ORIGINAL REPORT

Increased Neutrophil–Lymphocyte Ratio and Platelet–Lymphocyte Ratio in Chronic and Severe Urticaria

Sarah WEISSMANN[1,2], Nitzan BURRACK[1,2], Inbal GOLAN-TRIPTO[1,3#] and Amir HOREV[1,4#]
[1]Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, [2]Clinical Research Unit, Beer Sheva, [3]Pediatric Pulmonary Unit, and [4]Pediatric Dermatology Service, Soroka University Medical Center, Beer Sheva, Israel
[#]These authors contributed equally to this manuscript

Chronic spontaneous urticaria (CSU) is a disturbing skin condition often severely detrimental to quality of life. Haematological markers of inflammation such as neutrophil-to-lymphocyte and platelet-to-lymphocyte may be used in the assessment of inflammatory skin diseases. Their usefulness in urticaria is unknown. Neutrophil-to-lymphocyte, platelet-to-lymphocyte, and total serum IgE were investigated in urticaria patients: acute spontaneous urticaria (ASU) versus CSU, children versus adults with CSU, and patients with mild-to-moderate versus severe CSU. This retrospective cohort study included patients of all ages diagnosed with urticaria between 2005 and 2020 and blood counts within 30 days of diagnosis. Patients with comorbidities influencing blood cells (infection, surgery, malignancy) were excluded. Neutrophil-to-lymphocyte and platelet-to-lymphocyte were evaluated in patients with ASU vs CSU and mild-to-moderate CSU vs severe CSU (defined by the use of systemic medications or hospitalizations). A total of 13,541 urticaria patients were included in the study. CSU patients ($n = 5,021$) had higher neutrophil-to-lymphocyte and platelet-to-lymphocyte, as well as serum IgE levels compared with ASU patients ($n = 8,520$). Adults had higher neutrophil-to-lymphocyte and platelet-to-lymphocyte than children. Severely affected patients ($n = 53$) had higher neutrophil-to-lymphocyte and platelet-to-lymphocyte compared with mild-to-moderately affected patients ($n = 4,968$). Patients with higher neutrophil-to-lymphocyte and platelet-to-lymphocyte had higher odds of having CSU rather than ASU and severe urticaria rather mild-to-moderate. In conclusion, neutrophil-to-lymphocyte and platelet-to-lymphocyte are simple and available markers that can be used to predict and assess severe and chronic urticaria.

Key words: neutrophil–lymphocyte ratio; platelet–lymphocyte ratio; chronic urticaria; national data.

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Corr: Sarah Weissmann, Faculty of Health Sciences, Soroka University Medical Center, Yitzhack I. Rager Blvd 151, POB 151, Beer Sheva 84101, Israel. E-mail: grzebins@post.bgu.ac.il

SIGNIFICANCE

This study sheds light on chronic spontaneous urticaria (CSU), a distressing skin condition impacting quality of life. Researchers examined common blood markers, neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, and found that higher ratios correlate with CSU and its severity, aiding in early detection and treatment. This insight offers a simple and accessible method for clinicians to better manage and understand this challenging skin disorder, ultimately improving patient care and well-being.

Urticaria is a skin condition defined as the development of wheals (hives), angioedema, or both (1). It is a common skin disorder affecting 15–20% of the general population at some point in their lifetime (2). Urticaria may be classified based on its duration (acute or chronic urticaria) and based on triggers (inducible or spontaneous urticaria). Acute urticaria is defined as the occurrence of wheals, angioedema, or both for 6 weeks or less while chronic urticaria occurs for more than 6 weeks. Inducible urticaria is defined by the development of wheals, angioedema, or both with definite and subtype-specific triggers. Wheals, angioedema, or both always occur in the presence of the trigger and never occur without the trigger subtypes of inducible urticaria include cholinergic urticaria, symptomatic dermographism, cold urticaria, and delayed-pressure urticaria (1). Spontaneous urticaria is defined as the presence of wheals, angioedema, or both due to known or unknown causes (1). Chronic spontaneous urticaria (CSU) is therefore defined as the appearance of wheals, angioedema, or both for >6 weeks due to known or unknown causes.

The pathophysiology of urticaria is primarily driven by mast cells (3). Histamine, platelet-activating factor (PAF), and cytokines are released from activated mast cells, resulting in sensory nerve activation, vasodilatation, plasma extravasation, and recruitment to urticaria lesion sites. The mast cell-activating signals in urticaria include T cell-driven cytokines and autoantibodies. Histologically, CSU presents with inflammatory infiltrate composed of neutrophils, eosinophils, T-helper lymphocytes, and activated macrophages (4).

Inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been used in the prediction of the presence and severity of inflammatory diseases, cardiovascular diseases, and cancer (5). Increased neutrophil and plate-

let counts compared with lymphocyte counts have been used to indicate acute inflammation in particular. It has been suggested that the inflammatory processes in acute inflammation stimulate the production of neutrophils while increasing the apoptosis rate of lymphocytes, causing an increased NLR (6). There are associations between NLR and urticaria, atopic dermatitis, psoriasis vulgaris, lupus erythematosus, vitiligo, rosacea, erythema nodosum, and dermatomyositis, among other inflammatory dermatological diseases (7). Studies have found correlations between NLR and severity indices of inflammatory conditions such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Psoriasis Area and Severity Index (PASI) scores (8). Due to the presence and pathogenesis of inflammatory cells in urticaria, we hypothesized that NLR and PLR will be elevated in patients with urticaria and may be used as a predictor for disease severity.

The main objective of this study was to evaluate the values of NLR and PLR among patients with urticaria in Southern Israel. In addition, we aimed to investigate IgE levels and: (1) compare these values between patients with ASU and CSU, (2) compare these values between children and adults with CSU, and (3) investigate these values according to CSU disease severity.

MATERIALS AND METHODS

Study design

This was a retrospective, semi-national cohort study including patient data from 2005 until 2020. Patients of all ages diagnosed with urticaria, either insured within the southern district of Clalit Health Maintenance Organization (HMO) or seen at Soroka University Medical Center (SUMC) were included. Clalit HMO is the largest public healthcare provider organization in Israel and serves more than half of Israel's population, covering 0.75 million people in the southern district. SUMC is a 1,200-bed tertiary hospital serving a large geographic area in Southern Israel. The study was approved by the Soroka University Medical Center Ethics Committee (No. 0434-15-SOR) and performed in accordance with all relevant guidelines and regulations.

Study population and blood count parameters

Children (aged 0–17 years) and adults diagnosed with urticaria, who were insured by Clalit HMO or visited SUMC, were included in this study. We obtained demographic and medical information recorded by the primary care physicians and/or the Admission-Discharge-Transfer (ATD) hospital system of SUMC. Data were extracted using Clalit's data-sharing platform powered by MDClone software (https://www.mdclone.com/). MDClone is a big-data platform with data-synthesizing capabilities. The diagnoses of urticaria were made by the patient's primary physician or a dermatologist and included in our study according to ICD-9 codes. We included all patients diagnosed with spontaneous urticaria. We excluded patients with inducible urticaria including cholinergic, symptomatic dermographism, cold, and delayed-pressure urticaria ICD-9 diagnoses. In order to exclude patients with comorbidities that may influence their blood count ratios, we excluded patients with ICD-9 codes indicating acute or chronic infections, malignancies, or a history of surgery within 30 days of their blood test. NLR and PLR were calculated from complete blood counts within 30 days of the first recorded urticaria diagnosis and 12–18 months before the urticaria diagnosis for a baseline comparison. Total serum IgE was taken from available medical records within the same time period. Blood parameters were determined using Siemens Advia i2120 (Siemens Healthineers, Erlangen, Germany) devices and Sysmax XN1000/XN2000 (Sysmex, Milton Keynes, UK). Patients with no blood tests within 30 days of their urticaria diagnosis were excluded.

Patients were classified as having either acute spontaneous urticaria (ASU) or chronic spontaneous urticaria (CSU). Patients were considered to have CSU if they had more than 2 separate recorded diagnoses of urticaria within a 6-week period. Though the standard definition of CSU is characterized by the presence of recurrent urticaria and/or angioedema for a period of 6 weeks or longer, we defined CSU using available data variables in accordance with previous literature (9). CSU patients were further subgrouped into mild-to-moderate and severe groups, and children and adults. Patients were considered to have severe CSU if they purchased systemic medications for urticaria after their diagnosis, either before or after their blood test (cyclosporin, dupilumab, methotrexate, mycophenolate, or omalizumab) ($n=53$) or were hospitalized for urticaria ($n=4$) and the remaining patients were considered to have mild-to-moderate CSU.

Patients' records included a baseline event (urticaria diagnosis), age, gender, socioeconomic status (SES), ethnicity, and insurance. In addition, neutrophil count, lymphocyte count, platelet count, and IgE levels were all recorded from laboratory results at the time of urticaria diagnosis as well as 12–18 months before. NLR and PLR for each lab result were calculated by dividing the neutrophil count and platelet count by the lymphocyte count, respectively.

Statistical analysis

Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U* test for variables not meeting normal distribution assumptions. Categorical variables were compared using the χ^2 test or Fisher's exact test. For the multivariable logistic regression, we took the range of NLR and PLR and divided it into quartiles. The association between variables was estimated with Spearman's rho test, and a multivariable logistic regression was subsequently performed, adjusted for age, gender, ethnicity, and socioeconomic status. We used 95% confidence intervals (95% CI), and a two-sided p-value <0.05 to indicate statistically significant. All statistical analyses were conducted using R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 13,541 patients with urticaria were included in this study: 8,520 (62.9%) with ASU and 5,021 (37.1%) with CSU. Demographic and clinical characteristics and laboratory parameters of the patients with urticaria (acute and chronic) are summarized in **Table I**. The mean age of patients with ASU was 33.46 ± 23.03 years, and the mean age of patients with CSU was 33.79 ± 21.34 years, with no significant difference. The minority of patients in both groups were male: 3,123 (36.7%), and 1,852 (36.9%) with ASU versus CSU, respectively. The socioeconomic score was determined by the National Institute for Statistics according to the zip code of the patient. A higher percentage of patients with ASU had a lower

Table I. Descriptive statistics of clinical, demographic, and laboratory characteristics of patients with acute urticaria compared with patients with chronic urticaria

Factor	Acute $n=8,520$	Chronic $n=5,021$	p-value
Gender, male, n (%)[a]	3,123 (36.7)	1,852 (36.9)	0.803
Age, years, mean (SD)[b]	33.46 (23.03)	33.79 (21.34)	0.401
Socioeconomic score, n (%)[a]			<0.001
High	1,181 (13.9)	741 (14.8)	
Medium	4,774 (56.0)	2,973 (59.2)	
Low	1,609 (18.9)	801 (16.0)	
No data	956 (11.2)	506 (10.1)	
Ethnicity (%)[a]			<0.001
Arab	1,620 (19.0)	730 (14.5)	
Jewish	6,719 (78.9)	4,175 (83.2)	
Other	157 (1.8)	110 (2.2)	
NLR, mean (SD)[b]	2.41 (3.82)	2.99 (5.23)	<0.001
PLR, mean (SD)[b]	125.98 (96.04)	134.46 (98.90)	<0.001
IgE, IU/mL, mean (SD)[b]	221.97 (370.09)	311.43 (1233.79)	0.014
NLR[c], mean (SD)[b]	2.25 (2.12)	2.30 (5.49)	0.616
PLR[c], mean (SD)[b]	124.11 (62.65)	127.16 (211.00)	0.423

[a]χ^2 test. [b]Student's t-test. [c]12–18 months before.
SD: standard deviation; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio.

socioeconomic score than those with CSU ($p<0.001$). In addition, a higher percentage of patients with ASU were Arab compared with CSU patients (19.0% vs 14.5%, $p<0.001$). It total, 5,446 patients had a record of NLR 12–18 months before diagnosis, and 5,479 patients had a record of PLR 12–18 months before diagnosis.

We found that patients with CSU had higher NLR, PLR, and serum IgE than ASU patients (2.99 vs 2.41, 134.46 vs 125.98, $p<0.001$, and 311.43 vs 221.97, $p=0.014$, respectively). Blood count ratios did not significantly differ between ASU and CSU, 12 to 18 months before diagnosis.

Children and adults with CSU are compared in **Table II**. The majority of patients with CSU were adults ($n=3,760$, 74.8%) with a mean age of 42.47 years, and the remaining patients were children ($n=1,261$, 25.2%) with a mean age of 7.95 years. Some 53.2% of children with CSU were male, while only 31.4% of adults were male. A higher percentage of children were in the lower socioeconomic status group compared with adults, and a higher percentage of children were Arab compared with adults. Adults had higher NLR and PLR than children (3.23 vs 2.28, 140.33 vs 116.97, $p<0.001$). Adults also had higher NLR and PLR 12–18 months before diagnosis (2.41 vs 1.56, $p=0.018$ and 131.15 vs 102.46, $p=0.036$, respectively).

Table II. Descriptive statistics of clinical, demographic, and laboratory characteristics of patients with chronic urticaria, stratified by age group

Factor	Adults $n=3,760$	Children $n=1,261$	p-value
Gender, male, n (%)[a]	1,179 (31.4)	673 (53.2)	<0.001
Age, years, mean (SD)[b]	42.46 (17.25)	7.95 (5.80)	<0.001
Socioeconomic score, n (%)[a]			<0.001
High	583 (15.5)	158 (12.5)	
Medium	2,287 (60.8)	686 (54.4)	
Low	559 (14.9)	242 (19.2)	
No data	331 (8.8)	175 (13.9)	
Ethnicity, n (%)[a]			<0.001
Arab	477 (12.7)	253 (20.1)	
Jewish	3,202 (85.2)	973 (77.2)	
Other	80 (2.1)	30 (2.4)	
Severity, n (%)[a]			<0.001
Mild-to-moderate			
Severe	15 (0.4)	38 (3.0)	
NLR, mean (SD)[b]	3.23 (3.38)	2.28 (8.61)	<0.001
PLR, mean (SD)[b]	140.33 (81.23)	116.97 (137.38)	<0.001
IgE, IU/mL, mean (SD)[b]	306.60 (1431.59)	322.42 (567.59)	0.829
NLR[c], mean (SD)[b]	2.41 (5.85)	1.56 (1.82)	0.018
PLR[c], mean (SD)[b]	131.15 (226.21)	102.46 (51.12)	0.036

[a]χ^2 test. [b]Student's t-test. [c]12–18 months before.
SD: standard deviation; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio.

Characteristics and blood parameters of patients with mild-to-moderate and severe CSU ($n=5,021$) can be seen in **Table III**. A minority of patients ($n=53$, 1.06%) with CSU were considered to have severe urticaria. Patients with severe CSU were significantly younger than patients with mild-to-moderate urticaria (average age of 18.9 years vs 33.95 years, respectively, $p<0.001$). In addition, a higher percentage of severe CSU patients were considered to have lower socioeconomic status (24.5% vs 15.9%, $p=0.017$). Patients with severe CSU had significantly higher NLR and PLR compared with mild-to-moderate CSU patients at the time of diagnosis (4.94 vs 2.97, $p=0.006$, and 165.62 vs 134.13, $p=0.021$, respectively). Other blood parameters did not significantly differ between groups.

Through multivariable analysis controlled for age, gender, ethnicity, and socioeconomic status (**Tables IV and V, and Figs 1–2**), we observed that patients with NLR and PLR in the highest quartile (NLR above 2.89 and PLR above 151) had higher odds of having severe urticaria rather than mild urticaria (OR 2.98, OR 1.54, $p<0.001$, $p=0.003$, respectively). We found that patients with NLR and PLR in the highest quartile (NLR above 2.89 and PLR above 151) also had higher odds of having

Table III. Descriptive statistics of clinical, demographic, and laboratory characteristics of patients with chronic urticaria, stratified by severity group

Factor	Mild-to-moderate $n=4,968$	Severe $n=53$	p-value
Gender, male, n (%)[a]	1,827 (36.8)	18.99 (24.04)	0.156
Age, years, mean (SD)[b]	33.95 (21.26)	18.9 (24.04)	<0.001
Socioeconomic score, n (%)[a]			0.017
High	738 (14.9)	3 (5.7)	
Medium	2,946 (59.3)	27 (50.9)	
Low	788 (15.9)	13 (24.5)	
No data	496 (10.0)	10 (18.9)	
Ethnicity, n (%)[a]			0.226
Arab	717 (14.4)	13 (24.5)	
Jewish	4,136 (83.3)	39 (73.6)	
Other	109 (2.2)	1 (1.9)	
NLR, mean (SD)[b]	2.97 (5.16)	4.94 (9.59)	0.006
PLR, mean (SD)[b]	134.13 (98.06)	165.62 (157.36)	0.021
IgE, IU/mL, mean (SD)[b]	309.93 (1,235.67)	534.26 (938.08)	0.587
NLR[c], mean (SD)[b]	2.30 (5.51)	1.99 (1.43)	0.826
PLR[c], mean (SD)[b]	127.13 (211.75)	132.14 (56.81)	0.927

[a]χ^2 test. [b]Student's t-test. [c]12–18 months before.
SD: standard deviation; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio.

Table IV. Regression for severe urticaria by quartile

Characteristic	OR	95% CI	*p*-value
NLR			
Q1			
Q2	0.88	0.61, 1.26	0.5
Q3	1.31	0.93, 1.84	0.12
Q4	2.98	2.22, 4.04	<0.001
PLR			
Q1			
Q2	0.79	0.57, 1.08	0.14
Q3	0.87	0.63, 1.19	0.4
Q4	1.54	1.16, 2.04	0.003

OR: odds ratio; CI: confidence interval.

Table V. Regression for chronic urticaria

Characteristic	OR	95% CI	*p*-value
NLR			
Q1			
Q2	1.09	0.98, 1.21	0.10
Q3	1.20	1.08, 1.33	<0.001
Q4	1.73	1.56, 1.92	<0.001
PLR			
Q1			
Q2	0.97	0.87, 1.07	0.5
Q3	1.01	0.92, 1.12	0.8
Q4	1.24	1.12, 1.37	<0.001

OR: odds ratio; CI: confidence interval.

CSU rather than ASU (OR 1.73, OR 1.24, $p<0.001$, respectively).

DISCUSSION

In this study, we evaluated the values of NLR, PLR, and total serum IgE among patients with ASU and CSU in a large semi-national cohort. We found significant differences in blood count parameters between patients with ASU and CSU, children and adults with CSU, and mild-to-moderate and severe CSU patients. In addition, we demonstrated that patients with higher NLR and PLR 12–18 months before urticaria diagnosis had higher odds of developing CSU from ASU.

Baseline characteristics demonstrated that most patients suffering from both ASU and CSU were females. This finding is consistent with previous studies, which suggest an average female-to-male ratio of 2 to 4 females to 1 male (10).

Our data reveal that a significantly higher percentage of patients with acute urticaria and severe urticaria had a lower socioeconomic score compared with those with mild-to-moderate urticaria. It is possible that this finding reflects differences in environmental exposures, access to healthcare, and stressors associated with lower socioeconomic status, all of which could influence the severity of urticaria and the presence of acute urticaria (11). Additionally, we found that a higher proportion of acute urticaria patients were Arab. This may be because of different environmental exposures and access to healthcare as well. Previous literature has similarly noted that CSU is associated with higher socioeconomic status (12).

Our findings indicated that patients with CSU had higher NLR, PLR, and IgE than those with ASU. These are markers that may be used to indicate inflammation. The proposed underlying pathogeneses of CSU are thought to include autoimmunity, autoallergy, pro-inflammation, and pro-coagulation states. These states, over long periods, may contribute to the increase in inflammatory parameters NLR and PLR. A previous study including 52 patients by Karaman et al. similarly suggested that NLR is positively correlated with chronic spontaneous urticaria disease duration (13) Interestingly, previous studies have not found significant associations between PLR and CSU. Total IgE, however, has been used previously as a marker in chronic spontaneous urticaria and is further associated with higher disease activity and longer disease duration, as well as a higher likelihood of responding to Omalizumab and a decreased likelihood of responding to cyclosporine (14).

Adults with CSU had higher NLR and PLR than children with CSU. Our findings regarding increased

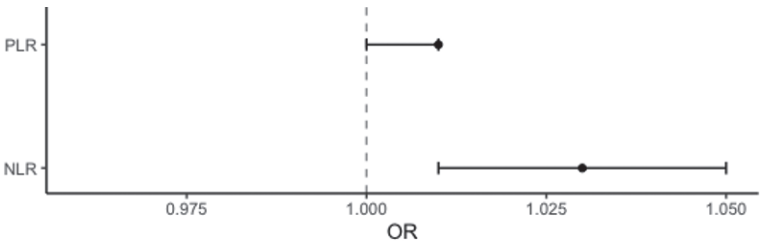

Fig. 1. Multivariable regression for severe chronic urticaria.

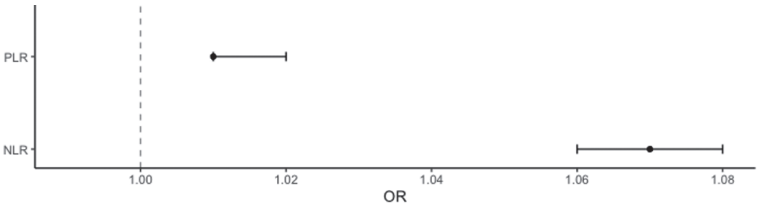

Fig. 2. Multivariable regression for chronic spontaneous urticaria (CSU).

NLR in adults are similar to those in patients with atopic dermatitis and brucellosis (15). However, this study did not find any significant difference in PLR between children and adults. Our findings may result from an increase in an acute neutrophilic inflammatory response in adults and/or an increase in apoptosis of lymphocytes under conditions of stress in adults.

Patients with severe CSU had significantly higher NLR and PLR at the time of diagnosis than patients with mild-to-moderate CSU. Our findings are again consistent with Karaman & Turedi (13), who demonstrated that an elevation in NLR was associated with poor prognosis of CSU. One previous study investigated inflammatory parameters in relation to urticaria severity according to the Urticaria Activity Score (UAS), a measure of severity based on the number of wheals and self-reported pruritis. However, they did not find a significant difference in NLR or high-sensitivity C-reactive protein (16). PLR is also known to be a common marker of the severity in disease. Our findings indicated a positive association between CSU severity and PLR; however, previous studies have found no such significant association (17). It is possible that our difference in findings is related to our definition of CSU severity. Due to our lack of recorded UAS indices, we used an alternative severity measure, as delineated earlier. It is also possible that our findings regarding NLR and PLR were significant compared with previous literature due to the large semi-national cohort we were able to use. Interestingly, we were not able to identify a significant difference in blood markers 12–18 months before diagnosis of severe CSU. This may indicate a pathogenesis and underlying systemic inflammation that occurs long before the initial clinical presentation of urticaria. We have demonstrated increased NLR and PLR in relation to urticaria severity. In the context of other dermatologic diseases, NLR and PLR have been shown to be associated with severity of atopic dermatitis, however negatively associated with psoriasis severity (18, 19).

Our multivariable analysis indicated that high NLR and PLR at the time of diagnosis are statistically significant in association with CSU compared with ASU and severe chronic urticaria compared with mild-to-moderate urticaria. Patients with NLR and PLR above 2.89 and 151, respectively, may alert physicians to a higher likelihood of developing CSU and severe CSU.

Limitations

Our study has a few limitations to be noted. First, the study population excluded patients with recorded infection, history of surgery, and malignancy before the blood test; however, we may have included patients with other conditions that may affect blood count values and patients may have had underlying infections not recorded in the medical records. Second, lab values were taken 30 days before and after the diagnosis of urticaria; however, it is uncertain whether the disease was present at that time or controlled due to external interventions. Additionally, it has been shown that smoking status impacts NLR, but we were unable to control for this. Finally, we included patients who were diagnosed with urticaria by primary care physicians in addition to board-certified dermatologists, so there may be differences in urticaria diagnosis criteria, including a lower percentage of severe patients within our population than expected. Due to the retrospective nature of the study, diagnoses were determined using ICD-9 codes and no patient-reported data on severity were available. However, to our knowledge, this is the first study to investigate blood count values in a semi-national population thoroughly, including patients with ASU and CSU, children and adults with CSU, and mild-to-moderate and severe CSU patients.

Conclusion

Novel findings regarding blood count ratios in urticaria were demonstrated in this study. We found that NLR and PLR significantly differed between patients with ASU and CSU, children and adults, and mild-to-moderate and severe CSU patients. We further demonstrated that high NLR and PLR at the time of diagnosis is associated with CSU as opposed to ASU. NLR and PLR can be used as markers for disease natural history and severity, providing an easy tool for physicians to use in the management and follow-up of patients with urticaria. Future studies are warranted to investigate underlying mechanisms of change in NLR and PLR in urticaria patients and create validated ranges and cut-off values of these parameters for proper use in the management and follow-up of urticaria patients.

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Study approval statement: This study protocol was reviewed and approved by the local Ethics Committee of SUMC, approval number (0434-15-SOR).

Consent to participate statement: This study has been granted an exemption from requiring informed written consent according to the Ethics Committee of SUMC, approval number (0434-15-SOR).

Data are available only on request due to privacy or other restrictions. For requests, please contact the corresponding author, Sarah Weissmann.

The authors have no conflicts of interest to declare.

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