Angioedema severity and impact on quality of life: Chronic histaminergic angioedema versus chronic spontaneous urticaria

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Clinical Implications

The impact of angioedema on quality of life is greater for patients with angioedema associated with chronic spontaneous urticaria than chronic histaminergic angioedema. Biomarkers for monitoring disease activity in chronic spontaneous urticaria are not useful in chronic histaminergic angioedema.

Histamine-mediated angioedema is the most frequent form of angioedema. It is classified as idiopathic histaminergic acquired angioedema (IH-AAE)[1] when allergies and other causes have been excluded and a positive treatment response to antihistamines, corticosteroids, or omalizumab has been reported. Idiopathic histaminergic acquired angioedema may occur in isolation, when it is termed chronic histaminergic angioedema (CHA), or it may be associated with wheals in chronic spontaneous urticaria angioedema (CSU-AE). The term CHA is equivalent to IH-AAE and mast cell-mediated angioedema. However, this term reflects the chronic and recurrent course of the disease. Therefore, we propose that the term CHA be internationally discussed in the following guidelines. Chronic spontaneous urticaria is classically characterized by the presence of recurrent episodes of wheals (hives) with or without angioedema for at least 6 weeks.[2] Chronic histaminergic angioedema is typically considered a subtype of CSU without wheals. However, a recent study[3] found several features that differentiate CHA from CSU, which suggests that CHA is a separate entity. Quality of life (QoL) studies specifically for CHA patients have not been performed, and their QoL has been assessed only in the context of CSU-AE.

We previously reported differences in cellular activation and autoimmunity parameters between CHA and CSU in the same cohort of patients.[3] The current work investigated the direct impact of angioedema in CSU and CHA (isolated angioedema) and assessed biomarkers for CSU activity[4] in the study population.

We performed a prospective study comparing 131 patients with CHA or CSU-AE who were recruited in six Spanish university hospitals between 2016 and 2018. Patient-reported questionnaires were used to analyze QoL and disease activity. Blood and serologic parameters, including cell blood count, C-reactive protein, D-dimer, and total IgE, were also analyzed. Inclusion and exclusion criteria and statistical analyses are described in the Supplemental Text (in this article's Online Repository at www.jaci-inpractice.org). Patients were prospectively included when they attended their corresponding center. At the first visit and after we obtained informed consent, we collected clinical and demographic features, blood samples, and QoL questionnaires. Patients answered disease activity questionnaires and were requested to send them back 4 weeks after the first visit.

A total of 131 patients were registered, including 68 with CHA and 63 with CSU-AE. As previously reported for this cohort,[3] significantly different sex and age distributions were found (Table I). We observed a trend for a longer duration of angioedema episodes in CHA, but without significant differences. However, when we categorized the duration of angioedema attacks between 0 and 48 hours or longer, 32.35% of CHA patients and 14.29% of CSU-AE patients had angioedema episodes longer than 48 hours ($P = .015$). The proportion of patients who followed treatment with second-generation H1-antihistamines was higher in CSU-AE patients (79.37% vs 52.94%; $P = .001$). Up-dosing and the number of patients who were prescribed a fourfold standard dose of H1-antihistamines were significantly higher in CSU-AE than CHA patients. Most patients needed at least one emergency department visit after the diagnosis, but CSU-AE patients had more emergency department visits within the previous 12 months ($P = .015$).

We found significant differences in angioedema severity (Table I). The Angioedema Activity Score over 7 days (AAS7) was higher in CSU-AE than CHA patients ($P = .022$). Some patients in the CSU-AE group experienced severe angioedema episodes (severe AAS7 range, 19-105). We found a significant association relationship between AAS7 and the Urticaria Activity Score over 7 consecutive days (UAS7) in the CSU-AE group ($P < .001$) with a strong positive correlation ($r = 0.7206$) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Multinomial logistic regression analysis was used to assess the influence of potential confounding variables such as sex and age, as well as group or angioedema episode characteristics, in AAS7. Not surprisingly, angioedema episodes in the past 12 months was a significant predictor of activity (low level presented with an odds ratio [OR] of 1.056 [95% CI, 1.011-1.103]; $P = .014$ and moderate to severe with 1.061 [95% CI, 1.013-1.110]; $P = .012$). The group variable (CHA or CSU-AE) presented a high OR for the moderate to severe level (OR = 3 [95% CI, 0.972-9.262]; $P = .056$) but was not significant, although the lack of differences in group sizes (no episodes = 58; low = 38; and moderate to severe = 17) was a limitation of the analysis.

Quality of life was significantly lower in CSU-AE than CHA patients ($P = .005$) (Figure 1). Across all dimensions, angioedema QoL scores were significantly higher (worse QoL) in CSU-AE patients, and mean angioedema QoL scores were generally higher in patients who reported a higher disease severity in the AAS7 score. This finding was reflected in the moderate positive

TABLE I. Demographics, episodes, treatment, emergency features, disease activity, and quality of life of patients

Features	CHA (n = 68)	CSU-AE (n = 63)	*P*
Sex, male, n (%)	30 (44.1%)	17 (27.0%)	**.047**
Male/female ratio	0.78	0.36	
Age, y (mean [range])	53.1 (20-85)	47.4 (20-76)	**.035**
Angioedema episode, duration, n (%)			.181
1-3 h	2 (2.9%)	3 (4.8%)	
3-6 h	9 (13.2%)	6 (9.5%)	
6-12 h	14 (20.6%)	15 (23.8%)	
12-24 h	9 (13.2%)	13 (20.6%)	
24-48 h	12 (17.7%)	17 (27.0%)	
2-3 d	15 (22.1%)	8 (12.7%)	
3-6 d	7 (10.3%)	1 (1.6%)	
Angioedema episodes past 12 mo (median [IQR])	6 (3-14)	4.5 (2-12)	.390
Treatment, n (%)	47 (69.12%)	52 (82.54%)	.096
Second-generation H1-antihistamine, n (%)	36 (52.94%)	50 (79.37%)	**.001**
Single-dose, n (%)	24 (35.29%)	27 (42.86%)	.375
Up-dosing, n (%)	12 (17.65%)	23 (36.51%)	**.015**
Double dose, n (%)	10 (14.71%)	13 (20.63%)	.373
Triple dose, n (%)	1 (1.47%)	4 (6.35%)	.145
Quadruple dose, n (%)	1 (1.47%)	6 (9.52%)	**.041**
Corticosteroid, n (%)	9 (13.24%)	13 (20.63%)	.694
Omalizumab, n (%)	3 (4.41%)	0	.086
Others, n (%)	4 (5.88%)	9 (14.29%)	.285
Treatments, n (median [IQR])	1 (1-1)	1 (1-2)	**.040**
Patients visiting emergency department since diagnosis, n (%)	41 (60.3%)	45 (71.4%)	.180
Visits to emergency department, n (%)			.333
0	0	2 (4.2%)	
1	9 (22.5%)	7 (14.6%)	
2	10 (25%)	7 (14.6%)	
3	2 (5%)	7 (14.6%)	
4	7 (17.5%)	5 (10.4%)	
5	4 (10%)	6 (12.5%)	
>5	8 (20%)	14 (29.2%)	
Visits to emergency department past 12 mo, n (median [IQR])*	1 (0-2)	2 (1-4)	**.015**
AAS7 (median [IQR])	0 (0-1)	1 (0-1)	**.022**
AAS7 levels, n (%)†			.089
No	36 (58.1%)	22 (42.3%)	
Low	20 (32.3%)	20 (38.5%)	
Moderate	6 (9.7%)	6 (11.5%)	
Severe	0	4 (7.7%)	
Angioedema quality of life (median [IQR])‡	18 (4-40)	37 (10-65)	**.005**
Functioning	0 (0-19)	25 (0-56)	**<.001**
Fatigue/mood	15 (0-40)	35 (0-65)	**.012**
Fear/shame	38 (0-58)	50 (21-79)	**.031**
Nutrition	0 (0-13)	25 (0-50)	**.007**
UAS7 (median [IQR])		3.75 (0-17)	
UAS7 levels, n (%)§			
No		15 (33.3%)	
Low		14 (31.1%)	
Moderate		13 (28.9%)	
Severe		3 (6.7%)	
Chronic Urticaria Quality of Life (median [IQR])		49 (27-66)	

AAS7, Angioedema Activity Score over 7 days; *CHA*, chronic histaminergic angioedema; *CSU-AE*, chronic spontaneous urticaria angioedema; *IQR*, interquartile range; *UAS7*, Urticaria Activity Score over 7 consecutive days.

The AAS7 level was categorized as: no episodes (0), low (1-6), moderate (7-18), and severe (19-105).[5] The UAS7 levels were categorized as: no episodes (0), low (1-6), moderate (7-27), and severe (28-42). Statistically significant differences are highlighted in bold.

*Results from 43 patients were not obtained (28 in the CHA group and 15 in the CSU-AE group).

†Results from 17 patients were not obtained (six in the CHA group and 11 in the CSU-AE group).

‡Results from five patients were not obtained (one in the CHA group and four in the CSU-AE group).

§Results from 18 patients were not obtained.

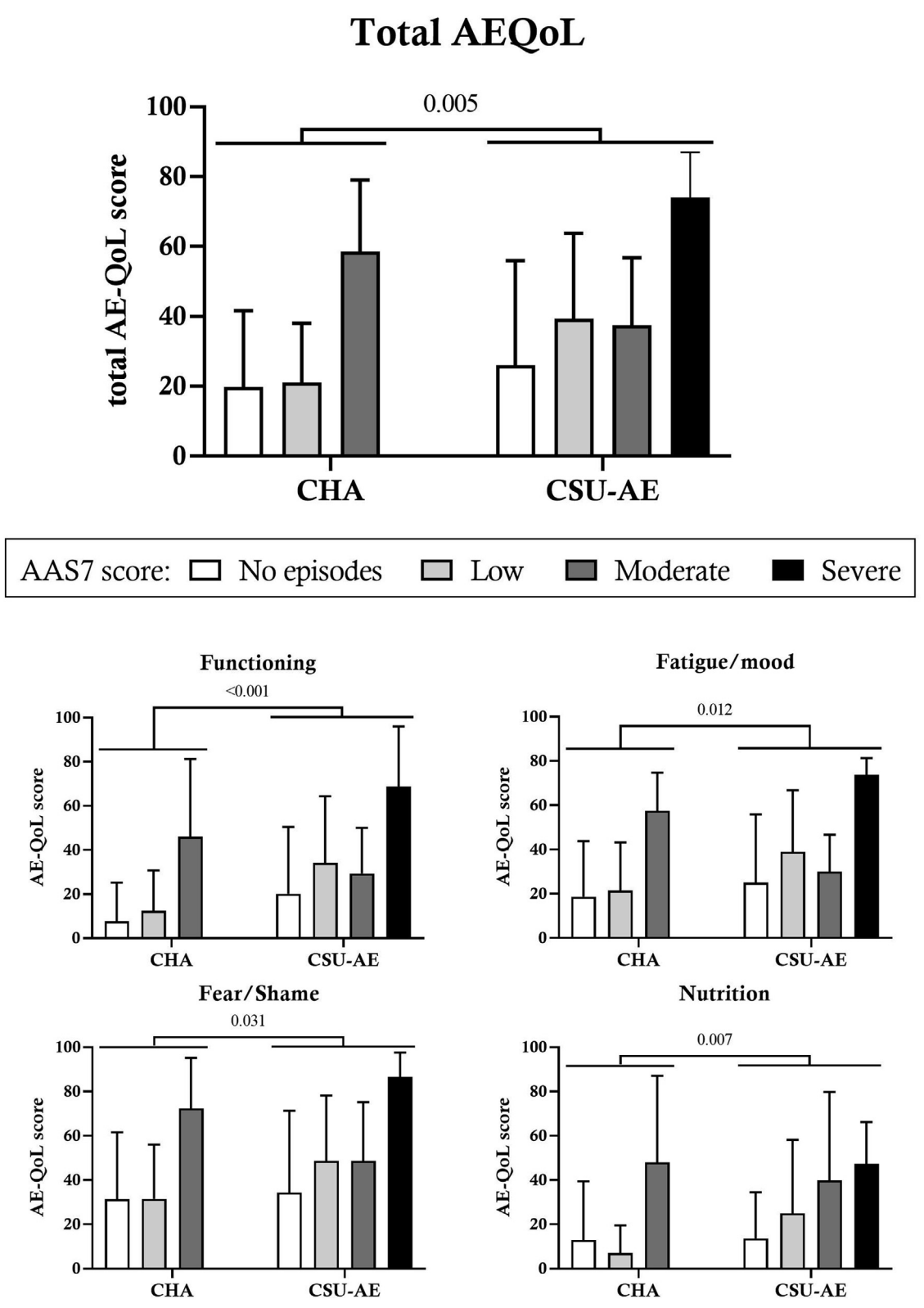

FIGURE 1. Angioedema Quality of Life (AEQoL) questionnaire using the severity of attacks recorded on Angioedema Activity Score (AAS). Total AEQoL scores in chronic histaminergic angioedema (CHA) and chronic spontaneous urticaria angioedema (CSU-AE) patients are grouped according to levels of AAS score over 7 days (AAS7): no episodes (AAS7 = 0), low (1-6), moderate (7-18), and severe (19-105). The AEQoL scores of different dimensions with patients grouped according to AAS7 score levels are presented.

correlation between AAS7 and angioedema QoL (r = 0.3892; $P < .001$). We found a very strong positive correlation between angioedema QoL and Chronic Urticaria Quality of Life (CU-Q_2oL) (r = 0.8819; $P < .001$) and a moderate positive correlation between UAS7 and CU-Q_2oL (r = 0.5455; $P < .001$) (Figure E1).

We observed a significant inverse correlation between UAS7 and eosinophil count (r = −0.3086; $P = .0392$) in CSU-AE patients, but the other four parameters did not reach statistical significance in Spearman's correlation analysis. However, a trend was observed for some of these parameters. For CSU-AE patients, no significant correlation was observed between AAS7 and any biomarker. The Angioedema Activity Score over 7 days showed a significant inverse correlation with D-dimer in CHA patients (r = −0.3007; $P = .0243$), but no correlations were observed with any other biomarkers (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

We also assessed the QoL score correlations with the selected biomarkers. For CU-Q_2oL, moderate correlations were obtained for D-dimer (r = 0.4479; $P = .0005$) and eosinophil counts (r = −0.3780; $P = .0034$). Angioedema QoL also correlated with D-dimer (r = 0.4636; $P = .0003$) and eosinophil counts (r = −0.2867; $P = .0291$). Angioedema QoL did not exhibit a significant correlation with any of the biomarkers analyzed in CHA patients.

Chronic spontaneous urticaria has a significant impact on QoL, and although itch is responsible for much of this effect, angioedema is also a key factor. However, angioedema is underdiagnosed,[6] it is not included in the most widely used severity scores (UAS or UAS7), and it is frequently overlooked in clinical trials.[7] Some studies showed the influence of angioedema in CSU and compared CSU patients with and without angioedema attacks.[6] However, the disease severity and QoL of patients with CHA alone has not been clarified. Our study compared CSU-AE and CHA for the first time.

Angioedema in the context of CSU was more severe and resulted in a greater need for medication and emergency visits than did angioedema in CHA. We showed that the AAS7 tool had a good correlation with CSU severity. Therefore, a new urticaria activity score that incorporates AAS items may be useful. The Urticaria Control Test is more comprehensive[5] because it includes swelling in the main control question. However, the Urticaria Control Test is not a severity scoring system.

We also revealed the considerable impact on QoL in CHA and CSU-AE. Patients with a higher frequency of attacks generally showed worse QoL in both groups. It was reported that patients with high severity scores on the UAS7 also have a poorer QoL.[8]

Many biomarkers for monitoring CSU were recently described.[4] Kolkhir et al[9] found that eosinopenia in patients with CSU was associated with high disease activity and poor treatment response. However, biomarkers associated with histamine-mediated angioedema have not been identified. The presence of angioedema in CSU (compared with CSU without angioedema) has not been associated with altered levels of anti-FCεRI, anti-IgE, substance P, β-cell activation factor, or tryptase.[4] Our study found that D-dimer inversely correlated with CHA disease activity, but this relationship was not observed for CSU-AE patients.

Some limitations must be acknowledged in this study. First, the presence of hives and itch may influence the higher severity of angioedema in CSU patients. Second, the impact on QoL is subject to patients' individual interpretations of symptoms.

The differences between CSU-AE and CHA suggest that these conditions are different entities or differing endotypes, and we favor the former view. Angioedema deserves better representation in CSU severity and QoL questionnaires. Experts designing these tools should highlight angioedema when it is associated with CSU so that questionnaires for angioedema alone may be used for angioedema without urticaria.

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SUPPLEMENTAL TEXT

Inclusion criteria. All patients were aged greater than 18 years and provided signed informed consent to participate in the study. Ethical approval was obtained in each collaborating center and the study followed Good Clinical Practice guidelines and the Helsinki Declaration. The inclusion criterion to fulfill the diagnosis of chronic histaminergic angioedema (CHA) was the presence of recurrent angioedema (AE) that responded to treatment with antihistamines, corticosteroids, adrenaline, or omalizumab. All patients had normal C1INH, C1q, C3, and C4 protein levels and normal C1INH activity.

Exclusion criteria. Exclusion criteria were the presence of bradykinergic AEs, ACE inhibitor intake, delayed-pressure AEs, vibratory AEs, or edema induced by nonsteroidal anti-inflammatory drugs.

Disease activity and quality of life questionnaires. Patients completed the Spanish versions of patient-reported questionnaires. Disease activity was determined using the following questionnaires: Angioedema Activity Score over 7 days (AAS7) in CHA and CSU-AE patients and Urticaria Activity Score over 7 days (UAS7) in CSU-AE patients. The AAS7 score was categorized into four score levels: no episodes (0), low (1-6), moderate (7-18), and severe (19-105). The UAS7 questionnaire was also divided into four score levels: no episodes (0), low (1-6), moderate (7-27), and severe (28-42). The impact on quality of life was measured using the Angioedema Quality of Life (AE-QoL) in CHA and CSU-AE patients and the Chronic Urticaria Quality of Life questionnaires in CSU-AE patients. The Spanish versions of AAS and AE-QoL are available on the MOXIE GmbH website (https://moxie-gmbh.de/our-products/). Validated UAS and Chronic Urticaria Quality of Life questionnaires translated into Spanish are also available in the literature.

Statistical analysis. Statistical analyses were performed using Stata (version 12.0, StataCorp, College Station, TX). Graphics were generated using GraphPad Prism 8 (GraphPad Software, San Diego, CA). Qualitative variables are reported as the total number and percentage and were compared using χ^2 tests. Quantitative variables are reported as the mean with SD or median with range and were compared using Student *t* test with Welch's correction (normally distributed) or Mann-Whitney *U* test and Kruskal-Wallis test (nonnormally distributed). Spearman's correlation coefficient (r) is reported for correlations. To test for normality distribution, we used the D'Agostino-Pearson test. Because AAS7 scores did not fulfill requirements for linear regression analysis, multinomial logistic regression analysis was used to evaluate the effect of various factors (sex, group, and AE characteristics) on AAS7 groups (no episodes, low, and moderate to severe).

Values were considered significant at P less than .05. No P value correction was applied for multiple comparisons because the study was exploratory.

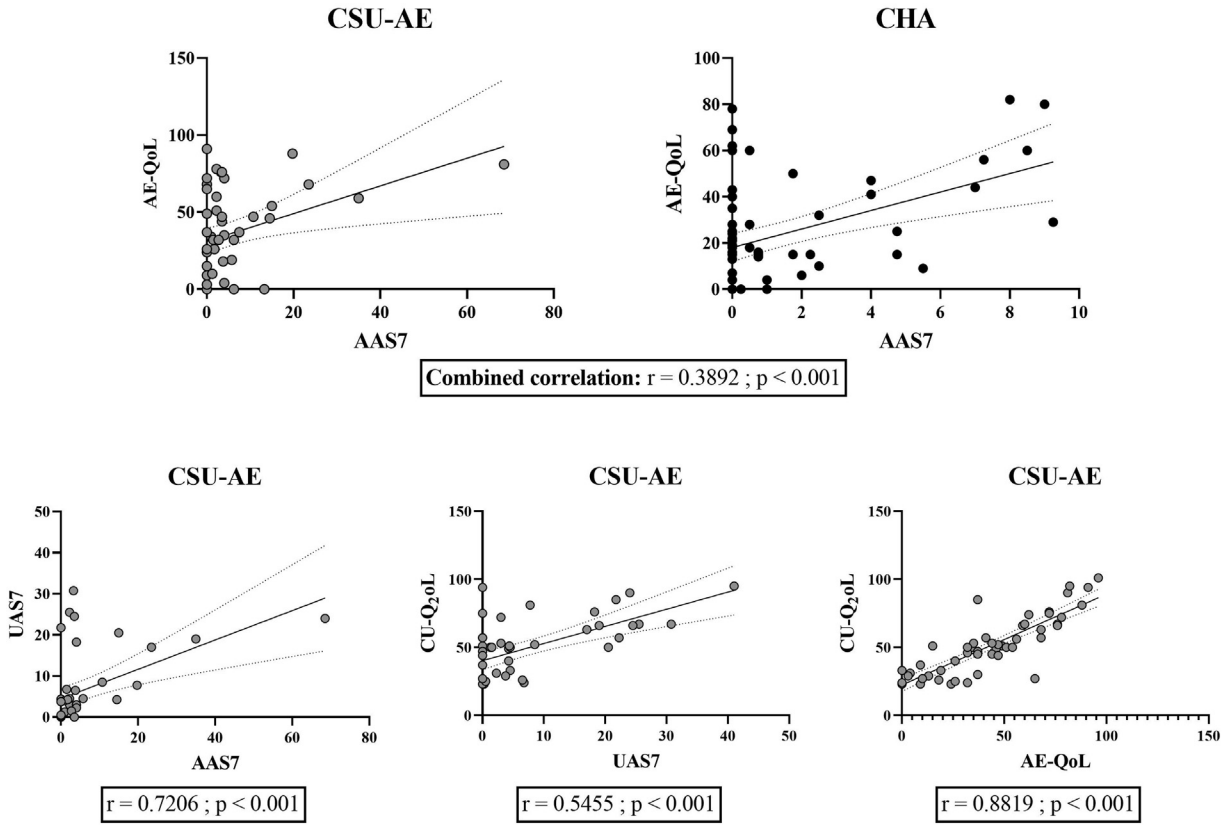

FIGURE E1. Correlations observed between different questionnaire scores in chronic spontaneous urticaria angioedema (CSU-AE) patients (gray) and chronic histaminergic angioedema (CHA) patients (black). Top, left to right: Angioedema Activity Score over 7 d (AAS7) vs Angioedema Quality of Life (AE-QoL) questionnaire in CSU and AAS7 vs AE-QoL in CHA. Bottom, left to right: Urticaria Activity Score over 7 consecutive d (UAS7) vs AAS7, Chronic Urticaria Quality of Life (CU-Q_2oL) vs UAS7, and CU-Q_2oL vs AE-QoL, all in CSU-AE. Linear regression and 95% confidence interval of the regression are shown. Spearman's correlation coefficients (r) and *P* values are presented.

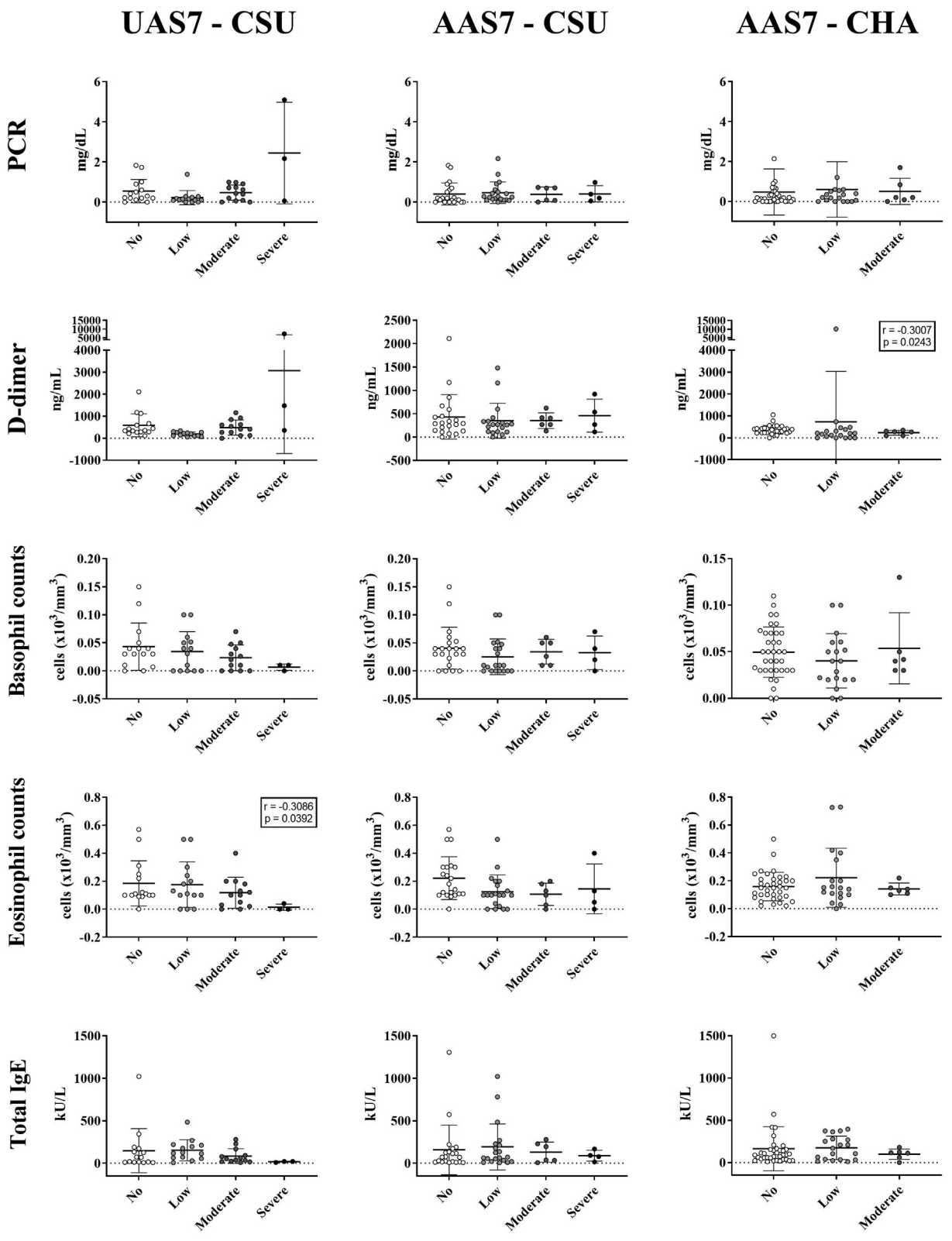

FIGURE E2. Levels of different biomarkers (C-reactive protein, D-dimer, basophil counts, eosinophil counts, and total IgE) in patients categorized according to Urticaria Activity Score over 7 consecutive d (UAS7) in CSU-AE (first column) and AAS7 in chronic spontaneous urticaria angioedema (CSU-AE) (second column) and chronic histaminergic angioedema (CHA) (third column). Individual data are presented; means and SDs shown.