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Original Research Article

ASSOCIATION OF ELEVATED D-DIMER LEVELS WITH DISEASE SEVERITY AND QUALITY OF LIFE IN CHRONIC URTICARIA: A PROSPECTIVE COHORT STUDY

Anup Kumar Tiwary[1]

[1]*Associate Professor, Department of Dermatology, Venkateshwara Institute of Medical Sciences, Gajraula, Uttar Pradesh, India.*

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Corresponding Author:
Dr. Krishna Nitin Jadhav,
Associate Professor, Department of Dermatology, Venkateshwara Institute of Medical Sciences, Gajraula, Uttar Pradesh, India..
Email: anup07tunnu07@gmail.com

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ABSTRACT

Background: Chronic urticaria (CU) is a distressing condition with significant impact on patients' quality of life. Emerging evidence suggests a potential role of D-dimer levels as a biomarker for disease severity and treatment response. This study aimed to assess the clinicoepidemiological profile of CU patients and investigate the association between D-dimer levels and disease outcomes.

Materials and Methods: This prospective cohort study was conducted at a tertiary care center in India, enrolling adult patients diagnosed with CU. Detailed clinical history, comorbidities, and exacerbating factors were recorded. Disease severity was assessed using the Urticaria Activity Score over 7 days (UAS7), Dermatology Life Quality Index (DLQI), and pruritus severity scores. D-dimer levels, along with inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were measured. Treatment response was categorized as complete, partial, or no response based on symptom resolution. Statistical analyses included chi-square tests and independent t-tests to assess associations.

Results: The mean age of participants was 38.7 years, with a slight female predominance (56.5%). Elevated D-dimer levels were identified in 28.6% (mild), 14.3% (moderate), and 8.1% (severe) of participants. Elevated D-dimer levels were significantly associated with higher UAS7 scores (22.4 vs. 17.1; $p < 0.001$). Poorer quality of life (DLQI ≥ 11 in 65.3% vs. 36.1%; $p = 0.002$) was also significantly linked to elevated D-dimer levels. Patients with complete or partial treatment response demonstrated significant reductions in D-dimer levels ($p < 0.001$ and $p = 0.012$, respectively), while non-responders had persistently elevated D-dimer levels ($p = 0.684$).

Conclusion: Elevated D-dimer levels were significantly associated with increased CU severity, poorer quality of life, and impaired treatment response. D-dimer monitoring may serve as a valuable prognostic marker to guide therapeutic interventions in CU patients.

Keywords: Chronic urticaria, D-dimer, UAS7, Quality of life, Inflammatory markers.

INTRODUCTION

Chronic urticaria (CU) is a persistent inflammatory skin disorder characterized by recurrent wheals, pruritus, and/or angioedema that persist for six weeks or longer. Globally, CU affects approximately 0.5% to 1% of the population, with a higher prevalence noted among women, particularly those aged 30 to 50 years.[1] In India, the reported prevalence is around 0.7% to 1.2%, with a significant proportion of cases being attributed to environmental allergens, food additives, and psychosocial stressors.[2,3] CU is classified into chronic spontaneous urticaria (CSU), where no definite external trigger is identified, and chronic inducible urticaria (CIndU), which arises from specific stimuli such as pressure, cold, or heat.[4] Among these, CSU is the most common subtype, accounting for nearly 80% of all CU cases.[5]

The pathogenesis of CU is multifactorial, involving immune dysregulation, autoimmune mechanisms, and emerging evidence of coagulation abnormalities. Autoimmune CU, characterized by autoantibodies targeting the high-affinity IgE receptor or IgE itself, is reported in up to 40% to 50% of CSU patients.[6] Additionally, recent studies have identified an intricate interplay between coagulation and inflammatory pathways in CU pathophysiology. Activation of the coagulation cascade, particularly thrombin generation and fibrinolysis, is increasingly recognized as a contributory factor in CU pathogenesis.[7]

D-dimer, a fibrin degradation product and a marker of fibrinolytic activity, has gained attention as a potential biomarker for CU severity and treatment response. Elevated D-dimer levels have been reported in 30% to 50% of patients with severe CU, with higher levels linked to poor disease control, frequent relapses, and resistance to first-line antihistamine therapy.[8] Also, CU patients with elevated D-dimer levels were significantly more likely to require corticosteroids or omalizumab for symptom control, and D-dimer levels were positively correlated with urticaria activity scores (UAS), indicating its potential utility in monitoring disease progression and predicting treatment outcomes.[9,10]

In the Indian context, limited studies have explored the association between D-dimer levels and CU severity. Given the potential role of D-dimer in guiding therapeutic decisions, there is a pressing need to evaluate this biomarker in Indian CU patients. So, this prospective cohort study aimed to investigate the clinicoepidemiological characteristics of CU patients and assess the correlation between D-dimer levels and disease severity. By addressing this knowledge gap, the study seeks to improve diagnostic accuracy, guide treatment strategies, and enhance overall patient outcomes in resource-constrained settings.

MATERIALS AND METHODS

Study Design and Setting: This prospective cohort study was conducted in the Dermatology Outpatient Department (OPD) of a tertiary care center in North India for a period of 2 years from June 2022 to May 2024. The study protocol was approved by the Institutional Ethics Committee (IEC) and written informed consent was obtained from all participants prior to enrollment.

Study Population: The study population included patients diagnosed with CU based on clinical criteria outlined in the EAACI/GA²LEN/EDF/WAO guidelines. CU was defined as the presence of recurrent wheals, pruritus, and/or angioedema persisting for six weeks or longer. Both chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) cases were included. Patients eligible for the study were adults aged 18 years and above who were willing to participate and adhere to follow-up visits. Exclusion criteria included individuals diagnosed with acute urticaria, urticarial vasculitis, autoimmune conditions, known malignancies, or systemic infections. Patients who were receiving systemic anticoagulants, immunosuppressive therapy, or biologics such as omalizumab in the preceding three months were also excluded. Pregnant and lactating women were not included in the study.

Sample Size Calculation: The sample size determination was based on previous study by Chauhan et al., that reported 65% of CU patients had elevated D-dimer levels, and based on that the estimated sample size was calculated to be 144.[2] To account for potential dropouts and ensure adequate statistical power, the final sample size was adjusted to 147 participants.

Data Collection: Data collection involved detailed documentation of patient demographics, clinical history, and disease characteristics. Information recorded included age, gender, socioeconomic status, duration of CU, frequency and duration of urticaria episodes, presence of angioedema, and associated comorbidities such as hypothyroidism, hypertension, or diabetes mellitus. Details regarding potential triggers like food, medications, and stress were noted, along with prior treatment history and family history of allergic conditions. Disease severity was assessed using the Urticaria Activity Score over seven days (UAS7), a validated scoring system that considers daily scores for wheal count and itch severity. The total score ranges from 0 to 42, with severity categorized as mild (UAS7 score 0–15), moderate (UAS7 score 16–27), or severe (UAS7 score 28–42).

Laboratory Investigations: Laboratory investigations were conducted to assess D-dimer levels and other inflammatory markers. Venous blood samples (5 mL) were collected under aseptic conditions and processed within two hours of collection. D-dimer levels were measured using an enzyme-linked immunosorbent assay (ELISA) method with values greater than 500 ng/mL considered elevated. In addition to D-dimer estimation, routine investigations such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were performed to assess systemic inflammation. Thyroid function tests (TSH, T3, T4) were conducted to identify underlying thyroid disorders, given their known association with CU. Serum IgE levels were also measured to evaluate allergic response patterns.

Follow-up and Outcome Measures: Participants were followed monthly for a total of three months to assess disease progression, treatment response, and changes in D-dimer levels. At each visit, UAS7 scores were recorded to monitor symptom severity, and adherence to prescribed medications was documented. Treatment response was categorized as complete (complete resolution of symptoms), partial (≥50% reduction in UAS7 score), or no response (<50% reduction in UAS7 score). Any escalation of therapy, including the introduction of corticosteroids, cyclosporine, or omalizumab, was recorded.

Statistical Analysis: Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparative analyses between groups with elevated and normal D-dimer levels were conducted using the chi-square test for categorical variables and the independent t-test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among 147 patients with chronic urticaria, the mean age was 38.7 ± 12.5 years, with 43.5% males. The mean BMI was 24.6 ± 3.4 kg/m², and the average disease duration was 14.2 ± 8.6 months. Angioedema (38.1%) and atopic dermatitis (19.7%) were common. Known triggers included stress (32.0%), food (29.3%), drugs (14.3%), and unknown factors (24.4%). Hypertension (19%), diabetes (11.6%), and hypothyroidism (9.5%) were notable comorbidities. Smoking (21.1%), alcohol use (27.2%), and occupational exposures (15%) were reported. Seasonal exacerbation was seen in 41.5% of cases, with a mean of 3.2 ± 1.8 episodes per month. Antihistamine use was common (63.3%), while systemic corticosteroids (14.3%) and immunosuppressants (6.1%) were less frequent. Hospitalization for severe episodes occurred in 8.8% of participants [Table 1].

Table 1: Demographic and Clinical Characteristics of Study Participants.

Variable	Frequency (%) or Mean ± SD
Age (years)	38.7 ± 12.5
Gender	
Male	64 (43.5%)
Female	83 (56.5%)
BMI (kg/m²)	24.6 ± 3.4
Duration of CU (months)	14.2 ± 8.6
Family History of Allergic Conditions	38 (25.9%)
Presence of Angioedema	56 (38.1%)
Presence of Atopic Dermatitis	29 (19.7%)
Known Triggers	
Food	43 (29.3%)
Drugs	21 (14.3%)
Stress	47 (32.0%)
Unknown	36 (24.4%)
Comorbidities	
Hypertension (HTN)	28 (19%)
Diabetes Mellitus (DM)	17 (11.6%)
Hypothyroidism	14 (9.5%)
Autoimmune Disorders	10 (6.8%)
Smoking History	31 (21.1%)
Alcohol Use	40 (27.2%)
Occupational Exposure	
Chemical Exposure	10 (6.8%)
Dust Exposure	8 (5.4%)
Other Occupational Exposures	4 (2.7%)
Seasonal Exacerbation	61 (41.5%)
Frequency of Exacerbations (per month)	3.2 ± 1.8
Use of Antihistamines	
Current Use	93 (63.3%)
Previous Use	54 (36.7%)
Use of Systemic Corticosteroids	
Current Use	21 (14.3%)
Previous Use	18 (12.2%)
Use of Immunosuppressants	9 (6.1%)
Previous Hospitalization for Severe Urticaria	13 (8.8%)

The mean ESR and CRP levels were 26.4 ± 11.7 mm/hr and 8.2 ± 4.5 mg/L, respectively. Hemoglobin averaged 12.3 ± 1.8 g/dL, with leukocyte, neutrophil, and lymphocyte counts of 8217.3 ± 1582.7/µL, 5203.4 ± 1120.5/µL, and 2468.5 ± 682.1/µL, respectively. Serum IgE and eosinophil counts were 244.6 ± 112.9 IU/mL and 489.3 ± 133.2/µL. Mean D-dimer was 686.4 ± 438.5 ng/mL, with 49% normal and 28.6%, 14.3%, and 8.1% showing mild, moderate, and severe elevation. Liver and renal function parameters were within normal ranges [Table 2].

Table 2: Laboratory Parameters of Study Participants.

Parameter	Frequency (%) or Mean ± SD
ESR (mm/hr)	26.4 ± 11.7
CRP (mg/L)	8.2 ± 4.5
Hemoglobin (g/dL)	12.3 ± 1.8

Total Leukocyte Count (/µL)	8217.3 ± 1582.7
Neutrophil Count (/µL)	5203.4 ± 1120.5
Lymphocyte Count (/µL)	2468.5 ± 682.1
Monocyte Count (/µL)	480.2 ± 135.3
Serum IgE (IU/mL)	244.6 ± 112.9
Platelet Count (x10³/µL)	287.1 ± 62.8
Serum Eosinophil Count (/µL)	489.3 ± 133.2
Serum Total Protein (g/dL)	7.1 ± 0.6
Serum Albumin (g/dL)	4.3 ± 0.5
Serum Globulin (g/dL)	2.8 ± 0.4
Mean D-dimer Levels (ng/mL)	686.4 ± 438.5
D-dimer Category	
Normal (≤500 ng/mL)	72 (49.0%)
Mildly Elevated (501–1000 ng/mL)	42 (28.6%)
Moderately Elevated (1001–2000 ng/mL)	21 (14.3%)
Severely Elevated (>2000 ng/mL)	12 (8.1%)
Liver Function Tests (LFTs)	
ALT (U/L)	28.6 ± 11.4
AST (U/L)	32.3 ± 10.8
Alkaline Phosphatase (U/L)	78.2 ± 23.7
Bilirubin (mg/dL)	0.8 ± 0.3
Renal Function Tests (RFTs)	
Blood Urea (mg/dL)	24.1 ± 8.9
Serum Creatinine (mg/dL)	0.9 ± 0.2

Participants had a mean UAS7 score of 19.8 ± 7.2 and a pruritus severity score of 6.8 ± 2.1. Sleep disturbance occurred on average 3.7 ± 1.4 days per week, with 28.6% reporting disturbance ≥3 days/week. The mean DLQI score was 12.5 ± 5.9, with 39.5% experiencing moderate and 36.7% severe quality of life impairment. Regarding daily activities, 30.6% reported mild and 21.1% severe impact. Work productivity was affected in 64.6% of participants, with 26.5% experiencing mild, 22.4% moderate, and 15.7% severe impairment [Table 3].

Table 3: Disease Activity, Quality of Life, and Functional Impact in Study Participants.

Parameter	**Frequency (%) or Mean ± SD**
UAS7 Score (Urticaria Activity Score over 7 days)	19.8 ± 7.2
Pruritus Severity Score (0-10 scale)	6.8 ± 2.1
Sleep Disturbance (Days/Week)	3.7 ± 1.4
Sleep Disturbance (≥3 days/week)	42 (28.6%)
Dermatology Life Quality Index (DLQI) (0-30 scale)	12.5 ± 5.9
Impact on Quality of Life (Measured via DLQI)	
Mild Impact	35 (23.8%)
Moderate Impact	58 (39.5%)
Severe Impact	54 (36.7%)
Impact on Daily Activities (Measured via CUPRO)	
No Impact	71 (48.3%)
Mild Impact	45 (30.6%)
Severe Impact	31 (21.1%)
Impact on Work Productivity (Measured via WPAI)	
No Impact	52 (35.4%)
Mild Impact	39 (26.5%)
Moderate Impact	33 (22.4%)
Severe Impact	23 (15.7%)

Among participants, those with elevated D-dimer levels had significantly higher UAS7 scores (22.4 ± 6.8 vs. 17.1 ± 7.1; $p < 0.001$) and greater pruritus severity (7.4 ± 1.9 vs. 5.8 ± 2.0; $p < 0.001$). Elevated D-dimer levels were associated with higher rates of angioedema (53.3% vs. 22.2%; $p < 0.001$), prolonged CU duration (18.7 ± 9.2 vs. 10.5 ± 7.3 months; $p < 0.001$), and increased sleep disturbance (38.7% vs. 18.1%; $p = 0.01$). Quality of life was notably worse in the elevated D-dimer group, with 65.3% reporting a DLQI ≥ 11 compared to 36.1% in the normal D-dimer group ($p = 0.002$). Additionally, impaired daily activities ($p = 0.003$), reduced work productivity ($p = 0.006$), and more frequent comorbidities ($p = 0.043$) were observed in participants with elevated D-dimer levels [Table 4].

Table 4: Comparison of Clinical and Quality of Life Parameters in Patients with Elevated and Normal D-dimer Levels.

Variable	**Elevated D-dimer (n = 75)**	**Normal D-dimer (n = 72)**	**p-value**
	Frequency (%) or Mean ± SD		
Age (years)	40.2 ± 11.8	37.2 ± 12.1	0.125
UAS7 Score	22.4 ± 6.8	17.1 ± 7.1	<0.001
Presence of Angioedema (n=56)	40 (53.3%)	16 (22.2%)	<0.001
ESR (mm/hr)	32.1 ± 9.5	20.4 ± 8.7	<0.001

CRP (mg/L)	10.5 ± 4.2	6.3 ± 3.1	<0.001
Serum IgE (IU/mL)	311.2 ± 109.4	199.3 ± 95.4	0.004
Platelet Count (x10³/µL)	312.6 ± 74.9	261.9 ± 67.3	0.021
Duration of CU (months)	18.7 ± 9.2	10.5 ± 7.3	<0.001
Pruritus Severity Score	7.4 ± 1.9	5.8 ± 2.0	<0.001
Sleep Disturbance (≥3 days/week, n=42)	29 (38.7%)	13 (18.1%)	0.011
Impact on Daily Activities (n = 76)	41 (53.9%)	35 (46.1%)	0.003
Impact on Work Productivity (n = 95)	51 (53.7%)	44 (46.3%)	0.006
Impact on Quality of Life (DLQI ≥ 11)	49 (65.3%)	26 (36.1%)	0.002
Presence of Comorbidities (n=50)	31 (41.3%)	19 (26.4%)	0.043

D-dimer levels significantly decreased among participants with a complete response (712.4 ± 368.6 to 432.4 ± 229.7; $p < 0.001$), partial response (912.6 ± 422.5 to 683.7 ± 320.9; $p = 0.012$), and overall improvement (949.1 ± 451.8 to 654.8 ± 312.3; $p = 0.004$). However, no significant reduction was observed in the no-response group (1221.7 ± 530.9 to 1177.3 ± 499.8; $p = 0.684$) [Table 5].

Table 5: D-dimer Levels at Baseline and Follow-up Based on Treatment Response.

Variable	Baseline D-dimer	Follow-up D-dimer	p-value
	Mean ± SD		
Complete Response	712.4 ± 368.6	432.4 ± 229.7	<0.001
Partial Response	912.6 ± 422.5	683.7 ± 320.9	0.012
No Response	1221.7 ± 530.9	1177.3 ± 499.8	0.684
Overall Improvement	949.1 ± 451.8	654.8 ± 312.3	0.004

DISCUSSION

In our study assessing the clinicoepidemiological profile of chronic urticaria (CU) patients and its association with D-dimer levels, several significant observations were made. The mean age of participants was 38.7 years, aligning with Ashraf et al., that have reported CU to predominantly affect individuals in their 30s and 40s.[11] The slight female predominance (56.5%) observed is consistent with existing literature highlighting a higher prevalence of CU in women, possibly due to hormonal influences and autoimmune predisposition.[12]

The presence of common comorbidities such as hypertension (19%), diabetes mellitus (11.6%), and hypothyroidism (9.5%) aligns with previous findings that CU patients frequently exhibit metabolic and autoimmune conditions.[13] Notably, our study found that 41.5% of participants reported seasonal exacerbation, comparable to rates reported in prior studies, emphasizing the role of environmental triggers.[14]

D-dimer levels were significantly elevated in a considerable proportion of participants, with 28.6% having mild elevation, 14.3% moderate elevation, and 8.1% severe elevation. Patients with elevated D-dimer levels demonstrated significantly higher UAS7 scores, suggesting greater disease severity. This aligns with studies by Asero et al. and Kolkhir et al., which reported that elevated D-dimer levels correlate with severe urticaria symptoms and poor treatment response.[15,16] The elevated UAS7 scores in our study suggest that heightened coagulation and fibrinolysis pathways may contribute to the inflammatory burden, potentially through thrombin generation and mast cell activation, as previously described in CU pathophysiology.[17]

Angioedema was significantly more prevalent in the elevated D-dimer group (53.3%) compared to the normal D-dimer group (22.2%), consistent with findings from Chu et al., where patients with persistent angioedema exhibited higher D-dimer levels.[18] This supports the hypothesis that fibrin degradation products may perpetuate vascular leakage and tissue edema, intensifying clinical manifestations.[19]

Inflammatory markers such as ESR and CRP were markedly elevated in patients with elevated D-dimer levels, reinforcing the link between systemic inflammation and coagulation activation in CU. Previous study by Criado et al., has demonstrated that heightened ESR and CRP values are associated with more severe CU presentations, suggesting a common inflammatory pathway.[20] Elevated serum IgE levels, as observed in our study, further align with reports indicating IgE-mediated mast cell degranulation as a key mechanism in CU exacerbation.[21]

Our data showed a longer duration of CU in the elevated D-dimer group (18.7 ± 9.2 months vs. 10.5 ± 7.3 months), corroborating observations by Kaur et al., who identified prolonged disease courses in patients with elevated thrombin-antithrombin complexes.[22] This extended disease duration may reflect a chronic inflammatory state that perpetuates coagulation abnormalities and delays resolution.[23]

Significant differences were observed in quality-of-life parameters. Patients with elevated D-dimer levels had more pronounced impairments in daily activities (53.9% vs. 46.1%) and work productivity (53.7% vs. 46.3%), reinforcing the substantial impact of CU on functional outcomes. These findings align with a study by Sánchez-Díaz et al., which highlighted that severe CU negatively affects social, occupational, and psychological well-being, particularly in patients with persistent inflammation.[24]

Treatment responses also varied significantly. Patients who achieved complete or partial response exhibited substantial reductions in D-dimer levels, whereas those without response showed persistently elevated D-dimer values. This finding mirrors results

reported by Dabas et al., where successful treatment correlated with decreased D-dimer levels, emphasizing the utility of D-dimer as a potential biomarker for disease monitoring and therapeutic response.[25]

The significantly higher prevalence of comorbidities (41.3% vs. 26.4%) in patients with elevated D-dimer levels may indicate a shared inflammatory and thrombotic pathway linking CU with systemic conditions such as hypertension, diabetes, and autoimmune disorders. This aligns with reports suggesting that CU patients with elevated inflammatory markers are more likely to have concurrent comorbidities, potentially exacerbating disease severity.[26]

The observed improvement in D-dimer levels following treatment highlights the potential therapeutic benefit of targeting inflammation-driven coagulation pathways. Agents such as omalizumab and anticoagulant therapies have been previously reported to reduce D-dimer levels and improve CU symptoms, underscoring the need for personalized treatment approaches in patients with refractory CU and elevated coagulation markers.[27,28]

Limitations: Our study's limitations include its single-center design and limited follow-up duration. Future multicentric studies with larger cohorts and longer follow-up are recommended to validate these findings and further explore the prognostic role of D-dimer in CU management.

CONCLUSION

In conclusion, our study underscores the association between elevated D-dimer levels and more severe CU phenotypes, prolonged disease duration, and impaired quality of life. These findings reinforce the utility of D-dimer as a valuable biomarker for disease severity and treatment response. Further research exploring targeted therapies addressing coagulation pathways may improve outcomes in this challenging patient population.

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