

## Evaluation of Neutrophil to Lymphocyte Ratio in Patients with Chronic Spontaneous Urticaria

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### ABSTRACT

**Background:** Chronic spontaneous urticaria (CSU) is an immune-inflammatory disorder. The urticaria activity score (UAS 7) is used to assess urticaria activity. The neutrophil to lymphocyte ratio (NLR) is a reliable indicator for inflammatory conditions. Parameters useful for the evaluation of patients with CSU are not currently available.

**Objectives:** To assess NLR in CSU patients and its correlation with urticaria activity score.

**Patients and methods:** Of the patients attending the allergy clinic of Ain Shams University Hospital, 200 patients with CSU, including 62 patients with mild disease, 68 with moderate disease, and 70 with severe disease according to urticaria activity score 7 (UAS7), and 200 controls, were included in this study. NLR values were compared among various study groups.

**Results:** NLR values were significantly higher among CSU patients than controls ( $p < 0.001$ ), with no significant correlation with urticaria activity score.

**Conclusion:** NLR is a rapid, simple, and low-cost blood marker that can be used to detect systemic inflammatory processes in patients with CSU.

**Keywords:** Neutrophil to lymphocyte ratio, Chronic spontaneous urticaria, Urticaria activity score.

### INTRODUCTION

Chronic urticaria (CU) is a mast cell-driven dermal disease, presented by at least 6 weeks of daily or intermittent itchy wheals with or without angioedema<sup>(1)</sup>. Chronic spontaneous urticaria (CSU) is the most prevalent type of chronic urticaria. CSU occurs spontaneously in the absence of any definite stimulus<sup>(1)</sup>. The urticaria activity score (UAS 7) is a frequently used patient-reported CSU score based on symptoms, such as the number of hives and severity of pruritis, to assess disease activity and therapy response<sup>(1)</sup>.

Therefore, the UAS7 lacks objectivity, so different markers have been studied to evaluate the activity of the disease.

Mast cells are the key cells in CSU pathogenesis. However, various inflammatory cells, including basophils, eosinophils, T-lymphocytes, and neutrophils, are essential in the pathogenesis of CSU<sup>(2)</sup>

The neutrophil-lymphocyte ratio (NLR) is the division of absolute neutrophil count by absolute lymphocyte count. It is a simple, cheap, and easily accessible hemogram, which increases in a lot of inflammatory disorders, such as diabetes mellitus, ulcerative colitis, and psoriasis<sup>(3-5)</sup>. Correlations between parameters of inflammation such as NLR and disease severity or activity have been defined in other skin disorders<sup>(6-7)</sup>.

The aim of the current study is to evaluate NLR in CSU patients and its correlation with UAS7.

### PATIENTS AND METHODS

A case-control study was conducted on 200 CSU patients presenting to the allergy clinic of Ain Shams University Hospital, and 200 healthy control volunteers without any dermatological or systemic disease, matched for gender and age, were included in this study. Any

triggers or causes of chronic spontaneous urticaria were ruled out by history and proper investigations for all patients. Patients were diagnosed according to EAACI/GA2LEN/EDF/WAO guideline<sup>(1)</sup>.

Each patient underwent the following investigations to exclude other causes of chronic urticaria: differential blood count, C-reactive protein (CRP), antithyroid antibodies, thyroid function tests, and erythrocyte sedimentation rate (ESR). Patients with acute or chronic infection, autoimmune disease, acute or chronic inflammation, tumors, any other dermatological or systemic disorder, or pregnant women were excluded from this study.

Also, patients on immunosuppressive drugs, omalizumab, or corticosteroid treatment for CSU, as well as smokers or alcoholic patients, were excluded. The body mass index (BMI) was within the normal range for all subjects.

### Assessment of urticaria activity score (UAS7):

According to the EAACI/GA2LEN/EDF/WAO guideline<sup>(1)</sup>, urticaria activity is determined by urticaria activity score 7. Itching and hives (wheals), the two main urticaria symptoms, are evaluated by the UAS7.

Depending on the number of wheals and the level of pruritis, the UAS7 values were assessed during the previous 7 days. Then the scores of wheals and pruritis were summed up over seven days (minimum score 0–maximum score 42). UAS7  $\leq 6$  is considered a controlled urticaria, UAS7 (7–15) is a mild urticaria, UAS7 (16–27) is a moderate urticaria, and UAS7 (28–42) is a severe urticaria<sup>(8)</sup>.

### Assay of NLR:

For all participants, blood samples were drawn and analyzed using (Sysmex XN-1000, Sysmex corp., Japan) hematology analyzer. Total and differential white blood cell counts were assessed in terms of the

NLR by division of the absolute neutrophil count by the absolute lymphocyte count.

**Ethical consent:**

This study was ethically approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Ain Shams University. Written informed consent was taken from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

**Statistical analysis**

For all statistical tests, the Statistical Package for Social Sciences (IBM SPSS) version 23 was used. The parametric distribution of the quantitative variables was expressed by the mean, standard deviations (SD), and range, while the non-parametric distribution was expressed by the median and interquartile range (IQR). The qualitative variables were represented by numbers and percentages. The chi-square test was used to

compare between groups regarding qualitative data. The independent t-test was used to compare two independent groups with quantitative data and parametric distribution, while the Mann-Whitney test was performed to compare two independent groups with quantitative data and non-parametric distribution.

For comparison of more than two independent groups with quantitative data and a non-parametric distribution, the Kruskal-Wallis test was used. The correlation between two parameters within the same group was assessed using Spearman correlation coefficients. P value  $\leq 0.05$  was considered significant.

**RESULTS**

Of the 200 CSU patients, 65% were females and 35% were males; all patients were within the age group of 18–56 years. Of the 200 controls, 60% were females and 40% were males; all controls were within the age group of 18–55 years. Patients and controls were comparable in age and sex with no significant difference (Table 1).

**Table (1):** Gender and age distributions of all participants

Variable		Control group	Cases group	Test value	P-value
		No. = 200	No. = 200		
Age	Mean $\pm$ SD	33.04 $\pm$ 10.01	32.13 $\pm$ 9.57	0.929•	0.353
	Range	18 – 55	18 – 56		
Gender	Females	120 (60.0%)	130 (65.0%)	1.067*	0.302
	Males	80 (40.0%)	70 (35.0%)		

•: Independent t-test; \*: Chi-square test SD: standard deviation

As shown in table 2, there was no statistically significant difference in WBC count between CSU patients and controls, but there was a statistically significant difference in absolute lymphocyte count, absolute neutrophil count, and NLR. In CSU patients, NLR values were higher than in controls ( $p < 0.001$ ).

**Table (2):** Comparison of NLR and other laboratory findings between patients and controls.

Variable		Control group	Cases group	Test value	P-value
		No. = 200	No. = 200		
WBC count ( $\times 10^3/\mu\text{L}$ )	Median (IQR)	7.1 (5.9 - 8.5)	7.65 (5.95 - 9.1)	-1.565 $\neq$	0.117
	Range	3.9 – 11	3.1 – 14.5		
Absolute neutrophil count ( $\times 10^3/\mu\text{L}$ )	Median (IQR)	3.9 (3.1 - 4.71)	4.61 (3.4 - 5.58)	-4.373 $\neq$	<0.001
	Range	2.14 – 6.7	1.82 – 10.21		
Absolute lymphocyte count ( $\times 10^3/\mu\text{L}$ )	Median (IQR)	2.51 (2.08 - 2.9)	1.89 (1.4 - 2.64)	-6.394 $\neq$	<0.001
	Range	1.3 – 4.84	0.5 – 7.35		
NLR	Median (IQR)	1.5 (1.16 - 1.9)	2.05 (1.6 - 3.37)	-7.878 $\neq$	<0.001
	Range	0.7 – 3	0.76 – 11		

$\neq$ : Mann-Whitney test

WBC; white blood cells; IQR; inter-quartile range; NLR neutrophils to lymphocyte ratio

Regarding the urticaria activity, 62 CSU patients had mild urticaria, 68 had moderate urticaria, and 70 had severe or intense urticaria. There was no significant relation between WBC count, absolute lymphocyte count, absolute neutrophil count, NLR values, and urticaria activity. NLR did not differ significantly between severe urticaria cases and mild or moderate cases (Table 3).

**Table (3): Relation of NLR and differential WBC count with urticaria activity.**

Variable		Mild cases	Moderate cases	Severe cases	Test value	P-value
		No. = 62	No. = 68	No. = 70		
WBC count (x 10 <sup>3</sup> /μL)	Median (IQR)	7.4 (6.0 – 8.8)	8.0 (6.1 – 10.5)	7.7 (5.8 – 9.0)	3.812 <sup>‡</sup>	0.149
	Range	3.5 – 10.5	3.1 – 14.5	4.3 – 13.8		
Absolute neutrophil count (x 10 <sup>3</sup> /μL)	Median (IQR)	4.56 (3.3 – 5.17)	4.81 (3.36 – 6.75)	4.31 (3.44 – 5.61)	2.682 <sup>‡</sup>	0.262
	Range	2.1 – 7.9	1.82 – 9.75	2.06 – 10.21		
Absolute lymphocyte count (x 10 <sup>3</sup> /μL)	Median (IQR)	1.82 (1.3 – 2.62)	1.96 (1.34 – 2.69)	1.90 (1.65 – 2.64)	1.312 <sup>‡</sup>	0.519
	Range	0.5 – 4.73	0.72 – 7.35	0.79 – 3.83		
NLR	Median (IQR)	2.00 (1.66 – 3.80)	2.12 (1.60 – 3.43)	2.10 (1.63 – 3.20)	0.009 <sup>‡</sup>	0.996
	Range	0.76 – 7.3	0.8 – 11	0.89 – 8.67		

<sup>‡</sup>: Kruskal-Wallis test

There was no statistically significant correlation between NLR and urticaria activity score, with p-value = 0.229 and r = -0.085 (Table 4).

**Table (4): Correlation between NLR and urticaria activity score (UAS7).**

Variable	Urticaria activity score (UAS7)	
	R	P-value
NLR	-0.085	0.229

r: Spearman correlation coefficients.

## DISCUSSION

Chronic urticaria (CU) is an inflammatory disorder of the skin characterized by the degranulation of mast cells with infiltration of other inflammatory cells such as neutrophils, basophils, and lymphocytes (2). The final common pathway for CSU pathogenesis is thought to be the release of proinflammatory mediators (9-10).

The CU is divided into inducible and spontaneous types according to recent classification. CSU is the commonest type of chronic urticaria that develops without a definite trigger (1).

NLR is a novel peripheral blood parameter to detect systemic inflammation. It has been studied in different inflammatory and autoimmune diseases such as familial Mediterranean fever and psoriasis (5,11).

In this study, the age of CSU patients was between 18 and 56 years; 35% were males, and 65% were females. Females are more susceptible to chronic urticaria (12), which is why they are the majority of participants in this study.

A few recent studies have assessed NLR in CSU. In the current study, the author found that the level of neutrophil to lymphocyte ratio was significantly higher in CSU patients in comparison to controls. In agreement with this finding, Karabay *et al.* (13) found an increase in NLR in CSU patients compared to controls. Akca *et al.* (14) also found the neutrophil/lymphocyte ratio to be higher in CSU patients than in the control group. Also,

Sarce *et al.* (15) found high NLR values in patients with chronic urticaria in comparison to controls. Moreover, Karaman *et al.* (16) in children found that elevation in the neutrophil/lymphocyte ratio was associated with a poor prognosis in children with CSU.

Higher levels of NLR were observed by Ertas *et al.* (17) in patients with severe CSU compared to controls, although this result was not statistically significant. On the other hand, the reduction in the NLR during the treatment of CSU patients with omalizumab was statistically significant.

Acer *et al.* (18) also reported that following omalizumab therapy, NLR levels in patients with CSU had lowered. This result can be interpreted as a reduction in the inflammatory process while receiving treatment for CSU (17,18).

In contrast, Duman *et al.* (19) conducted a study on 46 children with CU and 30 healthy children. They did not find a significant difference in NLR between CU patients and controls, but it was a retrospective study with a small number of patients and a different age group than the present study. Also, NLR was not compared between the equal number of cases and controls.

Regarding urticaria activity, Karabay *et al.* (13) found no significant relation between NLR and urticaria activity. Akca *et al.* (14) also found no significant correlation between NLR and UAS7. Similarly, the author also did not find a significant correlation

between NLR and urticaria activity score. NLR values did not differ significantly with urticaria activity. Although the NLR may not be related directly to CSU activity, more studies are needed.

The limitations of the present study include the small sample size and the small number of patients in the subgroups. Therefore, more research on a larger number of cases is needed.

The strength of the current study includes that any infections, inflammatory conditions, or drugs that could affect NLR were excluded.

## CONCLUSION

CSU is correlated with systemic inflammation. NLR is elevated among CSU patients, with no correlation with disease activity.

**Conflict of interest:** Nil .

**Funding:** Nil.

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