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Development and construct validation of the angioedema quality of life questionnaire

K. Weller[1], A. Groffik[2], M. Magerl[1], N. Tohme[1], P. Martus[3], K. Krause[1], M. Metz[1], P. Staubach[2] & M. Maurer[1]

[1]Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Department of Dermatology, University Medical Center Mainz, Mainz, Germany; [3]Institute for Clinical Epidemiology and Applied Biometry, Eberhard-Karls University Tübingen, Tübingen, Germany

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Correspondence
Prof. Dr Marcus Maurer,
Allergie-Centrum-Charité
Department of Dermatology and Allergy,
Charité – Universitätsmedizin Berlin,
Charitéplatz 1, D-10117 Berlin, Germany.
Tel.: +49 30 450 518043
Fax: +49 30 450 518972
E-mail: marcus.maurer@charite.de

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Abstract

Background: Recurrent angioedema is a frequent clinical problem characterized by unpredictably and rapidly occurring cutaneous and mucosal swellings. These swellings may be painful and/or disfiguring. Upper airway involvement can also lead to dyspnea and suffocation. Although the disease burden is high, there is currently no specific instrument to measure health-related quality of life (QoL) impairment.

Objective: To develop and validate the first symptom-specific tool to assess QoL impairment in recurrent angioedema patients, adhering to established methodological recommendations.

Methods: During the development phase, 29 questions (items) were generated. Subsequently, item reduction was performed by means of impact analysis and factor analysis as well as by checking for content and face validity. As a result, 17 items were selected and included in the final instrument, the Angioedema QoL Questionnaire (AE-QoL). AE-QoL was then tested for its validity, reliability, and influence factors.

Results: One hundred and ten angioedema patients took part in the validation of AE-QoL. AE-QoL was found to have a four-dimensional structure as well as a valid total score. All of its four domains (functioning, fatigue/mood, fears/shame, food) showed good levels of internal consistency with Cronbach's alpha > 0.8. Test–retesting revealed a good reliability of the instruments total score and domain scores. Gender as well as the patients' self-rated disease activity was found to be predictors of the AE-QoL total score.

Conclusions: Angioedema Quality of Life Questionnaire is the first angioedema-specific QoL questionnaire. It is a short, valid and reliable instrument that may serve as a valuable tool in future clinical studies and in routine patient care.

Angioedema is defined as nonpruritic, nonpitting swellings of deeper cutaneous and mucosal tissues (1). Swellings may be erythematous or skin-colored (2). Recurrent angioedema is either mast cell mediator mediated, for example, in patients with chronic spontaneous urticaria (csU), bradykinin mediated, for example, in patients with hereditary angioedema because of C1-inhibitor defects or deficiency (HAE1&2), or idiopathic. The prevalence of HAE1&2 is low (1 : 10 000–1 : 50 000) (3), whereas csU prevalence is high (1 : 100–1 : 200) (4). All HAE1&2 patients and 30–50% of csU patients develop recurrent angioedema (4). In addition, there is a third but not well-characterized group of patients with recurrent idiopathic angioedema. For this group, no reliable data regarding its prevalence exists.

Depending on the size and location, angioedema may be painful and/or disfiguring, thereby leading to limitations of daily activities. Airway swellings can be life-threatening, and the risk of dying from airway obstruction is significant in laryngeal edema if left untreated (5). A major feature of recurrent angioedema is the unpredictability and the rapid onset of attacks. This may lead to unexpected and frequent absence from work or school, and negatively impact

education, career, and work productivity (6). Patients with recurrent angioedema are commonly regarded as unreliable employees, and many constantly fear the appearance of new attacks. Accordingly, recurrent angioedema is a major burden for the patients and severely impacts their quality of life (QoL).

As of yet, there is no validated and reliable instrument to measure QoL impairment of patients with recurrent angioedema. Here, we report such an instrument, which we developed in adherence to established methodological recommendations (7).

Methods

Patient sample and data acquisition

Data were collected from April 2011 until January 2012 by the Department of Dermatology and Allergy of the Charité – Universitätsmedizin Berlin and at the Department of Dermatology of the University Medical Center Mainz. In total, 120 adult patients with recurrent angioedema participated in the development of the instrument (item generation: $n = 10$; item reduction and instrument validation: $n = 110$).

Development procedure

To ensure that AE-QoL items address frequent and important areas of QoL impairment in recurrent angioedema patients, we first performed item generation steps according to current recommendations for patient reported outcome development (7). This was followed by item reduction using impact analysis (8). The Urticaria Quality of Life Questionnaire (CU-Q_2oL) (9, 10) served as an intellectual and structural model during the development of AE-QoL.

Item generation

To identify and generate items appropriate for an angioedema-specific QoL instrument, we used three complementary strategies: We (1) performed exploratory semi-structured interviews with 10 recurrent angioedema patients (HAE1&2: $n = 4$, csU: $n = 3$, other: $n = 3$); (2) conducted a systematic review of the literature and (3) obtained opinions from clinical angioedema experts of both participating centers on the areas most troublesome for angioedema patients. All item responses were formatted as 5-point Likert scales with the following answer options: never, rarely, sometimes, often, and very often. The time frame covered by the items was chosen to be the last 4 weeks.

Item reduction

All generated items were administered to recurrent angioedema patients ($n = 110$, for details on population characteristics, see Results section) who were asked, first, which of the problems indicated in the items they had experienced during the last year (response options: yes or no), and, second, to rate the importance of the items (response options: 1 – not important to 5 – extremely important). The results were expressed as 'frequency' of patients (proportion who had experienced the problem indicated in the respective item during the last year) and as 'importance' (mean importance of each item). The 'impact' of the items was then calculated as the product of 'frequency' and 'importance' (impact analysis). All items with an impact score < 1.5 were excluded (Table 2). In addition, items 1–4 were removed for reasons of face validity: These items only assess symptoms rather than facets of symptom-related quality of life impairment.

Instrument validation

The aim of this phase was to determine the dimensions (domains) of AE-QoL as well as to evaluate its validity, internal consistency, and reliability. To this end, recurrent angioedema patients ($n = 110$) received a self-administered questionnaire asking for sociodemographic data, overall self-rating of their angioedema-related QoL impairment and angioedema activity. In addition, it contained the Dermatology Life Quality Index (DLQI), the generic SF-36 health survey and all generated items for the AE-QoL. In a separate document, 46 patients completed all AE-QoL items twice at an interval of 3 weeks during follow-up to assess its test–retest reliability. All questionnaires were completed by the patients at home.

Determination and scoring of AE-QoL domains

To determine the appropriate domains of AE-QoL, we performed an exploratory factor analysis. The approach employed was a principal component analysis with Varimax rotation and Kaiser normalization. The criterion chosen to retain factors (domains) was an eigenvalue ≥ 1. Individual items loading onto a domain with a factor loading ≥ 0.5 were assigned to that domain.

After all AE-QoL domains were defined, the raw domain scores (mean of the item scores within each domain) and the raw total score (mean of all item scores) were computed. If single items were missing, the total of the items within each domain was divided by the number of the nonmissing items. In a second step, all raw domain scores and the raw total score were transformed into percentage scores, indicating the location of the raw scores in relation (in percent) to its maximum possible score (linear transformation). Accordingly, the minimum and highest possible domain and total score were 0 and 100, respectively. An AE-QoL domain score was not calculated in case of more than one item missing in that domain. The AE-QoL total score was not calculated if more than 25% of items (>4 items) were missing.

Internal consistency

Internal consistency measures the homogeneity of a domain. The internal consistency of each AE-QoL domain was tested by computing Cronbach's α. The commonly suggested interpretation of Cronbach's α coefficient is as follows: <0.60 unacceptable, 0.60–0.65 undesirable, 0.65–0.70 minimally

acceptable, 0.70–0.80 respectable, 0.80–0.90 excellent and > 0.90 excessive consistency (11).

Convergent validity

Convergent validity tests whether items, domains, or total instruments that should theoretically be related really are related. The convergent validity of AE-QoL was determined by calculating the correlation of its domains with those of the DLQI and the SF-36 (Pearson correlation). The DLQI is one of the most widely used dermatosis-specific questionnaires to measure health-related QoL impairment (12). It is composed of 10 items that are summed up to a total score (minimum 0 points, maximum 30 points) (13). In addition, six subdomains (headings) can be computed: 'symptoms and feelings', 'daily activities', 'leisure', 'work and school', 'personal relationships' and 'treatment'. The SF-36 is a generic questionnaire that has also been used extensively to detect and compare health-related QoL impairment in dermatologic and nondermatologic diseases (9, 14–17). It consists of 36 items corresponding to eight domains: 'physical function', 'role limitation (physical)', 'bodily pain', 'general health', 'vitality', 'social function', 'role limitation (emotional)', and 'mental health'. In addition, two composite scores can be computed, the 'physical component summary' and the 'mental component summary'.

Known-groups validity

One criterion for validity is that an instrument should be able to discriminate between patient groups that are assumed to differ. Known-groups validity of AE-QoL was tested by determining whether it was able to discriminate between patients who exhibit differences in their overall angioedema-related QoL impairment and their disease activity as assessed by the use of five-point Likert scales (response options: none, mild, moderate, severe, and very severe) to self-rate the last 4 weeks (the same period as covered by the AE-QoL items). Depending on their self-rating, all patients were assigned to one of five groups (none, mild, moderate, severe, and very severe), and the analysis of variance (ANOVA) trend test (one degree of freedom) was used to test for a linear relationship between these groups and increasing AE-QoL scores. Taking into account the limited group sizes, we decided to not compute tests of significance between the five groups but to present the results of a descriptive analysis including mean and standard deviation of each group.

Test–retest reliability

To test the ability of AE-QoL to yield stable scores over a short period of time, the AE-QoL was administered twice in a subsample of 46 patients. The time interval between both AE-QoL administrations was three weeks. The results of the domain scores and total scores were compared by computing the interclass correlation coefficient. An interclass coefficient of > 0.70 indicates good reproducibility (7).

Multiple linear regression

To detect drivers of AE-QoL scores (domain scores and total score), multiple linear regression analysis (stepwise) was used. Age, gender, and patients' self-rated disease activity were set as independent variables, and the AE-QoL domain scores or its total score was set as dependent variables.

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics Version 19, IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered as statistically significant.

Results

Population characteristics

A total of 110 angioedema patients (66% women, mean age ± SD: 53 ± 15 years, age range 19–85 years) participated in the item reduction and AE-QoL validation. The sociodemographic and clinical data of this sample are shown in Table 1. While the current guideline classification (18) regards patients with recurrent angioedema without C1-inhibitor deficiency and without wheals as a subset of chronic spontaneous urticaria, we decided to list the latter as a

Table 1 Population characteristics

	n	%
Gender		
Female	73	66.4
Male	37	33.6
Age		
18–40 years	24	21.8
40–60 years	50	45.5
60–80 years	34	30.9
>80 years	2	1.8
Marital status		
Single	11	10.0
Long-lasting relationship	13	11.8
Married	72	66.5
Divorced	6	5.5
Widowed	6	5.5
Unknown	2	1.8
School education		
9 years	18	16.4
10 years	49	44.5
12–13 years	39	35.5
Unknown	4	3.6
Diagnosis		
HAE1&2	21	19.1
Chronic spontaneous urticaria (patients with wheals and angioeedma)	55	50.0
Other*	34	30.9

*Recurrent angioedema without C1-inhibitor deficiency and without wheals ($n = 30$); recurrent angioedema with no clear allocation ($n = 4$) to 'chronic spontaneous urticaria'; or 'Recurrent angioedema without C1-inhibitor deficiency and without wheals'.

separate group. The reason is that these patients clinically differ from those urticaria patients who develop recurrent wheals in addition to angioedema, and this might be important for the interpretation of our results.

To obtain information on the attack frequency, the participating patients were asked, at the time of completion of the AE-QoL items, when the last swelling episode had occurred. Response options (chosen by *n* of patients) were 'today or yesterday' (*n* = 29), 'during the last week' (*n* = 31), 'between 1 and 4 weeks ago' (*n* = 23), 'between 4 weeks and 3 months ago' (*n* = 10), and 'more than 3 months ago' (*n* = 6). Eleven patients provided no answer to this question.

AE-QoL development

The item generation phase resulted in 29 items possibly relevant to patients with recurrent angioedema, each covering a recall period of 4 weeks. For item reduction, the impact of each item was computed (Table 2). Items 21 to 23 and 26 to 28 were removed, because their impact scored < 1.5. In addition, items 1 to 4 were excluded for reasons of face validity as these four items assess symptoms rather than facets of symptom-related QoL impairment.

AE-QoL validation

Factor analysis and internal consistency

The remaining 19 items were subjected to an exploratory factor analysis, which identified a four-factor (domain) structure of the AE-QoL. Of these 19 items, two (items 7 and 15) were removed from the final AE-QoL instrument because they did not meaningfully predict the value of its domains. Thus, a total of 17 items remained in the final instrument (Table 3). Its four-domain structure explained 69.5% of the total variance. The eigenvalues of the four factors were 6.26, 2.27, 1.81, and 1.48. While 16 of the 17 items could be clearly assigned to one factor (factor loading > 0.5), the item 29 ('Fear of long-term negative drug effects') was assigned to the factor with the highest loading (factor loading 0.4). Notably, an additional factor analysis that included items 1 to 4 revealed that these did not load to one of the four domains, thus further backing their exclusion from the final instrument.

As a last step of the instrument generation, the face validity and content validity of the 17 included items and the four domains were reviewed again, both in terms of the items and domains' global meanings as well the fitting of each item to its assigned domain. No further changes were regarded to be nec-

Table 2 Item impact analysis. Low impact scores (<1.5) are printed in bold

Item no.	Item name	Frequency (in %)	Importance (mean)	Impact
1	Swelling in the face	0.81	3.79	3.07
2	Swelling in the mouth/larynx	0.74	4.02	2.97
3	Swelling at hands and/or feet	0.80	3.29	2.63
4	Swelling at other location	0.86	3.32	2.86
5	Impairment of work	0.67	3.35	2.24
6	Impairment of physical activity	0.78	3.40	2.65
7	Impairment of sleep	0.78	3.80	2.96
8	Impairment of spare time activities	0.79	3.19	2.52
9	Impairment of social relations	0.63	3.32	2.09
10	General limitations in foods and eating	0.59	3.41	2.01
11	Difficulties of falling asleep	0.63	3.34	2.10
12	Waking up during the night	0.86	3.46	2.98
13	Feeling tired during the day	0.75	3.51	2.63
14	Difficulties in concentrating	0.60	3.32	1.99
15	Feeling nervous	0.64	3.10	1.98
16	Feeling downhearted	0.71	3.31	2.35
17	Limitations in the selection of food and beverages	0.58	3.34	1.94
18	Feeling burdened at having swellings	0.92	3.87	3.56
19	Fear of new suddenly appearing swellings	0.78	3.68	2.87
20	Fear of increased frequency of swellings	0.86	3.74	3.22
21	Tend to stay at home	0.42	3.14	**1.32**
22	Less meeting other people	0.49	2.97	**1.46**
23	Tend to do things alone	0.34	2.74	**0.93**
24	Ashamed to visit public places	0.53	2.92	1.55
25	Embarrassed by the appearance of swellings	0.58	2.98	1.73
26	Limitations in choosing clothes	0.39	2.83	**1.10**
27	Limitations in doing sport	0.51	2.91	**1.48**
28	Suffer from drug side effects	0.37	3.43	**1.27**
29	Fear of long-term negative drug effects	0.64	3.66	2.34

Table 3 Item factor loadings. Items with a factor loading > 0.5 are printed in bold

Item no.	Item	Factor 1	Factor 2	Factor 3	Factor 4
5	Impairment of work	**0.785**	0.198	0.120	−0.023
6	Impairment of physical activity	**0.878**	0.142	0.018	0.150
8	Impairment of spare time activities	**0.855**	0.208	0.157	0.071
9	Impairment of social relations	**0.782**	0.178	0.309	0.125
11	Difficulties of falling asleep	0.163	**0.763**	0.050	0.039
12	Waking up during the night	0.008	**0.884**	0.042	0.078
13	Feeling tired during the day	0.293	**0.832**	0.171	0.030
14	Difficulties in concentrating	0.228	**0.696**	0.171	0.248
16	Feeling downhearted	0.336	**0.636**	0.134	0.120
18	Feeling burdened at having swellings	0.401	0.286	**0.593**	0.019
19	Fear of new suddenly appearing swellings	0.059	0.008	**0.873**	−0.040
20	Fear of increased frequency of swellings	0.079	0.208	**0.772**	−0.046
24	Ashamed to visit public places	0.222	0.005	**0.778**	0.212
25	Embarrassed by the appearance of swellings	0.181	0.044	**0.753**	0.236
29	Fear of long-term negative drug effects	−0.053	0.343	0.424	0.089
10	General limitations in foods and eating	0.242	0.193	0.116	**0.851**
17	Limitations in the selection of food and beverages	−0.008	0.128	0.118	**0.919**

essary. According to the content of the domains, these received the headings 'Functioning', 'Fatigue/Mood', 'Fears/Shame', and 'Food' (the final German version of AE-QoL can be found as supporting information (Appendix S1) to his article).

The internal consistency of each domain was tested by computing Cronbach's α (Table 4). All values were > 0.8 and < 0.9, indicating excellent internal consistency. In addition, the Cronbach's α for the whole instrument was 0.89, which indicates that it is appropriate to calculate a total score in addition to domain scores. This is further supported by the fact that in an additional factor analysis with a one factor solution, only three of the included items (17, 19, 29) did not load to that factor when using the threshold of $\geq$ 0.5 for factor loading (results not shown).

Quality of life scores

The AE-QoL domain and total scores of the recurrent angioedema patients investigated are shown in Fig. 1. All scores represent linear transformations of raw scores to a 0 to 100 scale, with higher scores indicating a stronger impairment. The domain 'Fears/Shame' was most affected, followed by 'Fatigue/Mood'. In contrast, 'Functioning' and 'Food' exhibited lower domain scores. The distribution of the domain scores as well as the total score was broad, suggesting significant differences of QoL impairment between individual patients.

Convergent validity

To test the convergent validity of AE-QoL, correlations were computed between the AE-QoL total score and the DLQI total score ($r = 0.52$, $P < 0.001$) as well as between the AE-QoL domain scores and the six DLQI subdomains (headings) (Table 5). Similar correlations were also performed between the AE-QoL scores and the SF-36 scores (Table 6). All correlations were in the expected direction. The correlation of the AE-QoL total score and the SF-36 'Mental Component Summary' was particularly high ($r = -0.68$, $P < 0.001$), while the correlation with the SF-36 'Physical Component Summary' was lower ($r = -0.24$) but still significant ($P < 0.05$). The

Table 4 Domain structure and internal consistency of AE-QoL

Domain	Item	Crohnbach's α
Functioning	Impairment of work Impairment of physical activity Impairment of spare time activities Impairment of social relations	0.896
Fatigue/Mood	Difficulties of falling asleep Waking up during the night Feeling tired during the day Difficulties in concentrating Feeling downhearted	0.870
Fears/Shame	Feeling burdened at having swellings Fear of new suddenly appearing swellings Fear of increased frequency of swellings Ashamed to visit public places Embarrassed by the appearance of swellings Fear of long-term negative drug effects	0.825
Food	General limitations in foods and eating Limitations in the selection of food and beverages	0.851
Total Instrument		0.889

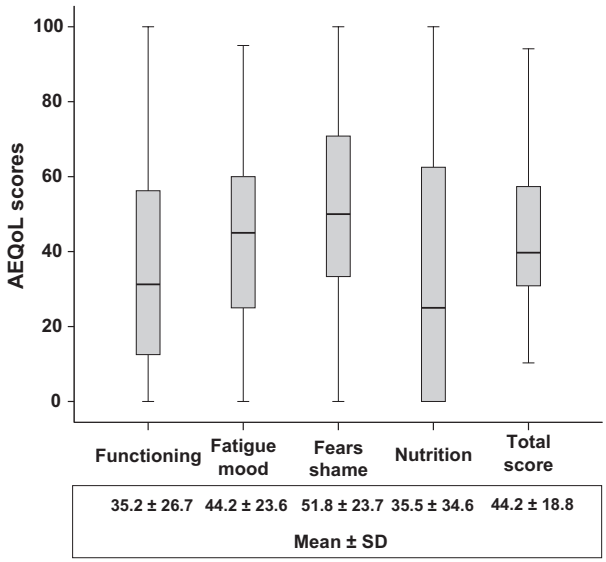

Figure 1 Results of the AE-QoL. Box and whisker plots show the distribution of the AE-QoL scores in the population. (The bottom and top of the box represent the 25th and 75th percentile, the band near the middle of the box represents the median, and the ends of the whiskers represent the minimum and maximum values.) In addition, the mean values ± SD of each domain score and of the total score are shown. The higher the values of the domain and the total score, the higher the impairment.

correlations with the SF-36 are negative, because, in contrast to AE-QoL, lower scores in this instrument represent a stronger QoL impairment.

Known-groups validity

Known-groups validity was tested by investigating whether the AE-QoL was able to discriminate between patients who showed differences in self-rated disease activity and QoL. Using the ANOVA trend test, a statistically significant linearity was found between increasing AE-QoL total scores and increasing levels of self-rated angioedema activity ($P < 0.001$) and QoL impairment ($P < 0.001$) (Table 7). Notably, the AE-QoL total score showed a particularly good linearity with the disease activities and QoL impairments self-rated from 'mild' to 'severe'. However, no sufficient discriminative ability was seen between the categories 'none' and 'mild' as well as 'severe' and 'very severe'.

Test–retest reliability

The AE-QoL domain scores and the AE-QoL total score were compared in a subsample of 46 patients who completed the questionnaire twice in an interval of three weeks (Table 8). No meaningful differences could be detected. The interclass correlation coefficients were > 0.70 for 'Functioning', 'Fears/Shame', 'Food' as well as for the AE-QoL total score, indicating good reproducibility. Only the coefficient for 'Sleep/Mood' was slightly lower ($r = 0.68$).

Multiple linear regression analysis

Multiple linear regression analysis was performed to identify drivers of QoL impairment in angioedema patients. This revealed that gender ($P < 0.05$) as well as the patients' self-rated disease activity ($P < 0.001$) was significant predictors of the AE-QoL total score (women and patients with a higher disease activity showed higher AE-QoL values). In terms of the AE-QoL domain scores, disease activity affected all domains ('Functioning' $P < 0.001$, 'Sleep/Mood' $P < 0.001$, 'Fears/Shame' $P < 0.005$, 'Food' $P < 0.05$), while gender was only a predictor of 'Sleep/Mood' ($P < 0.05$). Age predicted neither the AE-QoL total score nor any of the AE-QoL domain scores.

Discussion

Recurrent angioedema is a frequent clinical problem that causes a high disease burden. Currently, clinical research is mired by the lack of appropriate and validated outcome instruments. Here, we report the first validated specific instrument to measure health-related QoL impairment in patients with recurrent angioedema (AE-QoL). AE-QoL is easy to administer (self-administered questionnaire), and its completion takes less than 5 min. It may serve as a valuable

Table 5 Convergent validity of the AE-QoL. Correlations were computed between the AE-QoL scores and the DLQI scores. The results are expressed as Pearson correlation coefficients

	AE-QoL domains				
DLQI headings	Functioning	Fatigue mood	Fears shame	Food	AE-QoL total score
Symptoms and feelings	0.103	0.195*	0.235*	0.110	0.235*
Daily activities	0.317**	0.245*	0.217*	0.267*	0.328**
Leisure	0.388***	0.238**	0.366***	0.219*	0.447***
Work and school	0.402***	0.243*	0.233*	0.117	0.336***
Personal relationships	0.357***	0.317**	0.345***	0.267*	0.439***
Treatment	0.339**	0.192*	0.343***	0.247*	0.380***
Total score	0.443***	0.377***	0.403***	0.309**	0.535***

*$P < 0.05$, **$P < 0.005$, ***$P < 0.001$.

Table 6 Convergent validity of the AE-QoL. Correlations were computed between the AE-QoL scores and the SF-36 scores. The results are expressed as Pearson correlation coefficients

	AE-QoL domains				
SF-36 domains	Functioning	Fatigue mood	Fears shame	Food	AE-QoL total score
Physical function	−0.366***	−0.277**	−0.101	−0.107	−0.301**
Role limitation (Physical)	−0.467***	−0.267**	−0.154	0.018	−0.327**
Bodily pain	−0.520***	−0.279**	−0.204*	−0.151	−0.397***
General health	−0.218*	−0.344***	−0.308**	−0.187	−0.355***
Vitality	−0.498***	−0.596***	−0.340***	−0.116	−0.551***
Social function	−0.547***	−0.469***	−0.403***	−0.275**	−0.588***
Role limitation (Emotional)	−0.357***	−0.458***	−0.348***	−0.304**	−0.503***
Mental health	−0.392***	−0.570***	−0.504***	−0.249**	−0.617***
Physical component summary	−0.466***	−0.189	−0.031	0.011	−0.235*
Mental component summary	−0.375***	−0.587***	−0.525***	−0.345***	−0.680***

*$P < 0.05$, **$P < 0.005$, ***$P < 0.001$.

Table 7 Known-groups validity. The results are expressed as AE-QoL total score in relation to the patients self-rated QoL impairment and self-rated disease activity

Patients self-rated disease activity and QoL impairment*		*n*	AE-QoL total score (mean ± SD)	Minimum	Maximum
Disease activity	None	9	29.6 ± 15.8	10.3	51.6
	Mild	29	31.4 ± 13.2	11.8	67.7
	Moderate	36	47.7 ± 15.6	14.7	83.8
	Severe	26	55.8 ± 18.1	23.5	83.3
	Very severe	9	53.0 ± 20.9	25.0	94.1
QoL impairment	None	7	29.6 ± 15.8	10.3	51.6
	Mild	27	31.4 ± 14.3	10.3	67.7
	Moderate	44	44.4 ± 14.8	19.1	79.4
	Severe	24	56.5. ± 18.4	20.6	83.3
	Very severe	7	64.4. ± 17.7	50.0	94.1

*During the previous 4 weeks.

Table 8 Test–retest results in a subsample of 46 angioedema patients. Patients completed the AE-QoL twice at a distance of three weeks. The subsample consisted of 15 patients with recurrent angioedema because of C1-INH deficiency, 22 patients with urticaria and angioedema and nine patients with recurrent angioedema without urticaria/C1-INH deficiency

AE-QoL domains	Mean score ± SD First assessment	Mean score ± SD Second assessment	Inter class coefficient
Functioning	24.5 ± 22.2 (*n* = 44)	25.5 ± 21.1 (*n* = 45)	0.78
Fatigue/Mood	44.0 ± 21.8 (*n* = 46)	44.2 ± 17.9 (*n* = 46)	0.68
Fears/Shame	45.0 ± 23.5 (*n* = 46)	48.1 ± 21.7 (*n* = 46)	0.84
Food	34.2 ± 32.9 (*n* = 46)	39.7 ± 34.7 (*n* = 45)	0.90
Total Score	39.0 ± 16.4 (*n* = 46)	40.8 ± 13.5 (*n* = 46)	0.83

instrument for future clinical studies but also for routine patient care. It may also help to better characterize affected patients as well as to aid treatment decisions.

Measuring health-related QoL impairment is a comprehensive way of determining and monitoring disease burden (4). In contrast to just scoring disease symptoms, it assesses the impact of diseases on different aspects of the patient's life. In other words, it is a more holistic approach to find out how patients are actually doing with their disease, how they feel, and which aspects of their everyday life are impaired by their symptoms. The detection of health-related QoL is particularly important and useful in disorders with suddenly appearing, transient attacks such as in asthma, epilepsy, and also recurrent angioedema. Symptoms may be infrequent in these

diseases, but patients can, nevertheless, suffer tremendously because of the unpredictability, the visibility, and the life-threatening nature of attacks.

Although leading health authorities have recommended the use of patient-reported outcomes, such as health-related QoL impairment, to measure benefit of therapy in clinical studies for years (19, 20), there is still a lack of suitable instruments to do so. Generic tools such as the SF-36 lack sufficient specificity and sensitivity, because they omit or carry items that are relevant or not relevant for different disorders. Disease-specific health-related QoL instruments are much better suited to detect the real extent and pattern of QoL impairment as well as to detect QoL changes, for example during treatment.

Considerable research activities during recent years have helped to improve our understanding of recurrent angioedema because of C1-INH deficiency, and important new therapeutic strategies have become available (21–26). Future studies in this field will need to compare different HAE therapies as well as different treatment strategies such as prophylaxis *vs* on-demand therapy or combinations of both. Currently, only based on clinical experience, it has been suggested to consider long-term prophylaxis when patients, despite optimized on-demand treatment of angioedema attacks, continuously experience more than 12 moderate-to-severe attacks per year or more than 24 days per year affected by HAE (27). In addition, future studies will need to compare different subgroups of hereditary angioedema such as HAE1&2 *vs* HAE type 3. For these trials, appropriate angioedema-specific patient reported outcome instruments such as health-related QoL measures are required.

Recurrent angioedema is a frequent symptom of csU patients. Nevertheless, csU patients with recurrent angioedema are often excluded from the participation in clinical trials. A major reason for this is that the current validated and recommended outcome instruments for csU, the Urticaria Activity Score (UAS) (28, 29), and CU-Q_2oL (9, 10) do not or only insufficiently consider angioedema. Accordingly, many of the current studies in csU do not fully represent the entire csU population, and there is, as of yet, no sufficient information on the impact of angioedema on disease burden of csU patients.

Idiopathic angioedema, that is, angioedema without wheals or bradykinin-mediated angioedema, remains ill identified, not only in terms of the underlying causes and pathogenic pathways, but also regarding its prevalence, course, prognosis, subtypes, disease burden, and possible treatment options.

Taken together, there are shortcomings in the understanding of all subforms of recurrent angioedema, and there is a clear need for new and valuable outcome measures to enable further research. AE-QoL could facilitate the studies that need to be carried out and may help to better characterize and compare angioedema patient subgroups, and to develop new and/or better treatment options.

For AE-QoL, we decided to choose a recall period of 4 weeks. To minimize a recall bias, it is generally advisable to select a recall interval that is as short as possible, while balancing recall bias and respondent burden (30). While some health-related QoL instruments apply recall periods of only one or two weeks, disorders with relatively rare yet salient events, such as recurrent angioedema, may be best assessed using longer recall intervals. No single recall period will fit all applications; thus, it is recommended that a variety of factors such as saliency, frequency of occurrence, and respondent burden should be considered for choosing the optimal observation period to optimize data quality and completeness (30). Our decision for a 4-week recall period is backed by other well-established health-related quality of life instruments such as the SF-36 that successfully apply the same time period.

Limitations of this work include that the study sample was relatively small. However, the results of the impact analysis and the factor analysis were found to be convincing. In addition, a minimum sample size of five subjects per item for factor analysis has been suggested (31). Because 19 items were included, the development of AE-QoL needed a minimum of 95 patients. Thus, the sample size was at least satisfactory. A second limitation might be that this work was performed in two specialized centers in Germany but not in populations of other levels of care (primary and secondary care) and other cultural backgrounds. This most probably has led to a selection bias. While this is primarily important for the results obtained by the instrument (extent of QoL impairment measured in the observed population), this should be far less important for the validation of the instrument. A third limitation that should be considered is that AE-QoL was not tested for responsiveness (sensitivity to change) and for its minimal important difference. Further studies are needed to determine these properties of AE-QoL. In addition, the translation of AE-QoL into different languages together with cross-cultural validation studies are needed to enable the multinational application of this instrument as well as to detect regional differences in angioedema-specific QoL impairment. Finally, it is important to recognize that the included study population did not comprise children and adolescents. Therefore, AE-QoL is currently only validated for adults.

In conclusion, the AE-QoL is a valid and reliable instrument to assess the symptom-specific health-related QoL impairment in patients suffering from recurrent angioedema. It is the first angioedema-specific QoL instrument, and it will not only help to improve the quality and performance of clinical studies, but also to trigger further angioedema research in general, which is strongly needed.

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Author contributions

K. Weller substantially contributed to the conception and design, acquisition of data, analysis and interpretation of data, drafted the article, and given final approval of the version to be published. *A. Groffik, K. Krause, M. Metz, and P. Staubach* substantially contributed to the acquisition and interpretation of data, reviewed the article critically for important intellectual content, and given final approval of the version to be published. *M. Magerl and N. Tohme* substantially contributed to the conception and design, acquisition and interpretation of data, reviewed the article critically for important intellectual content, and given final approval of the version to be published. *P. Martus and M. Maurer* substantially contributed to the conception and design, analysis and interpretation of data; reviewed the article critically for important intellectual content, and given final approval of the version to be published.

Conflict of interest

None of the authors declare that they have conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 AE-QoL – validated German version.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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