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REVIEW

The Role of Coagulation/Fibrinolysis Biomarkers in Pathophysiology, Disease Severity, and Treatment Response in Patients with Urticaria: A Scoping Review

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Abstract

The pathology of urticaria is complex. Recently, researchers have widely focused on the role that the coagulation/fibrinolysis system plays in the pathology of urticaria. The potential of coagulation/fibrinolysis biomarkers as disease severity or treatment response biomarkers remains uncertain, lacking comprehensive analysis in previous studies. Hence, we performed a scoping review to thoroughly analyze coagulation/fibrinolysis biomarkers that may predict disease progression and treatment response of urticaria. Data from 71 studies showed that chronic spontaneous urticaria (CSU) was the most-studied subtype (39 articles), with D-dimers being the most researched marker (56 articles). Twenty-one biomarkers were investigated, and ten biomarkers were significantly correlated with disease severity. Specifically, D-dimers (26 articles) and prothrombin fragment 1 + 2 (F_{1+2}) (12 articles) plasma levels increased with exacerbation and decreased with remission. Biomarkers such as D-dimer also correlated significantly with inflammatory cytokines and complement, suggesting interactions among coagulation, immunity, and inflammation in the pathology of urticaria. While these biomarkers may predict treatment response, more evidence is needed. Additionally, anticoagulants such as warfarin, heparin sodium and tranexamic acid have been proved effective for urticaria. This review emphasizes that some coagulation/fibrinolysis biomarkers (such as D-dimer and F_{1+2}) may be not only indicators of disease status but also potential predictors of treatment response. It aims to assist researchers and practitioners in gaining a better understanding of the close relationships among coagulation/fibrinolysis biomarkers, the condition of urticaria (especially chronic urticaria, CU), and its prognosis. It also provides new directions for future research on exploring treatment methods via the coagulation/fibrinolysis pathways.

Keywords Coagulation/fibrinolysis biomarkers · D-dimer · Prothrombin fragment 1 + 2 · Urticaria · Scoping review

Introduction

Urticaria, characterized by hives, angioedema, or both, is an inflammatory skin disorder [1]. It is also recognized as a mast cell-driven disease associated with histamine and other inflammatory mediators [2] and is more commonly diagnosed in women [3]. The high recurrence rate and bothersome symptoms, such as itching and hives, may cause severe negative impact on patients' quality of life [4]. Although it is most often a self-limited disease, effectively treating patients with refractory urticaria remains a tremendous challenge. Its pathogenesis has not been fully elucidated and is a topic of debate. Exploring its underlying pathological mechanisms is conducive to better managing urticaria. Urticaria, especially chronic urticaria (CU) and its subtype chronic spontaneous urticaria (CSU), is frequently associated with autoimmunity and inflammatory responses [5–12]. A suspected link

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between urticaria and coagulation cascade activation also exists. Recent researches indicate a multifaceted pathophysiology, involving the immune system, the inflammatory response and the coagulation/fibrinolysis process [13, 14]. Skin immune cells not only produce pro-inflammatory cytokines, but also promote the over-expression of coagulation factors, such as tissue factor (TF) [15, 16]. The intricate interactions between the coagulation/fibrinolysis system and the immune system exacerbate the inflammatory response of urticaria and also increase the complexity of this disease [16], but the causal relationship among the three systems needed to be supported by stronger evidence.

Asero, R [17] found that patients with a negative autologous serum skin test (ASST) may be positive in the autologous plasma skin test (APST) and the positive rate of APST in CSU patients is much higher than that of ASST. The plasma component in APST is rich and contains factors such as thrombin, which suggests that abnormal activation of the coagulation system may be related to the pathogenesis of CSU [17]. However, another study [18] also found that APST and ASST results are mainly unaffected by coagulation abnormalities (like thrombin generation), implying thrombin may not directly be involved in skin autoreactivity. Studies on APST/ASST in CSU showed conflicting results, needing further research. The degranulation of skin mast cells in urticaria has been reported to be linked to elevated plasma levels of thrombin, and thrombin-induced activation of mast cells is contingent upon Ca^{2+} [19–21]. Coagulation factors may activate mast cells via multiple pathways. For instance, in the skin of patients with CSU, TF activates coagulation factors, then activates mast cells through protease-activated receptors 2 (PAR-2), and can also induce thrombin production to trigger mast cell degranulation, giving rise to the symptoms of urticaria [14]. Some researchers [22, 23] also have evaluated the relationship between coagulation cascade and urticaria by measuring coagulation/fibrinolysis products. For example, higher plasma levels of D-dimer and Prothrombin fragment 1 + 2 (F_{1+2}) might be associated with the severity of the disease, which implied that the exogenous coagulation and fibrinolysis system might be activated [24, 25]. In addition, previous studies have provided evidence that dipyridamole, heparin sodium, and warfarin can be effective for CU [26–28]. Nevertheless, currently, the literature regarding the association between urticaria and coagulation/fibrinolysis is confined to a few isolated studies, limited case collections, and a few reviews of pathological mechanisms. Furthermore, these reviews concerning urticaria and coagulation were all founded on restricted search biomarkers, leading to generally small patient populations. Hence, there are still uncertainties regarding the potential utility of coagulation/fibrinolysis biomarkers as bioactive markers to gauge the disease severity, and treatment responsiveness in urticaria.

Taking all these into consideration, we performed a comprehensive scoping review to reveal the relation between coagulation/fibrinolysis biomarkers and disease severity, and to assess whether these biomarkers can predict treatment response in patients with urticaria. We also aim to map all anticoagulants for urticaria, in order to gain a deeper understanding of their application scenarios and usage details. This study will improve our understanding of the immunological, inflammatory, and coagulation mechanisms driving urticaria, offer insights into treatment response prediction, and guide more targeted therapeutic interventions, thereby optimizing patients' care.

Methods

Search Strategy

A search was performed in Pubmed, Web of Science, Embase, and Cochrane from inception to November 1, 2024, and was limited to the English language, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews methodology (according to PRISMA-ScR [29]; see Supplementary Table 1). The detailed search strategy was available in Supplementary Text 1.

Eligibility Criteria

Population, Intervention, Outcomes

We included studies that met the following criteria: patients with urticaria, without any age restriction or type specification, in which coagulation/fibrinolysis biomarkers were measured or anticoagulants were used as intervening drugs.

Study Types

We included observational studies and interventional studies. Animal studies, conference abstracts, reviews, and editorials were excluded.

Selection About Sources of Evidence

Titles and abstracts were screened by two reviewers. All potentially relevant references were retrieved in full-text and independently assessed by two reviewers. Any disagreements were resolved by consensus or through discussion with a third reviewer.

Data Extraction and Cataloging

Two reviewers independently charted the data from each source of evidence in a standardized fashion for aggregated analysis. Standard data elements included: study type (observational studies and interventional studies), countries, journals, population of patients, sex composition, age, coagulation/fibrinolysis biomarkers, and anticoagulants.

Synthesis Methods

For some continuity data, meta-analysis was performed using R 4.1.3 "meta" package 6.1.0. In a qualitative approach, we organized the content of the studies thematically, and reviewed how clinical coagulation/fibrinolysis biomarkers associated with urticaria. For the basic information data, GraphPad Prism 8 was used to perform simple quantitative analyses and visualize the number of authors, countries, and Journal Citation Reports (JCR) categories. In addition, VOS viewer (version 1.6.16, Leiden University Center for Science and Technology Studies, Leiden, Netherlands) was used in this study to draw co-occurrence maps of the authors and keywords.

Results

Study Characteristics

Search Results

A total of 1813 records were identified. After eliminating duplicate documents, 1,307 remained. Following title/abstract screening, only 176 studies were left. Subsequently, after screening for literature types, 79 full-text articles were left for eligibility assessment. Finally, 71 studies [17, 19, 24, 26–28, 30–94] were included in the scoping review. The detailed flowchart of the literature search is shown in Fig. 1. The characteristics of the included studies and the baseline characteristics of the patients are detailed in Tables 1 and 2.

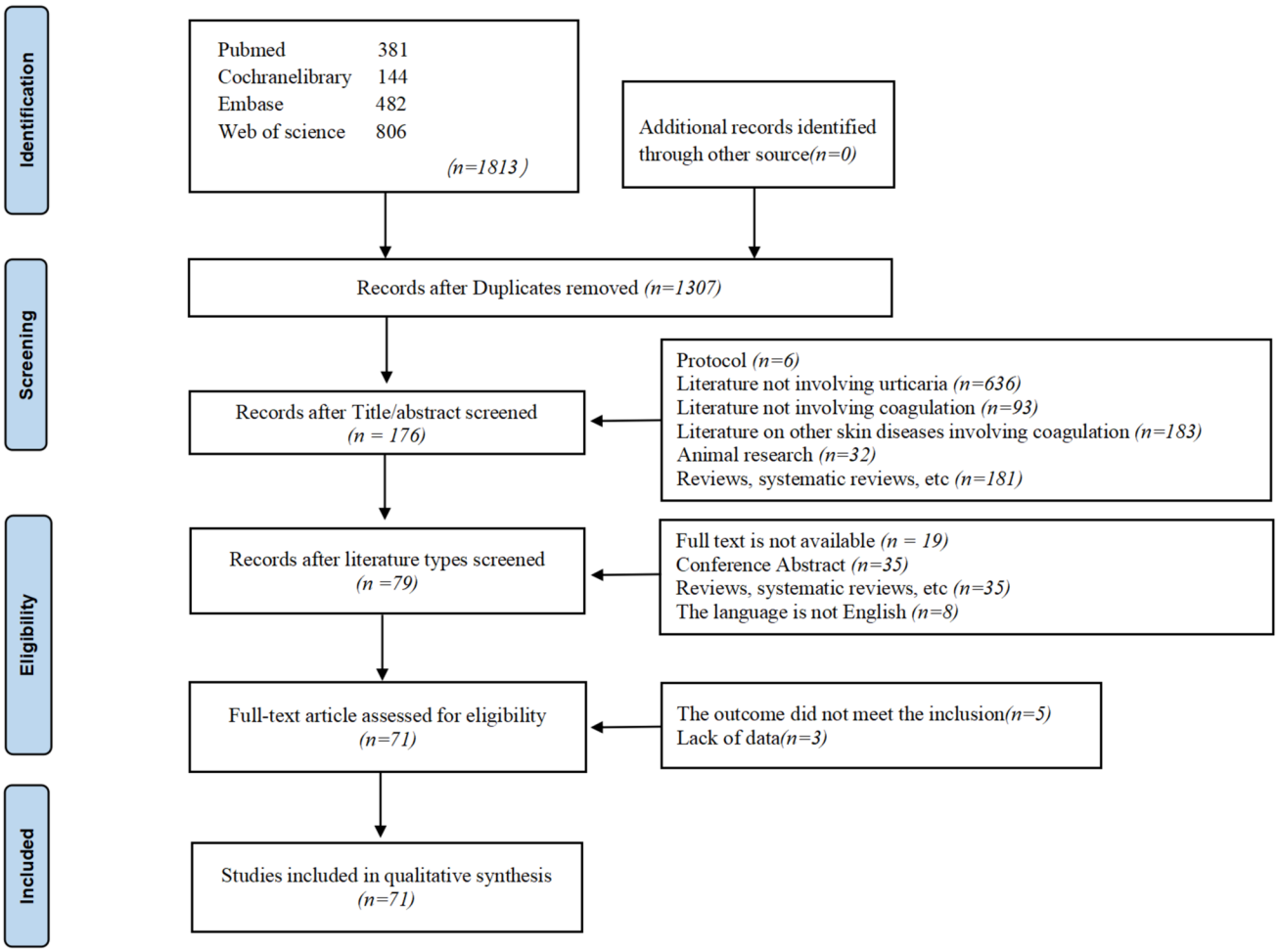


Fig. 1 Study flowchart. Subscript: PRISMA diagram of the literature search

Table 1 Characteristics of the included observational trials

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ $ASST^+$/ $APST^+$n(%)	Correlation	Outcomes
Berth-Jones, J 1988 [30]	CU	Case report	UK	0	1	42	2	FXIIa, AT III, INR	NA	NA	1. The use of warfarin in CU is valuable 2. The coagulation system is associated with the onset of diseases in CU
Asero, R. 2001 [45]	CIU	Cross-sectional study	Italy	201 (65.7)	306	> 16	NA	NA	/205 (67)/8 (14)	NA	1. Heparin sodium inhibits histamine release from both basophils (in vitro) and mast cells (in vivo)
S L Chua 2005 [27]	CU	Case report	UK	1 (100)	1	43	5	NA	NA	NA	1.S L Chua first reported that heparin sodium had dramatic effect in patient with CU
Asero, R. 2006a [17]	CU	Case–control study	Italy	72 (75)	96	18–70	NA	F_{1+2}	/51 (53.1)/61 (86)	1. F_{1+2} and urticaria severity were correlated ($r = 0.37$; $P < 0.05$)	1. Patients showed a significantly higher levels of F_{1+2} than normal controls (3.06 [3.36] vs 0.80 [0.34] nmol/L; $P < 0.001$) 2. Mean plasma F_{1+2} levels were higher in $ASST^+/APST^+$ than in $ASST^+$ /$APST^+$ patients
Asero, R. 2006b [84]	NSAID-induced urticaria	Case report	Italy	0 (0)	1	55	NA	NA	NA	NA	1.Anticoagulant therapy may interfere with pathogenic mechanisms involved both in spontaneous urticaria and NSAID-induced exacerbations
C Shedden 2006 [44]	DPU	Case report	UK	1 (100)	1	41	1.5	NA	1(100)		1.Tranexamic acid can be an effective treatment for DPU

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Asero, R. 2007 [24]	CU	Case–control study	Italy	29 (78.4)	37	45 (14–82)		F_{1+2}, FXIIa, FXIIa, D-dimer, TF	/21 (67.7)/36 (97.3)	1. FVIIa and F_{1+2} were correlated ($r=0.529$; $P=0.008$)	1. The levels of F_{1+2} were higher in patients than controls (2.54 [2.57] vs 0.87 [0.26] nmol/L; $P<0.001$); 2. 30% of patients showed significantly elevated levels of F_{1+2} 3. D-dimer levels were higher in patients than controls (329 [188.00] vs 236 [81.0080] ng/mL; $P<0.01$); 4. The levels of FIIa were higher in patients than controls (2.86 [0.66] vs 1.97 [0.65] ng/mL; $P<0.001$).; 5. The levels of TF were significantly higher in patients with CU than controls ($P<0.01$)
FujII, K. 2008 [41]	CU	Case–control study	Japan	12 (60)	20	36.9 (28–72)	NA	D-dimer, TAT, SFMC, AT III *PLT, PT, APTT, Plasma protein C and S, compliment C3 and C4, plasma fibrinogen and FIIa*		1.The extent of skin rash was roughly correlated with TAT and D-dimer	1. A large proportion of urticaria patients showed elevated levels of TAT (17/20) and D-dimer (13/20) 2. Abundant fibrinogen deposits were found in the dermis of biopsy specimens from urticaria

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Asero, R. 2008 [43]	★CU	Case–control study	Italy	5 (62.5)	8	47 (22)	NA	D-dimer, F_{1+2}	NA	1. D-dimer was significantly correlated with F1 + 2 (r = 0.64, P = 0.002)	1. Patients with severe CU, who had median levels of both D-dimer (11.20 nmol/L) and F1 + 2 (0.59 nmol/L), had levels that largely exceeded those found in patients with slight CU 2. The D-dimer level in slight CU patients was 2.66 nmol/L ($P = 0.001$ compared to severe CU patients), and the F1 + 2 level was 0.228 nmol/L ($P = 0.003$ compared to severe CU patients) 3. For normal subjects, the D-dimer level was 1.41 (0.96—1.62 nmol/L, $P = 0.001$ compared to severe CU patients), and the F1 + 2 level was 159 (123—196 pmol/L, $P = 0.0001$ compared to severe CU patients)
Cugno, M. 2009 [42]	★CU	Case–control study	Italy	13 (65)	20	39 (18–70)	NA	TF	NA	NA	1. A strong expression of TF has been found in CU lesional skin 2. Eosinophils were the main source of TF in CU lesional skin

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Kasperska-Zajac, A. 2009 [40]	★AU	Case–control study	Poland	10 (59)	17	32 (21–42)	NA	D-dimer	NA	1. *There was no significant correlation between disease severity and D-dimer*	1. The levels of D-dimer were significantly higher in patients with severe AU compared with patients with mild/moderate AU and healthy subjects (260 [220 −450] vs. 17 [50—180] and 140 [80 −220] ng/mL, respectively; $P<0.001$); 2. D-dimer concentrations were above the normal laboratory range (< 500 ng/mL) in all patients with severe AU
Tedeschi, A. 2009 [39]	CU	Case–control study	Italy	61 (76.2)	80	43.4 (14.1)	NA	F_{1+2}	//63 (85.1)	1. F1 + 2 was correlated with VEGF ($P=0.043$)	1. F1 + 2 levels increased to a concentration of 0.55 [0.076] nmol/L 2. The levels of VEGF were significantly higher in CU patients (8.00 ± 0.90 pmol/L) than in normal subjects (0.54 ± 0.08 pmol/L) ($P=0.0001$)
Mahesh, P. A. 2009 [28]	CIU‡	Case report	India	3 (60)	5	37.6 (5.0)	0.75 (0.21)	PT INR	1 (20)/5 (80)/5 (100)	NA	1. In three patients, there was no recurrence of CIU after warfarin withdrawal 2.Two patients, who had an onset of clinical response within 2 weeks, had an adverse response, possibly due to warfarin

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
S Takahagi 2010 [37]	CU/IU	Case–control study	Japan	60 (73.2)	82	39.5 (4–80)		D-dimer, FDP	/18 (28.1)	1. The levels of FDP, D-dimer and CRP were correlated with the disease severity of CU	1. The levels of FDP in 17 of 81 (21%) patients with CU exceeded the normal range, and 29 of 82 (35%) patients showed an increase in the level of D-dimer
Kasperska-Zajac, A. 2011 [35]	DPU	Case–control study	Poland	3 (37.5)	8	37 (28–43)		D-dimer		1. The haemostatic activation state depended on the severity of the disease	1. DPU had significantly higher the levels of D-dimer compared with the healthy subjects ($P=0.012$, 350 [175 −195] vs. 140 [80—220] ng/mL, respectively)
Takeda, T. 2011 [34]	CU	Case–control study	Japan	NA	36	47 (18)	NA	D-dimer, F_{1+2}, FDP, Fibrinogen, SFMC	NA	1. The disease severity was correlated with the levels of D-dimer ($P<0.05$), F1 + 2 ($P<0.01$), and positive rates of SFMC ($P<0.05$)	1. The levels of fibrinogen, D-dimer, and FDP, and positive rates of SFMC were significantly elevated in patients with CU
Yildiz, H. 2011 [33]	CIU	Case–control study	Turkey	23 (54.8)	42	35.7 (28–76)	NA	F_{1+2}	/26 (62)/28 (66.7)	NA	1. The levels of F_{1+2} were found to be elevated in patients with CSU
Asero, R. 2011 [36]	CU	Case–control study	Italy	28 (65.1)	43	43.5 (17–72)	NA	D-dimer, F_{1+2}	*II*27 (62.8)	1. The disease severity was correlated with the levels of F1 + 2 ($r=0.685$, $P=0.003$) and D-dimer ($r=0.704$, $P=0.002$)	1. The levels of F_{1+2} and D-dimer were elevated in 7/16 APST-negative CU patients 2. The mean D-dimer level was higher in these patients than in normal controls (484.2 [148.3] vs. 229.5[16.7] ng/mL; $P=0.03$)

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ $ASST^+$/ $APST^+$n(%)	Correlation	Outcomes
Spring, P. 2012 [32]	CIU	Case report	Singapore	1	1(100)	59	9	D-dimer, TAT, F_{1+2}	NA	NA	1. The levels of F_{1+2}, TAT and D-dimer were elevated in CIU
Huilan Zhu 2013 [19]	AU/CU	Case–control study	China	19 (47.5)	40	33 (12–63)/38 (17–69)	NA	D-dimer, TAT, $F_{1+2,}$ HMWK, t-PA, FVIIa	NA	1. The levels of F1 + 2, TAT, D-dimer, HMWK, and t-PA were correlated with symptom scores in CU patients ($r = 0.81$, $P < 0.01$; $r = 0.55$, $P < 0.01$; $r = 0.73$, $P < 0.01$; $r = -0.39$, $P < 0.05$; $r = 0.35$, $P < 0.05$; respectively)	1. The levels of D-dimer increased significantly ($P < 0.01$) in AU and CU patients; the levels of HMWK were increased significantly ($P < 0.01$), while the levels of t-PA were decreased ($P < 0.01$) in patients 2. The levels of FIIa were higher in AU patients ($P < 0.01$) 3. The levels of TAT and F1 + 2 were significantly higher ($P < 0.01$) 4. The levels of FIXa were higher in CU patients ($P < 0.01$) 5. The levels of C5a and C4 in CU patients were superior to those in healthy controls ($P < 0.01$). The levels of C3 were not significantly different from healthy controls
Triwongwaranat, D. 2013 [31]	CIU	Case–control study	Thailand	90 (75)	120	38.8 (16–73)	1 (0.25–30)	D-dimer	6 (5)/33 (34.4)/35 (36.5)	1. The disease severity was correlated with the levels of D-dimer ($p < 0.05$, $r = 0.537$)	1. There was an elevated D-dimer level in nearly half of Thai patients with CIU 2. D-dimer level was abnormal in 58 patients (48.3%)

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Baek, Y. S. 2014 [50]	CU/AU	Cohort study	South Korea	57 (60.6)	94	39 (17.4)	NA	D-dimer	13 (13.8)	1. The levels of D-dimer significantly were correlated with UAS (AU $r=0.30$, $P<0.001$; CU $r=0.37$, $P<0.05$) *2. There was no significant correlation between disease severity and CRP and total IgE*	1. There were 39 patients (41.8%) with a raised D-dimer level; AU 43.5%/ CU 39.6% had an increased D-dimer level 2. The raised D-dimer group had significantly higher UAS than the normal D-dimer group
Kirchhof, M. G.2014 [49]	Atypical Recurrent Urticaria	Case report	Canada	1 (100)	1	20	NA	D-dimer	NA	NA	1. The levels of D-dimer were more than 4000 µg/mL during the active phase of the disease 2. The levels of D-dimer turned normal after treatment
Asero, R. 2015 [52]	★CSU‡	Cross-sectional study	Italy	20 (69)	29	46 (11–75)	2.9 (3.7)	D-dimer	NA	1. There was a significant correlation between disease activity and the levels of D-dimer	1. The levels of baseline D-dimer were elevated in 18 of 29 (62%) patients; 2. Baseline D-dimer levels showed a highly significant negative correlation with the response to cyclosporine (t=20.44; $P<0.02$)

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Farres, M. N. 2015 [51]	CSU	Case–control study	Egypt	18 (60)	30	29.57 (8.8)	2.0 (1.0, 6.5)	D-dimer, FVIIa	NA	1. The disease severity was correlated with D-dimer	1. The levels of D-dimer and FIIa were significantly higher among patients with CSU than among healthy controls 2. FIIa levels did not differ significantly according to disease severity grades
Duoqin Wang 2015 [53]	CSU	Case–control study	China	73 (70.9)	103	38.7 (16–75)	2–10	D-dimer, F_{1+2}, FVIIa, FXIIa	NA	1. D-dimer ($r=0.480$, $P<0.001$), FIIa ($r=0.284$, $P=0.003$), and F_{1+2} ($r=0.229$, $P=0.04$) were significantly correlated with disease severity	1. The levels of D-dimer were higher in patients than controls (410[440.00] vs. 210[260.00] ng/mL; $P<0.001$) 2. The levels of F_{1+2} were higher in patients than controls (11.17 [17.65] vs. 5.97 [9.42] nmol/ml; $P=0.048$) 3. The levels of FIIa were higher in patients than controls (4.09 [4.22] vs. 2.97 [1.59] ng/mL; $P=0.03$)
Asero, R. 2017 [56]	★CSU※	Case report	Italy	1 (100)	1	47	0.25	D-dimer	1 (100)	1. The levels of D-dimer strictly paralleled the severity of the disease	1. The levels of D-dimer were elevated (3929 ng/mL) 2. After the second dose of omalizumab, D-dimer plasma levels had decreased further to 419 ng/Ml 3. After the fourth dose of omalizumab, D-dimer plasma levels were 2269 ng/mL

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
R Grzanka 2018 [58]	CSU	Case–control study	Poland	41 (70.7)	58	39 (21–45)	2.5 (0.6–5.2)	D-dimer	NA	1. The levels of D-dimer were correlated with the biomarkers, CRP and IL-6 as well as UAS7	1. The levels of D-dimer were significantly higher in CSU patients compared with the controls
Kolkhir, P. 2018 [61]	CSU	Cohort study	Germany Russian	922 (73.6)	1253	42 (30–53)	NA	D-dimer, Fibrinogen	296 (29.7)	NA	1.CRP was also correlated with fibrinogen and D-dimer
Magen, E. 2018 [60]	CSU※	Case report	Israel	1 (100)	1	27	0.6	NA	NA	NA	1. After being treated with Warfarin, coagulation—related clinical parameters and biomarkers were normal
Takahashi, T. 2018 [57]	infectious AU	Case report	Japan	1 (25)	4	20–70	NA	D-dimer	NA	1. The levels of D-dimer strictly paralleled the severity of the disease	1. There was a significant elevation of D-dimer levels in all patients
Shailja Chauhan 2019 [85]	CSU‡	Case–control study	India	75 (75)	100	36.12 (10.9)	0.1–20	D-dimer, PT, APTT	NA	1. The levels of D-dimer strictly paralleled the severity of the disease	1. D-dimer levels in 23% of patients, PT levels in 63% of patients, and APTT levels in 5% of patients were significantly higher compared with the controls
Marzano, A. V. 2019 [65]	CSU‡	Case–control study	Italy	310 (66)	470	49 (37–61)	NA	D-dimer	NA	1. The levels of D-dimer did not correlate with response to omalizumab	1.D-dimer mean values were similar in responders (327 [874.10]) ng/mL and non-responders (292.9 [689.60]) ng/mL; $P=0.556$)

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Grieco, T. 2020 [66]	CSU‡	Case–control study	Italy	31 (73.8)	42	48.89 (18.7)	NA	D-dimer	NA	1. High levels of D-dimer were associated to disease severity in late responders; 2. *The possible relation to relapse was unclear*	1. The levels of D-dimer were elevated above 900 ng/mL in late responders of omalizumab
Obtulowicz, A. 2020 [67]	CSU	Cohort study	Poland	108 (76)	142	19–87	NA	D-dimer, fibrinogen, MPV, PLT	/92 (65)	*1. No statistically significant increase in fibrinogen, D-dimer, CRP, vitamin D, and the mean MPV concentration as the activity of urticaria increased was observed*	1. An increased D-dimer level in patients with severe urticaria should be considered not only as an indicator of its activity but also as something else
Saito, R. 2020 [68]	CSU	Case–control study	Japan	NA	79	NA	NA	TF	NA	NA	1. TF expression was enhanced in CSU patients compared with healthy donors
Asero, R. 2021 [73]	CSU‡	Case–control study	Italy	77 (59.2)	130	50.6 (13–89)	NA	D-dimer	NA	NA	1. The median D-dimer levels of late responders (9 out of 21, accounting for 43%) of omalizumab were much higher than those of early responders (42, accounting for 39%)

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Dabas, G. 2021 [74]	CSU	Cohort study	India	88 (62.4)	141	34.5 (11.9)/36.2 (11.2)	44.9 (22.5)	D-dimer PT APTT	65 (46.1)	1. D-dimer levels paralleled the disease severity	1. The levels of D-dimer were raised in 46 CSU patients (32.6%) 2. The proportion of patients with raised D-dimer levels was higher in patients with severe CSU. The proportions in mild, moderate, and severe disease were 12.9%, 27.2%, and 54.5% respectively, with $P<0.001$
Zaryczański, J. 2021 [82]	AU	Cohort study	Poland	59 (55.7)	106	5.57 (4.9)	NA	D-dimer	NA	NA	1. The levels of D-dimer were elevated in 51% of the patients 2. There was a tendency for higher D-dimer in patients who required a longer GCS treatment
Criado, R. F. 2021 [71]	CSU	Case–control study	Brazil	40 (72.72)	55	41 (14.1)	NA	D-dimer	26 (47.22)/18 (62.1)	1. There was a strong and positive relationship among D-dimer, UAS, and the number of drugs needed to control CSU	1. Forty percent (22 out of 55) of the patients with CSU presented high D-dimer levels; 2. D-dimer and UAS levels demonstrated a strong and positive relationship (53.1%)
Sadowska-Przytocka, A. 2021 [69]	CU	Case–control study	Poland	46 (76.7)	60	42.4 (13–84)	NA	D-dimer	NA	1. The levels of D-dimer strictly paralleled the severity of the disease and UAS index	1. Patients with severe urticaria had increased D-dimer levels

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Aleksandra Plavsic 2021 [70]	CSU	Case–control study	Serbia	38	44	50.4 (3.1)	3.1	D-dimer, C3, PT, APTT	24 (54.5)	*1. There was no correlation between D-dimer, CRP, C3, Prothrombin time, APTT and disease activity*	1. Twenty—one (47.7%) of the patients had elevated D-dimer levels 2. Patients had statistically significantly elevated D-dimer levels as compared with controls
Anil, H. 2021 [86]	CSU	Case–control study	Turkey	11	24	13.9 (4.5)	NA	*PT, APTT, Fibrinogen*	NA	NA	*1. There was no difference between groups in the biomarkers: PT, APTT, and fibrinogen levels*
Baskurt, D. 2022 [75]	★CSU	Case report	Italy	1 (100)	1	45	0.42	D-dimer	/1 (100)	*1. The correlation between D-dimer levels and disease activity may indicate the need for more evidence*	*1. There was an omalizumab—refractory case of severe CSU with high D-dimer levels. The levels declined only after disease remission with cyclosporine treatment but not with anticoagulation*
Kitao, R. 2022 [88]	CSU	Case–control study	Japan	34 (65.4)	52	46.1 (16.9)/57.1 (22.1)	NA	D-dimer	/4 (25)/1 (16.7)	NA	1. D-dimer levels were lower in the < 65 group than in the ≥ 65 group, but D-dimer levels were not significantly associated with age
Veleiro-Pérez, B. 2022 [77]	DPU	Cohort study	Spain	9 (64.3)	14	43.64 (13.8)	NA	D-dimer	NA	NA	1. High D-dimer levels (> 500 ng/mL) were present in 30% of the patients

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Mehta, H. 2022 [87]	CSU‡	Real-world study	India	41	56	30 (18–47)	NA	D-dimer	/56 (49.1)	NA	1. Elevated baseline D-dimer levels: omalizumab responders (65.3%) and non-responders (60%) 2. Elevated baseline D-dimer levels: cyclosporine responders (41.3%) and non-responders (73.3%)
Góra, A. 2022a [79]	AU	Case–control study	Poland	34 (44.3)	76	9.04 (6.3–12.7)	NA	D-dimer, PLT, MPV,	/8 (16.3)	1. Disease activity was positively correlated with CRP and D-dimer (AU) 2. There was a positive correlation between disease activity and CRP (CU)	1. The biomarkers PLT, MPV, MPR and PLR were not assessed as biomarkers of urticaria 2. The best predictor of urticaria development was an increase in the levels of D-dimers
Relvas, M. 2022 [83]	CSU	Cohort study	Portugal	74 (84.1)	88	45 (15.8)	NA	D-dimer	NA	1. D-dimer levels correlated with disease activity	1. Median D-dimer levels were 181 ng/mL [85–306], with 33 patients (37.5%) exhibiting values above normal
Şengül Beyaz 2023 [78]	CSU	Case–control study	Turkey	52 (74.3)	70	37.51 (11.8)	1 (0.5–2)	D-dimer	NA	1. D-dimer levels were elevated and positively correlated with UAS7 and disease activity	1. Patients had higher D-dimer levels than the controls
Brás, R. 2023 [80]	CSU	Case–control study	Portugal	114	138	49 (40–58)	NA	D-dimer	97 (68)	NA	1. A total of 71 (51%) patients lengthened the treatment interval, presenting higher median D-dimer levels and CRP levels than those with a standard dose

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ ASST$^+$/ APST$^+$n(%)	Correlation	Outcomes
Pesqué, D. 2023 [76]	CSU	Cohort study	Spain	269 (71.4)	377	46.0 (34–58)	NA	D-dimer	164 (43.5)/112 (59.3)	NA	1. Higher baseline D-dimer values were found in patients with CSU (373.29[264.18] ng/mL)
Di Pino, M. 2023 [81]	CSU	Case–control study	Italy	39 (83)	47	44 (14–71)	NA	D-dimer, F_{1+2}, APTT, PLT, MPV	NA	NA	1. A statistically significant increase in APTT ratio, D-dimer, F_{1+2}, PLT and MPV was found when these parameters were compared with healthy controls
Chinthada, D. 2023 [90]	CSU	Cohort study	India	60 (60)	100	30 (18–75)	20.5	D-dimer	NA	1. Elevated D-dimer levels were correlated with age range, duration of chronic urticaria, disease severity, angioedema, and response to antihistamines	1. D-dimer levels may be used as a laboratory parameter for determining antihistamine resistance and severity in these patients
A. Gonzalez Ruvalcaba. 2024 [91]	CSU※	Case report	Mexico	NA	40	NA	NA	D-dimer	NA	*1. No relationship was found between the D-dimer and the clinical evaluation*	*1. D-dimer was not considered useful as a prognostic factor*
Ashraf, R.2024 [89]	CSU	Case–control study	India	676 (61.2)	1104	33.03 (14.3)	3.46 (4.6)	D-dimer	NA	1. D-dimer levels correlated with disease activity	1. IgE and D-dimer levels could identify a CSU patient who could warrant a higher dose of antihistamine or has antihistamine—refractory urticaria

Table 1 (continued)

Author year	Disease	Study design	Site	Females *n* (%)	Patients *n*	Age (y)	Duration (y)	Biomarkers	Angioedema/ $ASST^+$/ $APST^+$n(%)	Correlation	Outcomes
Baskurt, D.2024 [92]	CSU	Cohort study	Turkey	1	1	45	5	D-dimer	/1 (100)	1.The correlation between D-dimer levels and disease activity may indicate the need for more evidence	1. There was a case of severe CSU with high D-dimer levels. The levels declined only after disease remission with cyclosporine treatment but not with anticoagulation
Carvallo, A. 2024 [93]	CSU/CIU	Cohort study	Spain	43 (64.2)	67	50.9 (1.8)	NA	D-dimer	54 (80.6)	1. UAS7 showed a moderate positive correlation with D-dimer levels	1. SAA-1 levels showed a strong positive correlation with CRP levels and a moderate positive correlation with D-dimer levels 2.D-dimer and CRP levels showed a moderate positive correlation with each other
Relvas, M.2024 [94]	CSU	Cohort study	Portugal	74 (84.1)	88	45 (15.8)	16.5 (5–6)	D-dimer	59 (67.1)	1. Both the levels of D-dimer and CRP significantly correlated with CSU activity	*1. D-dimer and C-RP serum levels were sensitive biomarkers for CSU activity, but their concomitant use did not seem to increase their sensitivity in detecting higher disease activity*

★, severe; ‡, with nonresponsive to antihistamines; ※, with nonresponsive to omalizumab; (y) Mean (SD)/Median (range)

Abbreviations: *CSU* chronic spontaneous urticaria, *CU* chronic urticaria, *CIU* chronic idiopathic urticaria, *DPU* delayed pressure urticaria, *AU* acute urticaria, *IU* idiopathic urticaria, F_{1+2} Prothrombin fragment $_{1+2}$, *FIIa* activated factor VII, *FIIa* activated factor XII, *FXa*, activated factor X, *TF* tissue factor, *TAT* thrombin–antithrombin III complex, *FDP* fibrin degradation products, *HMWK* high molecular weight kininogen, *t-PA* tissue-type plasminogen activator, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *INR* international normalized ratio, *MPV* mean platelet volume, *AT III* antithrombin III, *SFMC* soluble fibrin monomer complex, *FII* prothrombin (Factor II), *CRP* C-reactive protein, *IL-6* interleukin 6, *UAS* urticaria activity score, *CU-Q2oL* Chronic Urticaria Quality of Life Questionnaire, *APST* autologous plasma skin test, *GCS* glucocorticoids, *PLR* platelet-lymphocyte ratio, *SAA-1* Serum Amyloid A1, $ASST^+$ autologous serum skin test were positive, *APST* autologous plasma skin test were positive, *VEGF* vascular endothelial growth factor

Tips: the italic font represents a negative correlation

Table 2 Characteristics of the included interventional trials

Author year	Disease	Study design	Site	Patients *n*	Females *n* (%)	Age (y)	Biomarkers	Drugs	Baseline outcomes	Post-treatment outcomes
R. Parslew 2000 [46]	CIU‡	Double-blind placebo-controlled, non-randomised controlled study	UK	3	2 (66.7)	43.3 (38–54)	NA	Warfarin	1. Three patients obtained and sustained significant benefits from the use of warfarin	
Khalaf, A.T. 2008 [26]	CU	Double-blind, parallel-group, RCT	China	64	37 (57.8)	3.25–71	F_{1+2}	Desloratadine and dipyridamole	1. The levels of F_{1+2} in patients had been elevated	1. The levels of F_{1+2} in patients had decreased obviously after treatment (3.27 [2.74] vs. 0.87 [0.46], $P<0.001$)
Asero, R. 2010 [38]	CU	Non-randomised controlled study	Italy	68	52 (76.5)	49 (14–84)	D-dimer	Nadroparin and tranexamic acid	1. The levels of D-dimer were elevated in 14/68 (20.6%) patients (306–7317 ng/mL); 2. 10/14 patients showing elevated D-dimer levels had a severe disease activity score	1. Therapy caused a dramatic drop in D-dimer levels in 6/6 patients 2. 12/14 patients with elevated D-dimer levels did not respond to anti-histamine treatment ($P=0.0001$)
Yalcin, A. D. 2014 [48]	CU	Non-randomised controlled study	Taiwan	8	NA	47.5 (10.04)	D-dimer	Omalizumab	1. There was a significant positive correlation between D-dimer and age	1. A significant decrease of D-dimer levels was observed after omalizumab therapy
Asero, R. 2017 [56]	★CSU	Non-randomised controlled study	Italy	32	21 (65.6)	50 (17–78)	D-dimer	Omalizumab	1. The levels of D-dimer were elevated in 19 (59%) cases	1. Responders showed a dramatic decrease of D-dimer levels after the first administration of omalizumab (from 1024 [248.00] to 251 [30.00] ng/mL; $P=0.003$); 2. 14/25 responders had increased D-dimer levels versus 5/7 non-responders

Table 2 (continued)

Author year	Disease	Study design	Site	Patients *n*	Females *n* (%)	Age (y)	Biomarkers	Drugs	Baseline outcomes	Post-treatment outcomes
Kitsioulis, N. A. 2017 [55]	CSU※‡	Non-randomised controlled study	Greece	19	12 (63.2)	54 (20.8)	D-dimer	Autologous whole-blood injection (AWBI)	1. There was a negative correlation between patients' baseline D-dimer levels and UAS7 and DLQI scores, before and after AWBI intervention ($P=0.002$, $P=0.001$)	1.D-dimer levels ≥ 292 ng/mL were associated with poor responsiveness (sensitivity 75%; specificity 83.3%)
Kolkhir, P. 2017 [54]	CSU	Non-randomised controlled study	Russia	84	59 (70.2)	NA	D-dimer	Levocetirizine	1. D-dimer and fibrinogen seem to be useful biomarkers for prediction of response to levocetirizine in CSU patients 2. Responders had lower levels of D-dimer and fibrinogen compared to non-responders 3. There was a negative correlation between values of D-dimer and CU-Q2oL;	NA
Cugno, M. 2018 [59]	CSU	Non-randomised controlled study	Italy	25	14 (56)	40.3 (15–69)	D-dimer	Omalizumab	1.Baseline D-dimer levels were significantly lower in non-responders (162 [82.00] ng/mL) than in partial responders (676 [1957.00] ng/mL, $P=0.017$) and complete responders (619 [1599.00] ng/mL, $P=0.004$)	1. D-dimer was potentially involved in the mechanism of action of omalizumab in CSU, and may be a predictor of the therapeutic effectiveness of this drug

Table 2 (continued)

Author year	Disease	Study design	Site	Patients *n*	Females *n* (%)	Age (y)	Biomarkers	Drugs	Baseline outcomes	Post-treatment outcomes
Uysal, P. İ 2018 [62]	CIU/CSU	Non-randomised controlled study	Turkey	31	24 (77.4)	47.19 (12.5)	D-dimer, PT, INR, APTT	Omalizumab	1. Baseline PT, INR, and APTT were not associated with lack of therapy response ($P > 0.05$)	1. Dramatic decrease in the levels of D-dimer, PT and INR were observed in CIU/CSU ($P = 0.001$, $P = 0.025$, $p = 0.017$), except for APTT and Fibrinogen ($P = 0.057$, $P = 0.82$); 2. D-dimer levels showed a dramatic decrease after the first dose of omalizumab in responders ($P = 0.003$), but the decrease was not significant among non-responders ($P = 0.068$)
Asero, R. 2019 [64]	CSU‡	Non-randomised controlled study	Italy	161	118 (73.2)	48 (15–80)	D-dimer	Omalizumab	1. Early and complete responders: baseline D-dimer level (1186 [1199]) ng/ml 2. Late and complete responders: baseline D-dimer level (892 [1045]) ng/mL 3. Late and partial responders: baseline D-dimer level (988 [1762]) ng/mL; 4. Non-responders: baseline D-dimer level (826 [973]) ng/mL 5. A significant correlation between D-dimer and UAS7 at baseline was found ($P = 0.014$)	

Table 2 (continued)

Author year	Disease	Study design	Site	Patients *n*	Females *n* (%)	Age (y)	Biomarkers	Drugs	Baseline outcomes	Post-treatment outcomes
Bérard, F. 2019 [63]	CSU‡	Non-randomized multicentre, phase IV study	French	136	106 (77.9)	44.4 (12.7)	D-dimer	Omalizumab	1. The levels of D-dimer were elevated at baseline (1002.1 ng/mL) 2. There was a weak positive correlation of UCT / UAS7 with baseline D-dimer (0.059, 0.108)	1. The levels of D-dimer were decreased after omalizumab therapy at Week 8 (455 ng/mL) 2. Among the 9 patients with a very high baseline D-dimer concentration (> 3000 ng/mL), 8 were responders
deMontjoy, L. 2021 [72]	CSU	Intervention prospective study	Belgium	95	68 (71.6)	45 (16)	D-dimer	Omalizumab	1. The levels of D-dimer were 1278.2 [1939] ng/ml, with 56.3% (40/71) of patients having levels higher than 500 ng/mL 2. D-dimer were higher in H1-antihistamines non-responders ($P = 0.008$)	1. Under omalizumab, a decrease of D-dimer levels ($P = 0.0002$) was observed

★, severe; ‡, with nonresponsive to antihistamines; ※, with nonresponsive to omalizumab; §, refractory; age (y) Mean (SD)/Median (range)

Abbreviations: *CSU* chronic spontaneous urticaria, *CU* chronic urticaria, *CIU* chronic idiopathic urticaria, *DPU* delayed pressure urticaria, F_{1+2} prothrombin fragment $_{1+2}$, *TAT* thrombin–antithrombin III complex, *AT III* antithrombin III, *FIIa* activated factor II, *INR* international normalized ratio, *UCT* urticaria control test, *UAS7*, weekly urticaria activity score, *CU-Q2oL* Chronic Urticaria Quality of Life Questionnaire

Table 3 Urticaria patients demographics

Variable	Cases report	Case–control study	Cohort study	Cross-sectional study	Interventional study	Combined dataset
Patients, (*n*)	19	2031	2448	410	698	5606
Male, *n* (%)	8 (42.1)	633 (31.2)	987 (40.3)	136 (33.2)	197 (28.2)	1961 (35)
Female, *n* (%)	11 (57.9)	1398 (68.7)	1461 (59.7)	274 (66.8)	501 (71.8)	3645 (65)
Age (y), mean	38.7	40.3	39.1	43.5	40.5	40.4

n the number of patients

Research Types and Population Characteristics

Among these studies, 84.5% were observational studies, while the remaining 15.5% were interventional studies. The collective population across the 71 studies totaled 5606 patients, predominantly female (65%) and middle-aged (40.42 years) (Table 3).

Analysis of Countries and Authors

These studies were conducted in 24 countries from 1988 to 2024. Figure 2A presented the top 10 prolific countries, with Italy leading in publication volume with 19 articles, followed by Poland with 7 articles. Besides, the team of Asero, R. emerged as the most prolific, contributing with 12 articles, followed by Cugno, M., Kasperska-Zajac, A., and Kolkhir, P. (all two articles) (Fig. 2B). Meanwhile, a co-occurrence map shown that the node of "Asero, R." had a high degree, indicating that the author had collaborative relationships with many other authors and may be a key figure in this field (Fig. 2C). The cooperation network among authors was rather complex. The network formed by red lines had a wide coverage, indicating that the cooperation among this group of authors is quite common.

Analysis of Journals, Type of Disease, and Keywords

The 71 articles were published in 33 journals. The most productive journal was Allergy (seven articles), and nearly 50% of the included articles were published in high-quality journals (Fig. 3A). In addition, CSU is the most researched subtype (39 articles), followed by CU (16 articles), chronic inducible urticaria (CIU) (7 articles), and non-chronic urticaria (9 articles). "D-dimer," "chronic spontaneous urticaria," "urticaria," "disease activity," and "coagulation" were the most prominent keywords (Fig. 3B).

Coagulation/Fibrinolysis Biomarkers Were Predictive Markers of Urticaria Severity

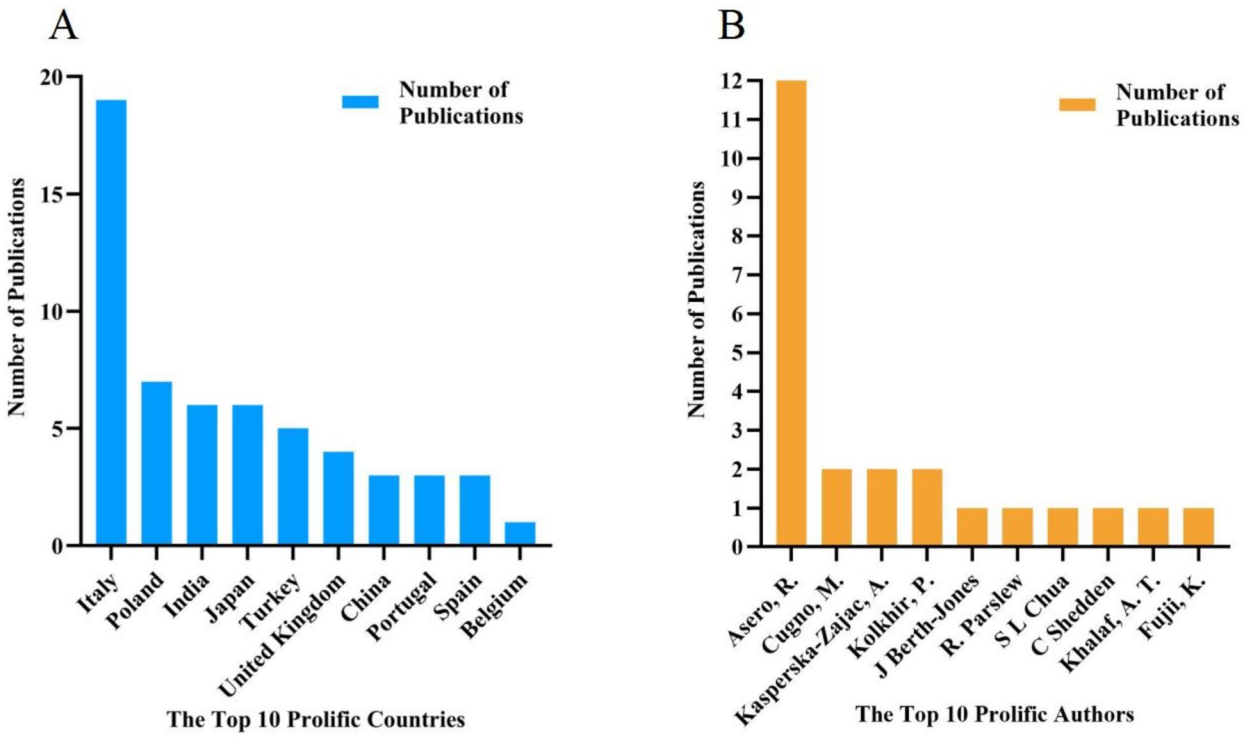
Coagulation/Fibrinolysis Biomarkers Related to Urticaria

In total, 21 biomarkers involved in the coagulation/fibrinolysis system were investigated in the included articles (Tables 1 and 2). D-dimer was the most investigated biomarker, which was evaluated in 56 studies. F_{1+2} was evaluated in 12 studies, prothrombin time (PT) in 8 studies; activated partial thromboplastin time (APTT) in 7 studies; platelet counts (PLT), fibrinogen, and thrombin–activated factor VII (FIIa) in 4 studies; TF, mean platelet volume (MPV), activated factor XII (FIIa), international normalized ratio (INR), and thrombin–antithrombin complex (TAT) in 3 studies; complement component 3 (C3), soluble fibrin monomer complex (SFMC), and Antithrombin III (AT III), and fibrin degradation products (FDP) in 2 studies; Plasma protein C/S, activated factor II (FIIa), high molecular weight kininogen (HMWK), and tissue-type plasminogen activator(t-PA) in 1 study (Table 4).

A total of 47.6% (1014/2132) of urticaria cases were ASST positive, and 66.9% (328/490) of cases were APST positive. In 60% (24/40) of the urticaria cases, ASST was negative, while APST was positive. In 69.1% (105/152) of the urticaria cases, both the ASST and APST were positive. 39.5% (826/2089) of cases had angioedema (Table 4).

D-Dimer and F_{1+2} Plasma Levels Were Upregulated in Patients with Urticaria

First, the included studies [24, 35, 51, 53, 62, 81] ($n = 256$) were analyzed for the baseline D-dimer levels of both patients and healthy controls. Four records were observational studies, and two records were non-randomized controlled trials. CSU [51, 53, 62, 81], CU [24], and delayed pressure urticaria (DPU) [35] were included in this analysis. Overall, when compared with healthy controls, plasma levels of D-dimer were significantly higher among patients (MD 255.82; 95% CI [85.00 to 426.64] ng/mL) (Fig. 4A). However, there was significant heterogeneity among different studies. In over half of the studies, the D-dimer levels of patients were within the normal threshold (< 500 ng/mL). Among the included studies, baseline D-dimer plasma levels were higher than 500 ng/mL in two observational studies [35, 51]. To further explore D-dimer levels in patients with urticaria, a single-arm meta-analysis was conducted, including 16 studies ($n = 1359$) [24, 35, 37, 50, 51, 53, 62, 69, 71, 72, 74, 80–83]. For D-dimer, the pooled MD was 628.38 (95% CI [437.67 to 819.08] ng/



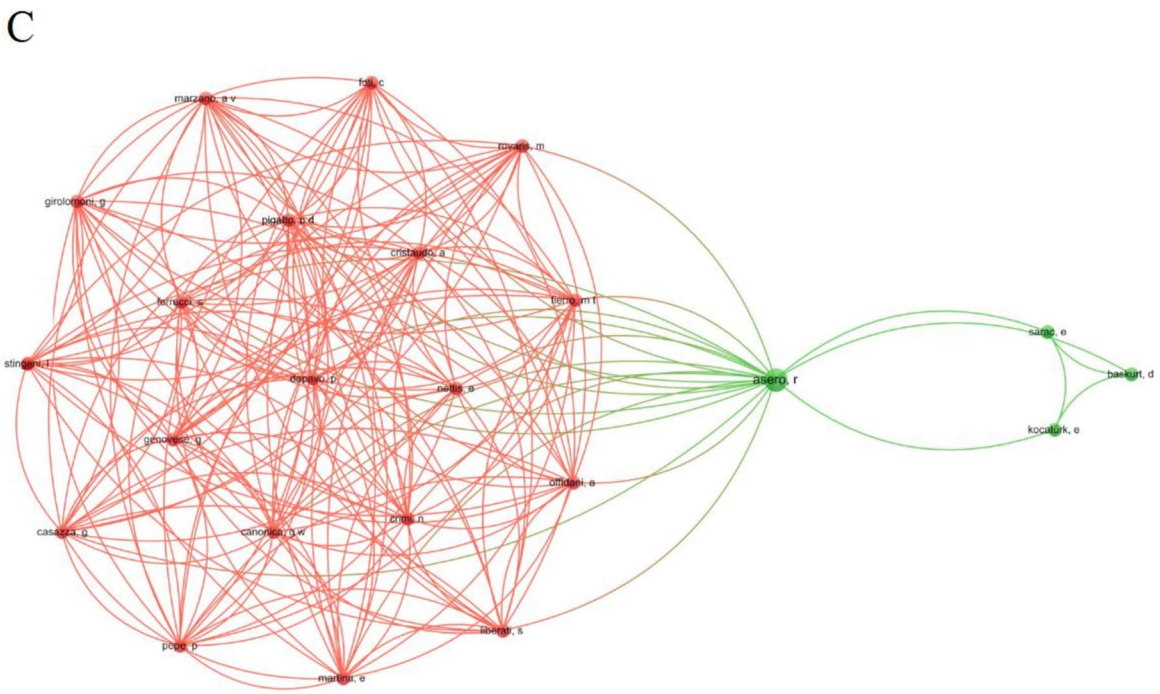


Fig. 2 Number of publications: **A** Top 10 prolific countries; **B** Top 10 prolific authors; **C** Co-occurrence map of authors

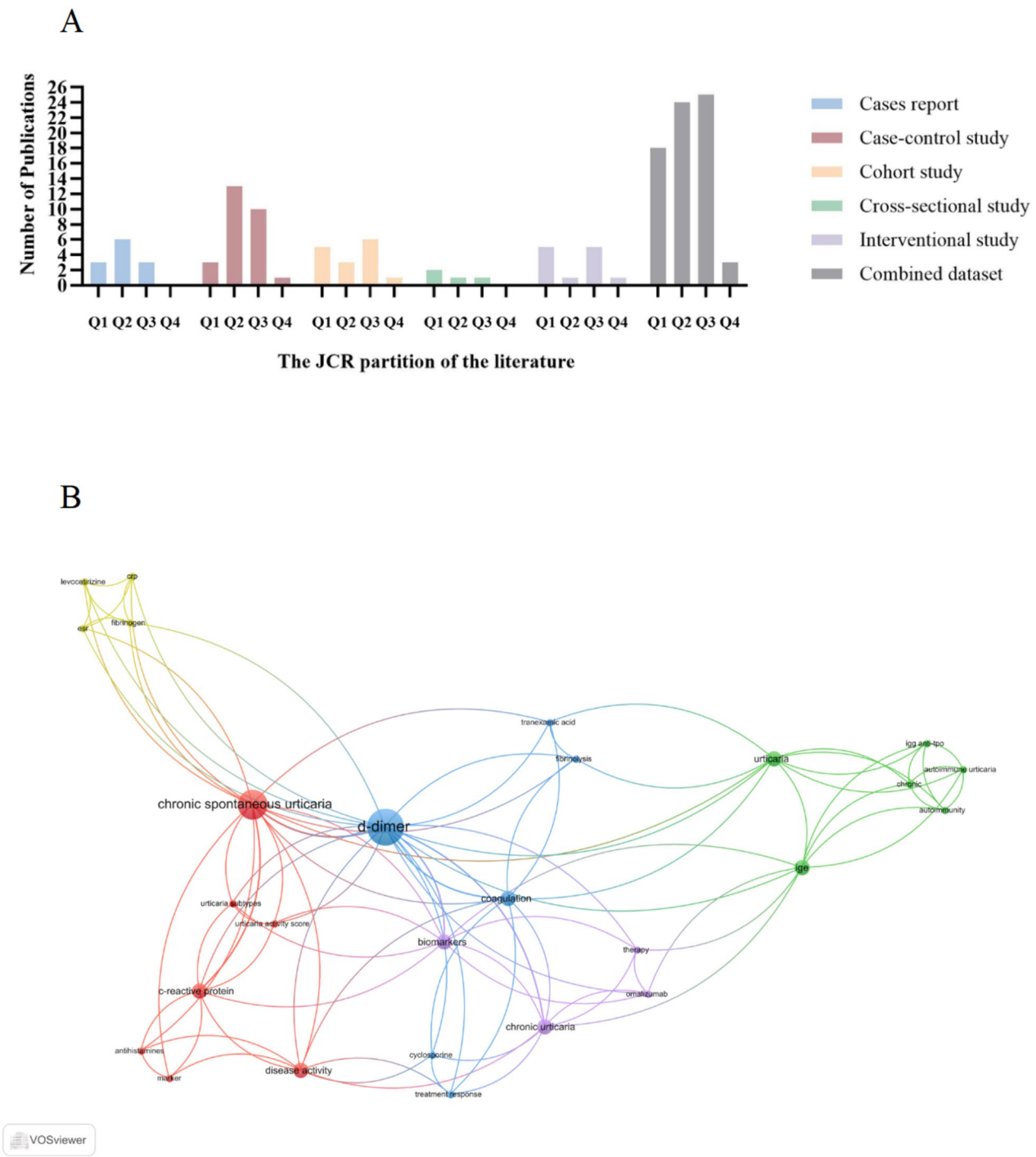


Fig. 3 **A** The JCR partition of literature; **B** Co-occurrence map of keywords

mL), and D-dimer plasma levels surpassed upper limit of normal values (500 ng/mL) in the majority of the included studies (56.3%) (Fig. 4B) [35, 37, 50, 51, 69, 71, 72, 82].

Second, compared with healthy controls, F_{1+2} levels were significantly elevated in patients with CSU [53], and CU [24, 26, 84] (1.61, 95% CI [0.43 to 2.80] nmol/L) (Fig. 4C). Furthermore, F_{1+2} levels in three studies [24, 53, 84] were higher than the normal F_{1+2} values (< 0.229 nmol/L).

D-Dimer and Disease Activity May Be Correlated

Coagulation/fibrinolysis biomarkers were often used to assess disease activity in patients with urticaria. D-dimer, 26

Table 4 Clinical characteristics

Variable	Cases report	Case–control study	Cohort study	Cross-sectional study	Interventional study	Combined dataset
ASST$^+$, n/N (%)	6/7 (85.7)	161/205 (78.5)	590/1506 (39.2)	223/335 (66.6)	34/79(43)	1014/2132 (47.6)
APST$^+$, n/N (%)	5/5 (100)	/369 (68)	—	8/57 (14.1)	64/64 (100)	328/490 (66.9)
ASST-, APST$^+$ n/N (%)	1/5 (20)	23/35 (65.7)	—	—	—	24/40 (60)
ASST$^+$, APST$^+$ n/N (%)	4/4 (100)	93/140 (97.6)	—	8/8(100)	—	105/152 (69.1)
Angioedema$^+$, n/N (%)	4/7 (57.1)	—	813/2048 (39.7)	—	9/34 (26.5)	826/2089 (39.5)
D-dimer, No	6	23	15	2	10	56
F_{1+2}, No	1	9	—	1	1	12
FVIIa, No	—	4	—	—	—	4
FXIIa, No	1	2	—	—	—	
TAT, No	1	3	1	—	—	5
AT III, No	—	2	1	—	—	3
FDP, No	—	2	—	—	—	2
HMWK, No	—	1	—	—	—	1
t-PA, No	—	1	—	—	—	1
SFMC, No	—	2	1	—	—	3
APTT, No	1	5	—	—	—	6
PT, No	1	4	1	—	1	7
TF, No		3	—	—	—	3
Platelet counts, No	—	1	—	—	—	1
Plasma protein C, No	—	1	—	—	—	1
Fibrinogen, No	—	3	1	—	2	6
MPV, No	—	2	1	—	—	3
PLT, No	—	1	1	—	—	2
C3, No	—	4	—	—	1	4
TNR, No	1	1	—	—	1	3

n the number of patients. *N* the total number of patients. *No* the number of literatures

Abbreviations are the same as those in Table 1

studies suggested a statistically significant positive correlation with disease severity (Table 5). In other words, the more severe the symptoms of urticaria, the higher the D-dimer levels. Meanwhile, coagulation/fibrinolysis biomarkers such as D-dimer levels have also been confirmed to be positively correlated with F_{1+2} levels [37], C-reactive protein (CRP) [58] and interleukin 6 (IL-6) [58], which suggested that the coagulation system, immune system and inflammatory response may interact with each other in the pathology of CU to accelerate the advancement of the disease condition (Table 6). However, 5 studies reported negative correlations among D-dimer values and the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), total immunoglobulin E (IgE), and Urticaria Activity Score 7 (UAS7) [40, 41, 67, 71, 76]. These contradictions could stem from variations in urticaria subtypes, the sample size, and other factors. Specifically, D-dimer levels were more likely to be elevated in patients with CSU/CU with nonresponsive to antihistamines/omalizumab than in other types of urticaria. In addition, the detection methods affected the results. For instance, by latex agglutination immunoassay, plasma from only 2 of 21 (10%) patients contained increased D-dimer levels, but by enzyme-linked immunosorbent assay (ELISA), the D-dimer levels were elevated in 8 of 37 (22%) patients [24]. Currently, ELISA stands as the most widely used measurement modality.

F1+2 and Disease Activity May Be Correlated

Six studies had also shown a positive relationship between urticaria severity and F_{1+2} levels (Table 5). Significant correlations between F_{1+2} and other coagulation/fibrinolysis

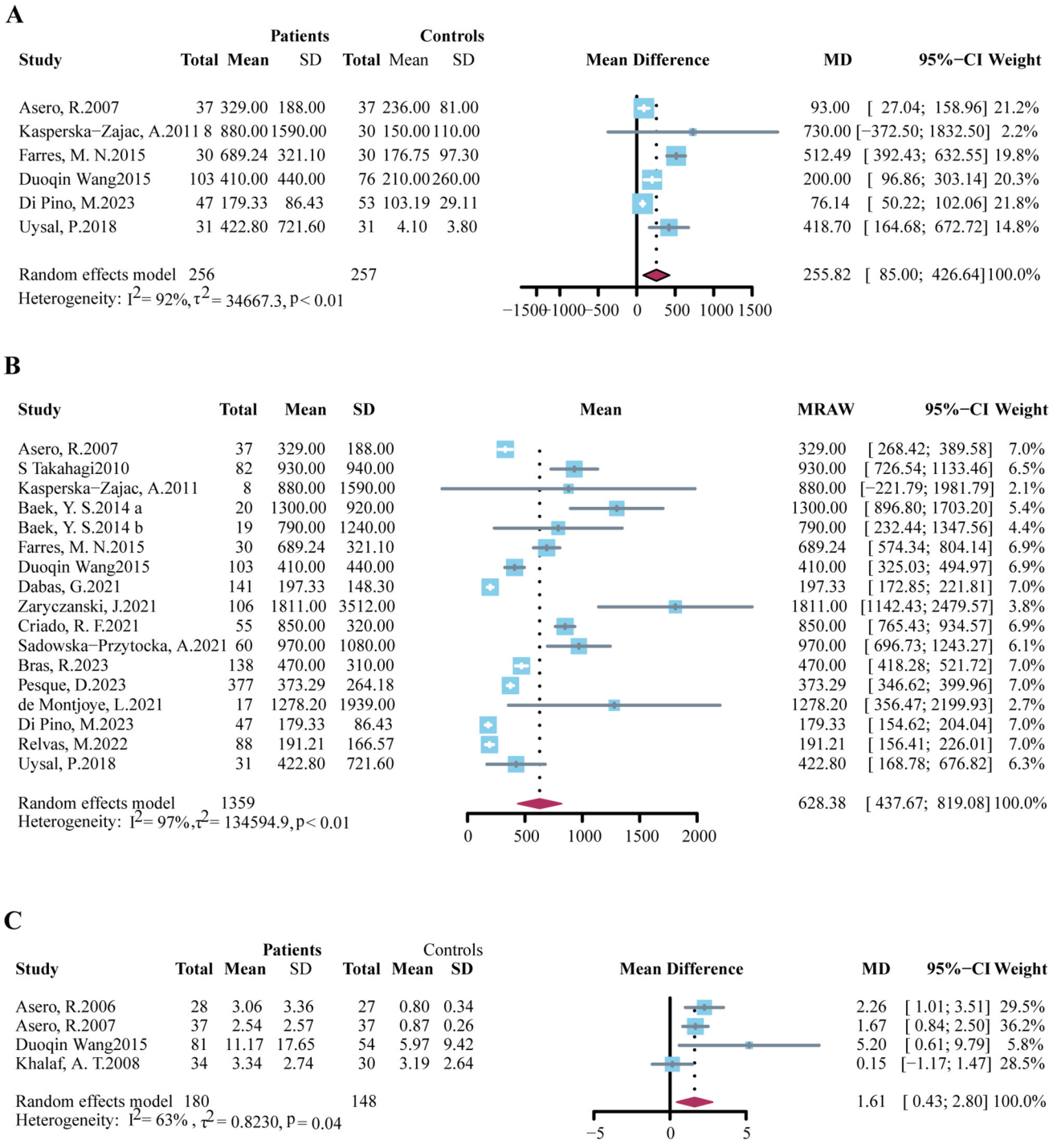


Fig. 4 Forest plots. **A** Pooled results of plasma levels of D-dimer; **B** Pooled results of plasma levels of D-dimer (single-arm meta-analysis); **C** Pooled results of plasma levels of F_{1+2}

Table 5 The relationship between coagulation/fibrinolysis biomarkers and the severity of urticaria

Severity of urticaria	D-dimer, No	$F_{1+2,}$ No	FVIIa, No	TAT, No	FDP, No	HMWK, No	t-PA, No	APTT, No	SFMC, No
Positive correlation	26	6	2	3	1	1	1	0	1
Negative correlation	5	—	—	—	—	—	—	1	—

Abbreviations are the same as those in Table 1

Table 6 The relationship between coagulation/fibrinolysis markers and other factors

Positive correlation	$F_{1+2,}$ No	CRP, No	FVIIa, No	IL-6	Positive correlation	D-dimer, No	VEGF, No	FVIIa, No
D-dimer	1	1	1	1	**F_{1+2}**	1	1	1

Abbreviations are the same as those in Table 1

biomarkers also were found. For example, FVIIa [24], D-dimer [43], and F_{1+2} levels were significantly correlated (Table 6).

Other Coagulation/Fibrinolysis Biomarkers and Disease Activity May Be Correlated

FDP [34, 37], TAT [32, 41, 95], HMWK [19], and FVIIa [51, 53] plasma levels were significantly correlated with the disease activity of patients with urticaria (Table 5). Moreover, TF was described upregulated in the lesioned skin of patients with CU and CSU [24, 42, 68]. Furthermore, compared to healthy individuals, a statistically significant increase in APTT [81, 85], PT [85], thrombin time (TT) [85], and PLT [81] were found in patients with CSU. Conversely, another study found no difference in PT, APTT, and fibrinogen levels between children with CSU and healthy children [86]. Lastly, no significant difference was found on FXIIa plasma levels in patients with CSU compared to the healthy participants [53].

Coagulation/Fibrinolysis Biomarkers, as Predictors of the Treatment Response in Urticaria, Still Require Support from More Evidence

As the activation of the coagulation cascade played a role in the pathophysiology of urticaria, we explored the potential use of coagulation/fibrinolysis biomarkers as predictors of treatment response. Notably, four studies demonstrated a significant decrease in plasma D-dimer concentration after omalizumab therapy [48, 63, 72, 96]. In addition, omalizumab non-responders tended to exhibit higher D-dimer plasma levels [56, 59, 63, 96]. However, some studies reached an opposite conclusion [59, 64]. Asero, R [64] investigated 161 adult patients with severe CSU and found that there was no clear trend in baseline D-dimer levels among the different response groups to omalizumab, which implied that it cannot be used to predict the response to omalizumab.

Besides, a few studies explored the predictive role of D-dimer on the efficacy of other drugs. Cyclosporine non/low-responders [87] and H1-antihistamines (sgAHs) non/low-responders [38, 54, 72, 97] had significantly higher baseline D-dimer levels than responders. Furthermore, in the subgroup of patients with urticaria who underwent a longer course of glucocorticoid (GCS) treatment, the concentration of D-dimer was significantly higher than that in patients with a shorter GCS treatment duration [82]. However, two studies also found that D-dimer levels showed no significant correlation with the response to cyclosporine [52] and autologous whole-blood injection (AWBI) intervention [55]. Researchers also hold the view that D-dimer was not considered useful as a prognostic factor [91], and did not seem to increase their sensitivity in detecting higher disease activity of urticaria [94].

Anticoagulants Showed Promising Results as a New Therapeutic Option for Urticaria

Some studies [28, 46, 60] have shown the potential efficacy of anticoagulants in relieving the symptoms of urticaria, especially in severe CSU/CU that were unresponsive to antihistamines/omalizumab. Predominantly, these findings came from case reports ($n=6$), with fewer clinical intervention studies ($n=4$). These case reports revealed the potential beneficial effects of warfarin [28, 30], heparin sodium [27], and tranexamic acid [44, 60] in various urticaria types, including CU, CIU, CSU, and NSAID-induced urticaria [84]. Besides, several anticoagulant intervention studies have confirmed reduced F_{1+2}, TAT, and D-dimer levels following treatment with tranexamic acid [38], acenocoumarol [32], warfarin [46], and dipyridamole [26]. However, current research also has found that in a severe CSU case refractory to omalizumab, high D-dimer levels decreased only after the disease was remitted by cyclosporine treatment, not by anticoagulation drugs [75].

Discussion

Summary of Findings

This scoping review provides a comprehensive analysis of the relationship between coagulation/fibrinolysis biomarkers and disease progression, predictors of the treatment response, as well as the efficacy of anticoagulants in patients with urticaria, especially those with CU (Fig. 5).

Coagulation/Fibrinolysis System and Immune-Inflammatory Responses Combine in the Pathogenesis of Urticaria

This review emphasizes the involvement of the coagulation/fibrinolysis system in urticaria pathogenesis. Patients with urticaria, especially those with CU, typically exhibit

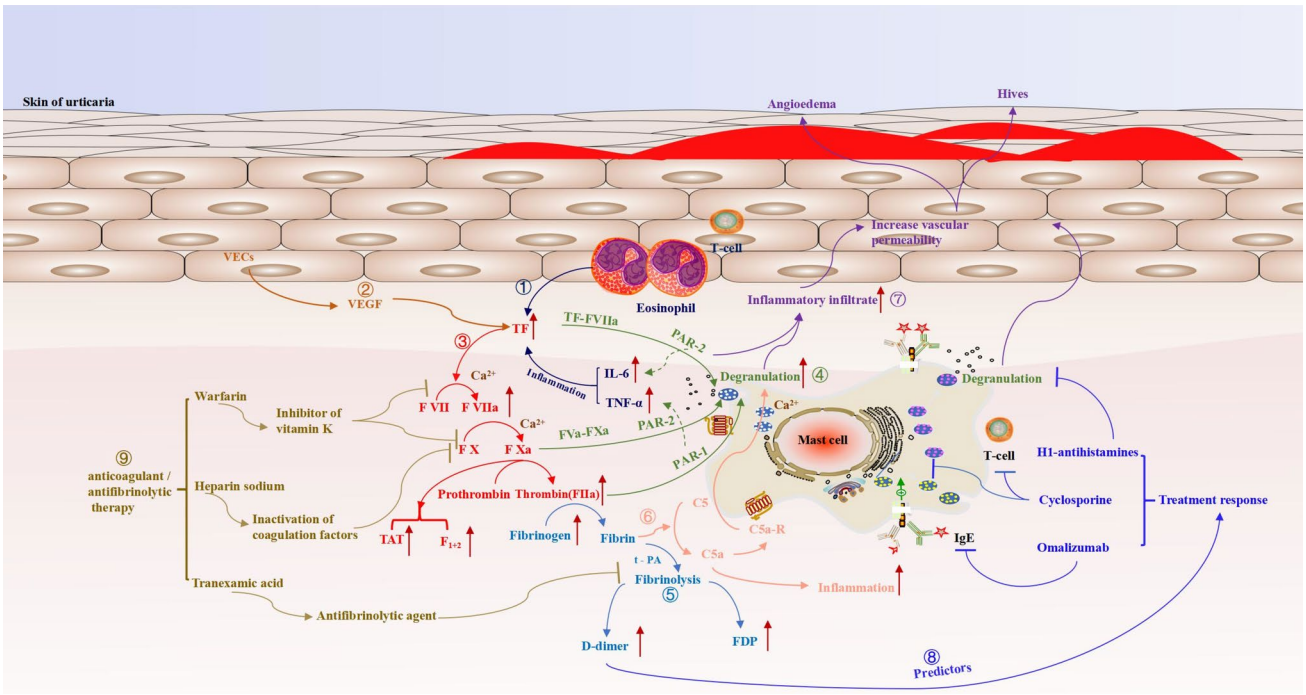


Fig. 5 The relationship between coagulation/fibrinolysis biomarkers and the pathology of urticaria as well as anticoagulant drugs.① Eosinophils or pro-inflammatory cytokines elevate TF levels in urticaria skin; ② Vascular endothelial cells secrete VEGF, raising TF levels in urticaria skin; ③ The extrinsic coagulation cascade is activated; ④ Multiple coagulation-related pathways lead to mast cell degranulation; ⑤ Fibrinolysis system is activated; ⑥ Fibrin activates the complement system; ⑦ Skin inflammatory reactions or substances released during mast cell degranulation can lead to urticaria or angioedema; ⑧ D-dimer as a predictor of the treatment response; ⑨ Anticoagulant or anti-fibrinolysis therapy for urticaria. Abbreviations: F1+2, Prothrombin fragment 1+2; FVIIa, activated factor VII; FVa, activated factor V; FXa, activated factor X; TF, Tissue factor; FDP, Fibrin degradation products; TAT, thrombin–antithrombin complex; PAR-1, protease-activated receptors 1; PAR-2, protease-activated receptors 2; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; t-PA, Tissue-type plasminogen activator; VEGF, Vascular Endothelial Growth Factor; C5aR, C5a Receptor; VECs, Vascular endothelial cells

higher levels of coagulation/fibrinolysis biomarkers than healthy controls, indicating an activated coagulation/fibrinolysis system [35, 51, 98, 99]. Notably, the APST positive rate (66.9%) in urticaria patients is significantly higher than the ASST positive rate (47.6%), and in 60% of patients, APST is positive while ASST is negative, suggesting plasma coagulation factors' role. Meanwhile, studies have shown a positive correlation between coagulation/fibrinolysis biomarkers and immune inflammatory factors like CRP [61] and IL-6 [58], indicating crosstalk among immunity, inflammation, and the coagulation/fibrinolysis system. In urticaria development, the link between the coagulation/fibrinolysis system and urticaria is extremely close and complex, involving multiple mechanisms.

The Extrinsic Coagulation Pathway Triggered by TF has Been Proven to be Involved in the Pathogenesis of Urticaria TF, originating from eosinophils in urticaria inflammatory skin lesions [42, 100] or induced by IL-6 and tumor necrosis factor alpha (TNF-α) [101, 102], triggers the extrinsic coagulation cascade in the skin and induces degranulation of skin mast cells in urticaria [24, 103]. Specifically, TF combines with factor VII (FVII) in the presence of Ca^{2+} to form the TF-FVIIa complex [103]. The complex of TF-FVIIa converts FX to Xa by calcium, which would form the prothrombinase complex with activated factor V (FVa), prothrombin factor II (FII), thereby generating FIIa [104]. During the production of FIIa, F_{1+2} is generated, and an increase in its level indicates the activation of the coagulation system. Some studies [24, 26, 84] have confirmed that the F1+2 level in the serum of urticaria patients is significantly elevated. Meanwhile, animal studies have shown that FIIa can increase vascular permeability [105] and induce mast cell degranulation via PAR-1 during inflammation [106, 107]. TF-FVa and FVa-FXa complexes act via PAR-2, leading to mast cell degranulation [108, 109]. In addition, the expression of PAR-2 in mast cells at the lesional sites of urticaria is upregulated [109]. In turn, activated coagulation factors (FVIIa, FXa, FIIa) trigger intracellular activation via PARs, induce pro-inflammatory mediators, and initiate an inflammatory response [110, 111]. Plasma levels of F_{1+2}, TAT, and FVIIa are significantly increased in CU patients [17,

41, 51], without elevated FXIIa [24, 53], further suggesting that the generation of thrombin in CU patients occurs and only the extrinsic coagulation pathway is involved in the pathogenesis of CU.

The Activated Fibrinolysis System Might be Involved in the Pathological Mechanism of Urticaria Moreover, FIIa can convert fibrinogen into fibrin. Fibrin can promote the occurrence of inflammatory responses through Toll—like receptor 4 (TLR-4). At the same time, FIIa can further affect the activities of t—PA and u—PA by regulating plasminogen activator inhibitor—1 (PAI-1), thus regulating the fibrinolysis process. Fibrin degradation during fibrinolysis produces D-dimer. Increased D-dimer and decreased t-PA concentrations also suggest the activation of fibrinolysis [19, 43]. Multiple studies [35, 37, 50, 51, 69, 71, 72, 82] have found that D-dimer is significantly increased in the serum of patients with urticaria, especially those with CU. Researchers have also confirmed that HMWK is elevated and t-PA is decreased in patients with CU [19]. In addition, the immune-inflammatory response in urticaria also promotes fibrin formation and fibrinolysis, resulting in elevating D-dimer plasma levels [41]. This significant correlation has been confirmed among IL-6, CRP, and D-dimer in CSU [58], which further indicates the potential interplay between fibrinolysis system and inflammatory response in CSU. Coagulation/fibrinolysis biomarkers such as D-dimer and F1 + 2 can, to some extent, also reflect the severity of urticaria, especially CU. This suggests their potential value in assessing the disease state and guiding further research into urticaria pathophysiology and treatment strategies.

The Coagulation Cascade, Vascular Endothelial Cells, and the Complement System may Jointly Participate in the Pathological Mechanism of Urticaria Vascular endothelial cells play a crucial role in the early stage of urticaria onset. After being stimulated by vascular endothelial growth factor (VEGF) and other factors, vascular endothelial cells will express a large amount of TF on their surface and produce activated coagulation factors such as FIIa. FIIa and FXa can also induce endothelial cell gap formation via PAR-1, disrupt the vascular endothelial barrier, increase vascular permeability, and cause plasma leakage, triggering the inflammatory reaction and urticaria symptoms like skin edema and wheals [112]. Researcher has also found that the level of VEGF was significantly higher in CU patients than in normal subjects [39]. Additionally, mast cells express C5a receptors. As an activated complement product, C5a activates macrophages, neutrophils, mast cells, triggering inflammatory-substance release and promoting inflammation. FIIa can convert C5 into C5a, and the latter induces the release of histamine from skin mast cells and peripheral blood basophils through the C5a receptor (without the involvement of antigens and IgE), thereby promoting the occurrence and development of urticaria symptoms [25, 112]. Meanwhile, FIIa participates in the interaction between the coagulation and complement systems, affecting the pathological process of CSU [25, 112]. Research has confirmed that the levels of C5a and C4 in patients with CU are significantly higher than those in healthy controls [19]. Therefore, the coagulation cascade, vascular endothelial cells, and the complement system are closely linked in urticaria pathology. But the exact mechanism remains unclear and requires further study.

In conclusion, the interplay of immunity, inflammation, and coagulation/fibrinolysis in urticaria may amplify its inflammation, yet the causal links among these three systems lack strong evidence. Future research may validate their clinical utility and explore targeted therapies based on these insights.

Coagulation/Fibrinolysis Markers as Predictors of the Treatment Response

Regarding predictors, nonresponse or low-response to antihistamines, omalizumab and cyclosporine can be predicted by some coagulation/fibrinolysis biomarkers, such as D-dimer, albeit with unknown sensitivity. A series of studies have found that D-dimer levels have shown a dramatic decrease in patients with CIU/CSU after omalizumab or cyclosporine treatment [52, 59, 62, 96]. Although elevated plasma levels of D-dimer lack specificity, the identification of D-dimer may play a pivotal role in evaluating the treatment effectiveness or the disease exacerbation. However, current studies on other coagulation/fibrinolysis predictors lack a robust and unified conclusion on this predictive aspect. Future studies should focus on establishing the sensitivity and specificity of these biomarkers in predicting treatment responses.

Prospects for Anticoagulants and Anti-Fibrinolysis Therapy

The activation of coagulation/fibrinolysis may provide the rationale for an anticoagulant and antifibrinolytic therapy in patients with severe urticaria or special subtypes of urticaria [99]. Anticoagulants have been infrequently used in urticaria treatment, primarily reported in case reports of refractory cases. Chua and Gibbs first reported the effectiveness of heparin sodium as a treatment for CU [27], and heparin sodium can turn apparently positive ASST negative [45]. Magen and Chikovani successfully treated angioedema after omalizumab injections in a patient with CSU using tranexamic acid [60], which is an antifibrinolytic agent. Some researchers reported that warfarin, a competitive inhibitor of vitamin K, was effective in patients with CIU [30, 113]. Khalaf et al. found that the desloratadine combined with dipyridamole, which is a platelet adhesion inhibitor, is more effective for patients with CU

[26]. It has been speculated that suppressing inflammation is the one of reasons this anticoagulant/ antifibrinolytic therapy works [38]. It is worth noting that most of the current findings were based on short-term clinical observations. It needs to be investigated, whether anticoagulant therapy could be the one of the solutions to the current dilemma of urticaria treatment.

Comparison with Other Literature Findings

This scoping review is the first of its kind to comprehensively and extensively analyze the published coagulation/fibrinolysis biomarkers and their association with anticoagulant use in urticaria, especially CU, thus setting it apart from previous literature in this field. While previous reviews have delved into this research area, the review uniquely has consolidated and expanded upon these findings, encompassing a broader range of relevant studies. Regarding the pathological mechanisms, researchers posited that the coagulation/fibrinolysis system contributed to the pathogenesis of urticaria [99, 114]. Yanase et al. [103] suggested that activating the extrinsic coagulation pathway may induce degranulation of skin mast cells and edema. Regarding disease severity prediction, Kolkhir et al. [115] found a significant association between CSU activity and blood levels of D-dimer and F_{1+2}. Another review [116] also found that thrombin generation and fibrinolysis were increased during exacerbations of urticaria and angioedema, with the biomarker levels decreasing to normal during remission. In terms of predictors of treatment response, some reviews found that D-dimers were robust predictors of a poor or no response to sgAHs [117, 118] and were associated with better responses to cyclosporine [119]. Most reviews supported that coagulation activation contributed to the pathophysiology of urticaria, especially CU and CSU, and it may predict drug responses, conforming to our results. Previous researches were mostly qualitative analysis or cases summaries. Our study quantifies coagulation/fibrinolysis biomarkers-urticaria-severity links, comprehensively analyzes the efficacy-predictive role of existing biomarkers and the types of anticoagulants used, and offers a relatively precise overview of the field.

Potential Applications and Implications of These Findings in Urticaria Diagnosis and Intervention

This review may provide some guidance for clinicians and patients regarding the potential applications of coagulation/fibrinolysis biomarkers in formulating diagnostic and treatment plans for urticaria, especially CU. Through the detection of related biomarkers, such as D-dimers, physicians may be able to determine the patient's condition at an early stage and develop a more individualized treatment plan. There is a possibility that identifying patients with drug-resistant urticaria and facilitate the implementation of stratified medication could potentially be extended. Finally, standardized anticoagul ant and antifibrinolytic therapies may potentially open new avenues in the treatment of urticaria, especially CU. However, this requires further verification through future studies.

Future Directions for Research

The coagulation/fibrinolysis biomarkers in literature identified in this review may provide new directions for future clinical and mechanism research. This scoping review underscores the existing unmet clinical needs in urticaria while highlighting the insufficiency of mechanistic studies exploring the involvement of the coagulation/fibrinolysis system in the disease progression. To address these gaps, urgent steps are warranted. First, existing studies in anticoagulants are mostly observational; therefore, gaps in the current literature suggest that there is an urgent need for high-quality RCTs to prove their effectiveness. Second, potential confounding factors such as the individual differences among patients with different types of urticaria in clinical practice still need to be carefully considered. Relevant studies may focus on a specific type of urticaria to generalize the research findings. Third, the specific effect of biomarkers in predicting drug response needs further substantiation. Fourth, further evidence is needed to elucidate the relationship between refractory urticaria and the coagulation/fibrinolysis system. This may be a new therapeutic target for refractory urticaria. Furthermore, whether abnormalities in coagulation/fibrinolysis biomarkers can explain urticaria resistance is worth exploring.

Limitations

The following study limitations are acknowledged. (1) Our review covered diverse urticaria types and age groups, causing inter-study heterogeneity that could veil subgroup-specific trends. (2) Quantitative subgroup analyses have not been applied according to different types of urticaria. Different types of urticaria vary widely in coagulation biomarkers. (3) All three meta—analyses had substantial heterogeneity. Diverse study designs and urticaria subtypes likely contributed to result variance. Also, bias risk was present in most studies, so results need cautious interpretation. (4) Different biomarker detection methods were used. Even after value normalization, they may bias results. Each method has pros and cons. Appropriate methods should be chosen per situation, with strict quality control and verification for accurate results. (5) Hematological or inflammatory diseases can skew coagulation/fibrinolysis biomarkers and such cases should be excluded in our study. After examining the inclusion and exclusion criteria for urticaria patients in 71 included studies, none of the studies mentioned whether the included urticaria patients had hematological diseases or other inflammatory diseases, nor did they clearly exclude urticaria patients with high coagulation/fibrinolysis markers caused by such diseases. In studies

involving anticoagulant drugs, only patients at risk of bleeding were excluded. Hence, we can't tell if biomarker changes relate to urticaria or underlying hematological diseases. Most inflammatory diseases have coagulation biomarkers abnormalities [16]. And it is hard to tell if coagulation/fibrinolysis biomarkers are due to urticaria or inflammatory diseases. Future studies should exclude urticaria patients with these comorbidities.

Conclusions

This scoping review of urticaria and coagulation/fibrinolysis system is a starting point to summarize research in this area, generate hypotheses, and direct future research. Two critical points were revealed: positive correlations between the coagulation/fibrinolysis biomarkers levels (D-dimers [26 articles] and F_{1+2} [12 articles]) and disease severity were confirmed; coagulation/fibrinolysis biomarkers may hold predictive value for treatment response (D-dimers). However, these results were mostly derived from observational studies, all of which need to be supported by more rigorous research evidence. Furthermore, although the field of pharmacological treatment of urticaria, especially CU, is ripe, the coagulation/fibrinolysis system shows promise as a new therapeutic target for urticaria.

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Author contributions Li—Tao Pan and Yun—zhou Shi: conceptualization and methodology. Hai—yan Qin and Xian—jun Xiao: investigation and resources. Di Qin and Siqi Wang: data curation and validation. Hai—yan Qin: software and formal analysis. Hai—yan Qin, Xian—jun Xiao and Peiwen Xue: writing—original draft and visualization. Yun—zhou Shi and Xian—jun Xiao: funding acquisition. Ying Li: supervision.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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