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Original Article

Intersecting pathways: evaluating inflammatory markers and metabolism in chronic spontaneous urticaria with a multi-marker approach

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Abstract

Background Chronic spontaneous urticaria (CSU) is an inflammatory skin disease with intricate mechanisms. This study comprehensively assessed markers from diverse metabolic pathways, including novel inflammatory indicators, to evaluate their potential for diagnosing and monitoring CSU.

Materials and methods In the study involving 90 CSU patients and 90 healthy controls, the levels of albumin, high-density lipoprotein (HDL), fibrinogen, uric acid, D-dimer, C-reactive protein (CRP), and white blood cells (WBC) values were analyzed. The D-dimer/albumin ratio (DAR), fibrinogen/albumin ratio (FAR), and uric acid/HDL ratio (UHR), considered novel inflammatory markers, were calculated. The Urticaria Activity Score 7 (UAS7) was also calculated. Pearson chi-squared test, Mann–Whitney *U* test, Spearman correlation coefficient, and univariate logistic regression analysis were employed for data analysis.

Results In the patient group, significant elevations were observed in DAR, FAR, fibrinogen, CRP, D-dimer, and UHR values. Additionally, albumin, HDL, and uric acid values exhibited significant decreases. HDL and albumin provided the most accurate results in the univariate logistic regression analysis. CRP had less accuracy, FAR exhibited greater accuracy than fibrinogen, and DAR demonstrated higher accuracy than D-dimer. There was no statistically significant correlation between the UAS7 and parameters. The considerable correlation of CRP with other parameters, except D-dimer, was also remarkable.

Conclusions Indicators from diverse metabolic pathways, including albumin, HDL, uric acid, fibrinogen, D-dimer, and CRP, can be valuable in assessing CSU. In particular, FAR and DAR are emerging as potential markers to consider in the assessment of CSU.

Introduction

Urticaria is a skin disease characterized by itchy and edematous plaques that appear suddenly and disappear independently.[1] The lifetime prevalence rate is approximately 8%–9%, with a higher occurrence among females.[2,3] Chronic urticaria (CU) is defined as urticarial papules and plaques lasting longer than 6 weeks, assuming symptoms are present most days.[4] It may be due to a triggerable cause called chronic inducible urticaria or without an underlying cause, known as chronic spontaneous urticaria (CSU).[5]

CSU comprises the majority of cases of CU. It affects 1%–2% of the population, with a higher prevalence among females.[2,3] The pathogenesis of it remains incompletely understood, believed to arise from the release of immune mediators, including histamine, proteases, and cytokines, triggered by mast cell activation.[4] Mast cells also release leukotrienes, prostaglandin D2, platelet-activating factor, and thromboxanes. These mediators predominantly mediate the manifestation of symptoms, including redness, swelling, and itchiness. Furthermore, biopsies indicate a perivascular infiltrate, including $CD4^+$ lymphocytes, neutrophils, monocytes, basophils, and eosinophils, which mediate inflammation.[6,7] Studies have also demonstrated an elevation in proinflammatory cytokines, such as IL-6, IL-18, IL-17, IL-23, and TNF-α, with some of these elevations associated with the severity of the disease.[8–10] Similarly, C-reactive protein (CRP), an acute-phase reactant, was found to be associated with disease activity.[11]

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In the past few years, investigations into the pathophysiology of CSU have examined a range of mechanisms. In CSU, there are inflammatory cellular infiltrates in the perivascular and interstitial spaces consisting of eosinophils, neutrophils, lymphocytes, and basophils. Eosinophils can express a significant quantity of tissue factors on their surface.[12] The activation of these tissue factors can trigger the extrinsic coagulation cascade, generating activated coagulation factors, including factor Xa and factor IIa (thrombin).[13] In addition, a series of reactions occur, including protease-activated receptor (PAR) 1, PAR 2, plasmin, complements, and leukotrienes.[14] Increased coagulation and fibrinolysis in CSU increases the levels of D-dimer, fibrinogen, fibrin, and fibrinogen degradation products.[15]

Considering the known mechanisms of CSU, there seems to be a connection between inflammation, autoimmunity, activation pathways of coagulation systems, and other metabolic pathways in the development of CSU. These factors may collectively contribute to the onset of urticarial inflammation.[16]

In addition to conventional inflammatory markers such as white blood cells (WBC), CRP, interleukins, and TNF-alpha, recent studies have shifted attention towards alternative indicators such as fibrinogen, D-dimer, albumin, uric acid, and high-density lipoprotein (HDL). Additionally, the fibrinogen/albumin ratio (FAR), D-dimer/albumin ratio (DAR), and uric acid/HDL ratio (UHR) have recently emerged as novel inflammatory markers.[17–22] Exploring the connection between these ratios and CSU, an inflammatory disease, may offer insights into the disease's pathophysiology and may prove valuable in assessing its severity, progression, and response to treatment.

Considering the complex mechanism of CSU, our study was comprehensive and included markers belonging to different pathways. Fibrinogen, D-dimer, CRP, WBC, albumin, uric acid, and HDL values were analyzed in our study. In addition, FAR, DAR, and UHR ratios, which are considered novel inflammatory markers, were also included in the study. The correlations of these markers with each other and the Urticaria Activity Score 7 (UAS7) were examined. The study aimed to investigate the potential of these markers as indicators in assessing CSU and, if deemed suitable, to identify which markers might be more effective. To the best of our knowledge, this study is the first to collectively evaluate a variety of markers related to CSU and assess novel inflammatory markers.

Materials and methods

Study design and patients

This cross-sectional study's total number of participants was 180, comprising 90 patients diagnosed with CSU and 90 individuals in the healthy control group. Participation in the study was voluntary for all individuals, and each participant provided written informed consent. Both the patient and the control group included individuals aged 18 and above.
The research adhered to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Karamanoglu Mehmetbey University (Date: 20.11.2023/no.10-2023/12).

Demographic information, including age, gender, and medical history, was documented for each participant. Participants in the patient group were required to have a confirmed diagnosis of CSU as determined by experienced dermatologists. The control group comprised individuals who were healthy, without any ongoing complaints, and attended the outpatient clinic for a regular check-up. The exclusion criteria included individuals in both groups who used medications potentially affecting the determined laboratory markers. Additionally, participants were excluded if they had chronic comorbidities or metabolic disorders that might impact systemic inflammation.

For both the patient and the control group, the levels of albumin (g/L), HDL (mg/dL), fibrinogen (mg/dL), uric acid (mg/dL), D-dimer (mg/L), CRP (mg/L) and WBC were assessed. Additionally, calculations were performed for the ratios of fibrinogen to albumin, D-dimer to albumin, and uric acid to HDL. All these variables were systematically compared between the two groups to discern potential associations.

In the patient group, the disease severity was assessed using UAS7. This subjective scale documents the patient's severity of itching (0 = none, 1 = mild, 2 = moderate, 3 = severe) and the number of wheals (0 = none, <20 = mild, 20–50 = moderate, >50 = severe) complaints for seven consecutive days, providing a comprehensive evaluation of disease severity. The scale's total score ranges from 0 to 42, with higher scores indicating more significant disease activity. The UAS7 categories are defined as follows: UAS7 = 0 for urticaria-free, UAS7 $\leq$ 6 for well-controlled, UAS7 = 7–15 for mild, UAS7 = 16–27 for moderate, and UAS7 = 28–42 for severe urticaria.[23] The correlations of UAS7 and other variables were explored in the study.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics 29 package program. Frequency tables and descriptive statistics were used to interpret the findings. Continuous variables were expressed as mean $\pm$ standard deviation, median [minimum–maximum], and categorical variables as frequency and percentage. Non-parametric methods were used to evaluate measurement values that did not conform to normal distribution. Pearson chi-squared test was used to examine the relationship between two qualitative variables. Analysis of quantitative independent data involved the use of the Mann–Whitney *U* test. Effect level analysis was conducted through univariate logistic regression. Spearman correlation coefficient was used to determine the relationship between two non-normally distributed variables. A *P*-value of <0.05 was considered statistically significant.

Results

The research involved 180 individuals; 90 identified as CSU patients and 90 as the control group, comprising healthy

Table 1 Comparison of the parameters and the relationship between the patient and control groups

Parameters	Status	Mean ± SD	Median [Min-Max]	Mann–Whitney U
Age	Patient	44.40 ± 14.44	45 [18–71]	$Z = 3.858$
	Control	36.19 ± 12.74	33.5 [18–65]	$\mathbf{P < 0.001}$
Fibrinogen	Patient	339.81 ± 66.92	325 [227–548]	$Z = 4.067$
	Control	300.38 ± 54.78	296 [202–445]	$\mathbf{P < 0.001}$
Albumin	Patient	46.53 ± 2.18	46 [42–53]	$Z = 22125.050$
	Control	48.13 ± 2.02	48 [43–52]	$\mathbf{P < 0.001}$
D-dimer	Patient	0.3344 ± 0.2396	0.2 [0.2–1.05]	Z = 2.710
	Control	0.2269 ± 0.0765	0.2 [0.2–0.68]	$\mathbf{P = 0.007}$
Uric Acid	Patient	4.40 ± 0.80	4 [3–7]	$Z = -2.826$
	Control	4.96 ± 1.36	5 [3–7]	$\mathbf{P = 0.005}$
HDL	Patient	48.00 ± 11.15	46 [29–82]	$Z = -5.758$
	Control	58.61 ± 11.67	63 [32–77]	$\mathbf{P < 0.001}$
CRP	Patient	3.57 ± 4.54	2 [0–24]	$Z = 3.030$
	Control	1.99 ± 2.13	2 [0–13]	$\mathbf{P = 0.002}$
WBC	Patient	8.46 ± 2.44	8.30 [4.05–16.28]	$Z = 0.946$
	Control	8.05 ± 1.72	7.81 [4.53–13.36]	$P = 0.344$
FAR	Patient	7.3244 ± 1.5108	7.0851 [4.9348–12.1778]	$Z = 5.007$
	Control	6.2470 ± 1.1540	6.1314 [4.3913–9.4681]	$\mathbf{P < 0.001}$
DAR	Patient	0.0072 ± 0.0052	0.0045 [0.0038–0.0248]	$Z = 4.717$
	Control	0.0047 ± 0.0017	0.0043 [0.0038–0.0142]	$\mathbf{P < 0.001}$
UHR	Patient	0.0974 ± 0.0303	0.0980 [0.0429–0.1724]	$Z = 2.046$
	Control	0.0891 ± 0.0334	0.0851 [0.0390–0.2000]	$\mathbf{P = 0.041}$

The bold values indicate a statistical significance of $P < 0.05$.
CRP, C-reactive protein; DAR, D-dimer/albumin ratio; FAR, fibrinogen/albumin ratio; HDL, High-density lipoprotein; UHR, uric acid/HDL ratio; WBC, white blood cell count.

Table 2 Univariate logistic regression analysis

Parameters	Coefficient	Odds ratio	95% CI	*P*-value	Accuracy (%)	Nagelkerke R^2
HDL	−0.077	0.925	0.899–0.952	**<0.001**	69.4	0.233
Albumin	−0.367	0.693	0.590–0.813	**<0.001**	68.9	0.171
FAR	0.639	1.895	1.447–2.481	**<0.001**	61.7	0.192
Fibrinogen	0.011	1.011	1.006–1.017	**<0.001**	61.1	0.129
DAR	245.086	2.8E+106	7.3E+41-1E+171	**0.001**	61.1	0.146
Uric acid	−0.449	0.638	0.483–0.842	**0.002**	61.1	0.078
D-dimer	4.621	101.568	5.972–1727.442	**0.001**	58.3	0.128
CRP	0.165	1.180	1.043–1.335	**0.009**	58.9	0.072
UHR	8.231	3755.488	0.33–43,338,643	0.085	57.2	0.022
WBC	0.095	1.099	0.954–1.267	0.190	57.8	0.013

The bold values indicate a statistical significance of $P < 0.05$.
CRP, C-reactive protein; DAR, D-dimer/albumin ratio; FAR, fibrinogen/albumin ratio; HDL, High-density lipoprotein; UHR, uric acid/HDL ratio; WBC, white blood cell count.

individuals. Within the patient group, 63 individuals (70%) were females, and 27 (30%) were males. To avoid the effect of gender on the study, the control group was structured to maintain a similar gender ratio.

The mean age of patients (44.40 ± 14.44) was significantly higher than the control group (36.19 ± 12.74; $P < 0.001$). In the patient group, significant elevations were observed in DAR ($P < 0.001$), FAR ($P < 0.001$), fibrinogen ($P < 0.001$), CRP ($P = 0.002$), D-dimer ($P = 0.007$), and UHR ($P = 0.041$) values. Additionally, there were notable decreases in albumin ($P < 0.001$), HDL ($P < 0.001$), and uric acid ($P = 0.005$) values. No statistical relationship was found in WBC values ($P > 0.05$; Table 1).

In the univariate logistic regression analysis (Table 2), all variables, except UHR and WBC values, exhibited significant efficiency ($P < 0.05$) in differentiating between patient and control groups. The findings indicate that an increase in FAR, fibrinogen, DAR, D-dimer, and CRP values heightens the risk of CSU, while

Table 3 Correlations of parameters within the patient group

	CRP	Fb	Ab	Dd	Ua	HDL	FAR	DAR	UHR
UAS7									
r	0.026	−0.058	0.027	−0.075	−0.055	−0.008	−0.082	−0.123	−0.005
P	0.808	0.590	0.803	0.481	0.610	0.938	0.442	0.249	0.965
CRP									
r		0.436	−0.241	0.197	0.359	−0.280	0.454	0.245	0.398
P		**<0.001**	**0.022**	0.063	**0.001**	**0.007**	**<0.001**	**0.02**	**<0.001**
Fb									
r			−0.154	0.037	0.209	−0.329	0.962	0.071	0.359
P			0.146	0.727	**0.048**	**0.002**	**<0.001**	0.504	**0.001**
Ab									
r				−0.023	−0.076	0.151	−0.391	−0.348	−0.124
P				0.828	0.478	0.156	**<0.001**	**0.001**	0.244
Dd									
r					0.101	0.006	0.017	0.914	0.060
P					0.344	0.953	0.871	**<0.001**	0.574
Ua									
r						−0.316	0.221	0.133	0.721
P						**0.002**	**0.036**	0.212	**<0.001**
HDL									
r							−0.340	−0.085	−0.850
P							**0.001**	0.427	**<0.001**
FAR									
r								0.128	0.369
P								0.228	**<0.001**
DAR									
r									0.139
P									0.191

The bold values indicate a statistical significance of $P < 0.05$.
Ab, albumin; CRP, C-reactive protein; DAR, D-dimer/albumin ratio; Dd, D-dimer; FAR, fibrinogen/albumin ratio; Fb, fibrinogen; HDL, high-density lipoprotein; *r*, Spearman correlation coefficient; Ua, uric acid; UAS7, Urticaria Activity Score 7; UHR, uric acid/HDL ratio.

a decrease in HDL, albumin, and uric acid values heightens the risk of CSU. It is essential to highlight that HDL (69.4%) and albumin (68.9%) provided the most accurate results, FAR (61.7%) exhibited greater accuracy compared to fibrinogen (61.1%), and DAR (61.1%) demonstrated higher accuracy than D-dimer (58.3%). All other results are shown in Table 2.

According to UAS7 scoring, there were 26 (28.9%) patients in the "urticaria-free" group, 28 (31.1%) in the "well-controlled" group, 29 (32.2%) in the "mild severity" group, and 7 (7.8%) in "moderate severity" group. There was no patient in the "severe urticaria" group.

Based on the correlation analysis within the patient group itself, no statistically significant correlations were found between the UAS7 and other parameters ($P > 0.05$) (Table 3). CRP demonstrated a moderate positive correlation with FAR ($r = 0.454$, $P < 0.001$), fibrinogen ($r = 0.436$, $P < 0.001$) and UHR ($r = 0.398$, $P < 0.001$), a weak positive correlation with uric acid ($r = 0.359$, $P = 0.001$), and DAR ($r = 0.245$, $P = 0.02$), and a weak negative correlation with HDL ($r = -0.280$, $P = 0.007$) and albumin ($r = -0.241$, $P = 0.022$). There was a weak positive correlation between CRP and D-dimer, but it was not statistically significant ($r = 0.197$, $P = 0.063$). Apart from these, UHR's positive correlation with fibrinogen ($r = 0.359$, $P = 0.001$) and FAR ($r = 0.369$, $P < 0.001$) and HDL's negative correlation with FAR ($r = -0.340$, $P = 0.001$) and fibrinogen ($r = -0.329$, $P = 0.002$) was also remarkable. All other related results are presented in Table 3.

Discussion

CSU is an inflammatory and immune-related disease that can impact individuals of all age groups. However, it commonly manifests between the ages of 20 and 40 and is more than twice as prevalent among women.[24] In our study, the mean age of patients with CSU was 44.40 ± 14.44, and 70% of patients were women, which is consistent with literature findings. Since age and gender may affect the laboratory findings, we tried to make the control group as similar to the patient group in terms of age and gender as possible. While the gender composition in the control group mirrored that of the patient group, including healthy individuals in the control group reduced the mean age. Consequently, the mean age of the patient group was significantly higher than that of the control group ($P < 0.001$; Table 1).

CSU involves intricate metabolic processes encompassing autoimmunity, inflammation, metabolic pathways, and the coagulation cascade. Indeed, numerous factors within these pathways could serve as valuable markers for diagnosing and monitoring CSU. Fibrinogen, D-dimer, albumin, CRP, WBC, uric acid, HDL, FAR, DAR, and UHR, assessed as markers within these pathways, will only offer insights into this intricate mechanism when collectively analyzed.

D-dimer and fibrinogen play a role in the coagulation process and serve as an acute-phase reactant, providing information about the systemic inflammatory state. Therefore, considering that D-dimer and fibrinogen are involved in the key mechanisms of CSU, it is clear that they may be potential indicators in the diagnosis and follow-up of CSU.

Studies have shown that D-dimer levels are high in CSU patients and correlate with disease severity.[15,25,26] In CSU patients, Grzanka et al. noted a correlation between D-dimer and inflammatory markers (IL-6 and CRP) and UAS7.[27] On the other hand, Asero et al. suggested that D-dimer levels are elevated in severe cases of CSU, but this elevation varies among individuals, attributed to distinct underlying mechanisms.[28,29] Similar to D-dimer, elevated fibrinogen levels were also observed in CSU.[15]

Albumin acts as a negative acute phase reactant, and new studies emphasize that it can also function in both procoagulant and anticoagulant mechanisms.[30,31] The fact that albumin levels were found to be low in CSU patients in certain studies suggests its potential involvement in specific pathways of CSU pathogenesis, hinting at its utility as an indicator.[32]

In the context of the inflammation and coagulation mechanisms involved in CSU, there is a possibility that DAR and FAR, recognized as novel prognostic indicators in conditions like chronic diseases, infections, inflammatory diseases, acute disorders, and malignancy, may also serve as an indicator for CSU.[21,33–35]

In our study, D-dimer ($P = 0.007$), DAR ($P < 0.001$), fibrinogen ($P < 0.001$), and FAR ($P < 0.001$) values were found to be significantly higher in CSU patients compared to the control group. At the same time, albumin levels were significantly lower in the CSU patients ($P < 0.001$; Table 1). According to the univariate logistic regression model in Table 2, FAR demonstrated greater accuracy than fibrinogen, and DAR exhibited higher accuracy than D-dimer. In addition, the reduced albumin levels in CSU patients provide a high level of accuracy in the differentiation from the control group. In this context, it can be suggested that albumin is a significant marker. DAR and FAR values may be preferred over D-dimer and fibrinogen in the differentiation of CSU patients. The number of severe cases was limited in our study, so different accuracy values may be obtained in a study of severe CSU cases.

Uric acid inhibits the release of nitric oxide and impacts various mechanisms, including inflammation and oxidative stress.[36] Recent studies propose the applicability of UHR as an indicator in inflammatory conditions. This indicates that UHR could be a promising research area for CSU. The role of uric acid in CSU has not yet been thoroughly investigated. Although Karabay et al. did not find a significant elevation in uric acid levels in CSU patients, there are not enough studies on this subject.[37]

Amin et al. demonstrated that CSU patients had reduced HDL levels and suggested that a common pathogenic mechanism linking CSU and hyperlipidemia might entail systemic inflammation associated with IL6 and TNF-α.[38]

In our study, increased UHR value ($P = 0.041$) and decreased uric acid ($P = 0.005$) and HDL values ($P < 0.001$) were found to be significant in the differentiation of CSU (Table 1). In the patient group, the univariate logistic regression analysis revealed that UHR did not exhibit substantial efficacy ($P = 0.085$), while HDL was significant ($P < 0.001$) with the highest accuracy value (69.4%; Table 2). Herein, the same directional variation of HDL and uric acid within the group seems to reduce the efficacy of UHR. Nevertheless, the potential efficacy of uric acid, especially HDL, in CSU differentiation should be emphasized.

CRP and WBC, considered classical indicators of inflammation, were found to be associated with CSU in various studies.[8,11,37] In our study, a significant elevation of CRP was observed in the differentiation of the patient group ($P = 0.002$), while no significant result was found for WBC ($P = 0.344$; Table 1). Although CRP is significant in the univariate logistic regression analysis, it is noteworthy that it demonstrates a lower accuracy value than other variables (Table 2).

Despite encountering diverse results in the literature concerning the correlations of identified variables with UAS7, it is noteworthy that none of the variables in our study exhibit a correlation with UAS7 (Table 3). In this study, a low number of patients with moderate and severe CSU seems to have contributed to this result. Hence, it would be beneficial to assess the correlation of UAS7 in severe cases of CSU in further studies.

Except for D-dimer, other parameters demonstrated a statistically significant correlation with CRP. These results highlight the capability of the identified parameters to function as inflammatory markers in CSU patients. While specific studies indicate a correlation between D-dimer and CRP in CSU cases, Asero et al. highlighted an elevation of D-dimer in severe CSU cases, suggesting distinct underlying mechanisms.[27–29] Our study's absence of correlation between D-dimer and CRP may be attributed to the limited number of patients with severe CSU. Nevertheless, the correlation between DAR and CRP, even in non-severe CSU patients, suggests that DAR may serve as a more sensitive indicator compared to D-dimer in this patient population.

The observed correlation among FAR, uric acid, HDL, and UHR in Table 3 is also noteworthy. While a mechanism explaining this relationship in CSU patients has not been established, more comprehensive studies are needed for detailed results.

Conclusion

The pathophysiology of CSU is still poorly understood due to the complex underlying mechanism. Accordingly, no objective criteria for diagnosis and treatment follow-up have been established. Therefore, utilizing markers that are highly specific, sensitive, and involved in multiple pathways is of significant importance in managing the disease. Our study is noteworthy as it highlights the greater significance of FAR and DAR over fibrinogen and D-dimer. It also suggests that indicators from diverse metabolic pathways, including fibrinogen, D-dimer, albumin, uric acid, HDL, and CRP, can be valuable in assessing CSU.

In conclusion, our study contributes to understanding CSU pathophysiology by collectively evaluating a diverse set of markers. The identified markers, especially novel ratios like FAR and DAR, are promising indicators for assessing the severity, progression, and treatment response of CSU. Further research and validation studies are warranted to establish these markers' clinical significance and potential integration into routine diagnostic and management protocols for CSU. Analyzing how the levels of these markers respond to various treatment options, including monoclonal antibodies, might also contribute to evaluating treatment superiority in further studies.

Limitations

The limitations of our study include the high mean age of the patient group, the low number of moderate CSU cases, and the absence of severe CSU cases. Additionally, a multivariate logistic regression model could not be created due to the insufficient number of patients and the large number of variables. Further studies, including more patients and severe CSU cases, will provide more comprehensive results.

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Author contributions

The design of the study and the writing of the first draft manuscript were performed by ZM. HMA performed data collection. ZM and KT performed material preparation. SA performed analysis. All authors provided critical feedback throughout the study, interpreted the data, reviewed, and edited subsequent drafts, and approved the final draft.

Patient consent

Informed consent was obtained from all participants in the study.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on a reasonable request.

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