

# Serum C-Reactive Protein, Neutrophil-Lymphocyte Ratio and Uric Acid Levels in Chronic Spontaneous Urticaria

## Kronik Spontan Ürtikerde Serum C-Reaktif Protein, Nötrofil-Lenfosit Oranı ve Ürik Asid Düzeyleri

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**ABSTRACT Objective:** Recent studies implicate the role of inflammatory responses in chronic spontaneous urticaria (CSU). The purpose of this study was to analyse the levels of neutrophil-lymphocyte ratio (NLR), serum C-reactive protein (CRP) and uric acid levels in CSU patients, and to investigate the relationship between these inflammatory parameters and disease activity. **Material and Methods:** A total of 100 people, consisting of 50 chronic urticaria patients and 50 healthy controls, who have no systemic disease, inflammatory, infectious or autoimmune disease, malignancy, were included in the study. **Results:** NLR and serum CRP levels were significantly higher in patients with CSU than in healthy controls ( $p < 0.001$ ,  $p < 0.001$ , respectively). The levels of uric acid did not show a statistically significant difference between CSU patients and controls ( $p = 0.359$ ). A significant positive correlation was found between NLR and CRP in patients with CSU ( $p = 0.001$ ,  $r = 0.442$ ). When CSU patients were evaluated according to disease severity, serum CRP levels were significantly higher in patients with severe CSU than in patients with mild-moderate CSU ( $p = 0.038$ ). **Conclusion:** Several biomarkers have been studied in systemic diseases to determine the inflammatory process ongoing and the relationship between these markers and disease activity has been investigated. It can be concluded that CRP and NLR can be used to assess the inflammatory status in CSU and may be useful parameters during the follow-up of these patients. It is known that NLR and CRP are diagnostic and prognostic markers of cardiovascular diseases. Elevated values of NLR and CRP may demand caution regarding cardiovascular comorbidities that may accompany chronic urticaria.

**Key Words:** C-reactive protein; neutrophils; uric acid; urticaria

**ÖZET Amaç:** Son dönemde yapılan çalışmalarda kronik spontan ürtikerde (KSÜ) inflamatuvar yanıtın üzerinde durulmaktadır. Bu çalışmanın amacı KSÜ hastalarında nötrofil-lenfosit oranı (NLO), serum C-reaktif proteini (CRP) ve ürik asid düzeylerini belirlemek ve bu inflamatuvar parametreler ile hastalık aktivitesi arasında ilişki olup olmadığını araştırmaktır. **Gereç ve Yöntemler:** Herhangi bir sistemik hastalığı, inflamatuvar veya enfeksiyöz hastalığı, malignitesi, otoimmün hastalığı olmayan 50 kronik ürtiker hastası ve 50 sağlıklı kontrol olmak üzere toplam 100 kişi çalışmaya dahil edildi. **Bulgular:** NLO ve CRP düzeyleri KSÜ hastalarında sağlıklı kontrollere göre anlamlı olarak daha yüksekti ( $p < 0.001$ ,  $p < 0.001$ , sırasıyla). Ürik asid düzeyleri açısından KSÜ hastaları ve sağlıklı kontroller arasında anlamlı bir fark izlenmedi ( $p = 0.359$ ). KSÜ hastalarında NLO ve CRP arasında anlamlı pozitif korelasyon mevcuttu ( $p = 0.001$ ,  $r = 0.442$ ). KSÜ hastaları hastalık şiddetine göre incelendiğinde serum CRP düzeyleri şiddetli KSÜ hastalarında hafif-orta şiddetli KSÜ hastalarına göre anlamlı olarak daha yüksekti ( $p = 0.038$ ). **Sonuç:** Çeşitli inflamatuvar belirteçler sistemik hastalıklarda devam eden inflamatuvar süreci belirlemek için çalışılmıştır ve bu parametrelerin hastalık aktivitesiyle ilişkisinin incelendiği pek çok çalışma mevcuttur. CRP ve NLO değerleri KSÜ'de inflamatuvar durumu belirlemede ve hastalık takibinde kullanılabilir. NLO ve CRP'nin kardiyovasküler hastalıklarda tanılma ve prognostik belirteçler olduğu bilinmektedir. Yükselmiş NLO ve CRP değerlerine kronik ürtikere eşlik edebilecek kardiyovasküler komorbiditeler açısından dikkat edilmelidir.

**Anahtar Kelimeler:** C-reaktif protein; nötrofiller; ürik asid; ürtiker

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Chronic spontaneous urticaria (CSU) is a mast cell and basophil-dependent inflammatory skin disease accompanied by the acute phase response.<sup>1</sup> The urticaria activity score (UAS), based on the urticarial symptoms of the patient such as wheals and pruritus, is used to evaluate the disease activity.<sup>2</sup> This scoring system depends on the patients' documentations of their symptoms and, therefore lacks objectivity. This is why various biomarkers have been investigated to assess the disease activity.

C-reactive protein (CRP) is a well-known inflammatory biomarker. Elevated serum CRP levels have already been shown in CSU patients.<sup>1</sup> The neutrophil-lymphocyte ratio (NLR) is a simple hemogram test which is the division of total neutrophil count by the total lymphocyte count. Recently, NLR has been found to be elevated in many inflammatory diseases, such as myocardial infarction (MI), diabetes mellitus (DM), hypertension (HT), ulcerative colitis (UC) and psoriasis.<sup>3,4</sup> Also, elevated serum uric acid (SUA) concentrations have been observed in HT, cardiovascular diseases, chronic kidney diseases and metabolic syndrome related with inflammatory status.<sup>5,6</sup>

In this study, serum NLR, CRP and uric acid levels of patients with CSU were measured and it was investigated whether or not these parameters have an association with clinical disease activity.

## MATERIAL AND METHODS

A cross-sectional study was planned to investigate the relationship between inflammatory markers, such as NLR, CRP and SUA, and the disease activity of CSU patients. Fifty patients with CSU, and 50 healthy volunteers without any systemic disease matched for age and sex were included in the study. In all cases, any known causes of CSU were ruled out by appropriate investigations. Each patient underwent the following tests: routine laboratory tests (full blood count, urine analysis, ESR, C-reactive protein, serum glucose, hepatic functions, and creatinine), stool (for parasites), hepatitis serology, antinuclear and antithyroid microsomal antibodies, thyroid function. Patients

with any other inflammatory, autoimmune or infectious diseases, malignancy, any systemic diseases or pregnancy were excluded from the study. In addition, patients receiving treatment for CSU or for any other reason, as well as those patients with smoking and/or alcohol consumption habits, were excluded. All of the participants were within the normal limits of body mass index (BMI).

All participants provided written informed consent after a full explanation of the purpose and nature of the study and all procedures. The study was approved by Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee.

## EVALUATION OF UAS

Disease activity in spontaneous urticaria was assessed with the UAS as recommended by EAACI/GA2LEN/EDF guidelines. The UAS is based on the assessment of the two key urticaria symptoms, wheals and pruritus. The mean UAS values of the patients were evaluated according to the symptoms of the last seven days, depending on the number of wheals (0-3 points) and the intensity of pruritus (0-3 points). Then, the scores of wheals and pruritus were added up between 0-6 and graded as follows: mild disease (score 1-2), moderate disease (score 3-4), severe disease (score 5-6).

## ASSAY OF NLR, CRP AND SUA

Venous blood samples were drawn from the participants between 09:00 and 11:00 hours following a 12-hour fasting period to assess CRP, NLR and uric acid levels. Measurements of serum CRP levels were performed with a spectrophotometric system (Cobas c 501; Roche Diagnostics, Mannheim, Germany). Hemogram tests were assessed by an autoanalyzer system (Sysmex XE-2100; Roche Diagnostics, Mannheim, Germany). SUA concentrations were measured with uricase calorimetric system (Cobac c 701; Roche Diagnostics, Mannheim, Germany).

## STATISTICAL ANALYSIS

Statistical analyses were carried out using SPSS version 15 (IBM, Armonk, NY, U.S.A.). Quantitative data were presented as mean  $\pm$  SD, while qualitative data are presented as number (n) and percent-

age. The Mann-Whitney U-test was used for the statistical analysis. The Kruskal-Wallis test was used to determine whether there was a difference between the two groups. To compare categorical data, the chi-square test was performed. Correlations were performed using Spearman's correlation analysis.  $p$ -values  $<0.05$  were considered to be statistically significant.

## RESULTS

### STUDY POPULATION

The sex and age ratios were not substantially different for each variable among patients with CSU (34 women, 16 men; mean age  $35.6 \pm 12.3$  years), and healthy controls (27 women, 23 men; mean age  $35 \pm 10$  years) ( $p=0.151$ ,  $p=0.855$ , respectively).

In the CSU group, the mean duration of the disease was  $34.7 \pm 59.5$  months (mean  $\pm$  SD). The CSU group consisted of 29 (58%) patients with mild-moderate disease and 21 (42%) patients with severe symptoms of urticaria (Table 1).

### CRP, NLR AND SUA CONCENTRATION

Serum CRP concentrations and NLR levels were significantly higher in CSU patients compared with the healthy subjects ( $p < 0.001$ ). There was no significant difference in SUA levels between patients with CSU and healthy controls ( $p=0.359$ ) (Table 2). A significant positive correlation between serum CRP and NLR was found in patients with CSU ( $p=0.001$ ,  $r=0.442$ ) (Figure 1).

**TABLE 1:** Demographic characteristics of subjects.

	CSU (n= 50)	Healthy controls (n= 50)	P
Age (mean $\pm$ SD, year)	35.6 $\pm$ 12.3	35 $\pm$ 10	<sup>a</sup> 0.855
Sex, n (%)			
Male	16 (32)	23 (46)	<sup>b</sup> 0.151
Female	34 (68)	27 (54)	
Disease duration (month) (mean $\pm$ SD)	21.16 $\pm$ 1.86		
Urticaria severity, n (%)			
Mild-moderate	29 (58)		
Severe	21 (42)		

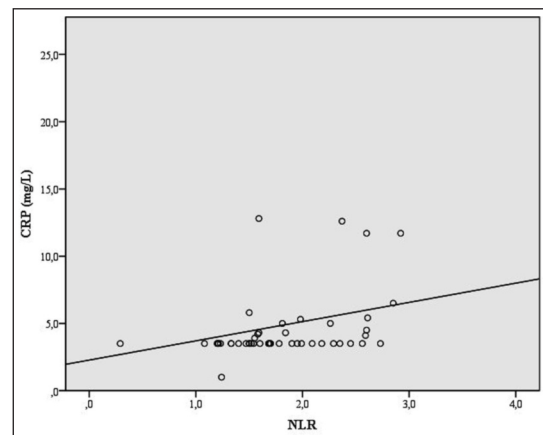
<sup>a</sup>P- value for the Mann-Whitney U test comparing age among patients with CSU and healthy controls. <sup>b</sup>P- value for the Pearson's chi square test comparing gender ratio among patients with CSU and healthy controls. CSU; chronic spontaneous urticaria.

**TABLE 2:** C-reactive protein, neutrophil lymphocyte ratio and uric acid levels of chronic spontaneous urticaria patients and healthy controls

	CSU (n= 50) Mean $\pm$ SD (med)	Healthy controls (n= 50) Mean $\pm$ SD (med)	p
CRP, mg/L	4.9 $\pm$ 4.2 (4)	3.4 $\pm$ 0.4 (4)	$<^a0.001^*$
NLR	1.88 $\pm$ 0.68 (1.7)	1.4 $\pm$ 0.4 (1.4)	$<^a0.001^*$
SUA, mg/dL	4.2 $\pm$ 1.2 (4)	4.0 $\pm$ 1.1 (4)	<sup>a</sup> 0.359

<sup>a</sup>Mann Whitney U Test; <sup>\*</sup> $p < 0.01$ .

CSU: Chronic spontaneous urticaria; CRP: C-reactive protein; NLR: Neutrophil lymphocyte ratio; SUA: Serum uric acid.

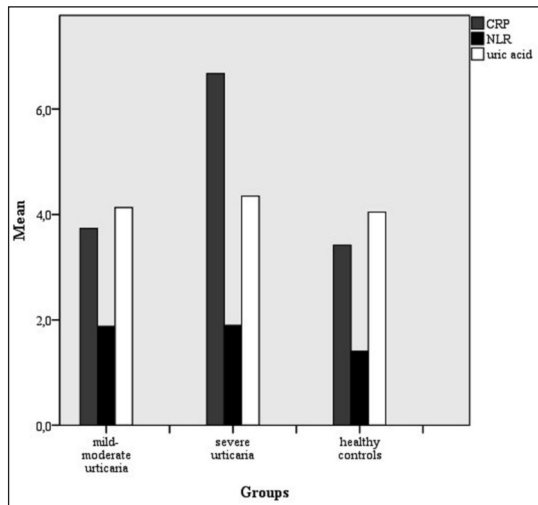


**FIGURE 1:** Correlation of C-reactive protein (CRP) with neutrophil lymphocyte ratio (NLR) in patients with chronic spontaneous urticaria (CSU).

When patients with CSU were evaluated according to disease severity, serum CRP concentration was significantly higher in patients with severe CSU ( $6.67 \pm 6.06$ ) than in patients with mild-moderate CSU ( $3.73 \pm 0.48$ ) and healthy controls ( $3.4 \pm 0.4$ ) ( $p=0.038$ ). However, there were no significant differences in NLR and SUA levels between patients with mild-moderate CSU, severe CSU and healthy controls ( $p=0.637$ ,  $p=0.555$ , respectively) (Figure 2, Table 3).

### ASSOCIATION BETWEEN THE DISEASE DURATION AND THE URTICARIA ACTIVITY SCORE

The mean disease duration in patients with severe CSU was higher than that of the mild-moderate CSU patients, but the difference was not statistically significant ( $43.57 \pm 62.0$  months vs.  $28.21 \pm 57.81$  months,  $p=0.106$ ) (Table 3). There was a positive correlation with the disease duration and UAS in patients with CSU ( $p=0.033$ ,  $r=0.301$ ) (Figure 3).



**FIGURE 2:** Mean C-reactive protein (CRP), neutrophil lymphocyte ratio (NLR) and serum uric acid (SUA) levels of the study groups.

## DISCUSSION

Chronic urticaria is a persistent inflammatory disorder of the skin characterized by mast cell degranulation and perivascular, non-necrotizing infiltrate of CD4(+) lymphocytes, consisting of a mixture of Th1 and Th2 subtypes, as well as monocytes, neutrophils, eosinophils and basophils.<sup>1</sup> Although systemic inflammation and infiltration of the skin with these inflammatory cells contribute to the development of CSU, little is known about the underlying pathogenic mechanisms.

The assessment of disease activity and severity of CSU are important processes in the management

of CSU. In the EAACI/GA2LEN/EDF guidelines, it is recommended to evaluate the disease activity before the treatment and during the follow-up of CSU. For the assessment of disease activity of CSU, the guideline proposes the scoring system UAS, based on urticarial symptoms, such as wheals and pruritus. It largely relies on patients' subjective descriptions.<sup>2</sup> Therefore more reliable and objective parameters for evaluating disease activity in CSU should be developed, with the objective of proper management of the disease. Several biomarkers have been suggested to reflect disease activity and severity of CSU.<sup>7</sup> It is well known that CSU affects the quality of life of patients. Quality of life (QoL) index is used to assess the disease activity. Chronic urticaria quality of life questionnaire (CU-Q2oL), is another tool for determining the severity of CSU quality of life impairment which has also been validated to Turkish language by Kocatürk et al.<sup>8,9</sup> Visual analogue scale (VAS) and itch severity score (ISS) are also used to determine the disease activity.<sup>10</sup> In the present study UAS was evaluated since guideline proposes this scoring system in the assessment of disease activity. In the present study it is investigated if there is a correlation between the inflammatory markers and the disease activity. Relation between quality of life in CSU patients and inflammatory biomarkers may be the issue of another study.

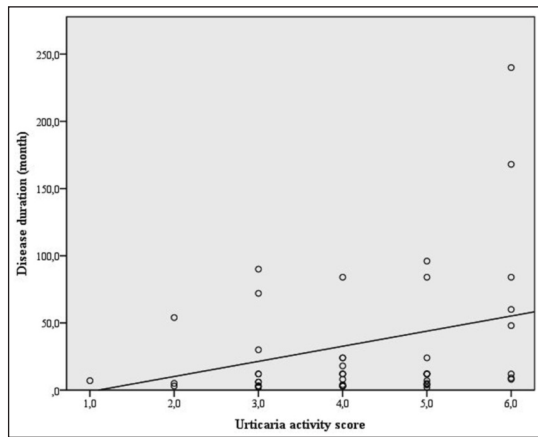
Currently, CRP is the most extensively studied biomarker of inflammation. CRP is an acute phase protein that is produced predominantly by hepato-

**TABLE 3:** C-reactive protein, neutrophil lymphocyte ratio and uric acid levels according to urticaria severity.

		Urticaria severity		
		Mild-moderate (n=29) mean±SD (med)	Severe (n=21) mean±SD (med)	P
CRP		3.73±0.48 (3.5)	6.67±6.06 (3.5)	<sup>a</sup> 0,038*
NLR		1,88±0.71 (1.69)	1,89±0.67 (1.84)	<sup>a</sup> 0,637
SUA		4.13±1.38 (4.3)	4.35±0.97 (4.1)	<sup>a</sup> 0,555
Disease duration		28.21±57.81 (8)	43.57±62.0 (12)	<sup>a</sup> 0.106
Age (year)		37.83±12.99 (38)	32.52±10.8 (30)	<sup>a</sup> 0,125
		n (%)	n (%)	
Sex	Female	20 (68.97)	14 (66.66)	<sup>a</sup> 0,863
	Male	9 (31.03)	7 (33.33)	

<sup>a</sup>Kruskal Wallis Test; <sup>a</sup>Pearson Chi-Square Test; \*p<0,05

CRP: C-reactive protein; NLR: Neutrophil lymphocyte ratio; SUA: Serum uric acid.



**FIGURE 3:** A positive correlation with the disease duration and urticaria activity score (UAS) in patients with chronic spontaneous urticaria (CSU).

cytes under the influence of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha).<sup>11</sup> In some prospective studies, an elevated CRP concentration was defined as a principal risk factor for some chronic diseases, including DM and HT.<sup>12</sup> Danesh et al. observed that increases in CRP concentration, even within the normal laboratory range, in patients with coronary heart diseases, are found to be associated with an increased risk of cardiovascular disease.<sup>13</sup> Moreover, it has been reported that the circulating CRP concentration is increased in CSU.<sup>1</sup> Kasperska-Zajac et al. showed not only elevated serum CRP levels in chronic urticaria patients, but also a positive relationship between urticaria activity and CRP levels.<sup>14</sup> In another study, Kasperska-Zajac et al. demonstrated elevated IL-6 and CRP levels in CSU patients, and a correlation between IL-6 and CRP concentration and the UAS.<sup>15</sup> Also, in the same study, decreases in IL-6 and CRP concentrations were observed during spontaneous remission.<sup>15</sup>

In the present study, the serum concentration of CRP was significantly elevated in CSU patients, which is consistent with the results of previous studies. In addition, when the CSU patients were considered separately as severe and mild-moderate CSU groups, serum CRP levels were statistically higher in the severe group than in the mild-moderate group. With these findings, it can be proposed that serum CRP concentration might be an objective parameter in the assessment of disease activity in CSU.

NLR obtained by dividing neutrophil count by lymphocyte count has recently been studied in various diseases, such as MI, DM, HT, UC, hepatic cirrhosis, familial mediterranean fever, cardiovascular diseases and malignancies.<sup>3,4,16-18</sup> During systemic inflammation, the release of cytokines, such as IL-1ra, IL-6, IL-7, IL-8, IL-12 and platelet derived growth factor (PDGF), is followed by neutrophil activation and elevation of NLR. NLR is a more stable measure than the individual neutrophil and lymphocyte counts, and is less affected by conditions which change the individual cell counts.<sup>19</sup> As far as the authors know, there is no study evaluating NLR in CSU patients. In the present study, NLR values were significantly higher in CSU patients compared with healthy controls. There was a positive correlation between the serum CRP and NLR levels in CSU patients. According to the clinical disease activity, there was no statistically significant difference in NLR values. There may be two explanations for this; first, NLR may really not be related to disease severity; and second, the small number of subjects and the variations of subgroup numbers may be responsible for the result.

Uric acid is the end product of purine metabolism in humans and higher primates.<sup>6</sup> There are epidemiological studies showing a relationship between SUA levels and the markers of systemic inflammation.<sup>20,21</sup> In several population-based studies, in healthy men and women, and also in patients with metabolic syndrome and patients with chronic heart failure, SUA has been shown to be positively correlated with CRP, IL-6 and TNF-alpha.<sup>6,20-24</sup> Recently, an association between hyperuricaemia and HT, atherosclerosis, cardiovascular diseases and chronic kidney diseases has been observed in several studies.<sup>20</sup> Epidemiological studies have demonstrated a close relationship between SUA levels and the prevalence of metabolic syndrome or its components, independent of classical risk factors.<sup>25</sup>

In the present study, the data did not show a statistically significant difference of SUA levels between CSU patients and healthy controls. SUA levels were associated neither with CRP nor with NLR. It may be due to different pathophysiologi-

cal pathways, rather than uric acid, playing a key role in the inflammation of CSU.

In this study, a positive correlation between the UAS scores and the disease duration was observed. With this information, it can be hypothesised that severe disease activity and increased inflammation may contribute to prolong the duration of the disease.

Interferon- (IFN-)  $\lambda$ 1, interleukin (IL)-18, pentraxin, IL-6, IL-13, CRP are some of the inflammatory biomarkers that have been shown to be elevated in CSU.<sup>26-30</sup> To the knowledge of the authors, this is the first study to compare CRP, NLR and SUA levels in patients with CSU with healthy controls. Additionally, this study is unique in investigating the relationship between the clinical activity of the disease and these inflammatory parameters. However, this study has some limitations, such as cross-sectional design and data on smoking that relied on patient self-reporting. Moreover, the lack of high sensitive (hs) CRP which is a more sensitive biomarker than CRP showing inflammation and the absence of autologous serum skin test performance are the other limitations of the study. NLR and CRP might be considered as inflammatory markers in CSU because they are easily accessed in daily routine measurements and are cost effective methods. It is known that increased levels of inflammatory biomarkers in systemic diseases is

also an indicator of ongoing inflammation in the body. It is not known if the elevated biomarkers in CSU might also be a predictor for the development of possible accompanying systemic inflammatory diseases in the future. Recently, inflammation has been identified as an independent risk factor for cardiovascular diseases.<sup>31</sup> An association between increased CRP levels, neutrophil activation, chronic systemic inflammation and risk for cardiovascular diseases has already been reported in the literature.<sup>32,33</sup> Specifically NLR and serum CRP levels, which were found to be elevated in CSU patients in the present study, have shown to be prognostic and predictor markers in cardiovascular diseases. What we discuss here is, if the patients with CSU without any systemic, inflammatory or autoimmune diseases might be under the risk of development of cardiovascular diseases in the future. Besides the traditional cardiovascular risk factors, NLR and CRP might be predictors of possible cardiovascular diseases among CSU patients who are already in a state of inflammatory disease. So far as this study has found, there is no information in the literature describing whether or not higher CRP and NLR levels in CSU patients are associated with any cardiovascular disease risks.<sup>1</sup> It can still not yet be concluded if CSU is a disease just affecting the skin, or one with systemic comorbidities. To confirm these findings, larger studies are required in the future.

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