New evidence for construct validity and interpretability of the German Quality of Life in Hand Eczema Questionnaire (QOLHEQ)

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Abstract
Background: The Quality of Life in Hand Eczema Questionnaire (QOLHEQ) is a disease-specific instrument used to assess health-related quality of life (HRQoL) in patients with hand eczema according to the domains of (a) symptoms, (b) emotions, (c) functioning, and (d) treatment/prevention. Today it is not clear what a single score of the QOLHEQ in its German-language version means to a patient.

Objectives: It was the aim of this study to band the QOLHEQ score to an anchor question (AQ) in order to obtain meaningful categories of the QOLHEQ to aid its interpretation. In addition, we assessed the minimal important change (MIC) by using anchor- and distribution-based methods.

Methods: Overall n = 440 hand eczema patients were included in the study. Mean age was 47.5 years (SD 11.9); 38.4% of the sample were female.

Results: With a weighted kappa of 0.62, the total QOLHEQ score showed the best agreement for the following band: QOLHEQ of <17 = no impairment; QOLHEQ of 18–28 = slight impairment; QOLHEQ of 29–41 = moderate impairment; QOLHEQ of 42–79 = severe impairment; and QOLHEQ of >79 = very severe impairment. The MIC for the total score was found to be 16.5 points.

Conclusion: This banding represents a standardized means of interpreting the QOLHEQ total score. Our results indicate that a banding study should be performed for each language version of the QOLHEQ.

KEYWORDS
hand eczema, health-related quality of life, interpretability, minimal important change, QOLHEQ, smallest detectable change

1 INTRODUCTION

Hand eczema is a frequent chronic disease with multifactorial etiology, often leading to long-term impairment in health-related quality of life (HRQoL) in those affected. The hand plays a special role when interacting with the world around us, not just while working in industry or at home, but also in social interactions with colleagues, friends, or family. Therefore it is not surprising that generic as well as dermatology-specific HRQoL instruments are not sufficient to assess HRQoL impairment in patients with hand eczema. To adequately
assess HRQoL impairment in patients with hand eczema, the Quality of Life in Hand Eczema Questionnaire (QOLHEQ) was developed by an international group involving hand eczema experts and patients from six countries (Australia, Denmark, Finland, Germany, Japan, and Sweden). The development process has been described in detail elsewhere. The QOLHEQ is composed of 30 questions assessing the disease-specific HRQoL of hand eczema patients according to the domains of (a) symptoms, (b) emotions, (c) functioning, and (d) treatment and prevention. The German-, Dutch-, and Japanese-language versions of the QOLHEQ have been shown to be valid, reliable, and responsive measures of HRQoL in patients with hand eczema. In addition, an international validation study was carried out assessing and resolving aspects of differential item functioning (DIF) in order to obtain a cross-culturally valid score by using the various translations of the QOLHEQ. The smallest real difference (SRD) for the QOLHEQ has already been reported, enhancing the interpretation of QOLHEQ score changes.

Although in a Dutch population an interpretability study on the Dutch and international QOLHEQ scoring has already been performed, such a study is lacking for the other language versions. National interpretability studies are necessary to allow for interpretation of data from national and multinational clinical studies or when someone simply wants to compare the meaning of results of clinical studies performed in different countries. The meaning of HRQoL scores as well as the meaning of change-scores are likely to vary between nations. This is true not only for instruments used in dermatology but also for prominent generic HRQoL instruments like the EuroQol (EQ-5D), which has just recently been noted. Therefore it is important to assess the interpretability of scores for each language version of an instrument separately. In accordance with a previously published study protocol concerning the cultural adaption and validation of the QOLHEQ and the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines, it was the aim of this study to identify meaningful categories (bands) for the interpretation of the total QOLHEQ as well as for the subscale scores in a German study population. In addition to generating a valid interpretation of cross-sectional QOLHEQ scores, we also aimed to identify the minimal important change (MIC) for the QOLHEQ to provide evidence as to which change in QOLHEQ score refers to a change in HRQoL that is perceived as important by patients.

2 | METHODS

2.1 | Study population

This study was performed at the occupational section of the University Hospital Heidelberg, Germany, Department of Dermatology. Patients were asked to participate in this study while taking part in a 3-week inpatient rehabilitation program for occupational skin diseases. Most patients presented with chronic hand eczema (duration longer than 3 months, or at least two relapses within 1 year), which was suspected to have an occupational background. Inclusion criteria were active hand eczema within the past week, which was diagnosed by a dermatologist. Patients completed the questionnaire when starting the rehabilitation program, and 3 to 4 weeks later when getting discharged.

2.2 | Study instruments

The QOLHEQ was assessed together with an anchor question for the global score (“How would you rate all the impairments caused by your hand eczema?”) as well as an anchor question for each subscale (a) “How would you rate all the impairments caused by the symptoms of your hand eczema? (eg, pain, fissuring, redness, or bleeding)”, (b) “How would you rate all emotional impairments caused by your hand eczema? (eg, being annoyed, depressed, or anxious about the future)”, (iii) “How would you rate functional impairments caused by your hand eczema? (eg, that you are impaired in daily activities or unable to perform them at all)”, (iv) “How would you rate impairments caused by measures of treatment and prevention? (eg, using creams, wearing gloves, side effects of treatment)”. For all anchor questions the following response options were given: “no”, “mild”, “moderate”, “strong”, or “very strong” impairments caused by symptoms, emotions, functioning, or treatment. In addition, we assessed the demographic data of the patients as well as itch by using a visual analog score (VAS). Severity of the hand eczema was rated by a dermatologist using the Osnabrück Hand Eczema Severity Index (OHSI).

2.3 | Analysis

To find evidence supporting construct validity of the QOLHEQ we assessed correlations between the QOLHEQ and the reference measures using the data of patients at T0. The Spearman correlation coefficient (r) was applied, strong correlation was defined as \( r > 0.7 \), moderate correlation as \( 0.7 > r > 0.4 \), and weak correlation as \( 0.4 > r > 0.2 \). The following hypotheses were formulated a priori:

1. Each anchor question score shows strongest correlation with its corresponding QOLHEQ subscale score (5 hypotheses)
2. All anchor question scores and QOLHEQ subscale scores intercorrelate at least with a moderate effect size (20 hypotheses)
3. OSHI and itch VAS scores show strongest correlation with the QOLHEQ symptoms subscale score (2 hypotheses)

To identify potential severity bands of the QOLHEQ we calculated mean, median, and modus of the anchor questions separately for each score of the QOLHEQ (or its subscales). Whenever one of those measures increased to the next full numeric value, the corresponding
QOLHEQ value was considered as a potential cut-off for categorization. In addition, we determined a set of bands by aiming at building a categorization of the QOLHEQ reflecting the same distribution of patients as gained by the corresponding anchor questions. For each set of bands received using this method we calculated the agreement between the QOLHEQ categorization and the corresponding anchor question using weighted kappa (κ), which was calculated according to Fleiss & Cohen.\textsuperscript{18} For the band with the highest κ-value as well as for all bands within a distance of 0.01 to the highest value, we checked the number of patients where the burden caused by the hand eczema would have been underestimated by using the band (higher impairment reported on the anchor question, than received by using the band). As the final band, the one was chosen where the amount of underestimated patients was the lowest.

The MIC was determined by using two anchor-based methods (a) the mean change in those with an one step increase to the anchor question and (b) by investigating the receiver-operating characteristic (ROC) plot,\textsuperscript{19} with a cut-off chosen at the point where the sum of sensitivity and specificity reaches its maximum. For both approaches, MIC was defined as an one step improvement according to the anchor questions for each QOLHEQ subscale. The QOLHEQ was defined to be responsive if the area under the curve (AUC) was >0.70.\textsuperscript{13,20} No MIC was determined for deterioration, because too few patients showed deterioration during the study period. All anchor questions were deemed to be an appropriate anchor if their correlation with the corresponding QOLHEQ score was >0.5.\textsuperscript{21} As a distribution-based approach for MIC calculation we assessed the smallest detectable change (SDC), which indicates a relevant change beyond measurement error. The SDC was calculated in those patients showing no change according to the anchor questions by using SDC = 1.96 * \sqrt{\text{SEM}}.\textsuperscript{22} All analyses were performed using SPSS Statistic 25 (IBM) and Excel 2010 (Microsoft).

### 3 | RESULTS

#### 3.1 | Sample characteristics

During the study period between January 2016 and April 2019, an overall number of 440 hand eczema patients were included into the study. Follow-up after 3–4 weeks was completed in n = 403 patients (response rate: 91.6%). The proportion of female patients was 38.4%; the mean age of male patients (48.9 years, SD 10.8) was slightly higher compared to female patients (46.0 years, SD 13.2). The OHSI showed a mean value of 2.3 (SD 2.4) and the mean disease duration was 7.1 years (SD 7.7). Only 9.1% of patients had a higher educational degree (Bachelor or higher), whereas 14.1% of the patients reported to have not completed vocational school or technical college. The prevalence of an atopic disease was more than twice as high in female (34.2%) compared to male (14.9%) patients, whereas a hyperkeratotic

| TABLE 1 Sample characteristic of the hand eczema population |
|-------------------------------------------------------------|
| Male (n = 271) | Female (n = 169) | Total (n = 440) |
|----------------|------------------|-----------------|
| Age in years, mean (SD)* | 48.9 (10.8) | 46.0 (13.2) | 47.5 (11.9) |
| (Ex-)smoker, %, (n) | 49.4% (134) | 45.0% (76) | 47.7% (210) |
| High education, %, (n) | 10.3% (28) | 7.1% (12) | 9.1% (40) |
| Disease duration in years, mean (SD) | 6.6 (7.4) | 8.1 (8.2) | 7.1 (7.7) |
| Atopic skin diatheses, %, (n) | 34.7% (94) | 52.1% (182) | 41.1% (182) |
| OHSI\textsuperscript{a} (mean, SD) | 2.4 (2.4) | 1.9 (2.0) | 2.3 (2.4) |
| Itch VAS, mean (SD)* | 4.4 (2.9) | 5.2 (2.8) | 4.7 (2.9) |
| Etiology of hand eczema, % (n) | | | |
| Irritant | 36.0% (87) | 29.8% (48) | 33.5% (135) |
| Allergic | 2.5% (6) | 3.7% (6) | 3.0% (12) |
| Atopic\textsuperscript{*} | 14.9% (36) | 34.2% (55) | 22.6% (91) |
| Vesicular genuine type | 25.2% (61) | 31.1% (50) | 27.5% (111) |
| Hyperkeratotic genuine type\textsuperscript{*} | 26.4% (64) | 16.1% (26) | 22.3% (90) |
| Mixed etiology | 23.6% (57) | 25.5% (41) | 24.3% (98) |
| QOLHEQ\textsuperscript{b} values, mean (SD) | | | |
| Symptoms\textsuperscript{*} | 9.2 (5.2) | 11.0 (5.8) | 9.9 (5.5) |
| Emotions\textsuperscript{*} | 8.3 (6.4) | 10.2 (7.0) | 9.1 (6.7) |
| Functioning\textsuperscript{*} | 8.8 (6.4) | 10.6 (7.2) | 9.5 (6.8) |
| Treatment/prevention | 10.1 (5.3) | 11.2 (5.7) | 10.5 (5.5) |
| Total\textsuperscript{*} | 36.2 (21.2) | 42.1 (23.1) | 38.6 (22.1) |

\textsuperscript{a}Osnabrück hand eczema severity index.

\textsuperscript{b}Quality of Life in Hand Eczema Questionnaire.

\textsuperscript{*}Significant difference (P < .05) between sexes.
type of hand eczema was more prevalent in male patients (male: 26.4% vs. female: 16.1%). Further sample characteristics can be found in Table 1; HRQoL impairment was more pronounced and itch VAS was higher in female compared to male patients.

3.2 | Construct validity of the QOLHEQ

As expected, all anchor questions showed the strongest correlation with the corresponding QOLHEQ subscale; the strongest correlation was found for the emotions subscale ($r = 0.76$). Moreover, the intercorrelations between all anchor questions and QOLHEQ subscales also were of moderate effect size ($0.44 < r < 0.64$). They are shown in Table 2 together with correlation coefficients for itch VAS and OHSI. Although itch VAS showed the strongest correlation with the symptom subscale as expected, this was not true for the OHSI. There the strongest correlation was found for the QOLHEQ functioning subscale, showing only a small effect size ($r = 0.26$).

3.3 | Banding of the QOLHEQ

Because all anchor questions showed a correlation of $r > 0.6$ with the corresponding subscale, they are deemed to be appropriate for anchoring the QOLHEQ. Detailed tables showing a cross-tabulation of the QOLHEQ score with the corresponding anchor question

| TABLE 2 | Correlation matrix for determining construct validity of the QOLHEQ |
|---|---|---|---|---|---|---|---|---|
| | QOLHEQ$^a$ symptoms | QOLHEQ$^a$ emotions | QOLHEQ$^a$ functioning & treatment & prevention | QOLHEQ$^a$ total | OHSI$^b$ | Itch VAS$^c$ |
| Symptoms anchor | Spearman’s rho | .590** | .437** | .533** | .419** | .548** | .194** | .402** |
| | P-value | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 |
| | N | 428 | 427 | 428 | 428 | 428 | 384 | 419 |
| Emotions anchor | Spearman’s rho | .507** | .761** | .579** | .478** | .681** | 0.022 | .350** |
| | P-value | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 |
| | N | 427 | 426 | 427 | 427 | 427 | 384 | 418 |
| Functioning anchor | Spearman’s rho | .533** | .474** | .624** | .449** | .585** | .156** | .325** |
| | P-value | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 |
| | N | 428 | 427 | 428 | 428 | 428 | 384 | 419 |
| Treatment & prevention anchor | Spearman’s rho | .472** | .476** | .469** | .605** | .565** | 0.007 | .294** |
| | P-value | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 |
| | N | 426 | 425 | 426 | 426 | 426 | 383 | 417 |
| Total HRQoL anchor | Spearman’s rho | .537** | .516** | .610** | .524** | .615** | .110** | .372** |
| | P-value | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 |
| | N | 424 | 423 | 424 | 424 | 424 | 380 | 415 |
| OHSI$^b$ | Spearman’s rho | .210** | 0.039 | .239** | 0.057 | .156** | 1000 | .263** |
| | P-value | < .001 | .44 | < .001 | .26 | .002 | < .001 | < .001 |
| | N | 395 | 395 | 396 | 396 | 396 | 396 | 377 |
| Itch VAS$^c$ | Spearman’s rho | .621** | .426** | .426** | .368** | .516** | .263** | 1000 |
| | P-value | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 |
| | N | 420 | 419 | 420 | 420 | 420 | 377 | 420 |

Strong correlation was defined as $r > 0.7$, moderate correlation as $0.7 > r > 0.4$, and weak correlation as $0.4 > r > 0.2$.

$^a$Quality of Life in Hand Eczema Questionnaire.

$^b$Osnabrück Hand Eczema Severity Index.

$^c$Visual Analogue Score.

*p < 0.05

**p < 0.01

Bold values show the strongest effect in this line.
together with mean, median, and mode can be found for each subscale and the QOLHEQ total score as supplemental information to this article (Tables S1–S5). From those tables we retrieved 24 possible bands for the categorization the total score and 5 to 10 bands for each of the four QOLHEQ subscales. Those bands are shown in the online supplement (Tables S1a–S5a) together with weighted κ and the amount of patients where the burden of disease would have been underestimated when using the corresponding band. The final banding chosen for interpreting the total score was 0–17 "none," 18–28 "slight," 29–41 "moderate," 42–79 "strong," and each score higher than 79 as "very strong impairment." This band received a weighted κ of 0.624; by using this banding the burden of diseases was underestimated in 13.3% of the patients compared to their rating on the anchor question. The weighted κ values for the finally selected bands for the QOLHEQ subscales were as follows: (a) symptoms κ = 0.599, (b) emotions κ = 0.758, (c) functioning κ = 0.653, and (d) treatment and prevention κ = 0.575—the range of those bands can be seen in Figure 1. Table 3 shows the HRQoL impairment according to the new QOLHEQ banding for each subscale together with κ-value and amount of patients underestimated. For all subscales the fraction of patients for whom severity would be overestimated by more than one category was <5%. The highest impairment was found on the symptoms subscale where 68.1% of the patients were classified as having a "strong" and 19.1% as having a "very strong" HRQoL impairment in daily life because of symptoms.

### 3.4 | Minimal important change (MIC)

Overall, n = 116 patients reported a minimal improvement of hand eczema according to the anchor question. Those patients reported a mean improvement of 20.9 points on the QOLHEQ total score, which reflects the MIC according to our first approach. According to the

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**FIGURE 1** Categories indicating no, slight, moderate, strong, or very strong impairment for each QOLHEQ domain of the German-language version

**TABLE 3** HRQoL impairment of patients for each QOLHEQ subscale according to the new banding together with the agreement between anchor question and selected band and the amount of patients underestimated by using the banding

| QOLHEQ subscale       | Patients rating of impairment according to new banding | Coefficient of agreement | % of patients underestimated |
|-----------------------|--------------------------------------------------------|--------------------------|-----------------------------|
|                       | Not at all | Slight | Moderate | Strong | Very strong | weighted κ | % of patients underestimated |
| Symptoms              | 6 1.4%   | 12 2.7% | 38 8.7%  | 299 68.1% | 84 19.1% | 0.599 | 14.9% |
| Emotion               | 26 6.1% | 80 18.8% | 111 26.1% | 136 31.9% | 73 17.1% | 0.758 | 20.4% |
| Treatment & Prevention| 19 4.3% | 28 6.4% | 115 26.1% | 234 53.2% | 44 10.0% | 0.575 | 21.0% |
| Functioning           | 5 1.1%   | 59 13.4% | 143 32.5% | 190 43.2% | 43 9.8% | 0.653 | 18.4% |
| Total score           | 16 3.6% | 33 7.5% | 52 11.8% | 269 61.1% | 70 15.9% | 0.624 | 13.3% |

**TABLE 4** Minimal important change values together with smallest detectable change for the QOLHEQ and its subscales

|                      | Total QOLHEQ | symptoms | emotions | functioning | treatment & prevention |
|----------------------|--------------|----------|----------|-------------|------------------------|
| N unchanged          | 116          | 112      | 95       | 93          | 112                    |
| Mean cut-off (SD)    | 20.9 (17.5)  | 6.3 (4.6) | 5.9 (5)  | 5.9 (5)     | 4.6 (4.9)              |
| ROC cut-off (AUC)    | 16.5 (0.73)  | 6.5 (0.74)| 4.5 (0.77)| 4.5 (0.77)  | 4.5 (0.71)             |
| SEM                  | 5.6          | 1.6      | 1.6      | 1.6         | 1.4                    |
| SDC                  | 15.5         | 4.5      | 4.4      | 4.4         | 3.9                    |

*Standard deviation.
*Receiver-operating characteristic.
*Area under the curve.
*Standard error of measurement.
*Smallest detectable change.
second approach (the ROC-based cut-off) the MIC is reflected by a change of 16.5 points of the QOLHEQ total score. Those values are given for the total score and all QOLHEQ subscale together with the SDC in Table 4. The AUC value was >0.7 in all subscales of the QOLHEQ. The SDC, which was calculated in n = 116 patients who reported no change according to the anchor questions, was 15.5 for the QOLHEQ total score.

4 | DISCUSSION

In this study we generated new evidence for the construct validity of the QOLHEQ. We were able to confirm 96.3% of the a priori set hypotheses, an excellent result supporting the construct validity. Only the hypothesis that hand eczema severity (assessed using OHSI) should show strongest correlation with the symptoms subscale of the QOLHEQ was rejected. However, the OHSI did not only show weak associations with the QOLHEQ but also with the anchor questions and the itch VAS, where one would expect an association of at least moderate strength. Besides this, it is known that patient-reported and physician-reported hand eczema severity assessments may sometimes be only poorly correlated.²³

It can be seen as a limitation of our study that it was performed as a single-center study with inpatients only. In most countries patients are treated primarily as outpatients and the proportion of male patients in our sample is higher compared to other studies. However, since we had a well-balanced distribution of hand eczema severity, the categorical distribution of the anchor questions, as well as the response categories may vary slightly in different translations, leading to different observed MIC values. Besides this it is also advised to use multiple independent anchors to confirm responsiveness,¹³ which reflects the fact that slightly varying questions and/or anchor categories can influence the MIC even within one language.²⁴ It is difficult to draft exactly the combination of best questions and response options to assess the smallest change in patients’ HRQoL. To identify the smallest MIC value, researchers have to find the best wording in each language for the anchor question in order to enable the patient to respond appropriately. It is a limitation of our study that we have assessed only one anchor question for each QOLHEQ subscale; however, we suggest that it might overburden a patient to answer several questions about the same topic with only very slight variations in wording at one session. Therefore we provide the exact wording of our anchor questions as a supplemental file to this article, enabling future researchers to perform studies using slightly different anchors. In order not to underestimate the benefit of a therapy given to a patient we suggest use of the MIC showing the lowest value as long as it is higher than the SDC that indicates change above measurement error.

When analyzing HRQoL of hand eczema patients using the QOLHEQ, researchers should use the coding and interpret the data according to the validation and interpretability studies performed in the referenced language version. If a national validation and interpretability study was not yet performed, the international scoring and interpretability cut-offs can be applied. Concerning interpretability, it should be noted that the international banding values have been obtained from a Dutch population only and should get updated in future studies using data from various countries and language versions.

AUTHOR CONTRIBUTIONS
Robert Ofenloch: Conceptualization; data curation; formal analysis; methodology; project administration; supervision; validation; visualization; writing-original draft; writing-review and editing. Elke Weisshaar: Data curation; investigation; project administration; supervision; writing-original draft; writing-review and editing. Christian
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SUPPORTING INFORMATION

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