

# Clinicoepidemiological Profile of Patients with Chronic Urticaria and its Association with D-dimer Levels at a Tertiary Care Centre: A Prospective Cohort Study

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## ABSTRACT

**Introduction:** Chronic urticaria is a commonly encountered, long-standing skin condition that typically lasts for more than six weeks and has various underlying aetiologies, including chronic infections, infestations, immunological and non immunological causes, and physical factors. In some cases, it may be idiopathic. Recent studies have shown that the activation of the coagulation cascade is involved in the development of chronic urticaria. This involvement is reflected in plasma D-dimer levels, which are explored in the current study.

**Aim:** To assess the epidemiological and clinical characteristics of urticaria and their association with D-dimer levels in a tertiary care centre.

**Materials and Methods:** This prospective cohort study was conducted at Department of Dermatology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India, from August 2022 to July 2023. The study included 100 chronic urticaria patients attending the dermatology Outpatient Department (OPD) to investigate various clinical types and their epidemiological factors. D-dimer levels were estimated using the latex-enhanced immunoturbidimetry assay method. The mean and range were calculated, and statistical analysis of various clinic-epidemiological characteristics was performed using Pearson's Chi-square test. A p-value <0.05 was considered statistically significant.

**Results:** Among the 100 patients with chronic urticaria, 40 (40%) were males and 60 (60%) were females. The mean age of presentation was 30 years, and the mean duration was 20.5 months. Elevated plasma D-dimer levels were noted in 40 (40%) of the study population. Chronic Spontaneous Urticaria (CSU) constituted 92 (92%) of the cases, followed by Chronic Inducible Urticaria (CIU) with 4 (4%) cases and 4 (4%) cases with CSU+CIU. Angioedema was noted in 20 (20%) of the cases in the present study. Thyroid disorder was seen in 12 (12%) of the study population. The majority of patients (44%) had mild urticaria. The mean Urticaria Activity Score (UAS) score before treatment was 21.08. A statistically significant association was found between elevated plasma D-dimer levels and age range, duration of chronic urticaria, disease severity, angioedema, and response to antihistamines. The response to antihistamines was graded based on the UAS7 score calculated before and after treatment.

**Conclusion:** The present study provides additional evidence to the existing literature by establishing an association between D-dimer levels and factors such as severity and angioedema. It also provides important insights into the relationship between age range, duration of chronic urticaria, and elevated plasma D-dimer levels by establishing statistical significance between these factors.

**Keywords:** Angioedema, Chronic inducible urticaria, Chronic spontaneous urticaria, Coagulation cascade, Histamine antagonists

## INTRODUCTION

Urticaria and angioedema belong to a heterogeneous group of diseases that can occur due to a multitude of causes. Urticaria may be caused by various factors such as antigen-antibody complexes, direct mast cell activation, and activation of the FcεR1 receptor, which are some of the pathogenic bases of urticaria. In most cases of acute urticaria, Immunoglobulin E (IgE) plays an important role, while Immunoglobulin G (IgG) is implicated in cases of chronic urticaria. Due to these multiple pathogenic bases, the management of this condition is challenging as the cause cannot always be ascertained [1].

Activation of the complement occurs due to various stimuli, and the release of the C5a fragment stimulates mast cells and acts chemotactically on neutrophils, eosinophils, and monocytes. Mast cells release both preformed mediators (e.g., histamine, heparin, bradykinin) and mediators produced immediately after activation (e.g., prostaglandins), [2], which ultimately cause vasodilation and a wheal and flare reaction.

Chronic urticaria is defined as the occurrence of wheals with or without angioedema for six weeks or longer [3,4]. There has been exploration of the interaction between immunological and coagulation pathways in recent years as a probable cause of chronic and treatment-resistant cases of urticaria [1]. It has been observed that tissue factor expressed by eosinophils can induce activation of the coagulation cascade, which in turn generates thrombin that can increase vascular permeability both directly by acting on endothelial cells and indirectly by inducing degranulation of mast cells [3].

D-dimer is a fibrin degradation product and a marker of thrombin activity, which increases vascular permeability and stimulates mast cell degranulation [5]. The present study has been conducted based on the assumption that a positive association exists between various clinicoepidemiological disease activities of chronic urticaria and elevated D-dimer levels.

Several studies have been conducted to evaluate the role of D-dimer in chronic urticaria in the past, showing a significant association. Positive associations between severity and elevated D-dimer levels have been observed in these studies [1,2]. The results of a study by

Sadowska-Przytocka et al., showed a statistically significant high positive association between serum D-dimer concentration and the severity of urticaria symptoms [1]. Another study conducted by Criado PR et al., revealed that patients with active chronic urticaria had the highest serum levels of D-dimer compared to those with chronic urticaria in remission [2].

The pathogenesis of chronic urticaria is idiopathic in many cases. There is a gap in the literature regarding the exact pathogenesis in these cases. Along with autoimmunity, the role of the coagulation system can be a causative factor [1]. The possibility of activation of the coagulation system was explored by using the D-dimer assay in the present study. The exact role of this immunological and coagulation interaction should be further determined. Hence, the aim of the present study was to assess the clinicoepidemiological characteristics of chronic urticaria and their association with D-dimer levels.

## MATERIALS AND METHODS

The present prospective cohort study was conducted at Department of Dermatology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India, for a duration of one year from August 2022 to July 2023. The study included 100 patients with chronic urticaria who attended the dermatology OPD during the study period. Institutional Ethical Committee clearance (07/IEC/GEMS&H/2023) was obtained, and written informed consent was obtained from all patients.

**Inclusion criteria:** Patients aged >18 years with a diagnosis of chronic urticaria (urticaria lasting >6 weeks) were included in the present study.

**Exclusion criteria:** Patients with a history of thromboembolic diseases, cardiovascular accidents, coronary artery disease, liver disease, severe renal disease, deep vein thrombosis, recent surgeries, malignancy, recent trauma, those on anticoagulants, autoimmune connective tissue diseases, or vasculitis were excluded from the study. Pregnant and lactating females were also excluded.

Clinicoepidemiological characteristics that were assessed included age, gender, duration of chronic urticaria, severity of disease, and antihistamine resistance with elevated D-dimer levels.

### Study Procedure

A detailed history was taken, and a complete cutaneous and systemic examination was performed. Urticaria Activity Score 7 (UAS7) was calculated for each patient before and after treatment with antihistamines. All routine investigations were conducted, including complete blood count, absolute eosinophil count, liver function tests, kidney function tests, and thyroid hormone levels. Bleeding time and clotting time were also noted. The evaluation of D-dimer levels [5,6] involved estimating D-dimer levels in the patients using the latex-enhanced immunoturbidimetry assay method. The cut-off value for normal D-dimer was 500 µg/mL [5,6].

To perform the test, a 3.6 mL blood sample was mixed with 0.4 mL sodium citrate in 10 mL tubes under sterile conditions. These samples were immediately sent to the laboratory within three hours. Centrifugation was then conducted at 1600 G for 10 minutes at 22°C to obtain platelet-poor plasma. Following this, a double spin was performed through centrifugation at 1500 G for six minutes at 9°C. D-Dimer concentration levels were quantified in the obtained serum sample using the latex-enhanced immunoturbidimetric assay method.

The cases were classified into CSU, CIU, and a combination of both CSU and CIU based on the patients' history and relevant investigations. The severity of urticaria was graded using the UAS7 score. The UAS7 score is the sum of scores obtained by assigning numerical values to the severity of wheals and pruritus for each day in a week. The score ranges from 0-42 [Table/Fig-1] [7]; UAS7 values were assigned to five score ranges (bands). A score between 1-6 is considered as well-controlled urticaria. Scores ranging from 7-15, 16-27, and 27-42 are considered as mild, moderate, and severe

urticaria, respectively. Post-treatment, the response was graded based on the reduction in UAS score. Patients with a UAS7 score between 0-6 were considered to show an adequate response. Patients with a UAS score between 7-42 were considered to show an inadequate response, reflecting urticaria disease activity [Table/Fig-2] [8].

Score	Wheals	Pruritus
0	None	None
1	Mild <20 wheals in 24 hours	Mild (Present but not annoying or troublesome)
2	Moderate. 20-50 wheals in 24 hours	Moderate - Troublesome but not causing sleep disturbances
3	Intense >50 wheals in 24 hours or large confluent area of wheals	Severe (Pruritus which is sufficiently troublesome to interfere with sleep)

[Table/Fig-1]: Urticaria activity score 7 (UAS7) [7].

UAS7 score	Disease severity
0	Itch and hive free indicative of no symptoms of CSU, considered a full treatment response
1-6	Well-controlled urticaria indicates a good response to treatment
7-15	Mild urticaria
16-27	Moderate urticaria
28-42	Severe

[Table/Fig-2]: UAS7 score and disease severity [8].



[Table/Fig-3]: Shows clinical picture of patient with chronic urticaria who was resistant to treatment with antihistamines.

## STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 29.0. Pearson's Chi-square test was applied to determine the statistical significance between D-dimer levels and clinicoepidemiological factors. A p-value <0.05 was considered statistically significant.

## RESULTS

In the present study population, CSU was the most common type of chronic urticaria, accounting for 92% of cases [Table/Fig-4]. The number of males (n=20) and females (n=20) with elevated plasma D-dimer levels was equal, but the proportion of male patients (50%) with elevated D-dimer levels was higher than that of females (33.33%). However, there was no statistically significant association between gender and plasma D-dimer levels (p-value=0.96) [Table/Fig-5].

Type of chronic urticaria	No. of patients	Percentage
CSU	92	92
CIU	4	4
CSU+CIU	4	4
Total	100	100

[Table/Fig-4]: Depict the types of urticaria in the study population. CSU: Chronic spontaneous urticaria; CIU: Chronic inducible urticaria

Gender	Elevated D-dimer	Normal D-dimer	Total	p-value
Male	20	20	40	0.96
Female	20	40	60	
Total	40	60	100	

**[Table/Fig-5]:** Shows association of plasma D-dimer levels with respect to gender. Chi-square test

The age range of the study group was 18-75 years, with a mean age of 30 years. A statistically significant association ( $p$ -value=0.03) was noted between age and D-dimer levels in patients with chronic urticaria [Table/Fig-6].

Age range	Elevated D-dimer	Normal D-dimer	Total patients value	p-value
18-25 years	4	20	24	0.03
26-50 years	29	31	60	
51-75 years	4	8	12	
>75 years	3	1	4	
Total	40	60	100	

**[Table/Fig-6]:** Shows depicts distribution of patients in various age ranges along with the relation to plasma D-dimer levels in various age groups.  $p$ -value was calculated using Chi-square test;  $p$ -value is 0.03

The mean duration of urticaria was 20.5 months, and the majority of patients (44%) presented with a duration of less than three months. There was a remarkably significant statistical association ( $p$ -value=0.0002) between duration and elevated plasma D-dimer levels [Table/Fig-7].

Duration of urticaria	Elevated D-dimer	Normal D-dimer	Total patients	p-value
8 weeks to 3 months	8	36	44	0.0002
3 months-6 months	13	3	16	
7 months-1 year	7	1	8	
>1 year	12	20	32	
Total	40	60	100	

**[Table/Fig-7]:** Shows number of patients with duration of urticaria at the time of presentation and association with D-dimer level.  $p$ -value was calculated using Chi-square test;  $p$ -value is 0.0002

Urticaria severity was graded as mild, moderate, or severe based on the UAS score. The majority of patients (44%) presented with mild urticaria. A large percentage of patients with severe urticaria (71%) had elevated D-dimer levels, compared to only 9% in mild cases. There was a strong statistical significance between severity and elevated plasma D-dimer levels ( $p$ -value=0.001). The mean UAS score before treatment was 21.08 [Table/Fig-8].

Severity of urticaria	Elevated D-dimer	Normal D-dimer	Total patients	p-value
Mild	4	40	44	0.001
Moderate	16	12	28	
Severe	20	8	28	
Total	40	60	100	

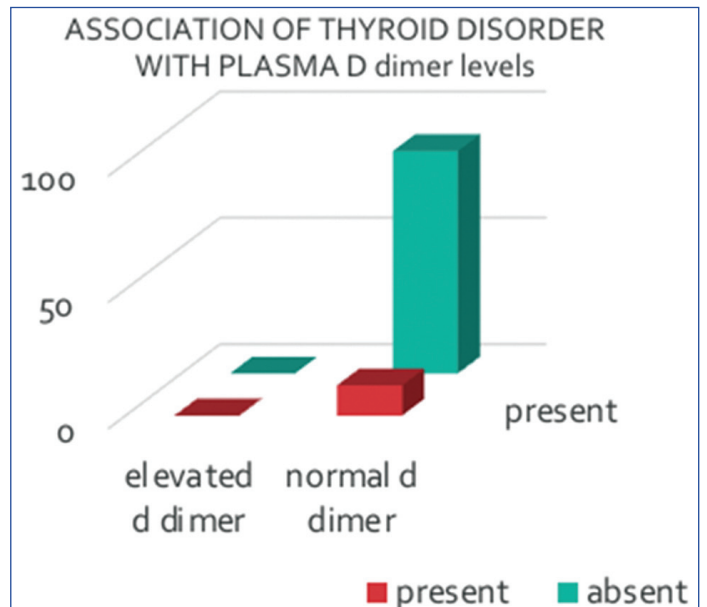
**[Table/Fig-8]:** Shows severity of urticaria in relation with plasma D-dimer levels.  $p$ -value was calculated using Chi-square test;  $p$ -value is 0.001

Elevated plasma D-dimer levels ranged from 617 ng/mL to 2681 ng/mL, with a mean of 1912.2 ng/mL. The mean for normal plasma D-dimer levels was 237.82 ng/mL. The percentage of patients with elevated D-dimer levels was higher (60%) in patients with angioedema, compared to 35% in patients without angioedema. There was a strong statistical significance ( $p$ =0.04) between the presence of angioedema and elevated D-dimer levels [Table/Fig-9]. Thyroid disorder was seen in 12 patients (12%) of the study population. Elevated D-dimer levels were not observed in patients with thyroid disorder. All chronic urticaria patients affected by thyroid

Angioedema	Elevated D-dimer	Normal D-dimer	Total patients	p-value
Present	12	8	20	0.04
Absent	28	52	80	
Total	40	60	100	

**[Table/Fig-9]:** Shows number of patients with and without angioedema with respect to D-dimer levels.  $p$ -value was calculated using Chi-square test;  $p$ -value is 0.04, which is statistically significant

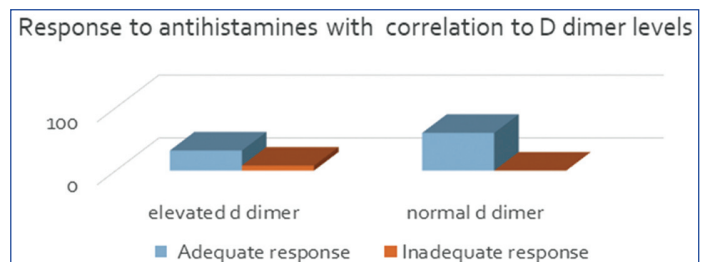
disorder had normal D-dimer levels [Table/Fig-10]. An adequate response with antihistamines was noted in 92% of patients. Among these patients, 64% had normal D-dimer levels. Inadequate response was observed in 8 patients, and 7 out of 8 (87.5%) had elevated D-dimer levels [Table/Fig-11,12].



**[Table/Fig-10]:** Shows presence of thyroid disorder in relation to plasma D-dimer in the study population in the form of a bar chart.

Response with antihistamines	Elevated D-dimer	Normal D-dimer	Total patients	p-value
Adequate response	33	59	92	0.0039
Inadequate response	7	1	8	
Total	40	60	100	

**[Table/Fig-11]:** Shows response to antihistamines in relation to plasma D-dimer levels.



**[Table/Fig-12]:** Shows response to anti-histamines in relation to plasma D-dimer levels in the form of a bar graph.

## DISCUSSION

The types of urticaria included in the present study were CSU, CIU, and CSU+CIU, accounting for 92%, 4%, and 4% of the patients, respectively. In a study conducted by Alen Coutinho I et al., [9], CSU accounted for 55.7% of the patients, while CSU associated with CIU accounted for 44.3%. These findings differ from the findings in the current study.

In the present study, elevated plasma levels of D-dimer were observed in 40 (40%) out of 100 patients, which is similar to the findings in a study conducted by Triwongwaranat D et al., [10], in which 48.3% of patients had elevated D-dimer levels. Additionally, a

female preponderance was noted in the present study, with females accounting for 60% of the study population and males accounting for 40%. This is in agreement with the findings of an epidemiological study conducted by Vijayabhaskar C and Venkatesan S, [11] in South India, where females constituted 62% of the population. Among the male patients in the present study, elevated D-dimer levels were seen in 20 (50%), while among the female patients, elevated D-dimer levels were seen in 20 (33.3%). However, there was no statistical significance between gender and the elevation of D-dimer levels ( $p$ -value=0.96).

The age range of patients in the present study was 18-76 years, which is higher than that of an Egyptian study conducted by Abo Alwafa HO et al., [12], where the age range was 18-52 years. In the present study, the mean age was 30 years, which was similar to an Egyptian study conducted by Farres MN et al., [13], where the mean age of patients was 29.6 years. The number of patients with elevated D-dimer levels was highest in the age range of 26-50 years, accounting for 28 (70%) out of 40 patients. There was a notable statistical significance between the age range and elevated levels of D-dimer, with a  $p$ -value of 0.032.

The duration of chronic urticaria in the present study ranged from eight weeks to one year. The majority of patients (44%) presented within a duration of less than three months. However, plasma D-dimer levels were found to be elevated in a high proportion (60%) of patients with a duration of more than one year, with 12 out of 20 patients showing elevated levels. This finding was further supported by a statistically significant association ( $p$ =0.00018) between the duration of chronic urticaria and elevated plasma D-dimer levels. These findings could not be corroborated with other studies as data pertaining to plasma D-dimer levels and duration of urticaria is scarce. Further studies are required to determine the relationship between plasma D-dimer levels and the duration of the disease.

The severity of the disease showed remarkable statistical significance with elevated D-dimer levels, as it was elevated in 20 (70%) out of 28 severe cases in the present study. These findings were consistent with multiple previous studies conducted by Triwongwanat D et al., Abo Alwafa HO et al., Farres MN et al., Dabas G et al., Asero R, In these studies, increased serum levels of D-dimer among patients with chronic urticaria were observed [2,10,12-15].

Angioedema was noted in 20 (20%) patients in the present study, which was lower compared to other studies such as Abo Alwafa HO et al., [12]. In the present study, elevated plasma D-dimer levels were observed in 12 (60%) out of 20 patients with angioedema, and this data was found to be statistically significant with a  $p$ -value of 0.04. This is in contrast to the study by Abo Alwafa HO et al., where they found no statistical significance [12].

An interesting finding is observed regarding the relationship between elevated plasma D-dimers and response to antihistamines. The proportion of patients with normal plasma D-dimer levels who showed a good response to antihistamines was greater, with 59 (98.3%) out of 60 patients, compared to the percentage of patients with elevated plasma levels, where 33 (82.5%) out of 40 patients responded well. These results are higher than the findings in the study conducted by Kaplan AP and Giménez-Arnau AM et al., where only 45-60% of cases with elevated plasma D-dimer levels were found to respond well to antihistamines [16,17]. This difference may be due to the inclusion of more severe cases in that study.

Seven out of 40 cases (17.5%) showed a lesser response to antihistamines and were considered relatively refractory to treatment. This percentage was significantly lower compared to the findings of the study by Abo Alwafa HO et al., where 35% of cases with elevated D-dimer were non responders to antihistamines [12]. Similar findings to the present study were noted in studies conducted by Humphreys F and Hunter JA, and Gattley N et al., [18,19].

In the present study, a patient with extremely high D-dimer levels was resistant to treatment with antihistamines but was successfully treated with cyclosporine. There are a few studies that emphasise the role of drugs like tranexamic acid and low molecular weight heparin, as well as cyclosporine [20,21]. Several multicentric studies need to be conducted to explore immunological and coagulation defects as a causation for this antihistamine-resistant chronic urticaria. The role of drugs like newer anticoagulants, biologicals, and biosimilars may form the future management armamentarium for chronic urticaria patients. D-dimer levels may be used as a laboratory parameter for determining antihistamine resistance and severity in these patients.

### Limitation(s)

The present study had a few limitations. It was conducted in a single tertiary care centre, so the results may not be directly applicable to a larger population. Further studies with a larger sample size can be conducted in the future.

### CONCLUSION(S)

The present study explores the importance of plasma D-dimer levels in cases of chronic urticaria and how these levels vary with factors such as gender and age. It also determines the statistical significance of these factors. The study provides important insights into the relationship between the duration of chronic urticaria and elevated plasma D-dimer levels, establishing a novel finding with statistical significance. Additionally, the study supports already established findings, such as the association between severity and elevated plasma D-dimer levels, as well as the decreased response to antihistamines in cases with elevated D-dimer levels. The role of the interaction between immune response and coagulation factors opens up new avenues for research in the management of antihistamine-resistant chronic urticaria. This includes the potential use of immunomodulators like cyclosporine and anticoagulants like low molecular weight heparin and tranexamic acid. Further studies are required to enhance the authors understanding and treatment of chronic urticaria with elevated D-dimers.

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