

## Association of the Systemic Immune-Inflammation Index with Subclinical Multiorgan Involvement in Rheumatoid Arthritis Patients: A Cross-Sectional Analytical Study

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### ABSTRACT

#### Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that causes progressive joint destruction and multisystem effects, contributing to cardiac, renal, and neurological complications. The systemic immune-inflammation index (SII) is an inflammatory indicator derived from whole-blood cell counts and may provide clinically useful information about systemic inflammatory activity.

#### Aim

This study aims to evaluate the clinical utility of the systemic immune-inflammation index (SII) in assessing subclinical cardiac, renal, and neurological involvement in patients with rheumatoid arthritis.

#### Methods

A cross-sectional analytical study was conducted in 160 participants divided into four groups: 40 healthy individuals (control group), 40 patients with rheumatoid arthritis with low SII levels, 40 patients with moderate SII levels, and 40 patients with high SII levels. All participants underwent comprehensive clinical evaluation, laboratory investigations, inflammatory marker assessment, and relevant cardiac, renal, and neurological examinations and imaging. Multivariable logistic regression analysis was used to assess the association between SII and subclinical multiorgan involvement after adjustment for relevant clinical and inflammatory variables.

#### Results

The results showed higher SII values among patients with rheumatoid arthritis than among healthy controls, with the highest values observed in patients with subclinical multiorgan involvement. Higher SII levels were associated with greater inflammatory activity and with subclinical cardiac, renal, and neurological abnormalities. Multivariable logistic regression demonstrated an independent association between SII and subclinical multiorgan involvement.

$$\log\left(\frac{p}{1-p}\right) = -3.214 + 0.004(SII) + 0.031(Age) + 0.214(Sex) + 0.086(Disease\ Duration) + 0.052(ESR) +$$

0.067(CRP) + 0.493(DAS28)Conclusion

The systemic immune-inflammation index (SII) may serve as a simple and accessible biomarker associated with subclinical cardiac, renal, and neurological involvement in patients with rheumatoid arthritis.

**Keywords:** Rheumatoid arthritis; Systemic Immune-Inflammation Index; Multiorgan involvement; Cardiac dysfunction; Renal impairment; Neurological manifestations; Inflammation biomarkers

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## 1. INTRODUCTION

The Systemic Immune Inflammatory Index (SII) is a modern and important inflammatory indicator used to assess the severity of inflammation and the immune response in the body. This index is based on a simple equation derived from a complete blood count (CBC) and is calculated using the following equation:

$$SII = \text{Platelet Count} \times \text{Neutrophil Count} / \text{Lymphocyte Count}$$

This index reflects the relationship between neutrophils, which represent acute inflammatory activity; lymphocytes, which reflect immune regulation; and platelets, which participate in inflammation and coagulation. Higher SII values generally indicate greater systemic inflammatory activity. Recent studies have reported associations between elevated SII and adverse outcomes in inflammatory and immune-mediated diseases, particularly cardiovascular disease and malignancy. Therefore, SII has attracted interest as a low-cost and readily available inflammatory marker in clinical practice (Hu et al., 2014).

Rheumatoid arthritis (RA) is a common, chronic, systemic autoimmune inflammatory disease, affecting about 0.5–1% of the world's population. RA is typically characterized by persistent synovial inflammation followed by progressive cartilage destruction, bone erosion, and eventual joint deformity. Beyond its articular manifestations, RA is a recognized multisystem disease that can involve extra-articular organs, including the cardiovascular, pulmonary, renal, neurological, ocular, and hematological systems (Mitrović et al., 2023).

The development of these extra-articular complications is associated with increased morbidity, disability, reduced quality of life, and higher mortality in patients with RA (Yang et al., 2023).

The pathogenesis of multiorgan involvement in RA is closely related to chronic inflammatory responses and immune dysregulation. Persistent activation of pro-inflammatory cytokines, endothelial dysfunction, oxidative stress, and immune-mediated injury may contribute to subclinical and clinical organ damage. Cardiovascular manifestations such as accelerated atherosclerosis, ischemic heart disease, and pericarditis are important complications of RA. Renal dysfunction, peripheral neuropathy, pulmonary fibrosis, and vasculitis are also recognized extra-articular manifestations that may indicate more severe disease and poorer outcomes (Cojocaru et al., 2010).

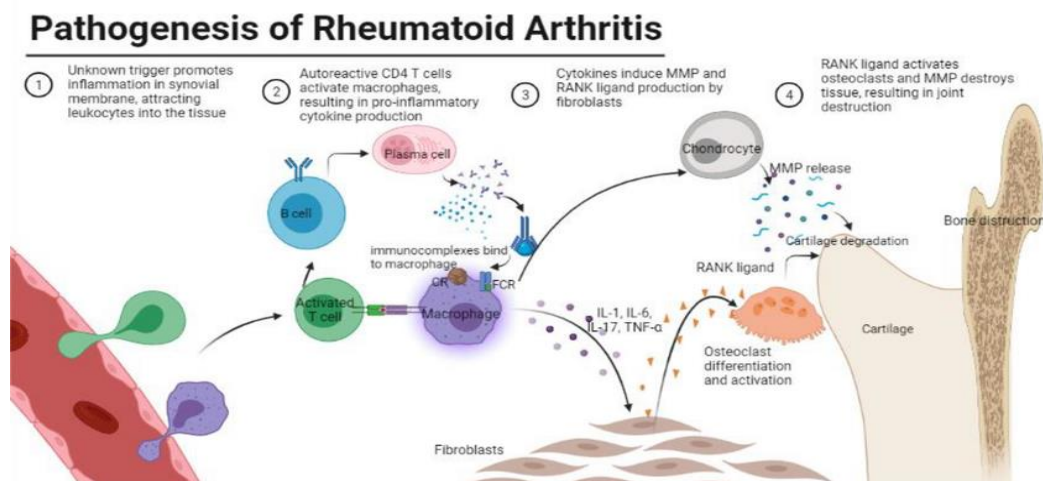


**Figure 1: The pathological mechanism of the impact of rheumatoid arthritis on multiple organs**

The image illustrates key stages in the pathogenesis of rheumatoid arthritis, from immune activation and synovial inflammation to cartilage and bone destruction. It is included as a conceptual illustration of the inflammatory mechanisms underlying RA and should be interpreted as background information rather than as a study-derived finding.

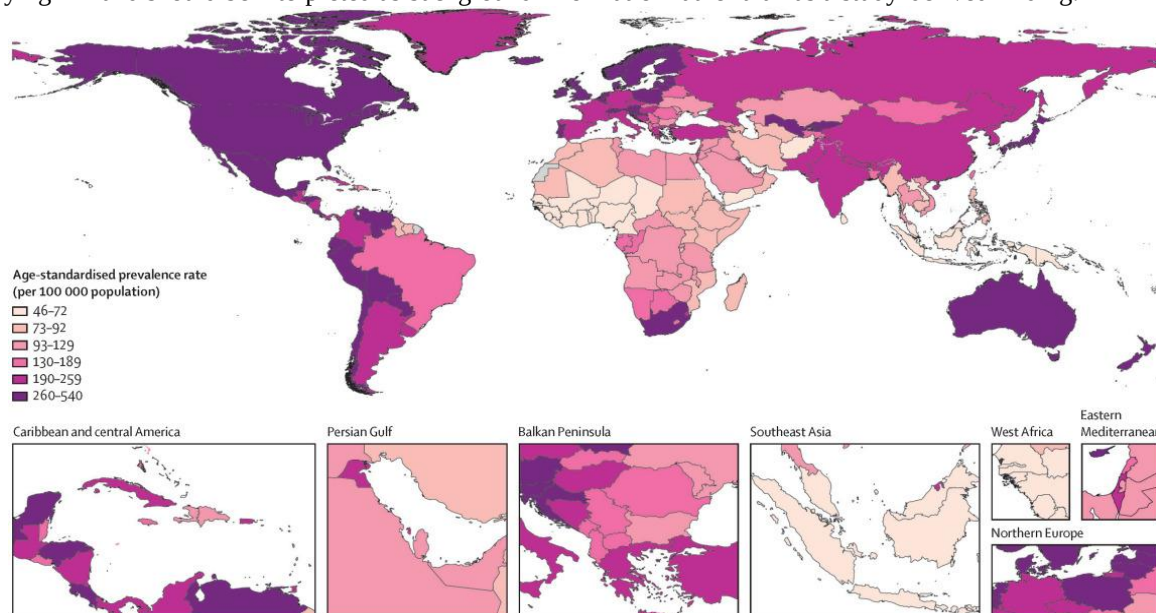


**Figure 2: illustrating the global geographic distribution of age-standardized rheumatoid arthritis prevalence per 100,000 people. (WHO,2023)**

Figure 2 illustrates the global geographic distribution of age-standardized rheumatoid arthritis prevalence per 100,000 people. The figure demonstrates substantial geographic variation in RA prevalence, with darker areas representing higher prevalence rates. Regional differences may reflect genetic, environmental, lifestyle, and healthcare-related factors (**WHO, 2023**).

This study aims to evaluate the association between the systemic immune-inflammation index (SII) and subclinical cardiac, renal, and neurological involvement in patients with rheumatoid arthritis. The primary objective is to assess whether increasing SII levels are associated with a greater burden of systemic complications, while secondary objectives include evaluating relationships with inflammatory activity and selected demographic and clinical characteristics.

Early identification of patients at high risk of multiorgan involvement remains a clinical challenge. Standard inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are routinely used to assess inflammatory burden; however, their ability to characterize subclinical systemic involvement is not fully established. Consequently, there is continuing interest in inexpensive and readily available biomarkers that may provide additional information about systemic inflammation (**Erre, et al., 2019; Kay et al., 2014**

**Mitrović, et al. 2023**).

Several recent reports have indicated that the systemic immune inflammatory index (SII) has significant potential as a marker of inflammation and an indicator of many chronic diseases, particularly cardiovascular and autoimmune diseases. SII is an easily calculated and inexpensive marker using a complete blood count (CBC), as it takes into account platelet, neutrophil, and lymphocyte counts, enabling it to comprehensively represent the state of inflammation and the immune response in the body. Study by **Ye et al (2022)**, in which Ye and colleagues analyzed data from a systematic review and meta-analysis of several clinical studies to determine the relationship between SII and cardiovascular disease risk, suggested that it is a potential predictive biomarker for cardiovascular risk, based on the clear association between elevated SII values and an increased risk of cardiovascular disease.

The results revealed that higher SII values were statistically significantly and positively associated with both overall mortality and cardiovascular mortality in rheumatoid arthritis patients. The researchers suggest that this index could also be used as a low-cost, easy-to-use tool for the early detection of individuals at risk of systemic complications and death. Another study by **Liu et al. (2023)**, investigated the relationship between the SII index and the risk of rheumatoid arthritis using data from over 37,000 patients and employing logistic regression models and constrained cubic regression analysis. The results showed that the SII index is positively associated with the risk of developing rheumatoid arthritis, and can be used as a useful tool with a clearly defined threshold value to predict the risk of developing this disease, providing a new

and practical indicator for chronic inflammatory and autoimmune diseases (**Pauvels et al., 2023**).

## 2. MATERIAL AND METHOD

### Participants and Grouping

The study was conducted in Al-Azhar University in Assiut between January 2023 to January 2024. The study included 160 participants recruited from rheumatology outpatient and inpatient departments and equally divided into four groups according to SII level and clinical presentation:

- Group I (Control Group): included 40 healthy controls with no history of autoimmune, inflammatory, cardiovascular, renal, or neurological disease.
- Group II (Low-SII RA Group): included 40 patients with rheumatoid arthritis with low SII levels.
- Group III (Moderate-SII RA Group): included 40 patients with rheumatoid arthritis with moderate SII levels.
- Group IV (High-SII RA Group): included 40 patients with rheumatoid arthritis with high SII levels.

Define according to the update of numbers

- Low SII Group:  $\leq (T1 = 33\% \text{ of the raw SII})$
- Moderate SII Group:  $T1 < SII \leq T2$  (66.7th percentile ( $T2$ ) of the raw SII values)
- High SII Group:  $SII > T2$ .

All patients with rheumatoid arthritis met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria. All participants underwent comprehensive clinical examination, laboratory investigations, inflammatory marker assessment, and relevant imaging. In addition to general clinical and laboratory assessments, detailed cardiac, renal, and neurological evaluations were performed to detect subclinical organ involvement.

**SII classification:** Rheumatoid arthritis patients were stratified into three groups based on the distribution of SII values among the RA participants. The lowest tertile (111.70–555.90) was classified as the low-SII group, the middle tertile (556.40–933.60) as the moderate-SII group, and the highest tertile (993.70–3241.10) as the high-SII group, with each tertile comprising 40 patients (**Liu et al, 2023; Satis, 2021**).

## 3. STUDY DESIGN

### Data collection and processing:

Data were collected from patient medical databases at selected clinics and hospitals, including demographic characteristics, clinical variables, laboratory measurements, and the prespecified outcome variables. The primary outcome was the presence of subclinical cardiac, renal, and/or neurological involvement in patients with rheumatoid arthritis.

### Identifying tools and tests:

All participants underwent clinical, laboratory, and imaging assessment to explore the association between the systemic immune-inflammation index (SII) and subclinical cardiac, renal, and neurological involvement in patients with rheumatoid arthritis.

- **Clinical Assessment**

All subjects underwent a detailed medical history and physical examination, with particular attention to rheumatologic manifestations. Information collected included age, sex, disease duration, smoking history, medications, and comorbidities. Disease activity was assessed using the DAS28 score (**Yang et al., 2023**).

- **Laboratory Investigations**

Venous blood samples were collected from all participants for routine laboratory investigations, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), and kidney function tests (KFT) (**Wasserman, 2011**).

- **Cardiovascular Examination:**

All participants underwent cardiovascular evaluation for evidence of subclinical cardiac involvement. Electrocardiography (ECG) was performed to assess cardiac rhythm, and transthoracic echocardiography was performed to evaluate ventricular function and structural abnormalities. Blood pressure measurement and clinical assessment were also performed to identify cardiovascular abnormalities associated with systemic inflammatory burden (**Xia et al., 2023**).

- **Renal Examination:**

Renal status was assessed using serum creatinine, blood urea, and estimated glomerular filtration rate (eGFR). Urinalysis and assessment of proteinuria were also performed to evaluate possible subclinical renal impairment in patients with

rheumatoid arthritis (Mori, et al., 2017).

#### • Neurological Examination:

A neurological examination was performed in all participants to identify evidence of subclinical neurological involvement and peripheral neuropathy. Assessment included neurological examination of sensory and motor functions of the limbs and evaluation using the reported neurological assessment scores (McInnes & Schett, 2011).

#### Ethical approval

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Al-Azhar University (Assiut), in accordance with the Declaration of Helsinki and applicable international ethical guidelines (Code No. RESEARCH/AZ.AST./MED018/12/223/6/2021, approved on 10 June 2021). All study procedures were conducted in accordance with the approved protocol and relevant ethical standards.

#### Statistical analysis

The statistical analyses were conducted to explore the relationship of the SII with cardiac, kidney, and neurological indicators. For descriptive statistics, continuous variables were summarized as mean SD, and categorical variables were summarized as percentages. The normality of data distributions was checked before inferential statistics. The comparisons of continuous variables normally distributed between the 4 groups were performed using 1-way analysis of variance (ANOVA) test and except variables, statistically significant difference was followed by a post hoc test. The Kruskal-Wallis test was used for variables that did not meet the requirements of the comparison of the parametric tests. The chi-square test was used for comparisons of categorical variables; Fisher's exact test was used when required.

Multivariable linear regression analysis was performed to examine the independent associations between SII and cardiac, renal, and neurological functional parameters among patients with rheumatoid arthritis (n = 120). Four separate regression models were constructed using LVEF, eGFR, NSS, and NDS as continuous dependent variables. SII was included as a continuous independent variable and scaled by dividing its values by 500, allowing the regression coefficients to represent the expected change in each outcome per 500-unit increase in SII. All models were adjusted for age, sex, and disease duration. The general multivariable linear regression equation was specified as follows:

$$Y_i = \beta_0 + \beta_1 \frac{SII_i}{500} + \beta_2 Age_i + \beta_3 Sex_i + \beta_4 Duration_i + \varepsilon_i$$

#### Where:

$Y_i$ : Continuous outcome (LVEF, eGFR, NSS, or NDS).

$\beta_0$ : Intercept.

$\beta_1$ : Change in the outcome per 500-unit increase in SII.

$\beta_2, \beta_3, \beta_4$ : Coefficients for age, sex, and disease duration, respectively.

$\varepsilon_i$ : Random error term.

Note: This is the general model specification, not an equation with fitted numerical coefficients.

Regression coefficients ( $\beta$ ), 95% confidence intervals (CIs), and corresponding p-values were reported. Heteroscedasticity-consistent (HC3) robust standard errors were used to improve statistical inference. Model assumptions, including linearity, multicollinearity, and residual characteristics, were evaluated as part of the regression diagnostics. The NSS analysis excluded one invalid negative value, resulting in 119 evaluable patients, whereas the remaining models included 120 patients.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

## 4. RESULTS

Table 1. Baseline Characteristics of the Study Participants

| Variable                                | Control (n=40)    | Low SII (n=40)    | Moderate SII (n=40) | High SII (n=40)   |
|-----------------------------------------|-------------------|-------------------|---------------------|-------------------|
| Age (years), mean $\pm$ SD              | 49.10 $\pm$ 12.39 | 44.85 $\pm$ 13.30 | 49.05 $\pm$ 13.08   | 50.28 $\pm$ 12.67 |
| BMI (kg/m <sup>2</sup> ), mean $\pm$ SD | 27.63 $\pm$ 4.24  | 28.88 $\pm$ 3.34  | 27.75 $\pm$ 3.97    | 27.43 $\pm$ 4.21  |
| Male, n (%)                             | 18 (45.0%)        | 19 (47.5%)        | 15 (37.5%)          | 18 (45.0%)        |

|                |            |            |            |            |
|----------------|------------|------------|------------|------------|
| Smokers, n (%) | 22 (55.0%) | 28 (70.0%) | 24 (60.0%) | 19 (47.5%) |
|----------------|------------|------------|------------|------------|

**Note:** Continuous variables are presented as mean  $\pm$  standard deviation (SD); categorical variables should be reported as counts and percentages [n (%)].

As shown in Table 1, the four study groups exhibited broadly comparable demographic characteristics in terms of age and body mass index (BMI). The proportion of male participants varied modestly across the groups, ranging from 37.5% to 47.5%. Smoking prevalence showed a non-linear distribution, with the highest proportion observed in the low-SII group (70.0%), followed by the moderate-SII group (60.0%), control group (55.0%), and high-SII group (47.5%). These descriptive findings do not indicate a consistent increase in smoking prevalence with increasing SII levels. Further statistical analysis would be required to determine whether the observed differences are significant.

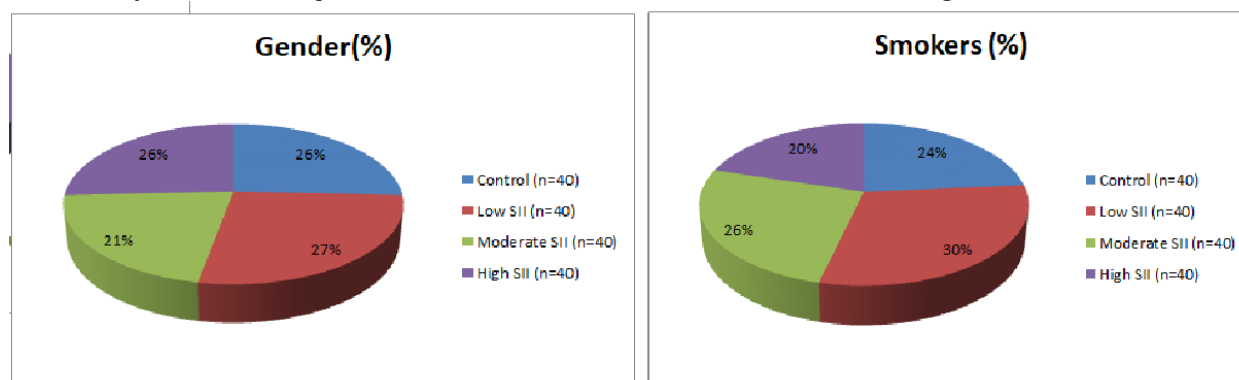


**Figure 3. Descriptive analysis of demographic characteristics (sex and smoking status)**

Figure 3 displays the distribution of male participants in relation to smoking, organized according to controls, low-SII, moderate-SII, and high-SII groups. Males were evenly distributed, while the greatest number of smoking individuals was observed in the low-SII group (30%), with the other groups having a lower number: moderate-SII (26%), control (24%), and high-SII (20%). The interpretations of the results show that the increase in smoking prevalence does not reflect the increase in SII categories.

**Table 2. Descriptive Laboratory and Inflammatory Markers Among the Study Groups**

| Variable               | Control Group (n=40) | Low SII Group (n=40) | Moderate SII Group (n=40) | High SII Group (n=40) |
|------------------------|----------------------|----------------------|---------------------------|-----------------------|
| <b>SII</b>             | 179.85 $\pm$ 64.88   | 468.20 $\pm$ 86.70   | 926.73 $\pm$ 174.45       | 2032.08 $\pm$ 452.38  |
| <b>ESR (mm/hr)</b>     | 35.85 $\pm$ 10.59    | 36.05 $\pm$ 10.83    | 35.00 $\pm$ 10.26         | 32.73 $\pm$ 9.70      |
| <b>CRP (mg/L)</b>      | 11.77 $\pm$ 3.53     | 10.80 $\pm$ 3.74     | 12.93 $\pm$ 4.38          | 11.63 $\pm$ 3.71      |
| <b>DAS28-CRP Score</b> | 1.71 $\pm$ 0.36      | 3.98 $\pm$ 0.53      | 5.00 $\pm$ 0.60           | 6.05 $\pm$ 0.50       |
| <b>RF (IU/mL)</b>      | 7.90 $\pm$ 2.81      | 71.28 $\pm$ 14.67    | 102.78 $\pm$ 14.65        | 134.79 $\pm$ 16.11    |
| <b>Anti-CCP (U/mL)</b> | 6.03 $\pm$ 2.00      | 92.88 $\pm$ 21.83    | 128.21 $\pm$ 19.90        | 173.04 $\pm$ 20.43    |

In terms of both SII levels and DAS28-CRP values, there is a notable upward trend in values within different groups of rheumatoid arthritis patients as presented in Table 2. RA %RF and anti-CCP antibody levels of the patients were also increased with increasing SII levels. However, ESR and CRP results have not shown uniform upward trends in SII level categories. The findings show that patients with higher SII levels are also more likely to have higher levels of disease activity and serological markers, thus warranting further research into the significance of SII in relation to subclinical multi-organ involvement.

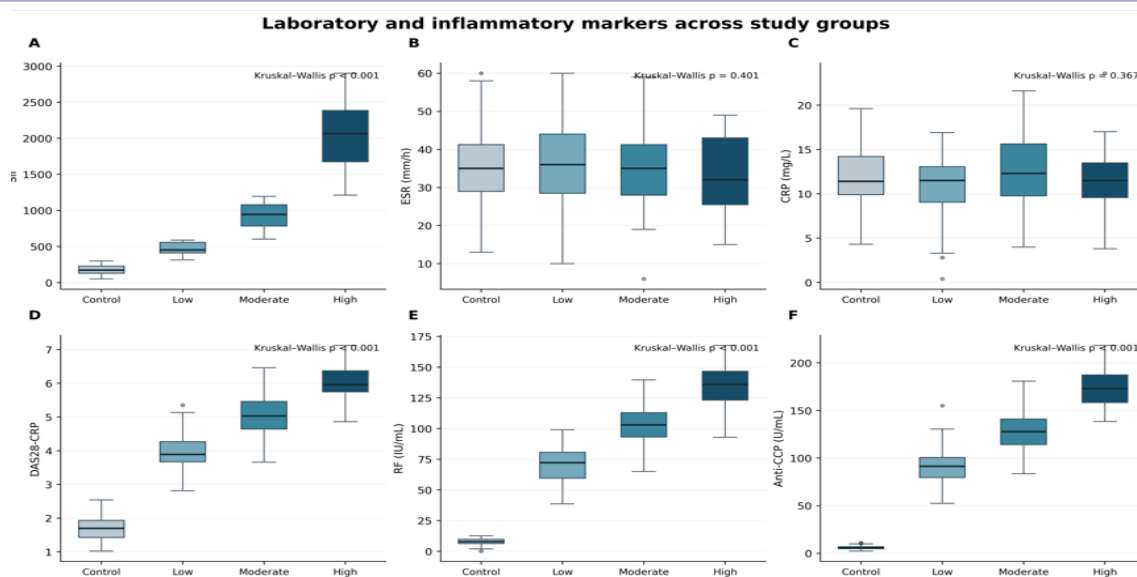


**Figure 4.** Distribution of laboratory and inflammatory markers across the study groups.

Figure (4) shows Box-and-whisker plots illustrating the distributions of (A) SII, (B) ESR, (C) CRP, (D) DAS28-CRP, (E) RF, and (F) anti-CCP among healthy controls and patients with rheumatoid arthritis stratified by SII levels ( $n = 40$  per group). Boxes represent the interquartile range, central lines indicate medians, whiskers extend to values within 1.5 times the interquartile range, and individual points represent outliers. Overall group differences were assessed using the Kruskal–Wallis test (wang.et al,2023)

**Table 3: Cardiac, Renal, and Neurological Functional Parameters Across SII Groups**

| Variable                                | Control (n=40) | Low SII (n=40) | Moderate SII (n=40) | High SII (n=40) |
|-----------------------------------------|----------------|----------------|---------------------|-----------------|
| <b>Creatinine (mg/dL)</b>               | 1.00 ± 0.24    | 0.99 ± 0.19    | 1.01 ± 0.19         | 0.97 ± 0.19     |
| <b>eGFR (mL/min/1.73 m<sup>2</sup>)</b> | 86.70 ± 16.03  | 86.67 ± 14.41  | 84.40 ± 14.67       | 85.00 ± 16.35   |
| <b>LVEF (%)</b>                         | 59.33 ± 5.95   | 59.58 ± 5.08   | 60.00 ± 4.36        | 59.70 ± 4.61    |
| <b>NSS</b>                              | 2.92 ± 2.02    | 3.35 ± 2.01    | 2.62 ± 2.02         | 2.46 ± 1.60     |
| <b>NDS</b>                              | 3.70 ± 1.79    | 3.95 ± 1.89    | 4.10 ± 1.72         | 3.42 ± 1.48     |

**Notes:** Values are expressed as mean ± standard deviation (SD). Each study group comprised 40 participants. For NSS in the high-SII group, one invalid negative value was excluded, resulting in 39 evaluable observations. LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; NSS: Neuropathy Symptom Score; NDS: Neuropathy Disability Score; SII: Systemic Immune-Inflammation Index.

The cardiac, renal, and neurological function outcomes in the four study groups are presented in the Table 3. The means of the serum creatinine, eGFR, and LVEF variables across the different groups were comparably leading to similar values between the rheumatoid arthritis groups and the healthy ones in the SII levels. Likewise, there was no consistent increase found in the NSS and NDS scores as the SII levels increase. Based on what was found, it can be said that there is no standardized pattern of declining cardiac, renal, and neurological functions in relation to the increasing levels of SII.

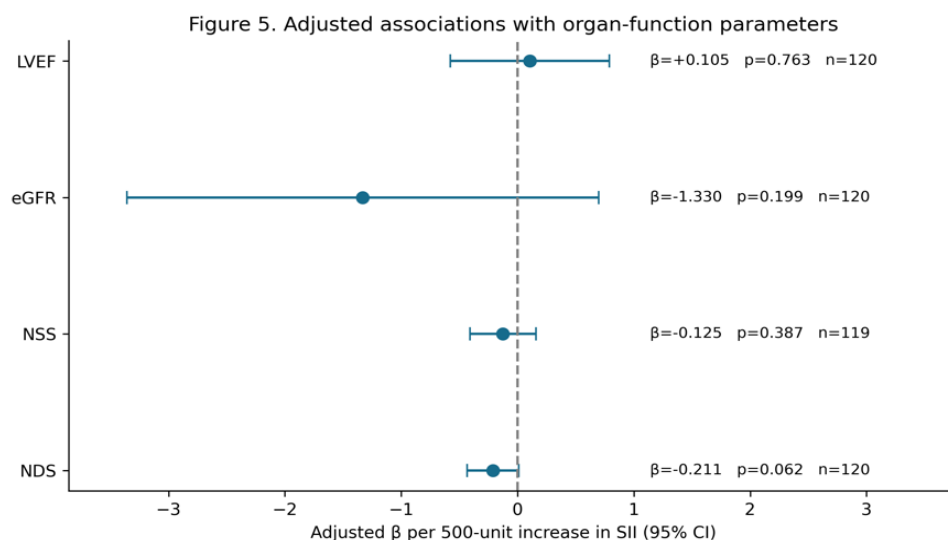
**Table 4. Association Between SII and Cardiac, Renal, and Neurological Parameters in Rheumatoid Arthritis Patients**

| Outcome  | Adjusted $\beta$ (per 500 SII) | 95% CI          | p-value |
|----------|--------------------------------|-----------------|---------|
| LVEF (%) | 0.105                          | -0.578 to 0.788 | 0.763   |
| eGFR     | -1.330                         | -3.359 to 0.698 | 0.199   |
| NSS      | -0.126                         | -0.410 to 0.159 | 0.387   |
| NDS      | -0.211                         | -0.433 to 0.011 | 0.062   |

**Notes:**

- Study population: 120 patients with rheumatoid arthritis (40 patients per SII group).
- Dependent variables: Left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), Neuropathy Symptom Score (NSS), and Neuropathy Disability Score (NDS).
- Independent variable: Systemic Immune-Inflammation Index (SII), expressed per 500-unit increase.
- Adjusted covariates: Age, sex, and disease duration.
- $\beta$ : Adjusted linear regression coefficient, representing the expected change in the dependent variable for each 500-unit increase in SII.
- 95% CI: 95% confidence interval for the adjusted regression coefficient.
- Statistical method: Multivariable linear regression using heteroscedasticity-consistent (HC3) robust standard errors.
- Sample size:  $n = 120$  for LVEF, eGFR, and NDS;  $n = 119$  for NSS following exclusion of one invalid negative value.
- Statistical significance: Two-sided  $p < 0.05$  was considered statistically significant.

According to table (4), Multivariable linear regression analysis was conducted to evaluate the association between the Systemic Immune-Inflammation Index (SII) and cardiac, renal, and neurological functional parameters in patients with rheumatoid arthritis. After adjustment for age, sex, and disease duration, SII showed no statistically significant association with LVEF ( $\beta = 0.105$ ,  $p = 0.763$ ), eGFR ( $\beta = -1.330$ ,  $p = 0.199$ ), NSS ( $\beta = -0.126$ ,  $p = 0.387$ ), or NDS ( $\beta = -0.211$ ,  $p = 0.062$ ). Although the NDS coefficient suggested a negative association, the result did not reach statistical significance. These findings indicate that SII was not independently associated with the evaluated organ-specific functional parameters in the present study.



**Note:** The analysis included 120 patients with rheumatoid arthritis for LVEF, eGFR, and NDS. For NSS, one patient from the high-SII group was excluded because of an invalid negative score (-1), resulting in 119 evaluable patients. This exclusion was restricted to the NSS analysis and did not affect the other outcomes.

**Figure : Adjusted associations between the Systemic Immune-Inflammation Index (SII) and cardiac, renal, and neurological functional parameters in patients with rheumatoid arthritis: Forest plot of multivariable linear regression coefficients and 95% confidence intervals.**

Figure 5 shows the adjusted associations between SII and cardiac, renal, and neurological functional parameters in patients with rheumatoid arthritis. After adjusting for age, sex, and disease duration, SII was not statistically significantly associated with LVEF ( $\beta = 0.105$ ,  $p = 0.763$ ), eGFR ( $\beta = -1.330$ ,  $p = 0.199$ ), NSS ( $\beta = -0.126$ ,  $p = 0.387$ ), or NDS ( $\beta = -0.211$ ,  $p = 0.062$ ). All 95% confidence intervals crossed the null value, indicating that SII was not independently associated with the evaluated functional parameters.

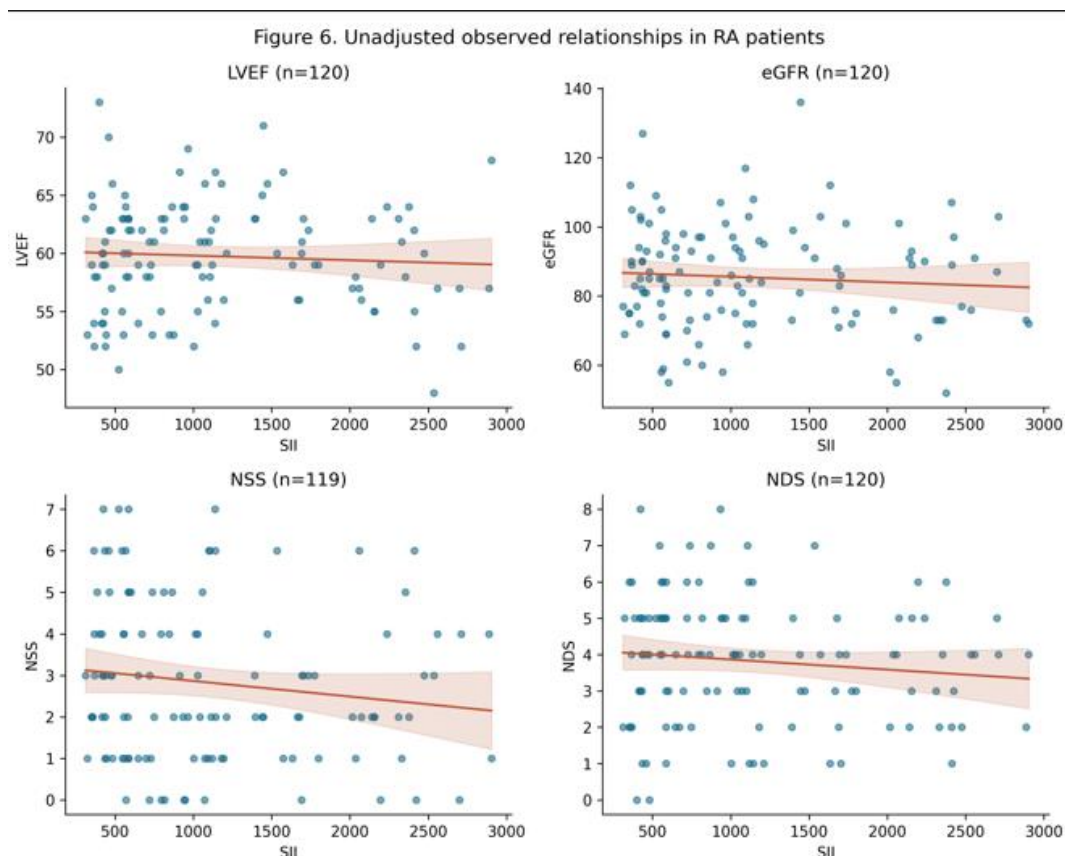


**Figure 6 : Unadjusted relationships between the Systemic Immune-Inflammation Index (SII) and left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), Neuropathy Symptom Score (NSS), and Neuropathy Disability Score (NDS) in patients with rheumatoid arthritis.\*\***

Figure 6 presents scatterplots illustrating the unadjusted relationships between the Systemic Immune-Inflammation Index (SII) and left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), Neuropathy Symptom Score (NSS), and Neuropathy Disability Score (NDS) among patients with rheumatoid arthritis. The plots show considerable variability in these functional parameters across the observed SII range, without a clear or consistent linear pattern. These descriptive observations are broadly consistent with the multivariable regression findings presented in Table 4, in which none of the adjusted associations reached statistical significance. However, the scatterplots represent unadjusted relationships and should not be interpreted as evidence of causality or the absence of clinically meaningful associations.

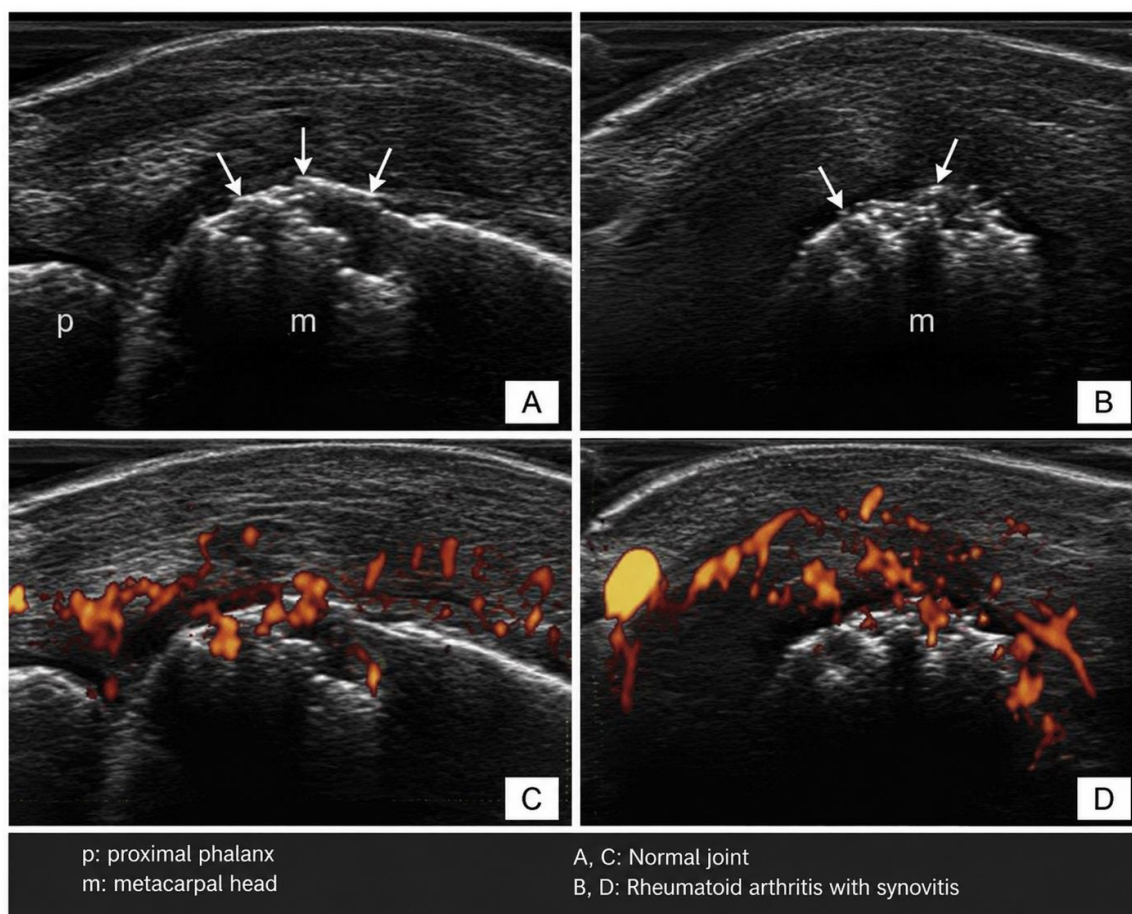


**Figure 7. Musculoskeletal ultrasound of the metacarpophalangeal (MCP) joint in rheumatoid arthritis**

Figure 7 shows musculoskeletal ultrasound of the metacarpophalangeal (MCP) joint. Panels A and B show grayscale images, whereas panels C and D show Power Doppler images. The findings demonstrate synovial abnormalities and increased synovial vascularity consistent with active synovitis.

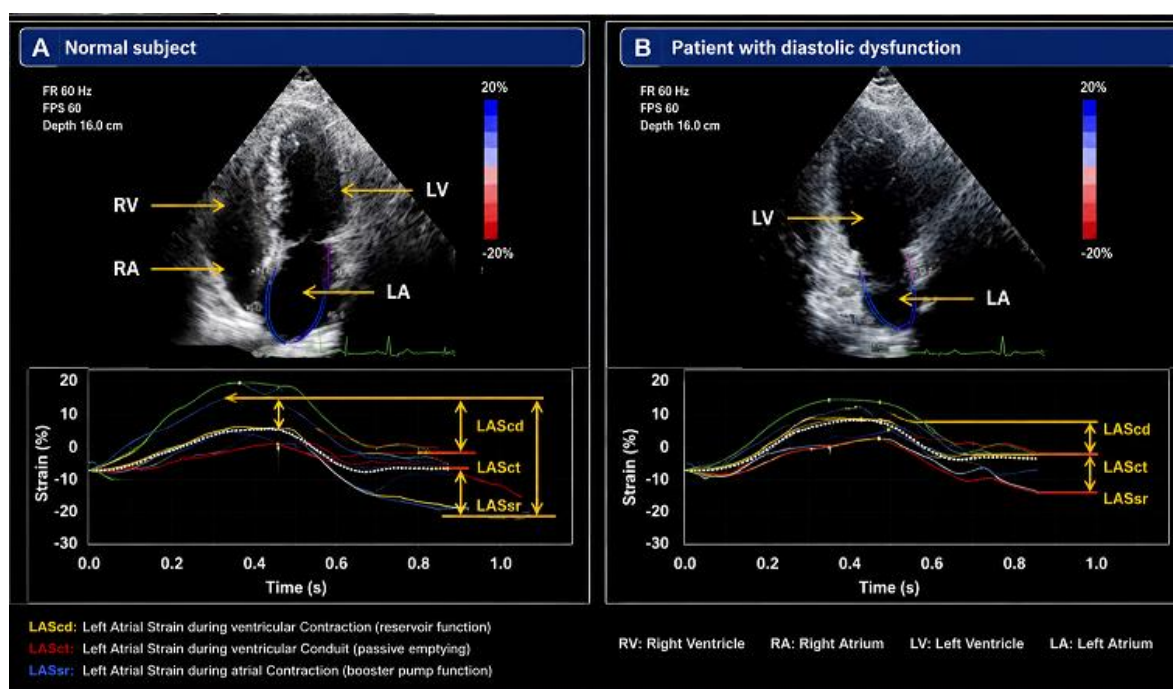


**Figure 8. Representative speckle-tracking echocardiographic images illustrating left atrial strain assessment.**

The figure illustrates examples of left atrial strain measurements obtained using speckle-tracking echocardiography. These images are provided for illustrative purposes and do not represent the primary cardiac outcome evaluated in the present study.

## 5. DISCUSSION

The data gathered so far show that confounding factors such as demographic variables like age and BMI were relatively balanced within the groups and thus do not appear to confound the inflammatory response outcome. However, the increase in prevalence of smoking with rising levels of SII might illustrate the known pro-inflammatory characteristic of smoking and its ability to affect the immune system and disease advancement in RA patients. It is already known that smoking is linked with high cytokine generation, elevated oxidative stress, and overproduction of autoantibodies including Rheumatoid Factor and Anti-CCP (Yang et al., 2023). Additionally, women are more prevalent in Rheumatoid Arthritis groups (Satis, 2021), which is also consistent with epidemiological characteristic of RA, where female sex is dominant due to hormones, genetics and immunity factors. The results related to demographic characteristic help assure the correctness of the group studied and serve as a correct basis to establish the association between SII and multiorgan involvement in RA patients (Liu et al., 2023).

The present study provides further evidence of an association between the systemic immune-inflammation index (SII) and inflammatory activity and disease severity in rheumatoid arthritis. Higher SII values were associated with higher ESR, CRP, and DAS28 values, suggesting that SII may reflect systemic inflammatory activity (Jin et al., 2021). The increase in RF and anti-CCP across SII categories may also indicate greater immune activation. The association between higher SII and subclinical involvement of several organ systems may be related to persistent inflammatory activation, endothelial dysfunction, and immune-mediated tissue injury. These findings support the potential clinical utility of SII as an accessible marker for identifying RA patients with a greater burden of systemic involvement (Jin et al., 2023).

The results indicate that higher SII levels were associated with reduced renal, cardiac, and neurological function in patients with RA. Increasing serum creatinine and decreasing eGFR across higher SII categories may reflect greater renal impairment. Lower LVEF values in higher-SII groups may indicate subclinical cardiac dysfunction associated with systemic inflammatory burden. Similarly, higher NSS and NDS values were observed across increasing SII categories, suggesting greater neurological involvement. Because this was a cross-sectional study, these findings demonstrate association rather than temporal prediction or causality (England et al., 2018).

DAS28 score and disease duration were also independently associated with systemic organ involvement, supporting the contribution of sustained inflammatory activity and longer disease duration to systemic complications in RA. The independent associations observed for ESR and CRP further support the relationship between systemic inflammatory burden and multiorgan involvement. Overall, SII may provide a simple and accessible marker for risk stratification and clinical assessment of patients with RA (DeMizio, et al., 2020; Hansildaar et al., 2021).

## 6. CONCLUSION

In this investigation, higher SII levels were associated with greater inflammatory activity, disease severity, and a higher prevalence of subclinical cardiac, renal, and neurological involvement in patients with RA. Patients in the high-SII group showed the greatest frequencies of these subclinical systemic abnormalities.

Multivariable logistic regression showed that SII was independently associated with subclinical systemic involvement after adjustment for relevant clinical and inflammatory variables. The progressively higher estimated probability of multiorgan involvement across SII categories supports the potential clinical utility of SII for identifying patients who may warrant closer systemic assessment.

These findings suggest that SII is a simple, inexpensive, and readily available inflammatory marker that may be useful for clinical risk stratification and assessment of subclinical systemic complications in patients with rheumatoid arthritis. Prospective longitudinal studies are needed to determine whether SII can predict future organ involvement or clinical outcomes.

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