

The relationship of the systemic immune inflammation index to severity in chronic spontaneous urticaria

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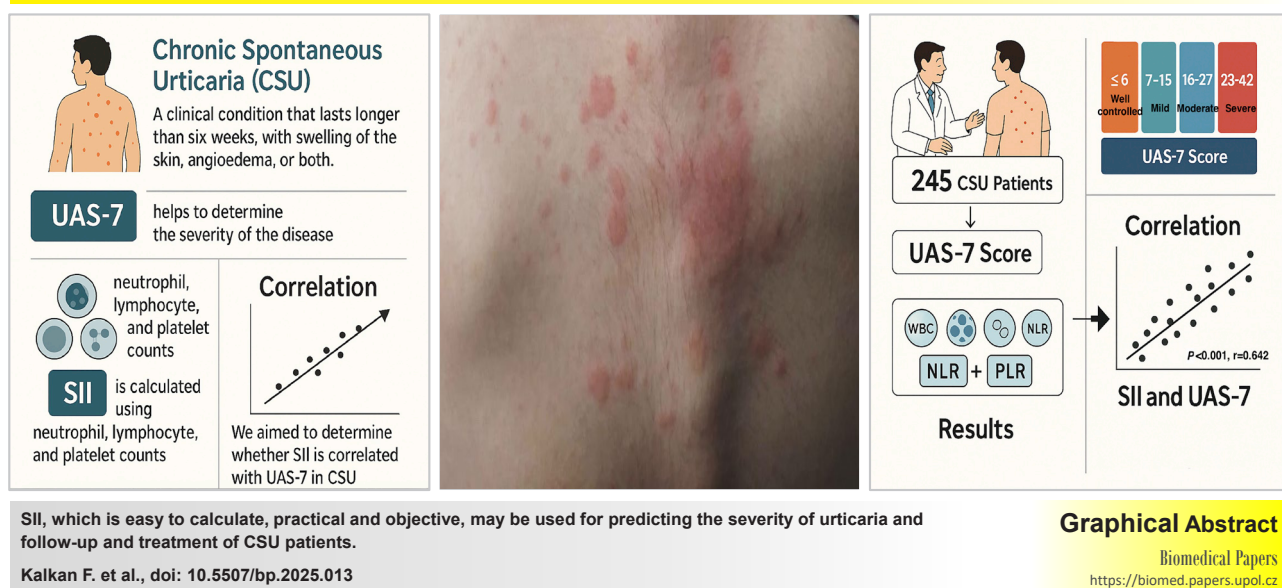
Background and aims. Chronic spontaneous urticaria (CSU) is a skin condition causing red, raised, itchy and sometimes painful hives which lasts longer than six weeks. While the cause is unclear, the Urticaria Activity Score-7 (UAS-7), can help to determine the severity of the disease while the Systemic Immune Inflammation Index (SII) defined as neutrophils $\times$ platelets/lymphocytes, is a recent marker that shows the inflammatory and immune status and can be easily calculated from routine blood tests using neutrophil, lymphocyte, and platelet counts. We aimed to determine whether the SII correlates with UAS-7 in CSU patients.

Methods. We conducted this study on 245 patients with CSU. The UAS-7 score was obtained from all patients. Four groups were generated according to the UAS-7 score as ≤ 6 , 7–15, 16–27, and 28–42. The correlation between the UAS-7 score and SII was evaluated.

Results. There was a statistically significant difference between the groups in terms of white blood cell count, neutrophil count, platelet count, Neutrophil-lymphocyte ratio (NLR), Platelet- lymphocyte ratio (PLR), and SII ($P < 0.05$). A positive correlation was found between SII, NLR and PLR, and UAS-7 score. The strongest correlation was between SII and UAS-7, with $P < 0.001$, $r = 0.642$.

Conclusion. SII, which is easy to calculate, practical, and objective can be used for predicting the severity of the urticaria and for guiding the follow-up and treatment of these patients.

THE RELATIONSHIP OF THE SYSTEMIC IMMUNE INFLAMMATION INDEX TO SEVERITY IN CHRONIC SPONTANEOUS URTICARIA



Key words: systemic immune inflammation index, chronic spontaneous urticaria, UAS-7 score

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a clinical condition that lasts longer than six weeks, with swelling of the skin, and angioedema¹. The pathogenesis of the skin lesions that develop in CSU is thought to be vasodilation caused by the release of histamine and other proinflammatory mediators following the activation of skin mast cells^{2,3}. Although it does not increase mortality, CSU affects the quality of life by negatively affecting the patient's social relations, sleep, and working life⁴. The Urticaria activity score (UAS), and urticaria control scale help to determine the severity of the disease^{5,6}. Treatment planning is made according to the severity of the disease itself and minimizing the negative sequelae⁷.

The systemic immune inflammation index (SII) is calculated using neutrophil, lymphocyte, and platelet counts⁴. SII is a tool that clinicians can use to demonstrate the immune and inflammatory status of the patient. In this context, it has been shown in many studies that the SII shows the disease severity and prognosis in patients with inflammatory diseases, cancer, pulmonary embolism, and acute coronary syndrome among others⁸⁻¹¹.

In our study, we aimed to determine whether SII, which is easy to calculate, is associated with the severity of the disease and compare it with UAS in CSU patients.

MATERIAL AND METHODS

A total of 245 patients with chronic spontaneous urticaria (CSU) admitted to our clinic August 2017 and August 2022 were included in the study retrospectively.

Patients with inflammatory or autoimmune disease, active infectious disease, malignancy, or pregnancy were excluded from the study. Patients taking corticosteroid and nonsteroidal anti-inflammatory drugs were also excluded from the study.

The clinical research ethics committee of our hospital approved our study protocol. The data of the patients were collected from the hospital automation system and patient files.

Urticaria activity score-7 (UAS-7) was calculated from the patients. The UAS-7 score is calculated by giving 1,2,3 point, respectively, as mild-moderate-severe itching and swelling symptoms for 7 days. It is scored between 0-42 in total. A UAS-7 score of ≤ 6 was considered well-controlled (UAS grade 1), a score of 7-15 was considered mild (UAS grade 2), a score of 16-27 was considered moderate (UAS grade 3), and a score of 28-42 (UAS grade 4) was regarded as severe urticaria⁵.

SII, Neutrophil-lymphocyte ratio (NLR) Platelet/lymphocyte ratio (PLR) was calculated using the formulas. Neutrophil lymphocyte ratio (NLR) = neutrophils/lymphocytes, Platelet/lymphocyte ratio (PLR) = platelet/lymphocytes, and SII = platelets x neutrophils/lymphocytes^{9,12}.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation, while categorical variables are given as percentages. The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Statistical analysis of clinical data between the two groups consisted of unpaired t-tests for parametric data and Mann-Whitney U-test analysis for nonparamet-

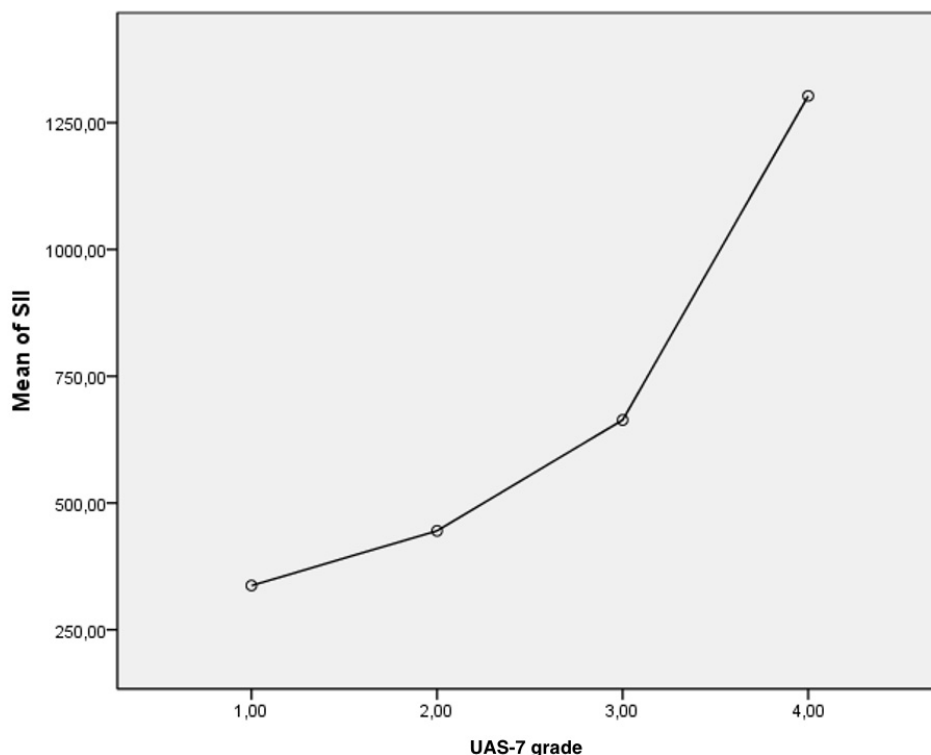


Fig. 1. The relationship between SII and UAS-7 grades.

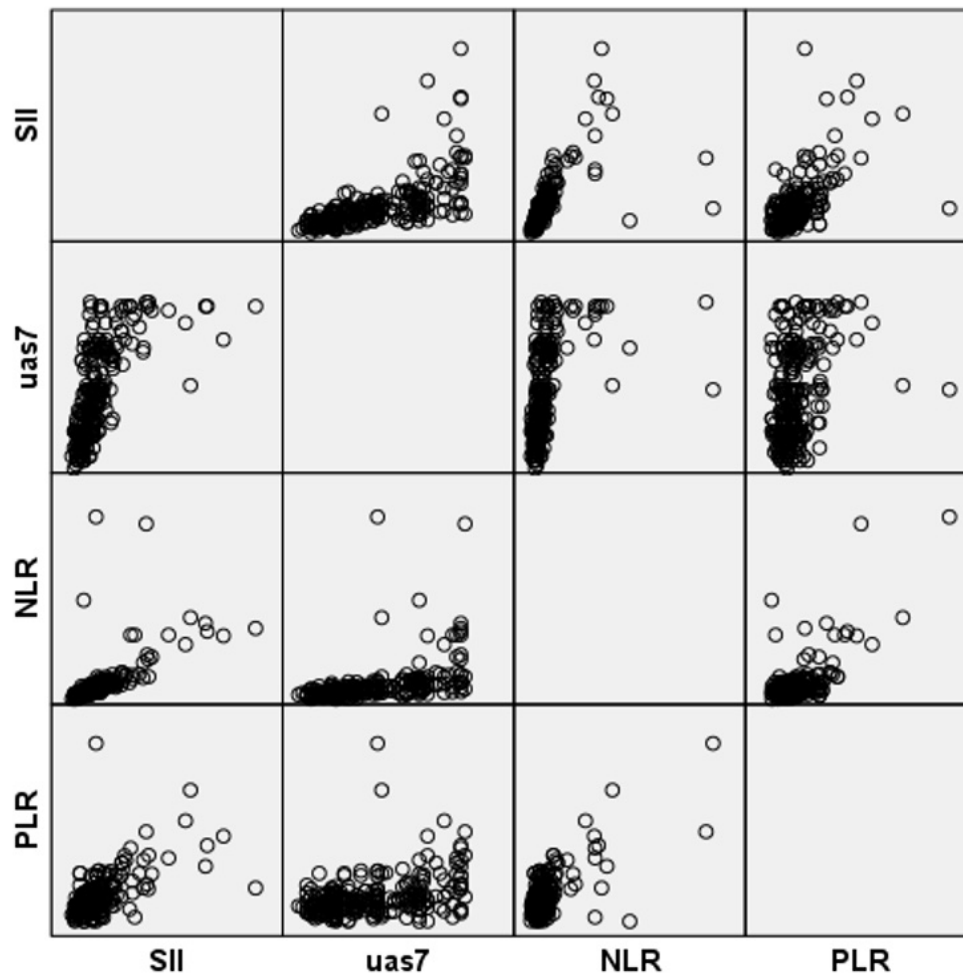


Fig. 2. Scatter dot plot of the correlation between SII, NLR and PLR and the UAS-7 score. UAS, Urticaria activity score; SII, Systemic immune-inflammation index; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio.

ric data. Continuous variables and categorical variables were analyzed by the chi-squared test and Student's t-test as appropriate. Spearman correlation analyses were conducted to investigate the relationship between SII and UAS-7 scores. A two-tailed $P < 0.05$ was accepted as statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 245 patients with chronic spontaneous urticaria (CSU) were included in the study, with a mean age of 39 ± 11 years. Of these, 101 (41.2% male) patients were male. Demographic, clinical and laboratory findings are shown in Table 1 by grouping them according to the grading of the whole population and UAS-7 scores.

There was a statistically significant difference between the groups in terms of white blood cell count, neutrophil count, platelet count, NLR, PLR and SII ($P < 0.05$).

Parameters with significant differences were included in the Spearman correlation analysis. A positive correlation was found between SII, NLR and PLR, and UAS-7

scores (Table 2). Between SII and UAS-7 score; $P < 0.001$, $r = 0.642$, UAS-7 with NLR; $P < 0.001$, $r = 0.447$, UAS-7 with PLR; $P < 0.001$, $r = 0.376$. The strongest correlation was found between SII and UAS-7. The relationship between SII and UAS-7 rating is shown in Fig. 1. The correlation between SII, NLR, and PLR and the UAS-7 score is shown in Fig. 2 as a scatter dot plot.

71.2% of patients had no comorbidities. The most observed comorbidities were allergic diseases in 21.1% of patients and cardiovascular diseases in 7.8%. Among cardiovascular diseases, the most prevalent was hypertension (HT), found in 13 patients (73%). Among autoimmune diseases, the most common was Hashimoto's thyroiditis, observed in 4 patients (75%). Among thyroid disorders, the most frequent was hypothyroidism, seen in 7 patients (70%). We detected allergic diseases in 21% of the patients, with allergic rhinitis being the most frequent, occurring in 30 patients (57%). No statistically significant relationship was found between comorbidities and SII, NLR, and PLR.

The Spearman correlation analysis showed that there was no significant correlation between CRP and UAS-7

Table 1. Baseline demographic, clinical and laboratory characteristics of the study population according UAS-7 score stages.

	Total study population, n = 245	UAS stage 1, n = 29	UAS stage 2, n = 89	UAS stage 3, n = 60	UAS stage 4, n = 67	<i>P</i>
Male,%	101 (41.2)	14 (48.3)	37 (41.6)	22 (36.7)	28 (41.8)	0.772
WBC, median (min-max), cells/mm ³ 10 ³	8384 (3400–26100)	6574 (3400–11600)	7696 (3541–20000)	8671 (5100–19000)	9847 (10877–26100)	0.020
Platelet/mm ³ ±SD	264±55	231±43	254±49	275.28±50	281±53	0.002
Hemoglobin, g/dL±SD	14.57±5.58	13.75±2.54	14.06±1.82	14.22±1.97	14.11±1.73	0.671
Total IgE, median (min-max)	222 (42–1602)	241 (24–710)	209 (2–1602)	192 (2–1602)	261 (2–1168)	0.998
Eosinophil, median (min-max) 10 ³ /mL	0.15 (0–1.96)	0.18 (0.05–0.66)	0.15 (0.02–0.60)	0.16 (0.02–0.196)	0.11 (0.01–0.40)	0.447
Basophil, 10 ³ /mL median (min-max)	0.03 (0–1.20)	0.03 (0–01)	0.03 (0–0.1)	0.02 (0–0.18)	0.05 (0–1.20)	0.138
Neutrophil, 10 ³ /mL ± SD	5.27±2.73	3.45±1.31	4.39±1.83	5.50±2.18	7.03±2.54	0.001
SII, median (min-max)	662 (170–3701)	337 (170–585)	445 (213–951)	663 (361–2450)	1092 (400–3701)	<0.001
NLR, median (min-max)	2.78 (0.75–27.1)	1.47 (0.76–2.62)	1.77 (0.75–3.26)	2.90 (1.25–27.10)	4.58 (1.44–26.00)	0.014
PLR, median (min-max)	130 (49–647)	104 (58–210)	107 (49–220)	141 (57–647)	163 (49–386)	0.041

UAS, Urticaria activity score; WBC, White blood cell; IgE, Immunoglobulin E; SII, Systemic immune-inflammation index; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio.

Table 2. Correlation of UAS-7 score and inflammatory parameters.

	Rho	<i>P</i>
SII	0.642	<0.001
NLR	0.447	<0.001
PLR	0.376	<0.001

UAS, Urticaria activity score; SII, Systemic immune-inflammation index; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio.

scores. It was also observed that there was no statistically significant relationship between SII and CRP ($P=0.847$).

DISCUSSION

Our study found that SII correlated with the UAS-7 score; that is, it predicted the severity of the disease in CSU patients. According to our knowledge, our study is the first to investigate the relationship between SII and UAS-7 scores. CSU is a disease that is difficult to diagnose, treat and follow. Treatment drugs and doses are adjusted according to the patient's response to treatment. Although UAS-7 is mostly used in follow-up, SII can also be used in follow-up as a more objective alternative method.

Urticaria is a skin disease with heterogeneous clinical features that occur due to different causes and different mechanisms^{1,13}. Urticaria is characterized by edematous papules/plaques involving the upper layers of the der-

mis, which are raised from the skin, fade with pressure, are pink or red, have clear borders, and usually have an erythema ring around them. The pathognomonic bumps' redness, swelling, and itching are caused by vasodilation, increased vascular permeability with fluid infiltration into the tissue, and stimulation of sensory nerve endings resulting in activation, degranulation, and release of vasoactive substances by dermal mast cells^{14,15}.

The UAS-7 score is a system that determines the clinical severity and response to treatment by questioning the urticaria swelling status and itching severity for seven days in CSU (ref.¹⁶). Although UAS-7 is useful in patients, it is calculated entirely based on the patient's subjective evaluation. In addition, following up and controlling the complaints for seven days is necessary. Seven days follow-up of patients to calculate the UA-7 may be difficult and may cause false results. In this context, there is a need for parameters that can show the severity of the disease and the response to treatment with instant evaluation.

SII is a parameter that can be calculated easily and has been associated with many diseases recently^{17,18}. NLR and PLR have been used in many studies before, and it has been found highin a study where inflammation plays a role in pathogenesis¹⁹. In another study by Maouia et al., a correlation was found between elevated CRP and UAS-7 in patients with urticaria²⁰. The neutrophil-to-lymphocyte ratio (NLR) can be a good indicator of systemic inflammation and can be easily calculated using routinely obtained complete blood counts. NLR has been associated with chronic inflammation in cardiovascular disease, hypertension, diabetes mellitus, various

malignancies, familial Mediterranean fever, hepatic cirrhosis, Behçet's disease, and sinonasal polyps^{4,21}. Similar to our study, in a survey by Akça et al., the relationship between UAS-7 score and NLR and high sensitive C reactive protein (hs-CRP) and Erythrocyte sedimentation rate (ESR) values were investigated. However, although there was no significant difference compared to the control group, NLR and ESR levels were higher in CSU patients²². In our study, we found that NLR, PLR, and SII were correlated with UAS-7 scores, especially SII, in the spearman correlation analysis, which we conducted to help with CSU patient groups.

As is known, NLR is calculated by using the ratio of neutrophils and lymphocytes, while PLR is calculated by using the ratio of platelets and lymphocytes. On the other hand, SII is a more sensitive index than NLR and PLR because it includes all NLR and PLR parameters. In our study, we investigated the relationship between SII and the UAS-7 score, indicating CSU disease severity. We found that SII increased as the severity of CSU increased, that is, as the UAS-7 score increased.

The systemic immune inflammation index (SII), determined by Hu B et al., is a promising new inflammation marker parameter calculated from the neutrophil X platelet/lymphocyte formula¹². In a study conducted by Coşansu et al., which supported our study, the response to omalizumab treatment was evaluated by calculating the UAS-7 score in patients with CSU who were treated with omalizumab. Then it was found to be helpful in predicting the response to SII treatment⁴. Unlike this study, the relationship between baseline SII values and disease severity of newly diagnosed CSU patients was investigated in our study rather than a response to treatment.

As a limitation, the retrospective design of our study and the low number of patients can be considered. In addition, no data shows the patients' SII responses and UAS follow-ups after treatment. Since erythrocyte sedimentation rate values were not available for all patients, the relationship between sedimentation rate and CSU severity was not investigated.

SII correlates with the UAS-7 score in patients with CSU. In this context, it can be used as an effective and objective parameter to predict the severity of urticaria. SII, which is easy to calculate and practical, can guide the follow-up and treatment of CSU patients..

Author contributions: All authors made equal contributions to the research design, the execution of the experiment, the analysis of the results, and the preparation of the manuscript.

Conflicts of interest statement: None declared.

Availability of data and materials: Data are however available from the authors upon reasonable request and with permission of the corresponding author.

Ethical approval statement: Study was approved by Ethics Committee of the our hospital.

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