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Concomitant evaluation of D-dimer and C-reactive protein in chronic spontaneous urticaria may show divergent values

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Key words

Chronic spontaneous urticaria; D-dimer; C-reactive protein; biomarkers; urticaria activity score.

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To the Editor,

two chronic spontaneous urticaria (CSU) subtypes with distinct pathomechanisms have been described: type IIb autoimmunity (IgG anti-FceRI/anti-IgE) and type I autoallergy (IgE anti-self/anti-thyroperoxidase/anti-interleukin-24) (1). In type IIb there is a higher female predominance, more angioedema, concomitant autoimmune diseases, positive basophil activation test (BAT) and autologous serum skin test (ASST), and a slow response to omalizumab, whereas in type I, response to this agent is usually fast (1). Recently, other concomitant pathomechanisms have been described, namely IgE anti-FceRI and immune-complexes with IgE, which may explain some overlap between the two subtypes and unexpected responses to omalizumab or in the ASST/BAT (2). Biomarkers that characterize these subtypes are still under evaluation, although high IgG anti-thyroperoxidase (anti-TPO) antibodies, low total serum IgE, basopenia and eosinopenia correlate better with type IIb autoimmunity (1). Other serum biomarkers, namely interleukin-6 (3), interleukin-17 (4), D-dimer (5) and C-reactive protein (C-RP) (6) seem to correlate with disease activity, but they are seldom studied simultaneously.

We conducted a retrospective study between 2019 and 2021 in our tertiary dermatology center, where we analysed data from 88 CSU patients, with the objective of evaluating the correlation between serum D-dimer and C-RP values, by comparing patients who had concordant levels of these biomarkers (both elevated or both normal) with those that had divergent values (one high and the other low). We also correlated these biomarkers with disease activity and with other markers that indicate CSU subtypes (type I and type IIb). Patients with pure chronic inducible urticaria or angioedema without wheals were excluded.

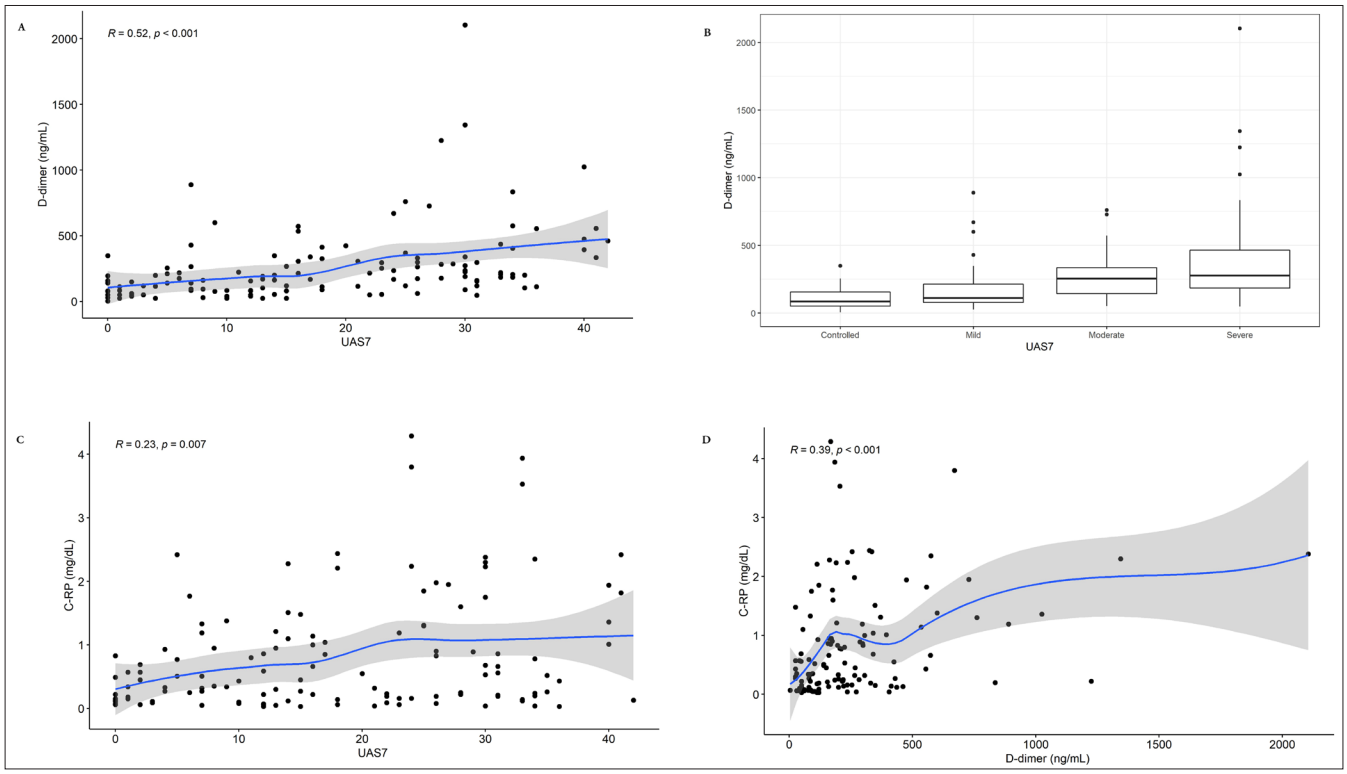
Clinical parameters included demographic data, CSU duration, concomitant angioedema, associated inducible urticaria, history of occasional wheals progressing to residual bruising and disease activity measured by Urticaria Activity Score over the last 7 days (UAS7; controlled, mild, moderate or severe for UAS7 between 0-6, 7-15, 16-27 or 28-42, respectively), evaluated the week before blood collection for the study. Venous blood was collected in the morning before the consultation and, for patients on omalizumab, 4-8 weeks after the last administration, depending on disease control and, consequently the interval between administrations. Parameters evaluated in the same blood sample included total serum IgE (normal < 100 UI/mL), eosinophil and basophil absolute counts, IgG anti-TPO and anti-nuclear antibodies (ANA, positive > 1:160), D-dimer (normal < 230 ng/mL) and C-RP (normal < 0.5 mg/dL) serum levels.

Statistical analysis was performed using R statistical software (version 4.0.5). Quantitative variables were tested for normality using Shapiro-Wilk test; group comparisons were made using Mann-Whitney test and Kruskal Wallis test. For pairwise comparisons P-values were presented with Bonferroni correction for multiple comparisons. Correlations between variables were made using Spearman correlation coefficient. The Chi-Square test of

A		B			
Patients' data	**Total n (%)**	**High D-dimer n (%) (n = 33)**	**High C-RP n (%) (n = 40)**	**Totally concordant n (%) (n = 49)**	**Totally divergent n (%) (n = 31)**
Age in years, mean ± SD	45 ± 15.8	50 ± 14.7	44.5 ± 14.4	43.6 ± 16.8	47.7 ± 14.3
Female	74 (84.1)	26 (78.8)	35 (87.5)	43 (87.8)	23 (74.2)
Angioedema	59 (67.1)	25 (75.8)	27 (67.5)	31 (63.3)	23 (74.2)
Concomitant inducible urticaria	39 (44.3)	/	/	/	/
Symptomatic dermographism	8 (9.1)	/	/	/	/
Delayed pressure urticaria	31 (35.2)	/	/	/	/
Cold urticaria	2 (2.3)	/	/	/	/
Heat urticaria	1 (1.1)	/	/	/	/
Solar urticaria	1 (1.1)	/	/	/	/
Residual bruising	21 (23.8)	11 (33.3)	9 (22.5)	9 (18.4)	7 (22.6)
ANA positive (> 1:160)	22 (25)	10 (30.3)	9 (22.5)	12 (24.5)	7 (22.6)
Anti-TPO positive	9 (11.4)	2 (6.1)	2 (5.0)	7 (14.3)*	1 (3.2)*
UAS7, median (IQR)	16 (7-29.5)	26 (19-33.5)	22 (13-30)	16 (8-26)	21 (13-30)
Controlled (0-6)	13 (14.8)	1 (3)	4 (10.0)	10 (20.4)	3 (9.7)
Mild (7-15)	24 (27.3)	4 (12.1)	11 (27.5)	13 (26.5)	9 (29.0)
Moderate (16-27)	24 (27.3)	13 (39.4)	12 (30.0)	15 (30.6)	7 (22.6)
Severe (28-42)	27 (30.7)	15 (45.5)	13 (32.5)	11 (22.4)	12 (38.7)
Low IgE (< 25 UI/mL)	21 (23.9)	7 (21.2)	14 (35)	12 (24.5)	6 (19.4)
Eosinopenia (< 100/mL)	25 (28.4)	11 (33.3)	10 (25)	18 (36.7)**	5 (16.1)**
Basopenia (0/mL)	26 (29.5)	11 (33.3)	25 (62.5)	17 (34.7)	8 (25.8)
		Median (IQR)			
CSU duration (months)	16.5 (5-60)	26 (6.5-78)	23 (8-69)	13 (5-54)	24 (5-60)
D-dimer (ng/mL)	181 (85-306)	405 (277.5-567.5)	188.5 (150-388)	150 (78.5-344)	185 (150-306)
C-RP (mg/dL)	0.45 (0.15-1.16)	0.55 (0.18-1.72)	1.32 (0.73-2.15)	0.27 (0.09-1.2)	0.83 (0.2-1.3)
Total IgE (UI/mL)	78 (20-255.5)	67 (27.8-261.0)	96 (31-265.5)	75 (25-249)	86 (24.8-275.3)
Eosinophils (mL)	130 (90-200)	110 (75-195)	140 (92-200)	100 (80-180)	170 (100-200)
Basophils (mL)	20 (0-50)	10 (0-95)	2 (2-40)	10 (0-45)	30 (10-80)

ANA: anti-nuclear antibodies; anti-TPO: anti-thyroperoxidase antibodies; C-RP: C-reactive protein; CSU: chronic spontaneous urticaria; IgE: immunoglobulin E; IQR: interquartile range; UAS7: urticaria activity score over 7 days; SD: standard deviation; *p = 0.142; **p = 0.052.

Figure 1 - (A) *The correlation between CSU activity and D-dimer serum levels;* ***(B)*** *Significant higher D-dimer values in patients with moderate-severe CSU versus mild disease;* ***(C)*** *The correlation between CSU activity and C-RP serum levels;* ***(D)*** *The correlation between D-dimer and C-RP serum levels.*



**Modified from Shaker et al. (72); subjectivity of studies regarding scoring anaphylaxis.*

independence was used to determine association between categorical variables. When more than 20% of cells have expected frequencies lower than 5, we used Fisher's exact test. We performed a local regression, a non-parametric approach that fits multiple regressions in local neighbourhood, using the loess () function. A P-value < 0.05 was considered significant.

Patients' demographic, clinical and laboratory data is summarized in **table IA**. From the 88 cases, 44.3% (n = 39) had one or more associated inducible forms of urticaria, including symptomatic dermographism (n = 8), delayed pressure urticaria (n = 31), cold (n = 2), heat (n = 1) and solar (n = 1) urticarias.

Patients were under treatment with second-generation H_1-antihistamines (n = 58) or omalizumab for 4-42 months (n = 30), with some in the latter group occasionally taking H_1-antihistamines on-demand when their disease was not completely controlled.

Median UAS7 was 16 (IQR 7-29.5) and 58% (n = 51) demonstrated moderate-severe disease (UAS7 > 15). Median D-dimer levels were 181 ng/mL (IQR: 85-306), with 33 patients (37.5%) exhibiting values above normal. D-dimer levels correlated with disease activity (p < 0.0001) (**figure 1A**), with significantly higher values in patients with moderate and severe CSU (median 254 (IQR: 120-240) and 277 (IQR 185-571.5), respectively) compared to mild disease (median 111.5 (IQR: 71.5-219.5); p = 0.026 and p = 0.01, respectively) (**figure 1B**). C-RP levels (median 0.45 mg/dL (IQR: 0.15-1.16)) were elevated in 40 patients (45.5%) and correlated with disease activity (p = 0.007) (**figure 1C**), but mean values of this marker for each of the four groups of urticaria activity (from controlled to severe) were not significantly different. Regarding the subgroup of patients with associated inducible forms of urticaria, we also found a correlation between D-dimer and UAS7 (p < 0.001) and C-RP and UAS7 (p = 0.141).

Median total serum IgE was 78 UI/mL (IQR: 20-255.5), with 23.9% of the patients showing low IgE levels (< 25 UI/mL). We did not find any correlation between D-dimer or C-RP and IgE levels.

Among patients with isolated high D-dimer (n = 16), isolated high C-RP (n = 23) or elevation of both biomarkers (n = 17), respec-

tively, 87.5%, 52.2% and 76.5%, demonstrated moderate-severe disease. Within the 51 patients with moderate-severe disease, both D-dimer and C-RP were normal in 11 of them (21.6%).

We did not find any association between high D-dimer or high C-RP and concomitant angioedema, history of bruising, eosinophil or basophil counts, IgE levels, anti-TPO or ANA positivity (**table IB**).

There was significant statistical correlation between D-dimer and C-RP levels ($r = 0.39$, $p < 0.001$) (**figure 1D**). In 57 patients (64.8%) both biomarkers were totally concordant (n = 49), either both normal or both elevated, or partially concordant (n = 8), meaning that only one biomarker was raised, but this elevation did no exceed 20% of the upper limit (*e.g.* 266 ng/mL for D-dimer and 0.6 mg/dL for C-RP). The remaining 31 patients (35.2%) showed totally divergent values. We found no significant differences in clinical or laboratory parameters between the groups with totally concordant or divergent values, although the percentage of patients with anti-TPO antibodies and eosinopenia was higher in the first group (**table IB**).

Our study confirms that both D-dimer and C-RP levels significantly correlate with CSU activity, as in previous studies (5, 6), and there is a positive correlation between these two biomarkers. Nevertheless, they fail to detect around 20% of moderate-severe CSU cases and assessing them, either separately or concomitantly, did not increase their sensitivity as markers of moderate-severe CSU activity.

Apart from CSU activity, there was no significant correlation between elevation of D-dimer or C-RP levels and the remaining clinical or laboratory parameters which are considered to target the two different CSU subtypes. Otherwise, as increasing overlap has been found between these subtypes (1, 7), these biomarkers may also be unable to distinguish them.

Interestingly, around one-third of the patients exhibited totally divergent D-dimer/C-RP levels. This may suggest the involvement of different pathways of inflammation or coagulation/fibrinolysis, either related to an individual response to mast cell degranulation or to specific CSU subtypes. Although we found no significant differences in the studied parameters between the patients with totally concordant or totally divergent D-dimer/C-RP values, the first group showed more frequently anti-TPO antibodies and eosinopenia, which, along with low IgE levels and basopenia, have been associated with type IIb autoimmune CSU (1, 8).

Limitations of this study include the reduced number of patients and their different therapeutic regimens, lack of ASST/BAT results, subjectivity of UAS7 as marker for CSU activity and other possible concomitant factors that may influence D-dimer and C-RP levels.

In conclusion, D-dimer and C-RP serum levels are sensitive biomarkers for CSU activity, but their concomitant use does not seem to increase their sensitivity in detecting higher disease activity. Nevertheless, we could not explain the divergent D-dimer and C-RP results in around one-third of the patients, which do not clearly correlate with the two main pathomechanisms recognized in CSU. More studies are needed to understand and define the particular group of patients who demonstrate a totally divergent response concerning these two biomarkers.

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Contributions

MR: conceptualization, investigation, methodology, resources, visualization, writing – original draft, writing – review & editing. JS: methodology, formal analysis, writing – original draft, writing – review & editing. ALM, FA: investigation, resources. MG: conceptualization, methodology, resources, supervision, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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