

# D-dimer levels in patients with chronic urticaria: A case–control study on a Kashmiri population

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## ABSTRACT

**Background:** Chronic urticaria (CU) is a common skin condition, affecting 0.5–1% of the population. Multiple studies have demonstrated that plasma D-dimer levels could be employed as a biomarker for disease activity and treatment response in patients with CU. **Aim:** The aim was to evaluate the correlation between D-dimer levels and the disease activity of CU. **Materials and Methods:** This study was a case–control study conducted on 120 patients suffering from CU and 50 healthy subjects. Plasma D-dimer levels were measured using ELISA. **Results:** Mean plasma D-dimer levels in the patients with CU (720.5 ng/mL) were significantly higher than those in the controls (405.6 ng/mL) ( $p < 0.001$ ). A significant correlation was observed between plasma D-dimer levels and the UAS (urticaria activity score). **Conclusion:** The patients with CU had higher plasma D-dimer levels than the control group. A positive statistical correlation was observed between plasma D-dimer levels and the severity of CU.

**Key words:** Chronic urticaria; D-dimer; Autoimmunity

## INTRODUCTION

Chronic urticaria (CU) is a pruritic skin condition characterized by wheals and/or angioedema lasting for at least six weeks or longer [1]. It is a common cause in patients presenting to primary care, emergency rooms, and dermatologists [2]. With a point prevalence of 0.5–1% in the population, it is one of the most common skin disorders encountered [3].

Chronic urticaria may severely affect the quality of life of the patient, due to the duration of symptoms, which may persist for years [4]. Nearly half of the patients have persistent symptoms even after three years of onset [5].

The release of histamine and other inflammatory mediators from mast cells causes an acute inflammatory response, including vasodilatation, increased fluid permeability, and the recruitment of various cells, which constitute the basic pathogenesis of the disease [1].

In CU, autoimmunity plays a major role. In a subset of patients, the coagulation cascade is also activated through the extrinsic pathway, which may increase plasma D-dimer levels [6,7].

Recent studies have demonstrated the correlation between plasma D-dimer levels and CU, suggesting the possibility of the use of plasma D-dimer levels as a biomarker for disease activity and response to treatment in patients with CU [8–11].

There is a paucity of data concerning plasma D-dimer levels in Kashmiri patients with CU. This study investigates the relationship between plasma D-dimer levels and disease activity in a Kashmiri population.

## MATERIALS AND METHODS

This study was conducted after receiving clearance from the institutional ethical committee. A total of 120 patients with CU (more than two episodes a week

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for more than six weeks) who visited the outpatient department of dermatology of the Government Medical College in Srinagar, India, from November 2020 to July 2021, aged at least eighteen years, and clinically diagnosed with CU were included in the study. Patients with diseases or taking medications that could have altered the coagulation pathways were excluded from the study.

A total of fifty age- and sex-matched healthy subjects undergoing routine check-ups comprised the control group.

All cases and controls voluntarily agreed to participate in the study and signed a written consent form. Demographic data and personal, family, and medical histories were recorded.

### Assessment of Disease Activity

All patients were interviewed by a dermatologist and the urticaria activity score (UAS) was determined. Disease activity was assessed on the basis of the EAACI/GA2LEN/EDF activity score [1], comprising the wheal score and pruritis score. Disease activity was scored from 0 to 6, where 0 was considered no disease, 1–2 mild disease, 3–4 moderate, and 5–6 severe.

### Methods

Plasma D-dimer levels were measured using the ELISA (enzyme-linked immunosorbent assay) in accordance with the manufacturer's recommendations (Instrumentation Laboratory Company, Bedford, MA, 01730-2443 (U.S.)). Levels below 500 ng/mL were regarded as normal.

### Statistical Analysis

The data was analyzed with the SPSS software. Descriptive statistics and percentages were used to describe the demographic data, clinical features, and plasma D-dimer levels. Non-parametric tests (e.g., chi-squared test) were employed to evaluate differences between the groups. Correlation was calculated using Spearman's rank test and logistic regression analysis. The statistical significance at  $p < 0.05$ .

## RESULTS

### Demographic and Clinical Characteristics

Out of the 120 patients, 52 were males (43.3%) and 68 were females (56.7%), with a mean age of  $33.5 \pm 8.4$  years. The average age of onset was  $31.5 \pm 8$  years. The duration of disease in the majority of the patients

was  $\leq 1$  year with a mean duration of 15 months. Out of the 120 patients, 29 (24%) had associated angioedema, whereas 15 (12.5%) had a family history of atopy (asthma, allergic rhinitis, etc.). A majority of the patients (56; 46.6%) had moderate disease severity, 41 (34%) had mild severity, and 14 (11.6%) had severe severity. Nine patients had the disease well under control.

### Correlation between Plasma D-Dimer Levels and Disease Severity

The patients were divided into three groups:  $< 1$  year, 1–5 years, and  $> 5$  years. It was noted that D-dimer levels in patients who had a longer duration of the disease were significantly higher ( $p < 0.05$ ).

The difference in the proportion of abnormal plasma D-dimer levels in the patients with CU and the control group was statistically significant (60.8% vs. 44%;  $p = 0.04$ ) (chi-squared test: 4.05). Plasma D-dimer levels were significantly higher in the patients with CU than in the control group (720.5 ng/mL vs. 405.6 ng/mL;  $p < 0.001$ ). Table 1 shows disease severity and plasma D-dimer levels among all groups.

## DISCUSSION

It is imperative to find reliable biomarkers to assess disease severity when determining the correlation between disease severity and treatment response. A study by Raffael et al. [11] found that disease severity may also predict the duration of chronic spontaneous urticaria.

Studies have shown a link in the pathogenesis of CU with the activation of the coagulation cascade [7,12,13]. The activation of this cascade results in thrombin formation and the activation of mast cells. This leads to the release of histamine from mast cells and causes edema formation in urticaria [7]. D-dimer, which is an FDP (fibrin degradation product) is formed after the lysis of thrombus. It may remain elevated in the serum for around one week [14].

In our study, we observed higher D-dimer levels in the patients with CU than in the control group. Similar results were found in other studies conducted in other regions [8,10,14]. Thus, our study provides further evidence of a possible mechanism of coagulation cascade activation in patients with CU.

Our study demonstrated statistically higher plasma D-dimer levels and a higher proportion of abnormal

**Table 1:** Disease severity and plasma D-dimer levels among all groups

Disease activity group	No. of patients (%)	Mean plasma D-dimer levels (ng/mL)	Proportion of abnormal D-dimer levels in each group (n (%))
None	9 (7.5%)	530.6	4 (44.4%)
Mild	41 (34%)	619.6	23 (56.1%)
Moderate	56 (46.6%)	765.8	37 (66%)
Severe	14 (11.6%)	950	9 (64.2%)
Total	120	720.5	73 (60.8%)

plasma D-dimer levels in patients with CU. This was corroborated in a study by Asero et al. [15]. This finding is also supported by a literature review by Pavel et al. [16].

D-dimer levels and CRP show a strong correlation with CSU activity [16]. Our study also found a positive correlation between disease severity and serum D-dimer levels. Hence, D-dimer may play a vital role as a biomarker for CU severity. Besides, D-dimer levels in the plasma may also be employed to assess treatment response and potential antihistamine resistance to CU [17]. Therefore, D-dimer may be a predictor of response to treatment, more so in refractory cases or antihistamine-resistant CU.

Although several studies show a possible correlation between plasma D-dimer levels and CU, larger studies are needed due to the lack of strong evidence.

### Limitations

The following limitations were noted in this study:

1. The correlation between D-dimer levels and treatment response was not assessed.
2. Other biomarkers were not assessed.

### CONCLUSION

In our study, the patients with CU had higher plasma D-dimer levels than the control subjects, and the levels of D-dimer were higher in more severe cases. D-dimer levels may be considered a biomarker for disease activity/severity.

### Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

### Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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