

Minimal important difference of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)

To the Editor,

Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by the sudden appearance of pruritic wheals, angioedema or both, for a period of at least 6 weeks.¹ CSU is typically associated with a high impact on patients' Health Related Quality of Life (HRQoL)² and needs to be treated effectively.¹ Despite the improvement of CSU pharmacotherapy over recent years, many patients have an unsatisfactory response to the currently available drugs. Moreover, CSU is a disease of long duration and its activity may vary considerably over time. For these reasons, the assessment of HRQoL is important to make decisions about treatment.^{1,3}

The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) is the only validated tool to evaluate disease-specific HRQoL impairment in patients with CSU.⁴ It was originally developed in Italian⁴ and is now available in German, Spanish, Polish, Brazilian-Portuguese, Turkish, Greek, Persian, Thai,⁵ and

Hebrew.⁶ CU-Q2oL has been shown to have the required psychometric properties in terms of construct validity, internal consistency, reliability, and responsiveness in all validated versions. The EAACI/GA²LEN/EDF/WAO guideline for urticaria¹ recommends the use of CU-Q2oL for assessing disease impairment and monitoring response to treatment. Therefore, it is important to understand how changes CU-Q2oL scores are linked to changes in HRQoL impairment and how to interpret the clinical relevance of changes in CU-Q2oL scores associated with disease variability and treatment responses.^{7,8}

Health Related Quality of Life changes over time may be evaluated in two ways: by calculating the mean change difference of scores between treatment and control groups (distribution-based approach) and by determining whether a minimal important difference (MID) has been achieved (anchor-based approach).⁹ The MID is defined as the smallest change in an outcome measure perceived as

GRS score category	No. of patients (%)	Coding for small improvement	Coding for moderate improvement	Coding for significant improvement
-3 = Significant worsening	3 (2.3)	-	-	-
-2 = Moderate worsening	1 (0.8)	-	-	-
-1 = Small worsening	8 (6.1)	-	-	-
0 = No change	29 (22.3)	0	0	0
+1 = Small improvement	40 (30.8)	1	0	0
+2 = Moderate improvement	30 (23.1)	1	1	0
+3 = Significant improvement	19 (14.6)	1	1	1

TABLE 1 Distribution of the answers to the GRS and coding for the ROC analyses

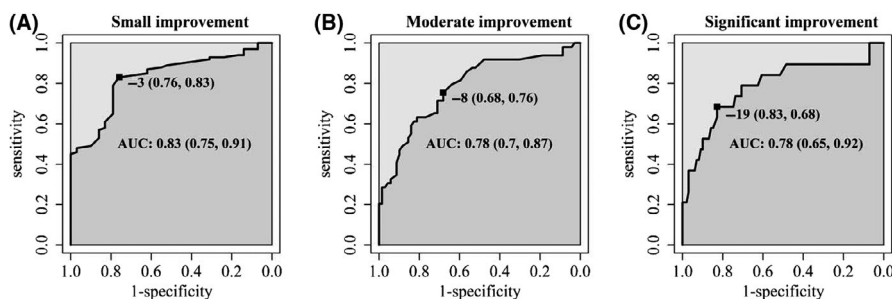


FIGURE 1 ROC curves for CU-Q2oL MID estimation: A, "small improvement", B, "moderate improvement", C, "significant improvement"

beneficial by patients.⁹ This concept evolved as a way to overcome the shortcomings of the “statistically significant difference.”

To date, the absence of a known MID for CU-Q2oL represents a limitation to the interpretation of score changes of this measure for patients, physicians, and researchers. To close this gap, we determined the MID of CU-Q2oL. We investigated 130 consecutive patients who were receiving treatment for CSU (66.7% antihistamine, 4.6% oral corticosteroids, 16.6% antihistamine plus oral corticosteroids, 4.6% antihistamine plus another drug, 7.5% a combination of three drugs) who participated in the CUPP study (Ethics Committee of the University of Genoa, approval no. PR 382REG2014).⁵ This observational study was designed to enroll consecutive adult patients with CSU treated at 13 Italian centers. Patients were assessed at baseline and after 4 weeks. CU-Q2oL was filled at both visits. To determine the CU-Q2oL's MID, an anchor-based approach was applied. To this end, a 7-point Global Rating Scale (GRS) was completed at visit two to evaluate any change in health status: 0 = “no change,” +1 (−1) = “small improvement (worsening),” +2 (−2) = “moderate improvement (worsening),” +3 (−3) = “significant improvement (worsening).”

The MID for small (GRS of 0 vs +1, +2, +3), moderate (GRS of 0, +1 vs +2, +3), and large (GRS of 0, +1, +2, vs +3) improvement was then calculated by applying the receiver operating characteristics (ROC) curve method, using the entire cohort for each dichotomization point in order to maximize precision (Table 1).⁹ The estimated MID was defined as the cut-off point of the CU-Q2oL score difference at which the second diagonal crossed the ROC curves. Sensitivity (Se), specificity (Sp), area under the curve (AUC), and 95% confidence interval for the AUC were calculated. The analyses were performed using R version 3.5.1. The distribution of the answers to the GRS is reported in Table 1.

As expected, changes in CU-Q2oL scores were significantly correlated to GRS scores at visit 2 (Spearman's $\rho = -0.58$, $P < 0.001$; Figure S1), and the correlation was in the expected direction (the higher the improvement detected by GRS, the higher the decrease in the CU-Q2oL score). The MID, that is, the cut-off point for the CU-Q2oL score change with the best balance of sensitivity and specificity for HRQoL improvement was −3 for small improvement (Se = 0.76, Sp = 0.83, AUC = 0.83 [0.75–0.91]), −8 for moderate improvement (Se = 0.68, Sp = 0.76, AUC = 0.78 [0.70–0.87]), and −19 for large improvement (Se = 0.83, Sp = 0.68, AUC = 0.78 [0.65–0.92]; Figure 1).

Our findings provide a better understanding of the clinical relevance of changes in CU-Q2oL scores in patients with CSU. Clinicians and researchers need to be able to determine whether a change in HRQoL is clinically relevant, rather than merely statistically significant. The results of our study enable them to do this.

In the present study, we calculated the MID by applying an anchor-based approach in a cohort of CSU patients from a single country. Future studies should aim to confirm our findings in larger and multinational cohorts of CSU patients, ideally by making use of anchor-based and other approaches. We also need studies that make use of our results to better characterize the link of clinically meaningful changes in QoL impairment with those in disease activity (eg,

assessed by the use of the urticaria score, UAS7) and disease control (eg, assessed by the use of the urticaria control test, UCT).

Taken together, the results of our analyses indicate that a change of at least three points in the CU-Q2oL score is clinically relevant. This will help the assessment of the clinical effectiveness of treatments for CSU and make it possible to interpret the meaning of changes of HRQoL scores, in clinical practice and in clinical trials.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Boxplots of the CU-Q2oL score change by GRS category.

