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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...
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.\(^3\)\(^,\)\(^4\) 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. 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 and overall results 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 H1-antihistamine, had been symptomatic for more than 12 months and were currently symptomatic despite treatment were eligible; patients with urticaria that was pre-dominantly 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.

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 or not 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-Q2oL) and Dermatology Life Quality Index (DLQI) and HCRU. The 7-day UPDD also included the twice-daily Urticaria Activity Score over 7 Days (UAS7TD), 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.

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 UAS7TD score bands: UAS7TD = 0-6 (urticaria-free or well-controlled urticaria activity), 7-15 (mild activity), 16-27 (moderate activity) and 28-42 (severe activity). 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 UAS7TD 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). UAS7TD 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) UAS7TD 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...
had severe (UAS7TD 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-Q2OL score for the overall patient sample was 33.6 (21.02). Mean (SD) CU-Q2OL 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-Q2OL 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 category had severe disease activity (18.9% vs 12.4%) (Figure S1).19

### Table 1

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

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total (n = 643)</th>
<th>Angioedema category</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt; (yes vs no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (n = 259)</td>
<td>No (n = 173)</td>
</tr>
<tr>
<td>Age at enrolment (years)</td>
<td>49.0 (15.56)</td>
<td>49.4 (14.45)</td>
<td>46.8 (16.50)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>19.0, 89.0</td>
<td>20.0, 81.0</td>
<td>19.0, 89.0</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>469 (72.9)</td>
<td>197 (76.1)</td>
<td>117 (67.6)</td>
</tr>
<tr>
<td>Race and ethnicity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>544</td>
<td>205</td>
<td>155</td>
</tr>
<tr>
<td>Caucasian/White (%)</td>
<td>491 (90.3)</td>
<td>189 (92.2)</td>
<td>138 (89.0)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>44 (8.1)</td>
<td>15 (7.3)</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>Data not available (%)</td>
<td>9 (1.7)</td>
<td>1 (0.5)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Disease duration from diagnosis to enrolment (months)</td>
<td>57.3 (77.73)</td>
<td>61.7 (76.64)</td>
<td>46.1 (69.06)</td>
</tr>
<tr>
<td>Comorbid conditions at enrolment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity to NSAIDs</td>
<td>52 (8.1)</td>
<td>28 (10.8)</td>
<td>10 (5.8)</td>
</tr>
<tr>
<td>Hashimoto’s disease</td>
<td>43 (6.7)</td>
<td>27 (10.4)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>71 (11.0)</td>
<td>33 (12.7)</td>
<td>18 (10.4)</td>
</tr>
<tr>
<td>CSU/CIU severity at the time of diagnosis (%)</td>
<td>642</td>
<td>259</td>
<td>173</td>
</tr>
<tr>
<td>Mild</td>
<td>71 (11.1)</td>
<td>27 (10.4)</td>
<td>32 (18.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>202 (31.5)</td>
<td>81 (31.3)</td>
<td>53 (30.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>233 (36.3)</td>
<td>98 (37.8)</td>
<td>45 (26.0)</td>
</tr>
<tr>
<td>Data not available (%)</td>
<td>136 (21.2)</td>
<td>53 (20.5)</td>
<td>43 (24.9)</td>
</tr>
<tr>
<td>UAS7TD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) UAS7TD</td>
<td>17.3 (10.46)</td>
<td>17.6 (10.55)</td>
<td>14.6 (8.97)</td>
</tr>
<tr>
<td>UAS7TD band (%)</td>
<td>600</td>
<td>244</td>
<td>161</td>
</tr>
<tr>
<td>0-6</td>
<td>98 (16.3)</td>
<td>41 (16.8)</td>
<td>28 (17.4)</td>
</tr>
<tr>
<td>7-15</td>
<td>204 (34.0)</td>
<td>75 (30.7)</td>
<td>73 (45.3)</td>
</tr>
<tr>
<td>16-27</td>
<td>182 (30.3)</td>
<td>82 (33.6)</td>
<td>40 (24.8)</td>
</tr>
<tr>
<td>28-42</td>
<td>116 (19.3)</td>
<td>46 (18.9)</td>
<td>20 (12.4)</td>
</tr>
</tbody>
</table>

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; UAS7TD, Urticaria Activity Score over 7 Days, twice-daily assessment.

<sup>a</sup>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.

<sup>b</sup><i>P</i> values shown from <i>t</i> 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.

<sup>c</sup>Race and ethnicity data were not collected in France. For some categories of race and ethnicity, different terms were used across countries.
category (20.4%) had DLQI scores [greater than] 10 (indicating a very to extremely large effect on HRQoL).

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-Q2oL (33.6 [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).
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-QoL, 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 UAS7TD 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. The current analysis also revealed the considerable impact of angioedema on HRQoL, as indicated by CU-QoL 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. In patients with recurrent angioedema, CSU should be considered as one of the differential diagnoses. 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. 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 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%...
(A) CU-QoL Total and Domain Scores

- High impairment 100
- Low impairment 0

- Mean ± SD score (0-100)

- Overall score*
- Pruritus*
- Swelling*
- Impact on life activities*
- Sleep problems*
- Limitations*
- Looks*

- Yes-angioedema (N = 212)
- No-angioedema (N = 147)
- Misaligned (N = 184)

(B) DLQI total score*

- High impairment 30
- Low impairment 0

- Mean ± SD score (0-30)

- Yes-angioedema (N = 259)
- No-angioedema (N = 173)
- Misaligned (N = 211)

(C) DLQI domain scores

- Symptoms and feelings*
- Daily activities*
- Leisure*
- Personal relationships*
- Work and school**
- Treatment*

- Mean ± SD score (0-6)

- Yes-angioedema (N = 259)
- No-angioedema (N = 173)
- Misaligned (N = 211)

(D) Severe interference

- No interference 0
- Mean ± SD score (0-21)

- Sleep Interference*
- Interference with daily activities**

- Yes-angioedema (N = 247)
- No-angioedema (N = 163)
- Misaligned (N = 196)
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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**Table 2: DLQI regression results**

<table>
<thead>
<tr>
<th>Angioedema Classification</th>
<th>n</th>
<th>LS Mean</th>
<th>SE</th>
<th>Comparison</th>
<th>LS Mean</th>
<th>SE</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>within Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary analysis: ANCOVA for DLQI total score by angioedema classification (assigning Misaligned category to Yes-angioedema category)</td>
<td></td>
<td></td>
<td></td>
<td>No-angioedema</td>
<td>150</td>
<td>7.27</td>
<td>0.850</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vs Yes</td>
<td>No-angioedema</td>
<td>163</td>
<td>-2.61</td>
<td>0.558</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes-angioedema</td>
<td>247</td>
<td>-2.96</td>
<td>0.586</td>
</tr>
<tr>
<td>Sensitivity analysis: ANCOVA for DLQI total score by angioedema classification (removing the Misaligned category)</td>
<td></td>
<td></td>
<td></td>
<td>No-angioedema</td>
<td>150</td>
<td>6.73</td>
<td>0.902</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vs Yes</td>
<td>No-angioedema</td>
<td>163</td>
<td>-2.96</td>
<td>0.586</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes-angioedema</td>
<td>232</td>
<td>9.69</td>
<td>0.795</td>
</tr>
</tbody>
</table>

LS means, 95% CIs and P values are from an ANCOVA model with covariates: angioedema classification, UAS7TD 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; UAS7TD, Urticaria Activity Score over 7 days, twice-daily assessment. 

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**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]

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION
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