was also found between PLR and DAS28. In conclusion, they noted that high PLR values are associated with an increased risk of RA. Erre et al. (9), stated that in a meta-analysis in which they included 13 of the studies published between 2015 and 2017, they confirmed that NLR and PLR values are associated with the presence of RA. Our results related to NLR and PLR values are compatible with the current literature.

SII variable can be more effective in demonstrating activity in RA patients than NLR and PLR, since neutrophil, lymphocyte and PLT values are calculated with a method that includes all three. SII was investigated in patients with malignant diseases (13-16). Apart from malignancies, studies have also been conducted in patients with aphthous stomatitis, psoriasis, hydradenitis suppurativa, interstitial lung disease, non-infectious uveitis and ulcerative colitis (19-24). The SII has been shown to be a useful index for monitoring disease activity in patients with ankylosing spondylitis, determining the activity of Behçet's disease, diagnosing AOSD and predicting the severity of psoriatic arthritis (25-27,34). It has also been reported to be an effective marker in studies on vasculitis (28,29).

There were three studies in the literature that investigated SII in RA patients (30-32). In one of these studies, some markers were calculated including SII in patients with active RA, AS and systemic lupus erythematosus. In contrast to healthy controls, RA patients had higher SII, which was statistically significant, but performed poorly in predicting RA disease activity (AUC: 0.622,

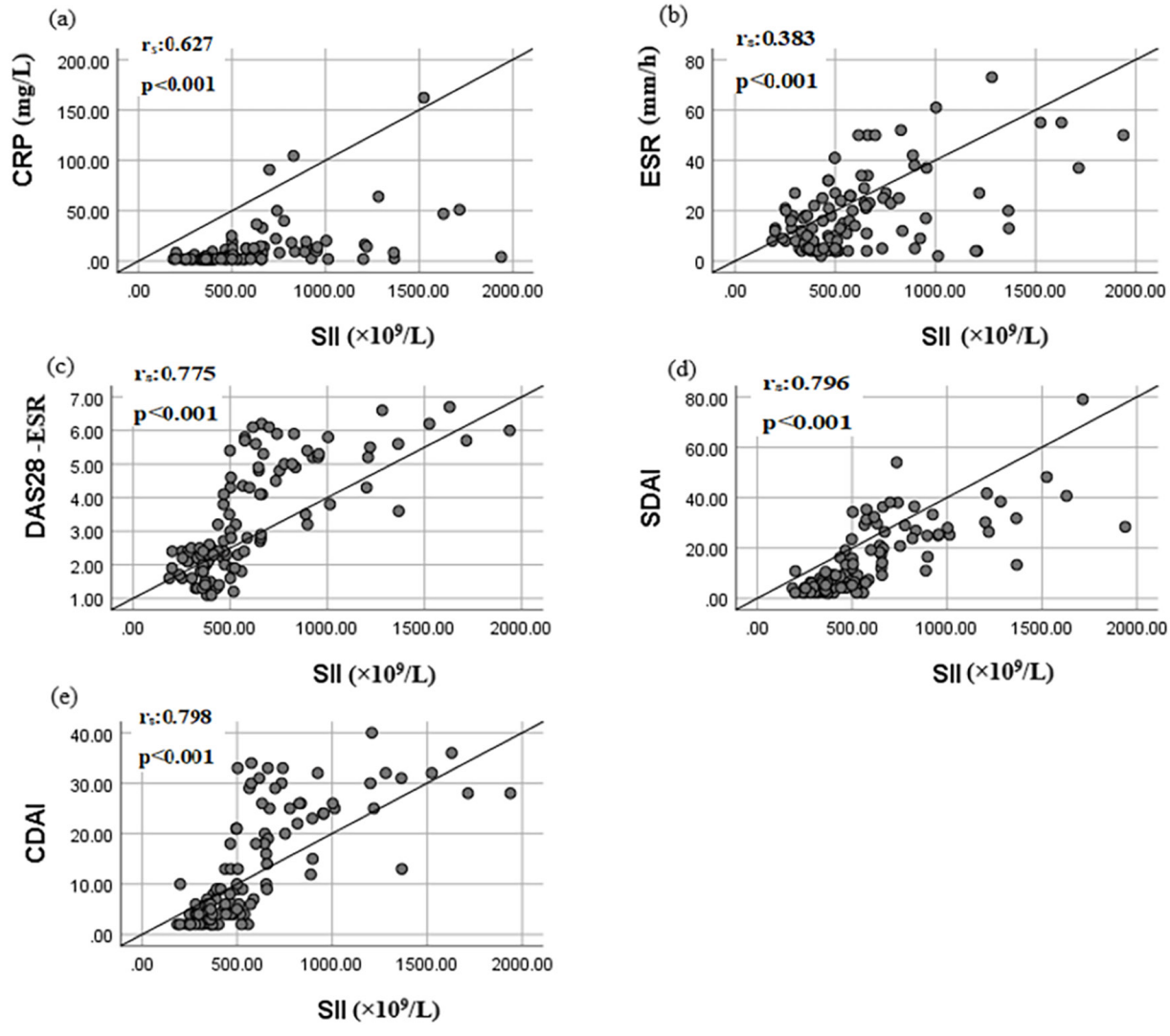

Figure 2. Correlations of SII with CRP (a), ESR (b), DAS28-ESR (c), SDAI (d) and CDAI (e)

CDAI: Clinical disease activity index, CRP: C-reactive protein, DAS28-ESR: Disease activity score 28-erythrocyte sedimentation rate, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, SDAI: Simplified disease activity index, SII: Systemic immune inflammation index, r_s: Spearmen correlation coefficient

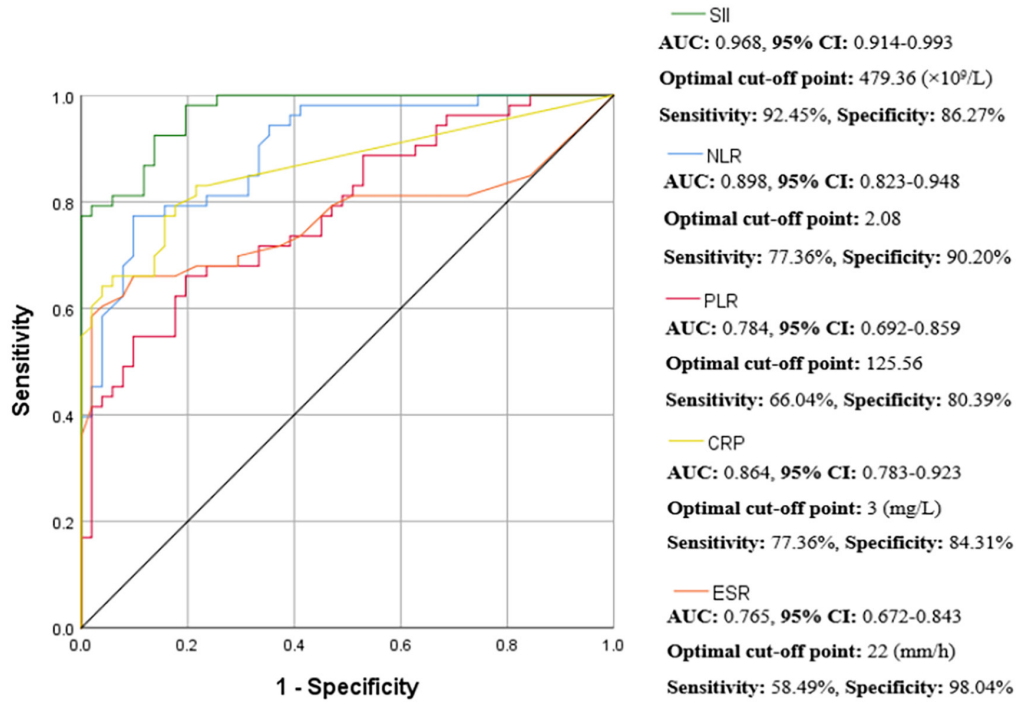

Figure 3. Receiver operating characteristic (ROC) curves
CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, ROC: Receiver operating characteristic, AUC: Area under the curve

95% CI: 0.449-0.794, cut-off point: 691.55, sensitivity: 54.00%, specificity: 61.50%) (32). Compared to this study, SII was a good predictor of RA disease activity in our ROC curve analysis.

In another RA study on SII by Choe and Kim (31), evaluation with janus kinase (JAK) inhibitors was performed before and after 24 weeks of treatment. They determined that SII, NLR and PLR values in RA patients were higher than healthy controls in the initial evaluation. The present results are also consistent with our study. It was stated also that after treatment with JAK inhibitors for 24 weeks, there was a decrease in SII and NLR values.

A separate investigation carried out in Türkiye demonstrated elevated SII levels in RA patients relative to healthy controls, with even greater elevations observed in those with active disease compared to patients in remission. (p=0.002 and p=0.030, respectively) (30).

On the other hand, another study came to the conclusion that SII levels are not a reliable indicator of RA disease activity (32). Unlike previous studies, our research holds particular value due to the inclusion of a larger number of healthy controls and a well-balanced distribution between patients with active RA and those in remission and had SII values that were highly predictive of disease activity.

Study Limitations

The main limitation of our work is that it was a case control study conducted in a single centre. In addition, the SII scores (remission) of the patients in the active RA group could not be assessed after treatment. Future research with larger cohorts and prospective design is warranted to evaluate the efficacy of RA SII.

Conclusion

The SII could be an innovative indicator for evaluating disease activity in patients with RA.

Ethics

Ethics Committee Approval: The study population consisted of patients who had received treatment at the Outpatient Clinic for Physical Therapy and Rehabilitation at Bursa Uludağ University (ethical approval date: February 23, 2022, protocol code: 2022-4/24).

Informed Consent: Written informed consent was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M., A.A., Concept: S.M., A.A., B.B.Y., Design: S.M., A.A., B.B.Y., Data Collection or Processing: S.M., A.A., Analysis or Interpretation: S.M., A.A., B.B.Y., Literature Search: S.M., A.A., Writing: S.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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