

Levels of C-Reactive Protein and D-Dimers in Chronic Urticaria as Markers of Severity

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ABSTRACT

Objective: To assess C-reactive protein (CRP) and D-dimers as possible indicators of disease severity in individuals with chronic spontaneous urticaria (CSU), and to investigate additional inflammatory, allergic, and coagulation factors.

Study Design: Cross sectional analytical study.

Place and Duration of Study: Dermatology Department, Pak-Emirates Military Hospital Rawalpindi, Pakistan, from Feb 2023 to Jan 2024.

Methodology: One hundred CSU patients and 100 age- and gender-matched healthy controls were enrolled. Disease severity was assessed using the Urticaria Activity Score over 7 days (UAS7). Serum CRP and D-dimer levels were measured by HS-CRP turbidimetric assay and ELISA, respectively. Additional parameters included serum IgE, prothrombin time (PT), and activated partial thromboplastin time (APTT). Data normality was tested, and correlations between biomarkers and UAS7 were analyzed using Pearson's or Spearman's correlation as appropriate.

Results: Median CRP [8.7 (4.9–13.5) mg/L vs. 2.1 (1.3–4.0) mg/L; $p < 0.001$] and D-dimer [468.8 (320.5–625.7) ng/mL vs. 190.4 (130.7–247.9) ng/mL; $p < 0.001$] were significantly higher in CSU patients compared to controls. Moderate positive correlations were observed between UAS7 and CRP ($r_s = 0.62$, $p < 0.001$) and UAS7 and D-dimer ($r_s = 0.58$, $p < 0.001$). Female patients had significantly higher UAS7 scores and a higher frequency of elevated IgE, prolonged PT/APTT, and inflammatory markers. No significant correlation was found between CRP and D-dimer levels.

Conclusion: CRP and D-dimer levels are elevated in CSU and correlate moderately with disease severity, suggesting their utility as adjunct biomarkers. Their limited specificity requires consideration of additional inflammatory, allergic, and coagulation markers in assessment.

Keywords: Biomarkers, Chronic Spontaneous Urticaria, CRP, D-dimers, Inflammation, Thrombosis, UAS7.

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INTRODUCTION

Chronic Spontaneous Urticaria (CSU) is a medical condition marked by the repeated occurrence of hives, angioedema, or both lasting over six weeks. CSU affects 0.5-1% of the Pakistani population and significantly influences the lives of those afflicted, as it can be quite persistent and unpredictable, making treatment outcomes also uncertain.¹ The exact pathophysiology behind CSU is not completely known, but it is thought to result from immune dysregulation, with possible roles of autoimmunity, infections, and other systemic diseases.² Thrombin-antithrombin and various byproducts of coagulation/fibrinolysis have been proposed to trigger activation of mast cells and heightened vascular permeability.³

There is a dire need for exploring the potential biomarkers for CSU that would address the issue of its

unpredictable duration, and would effectively predict its severity, duration of suffering and its management.⁴ Currently, UAS7 is commonly utilized as a measure of disease activity, scoring the primary signs and symptoms of urticaria (wheals and itching) noted by the patient over a span of 7 consecutive days.⁵ Heightened concentrations of prothrombin fragment 1+2 (F1+2), D-dimer, FVIIa, C-reactive protein (CRP), interleukin-6 (IL-6), matrix metalloproteinase 9 (MMP-9), mean platelet volume (MPV), tumor necrosis factor, dehydro-epiandrosterone sulfate, and vitamin D are also extensively recognized as reliable biomarkers for CSU.⁶⁻¹⁰ Nevertheless, the relationship between inflammation and thromboplastin time, in both patients and healthy controls, has yet to be investigated.

This study focused on examining the relationship between CRP, reflecting inflammation, and D-Dimer, a parameter of activated partial thromboplastin time, in both CSU patients and healthy individuals.

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METHODOLOGY

This cross-sectional analytical study was conducted at Department of Dermatology, Pak-Emirates Military Hospital Rawalpindi, Pakistan, between February 2023 to January 2024 following due approval by the Institutional Ethical Committee (A/29/ER/20.2024).

Inclusion Criteria: Newly diagnosed or untreated adults with CSU, of either gender, aged between 20 and 60 years were included.

Exclusion Criteria: Participants with acute urticaria, current autoimmune or inflammatory conditions, recent infections or thrombotic events within the past three months, or those who had used systemic corticosteroids, immunosuppressants, or anti-inflammatory medications within two weeks prior to enrollment were excluded.

The sample size was determined using the OpenEpi online calculator. Using an assumed prevalence of chronic spontaneous urticaria (CSU) at 1% in the general population, the estimated minimum sample size required was 196.1 This was increased to 200 to accommodate a potential attrition. A total of 100 CSU patients and 100 healthy controls were obtained from the Rawalpindi-Islamabad area through non-probability consecutive sampling, after obtaining informed consent.

Adult age range was selected to focus on the adult population most commonly affected by chronic spontaneous urticaria (CSU), as the condition typically presents in early to middle adulthood and peaks between the third and fifth decades of life. Participants had an average age of 40 ± 20.2 years, and the mean duration of illness was 20.6 ± 15.4 months, as they continuously received antihistamine treatment; treatment was maintained throughout the study.

The research was conducted to evaluate the levels of CRP and D-dimers in patients identified with CSU and to determine a correlation between these biomarkers and the disease's severity. Comprehensive clinicodemographic information about disease duration and treatment response was recorded, and patients with inadequate data were removed from the study. The Urticaria Activity Score over 7 days (UAS7) was utilized to evaluate disease severity and quality of life. UAS7 classifications included urticaria-free = 0; well-controlled urticaria = 1–6; mild = 7–15; moderate = 16–27; and severe urticaria = 28–42.

All participants underwent an extensive medical history, physical examination, and assessment of CSU severity utilizing UAS7, referencing a 7-day recall timeframe preceding blood collection. Venous blood samples were obtained to assess CRP and D-dimer concentrations. CRP was assessed with a high-sensitivity turbidimetric assay, and D-dimer was evaluated using ELISA. The reference ranges were 0–5 mg/L for CRP and 0–0.5 mg/L FEU for D-dimer. Other markers comprised serum IgE (evaluated through CLIA) and coagulation metrics, i.e., PT and APTT using coagulometric techniques, to offer extra understanding of allergic and coagulation characteristics in CSU.

Data were analyzed with Statistical Package for Social Sciences (SPSS) version 20. Shapiro-Wilk test was utilized to evaluate the normality of continuous variables. All variables exhibited a non-normal distribution; therefore, outcomes were reported as Median and Interquartile Range (IQR). Mann-Whitney U test was employed to compare continuous variables between patients with CSU and the control group. Chi-square test was utilized for categorical variables such as gender, allergy history, thyroid condition, and increased IgE levels. Spearman's rank correlation coefficient was employed to evaluate the correlation between UAS7 and biomarkers (CRP, D-dimer, IgE, PT, APTT). A p -value ≤ 0.05 was deemed statistically significant.

RESULTS

We recruited 200 individuals: 100 patients with chronic spontaneous urticaria (CSU) and 100 healthy participants. The median age of patients at CSU was 35.5 years (IQR: 28.6–42.5), and there was no statistically significant difference found between males and females ($p=0.37$). The duration of the disease was considerably longer in male patients (7.7 months, IQR: 0.0–15.3) compared to female patients (0.0 months, IQR: 0.0–11.3) ($p=0.001$). A greater percentage of females indicated a positive allergic history (83.3%) than males (65%) ($p=0.01$). Additional parameters, including angioedema and thyroid abnormalities, exhibited no notable differences between sexes ($p=0.098$ and $p=0.06$, respectively). The median serum IgE levels in male CSU patients (240.5 kU/L, IQR: 143.0–972.3) were noticeably greater than in female patients (162.3 kU/L, IQR: 129.8–691.5), which was significant ($p=0.003$). Table-I provides a summary of clinicodemographic characteristics.

Table-I: Clinicodemographic Data of Participants (n=200)

Parameter	Total (n=200) n (%)	Female (n=97) n (%)	Male (n=103) n (%)	p-value
Age in years, Median (IQR)	35.5 (28.6–42.5)	34.6 (28.4–41.6)	36.5 (28.6–44.0)	0.370
Duration of illness in months, Median (IQR)	0.0 (0.0–13.7)	0.0 (0.0–11.3)	7.7 (0.0–15.3)	0.001
Sex (F/M)	—	97	103	0.050
Angioedema	30(30.0%)	21 (35.0%)	9 (22.5%)	0.098
Allergic history	76(76.0%)	50 (83.3%)	26 (65.0%)	0.010
Thyroid abnormality	6(6.0%)	5 (8.3%)	1 (2.5%)	0.060
Serum IgE (kU/L), Median (IQR)	179.7 (133.7–842.5)	162.3 (129.8–691.5)	240.5 (143.0–972.3)	0.003
Elevated IgE (>100)	90 (90.0%)	40 (66.7%)	19 (47.5%)	0.370

The severity of disease, evaluated by the Urticaria Activity Score over 7 days (UAS7), demonstrated notable differences between genders. Of the female patients, 50% demonstrated severe disease (UAS7: 28–42), and 30.9% showed moderate disease (UAS7: 16–27). Conversely, 32.5% of male patients exhibited well-managed disease (UAS7: 0–6), while 20% experienced mild urticaria (UAS7: 7–15). The detailed breakdown of UAS7 severity grades is shown in Table-II.

Table-II: Urticaria Activity Score (UAS7) scores for patients Suffering from Chronic Spontaneous Urticaria (n=200)

UAS7 Score Range	Severity Category	Female (n=97) n (%)	Male (n=103) n (%)	Total (n=200)
0–6	Well-controlled	7(7.2%)	13(12.6%)	20(10.0%)
7–15	Mild	7(7.2%)	8(7.8%)	15(7.5%)
16–27	Moderate	18(18.6%)	12(11.7%)	30(15.0%)
28–42	Severe	30(30.9%)	5(4.9%)	35(17.5%)

Comparative analysis of biomarkers showed notably higher serum IgE, CRP, and D-Dimer levels in CSU patients versus controls. In the CSU group, the median serum IgE was 842.4 kU/L (IQR: 439.4–1327.5), whereas the control group had a median of 141.2 kU/L (IQR: 122.5–163.9) ($p=0.003$). CSU patients exhibited significantly elevated CRP levels (12.2 mg/L, IQR: 9.6–15.1) in comparison to controls (3.1 mg/L, IQR: 2.2–3.8) ($p<0.001$). Likewise, D-Dimer concentrations were elevated in the patient cohort (1.17 ng/mL, IQR: 0.96–1.49) compared to the control group (0.28 ng/mL, IQR: 0.23–0.36, $p<0.001$). Coagulation indicators also indicated a notable extension in the CSU group. Prothrombin time measured 23.0 seconds (IQR: 22.2–23.9) for CSU patients, in contrast to 13.0 seconds (IQR: 12.3–13.7) for controls ($p=0.002$). Meanwhile, activated partial thromboplastin time (APTT) was 74.0 seconds (IQR: 72.3–77.0) for CSU patients, whereas it was 34.7

seconds (IQR: 33.3–35.9) for healthy participants ($p<0.001$). Table-III displays the comparative data regarding biomarkers.

Table-III: Biomarker Comparison Between Chronic Spontaneous Urticaria (CSU) Patients and Healthy Controls

Biomarker	CSU Patients (n=100) Median (IQR)	Controls (n=100) Median (IQR)	p-value
Serum IgE (kU/L)	842.4 (439.4–1327.5)	141.2 (122.5–163.9)	0.003
Prothrombin Time (sec)	23.0 (22.2–23.9)	13.0 (12.3–13.7)	0.002
APTT (sec)	74.0 (72.3–77.0)	34.7 (33.3–35.9)	<0.001
UAS7	16.4 (14.8–18.0)	0.0 (0.0–0.0)	—
CRP (mg/L)	12.2 (9.6–15.1)	3.1 (2.2–3.8)	<0.001
D-Dimer (ng/mL)	1.17 (0.9–1.4)	0.28 (0.2–0.3)	<0.001

* UAS7 = Urticaria Activity Score over 7 days; CRP = C-reactive protein; APTT = activated partial thromboplastin time

DISCUSSION

The results of this study confirm that chronic spontaneous urticaria (CSU) includes not just allergic factors but also inflammatory and prothrombotic aspects. The notably high serum concentrations of C-reactive protein (CRP) and D-dimer in CSU patients, relative to healthy controls, reinforce their possible value as additional biomarkers for disease severity. The link between elevated CRP and disease activity has been recorded in prior studies. Our findings are consistent with an earlier study, which identified CRP as an important marker associated with the severity of CSU and treatment response.¹¹ Likewise, the current research corroborates previous results, indicating a notable relationship between increased D-dimer levels and CSU severity in Indian patients.¹² Both CRP and D-dimer levels were found to be significantly elevated in CSU patients relative to the control group. This aligns with multiple studies, which observed positive correlations between CRP, interleukin-6 (IL-6), and CSU activity.^{13,14} The role of inflammatory cytokines like IL-6 in the development of CSU may account for the increased CRP seen in our group.¹¹ Nonetheless, as highlighted in the results of Kuna *et al.*, variations in inflammatory responses at both individual and population levels may affect biomarker concentrations.¹⁵ The noted increase in serum IgE levels in CSU patients aligns with the recognized atopic characteristics of the condition.³ Increased IgE is a characteristic of allergic sensitization and promotes mast cell degranulation and basophil activation, which are essential to the urticarial response. These results reflect earlier studies that highlight the immunoglobulin-driven pathophysiology of CSU.^{3,16}

We also found markedly extended prothrombin time (PT) and activated partial thromboplastin time (APTT) in CSU patients. This reinforces the notion that CSU is linked to concealed coagulation irregularities, potentially driven by the expression of tissue factor from mast cells and activation of the endothelium³. These findings align with research conducted by Kasperska-Zajac *et al.* and Kolkhir *et al.*, indicating that both extrinsic and intrinsic coagulation pathways might play a role in CSU.^{16,17} Differences specific to gender were apparent in both the severity of the disease and the response to treatment. Female patients showed elevated UAS7 scores along with a higher incidence of raised CRP, D-dimer, and IgE levels, indicating increased inflammatory activation severity. On the other hand, male patients showed a greater disease duration and heightened resistance to antihistamine treatment. As illustrated in Figure, male patients often needed double, triple, or quadruple amounts of antihistamines for symptom management, and a portion (16%) still proved resistant even with maximum doses. Importantly, patients exhibiting the highest D-dimer levels were among the least likely to experience symptom resolution, emphasizing a potential connection between prothrombotic activity and ineffective treatment response, as also reflected in another study.¹⁷

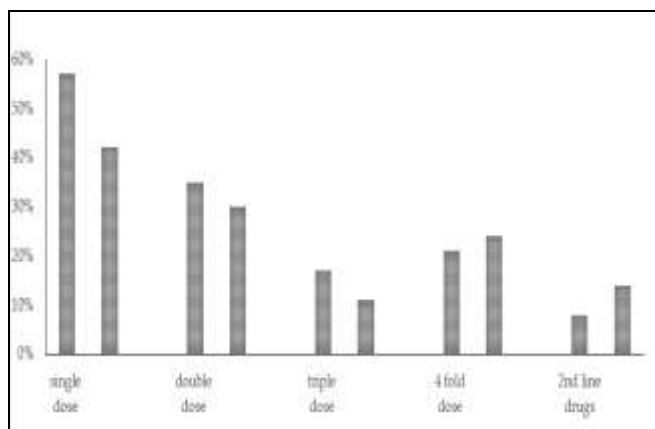


Figure. Gender-wise comparison of Antihistamine Dosage requirements for Symptom Control in Chronic Spontaneous Urticaria (CSU) patients (n=200)

Although CRP and D-dimer are potential indicators for tracking disease severity, their limited specificity should be recognized. Infections, autoimmune diseases, or cardiovascular conditions may also show elevated levels of these biomarkers. Thus, they need to be understood within the

framework of clinical parameters like UAS7 and treatment results.^{18,19}

LIMITATIONS OF STUDY

The research involves 200 Pakistani patients from the Rawalpindi-Islamabad area, so the results of this study cannot be applied to larger groups from various demographic or geographical backgrounds. Moreover, the influence of antihistamines could not be eliminated as the medication dosage was maintained throughout the duration of the study. Another constraint was that elements such as pregnancy and the menstrual cycle in female participants were not considered

CONCLUSION

CRP and D-dimer levels are elevated in CSU and correlate moderately with disease severity, suggesting their utility as adjunct biomarkers. Their limited specificity requires consideration of additional inflammatory, allergic, and coagulation markers in assessment.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

ZHA & AUB: Conception, study design, drafting the manuscript, approval of the final version to be published.

HFQ & SA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SFU & ANM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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