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Original Article

Systemic Immune-inflammation Index in Evaluation of Inflammation in Rheumatoid Arthritis Patients

Romatoid Artrit Hastalarında Enflamasyonun Değerlendirilmesinde Sistemik İmmün Enflamasyon

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ABSTRACT

Objective: To evaluate the systemic immune-inflammation (SII) index in patients with rheumatoid arthritis (RA) stratified by systemic inflammatory status.

Methods: Seropositive patients with RA (n=58) were divided into two groups based on serum hs-C-reactive protein (hs-CRP) levels: RA patients with hs-CRP levels of at or 3 mg/L or above (high systemic inflammatory status; n=38) and RA patients with hs-CRP levels of less than 3 mg/L (low systemic inflammatory status; n=20). The control group comprised 31 healthy individuals. Blood samples were tested for the next parameters: leukocytes, neutrophilic granulocytes, lymphocytes, thrombocytes [platelet (PLT)], high-sensitivity hs-CRP, sed rate [erythrocyte sedimentation rate (ESR)], neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). The SII index was derived as Neu x PLT/Lym.

Results: In patients with RA, the SII index was elevated compared with that of healthy individuals and positively correlated with hs-CRP, erythrocyte sedimentation rate, NLR, MLR, PLR, tender joint count, and swollen-to-tender joint count ratio. Patients with RA who had hs-CRP levels of 3 mg/L above exhibited a statistically significant increase in the SII compared with those with hs-CRP levels below 3 mg/L. Additionally, within the cohort of RA patients with hs-CRP levels at or above 3 mg/L, a positive correlation was found between the SII index and both NLR and PLR. The SII index was positively correlated with NLR, MLR, and PLR in RA patients with hs-CRP levels below 3 mg/L. The cut-off point of the SII index for distinguishing between RA cases with hs-CRP levels 3 mg/L and those with hs-CRP levels 3 mg/L or higher was ≥323.4, with a sensitivity of 77.6% and a specificity of 54.8%.

Conclusions: The serum SII index can be a potentially useful marker for evaluating the inflammatory process and clinical progression of RA.

Keywords: Systemic immune-inflammation index, inflammation, hs-CRP, rheumatoid arthritis

ÖZ

Amaç: Romatoid artritli (RA) hastalarda sistemik enflamatuvar duruma göre düzenlenmiş sistemik immün-enflamasyon (SII) indeksini değerlendirmektir.

Yöntemler: Seropozitif RA hastaları (n=58) serum hs-C-reaktif protein (hs-CRP) düzeylerine göre iki gruba ayrıldılar: hs-CRP düzeyleri 3 mg/L veya üzerinde olan RA hastaları (yüksek sistemik enflamatuvar durum; n=38) ve hs-CRP düzeyleri 3 mg/L'nin altında olan RA hastaları (düşük sistemik enflamatuvar durum; n=20). Kontrol grubu 31 sağlıklı bireyden oluştu. Kan örnekleri şu parametreler açısından test edildi: lökositler (beyaz kan hücresi), nötrofilik granülositler, lenfositler, trombositler [platelet (PLT)], yüksek hassasiyetli hs-CRP, sedimantasyon hızı [eritrosit sedimantasyon hızı (ESR)], nötrofil-lenfosit oranı (NLR), platelet-lenfosit oranı (PLR) ve monosit-lenfosit oranı (MLR). SII endeksi Neu x PLT/Lym olarak elde edildi.

Bulgular: RA'lı hastalarda, SII endeksi sağlıklı bireylere kıyasla yüksekti ve hs-CRP, eritrosit sedimantasyon hızı, NLR, MLR, PLR, hassas eklem sayısı ve şişmiş eklem sayısının hassas eklem sayısına oranı ile pozitif korelasyon gösterdi. Hs-CRP düzeyleri 3 mg/L'nin üzerinde olan RA'lı hastalar, hs-CRP düzeyleri 3 mg/L'nin altında olanlara kıyasla SII'de istatistiksel olarak anlamlı bir artış sergilediler. Ayrıca, hs-CRP düzeyleri 3 mg/L veya üzerinde olan RA hastaları kohortunda, SII endeksi ile hem NLR hem de PLR arasında pozitif bir korelasyon bulundu. SII indeksi, hs-CRP düzeyleri 3 mg/L'nin altında olan RA hastalarında NLR, MLR ve PLR ile pozitif korelasyon gösterdi. SII endeksinin hs-CRP düzeyi 3 mg/L olan RA olguları ile hs-CRP düzeyi 3 mg/L veya daha yüksek olan olguları ayırt etmek için kesme noktası ≥323,4 olup, duyarlılığı %77,6 ve özgüllüğü %54,8 idi.

Sonuçlar: Serum SII indeksi, RA'nın enflamatuvar sürecini ve klinik ilerlemesini değerlendirmek için potansiyel olarak yararlı bir belirteç olabilir.

Anahtar kelimeler: Sistemik immün-enflamasyon indeksi, enflamasyon, hs-CRP, romatoid artrit

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INTRODUCTION

Rheumatoid arthritis (RA) is a complex disorder of the immune system accompanied by inflammation and destruction of joint structures, with a global prevalence of 0.24%[1]. Patients diagnosed with RA can experience increasing pain, swelling, stiffness, and functional loss in any synovial joint, ultimately resulting in a reduced standard of living. Approximately 50% of patients with RA may exhibit extra-articular manifestations, primarily affecting the skin, eyes, heart, respiratory, urinary, nervous, and gastrointestinal systems[2]. Although the exact mechanisms underlying the pathophysiological process of RA remain unknown, a growing body of scientific evidence suggests that immune-mediated inflammation plays a crucial role in the onset and progression of RA. The interaction between immune and inflammatory responses, which leads to increased production of pro-inflammatory cytokines and chemokines, activates endothelial cells and promotes alterations in the production and activation of both innate and adaptive immune cells within the joint synovium[3]. Accurately monitoring the intensity of inflammation and disease status RA patients is crucial. Developing a straightforward and quantifiable biomarker would enable more efficient, rapid, and comprehensive assessment of pathological processes in RA. The ideal hematologic diagnostic marker of systemic inflammatory response should be simple, non-invasive, readily available, inexpensive, and exact. C-reactive protein (CRP) is frequently utilized to evaluate systemic inflammation in RA. Additionally, it functions as an immune regulator and contributes to the inflammatory processes linked to RA and its atherogenic effects. Elevated CRP levels in patients with RA indicate a higher degree of disease activity, which can also be assessed and confirmed through the components of the 28 joints Disease Activity score 28 (DAS28)[4].

New indirect hematological parameters, such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), have been recognized as valuable hematological indicators for numerous diseases[5].

The SII index is based on three peripheral immune and inflammatory cell types: thrombocytes, neutrophils, and lymphocytes (Lym) and is easily obtained from routine blood count data[6,7]. As a complex inflammatory biomarker, the SII index may better reflect systemic inflammatory status than other standard inflammatory markers, such as NLR or PLR alone[8]. To date, this inflammatory biomarker has been used to assess prognosis in various malignancies, including glioma, nasopharyngeal carcinoma, breast cancer, and hepatocellular carcinoma. In addition, research has shown its efficacy in various clinical conditions wherein inflammation is a key factor, including cardiovascular disease, ophthalmological disease, and autoimmune disorders[9].

Given the significance of inflammation in the pathogenesis of RA, this study aimed to determine the SII index levels in patients with RA categorized by systemic inflammatory status and to examine the association of the SII index with the DAS28-erythrocyte sedimentation rate (ESR) score, as well as with clinical and functional disease parameters.

MATERIALS and METHODS

Patients and Control Subjects

This single-institution, cross-sectional study included 58 patients of both sexes with a diagnosis of seropositive RA, all of whom were admitted to the Clinic for heart, blood vessels, and rheumatism at the Clinical Center University of Sarajevo. RA diagnosis was validated by an independent rheumatologist based on the 1987 American College of Rheumatology (ACR) revised classification criteria[10].

The experienced physician assessed disease activity in RA patients using DAS28, a formula with four components: DAS28 = 0.56 × √(TEN28) + 0.28 × √(SW28) + 0.70 × Ln(ESR) + 0.014x (GH). [TEN28: tender joint count; SW28: swollen joint count; Ln(ESR): the natural logarithm of Westergren's ESR; GH: general health, i.e., the patient's subjective assessment of disease activity based on a visual analog scale (VAS) of 100 mm][11].

Based on serum hs-CRP levels, which reflect the degree of systemic inflammation, RA patients were categorized into two groups: those with high systemic inflammation (n=38; hs-CRP ≥3 mg/L) and those with low systemic inflammation (n=20; hs-CRP <3 mg/L)[12].

The control group (n=31) consisted of healthy participants drawn from the general population, matched for age and gender, and exhibited neither subjective nor objective indicators of acute or chronic illness.

The inclusion criteria for the study were laboratory-confirmed seropositive RA patients aged 18 years or older, of both sexes, and who met the ACR diagnostic criteria for RA.

Participants were excluded from the study if they had any coexisting pathological conditions, including other forms of rheumatic diseases, malignant diseases, active inflammation of a local or systemic nature, thyroid gland dysfunction, liver or kidney diseases, coronary artery

diseases, hematological disorders, or other autoimmune disorders.

Patients who were taking enzyme-inducing or enzyme-inhibiting medications, as well as statins, were also excluded from the study.

We excluded current smokers, pregnant or lactating women, as well as individuals unable to provide informed consent from both the patient and control groups in this study.

After a detailed explanation of the research protocol, all participants voluntarily agreed to sign an informed consent form to complete the survey questionnaire and donate blood for biochemical analyses.

During blood collection, all patients were treated with disease-modifying anti-rheumatic drugs (DMARDs). In this cohort, methotrexate (MTX) was the most frequently used DMARD, administered in 51 cases. MTX was used as monotherapy in 36 cases, combined with sulfasalazine in 5 cases, with cyclosporine in 3 cases, and in 7 cases, it was combined with TNF-α inhibitors.

Of the remaining 7 cases treated with sulfasalazine, 5 received sulfasalazine alone, while 2 patients used cyclosporine in addition to sulfasalazine.

The most prevalent extra-articular complications observed among the 58 included patients were muscular weakness (14 patients, 24.1%), muscular hypotrophy (10 patients, 17.2%), rheumatoid scleritis (8 patients, 13.8%), conjunctivitis (6 patients, 10.3%), osteoporosis (12 patients, 20.7%), and Sy. Caplan (8 patients, 13.8%). Patients with other extra-articular manifestations, such as anemia, vasculitis purpura, pleuritis, and central nervous system injuries, were excluded from the study to preserve cohort homogeneity.

The study was approved by the Clinical Center of the University of Sarajevo Ethics Committee (approval no.: 0305-33957, date: 30.11.2010) and was conducted following a protocol that adhered strictly to the ethical guidelines established by the Declaration of Helsinki, as revised in 2000.

Laboratory Analysis

Samples of blood from both patients and healthy subjects were obtained in the early morning using the vacutainer technique, through venipuncture in the antecubital area, following a 12 h overnight fasting period and after a 30-min rest.

In the blood samples collected from all subjects, biochemical laboratory analyses were performed to determine the leukocyte count (WBC), neutrophilic granulocyte count, lymphocytes count (Lym), thrombocyte count (PLT), hs-CRP concentration, and sed rate (ESR).

All laboratory tests were conducted utilizing standardized and automated procedures at the Department of clinical chemistry and biochemistry.

Serum levels of hs-CRP were assessed using the particle-enhanced immunonephelometry technique with a BN II analyzer (Siemens Healthineers Global, Erlangen, Germany) and the Roche, Hitachi Cobas C system (Mannheim, Germany).

The SII index for each research participant was calculated by dividing the product of the number of neutrophil granulocytes and platelets by the number of Lyms.

The NLR represents the quotient of the total number of neutrophils and lymphocytes in peripheral blood. Similarly, the PLR was calculated by dividing the total number of platelets by the total number of lymphocytes. MLR was calculated by dividing the total number of monocytes by the total number of lymphocytes.

Statistical Analysis

The distribution of the analyzed data was assessed using the Shapiro-Wilk test. Normally distributed data are reported as mean and standard deviation, whereas non-normally distributed data are presented as median and interquartile range (25^{th} to 75^{th} percentile). Categorical data are expressed as a whole numbers (n) or percentages (%).

The independent t-test was used to compare normally distributed data, whereas the Mann-Whitney U test was employed for non-normally distributed data.

Spearman's correlation coefficient was used to examine the relationships between quantitative variables. Receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to determine the optimal cut-off values of the SII index for distinguishing patients with RA based on the level of systemic inflammation. Diagnostic accuracy was calculated with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) software for Windows (version 13.0; SPSS, Chicago, IL, USA).

RESULTS

The baseline parameters, including sex and age, along with the laboratory findings for patients with RA and healthy individuals are presented in Table 1.

The subjects in the observed groups did not differ significantly in terms of age or gender. RA patients had

significantly higher hs-CRP (p<0.001), ESR (p<0.001), PLT count (p=0.031), WBC count (p=0.002), neutrophil count (p=0.001), NLR (p=0.002) and SII index (p=0.001) compared to control individuals.

The observed differences in the numbers of monocytes (p=0.392), Lyms (p=0.743), MLR (p=0.524), and PLR (p=0.188) between RA patients and healthy individuals did not reach statistical significance.

We then analyzed the differences in laboratory parameters between RA patients exhibiting hs-CRP levels below 3.0 mg/L and those with hs-CRP levels at or above 3.0 mg/L. RA patients with hs-CRP levels of 3.0 mg/L demonstrated significantly elevated values for hs-CRP (p<0.001), ESR (p<0.001), PLT (p<0.001), neutrophil count (p=0.003), NLR (p=0.018), PLR (p=0.015), and SII index (p<0.001) in comparison to RA patients with hs-CRP levels below 3.0 mg/L.

The observed differences in the numbers of monocytes (p=0.382), WBCs (p=0.051), Lyms (p=0.765), and MLR (p=0.839) between the groups did not reach statistical significance (Table 2).

Table 1. Baseline characteristics and laboratory results observed in RA cases and healthy individuals.

Variables	RA group (n=58)	Control group (n=31)	p-value
Female (n/%)	56 (96.6)	27 (87.1)	0.09
Male (n/%)	2 (3.4)	4 (12.9)	
Age (years)	55.2±12.3	50.6±7.6	0.06
hs-CRP (mg/L)	6.4 (1.5-24.3)	0.8 (0.4-1.6)	**<0.001**
ESR (mm/h)	31.0 (19.8-55.0)	11.0 (7.0-20.0)	**<0.001**
Platelet count (10^9/L)	278.5±82.7	243.3±46.0	**0.031**
Monocyte count (10^9/L)	0.41±0.17	0.38±0.15	0.392
White blood cell count (10^9/L)	6.7±2.0	5.4±1.1	**0.002**
Neutrophil counts (10^9/L)	3.5 (2.7-4.8)	2.8 (2.1-3.7)	**0.001**
Lymphocyte count (10^9/L)	2.2±0.8	2.1±0.5	0.743
NLR	1.8 (1.3-2.5)	1.3 (1.0-1.7)	**0.002**
MLR	0.19 (0.13-0.28)	0.17 (0.14-0.23)	0.524
PLR	139.2 (91.6-184.4)	120.4 (102.4-150.0)	0.188
SII index	472.7 (342.3-712.9)	319.5 (252.0-342.0)	**0.001**

The findings are presented as mean values with standard deviations, median values with interquartile ranges (25th to 75th percentile), and percentages (%). RA: Rheumatoid arthritis, hs-CRP: hs-C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation

Table 2. Laboratory findings in patients with RA according to hs-CRP levels.

Variables	RA group hs-CRP <3 mg/L (n=20)	RA group hs-CRP ≥3 mg/L (n=38)	p-value
hs-CRP (mg/L)	1.5 (1.3-1.8)	17.2 (6.5-32.0)	**<0.001**
ESR (mm/h)	20.0 (12.0-22.0)	38.5 (24.3-61.5)	**<0.001**
Platelet count (10^9/L)	213.0 (184.0-268.0)	291.5 (233.5-258.8)	**0.001**
Monocyte count (10^9/L)	0.45±0.15	0.40±0.18	0.382
White blood cells count (10^9/L)	6.06±1.4	6.87±2.1	0.051
Neutrophil counts (10^9/L)	3.3±0.8	4.2±1.5	**0.003**
Lymphocytes count (10^9/L)	2.18±0.8	2.07±0.8	0.765
NLR	1.51 (1.26-1.9)	2.0 (1.4-2.7)	**0.018**
MLR	0.23±0.1	0.20±0.1	0.839
PLR	111.94 (86.5-142.5)	158.01 (102.2-226.8)	**0.015**
SII index	357.7 (236.4-434.9)	570.4 (391.7-918.8)	**<0.001**

The findings are presented as mean values with standard deviations, median values with interquartile ranges (25th to 75th percentile), and percentages (%). RA: Rheumatoid arthritis, hs-CRP: hs-C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation

Significantly higher tender joint count (p=0.008), VAS pain score (p=0.028), and DAS28-ESR (p=0.001) were observed in RA patients with hs-CRP levels of 3 mg/L or above compared with RA patients with hs-CRP levels below 3 mg/L.

The differences in disease duration (p=0.600), number of swollen joints (p=0.238), and swollen-to-tender joint count ratio (p=0.279) between the observed groups did not reach statistical significance (Table 3).

Among the RA patients, a statistically significant positive correlation was identified between the SII index and hs-CRP (rho=0.468; p<0.001), ESR (rho=0.302; p=0.021), NLR (rho=0.846; p<0.001), MLR (rho=0.287; p=0.029) and PLR (rho=0.715; p<0.001).

The SII index exhibited a linear positive correlation with NLR (rho=0.698; p=0.001), MLR (rho=0.538; p=0.017), and PLR (rho=0.765; p<0.001) among patients with RA and hs-CRP level of 3 mg/L or above. Likewise, in patients with RA and hs-CRP levels of 3 mg/L or above, the SII index showed a significant positive correlation with NLR (rho=0.895; p<0.001) and PLR (rho=0.664; p<0.001) (Table 4).

The SII index demonstrated a significant positive correlation only with tender joint count (rho=0.303; p=0.021) and swollen-to-tender joint count ratio (rho=0.293; p=0.026) in the sum of all RA patients. However, correlations did not occur between the SII index and clinical parameters of disease in the RA group with hs-CRP <3 mg/L and the RA group with hs-CRP ≥3 mg/L, as shown in Table 5.

Additionally, we performed ROC curve analysis to evaluate the ability of the SII index to distinguish RA cases with hs-CRP values lower than 3 mg/L and those with hs-CRP levels of 3 mg/L or above.

The ROC curve illustrated in Figure 1 identified an optimal cut-off value of the SII index that effectively distinguished between RA patients with hs-CRP levels below 3 mg/L and those with hs-CRP levels of 3 mg/L or higher, set at ≥323.4.

Table 3. Clinical characteristics of all RA patients and subgroups of RA patients stratified according to hs-CRP levels.

Variables	RA group (n=58)	RA group hs-CRP <3 mg/L (n=20)	RA group hs-CRP ≥3 mg/L (n=38)	p-value
Disease duration (months)	72.0 (24.0-180.0)	78.0 (45.0-183.0)	72.0 (24.0-180.0)	0.600
Swollen joint count	5.1±3.9	4.0 (0.0-8.0)	5.0 (2.0-8.75)	0.238
Tender joint count	5.0 (3.0-10.0)	4.0 (2.0-4.0)	6.0 (3.25-12.0)	**0.008**
STR	0.67 (0.31-1.0)	1.0 (0.0-1.0)	0.6 (0.35-0.96)	0.279
VAS of pain score (mm)	25.0 (15.0-50.0)	20.0 (10.0-30.0)	30.0 (16.25-70.0)	**0.028**
DAS28-ESR	4.7 (3.2-5.9)	3.75 (3.0-4.36)	5.32 (3.53-6.43)	**0.001**

The findings are presented as mean values with standard deviations, median values with interquartile ranges (25th to 75th percentile), and percentages (%). RA: Rheumatoid arthritis, hs-CRP: hs-C-reactive protein, DAS28-ESR: Diseases Activity score 28-erythrocyte sedimentation rate, STR: Swollen-to-tender joint count ratio, VAS: Visual analog scale

Table 4. Correlation between SII index and inflammatory markers in RA patients according to hs-CRP levels.

Variables	RA group (n=58)		RA group hs-CRP <3 mg/L (n=20)		RA group hs-CRP ≥3 mg/L (n=38)	
	SII index					
	rho	p-value	rho	p-value	rho	p-value
hs-CRP (mg/L)	0.468	**<0.001**	0.132	0.589	0.136	0.429
ESR (mm/h)	0.302	**0.021**	0.150	p=0.539	0.115	0.502
White blood cell count (10^9/L)	0.256	0.052	-0.154	p=0.528	0.287	0.090
NLR	0.846	**<0.001**	0.696	**p=0.001**	0.895	**<0.001**
MLR	0.287	**0.029**	0.538	**p=0.017**	0.323	0.055
PLR	0.715	**<0.001**	0.765	**p<0.001**	0.664	**<0.001**

RA: Rheumatoid arthritis, hs-CRP: hs-C-reactive protein, SII: Systemic immune-inflammation, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

The AUC for the established cutoff point was 0.721, accompanied by a 95% CI ranging from 0.613 to 0.829 (p=0.001). At the identified optimal SII cut-off of ≥323.4, the maximal sensitivity achieved was 77.6%, whereas the maximal specificity recorded was 54.8%.

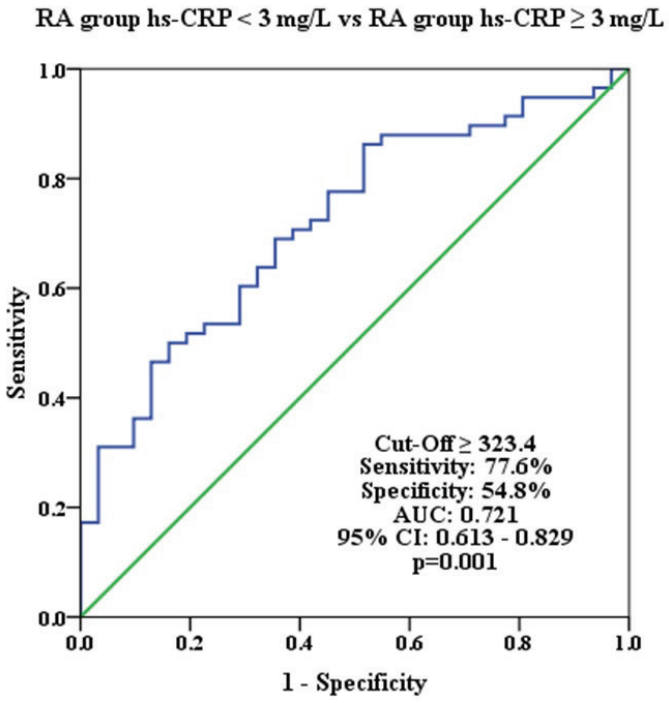

Figure 1. Receiver operating characteristic curve analysis of the SII index for distinguishing between RA patients with hs-CRP levels below 3 mg/L and those with hs-CRP levels at or exceeding 3 mg/L.

SII: Systemic immune-inflammation, RA: Rheumatoid arthritis, AUC: Area under the curve, CI: Confidence intervals, hs-CRP: hs-C-reactive protein

DISCUSSION

It has been documented that inflammatory processes, along with dysregulated immune responses, are crucial in the onset, development, and progression of RA[13,14].

However, no consensus has been established regarding the definite specific biomarkers that can be used to evaluate systemic inflammatory response in RA. The SII index is a circulating blood cell-derived index based on platelets and the two WBC subtypes neutrophils and Lyms. The importance of the SII index in identifying local immune responses and systemic inflammation is specified by the different roles that Lyms, neutrophils, and platelets play in the immune response.

This study represents the first study in which the SII index was examined in patients with RA categorized according to their systemic inflammation status. This finding underscores the significance of early inflammation assessment as a proactive measure to prevent the onset of cardiovascular comorbidities in this population.

The findings of our research indicated that patients with RA demonstrated significantly elevated SII index levels compared with healthy controls.

Elevated SII index levels suggest an intensified immune response, which may influence the mechanisms underlying the development and progression of RA. Previous research by Choe et al.[15] highlights the significance of the SII index as a marker for assessing clinical severity in RA and demonstrates significant associations with DAS28-ESR, DAS28 CRP, Clinical Disease Activity index, and Simplified Disease Activity index, indicating its potential diagnostic utility. However, its sensitivity in detecting disease remission was limited.

Table 5. Correlation between SII index and clinical indicators associated with RA according to hs-CRP levels.

Variables	RA group (n=58)		RA group hs-CRP <3 mg/L (n=20)		RA group hs-CRP ≥3 mg/L (n=38)	
	SII index					
	rho	p-value	rho	p-value	rho	p-value
Disease duration (months)	-0.211	0.115	-0.268	0.282	-0.256	0.132
Swollen joint count	0.134	0.315	0.005	0.983	0.136	0.428
Tender joint count	0.303	**0.021**	-0.003	0.991	0.174	0.309
STR	0.293	**0.026**	-0.035	0.888	0.026	0.881
VAS pain (mm)	0.257	0.051	-0.178	0.466	0.239	0.160
DAS28-ESR	-0.122	0.363	0.004	0.989	0.144	0.402

RA: Rheumatoid arthritis, hs-CRP: hs-C-reactive protein, SII: Systemic immune-inflammation, DAS28-ESR: Diseases Activity score 28-Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, STR: Swollen-to-tender joint count ratio, VAS: Visual analog scale

Based on a study by Aletaha et al.[16], Lyms, neutrophils, and platelets are recognized for their crucial roles in regulating inflammatory processes in RA patients, and their serum levels are considered valuable markers for assessing disease activity. Various T-cell-mediated immune processes are linked to inflammation and matrix degradation in RA. These processes encompass the migration of T-cells, their recruitment, and subsequent activation within synovial tissue, leading to the swift release of cytokines[17]. Neutrophils exhibit the highest cytotoxic capacity among the various cell types involved in the pathology of RA. In individuals with RA, neutrophils exhibit functional differences compared with those found in healthy individuals because the neutrophils present in the bloodstream of patients with RA are pre-activated to generate reactive oxygen species (ROS)[18]. Additionally, platelets enhance the recruitment of leukocytes into the vascular compartment of the RA synovium[19,20]. Our study suggests that systemic inflammatory status significantly influences not only parameters such as ESR, PLT count, neutrophil count, NLR, PLR, tender joint count, VAS of pain score, and DAS28-ESR but also SII index values in RA patients. The established correlation of the SII with hs-CRP, ESR, NLR, MLR, and PLR, as well as with the clinical and functional characteristics of disease activity, revealed significant changes in the immune system, including changes in both the quantity and role of immune cells, such as neutrophils and Lyms, in RA. In general, systemic inflammation is associated with variations in the number and composition of circulating inflammatory blood cells. The SII index combines the predictive value of three circulating inflammatory blood cell parameters from the complete blood count and is considered more powerful for predicting inflammation than single-component or two-component inflammatory markers[21].

The findings of our study align with those of the existing literature on juvenile arthritis patients, which has shown a significant positive correlation between the SII and various indicators of disease activity, encompassing both clinical assessments Juvenile Arthritis Disease Activity score-10 and laboratory evaluations (CRP and ESR)[22].

Similarly, the statistically significant positive linear associations between the SII index and both CRP and ESR in patients with ankylosing spondylitis (AS) highlight the importance of the SII index in assessing systemic inflammation in AS. However, this study also indicated that the SII is not effective in assessing disease activity, functional status, and general health status in AS[23].

Timely recognition of inflammatory processes in patients with RA is crucial for the outcome of the disease, with regard to CRP. CRP production shows a late response after infections, reaching a peak approximately 48 h after the onset of inflammation or initiation of infection[24].

Elevated SII index, platelet and neutrophil counts, NLR, and PLR in patients with high systemic inflammatory status indicate that inflammatory cytokines, along with ROS, contribute to increased disease severity in RA by promoting inflammation.

The findings of our study are consistent with those reported in prior research in which the SII index values of patients with RA were investigated. Satis[25] found that the SII index was higher in active RA patients than in remission RA patients.

In addition to disease activity, the author concluded that the SII index has the potential to be utilized as a novel index that efficiently reflects disease activity. By analyzing the ROC curve, the authors determined that a cut-off value of 574.20 was the optimal value for differentiating between patients with active RA and those in remission. Based on these findings, the SII index could be a valuable tool for monitoring inflammation and disease progression in patients with RA.

Liu et al.[26] Conducted their research on a large number of subjects using the National Health and Nutrition Examination Survey database.

In their study, all rheumatic cases had significantly higher SII index levels than control subjects. Additionally, the ROC analysis revealed that a cut-off value higher than 578.25 significantly increased RA risk. The authors concluded that the SII index, as a novel, valuable, and convenient inflammatory marker that can predict the risk of RA in adults.

The reasons for the different SII index cut-off values between studies is unclear. This explanation may be attributed to the sample size, study design, disease duration, or characteristics of the study population.

The interpretation of the results is limited by several factors. Conducted as a case-control study, this research has inherent limitations associated with its design.

The single-center observational study design made eliminating potential remnants of residual confounding. Only a single blood sample from each patient was utilized for the analysis, which may not accurately represent fluctuations in blood-derived parameters. Our subgroups were relatively small; therefore, the results we obtained need to be validated in controlled studies with more patients.

CONCLUSION

Our research results indicate a relationship between the SII index and the systemic inflammatory response in patients with RA, suggesting that the serum SII index could be a significant parameter for evaluating the inflammatory process and clinical progression of RA.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Committee of the University Clinical Center Sarajevo (UCCS) (approval no.: 0305-33957, date: 30.11.2010).

Informed Consent: After a detailed explanation of the research protocol, all participants voluntarily agreed to sign an informed consent form to complete the survey questionnaire and donate blood for biochemical analyses.

Author Contributions

Surgical and Medical Practices: E.J., Concept: A.D., E.J., E.A., A.Z., Design: A.D., E.J., E.A., A.Z., Data Collection and/or Processing: A.D., A.F., L.D., Analysis and/or Interpretation: A.D., L.D., Z.A., E.A., Literature Search: A.D., A.F., L.D., Z.A., A.Z., Writing: A.D., A.F., Z.A., A.Z.

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