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ORIGINAL PAPER

Analysis of blood count derivative parameters and selected biochemical and fibrinolysis parameters in children with urticaria

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ABSTRACT

Introduction: Urticaria is a common disease in the pediatric population. It is characterized by the presence of wheals, angioedema or coexistence of these changes. The pathomechanism of urticaria is associated with activation of the immune system, development of inflammation and changes in the coagulation system. The aim of the study was to analyze selected blood count parameters and their derivatives (neutrophil/lymphocyte ratio – NLR, platelet/lymphocyte ratio – PLR, mean platelet volume/platelet count ratio – MPR), C-reactive protein (CRP) and D-dimers in children with acute urticaria (AU) and chronic urticaria (CU) to assess their suitability for predicting the occurrence and activity of the disease.

Material and methods: We performed a retrospective analysis of the clinical data and selected laboratory results in 125 children with urticaria (76 with AU and 49 with CU) hospitalized in our center between 2013 and 2019. The control group consisted of 75 healthy children.

Results: Based on logistic regression analysis, we recorded an increased risk of AU and CU occurrence in the case of elevated NLR, neutrophil count, white blood cells (WBC), CRP and D-dimer values. Statistical analysis revealed that the best predictor of urticaria development was an increase in D-dimers (area under the curve –AUC = 0.84, sensitivity 86%, specificity 69%, cut-off 390.0). In patients with AU the disease activity was positively correlated with CRP ($r = 0.24$, $p = 0.04$) and D-dimer levels ($r = 0.28$, $p = 0.02$). In CU there was a positive correlation between disease activity and NLR ($r = 0.44$, $p < 0.001$), WBC ($r = 0.30$, $p = 0.04$) and CRP values ($r = 0.35$, $p = 0.01$).

Conclusions: Increased CRP, WBC, NLR, platelet and D-dimer levels reflect the activation of inflammation and fibrynolysis present in urticaria. Further studies are required to determine the utility of these parameters as biomarkers of urticaria activity in children.

KEY WORDS:

D-dimer, children, urticaria, biomarkers, C-reactive protein.

INTRODUCTION

Urticaria is a skin disease characterized by the presence of wheals, angioedema, or the coexistence of both symptoms [1]. Duration of skin lesions in acute urticaria (AU) does not exceed 6 weeks, whereas in chronic urticaria (CU) the lesions persist for more than 6 weeks [1]. Chronic urticaria can be classified as spontaneous urticaria (CSU) or as inducible urticaria – involving a specific triggering factor (e.g. cold, pressure, cholinergic stimulation) [1, 2]. Classified as spontaneous urticaria in some patients is associated with autoimmunity, however in most cases the cause of the disease remains unknown [3].

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The development of urticaria depends on the activation of mast cells and other immune cells [4, 5]. As a result of the degranulation of skin mast cells, histamine and other inflammatory mediators are released, which initiates the disease process [4–6].

The histopathological features of urticaria are skin edema, capillary dilation, and the formation of perivascular infiltrates composed of CD4+ lymphocytes, monocytes, neutrophils, eosinophils, and basophils [4]. In AU, approximately one hour after the onset of the wheal, mainly neutrophils are present in the infiltrate [7, 8].

Infections are the most common identified cause of AU in children [9, 10]. More rarely, AU is associated with hypersensitivity reactions to food and drugs [2, 11]. The pathogenesis of CU is multifactorial, involving activation of the immune mechanisms and coagulation disorders [4, 10, 12, 13]. It has been demonstrated that up to 40% of patients with CSU shows a positive result of the autologous serum skin test (ASST) [7]. In patients with CSU, the presence of autoantibodies specific either for the high-affinity IgE receptor (FcεRI) or for IgE is found [8].

Children and adults with AU and CU have increased levels of inflammatory markers and some coagulation markers, which are associated with the degree of disease activity [12, 14–16].

The white blood cells (WBC), neutrophil and lymphocyte count and neutrophil/lymphocyte ratio (NLR) are indicators of systemic inflammation. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio (PLR) and mean platelet volume/platelet count ratio (MPR) are markers that can be assessed easily and determine presence of systemic inflammatory response. These markers have been used to assess the severity of lesions in many diseases such as atopic dermatitis, IgA vasculitis, psoriasis, systemic lupus erythematosus, and cancer [17–21].

In the present study we evaluated selected blood morphology indices and their derivatives (NLR, PLR, MPR) as well as biochemical (C-reactive protein – CRP) and fibrinolysis (D-dimer) parameters in children with AU and CU to determine their usefulness in the assessment of disease occurrence and activity.

MATERIAL AND METHODS

STUDY POPULATION

The study included 125 children with urticaria: 76 subjects with AU and 49 subjects with CSU. Patients were hospitalized in 2013–2019. In each case the diagnosis of the disease was based on the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria [1], which include presence of wheals, angioedema, or both in a determined time period: acute (≤ 6 weeks) or chronic (> 6 weeks).

Urticaria activity was assessed using the total symptom score (TSS) [4, 22], which is defined as the sum of the scores for the number and size of wheals and severity of pruritus. The maximum diameter of the largest wheal was assessed according to the following scheme: 0 = 0, 1 = diameter ≤ 1.5 cm, 2 = diameter > 1.5 cm and ≤ 2.5 cm, 3 = diameter > 2.5 cm. The number of wheals was estimated consecutively as: 0 = no wheals, 1 ≤ 10 wheals, 2 ≥ 10 wheals, 3 = body covered with wheals. Severity of pruritus was scored as: 0 = absent, 1 = mild pruritus, 2 = moderate with slight disturbance of daily activities and/or sleep, 3 = intense unbearable itching with marked disturbance of daily activities and/or sleep. The control group (CG) consisted of 75 healthy children, selected in terms of age and gender. Children included into the CG attended the outpatient pediatric clinic for nonimmunological, noninflammatory health problems and needed venous puncture.

Patients with diagnoses of sepsis, immunological disorders, hematological diseases, genetic syndromes and patients using antihistamine treatment or systemic corticosteroids prior to blood sampling were excluded from the study. Retrospective data on the course of the disease, anthropometric data and results of additional, including laboratory tests were collected.

Informed consent was obtained from all study participants and/or their parents. The presented study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice on 26.02.2019 (decision no KNW/0022/KB1/6/I/19).

LABORATORY ANALYSIS

Venous blood samples for laboratory tests were collected on admission to the ward, before the administration of drugs that may modify the course of the disease. Samples were tested within the first hour after collection. Citrate tubes were used for D-dimer analysis, blood for the remaining laboratory test was collected into EDTA tubes. Complete blood count was determined by an automated method using an ABX Pentra XL 80. All laboratory parameters were determined with respect to age standards.

STATISTICAL DATA

Statistical evaluation was obtained using Statistica 13.1, Dell Inc. The descriptive statistical analysis was presented as median and quartiles (Q_{25}–Q_{75}). The Kruskall-Wallis test was used in the comparative analysis of groups, the normality of distribution was determined by Shapiro-Wilk test. Logistic regression analysis was performed to identify potential factors associated with the development of urticaria. The receiver operating curve (ROC) curve was determined to assess the sensitivity and specificity of analyzed variables. The correlation between the selected parameters was assessed using the Spearman's rank test. *P*-values lower than 0.05 were considered significant.

RESULTS

There were no significant differences in terms of age, gender and body mass index between the patient with urticaria and CG. The median length of hospitalization for patients with AU was 5 days, for CU 4 days. Children with AU were the predominant group (n = 76; 60.8%). Chronic urticaria was diagnosed in 39.2% (n = 49) of patients. In the CU group, ASST positivity was present in 16% (n = 8) of patients. Detailed characteristics are presented in the Table 1.

URTICARIA PATIENTS VS. CONTROL GROUP

In patients with AU compared to CG, significantly higher values of WBC, NLR, neutrophil count, platelet count (PLT) and CRP were found (for WBC, NLR, neutrophil count and CRP $p < 0.001$; for PLT $p = 0.01$) (Table 2). Similarly, values of WBC, neutrophil count, PLT and CRP were significantly higher in patients with CU compared to the CG (for WBC, neutrophil count and CRP $p < 0.001$, for PLT $p = 0.01$). Taking into account the activity of the disease these differences were found only in patients with severe CU. C-reactive protein levels higher than normal (CRP serum concentration > 5 mg/l), were noted in 43.4% (n = 33) of patients with AU and in 24.5% (n = 12) of patients with CU.

In AU and CU significantly lower median MPR values were found as compared to the CG (patients with AU, CU, severe CU vs. control: $p = 0.01$; $p = 0.01$; $p < 0.001$ respectively).

TABLE 1. General characteristic of study population

Parameter	Urticaria (n = 125)		Control group (n = 75)
	Acute urticaria (n = 76)	Chronic urticaria (n = 49)	
Median age (years)	9.04 (6.29–12.67)	10.67 (7.5–13.42)	10.99 (7.0–13.67)
Gender (M/F)	42/34	20/29	38/37
BMI [kg/m^2]	17.4 (15.25–20.3)	17.85 (15.59–21.23)	17.82 (16.15–20.16)
IgE [IU/ml]	77.51 (48.9–160.3)[b]	75.39 (29.5–185.4)	33.87 (20.2–89.9)
Eosinophilia [cells/µl]	116.5 (85.0–214.5)[c]	170.0 (118.0–272.0)[b]	104 (84–187)
Localization of skin changes, n (%)			
Whole body	20 (26.3)	8 (16.3)	
Limbs	8 (10.5)	17 (34.7)	
Trunck	24 (31.6)	9 (18.4)	
Trunck and limbs	16 (21)	11 (22.4)	
Face	8 (10.5)	4 (8.2)	
Fever > 38°C, n (%)	16 (21)	0	
Respiratory tract infection, n (%)	37 (48.7)	5 (10.2)	
Other infections, n (%)	9 (11.8)	4 (8.2)	
Parasitic infection, n (%)	7 (9.2)	5 (10.2)	
Allergic disease[a], n (%)	25 (32.9)	16 (32.7)	
Use of medications, n (%)	16 (21)	1 (2.0)	
Unknown cause, n (%)	18 (23.7)	23 (46.9)	
Concomitant diseases, n (%)	32 (42.1)	25 (51.0)	
Asthma	3 (3.9)	3 (6.1)	
Atopic dermatitits	3 (3.9)	6 (12.2)	
Allergic rhinitis	4 (5.2)	2 (4.0)	
Chronic tonsillitis/tonsillar hyperthrophy	22 (28.9)	14 (28.6)	
Median duration of hospitalization (days)	5 (4–6)	4 (3–5)	
Severity score[d], n (%)			
Mild (0–3 points)	9 (11.8)	23 (46.9)	
Moderate (4–6 points)	42 (55.3)	14 (28.6)	
Severe (7–9 points)	25 (32.9)	12 (24.5)	

BMI – body mass index, [a]positive specific IgE/skin prick tests, positive anamnesis of food and inhalation allergies, [b]$p < 0.05$ in comparison with control group, [c]$p < 0.05$ children with acute urticaria in comparison with chronic urticaria, [d]TSS – total symptom score, laboratory data presented as median, quartiles (Q_{25}–Q_{75})

TABLE 2. Selected laboratory parameters and calculated indices in acute utricaria, chronic urticaria and control group

Parameter	Urticaria ($n = 125$)		Control group ($n = 75$)
Hgb [g/dl]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	12.95 (12.24–13.9) 13.10 (12.7–13.9) 13.10 (12.5–13.9) 13.3 (13.0–13.7) 13.64 (12.9–15.5)	13.1 (12.3–14.0)
WBC ($\times 10^3$/µl)	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	10.97 (7.31–14.83)[a,b] 7.28 (5.9–9.0)[a] 6.57 (5.89–8.87)[c] 6.59 (5.2–8.13)[d] 9.71 (8.66–12.25)[a]	6.5 (5.3–7.8)
Lymphocytes ($\times 10^3$/µl)	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	2.71 (1.9–3.82) 2.57 (2.23–3.38) 2.87 (2.39–3.65)[a] 2.25 (2.05–2.70) 2.47 (2.17–3.88)	2.28 (1.87–3.12)
Neutrophils ($\times 10^3$/µl)	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	5.98 (3.53–10.86)[a,b] 3.32 (2.47–4.88)[a] 2.9 (1.92–3.44)[c] 2.89 (2.93–4.14)[d] 5.77 (4.25–8.67)[a]	2.8 (2.11–3.77)
NLR[e]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	1.89 (1.29–3.21)[a,b] 1.18 (0.79–1.95) 0.91 (0.64–1.46)[c] 1.2 (0.74–1.67)[d] 2.10 (1.61–3.34)[a]	1.09 (0.89–1.61)
PLT (x 10^3/µl)	AU ($n = 76$) CU (n = 49) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	314 (248.5–394.5)[a] 327.0 (291.0–366.0)[a] 319.0 (272.0–366.0)[a,c] 308.5 (238.0–327.0)[d] 369.0 (338.0–420.0)[a]	284 (236–324)
PLR[f]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	116.18 (76.18–167.68) 120.0 (97.94–140.5) 115.41 (73.6–135.32) 114.98 (103.25–152.09) 137.12 (103.37–235.79)	117.65 (81.11–154.74)
MPV [fl][g]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	8.6 (7.8–9.21) 8.7 (8.19–9.73) 8.96 (8.1–9.9) 9.59 (8.32–9.9)[d] 8.32 (8.15–8.5)	8.6 (7.94–9.4)
PDW [fl][h]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	12.0 (10.0–14.15) 11.8 (10.5–13.0) 11.6 (10.8–12.8) 12.3 (11.0–15.5) 11.65 (9.0–13.0)	12.2 (10.3–13.5)
MPR (MPV/PLT)[i]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	0.027 (0.02–0.035)[a] 0.028 (0.023–0.032)[a] 0.028 (0.023–0.033)[c] 0.032 (0.028–0.036)[d] 0.023 (0.02–0.025)[a]	0.031 (0.025–0.038)
CRP [mg/l]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	3.6 (0.86–13.57)[a] 0.93 (0.47–4.06)[a] 0.57 (0.29–1.99)[c] 0.82 (0.52–1.29)[d] 6.03 (0.88–8.58)[a]	0.6 (0.34–1.03)
D-dimer [ng/ml]	AU ($n = 76$) CU ($n = 49$) Mild CU ($n = 23$) Moderate CU ($n = 14$) Severe CU ($n = 12$)	1150.0 (450.0–2090.0)[b] 270.0 (270.0–410.0) 270.0 (270.0–370.0) 270.0 (260.0–490.0) 360.0 (270.0–850.0)	not studied

[a]$p < 0.05$ in comparison with control group, [b]$p < 0.05$ children with acute urticaria (AU) in comparison with chronic urticaria (CU), [c]$p < 0.05$ children with mild CU in comparison with severe CU, [d]$p < 0.05$ children with moderate CU in comparison with severe CU, CRP – C-reactive protein, [e]NLR – neutrophil/lymphocyte ratio, [f]PLR – platelet/lymphocyte ratio, [g]MPV – mean platelet volume, [h]PDW –platelet distribution width, [i]MPR – mean platelet volume/platelet count ratio, PLT – platelet count, WBC – white blood cells

TABLE 3. Logistic regression analysis of the association of selected factors and occurence of urticaria

Parameter	OR[b]	95% CI lower[c]	95% CI upper	*p*-value[d]
WBC	1.21	1.09	1.35	< 0.001
Neutrophil count	1.32	1.14	1.53	< 0.001
NLR[a]	1.35	1.06	1.70	0.01
CRP	1.06	1.02	1.12	0.01
D-dimer	1.002	1.001	1.003	< 0.001

[a]NLR – neutrophil/lymphocyte ratio, [b]OR – odds ratio, [c]95% CI lower and upper limits of the 95% confidence interval for the odds ratio, [d] bold values are statistically significant, CRP – C-reactive protein, WBC – white blood cells

There were no significant differences between groups regarding levels of haemoglobin (Hgb), lymphocyte count, PLR, platelet distribution width and MPV.

ACUTE VS. CHRONIC URTICARIA GROUP

There were statistically significant higher values of WBC, NLR, neutrophil count, CRP and D-dimer in patients with AU compared to the CU (for WBC, NLR, neutrophil count, D-dimer $p < 0.001$; for CRP $p = 0.01$).

MILD COURSE CHRONIC URTICARIA VS. SEVERE COURSE CHRONIC URTICARIA

There were significantly lower values of WBC, neutrophil count, NLR, PLT, CRP ($p = 0.01$; $p < 0.001$; $p < 0.001$; $p = 0.02$; $p = 0.01$) and significantly higher values of MPR ($p = 0.02$) in patients with mild CU vs. severe CU.

MODERATE COURSE CHRONIC URTICARIA VS. SEVERE COURSE CHRONIC URTICARIA

Patients with moderate CU compared to severe CU had significantly lower values of WBC, neutrophil count, NLR, MPV, PLT, CRP ($p < 0.001$; $p < 0.001$; $p = 0.02$; $p = 0.04$; $p < 0.001$; $p < 0.05$) and higher values of MPR ($p < 0.001$).

ADDITIONAL RESULTS

In both patients with AU and CU, we confirmed a significant correlation between CRP levels and the value of NLR ($r = 0.39$, $p < 0.001$; $r = 0.57$, $p < 0.001$), neutrophil count ($r = 0.47$, $p < 0.001$, respectively; $r = 0.38$, $p = 0.01$) and D-dimer levels ($r = 0.43$, $p < 0.001$; $r = 0.28$, $p < 0.05$).

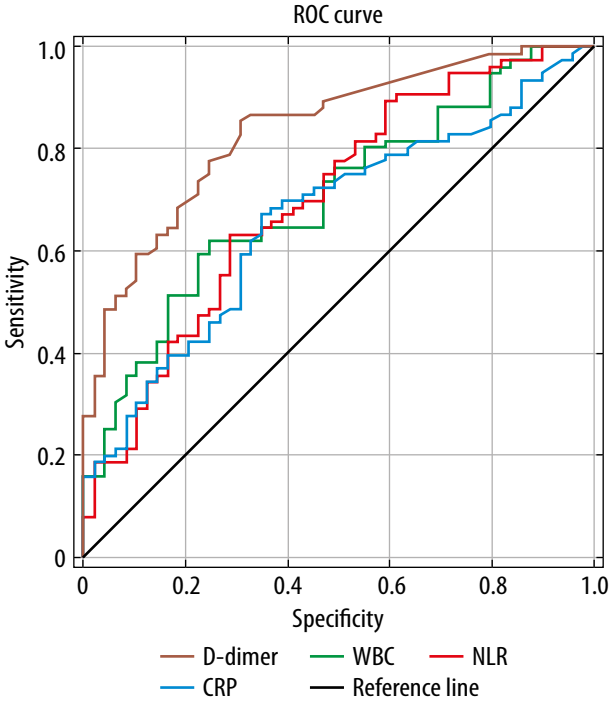

FIGURE 1. Comparison of receiver operating curves for white blood cells, neutrophil/lymphocyte ratio, C-reactive protein and D-dimer for predicting occurrence of urticaria

CRP – C-reactive protein, NLR – neutrophil/lymphocyte ratio, ROC – receiver operating curve, WBC– white blood cells

The duration of hospitalization in AU and CU patients positively correlated with CRP concentration ($r = 0.43$, $p < 0.001$; $r = 0.38$, $p = 0.01$, respectively). The disease activity assesed on the TSS scale in patients with AU positively correlated with the CRP concentration ($r = 0.24$, $p = 0.04$) and D-dimer levels ($r = 0.28$, $p = 0.02$). In CU, there was also a correlation between disease activity and CRP levels ($r = 0.35$, $p = 0.01$), WBC values ($r = 0.30$, $p = 0.04$) and NLR values ($r = 0.44$, $p < 0.001$).

TABLE 4. Receiver operating curve analysis of selected parameters as predictors of the occurrence of urticaria

Parameter	AUC[b]	95% AUC CI lower[c]	95% AUC CI upper	Cutoff	Sensitivity (%)	Specificity (%)	Youden index	*p*-value[d]
D-dimer	0.84	0.77	0.91	390.0	86	69	0.5491	< 0.001
WBC	0.70	0.61	0.79	9.16	62	76	0.3735	< 0.001
NLR[a]	0.70	0.61	0.80	1.68	63	71	0.3459	< 0.001
CRP	0.66	0.57	0.76	1.59	67	65	0.3241	< 0.001

[a]NLR – neutrophil/lymphocyte ratio, [b]AUC – area under the curve, [c]AUC CI – lower and upper 95% confidence limits for AUC, [d]bold values are statistically significant, CRP – C-reactive protein, WBC – white blood cells

Altogether in the group of patients with urticaria based on logistic regression analysis, it was found that the highest risk of developing urticaria is associated with elevated NLR, neutrophil count, WBC, CRP and D-dimer values (Table 3).

Receiver operating curve analysis revealed that statistically significant predictors of urticaria included D-dimer, WBC, NLR and CRP. The largest area under the curve (AUC) was demonstrated for D-dimer (AUC = 0.84; $p < 0.001$) (Fig. 1.) The optimal cut-off value for D-dimer determined by Youden index was 390.0. The parameter with the highest sensitivity (86%) turned out to be D-dimers, while the highest specificity (76%) was demonstrated for WBC (Table 4). In the logistic regression model and ROC analysis, the parameters PLT, MPV, MPR and PLR did not meet criteria for statistical significance, therefore they were not assessed as biomarkers of urticaria.

DISCUSSION

In this study, we found increased values of CRP, WBC and neutrophil count in patients with AU and severe CU in comparison to the CG.

Current reports indicate that patients with urticaria have elevated interleukin 6 (IL-6) levels [23]. In AU, there is an overproduction of IL-1, which stimulates the production of IL-6 and then acute phase proteins, including CRP [6]. According to Czarnecka-Operacz *et al*. in patients with AU, a severe course of the disease is associated with elevated serum CRP levels [4], a similar correlation was noted in our study. In the case of CU, regardless of its mechanism, significantly higher CRP values are found in comparison to the CG [4], similarly significantly higher CRP values are reported in patients with CSU poorly responsive to antihistamine treatment [23]. Receiver operating curve analysis showed moderate sensitivity and specificity (67% and 65%, respectively, cut-off 1.59) for CRP as an indicator of urticaria occurrence.

We also noted higher values of WBC, neutrophil count and NLR comparing patients with AU in relation to patients with CU, which may indicate a higher intensity of inflammation in the first group. In the ROC curve analysis, NLR and WBC, turned out to be moderately sensitive and specific in the prediction of urticaria (63% and 71%, cut-off 1.68 for the NLR; 62% and 76%, cut-off 9.16 for the WBC, respectively).

According to Antia *et al*., AU is associated with high leukocyte infiltration, leukocytosis and prolonged erythrocyte sedimentation rate [8]. Similar data were presented in the works of other authors [9, 24, 25]. The data we obtained are consistent with previous reports.

Considering the fact that infection is the most frequently documented cause of AU in children [3], identification of the cause of the increase in inflammatory and leukocyte parameters may pose difficulties. In our patients with urticaria, the development of urticarial lesions and the increase in WBC and NLR counts occurred independently of coexisting infection or allergy in an IgE-mediated mechanism. These indicate that upregulation of CRP and IL-6 in urticaria/angioedema does not necessarily reflect a concomitant infection, but first of all points to high activity of the urticarial inflammation itself.

We observed significantly higher values of WBC and NLR in patients with severe CU in comparison with mild and moderate CU. It is believed that the development of urticaria depends on the migratory ability of immune cells determined by the interaction of chemotactic factors and endothelium. During this process, T lymphocytes, monocytes, eosinophils, and basophils move from the blood into tissues, leading to the formation of perivascular infiltrates [26]. According to Karaman *et al*, in CU, due to an inflammatory response, there is a shift in the leukocyte pool in the body, resulting in an increase in neutrophil and a decrease in lymphocyte count in the blood [23].

Neutrophils are an important link in the immune response primarily due to their production of reactive oxygen species, degranulation abilities, and formation of neutrophil extracellular traps (NETs); they also have a regulatory function for the acquired immune system [27].

Increased neutrophil count and NLR values are associated with poor prognosis in children with CSU. Previous literature reports [23] as well as our study in CU reveal a positive correlation between NLR value and activity of urticarial lesions. Additionally, we found a correlation between WBC value and CU activity. It is worth mentioning that the NLR was also found to be useful as a marker for the presence of psoriasis and exacerbation of atopic dermatitis [18, 28].

The increase in leukocyte parameters in children with urticaria and their usefulness in predicting the activity of changes found in our study seems to have multiple causes due to the aforementioned complex etiopathogenesis of individual clinical manifestations of urticaria. In addition, we should mention a number of factors affecting the values of leukocyte parameters such as medications (including corticosteroids, epinephrine, lithium, β-mimetics), physical stress (surgery, trauma, excessive exercise), emotional stress, necrotic and inflammatory foci, bone marrow diseases [29].

We noted an increase in platelet count among patients with AU and CU compared to controls and a higher PLT in patients with severe CU compared to patients with mild and moderate CU. It seems that platelet activation in this case may be related to the activation of proinflammatory mechanisms, especially IL-6 stimulating megakaryocyte proliferation [30] and activation of coagulation supporting mechanisms in inflamed vessels [31, 32].

Different results were obtained for the MPR parameter (MPV/PLT), which was significantly lower among children with AU and severe CU than in controls.

The observed changes draw attention to the activation of the platelet system in the course of exacerbation of urticarial lesions, which in the case of our patients translated mainly into an increase in the number of PLT.

In previous reports lower MPV values were found in children with inflammatory diseases [24]. It is worth mentioning that in adult patients in contrast to children, elevated MPV values are usually observed in the course of CU [33]. Increased MPV has also been reported in patients with other skin diseases such as psoriasis, atopic eczema, and systemic lupus erythematosus (SLE) [19, 24].

The influence of genetic polymorphisms and variation of MPV with age, hormonal changes or lifestyle factors (smoking, obesity, hypertension, diabetes) should be considered in the evaluation of platelet parameters [30]. In our study, platelet parameter values proved to be useless as a predictor of urticarial lesion occurrence. Thus, there is a need for further studies in this regard.

We found significantly higher D-dimer levels among patients with AU compared to CU. Receiver operating curve analysis indicated that D-dimers were the best predictor of urticaria occurrence among the laboratory parameters tested (AUC = 0.84, sensitivity 86%, specificity 69%, cut-off 390.0). In addition, D-dimer levels correlated positively with disease activity in this group.

D-dimers are a fibrin degradation products formed by activation of the clotting cascade of blood and thrombin. Previously, elevated D-dimer levels have been found in patients with AU, including those requiring prolonged corticosteroid therapy [34]. According to Zhang *et al*. in AU there is an association of elevated D-dimers with the severity of skin lesions, moreover, high IgE levels may promote activation of the coagulation system in an extrinsic mechanism [35]. The development and severity of skin lesions have been shown to be related to thrombin production also in the case of CSU [32, 33, 36]. It is relevant that the absence of an increase in D-dimers plays an important role in excluding coagulation disorders [32].

A study by Kolkhir *et al*. in a group of patients with CSU reported a positive correlation between CRP levels and fibrinogen and D-dimer levels [37]. D-dimer levels also proved to be a significant marker of CSU activity among patients developing resistance to omalizumab treatment [38].

Inflammation is believed to be the link between the immune system and the coagulation system. Current reports indicate that CU is accompanied by systemic inflammation as well as activation of the coagulation and fibrinolysis systems [13–15].

It seems that in view of the complex pathomechanism of urticaria development, the parameters we analyzed in the study may constitute potential directions for further research.

This study has several limitations. First of all, it is a single-center retrospective study with a limited number of patients, which may affect the quality of the obtained data. The used disease activity scale was selected as for adult patients; there is no standardized scale assessing both AU and CU activity.

CONCLUSIONS

Increased values of WBC, NLR, PLT, CRP and D-dimers, regardless of coexistence of infection, reflect the presence of inflammation and activation of fibrinolysis in children with urticaria. The utility of parameters calculated from blood count as well as biochemical and fibrinolysis parameters as biomarkers of urticaria activity requires further study.

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DISCLOSURE

The authors declare no conflicts of interest.

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