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The Angioedema Quality of Life Questionnaire (AE-QoL) – assessment of sensitivity to change and minimal clinically important difference

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angioedema; minimal clinically important difference; quality of life; responsivity; sensitivity to change.

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Abstract

Background: The Angioedema Quality of Life Questionnaire (AE-QoL) has recently been developed and validated as the first specific patient-reported outcome tool to assess quality of life (QoL) impairment in recurrent angioedema patients. As of yet, its sensitivity to change and minimal clinically important difference (MCID) have not been established.
Methods: Recurrent angioedema patients with chronic spontaneous urticaria or hereditary angioedema were repeatedly asked to complete the AE-QoL along with the SF-12 and other anchors for QoL impairment and disease activity during routine care visits. The sensitivity to change of AE-QoL was determined by correlating changes in its scores over time with changes in the applied anchors. In addition, the MCID was determined using anchor-based and distributional criterion-based approaches.
Results: Two hundred and seventy-eight patients contributed data sets for analysis. Baseline AE-QoL values were found to correlate well with SF-12 results as well as all other applied anchors for angioedema-related QoL impairment and disease activity. In addition, AE-QoL score changes over time correlated significantly with changes in the above anchors, thus demonstrating its sensitivity to change. The MCID of the AE-QoL total score was found to be six points.
Conclusion: The AE-QoL is a valuable tool to assess changes of QoL impairment in recurrent angioedema patients over time, including changes due to treatment.

Recurrent angioedema (RA) is a frequent problem in the field of dermatology, allergology, otolaryngology and emergency medicine. It is characterized by repeated, sudden and unexpected swellings of deeper cutaneous and mucosal tissues (1). RA may occur as a sign of chronic spontaneous urticaria, of C1-inhibitor deficiency (hereditary angioedema – HAE), or as a side effect of ACE-inhibitor treatment (2). All types of RA may occur in the face; additional predilection sites include the tongue, upper airways, and the gastrointestinal tract (3).

RA is commonly associated with a high burden of disease and needs to be treated effectively (4). This has several reasons: one major feature of RA is the unpredictability and the rapid onset of attacks (5). Depending on the size, duration and location, angioedema may be painful, disfiguring, disabling and even life-threatening in case of upper airway swelling (6). The occurrence of angioedema markedly impacts daily activities, free time and social relations. Also, patients with RA exhibit high rates of absenteeism, missing school and/or work days (6). The psychosocial impact of RA is considerable. Patients constantly fear the appearance of new angioedema attacks and are unable to make or keep plans

Abbreviations
AAS, Angioedema Activity Score; AE-QoL, Angioedema Quality of Life Questionnaire; CSU, chronic spontaneous urticaria; HAE, hereditary angioedema; MCID, minimal clinically important difference; PGA, patients global assessment; PRO, patient-reported outcome; QoL, quality of life; RA, recurrent angioedema; SD, standard deviation; SF-12, 12-Item Short Form Health Survey.

(6). Many feel forced to avoid travelling, certain hobbies or social opportunities and consequently feel that their relationships suffer (6).

Recently, we developed and validated the Angioedema Quality of Life Questionnaire (AE-QoL) as the first specific patient-reported outcome (PRO) tool to assess quality of life (QoL) impairment in RA-affected patients (5). The AE-QoL exhibits good levels of internal consistency, convergent and known-groups validity as well as test–retest reliability (5).

An important property of PRO instruments such as the AE-QoL is their ability to determine changes over time, for example before and after treatment adjustment. However, as of yet, the sensitivity to change of AE-QoL has not been studied. In addition, the interpretation of AE-QoL score changes is difficult, because it is unclear which score changes are really meaningful to the patients, that is the minimal clinically important difference (MCID) of AE-QoL remains unknown.

To close this gap, we determined the ability of AE-QoL to assess changes during the course of disease as well as the MCID by applying anchor-based and distributional criterion-based approaches.

Methods

Patient population

Consecutive patients with RA due to CSU or HAE treated at the Department of Dermatology and Allergy of the Charité – Universitätsmedizin Berlin or the Department of Dermatology of the University Medical Center Mainz were asked to complete the AE-QoL along with other PRO tools during several successive routine care visits. In total, 278 patients (70.5% female) were included in this analysis, with a mean age of 47.8 ± 16.5 (median: 48) years. No selection of patients was performed.

Patient-reported outcome tools

Angioedema Quality of Life Questionnaire

The Angioedema Quality of Life Questionnaire (AE-QoL) is the first angioedema-specific, valid and reliable HR-QoL questionnaire (5). It can be used in all patients with RA, that is histamine-mediated RA (e.g. RA in CSU) and bradykinin-mediated RA (e.g. HAE). The AE-QoL consists of 17 questions with five answers each and has a recall period of 4 weeks. A total score can be computed over all questions, but it is also possible to apply the AE-QoL as a profile instrument by grouping the questions into four domains ('Functioning', 'Fatigue/Mood', 'Fears/Shame' and 'Food') and calculating the individual domain scores. After computation of raw scores, these are transformed to a linear 0–100 scale with higher scores indicative of a higher QoL impairment. Linguistically validated versions of AE-QoL are available for several languages (among other for American English, Canadian English, Canadian French, Danish, Dutch, French, German, Greek, Hungarian, Italian, Japanese, Mexican-Spanish, Polish, Portuguese, Romanian, Russian, Spanish and Swedish) and free for use in routine patient care as well as in noncommercial investigator-driven research projects (7).

Patients' global self-assessment of disease activity and QoL impairment

Along with the AE-QoL, all patients were asked to globally self-rate their angioedema disease activity (PGA disease activity) as well as their angioedema-related QoL impairment (PGA-QoL) during the past 4 weeks on a 4-point Likert scale (answer options: 'none', 'mild', 'moderate' and 'severe'). In addition, they reported the frequency of their angioedema attacks during the past 4 weeks (answer options: 'none', '1–2 attacks', '3–4 attacks', 'more than 4 attacks' and 'attacks almost every day').

12-Item Short Form Health Survey

The 12-Item Short Form Health Survey (SF-12) is a generic instrument originally developed for the Medical Outcomes Study (MOS) that examined patients with chronic conditions. The SF-12 contains 12 questions and is a widely used, validated short version of the SF-36. Its results are displayed as a Physical Composite Summary (PCS) and a Mental Composite Summary (MCS) ranging from 0 to 100 points with higher scores representing a better level of health (8).

Data analysis

Convergent validity of AE-QoL

Convergent validity tests whether a questionnaire measures what it is intended to measure. The convergent validity of AE-QoL was determined by correlating its scores (rank correlation with calculation of Spearman's *rho*) with the results of the SF-12, PGA-QoL and PGA disease activity. According to Cohen's conventions, a correlation coefficient of 0.1–0.3 was considered as weak correlation, 0.3–0.5 as moderate correlation and >0.5 as large correlation (9).

Sensitivity to change

Sensitivity to change is the ability of a PRO to measure change in the patient's disease status, regardless of whether this change is relevant or meaningful. To assess the sensitivity to change of the AE-QoL, we computed the rank correlation coefficient (Spearman's *rho*) for AE-QoL score changes between two different time points with changes in the PGA-QoL, SF-12 PCS and MCS, and PGA disease activity covering identical time periods.

Responsiveness and minimal clinically important difference

Responsiveness is the ability of an instrument to determine meaningful (clinically important) changes in the patient's disease status over time. It is an essential property of PROs that are applied repetitively and is commonly reported through the minimal clinically important difference (MCID). A change equal to or higher than the MCID can be considered a clinically meaningful change.

To determine the MCID of the AE-QoL, we applied different approaches, anchor-based and distributional criterion methods, as described previously (10–12). The anchor-based approaches were applied by computing the mean intra-

Table 1 Convergent validity of AE-QoL (baseline measurements). AE-QoL scores correlate with the results of the applied anchors (the results of the rank correlation are presented with the correlation coefficient Spearman's *rho*). A coefficient of 0.1–0.3 was considered as weak correlation, 0.3–0.5 as moderate correlation and >0.5 as large correlation

		AE-QoL domain scores			
	AE-QoL total score	Functioning	Fatigue/Mood	Fears/Shame	Food
PGA-QoL	0.753	0.752	0.574	0.564	0.339
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
	$n = 272$	$n = 260$	$n = 272$	$n = 270$	$n = 272$
SF-12 PCS	−0.470	−0.501	−0.412	−0.298	−0.218
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.01$
	$n = 220$	$n = 213$	$n = 220$	$n = 218$	$n = 220$
SF-12 MCS	−0.507	−0.427	−0.478	−0.414	−0.153
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.05$
	$n = 220$	$n = 213$	$n = 220$	$n = 218$	$n = 220$
PGA-disease activity	0.628	0.684	0.474	0.423	0.321
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
	$n = 271$	$n = 259$	$n = 271$	$n = 269$	$n = 271$

AE-QoL, Angioedema Quality of Life Questionnaire; PGA-QoL, patients' global assessment of their angioedema-related QoL impairment; PGA disease activity, patients' global assessment of their disease activity, SF-12 PCS, SF-12 Physical Health Composite Score; SF-12 MCS, SF-12 Mental Health Composite Score.

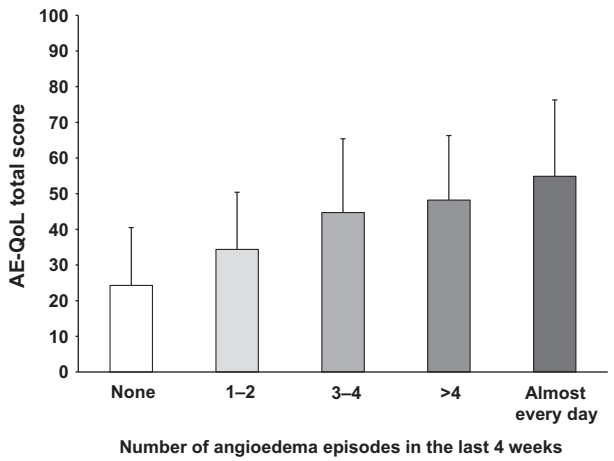

Figure 1 AE-QoL total scores increase with increasing angioedema frequency. The exact mean AE-QoL total score values ±SD are 24.2 ± 16.2 for 'none' ($n = 69$), 34.4 ± 16.0 for '1–2' ($n = 58$), 44.7 ± 20.7 for '3–4' ($n = 50$), 48.2 ± 18.1 for '>4' ($n = 43$), and 54.9 ± 21.4 for 'almost every day' ($n = 39$).

individual differences of AE-QoL total scores between assessments with different PGA-QoL ratings (defined as a change of one step in the PGA-QoL, e.g. from moderate to mild or moderate to severe). In addition, the intra-individual variation of AE-QoL total score values in case of stable disease (unchanged PGA-QoL rating) was analysed by computing the median and various percentiles. Finally, the PGA-QoL ratings were used to perform a receiver operating characteristic (ROC) curve analysis to identify the best cut-off point for clinically meaningful changes in the AE-QoL total score. For this analysis, patients were categorized as subjects with a changed QoL impairment (defined as at least one-step change in their PGA-QoL rating, e.g. from moderate to mild or from moderate to severe) and subjects with an unchanged QoL impairment (defined as unchanged PGA-QoL rating).

The distributional criterion approach was based on the finding that one-half of the SD (13) of an instrument's results may represent a good approximation of its MCID. Accordingly, the SD of all baseline AE-QoL total score values was computed and subsequently divided by two.

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics version 22, IBM Corporation, Armonk, New York, USA). The statistical methods applied are described at the respective methods and/or results section of this manuscript. $P \leq 0.05$ was considered as statistically significant.

Results

Confirmation of the convergent validity of the AE-QoL

Baseline AE-QoL values for each paired data set are shown in Figure S1. These were found to well correlate with the SF-12 Physical Composite Summary (PCS) and Mental Composite Summary (MCS), with PGA-QoL and with PGA disease activity, thus confirming the good convergent validity of the AE-QoL (Table 1). In line with these results, the AE-QoL total scores were also found to correlate significantly with the frequency of angioedema attacks ($r = 0.52$, $P < 0.001$), that is to be higher in patients with higher frequency of attacks (Fig. 1). For a total of 259 patients, the frequency of angioedema was available in addition to the AE-QoL total score. Of these subjects, 69 patients (27%) did not develop angioedema during the 4-week recall period of the AE-QoL, while the other 190 patients (73%) exhibited at least one angioedema attack.

Table 2 Changes in HRQoL impairment and disease activity correlate with changes in AE-QoL total and domain scores (the results of the rank correlation are presented with the correlation coefficient Spearman's *rho*). A coefficient of 0.1–0.3 was considered as weak correlation, 0.3–0.5 as moderate correlation and >0.5 as large correlation

	AE-QoL total score change	AE-QoL domain score changes			
		Functioning	Fatigue/Mood	Fears/Shame	Food
PGA-QoL change	0.489	0.592	0.366	0.231	0.252
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.01$
	$n = 112$	$n = 107$	$n = 112$	$n = 109$	$n = 112$
SF-12 PCS change	−0.262	−0.233	−0.089	−0.182	−0.033
	$P < 0.05$	$P = 0.060$	$P = 0.465$	$P = 0.138$	$P = 0.789$
	$n = 70$	$n = 66$	$n = 70$	$n = 68$	$n = 70$
SF-12 MCS change	−0.290	−0.273	−0.389	−0.184	−0.010
	$P < 0.05$	$P \leq 0.05$	$P < 0.01$	$P = 0.133$	$P = 0.932$
	$n = 70$	$n = 66$	$n = 70$	$n = 68$	$n = 70$
PGA-disease activity change	0.391	0.416	0.251	0.261	0.139
	$P < 0.001$	$P < 0.001$	$P = 0.01$	$P < 0.01$	$P = 0.150$
	$n = 109$	$n = 103$	$n = 109$	$n = 105$	$n = 109$

AE-QoL, Angioedema Quality of Life Questionnaire; PGA-QoL, patients' global assessment of their angioedema-related QoL impairment; PGA disease activity, patients' global assessment of their disease activity, SF-12 PCS, SF-12 Physical Health Composite Score; SF-12 MCS, SF-12 Mental Health Composite Score.

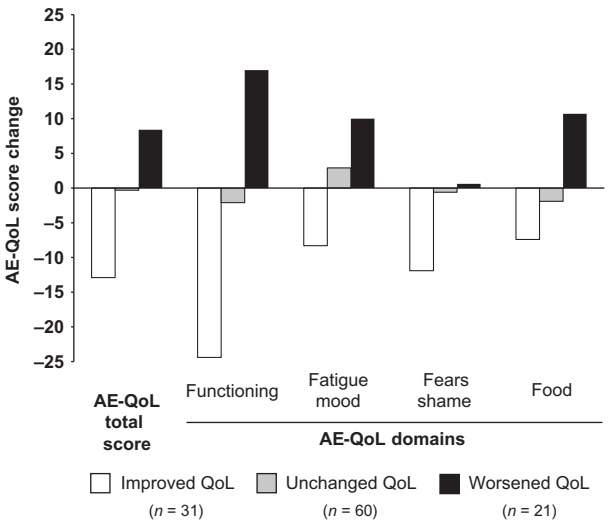

Figure 2 AE-QoL total scores change with changes in angioedema-related QoL impairment (PGA-QoL). Angioedema-related QoL impairment was considered to be 'improved' when the PGA-QoL improved by one step or more (e.g. from severe to moderate or from moderate to mild) between the baseline and follow-up evaluation, 'unchanged' when the PGA-QoL remained stable and 'worsened' when the PGA-QoL worsened by one step or more (e.g. from moderate to severe or from mild to moderate) between the baseline and follow-up evaluation.

The AE-QoL is sensitive to changes in HRQoL impairment

AE-QoL total score changes over time correlated significantly with changes in the PGA-QoL and changes in the PGA disease activity (Table 2). In addition, AE-QoL total score changes correlated with changes in the SF-12 PCS and MCS, thus demonstrating the AE-QoL's sensitivity to change. Notably, the magnitude of the correlations between changes in the different AE-QoL domains and changes in the anchors were different. While large correlations were found with changes in the AE-QoL 'Functioning' domain ($r > 0.5$), only moderate correlations were detected for changes in the domain 'Fatigue/Mood' and low correlations ($r < 0.3$) for the domains 'Fears/Shame' and 'Nutrition'. This indicates that the 'Functioning' domain has the best sensitivity to change, whereas the other domains are less responsive. The mean changes of the AE-QoL scores in relation to changed or unchanged PGA-QoL are displayed in Fig. 2.

Minimal clinically important difference of the AE-QoL

The MCID of AE-QoL was determined by applying anchor-based and distribution criterion-based approaches:

Anchor-based approaches

In a first step, the mean intra-individual differences of AE-QoL scores between phases of different levels of HR-QoL impairment (PGA-QoL) were computed (Table 3). The mean AE-QoL total score change ±SD was −12.5 ± 16.5 (median: −12.5) points in case of a one-step PGA-QoL improvement and 6.3 ± 12.4 (median: 6.5) points in case of a one-step PGA-QoL worsening. In a second step, the AE-QoL score changes were computed for patients with stable, unchanged PGA-QoL ratings (Table S3). Here, the mean AE-QoL total score change ±SD was found to be −0.3 ± 12.6 (median: 0) points, with an interquartile range of 11.8 points, ranging from −5.8 to 6 points.

As a second anchor-based method to determine the MCID of the AE-QoL total score, ROC curve analysis was applied in order to identify the best cut-off point for meaningful changes in the AE-QoL total score by using the PGA-QoL

Table 3 Magnitude of AE-QoL score changes (mean ± SD) during improved or worsened angioedema-related QoL impairment (in case of one-step change in the PGA-QoL, e.g. from severe to moderate, moderate to mild or mild to no impairment)

		AE-QoL domain score changes			
	AE-QoL Total Score change	Functioning	Fatigue/Mood	Fears/Shame	Food
Improved PGA-QoL by one step	−12.5 ± 16.5 Median: −12.5 *n* = 26	−23.0 ± 24.1 Median: −19.0 *n* = 25	−8.7 ± 16.5 Median: −10.0 *n* = 26	−10.3 ± 20.9 Median: −8.0 *n* = 25	−9.3 ± 23.4 Median: 0.0 *n* = 26
Unchanged PGA-QoL	−0.3 ± 12.6 Median: 0.0 *n* = 60	−2.1 ± 20.3 Median: 0.0 *n* = 58	2.9 ± 14.7 Median:0.0 *n* = 60	−0.6 ± 15.1 Median: 0.0 *n* = 58	−1.9 ± 22.8 Median: 0.0 *n* = 60
Worsened PGA-QoL by one step	6.3 ± 12.4 Median: 6.5 *n* = 18	15.5 ± 19.7 Median: 13.0 *n* = 17	10.8 ± 14.6 Median: 5.0 *n* = 18	−4.0 ± 18.9 Median: 0.0 *n* = 18	7.6 ± 12.3 Median: 0.0 *n* = 18

AE-QoL, Angioedema Quality of Life Questionnaire; PGA-QoL, patients' global assessment of their angioedema-related QoL impairment; SD, standard deviation.

as an anchor. The cut-off point with the best balance of sensitivity and specificity was found to be −5.5 points for QoL improvement (Table 4, Fig. S2a) and +5.5 points for QoL worsening (Table 5, Fig. S2b).

Distributional criterion approach

For the distributional criterion approach, the SD of all baseline AE-QoL total score values (20.9, see also Figure 1) was divided by two based on the finding of the remarkable universality of half a standard deviation as a good approximation of the MCID (13). Accordingly, a MCID of 10.5 points results for the AE-QoL total score from this approach.

Discussion

The angioedema-specific HR-QoL instrument AE-QoL is validated (5), widely used in clinical trials and practice, available in many languages (7), and recommended by current guidelines (2). Here we report, for the first time, sensitivity to change and responsiveness of the AE-QoL as well as its MCID. We show that the AE-QoL is suited to assess response to treatment, and we confirm its value for measuring HR-QoL impairment, that is its convergent validity.

RA is known to place a considerable burden on the life of patients and their families. In line with earlier results of the validation study (5), we found that AE-QoL scores correlate well with anchor instruments that measure HRQoL impairment and disease activity. Notably, the AE-QoL total score was linked to angioedema attack rates. However, at an angioedema frequency of more than four attacks per 4 weeks, the AE-QoL total score increase flattens, suggesting that the angioedema-related QoL impairment reaches a plateau when the number of angioedema exceeds a critical attack rate. This is important to consider when comparing patient groups with different levels of disease activity.

Table 4 Performance of the AE-QoL total score at various cut-off values in screening for a meaningful improvement in angioedema-related QoL impairment (improvement in PGA-QoL)*

AE-QoL total score decrease (cut-off value)	Sensitivity (patients correctly classified as PGA-QoL improved) (%)	Specificity (patients correctly classified as PGA-QoL not improved) (%)	Patients totally correctly classified (improved and nonimproved) (%)
−0.5	26/31 (83.9)	46/79 (58.2)	72/110 (65.5)
−1.5	25/31 (80.6)	48/79 (60.8)	73/110 (66.4)
−2.5	24/31 (77.4)	54/79 (68.4)	78/110 (70.9)
−3.5	24/31 (77.4)	56/79 (70.9)	80/110 (72.7)
−4.5	22/31 (71.0)	58/79 (73.4)	80/110 (72.7)
−5.5	20/31 (64.5)	61/79 (77.2)	81/110 (73.6)
−6.5	19/31 (61.3)	63/79 (79.7)	82/110 (74.5)
−8.0	18/31 (58.1)	65/79 (82.3)	83/110 (75.5)
−9.5	17/31 (54.8)	67/79 (84.8)	84/110 (76.3)
−10.5	16/31 (51.6)	69/79 (87.3)	85/110 (77.3)

*For this analysis of AE-QoL total score cut-off values, angioedema-related QoL impairment was categorized as 'improved' and 'not improved'. Angioedema-related QoL impairment was considered 'improved' when the PGA-QoL improved by one step or more (e.g. from severe to moderate or from moderate to mild) between the baseline and follow-up evaluation, whereas it was considered 'not improved' when the PGA-QoL did not change or worsened between the baseline and follow-up evaluation.

Table 5 Performance of the AE-QoL Total Score at various cut-off values in screening for a meaningful worsening in angioedema-related QoL impairment (worsening in PGA-QoL)*

AE-QoL total score increase (cut-off value)	Sensitivity (patients correctly classified as PGA-QoL worsened) (%)	Specificity (patients correctly classified as PGA-QoL not worsened) (%)	Patients totally correctly classified (improved and nonimproved) (%)
0.5	13/21 (61.9)	60/91 (65.9)	73/112 (65.2)
1.5	13/21 (61.9)	62/91 (68.1)	75/112 (67.0)
2.5	13/21 (61.9)	63/91 (69.2)	76/112 (67.9)
3.5	13/21 (61.9)	67/91 (73.6)	80/112 (71.4)
4.5	13/21 (61.9)	68/91 (74.7)	81/112 (72.3)
5.5	13/21 (61.9)	70/91 (76.9)	83/112 (74.1)
6.5	11/21 (52.4)	75/91 (82.4)	86/112 (76.7)
7.5	10/21 (47.6)	77/91 (84.6)	87/112 (77.6)
8.5	9/21 (42.9)	79/91 (86.8)	88/112 (78.6)

*For this analysis of AE-QoL total score cut-off values, angioedema-related QoL impairment was categorized as 'worsened' and 'not worsened'. Angioedema-related QoL impairment was considered 'worsened' when the PGA-QoL fell by one step or more (e.g. from moderate to severe or from mild to moderate) between the baseline and follow-up evaluation, whereas it was considered 'not worsened' when the PGA-QoL did not change or improved between the baseline and follow-up evaluation.

Our results also demonstrate that changes in AE-QoL total scores correlate with changes in the patients' self-rated QoL impairment and disease activity. Notably, the correlations between AE-QoL total score changes and changes in the PGA-QoL were higher as compared to the correlations between AE-QoL total score changes and changes in the PGA disease activity. This was not unexpected, because disease activity and HRQoL impairment represent different concepts. Previous studies have demonstrated that disease activity and HRQoL impairment may only moderately correlate with each other (14, 15). Although disease activity has a major influence on QoL impairment, there are additional drivers of HRQoL impairment in RA patients such as fear of the next attack or passing HAE on to their children, and this reduces the correlation between disease activity and QoL impairment.

The availability of a MCID is critical for the interpretation of results obtained by a PRO instrument. By applying different approaches (anchor-based and distribution criterion-based), we found the MCID of the AE-QoL total score to be 5.5–10.5 points. We clearly favour the anchor-based approach, a more direct and patient-centred method, over the distributional (half-SD) approach. The ROC curve analyses suggest an MCID of 5.5 points for both angioedema-related QoL improvement and QoL worsening. The interquartile range of AE-QoL total score changes in patients with unchanged angioedema-related QoL ranges from −5.8–6 points, that is only 25% of this 'stable' population exhibited AE-QoL total score changes of more than six points in either direction. We, therefore, recommend six points to be used as the MCID for the AE-QoL total score for both, improvement and worsening of angioedema-related QoL impairment. A change of six points in the AE-QoL total score can be regarded as a meaningful change to the patient. A MCID >6 points would go along with a decrease in the sensitivity of correctly classifying patients with improved or worsened QoL. Therefore, an MCID >6 points may be chosen in conservative approaches where the specificity is of much higher importance than the sensitivity.

A limitation of this study is that the numbers of patients who improved or got worse were not large enough to stratify the MCID analysis for different baseline levels of angioedema-related QoL impairment. It has been described by other authors that the absolute values that reflect meaningful change in disease status may be influenced by the starting level (16). Therefore, it cannot be excluded that patients with a low baseline AE-QoL total score may have a lower MCID as compared with patients with a high baseline AE-QoL total score.

In conclusion, the AE-QoL is a valuable tool to measure levels and changes of HRQoL impairment in RA patients and, thus, is a suitable tool for assessing treatment responses. The knowledge of the MCID of six points for improvement and worsening increases the interpretability of its results and further recommends its use in clinical trials and routine patient care.

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Conflict of interest

Karsten Weller, Markus Magerl and Marcus Maurer are scientific advisors for MOXIE, the company holding the copyright for the AE-QoL. All other authors have no conflicts of interest regarding this manuscript.

Author contributions

All authors made substantial contributions to (i) conception and design of or acquisition of data, or analysis and interpretation of data, to (ii) drafting the article or revising it critically for important intellectual content and to (iii) final approval of the version to be published.

Supporting Information

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

Figure S1. AE-QoL baseline results.

Figure S2a. ROC curve. Area under the ROC curve (AUROC) for AE-QoL total score changes related to improvement vs. non-improvement in patients' self-rated angioedema-related QoL impairment (PGA-QoL) = 0.79 (95% confidence interval: 0.69–0.88).

Figure S2b. ROC curve. Area under the ROC curve (AUROC) for AE-QoL total score changes related to worsening vs. non-worsening in patients' self-rated angioedema-related QoL impairment (PGA-QoL) = 0.73 (95% confidence interval: 0.61–0.85).

Table S1. AE-QoL scores remain stable in case of unchanged angioedema-related QoL impairment

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