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Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: Analyses from ASSURE-CSU

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Abstract

Background: ASSURE-CSU revealed differences in physician and patient reporting of angioedema. This post hoc analysis was conducted to evaluate the actual rate of angioedema in the study population and explore differences between patients with and without angioedema.

Methods: This international observational study assessed 673 patients with inadequately controlled chronic spontaneous urticaria (CSU). Physicians abstracted

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angioedema data from medical records, which were compared with patient-reported data. Patients in the *Yes-angioedema* category had angioedema reported in the medical record and a patient-reported source. For those in the *No-angioedema* category, angioedema was reported in neither the medical record nor a patient-reported source. Those in the *Misaligned* category had angioedema reported in only one source. Statistical comparisons between *Yes-angioedema* and *No-angioedema* categories were conducted for measures of CSU activity, health-related quality of life (HRQoL), productivity and healthcare resource utilization (HCRU). Regression analyses explored the relationship between Dermatology Life Quality Index (DLQI) score and angioedema, adjusting for important covariates.

Results: Among evaluable patients, 259 (40.3%), 173 (26.9%) and 211 (32.8%) were in the *Yes-angioedema*, *No-angioedema* and *Misaligned* category, respectively. CSU activity and impact on HRQoL, productivity, and HCRU was greater for *Yes-angioedema* patients than *No-angioedema* patients. After covariate adjustment, mean DLQI score was significantly higher (indicating worse HRQoL) for patients with angioedema versus no angioedema (9.88 vs 7.27, $P < .001$). The *Misaligned* category had similar results with *Yes-angioedema* on all outcomes.

Conclusions: Angioedema in CSU seems to be under-reported but has significant negative impacts on HRQoL, daily activities, HCRU and work compared with no angioedema.

KEYWORDS
angioedema, economic burden, observational study, quality of life, urticaria

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by the presence of hives, angioedema or both, recurring for 6 weeks or longer, in the absence of identifiable triggers.[1,2] Angioedema is defined as rapid swelling at a deeper level under the skin than hives, occurring on the face, inside the mouth or elsewhere on the body.[2,3] It is estimated that 33%-67% of patients with CSU exhibit both hives and angioedema, 29%-65% exhibit only hives and 1%-13% exhibit only angioedema.[4,5]

Patients who experience CSU as concurrent hives and angioedema often experience a longer duration of disease than patients who experience only hives.[6,7] Angioedema may be disfiguring or painful, may limit daily activities and may have a significant impact on quality of life.[8,9] Patients with CSU-associated angioedema often experience concern over their health status, at times worrying that swelling episodes may cause problems with breathing or may be life-threatening.[9] A real-world multicentre study in Germany has shown that in a 6-month period, more than 40% of patients with inadequately controlled CSU experienced angioedema; among these patients, 78% rated their angioedema as severe or moderate in intensity, and a mean of 34 days with angioedema was reported during the 6-month period.[5] In addition to its considerable symptom burden, recurrent angioedema (in those with hereditary angioedema) can lead to absenteeism and can have a negative impact on work productivity.[10]

The observational, multinational ASSURE-CSU (ASsessment of the Economic and Humanistic Burden of Chronic Spontaneous/Idiopathic URticaria PatiEnts) study aimed to characterize the patient population with inadequately controlled CSU and to evaluate the burden of disease.[11,12] Analyses of ASSURE-CSU data revealed

Highlights

- Nearly one-third of CSU patients in ASSURE-CSU reported having experienced angioedema in the past 12 months but did not have physician-reported angioedema as documented in their medical records.
- Patients with angioedema had greater CSU activity, HRQoL and productivity impairment, and resource utilization than those without. After controlling for other factors, angioedema significantly affected DLQI total score.
- Among patients with inadequately controlled symptomatic CSU, the proportion with angioedema may be higher than previously thought.

different rates of CSU-associated angioedema between physician and patient reports.[12] The objectives of this post hoc analysis were to provide a better estimate of angioedema rates among CSU patients in the ASSURE-CSU study by aligning patient and physician reports and to analyse differences in patient characteristics as well as humanistic and economic burden between individuals with and without angioedema.

2 | METHODS

2.1 | ASSURE-CSU study design

ASSURE-CSU was an observational, noninterventional, multinational, multicentre study conducted at urticaria specialty centres in Canada, France, Germany, Italy, Spain, the Netherlands and the United Kingdom. Methodology[11] and overall results[12] have been reported previously. In summary, recruitment of 700 patients was planned. Adult patients who had a clinician-confirmed CSU diagnosis, had received at least one treatment course with an H_1-antihistamine, had been symptomatic for more than 12 months and were currently symptomatic despite treatment were eligible[12]; patients with urticaria that was predominantly of the inducible form were ineligible. Study data were collected via a retrospective 12-month patient medical record abstraction (MRA) by physicians, a cross-sectional patient survey and a prospective 8-day patient diary. The appropriate national-, local- and site-level ethical approvals were obtained, and all patients provided written informed consent. The study complied with the Declaration of Helsinki.[13]

2.2 | Study measures

Study measures relevant to this analysis included the occurrence of angioedema as reported in the physician MRA, the cross-sectional patient survey and the patient diary. Specifically, physicians reported from the medical chart whether the patient had angioedema associated with his or her CSU ever, at the time of diagnosis, and/or within the past 12 months. In the patient survey, completed at enrolment, patients answered whether they had experienced angioedema ever, during the past 12 months, within the past 4 weeks and/or currently (at survey completion); patients also answered questions about the duration and location of angioedema, as well as the symptoms they experienced with angioedema (swelling, itching and pain) and what they would do to seek treatment (or not) during an angioedema episode. In the Urticaria Patient Daily Diary (UPDD), completed for each of 7 days following enrolment, patients indicated whether they had experienced "rapid swelling, also called angioedema," during the past 24 hours.

Additional measures explored in this analysis included demographic data, comorbidities and healthcare resource utilization (HCRU) related to CSU during the previous 12 months, as abstracted by physicians in the MRA. Additional measures collected in the patient survey included validated patient-reported outcome measures such as the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL)[14,15] and Dermatology Life Quality Index (DLQI)[16] and HCRU. The 7-day UPDD[17] also included the twice-daily Urticaria Activity Score over 7 Days ($UAS7_{TD}$),[18] daily sleep interference and activity impairment, in addition to the aforementioned occurrence and management of angioedema. On the 8th day, patients completed the Work Productivity and Activity Impairment (WPAI), which has a recall period of 7 days.[19]

2.3 | Statistical analysis

Frequency of angioedema within the past 12 months and misalignment of angioedema reporting between physician and patient data sources were evaluated. For patients in the *Yes-angioedema* category, physician and patient data sources agreed that the patient had experienced angioedema. For these cases, the MRA and either the patient survey or patient diary indicated that the patient had experienced angioedema in the past 12 months. For patients in the *No-angioedema* category, physician and patient data sources agreed that the patient had not experienced angioedema. For these cases, all 3 data sources indicated no angioedema in the past 12 months. For the *Misaligned* category, the physician and patient data sources (either patient survey or diary) did not agree as to whether the patient had experienced angioedema. For these cases, the physician data source indicated no angioedema during the past 12 months while one of the patient sources indicated that angioedema had occurred, or the physician source indicated that the patient had experienced angioedema in the past 12 months while the patient sources did not. If the angioedema classification was missing either from the MRA or from both patient data sources (survey and diary), the patient was assigned to a Missing category and excluded from analysis.

Descriptive statistics were used to characterize the study population by angioedema classification *(Yes-angioedema*, *No-angioedema*, *Misaligned*). Disease activity was determined by $UAS7_{TD}$ score bands: $UAS7_{TD}$ = 0-6 (urticaria-free or well-controlled urticaria activity), 7-15 (mild activity), 16-27 (moderate activity) and 28-42 (severe activity).[20] Health-related quality of life (HRQoL) measures were analysed by published methodology where available.

Statistical comparisons of patients with and without angioedema were conducted using *t* tests or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. Tests were performed between those in the *Yes-angioedema* and *No-angioedema* categories; patients who fell into the *Misaligned* category were not included in the statistical comparisons.

Regression modelling was used to explore whether the relationship between DLQI score and angioedema remained significant after adjusting for important covariates. An analysis of covariance model was used to evaluate the effect of angioedema on DLQI total score. Adjustment covariates included $UAS7_{TD}$ score, age, sex, country, disease duration from diagnosis to enrolment and selected comorbidities at enrolment (hypersensitivity to nonsteroidal anti-inflammatory drugs, Hashimoto's disease and asthma). $UAS7_{TD}$ score, age and disease duration were treated as continuous variables. Least-squares mean estimates and standard errors were estimated for each angioedema classification; patients in the *Misaligned* category were

combined with patients in the *Yes-angioedema* category for the primary analysis. A sensitivity analysis was also conducted in which the *Misaligned* category was excluded from the comparison.

All tests were performed at a nominal significance level of $\alpha = .05$ with 2-sided, single degree-of-freedom tests. No correction was made for multiple comparisons. All analyses were performed using SAS for Windows statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Initial angioedema frequency over the past 12 months

According to the MRA, physicians reported that 276 of 673 patients enrolled (41.0%) had experienced CSU-associated angioedema within the past 12 months, with a mean (standard deviation [SD]) of 19.0 (42.13) angioedema episodes during this period. Among the 649 patients who completed the survey, 427 (65.8%) patients reported having had angioedema within the past 12 months (Figure 1A).

Among the 614 patients who completed the diary over 1 week, 294 (47.9%) patients reported that they had angioedema at least 1 day; the mean (SD) patient-reported number of days with angioedema was 3.2 (1.92) over the 7 days. The occurrence of angioedema and number of days with angioedema increased with increasing disease activity over that week.[12]

3.2 | Postalignment angioedema frequency over the past 12 months

Of the 673 patients enrolled, 643 patients had recorded data for assigning the angioedema classification, and 30 patients had missing data either in the MRA or from both patient data sources (survey and diary) and could not be classified. Of the 643 patients included in the angioedema analyses, 276 (42.9%) had angioedema according to the MRA, and 467 (72.6%) had angioedema according to one of the patient sources (survey or diary).

For the analyses, 259 patients (40.3%) were in the *Yes-angioedema* category, 173 (26.9%) were in the *No-angioedema* category, and 211 (32.8%) were in the *Misaligned* category. Of the 211 patients in the *Misaligned* category, 205 (97.2%) had angioedema recorded in one of the patient sources (survey or diary) but not in the MRA (Figure 1B; Table S1).

3.3 | Patient demographics

There were no significant differences in baseline characteristics between patients in the *Yes-angioedema* and *No-angioedema* categories, except in duration of CSU and presence of Hashimoto's disease (Table 1). Patients in the *Yes-angioedema* category had longer mean (SD) duration of disease from diagnosis to enrolment (61.7 [76.64] months) than those in the *No-angioedema* category (46.1 [69.06]) ($P < .05$) and a higher prevalence of Hashimoto's disease (10.4% vs 2.9%; $P < .01$).

3.4 | Urticaria severity and activity

More patients in the *Yes-angioedema* category were reported to have severe CSU activity at diagnosis (37.8%) than those in the *No-angioedema* category (26.0%) (Table 1). Mean (SD) $UAS7_{TD}$ score reported in the patient diary was higher for patients in the *Yes-angioedema* category (17.6 [10.55]) than for those in the *No-angioedema* category (14.6 [8.97]) ($P < .01$) (Figure 2). In line with this observation, more patients in the *Yes-angioedema* category than in the *No-angioedema* category

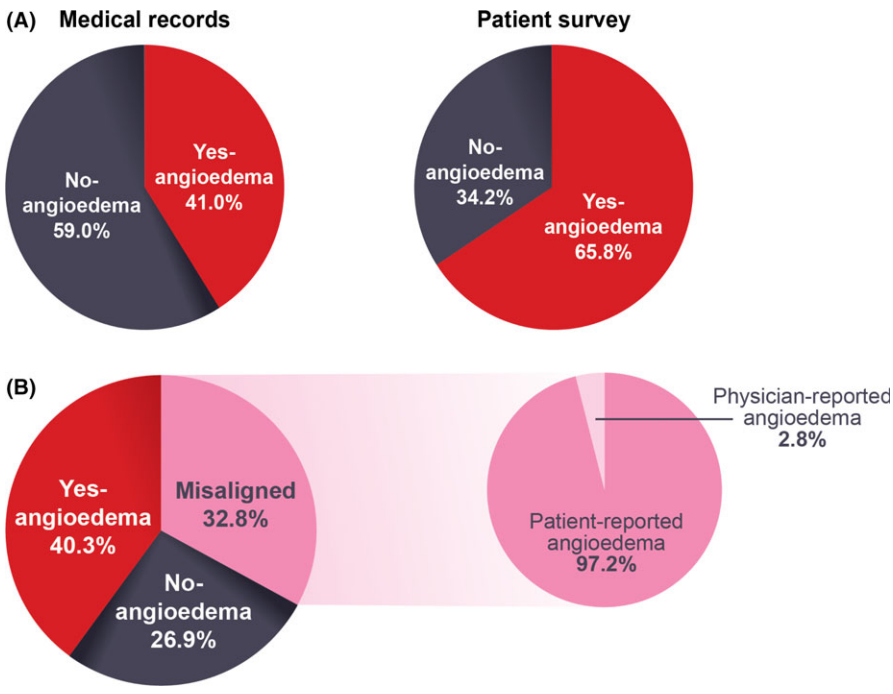


FIGURE 1 Frequency of angioedema in the past 12 months. (A) Initial frequency: Angioedema in the past 12 months was more frequently reported by patients who completed the survey (65.8%, 427/649 patients) than recorded in the medical record (41.0%, 276/673 patients). (B) Revised frequency: Of the 32.8% of patients (211/643) with misaligned reporting of angioedema in the past 12 months, 97.2% (205/211) reported having had angioedema when it was not noted in the medical record

TABLE 1 Patient and disease characteristics from the medical record abstraction, overall and by angioedema classification

Patient characteristics[a]	Total (n = 643)	Angioedema category: Yes (n = 259)	No (n = 173)	Misaligned (n = 211)	*P* value[b] (yes vs no)
Age at enrolment (years)					.0906
Mean (SD)	49.0 (15.56)	49.4 (14.45)	46.8 (16.50)	50.4 (15.95)	
Min, Max	19.0, 89.0	20.0, 81.0	19.0, 89.0	19.0, 87.0	
Female sex (%)	469 (72.9)	197 (76.1)	117 (67.6)	155 (73.5)	.0540
Race and ethnicity[c]	544	205	155	184	.5262
Caucasian/White (%)	491 (90.3)	189 (92.2)	138 (89.0)	164 (89.1)	
Other (%)	44 (8.1)	15 (7.3)	14 (9.0)	15 (8.2)	
Data not available (%)	9 (1.7)	1 (0.5)	3 (1.9)	5 (2.7)	
Disease duration from diagnosis to enrolment (months)					.0486
Mean (SD)	57.3 (77.73)	61.7 (76.64)	46.1 (69.06)	61.0 (85.43)	
Comorbid conditions at enrolment (%)					
Hypersensitivity to NSAIDs	52 (8.1)	28 (10.8)	10 (5.8)	14 (6.6)	.0833
Hashimoto's disease	43 (6.7)	27 (10.4)	5 (2.9)	11 (5.2)	.0042
Asthma	71 (11.0)	33 (12.7)	18 (10.4)	20 (9.5)	.5434
CSU/CIU severity at the time of diagnosis (%)	642	259	173	210	.0101
Mild	71 (11.1)	27 (10.4)	32 (18.5)	12 (5.7)	
Moderate	202 (31.5)	81 (31.3)	53 (30.6)	68 (32.4)	
Severe	233 (36.3)	98 (37.8)	45 (26.0)	90 (42.9)	
Data not available	136 (21.2)	53 (20.5)	43 (24.9)	40 (19.0)	
$UAS7_{TD}$					
Mean (SD) $UAS7_{TD}$	17.3 (10.46)	17.6 (10.55)	14.6 (8.97)	19.2 (11.05)	.0032
$UAS7_{TD}$ band (%)	600	244	161	195	.0140
0-6	98 (16.3)	41 (16.8)	28 (17.4)	29 (14.9)	
7-15	204 (34.0)	75 (30.7)	73 (45.3)	56 (28.7)	
16-27	182 (30.3)	82 (33.6)	40 (24.8)	60 (30.8)	
28-42	116 (19.3)	46 (18.9)	20 (12.4)	50 (25.6)	

CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; Q1, first quartile; Q3, third quartile; MRA, medical record abstraction; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; $UAS7_{TD}$, Urticaria Activity Score over 7 Days, twice-daily assessment.

[a]For categorical variables, the total number of patients with nonmissing data is presented by angioedema category for each question along with "n (%)" for each possible response to the question. Except where otherwise noted, percentage denominators are the number of patients with nonmissing data for the applicable question.

[b]*P* values shown from *t* tests for means of continuous variables and chi-square tests for frequencies of categorical variables to compare patients who experience angioedema (*Yes-angioedema*) with those who do not (*No-angioedema*). Patients in the *Misaligned* category were not included in the statistical comparison. For race and ethnicity, due to the small number of patients in many of the race/ethnicity categories, all races other than white were combined for these comparisons. Patients whose race/ethnicity group is "data not available" were excluded from the statistical comparison.

[c]Race and ethnicity data were not collected in France. For some categories of race and ethnicity, different terms were used across countries.

had severe ($UAS7_{TD}$ 28-42) disease activity (18.9% vs 12.4%) (Figure S1).[19] Moreover, a significant difference was observed between patients in the *Yes-angioedema* and *No-angioedema* categories in the mean (SD) absolute number of hives over a week collected in the UPDD (147.9 [266.37] vs 77.1 [123.87], respectively).

3.5 | Effect of angioedema on HRQoL, sleep and daily activities

The mean (SD) CU-Q_2oL score for the overall patient sample was 33.6 (21.02). Mean (SD) CU-Q_2OL scores differed significantly between patients in the *Yes-angioedema* and *No-angioedema* categories (37.6 [20.81] vs 23.4 [17.12], $P < .001$), reflecting significantly lower HRQoL for patients with angioedema (Figure 3A). Significant differences were observed between patients with and without angioedema on all CU-Q_2oL domains.

On the DLQI, mean (SD) overall score for the entire sample was 9.1 (6.63) and for *Yes-angioedema* and *No-angioedema* groups were 10.4 (6.85) and 6.6 (5.21), respectively ($P < .001$) (Figure 3B). Again, significant differences were observed between patients with and without angioedema on all DLQI domains (Figure 3C). More patients in the *Yes-angioedema* category (45.5%) than in the *No-angioedema*

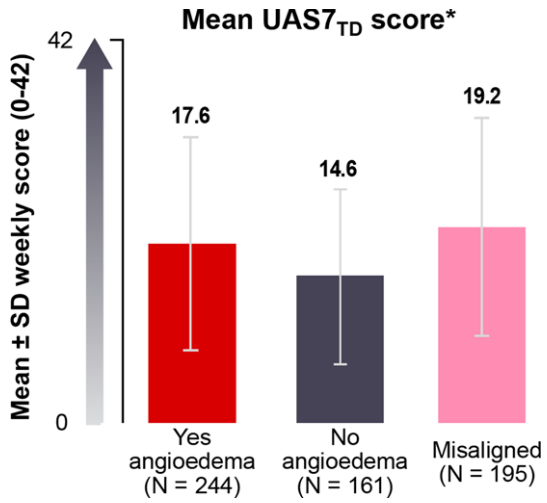


FIGURE 2 Mean urticaria activity score over 7 days, twice-daily assessment ($UAS7_{TD}$), by angioedema classification. $UAS7_{TD}$ scores were calculated by summing the average of twice-daily assessments of hive count and itch score and summing these daily scores over 7 days. *$P < .01$ (*Yes—angioedema* vs *No—angioedema*). Patients who fell into the *Misaligned* group were not included in the statistical comparisons. SD, standard deviation. [Colour figure can be viewed at wileyonlinelibrary.com]

category (20.4%) had DLQI scores >10 (indicating a very to extremely large effect on HRQoL[21]).

As patients reported on the UPDD, mean (SD) weekly scores for interference with sleep were higher for patients in the *Yes-angioedema* category (6.9 [6.14]) than for patients in the *No-angioedema* category (4.6 [4.92]) ($P < .001$), as were mean (SD) weekly scores for interference with daily activities (6.5 [5.68] vs 4.8 [4.39]; $P < .05$) (Figure 3D). Activity impairment measured by the mean percentage overall activity impairment score on the WPAI was also greater for patients in the *Yes-angioedema* category than for patients in the *No-angioedema* category (34.5% vs 23.8%; $P < .001$) (Figure 4).

3.6 | Economic and societal impact of angioedema

Patients in the *Yes-angioedema* category had greater HCRU, both documented in medical records and self-reported, than patients in the *No-angioedema* category (Table S2). According to the MRA, patients in the *Yes-angioedema* category were more likely to have a CSU-related emergency department visit than patients in the *No-angioedema* category (24.7% vs 5.2%, $P < .001$) and were more likely to have one or more inpatient hospital stays in the past 12 months (11.6% vs 3.5%, $P < .01$). As reported in the patient diary, patients with angioedema were more likely to call a healthcare provider during the 7-day window than patients without angioedema (7.3% vs 0.6%, $P < .01$).

Impact on work was greater among patients in the *Yes-angioedema* category than among patients in the *No-angioedema* category. Patients in the *Yes-angioedema* category who completed the diary were more likely to have missed 1 or more hours of work in the 7-day diary window than patients in the *No-angioedema* category (27.6% vs 5.8%, $P < .001$), and mean (SD) number of days of work missed in the past 3 months was significantly higher for patients in the *Yes-angioedema* versus the *No-angioedema* category (4.7 [11.64]) vs 0.8 [3.86], $P < .001$). WPAI scores showed significantly greater absenteeism among patients in the *Yes-angioedema* versus *No-angioedema* categories (mean [SD] percentage absenteeism: 9.1% [23.22%] vs 1.4% [9.08%], $P < .001$), as well as significantly greater overall work impairment (mean [SD] percentage overall work impairment: 29.2% [28.48%) vs 19.1% [21.37%], $P = .02$) (Figure 4). Overall, angioedema was the second most common reason for missing work, after itching.

3.7 | Characteristics of the misaligned angioedema category

Patients in the *Misaligned* category were compared descriptively with patients in the *Yes-angioedema* and *No-angioedema* categories and were found to be most similar to patients in the *Yes-angioedema* category in all outcomes. Demographics were similar in terms of age, sex, disease duration from diagnosis to enrolment and CSU severity at diagnosis (Table 1). Similar proportions of patients in the *Misaligned* and *Yes-angioedema* categories had moderate ($UAS7_{TD}$ 16-27) or severe ($UAS7_{TD}$ 28-42) disease activity (56.4% and 52.5%, respectively). When completing the survey, 52.2% of patients in the *Misaligned* category reported that their angioedema typically lasts more than 12 hours, compared with 47.8% of patients in the *Yes-angioedema* category. The mean (SD) amount of swelling, on a scale of 0 to 10, was similar for patients in the *Misaligned* category (7.1 [2.12]) and those in the *Yes-angioedema* category (7.2 [2.20]). In addition, the HRQoL impact of CSU was similar for patients in the *Misaligned* and *Yes-angioedema* categories, as indicated by mean (SD) overall scores on the DLQI (10.4 [6.85] and 9.7 [6.87], respectively) and CU-Q_2oL (37.6 [20.81] and 37.0 [21.49], respectively) (Figure 3A,B). Percentage overall work impairment due to CSU was similar for patients in the *Misaligned* and *Yes-angioedema* categories (mean [SD] = 31.5% [29.99%] and 29.2% (28.48%), respectively) (Figure 4).

3.8 | DLQI regression analysis

Given the similarities in characteristics and outcomes among patients in the *Misaligned* and *Yes-angioedema* categories, the *Misaligned* patients were combined with the *Yes-angioedema* patients in the primary regression analysis of DLQI total score. After covariate adjustment, mean DLQI score was significantly higher for patients with angioedema versus without (9.88 vs 7.27, $P < .001$) (Table 2). Results were similar in the sensitivity analysis in which patients in the *Misaligned* angioedema category were excluded: mean DLQI total score was significantly higher for patients with angioedema versus without (9.69 vs 6.73, $P < .001$).

4 | DISCUSSION

The results of this post hoc analysis revealed notable differences in reporting of angioedema between CSU patients and physicians in the ASSURE-CSU study. The objective of this analysis was to align angioedema data in order to better estimate the actual rate of angioedema and to analyse differences between patients with and without angioedema. Angioedema was more frequently reported by patients than by physicians: 65.8% of patients who completed the survey reported having experienced angioedema during the past 12 months, whereas physicians reported that 41.0% of patients had experienced angioedema during the same time period. A large majority (97%) of patients with misaligned angioedema data did not have physician-reported angioedema but reported having experienced angioedema in either the patient survey or diary. These findings suggest that the occurrence of angioedema may be under-recognized among physicians (who may not routinely ask patients about angioedema symptoms), that patients may not always report their angioedema symptoms to physicians or that patients characterize some CSU-related swelling as angioedema when a physician would classify it as hives or sometimes as swelling unrelated to urticaria.

ASSURE-CSU patients with misaligned angioedema data appear most similar to patients with angioedema, in terms of disease duration; disease activity; and scores on patient-reported outcome measures including the CU-Q_2oL, DLQI and WPAI. If patients in the *Misaligned* category were reclassified into the *Yes-angioedema* category, which they closely resembled, the percentage of patients in the ASSURE-CSU study with angioedema over 12 months would increase from 40.3% to 73.1%. Moreover, our analysis suggests that patients with more severe CSU are more likely to have angioedema. Physicians reported that more patients with angioedema than without had severe CSU at diagnosis, and patients with angioedema reported greater CSU activity as indicated by $UAS7_{TD}$ mean score than those without angioedema.

The primary ASSURE-CSU analysis found that angioedema had a significant impact on HRQoL in patients with CSU, particularly with respect to emotional well-being, fatigue and mood.[12] The current analysis also revealed the considerable impact of angioedema on HRQoL, as indicated by CU-Q_2oL and DLQI scores, and its additional negative impact on top of itch and hives. Even after controlling for other factors, angioedema has a significant effect on the DLQI total score. In addition, patients with angioedema have additional impairment on work productivity and more HCRU than those without it, indicating that angioedema further contributes to the economic burden of inadequately controlled CSU.

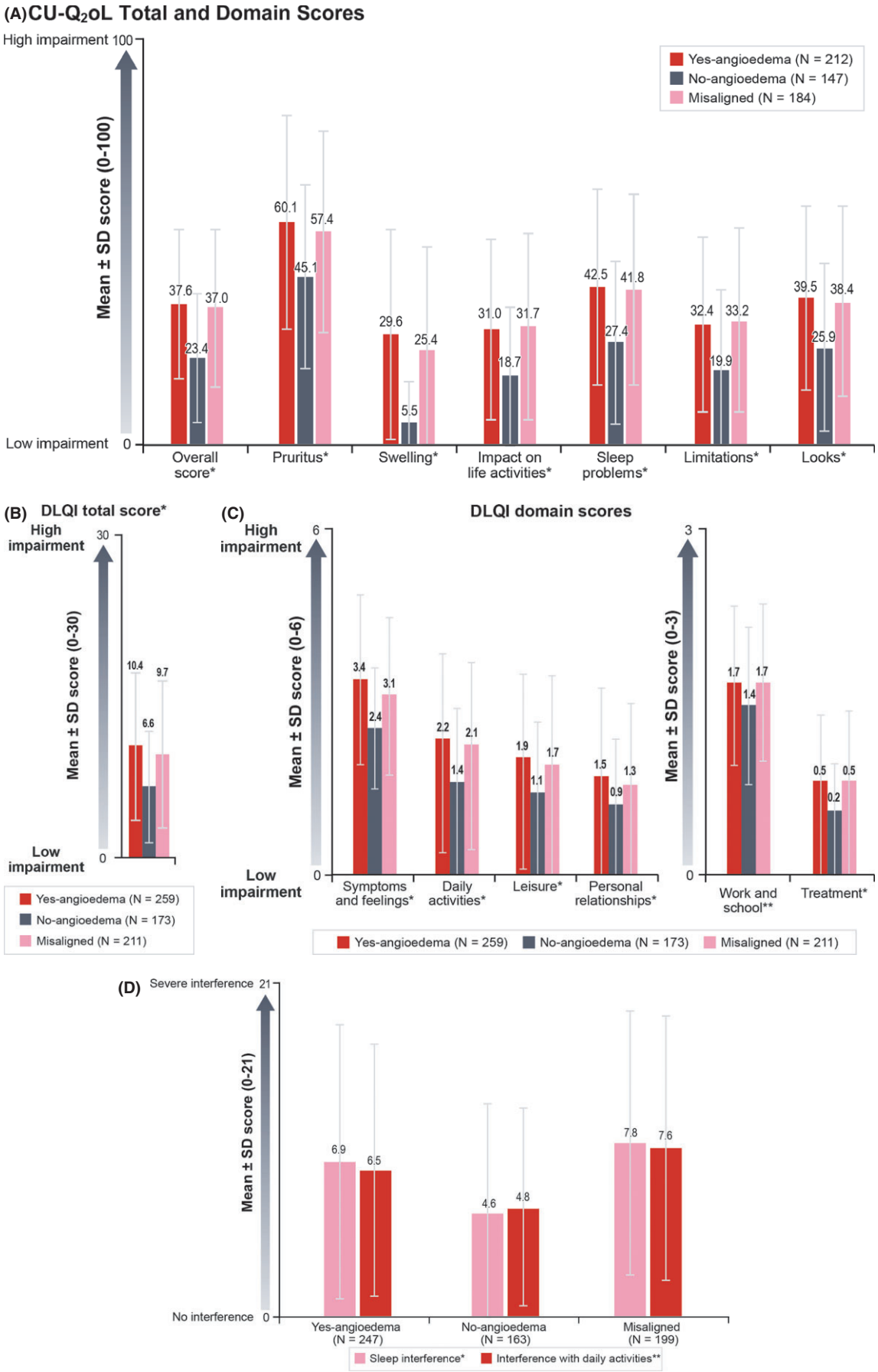
Taken together, findings from these analyses suggest that physicians should ensure that patients understand the manifestations of angioedema and should routinely assess patients with CSU for presence of angioedema, which may enable more accurate estimates of the true prevalence and burden of angioedema. Appropriate tools available for evaluating angioedema activity and its impact on CSU patients' lives should be used regularly in clinical practice.[22-24] In patients with recurrent angioedema, CSU should be considered as one of the differential diagnoses.[1,25] Additionally, angioedema in CSU should prompt adequate treatment. The development of new treatments specifically for CSU has been shown to prevent angioedema and improve angioedema-dependent and dermatology-related quality of life.[9,26-28] Future research should explore the clinical course of angioedema in CSU—including the most commonly affected areas, the clinical differences compared with hereditary angioedema and evolution of symptoms over time—as well as the distinct management patterns that patients with angioedema in CSU require. Understanding the underlying mechanisms of angioedema in CSU[29] and exploring differences in the general categories of angioedema (ie mast cell–induced and bradykinin-induced) are also important areas for additional research.

Several limitations must be considered when the results of this study are interpreted. First, the study was conducted in specialized centres only, and physicians and centres were not selected systematically, owing to the small number of specialist units for this population. The resulting sample is not guaranteed to be representative of all medical settings and physicians treating patients with CSU. Second, the target population had had CSU for at least 12 months and had not responded adequately to treatment at the time of inclusion in the study; thus, the study does not reflect the entire population of patients with CSU but more patients with inadequately controlled CSU. Moreover, although patients received training about identifying angioedema and reporting it in the patient survey or diary, like all patient-reported data, angioedema was still subject to patients' individual interpretation of the symptom description and manifestation. In addition, data extracted by physicians from medical records were not independently validated.

5 | CONCLUSIONS

Among this study population with inadequately controlled CSU, 40.3% had confirmed angioedema in the past 12 months, and 32.8%

FIGURE 3 Impact of CSU on HRQoL, sleep and daily activities, overall and by angioedema classification. (A) CU-Q_2oL total and domain scores. Different CU-Q_2oL scale scores are used in Germany than in Canada, France, Italy, the Netherlands, Spain and the UK. German CU-Q2oL overall score and scale scores are presented in Figure S2; (B) DLQI total score; (C) DLQI domain scores; (D) Interference with sleep and interference with daily activities over a week, as reported on the Urticaria Patient Daily Diary, by angioedema classification. For all scores, a higher score means higher impairment. *$P < .001$ (*Yes—angioedema* vs *No—angioedema*); **$P < .05$ (*Yes—angioedema* vs *No—angioedema*). Patients who fell into the *misaligned* category were not included in the statistical comparisons. CU-Q_2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; HRQoL, health-related quality of life; SD, standard deviation. [Colour figure can be viewed at wileyonlinelibrary.com]


(A) CU-Q2oL Total and Domain Scores
High impairment 100
Low impairment 0
Mean ± SD score (0-100)
Yes-angioedema (N = 212)
No-angioedema (N = 147)
Misaligned (N = 184)
37.6
23.4
37.0
60.1
45.1
57.4
29.6
5.5
25.4
31.0
18.7
31.7
42.5
27.4
41.8
32.4
19.9
33.2
39.5
25.9
38.4
Overall score*
Pruritus*
Swelling*
Impact on life activities*
Sleep problems*
Limitations*
Looks*
(B) DLQI total score*
High impairment
Low impairment
30
0
Mean ± SD score (0-30)
10.4
6.6
9.7
Yes-angioedema (N = 259)
No-angioedema (N = 173)
Misaligned (N = 211)
(C) DLQI domain scores
High impairment
Low impairment
6
0
Mean ± SD score (0-6)
3.4
2.4
3.1
2.2
1.4
2.1
1.9
1.1
1.7
1.5
0.9
1.3
Symptoms and feelings*
Daily activities*
Leisure*
Personal relationships*
3
0
Mean ± SD score (0-3)
1.7
1.4
1.7
0.5
0.2
0.5
Work and school**
Treatment*
Yes-angioedema (N = 259)
No-angioedema (N = 173)
Misaligned (N = 211)
(D)
Severe interference 21
No interference 0
Mean ± SD score (0-21)
6.9
6.5
4.6
4.8
7.8
7.6
Yes-angioedema (N = 247)
No-angioedema (N = 163)
Misaligned (N = 199)
Sleep interference*
Interference with daily activities**

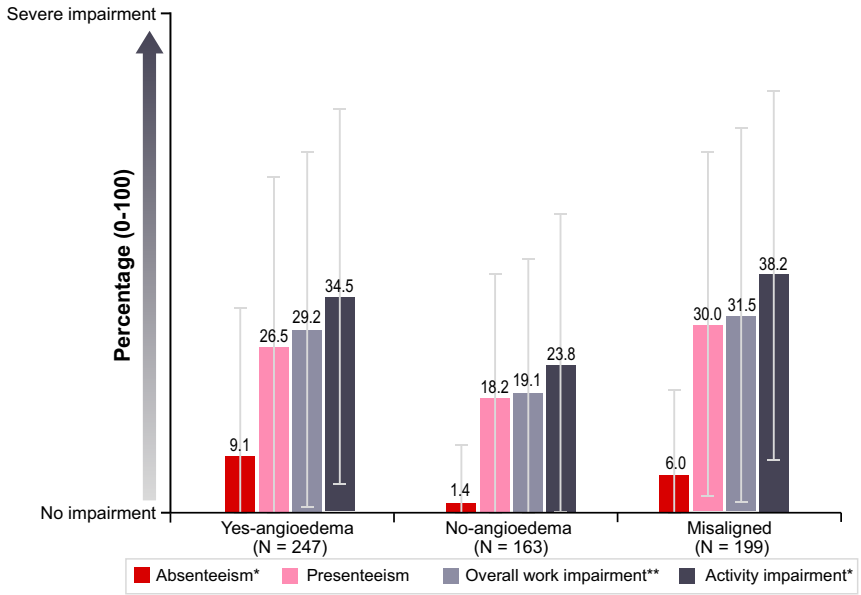


FIGURE 4 Work productivity and activity impairment (WPAI) results by angioedema classification. Absenteeism was defined as percentage of work time missed due to chronic spontaneous urticaria (CSU) in the past 7 days. Presenteeism was defined as percentage impairment while working due to CSU in the past 7 days. Overall work impairment was defined as percentage work impairment due to CSU in the past 7 days, incorporating both absenteeism and presenteeism using the following validated WPAI algorithm: overall work impairment = absenteeism + (1-absenteeism)*presenteeism. *$P < .001$ (*Yes—angioedema* vs *No—angioedema*); **$P < .05$ (*Yes—angioedema* vs *No—angioedema*). Patients who fell into the misaligned category were not included in the statistical comparisons. SD, standard deviation; WPAI, Work Productivity and Activity Impairment. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 DLQI regression results

Angioedema Classification	Within Group			Contrast in LS Mean				
	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	*P* value
Primary analysis: ANCOVA for DLQI total score by angioedema classification (assigning *Misaligned* category to *Yes-angioedema* category)								
No-angioedema	150	7.27	0.850	vs Yes	−2.61	0.558	−3.71 to −1.51	<.0001
Yes-angioedema	399	9.88	0.722					
Sensitivity analysis: ANCOVA for DLQI total score by angioedema classification (removing the *Misaligned* category)								
No-angioedema	150	6.73	0.902	vs Yes	−2.96	0.586	−4.12 to −1.81	<.0001
Yes-angioedema	232	9.69	0.795					

LS means, 95% CIs and *P* values are from an ANCOVA model with covariates: angioedema classification, $UAS7_{TD}$ score (continuous), age at enrolment (continuous), sex (male and female), country (Canada, France, Germany, Italy, Spain, the Netherlands and the UK), disease duration from diagnosis to enrolment (continuous) and comorbidities at enrolment (hypersensitivity to NSAIDs [yes/no], Hashimoto's [yes/no] and asthma [yes/no]). ANCOVA, analysis of covariance; CI, confidence interval; DLQI, Dermatology Life Quality Index; LS, least squares; n, number of subjects with data for all model inputs; NSAIDs, nonsteroidal anti-inflammatory drugs; SE, standard error; $UAS7_{TD}$, Urticaria Activity Score over 7 days, twice-daily assessment.

of patients had misaligned angioedema data (ie the majority reporting having experienced angioedema in the past 12 months without having it documented in their medical records). This suggests that a higher proportion of patients with inadequately controlled symptomatic CSU might have angioedema than previously thought. Patients with angioedema reported statistically significantly worse HRQoL and higher societal burden than patients without angioedema; patients in the Misaligned group reported similar impairment as patients with confirmed angioedema. Overall, the study found that angioedema has an incremental impact on societal and humanistic outcomes in CSU patients. These findings suggest the need for improved physician-patient communication regarding angioedema for better symptom control in patients with inadequately controlled CSU.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

M.M.B., K.H. and D.McB. initiated the study. M.M.B., K.H., D.McB, C.S. and D.W. designed the study; M.A., F.B., W.C., H.O.E., A.G-A., C.G., A.K., J-P.L., C.L., A.M., M.M., A.N., J.O.d.F., G.S. and K.W. provided clinical input on the study design. K.H., D.McB., C.S. and D.W. managed data collection, and M.M.B., K.H., D.McB., S.H., C.S., H.T. and D.W. led the data analyses. M.M.B., M.A., F.B., W.C., H.O.E., A.G-A., C.G., K.H., A.K., J-P.L., C.L., A.M., M.M., D.McB., A.N., J.O.d.F., C.P., G.S., C.S., H.T., K.W. and D.W. interpreted the data. M.M.B., K.H., S.H., D.McB. and G.S. drafted the manuscript, and M.A., F.B., W.C., H.O.E., A.G-A., C.G., A.K., J-P.L., C.L., A.M., M.M., A.N., J.O.d.F., C.S., H.T., K.W. and D.W. revised it critically for intellectual content. All authors reviewed and approved the final manuscript and agree to be accountable for the work as a whole.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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SUPPLEMENTARY APPENDIX

Table S-1. CSU Patient Groups Stratified by Angioedema Category (N = 673)

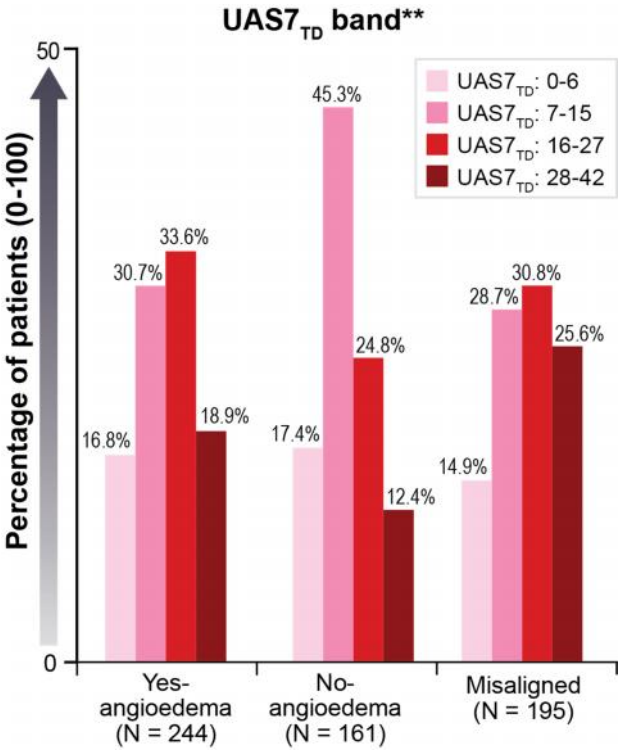
Angioedema Category	Definition	Patient Experienced Angioedema in the Past 12 Months				Number (Percentage) of Patients in Category[a]
		MRA	Survey	Diary	Number of Patients	
Yes-angioedema category	Physician and patient data sources agree that the patient has experienced angioedema in past 12 months	Yes	No	Yes	3	259 (40.3%)
		Yes	Yes	Missing	16	
		Yes	Yes	No	94	
		Yes	Yes	Yes	146	
No-angioedema category	Physician and patient data sources agree that the patient has not experienced angioedema	No	Missing	No	7	173 (26.9%)
		No	No	Missing	13	
		No	No	No	153	
Misaligned category	The physician and patient data sources do not agree as to whether the patient has experienced angioedema. Only 1 source (either physician or the patient) reported angioedema	No	Missing	Yes	1	211 (32.8%)
		No	No	Yes	35	
		No	Yes	Missing	13	
		No	Yes	No	48	
		No	Yes	Yes	108	
		Yes	No	No	6	

Angioedema Category	Definition	Patient Experienced Angioedema in the Past 12 Months				Number (Percentage) of Patients in Category[a]
		MRA	Survey	Diary	Number of Patients	
Missing	Angioedema classification was missing either from the MRA or from both patient data sources (survey and diary)	Missing	Missing	Missing	1	30 (NA)
		Missing	No	No	2	
		Missing	Yes	No	2	
		No	Missing	Yes	1	
		No	Missing	Missing	13	
		Yes	Missing	Missing	11	

CSU = chronic spontaneous urticaria; MRA = medical record abstraction.

[a] Percentage of patients among those with angioedema data available in one of the sources and included in the analysis.

Figure S-1. Urticaria Activity Score over 7 Days ($UAS7_{TD}$) Band, by Angioedema Classification[a]



** $P < 0.05$ (*Yes-angioedema* vs. *No-angioedema*, comparing the distribution of the $UAS7_{TD}$ score bands among the angioedema categories). Patients who fell into the *Misaligned* category were not included in the statistical comparisons.

$UAS7_{TD}$ = Urticaria Activity Score over 7 Days, twice-daily assessment.

Note: $UAS7_{TD}$ scores were assessed by summing the average of twice-daily assessments of hive count and itch score and summing these daily scores over 7 days.

[a] Data for angioedema from the medical record abstraction, patient survey, and patient diary were aligned. If the physician data source and at least one of the patient data sources indicate the patient experienced angioedema, then the angioedema category was set to *Yes-angioedema*. If all physician and patient data sources indicate no angioedema, then the angioedema category was set to *No-angioedema*. If physician and patient data sources disagreed, then the angioedema category was set to *Misaligned*. All data are from the past 12 months.

Table S-2. Health Care Resource Utilisation as Documented in Medical Records and by Patient Self-Report, Overall and by Angioedema Classification

		Angioedema Category[a]			
	Total	**Yes**	**No**	**Misaligned**	***P* Value (Yes vs. No)[b]**
Health care resource utilisation during previous 12 months, n (%) (reported in MRA)	**n = 643**	**n = 259**	**n = 173**	**n = 211**	
Had one or more CIU/CSU-related emergency department visits	95 (14.8%)	64 (24.7%)	9 (5.2%)	22 (10.4%)	< 0.0001
Had one or more CIU/CSU inpatient hospital stays	54 (8.4%)	30 (11.6%)	6 (3.5%)	18 (8.5%)	0.0028
Had one or more CSU-related visit to a health care professional,[c] n (%)	464 (72.2%)	195 (75.3%)	118 (68.2%)	151 (71.6%)	0.1065
Total number of CIU/CSU-related visits per patient, among those with one or more					0.0853
n	464	195	118	151	
Mean (SD)	3.3 (2.99)	3.4 (3.09)	2.8 (2.26)	3.4 (3.32)	
Length of visit (minutes), among UK patients with one or more visits[d]					< 0.0001
n	67	29	6	32	
Mean (SD)	21.9 (9.26)	27.2 (7.76)	16.6 (9.53)	19.3 (8.42)	
Health care resource utilisation during 7-day diary period, n (%)	**n = 609**	**n = 247**	**n = 163**	**n = 199**	
Called health care professional because of skin condition at least one day during 7-day diary period	29 (4.8%)	18 (7.3%)	1 (0.6%)	10 (5.0%)	0.0017

CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; MRA = medical record abstraction.

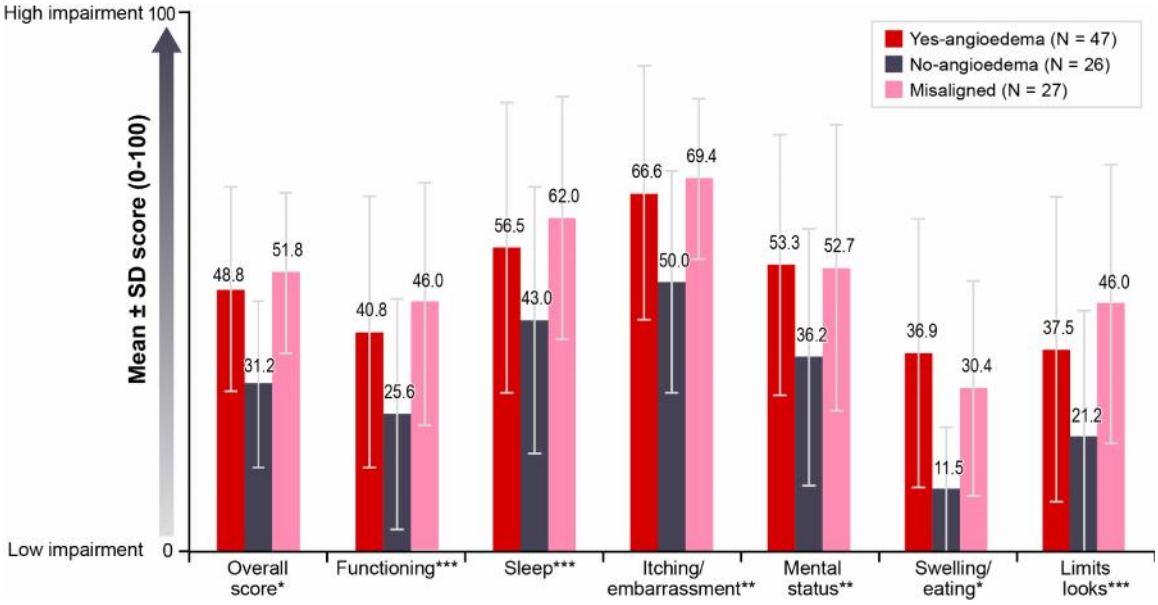
[a] Data for angioedema from the MRA, patient survey, and patient diary were aligned. If the physician data source and at least one of the patient data sources indicate the patient experienced angioedema, then the angioedema category was set to *Yes-angioedema*. If all physician and patient data sources indicate no angioedema, then the angioedema category was set to *No-angioedema*. If physician and patient data sources disagreed, then the angioedema category was set to *Misaligned*. All data are from the past 12 months.

[b] *P* values shown from chi-square tests to compare patients who experience angioedema (*Yes-angioedema*) with those who do not (*No-angioedema*). Patients in the *Misaligned* category were not included in the statistical comparison.

[c] Included routine visits, emergency visits, and visits where "Data not available" was selected as the primary reason for visit.

[d] Length of health care professional visits was collected only in the United Kingdom.

Figure S-2. CU-Q_2oL Total and Domain Scores for German Patients, by Angioedema Classification[a]



* *P* < 0.001 (*Yes-angioedema* vs. *No-angioedema*); ** *P* < 0.01 (*Yes-angioedema* vs. *No-angioedema*); *** *P* < 0.05 (*Yes-angioedema* vs. *No-angioedema*). Patients who fell into the *Misaligned* category were not included in the statistical comparisons.

CU-Q_2oL = Chronic Urticaria Quality of Life Questionnaire; SD = standard deviation.

Note: Higher scores indicate greater impairment.