

Systemic Immune Inflammation Index as a Reliable Disease Activity Marker in Psoriatic Arthritis

Ayşe Bahar Keleşoğlu Dincer¹ and Serdar Sezer²

¹Department of Rheumatology, Diskapi Yıldırım Beyazıt Research and Training Hospital, Ankara, Turkey

²Department of Rheumatology, Ankara Research and Training Hospital, Ankara, Turkey

ABSTRACT

Objective: To assess the utility of systemic immune inflammation index (SII) in predicting disease activity in psoriatic arthritis (PsA) patients.

Study Design: A descriptive study.

Place and Duration of Study: Diskapi Yıldırım Beyazıt Research and Training Hospital, Ankara, Turkey, from October 2020 to September 2021.

Methodology: This study included 106 PsA and 103 age and gender-matched healthy individuals. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and SII were calculated from complete blood count parameters. The PsA disease activity was assessed by using disease activity score-ESR and DAS-CRP based on 28 joints and the Disease Activity in Psoriatic Arthritis (DAPSA) scores. The receiver operating characteristic (ROC) curve was performed to evaluate the utility of SII in determining disease activity in PsA patients.

Results: The NLR, PLR, MLR, and SII were significantly higher in PsA patients compared to healthy control ($p=0.013$, $p=0.019$, $p=0.012$, and $p=0.002$, respectively). There were statistically significant positive correlations between the DAS28-ESR, DAS28-CRP, and DAPSA and SII ($p<0.001$, $p<0.001$, and $p<0.001$ respectively). The SII values were significantly higher in PsA patients with moderate to severe disease activity according to DAPSA scores when compared to patients with remission or low disease activity ($p<0.001$). The cut-off value of $800 \times 10^9/L$ was found for predicting disease activity in PsA.

Conclusion: SII may be an easy, practical, economical, and readily accessible tool for monitoring disease activity and the efficacy of treatment in PsA patients.

Key Words: Blood cell count, Psoriatic arthritis, Systemic immune inflammation index (SII).

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INTRODUCTION

Psoriasis is a chronic inflammatory multisystemic skin disease that is seen in 1-3% of the population.¹ Psoriatic arthritis (PsA) develops in 30% of psoriasis patients.² The annual incidence of the development of PsA in psoriasis patients was reported as 2-3%.³ PsA is a heterogeneous progressive inflammatory disease characterized with musculoskeletal (peripheral arthritis, axial disease, dactylitis, enthesitis) and extra-musculoskeletal manifestations resulting in disease-associated comorbidities and complications.^{4,5} The presence of arthritis and/or extensive cutaneous lesions is the hallmark of accompanying systemic inflammation in psoriasis.⁶

As articular involvement in PsA is erosive and debilitating, early diagnosis, immediate treatment to control inflammation, and achieving low disease activity are important for improved patient outcomes.⁷ Haroon *et al.* showed that even a six-month delay in diagnosis was associated with more erosion in peripheral joints, development of sacroiliitis, and higher Health Assessment Questionnaire scores.⁷ Therefore, monitoring disease activity in PsA patients is important not only for being able to assess treatment response but also for predicting the prognosis and outcome of the disease. While the markers that are most frequently used in daily practice to assess disease activity are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), they not only have low sensitivity and specificity but also show high levels in only 40% of PsA patients.^{8,9}

It has been shown that parameters like the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (PLR), and red cell distribution width (RDW), can be easily obtained from complete blood count tests nowadays, are practical markers for demonstrating systemic inflammation and disease activity.^{6,9-11} Systemic immune inflammation index

Correspondence to: Dr. Ayşe Bahar Keleşoğlu Dincer,
Department of Rheumatology, Diskapi Yıldırım Beyazıt
Research and Training Hospital, Ankara, Turkey
E-mail: bdincer@ankara.edu.tr

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(SII) is a novel complete blood count index that predicts systemic inflammation more precisely than NLR or PLR alone.^{9,12} It was first shown to be a good indicator of poor prognostic outcomes in patients with hepatocellular carcinoma in 2014. Since then, its utility has been observed in different malignancies.¹³⁻¹⁵

Studies of SII in autoimmune inflammatory diseases are lacking. In this study, the aim was to evaluate the efficacy of SII and its association with disease activity in patients with PsA.

METHODOLOGY

This descriptive study included PsA patients aged 18 years or older who were diagnosed according to the Classification Criteria for Psoriatic Arthritis (CASPAR),¹⁶ and was admitted to the Rheumatology outpatient clinic in Dışkapı Yıldırım Beyazıt Research and Training Hospital, Ankara between October 2020 and September 2021 and age and gender-matched healthy individuals. The demographic and clinical characteristics of the patients were obtained from hospital records retrospectively. The laboratory tests included complete blood count, ESR, CRP, and liver and renal function tests. NLR and PLR were obtained by dividing neutrophil counts by lymphocyte counts and platelet counts by lymphocyte counts, respectively. SII was calculated as platelet counts x neutrophil counts/lymphocyte counts. The exclusion criteria included recent or current corticosteroid treatment, active or chronic infections, solid or hematological malignancies, liver diseases, kidney diseases, pregnancy or lactation, and any rheumatic disease other than PsA.

The tender joint counts (TJC), swollen joint counts (SJC), and patients and physicians' visual analogue scores on a scale of 0-10 cm were evaluated retrospectively from patients' records. Disease activity was assessed by using the Disease Activity Index with ESR based on 28-joints (DAS28-ESR), Disease Activity Index with CRP (DAS28-CRP) and the Disease Activity in Psoriatic Arthritis (DAPSA) Score.¹⁷ DAPSA score is calculated as the sum of tender joint counts, swollen joint counts, CRP level, and patient's assessments of activity and pain on 0-10 scale. The total score of 0-4 shows remission, 5-14 points is low disease activity, 15-28 points is moderate disease activity and >28 points show high disease activity. In this study, the patients with DAPSA scores in the range of 0-14 points were accepted as remission and low disease activity; whereas the patients with scores above 15 points were accepted as moderate to high disease activity.

The data were analysed using the IBM SPSS (Statistical Package for the Social Sciences) version 25 package software. The normality of the distribution of the variables was investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics are presented using means and standard deviations for the normally distributed variables, medians and interquartile ranges for the non-normally distributed and ordinal variables, and frequencies for the categorical variables. In the comparisons between the groups, Student's t-test was

used for the normally distributed variables, Mann-Whitney U-test was used for the non-normally distributed variables and ordinal variables, and Chi-squared or Fisher test was used for the categorical variables. As both parameters were normally distributed, the correlation coefficients and their significance were calculated by Pearson's correlation analysis. While investigating the relationships between the non-normally distributed variables, the correlation coefficients and their significance were calculated using Spearman's correlation analysis. In order to assess the optimal cut-off value of SII for determining moderate to severe disease activity in PsA patients, receiver operating characteristics (ROC) analysis was performed. Youden index was applied to the ROC analysis to select the best cut-off value. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 106 PsA patients of whom 55.7% (n=59) were female and 44.3% (n=47) were male with a median age of 48.9 years, and 103 age and sex-matched healthy controls (HC) were enrolled in this study. The demographic and clinical features of the patients and HC were summarized in Table 1. The median duration of psoriasis was 102 (48-240) months. None of the patients were on corticosteroid treatment before recruitment for the study, methotrexate was the most commonly used disease-modifying anti-rheumatic drug (DMARD) followed by leflunomide and sulphasalazine. Twenty patients (18.87%) were on biological DMARD treatment, among whom TNF- α inhibitors were commonly preferred. The frequencies of comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia were similar in both groups.

Statistically significant differences were found regarding white blood cell, neutrophil, monocyte, and platelet counts between the PsA patients and the healthy individuals ($p=0.011$, $p=0.006$, $p=0.022$, and $p=0.018$, respectively) (Table 1). We also found statistically significant differences in NLR, PLR, monocyte to lymphocyte ratio (MLR), and SII between the two groups where all parameter values were higher in the PsA patients ($p=0.013$, $p=0.019$, $p=0.012$ and $p=0.002$, respectively, Table I).

There were statistically significant positive correlations between the PsA disease activity indices DAS28-ESR, DAS28-CRP and DAPSA and SII. There were positive correlations between the DAS28-CRP and NLR ($\rho=0.42$, $p<0.001$), PLR ($\rho=0.33$, $p=0.001$ and MLR ($\rho=0.33$, $p=0.001$) as well as between DAS28-ESR and NLR, PLR, and MLR ($\rho=0.33$ $p=0.001$, $\rho=0.34$ $p=0.001$, $\rho=0.25$ $p=0.012$).

When the patients were grouped according to their DAPSA scores, the patients with scores in the range of 0-14 points were accepted as remission and low disease activity; whereas the patients with scores above 15 points were accepted as moderate to high disease activity. The comparison of the clinical characteristics and laboratory findings of the patients with DAPSA scores of 0-14 and >15 is presented in Table II.

Table I: Demographic, clinical, and laboratory characteristics of PsA patients and healthy individuals

	PsA (n=106)	HC (n=103)	p-value
Sex, n(%)			
Female	59 (55.7)	63 (61.2)	0.42 ^a
Male	47 (44.3)	40 (38.8)	
Age (years) ⁺	48.9 (34.5-56.2) (20-82)	47 (38-55) (18-80)	0.96 ^b
Hypertension, n (%)	19 (17.9)	16 (15.5)	0.64 ^a
Diabetes mellitus, n (%)	7 (6.6)	5 (4.9)	0.59 ^a
Duration of psoriasis (months) ⁺	102 (48-240) (1-540)		
Laboratory features			
ESR (mm/h) ⁺	12 (5-20) (2-65)	9 (4-15) (2-37)	0.004 ^b
CRP (mg/dL) ⁺	5.7 (2.3-15.7) (0.1-75.4)	2.09 (1.19-4.49) (0.33-18.9)	<0.001 ^b
Red cell distribution width ⁺ (%)	13.5 (12.9-14.6) (11.8-19.6)	13 (12.5-13.8) (11.7-19.8)	0.001 ^b
White blood cell counts (x10 ⁹ /L) ⁺	7800 (6490-9435) (3870-14130)	7050 (5990-8300) (2900-14450)	0.011 ^b
Neutrophil counts (x10 ⁹ /L) ⁺	4570 (3520-5790) (1880-9830)	3840 (3190-4910) (890-9920)	0.006 ^b
Lymphocyte counts (x10 ⁹ /L) ⁺	2360 (1793-2753) (620-4470)	2270 (1890-2860) (1230-5080)	0.54 ^b
Monocyte counts (x10 ⁹ /L) ⁺	610 (470-763) (300-1890)	540 (450-650) (290-1270)	0.022 ^b
Platelet counts ⁺ (x10 ⁹ /L) ⁺	289 (247-330) (138-648)	261 (228-303) (151-474)	0.018 ^b
NLR ⁺	1.86 (1.49-2.83) (0.89-9.98)	1.72 (1.27-2.18) (0.57-4.42)	0.013 ^b
PLR ⁺	0.13 (0.1-0.16) (0.06-0.38)	0.12 (0.09-0.14) (0.05-0.21)	0.019 ^b
MLR ⁺	0.27 (0.2-0.33) (0.12-0.74)	0.23 (0.19-0.3) (0.11-0.63)	0.012 ^b
SII ⁺	541.5 (390.3-916.9) (211.9-2376.2)	447.3 (351.5-604.5) (171.1-1263.2)	0.002 ^b

⁺Median (Q1-Q3) (min-max); ^aChi-square; ^bMann-Whitney U.

Table II: Comparisons of clinical and laboratory features of PsA patients with remission-low disease activity and moderate-high disease activity based on DAPSA scores.

	Remission- Low Disease activity (n=73)	Moderate- High Disease activity (n=32)	p-value
Sex, n(%) ⁺			
Female	44 (60.3)	14 (43.8)	0.12 ^a
Male	29 (39.7)	18 (56.2)	
Age (years) ⁺	48.8 (32-57) (20-82)	46.5 (37.6-56) (21-77)	0.94 ^b
Hypertension ⁺	11 (15.1)	8 (25)	0.22 ^a
Diabetes mellitus ⁺	5 (6.8)	2 (6.3)	>0.99 ^c
Duration of psoriasis,(months) ⁺	120 (60-252) (1-480)	75 (48-189) (3-540)	0.28 ^b
Tender joint counts ⁺	0 (0-1) (0-3)	4 (2-8) (0-11)	<0.001 ^b
Swollen joint counts ⁺	0 (0-0) (0-1)	2 (1-5.8) (0-16)	<0.001 ^b
Patient's VAS (0-10 cm) ⁺	4 (3-6) (1-7)	7 (6-8) (4-9)	<0.001 ^b
Physician's VAS (0-10 cm) ⁺	2 (1-3) (0-6)	5 (4-6.8) (1-9)	<0.001 ^b
DAS28-CRP ⁺	2.67 (2.27-3.27) (1.31-4.93)	4.66 (3.9-5.25) (2.41-6.3)	<0.001 ^b
DAS28-ESR ⁺	2.01 (1.53-2.7) (0.78-4.5)	3.88 (3.28-4.83) (1.24-5.94)	<0.001 ^b
Treatment features			
Methotrexate ⁺	34 (46.6)	17 (53.1)	0.54 ^c
Leflunomide ⁺	3 (4.1)	3 (9.4)	0.37 ^c
Sulfasalazine ⁺	4 (5.5)	0 (0)	0.31 ^c
NSAIDs ⁺	25 (34.2)	7 (21.9)	0.21 ^a
TNF- α inhibitors ⁺	8 (11)	5 (15.6)	0.53 ^c
Secukinumab ⁺	6 (8.2)	1 (3.1)	0.67 ^c
Laboratory findings			
ESR, (mm/h) ⁺	10 (4.1-16) (2-50)	19 (8.3-28.8) (2-65)	0.002 ^b
CRP, (mg/dL) ⁺	4.1 (2-7.8) (0.1-31.1)	19.4 (5.6-37) (0.3-75.4)	<0.001 ^b
White blood cell counts, (x10 ⁹ /L) ⁺	7560 (6265-9105) (4160-11990)	8765 (6940-10628) (3870-14130)	0.029 ^b
Neutrophil counts, (x10 ⁹ /L) ⁺	4360 (3455-5300) (1880-9440)	5665 (4148-7289) (2440-9830)	0.002 ^b
Lymphocyte counts, (x10 ⁹ /L) ⁺	2400 (1900-2850) (1150-3910)	2040 (1643-2630) (620-4470)	0.026 ^b
Monocyte counts, (x10 ⁹ /L) ⁺	560 (470-705) (300-1890)	725 (540-858) (330-1550)	0.007 ^b
Platelet counts, (x10 ⁹ /L) ⁺	282 (243-319) (174-648)	314 (257-352) (138-567)	0.035 ^b
NLR ⁺	1.74 (1.36-2.31) (0.89-6.95)	2.78 (1.78-3.69) (1.37-9.98)	<0.001 ^b
PLR ⁺	0.12 (0.1-0.14) (0.06-0.26)	0.15 (0.12-0.18) (0.1-0.38)	<0.001 ^b
MLR ⁺	0.25 (0.18-0.3) (0.12-0.68)	0.31 (0.27-0.49) (0.16-0.74)	<0.001 ^b
SII ⁺	473.6 (359.8-699.4) (211.9-2014.9)	943.2 (497.4-1317) (311.1-2376.2)	<0.001 ^b
SII>800.0 ⁺	12 (16.4)	19 (59.4)	<0.001 ^b

⁺n (%) ⁺median (Q1-Q3) (min-max); ^aChi-square; ^bMann-Whitney U; ^cFisher's Exact Test.

The ESR and CRP levels were significantly higher among

$p < 0.001$, respectively).

The area under the ROC was calculated as 0.753 (95% CI 0.650-0.855 $p < 0.001$). The best cut-off value for SII was determined as 800.0 with a sensitivity of 62.5% and specificity of 83.6% among which the positive likelihood ratio was 3.8 and Youden index was 0.46.

DISCUSSION

To the best of the authors knowledge, this is the first study that evaluated SII in PsA patients which showed higher SII levels in the PsA patients than in the healthy individuals, and they were shown to be correlated with disease activity scores. In PsA, the synovial membranes are infiltrated by immune cells that release proinflammatory cytokines which results in synovial membrane inflammation, articular cartilage destruction, and bone erosions.¹⁸ The aim of the treatment in PsA is to achieve remission or the lowest disease activity in all aspects of PsA.¹⁹ However, there is no consensus on the most appropriate disease activity measure.²⁰ In studies, the 28- joint-DAS and the American College of Rheumatology response criteria are commonly used, in addition to composite indices such as DAPSA for articular diseases.²⁰ There is also no definite PsA-specific biomarker identified to reflect disease activity.²¹ Recently, components of complete blood cell parameters have emerged as useful and cost-effective indices to evaluate systemic inflammation in many rheumatic and non-rheumatic diseases. Proinflammatory cytokines and chemokines induce the recruitment, activation, and survival of neutrophils which results in an increase in the number and function of neutrophils.^{9,22} On the other hand, proinflammatory cytokines lead to lymphopenia by causing lymphocyte apoptosis.⁹ Platelets are an important source of inflammatory cytokines, in addition to being associated with hemostasis and coagulation, and they play an active role in inflammation by regulating immune system cells.²³ In this study, while the WBC, leukocyte, monocyte, and platelet counts of the peripheral blood samples of the PsA patients were significantly higher than those of the healthy control, there was no significant difference between the lymphocyte counts of the two groups. Similarly, while WBC, leukocyte, and monocyte values of PsA patients were found significantly higher in comparison to the psoriasis and control groups in the study by Kim *et al.*, lymphocyte counts were found similar in the three groups.²¹ There are a few studies evaluating the role of NLR, PLR, and MLR in patients with PsA. Kim *et al.* found NLR and PLR values significantly higher in PsA patients than in

psoriasis patients and controls.²¹ Similarly, Asahina *et al.* showed that both NLR and PLR increased in PsA patients, and these values were correlated with CRP.⁶ It was reported that MLR increased in many systemic autoimmune diseases such as rheumatoid arthritis, primary Sjögren syndrome, ankylosing spondylitis (AS), and systemic lupus erythematosus and showed correlations with acute phase reactants like ESR and CRP.¹¹ To the authors' knowledge, MLR values had not been studied in PsA patients earlier, and in this study, it was shown as in studies on other autoimmune diseases that MLR significantly increase in the PsA patients in comparison to the healthy controls.

As a novel inflammatory index, the Systemic Immune-Inflammation Index is a combination of these three parameters, and it is a better marker of inflammation than NLR or PLR alone.^{12,13} Due to the inflammatory immune response, an increase in the neutrophil and platelet counts and a decrease in lymphocyte counts occur which results in a rise in SII values.⁹ SII was defined for the first time in 2014, usually, its relationships with the prognosis of malignant diseases have been investigated, and its association with disease activity in systemic inflammatory diseases has gained importance in recent years.^{9,13} However, the utility of SII in PsA has not been evaluated before, our study was the first study that demonstrated a higher level of SII in PsA patients compared to healthy controls and SII was positively correlated with disease activity. In the study conducted with 71 psoriatic patients, SII values were found to be higher in comparison to healthy individuals and also were higher in patients with higher Psoriasis Area Severity Index (PASI) scores.¹²

Wu *et al.* showed significantly higher levels of SII in patients with AS compared to healthy controls and in their study SII, NLR, and PLR levels were significantly higher in active AS patients based on BASDAI scores.⁹ In the present study, similarly, DAS28-ESR, DAS28-CRP and DAPSA were used in the assessment of PsA disease activity, and statistically significant correlations of all three disease activity indices with SII, NLR, PLR, and MLR were shown. Moreover, when the PsA patients in this study were examined by dividing them into two groups as remission-low disease activity and moderate-severe disease activity based on their DAPSA scores, it was demonstrated that not only the SII values but also the NLR, PLR, and MLR values were significantly higher in the moderate-severe disease activity group than the remission-low disease activity group.

The study conducted by Tanacan *et al.* with Behçet syndrome (BS) patients included 103 active and 63 inactive BS patients and found significantly higher SII values in the active BS patients.²⁴ In the study by Chen *et al.* in patients with anti-neutrophil-cytoplasmic antibody-associated vasculitis (AAV), SII was shown to be positively correlated with ESR and CRP.²⁵ The authors also found the risk of developing end-stage renal disease to be lower in individuals with

high SII values. This finding was explained by the better response of individuals with higher disease activity to initial immunosuppressive treatment as high SII is associated with a higher inflammatory response.²⁵ In contrast, in the study conducted with 163 AAV patients by Kim *et al.*, it was shown that high SII was associated with more severe AAV activity, and these individuals had lower relapse-free and renal survival rates.²² These results were interpreted as that high SII values at the time of diagnosis showed poor prognosis in AAV cases.²²

The present study has several limitations. Firstly, the authors focused on the articular involvement of PsA. As enthesitis and dactylitis are both accompanied by inflammation, the utility of SII in these aspects of PsA should be evaluated in further studies. The second limitation was the retrospective design of the study, although, the number of patients was higher than those in the previous studies that focused on hematological indices in PsA patients. Additionally, as far as we know, this was the first study evaluating SII levels in PsA patients. Lastly, some of the patients were already on immunosuppressive agents other than corticosteroids (mostly conventional DMARDs) at the time of their inclusion in the study, which, however, did not affect the results of the study. Still, prospective studies evaluating differences in SII levels before and after initiating disease-modifying treatments must be conducted.

CONCLUSION

Systemic Immune Inflammation Index may be used to predict disease activity in PsA patients. It may be a helpful, cheap, and practical tool for physicians in the more effective modification of PsA treatments.

ETHICAL APPROVAL:

The study protocol was approved by the Health Sciences University Dışkapı Yıldırım Beyazıt Research and Training Hospital Ethics Committee (No. 119/06, Date: 06.09.2021).

PATIENTS' CONSENT:

As the study is retrospective, the patients' consents were waived.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

ABKD: Designed the study, selected patients, created the study plan, and wrote the manuscript.

SS: Selected patients analysed the data, and checked the final version of the manuscript to be published.

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