CLINICAL REPORT

Health-related Quality of Life in Epidermolysis Bullosa: Validation of the Dutch QOLEB Questionnaire and Assessment in the Dutch Population

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Defining the health-related quality of life (HRQoL) in patients suffering from the heritable blistering disease epidermolysis bullosa (EB) is important in assessing the efficacy of new treatments. The quality of life in EB questionnaire (QOLEB) is an English 17-item EB-specific HRQoL measurement tool. The aim of this study was to develop a validated and reliable QOLEB in Dutch and assess the HRQoL in Dutch EB patients. The QOLEB was translated to Dutch according to protocol. Fifty-five adult patients across 4 EB subtypes participated. The QOLEB had excellant correlation with the Skindex-29 ($\rho_s=0.86$), good correlation with the SF-36 physical score ($\rho_s=-0.75$), and moderate correlation with the SF-36 mental score ($\rho_s=-0.43$). The discriminative validity between the 4 different EB subtypes was significant ($p=0.002$). The internal consistency was excellent ($\alpha=0.905$), and the test–retest reliability strong ($\rho_s=0.88$). In conclusion, the Dutch QOLEB is a reliable and valid instrument for the assessment of the HRQoL in adult EB patients. *Key words: epidermolysis bullosa; health-related quality of life; validation; questionnaire; assessment.*

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Epidermolysis bullosa (EB) consists of a spectrum of heritable trauma-induced blistering diseases of skin and mucous membranes (1). Many subtypes exist, and their clinical severity is variable, ranging from an occasional palmoplantar blister to childhood lethality (1). The health-related quality of life (HRQoL) is the impact of a disease on the physical, psychological, and social health of a patient (2). Defining HRQoL in EB patients is important in patient care and management (3). Furthermore, in recent years more focus has been placed on finding specific treatments for EB and measuring HRQoL can help in assessing the efficacy of these new treatment modalities (4, 5). Also, measuring and comparing HRQoL to other diseases can help assign funding to this rather

unknown and rare disorder (4, 6). Measuring HRQoL is complicated by the wide range of phenotypes in EB, which all have their own clinical severity (3). Several studies have focused on qualitatively describing the impact of EB on patients' lives (7–11). Quantitative measurement of HRQoL has been performed using both generic and dermatology-specific instruments in EB patients (6, 12–15). However, due to ceiling effects and content validity issues of these instruments, the accuracy of the measurements is questionable. It has been hypothesised that, especially in the more severe EB subtypes, there has been an overestimation of the HRQoL (3). To overcome these problems, Frew et al. (3) developed and validated an EB-specific HRQoL measurement tool for older children and adults that can be used across all EB subtypes, called the QOLEB (quality of life in EB). Translation of the QOLEB, which was created and validated in English in Australia, to other cultures and languages may provide reliable comparisons of HRQoL in EB and the efficacy of clinical interventions across different countries (3). The aim of this study was to develop a validated and reliable QOLEB in Dutch, and to assess HRQoL in Dutch EB patients.

MATERIALS AND METHODS

This study was performed at the Center for Blistering Diseases at the University Medical Center Groningen, which is the single national referral centre for EB in the Netherlands. Ethical approval was granted by the Medical Ethical Committee of the University Medical Center Groningen in the Netherlands. A signed consent form was obtained from all participating patients.

Study measurement tools

The English QOLEB is a validated and reliable adult EB-specific HRQoL tool consisting of a 17-item questionnaire, and it was developed by 2 of the authors (JWF and DFM) (3). The QOLEB measures 2 factors: functioning (questions 1–7, 9–10, 12–13, 15) and emotions (question 8, 11, 14, 16–17). For each question 4 optional answers exist that are scored from 0 to 3 points, in which a higher score represents a worse HRQoL. The functioning scale ranged from 0–36, the emotions scale from 0–15, and the overall scale from 0–51 points. Recently proposed banding techniques by J.W.F and D.F.M. for the overall severity of the QOLEB score based upon the data reported in the original QOLEB validation are as follows: very mild (0–4 points), mild

(5–9 points), moderate (10–19 points), severe (20–34 points), and very severe (35–51 points) (3).

The Short Form-36 (SF-36) is a 36-item generic HRQoL instrument measuring 8 scales: physical functioning (PF, limitations in physical activities because of health problems), role-physical (RP, limitations in usual role activities because of physical health problems), bodily pain (BP, limitations and severity of pain), general health (GH, perceptions of the general health), vitality (VT, energy and fatigue experienced due to health problems), social functioning (SF, limitations in social activities because of physical or emotional problems), role-emotional (RE, limitations in usual role activities because of emotional problems), and mental health (MH, psychological distress and well-being) (16). Each scale is normalised to scores from 0 to 100 points, in which a higher score represents a better HRQoL (contrary to QOLEB). Two summary scales have been developed: the physical component summary (PCS) and the mental component summary (MCS) (17). The SF-36 has been translated and validated to Dutch, and age-and gender norm values are available for the Dutch population (18).

The Skindex-29 is a 30-item validated and reliable dermatology-specific HRQoL instrument for adults, measuring 3 factors: emotions ($n = 10$), functioning ($n = 12$) and symptoms ($n = 7$) (19–21). Each item can be answered on a 5-point scale ranging from "never" to "all the time", that are scored from 0 to 100 points. A higher score represents a worse HRQoL (similar to QOLEB). The overall Skindex-29 score indicates that the skin disease has very little (<5 points), mild negative (6–17 points), moderate (18–36 points), and severe (>37 points) effect on the HRQoL. Different intervals are used for the domains separately but with the same classification: emotions (<5; 6–24; 25–49; >50), functioning (<3; 4–10; 11–32; >33), and symptoms (<3; 4–10; 11–25; 26–49; and >50 for extremely severe) (22). The Skindex-29 has been translated to Dutch using a standard protocol (12).

Translation of the QOLEB to Dutch

Forward translation of the QOLEB to Dutch was performed by an independent qualified translator. The questionnaire was discussed by experts in EB (W.Y.Y. and M.F.J), who are native speakers in Dutch and fluent in English. There were no conceptual changes made. Content validity was obtained by back-translation to English by a different independent qualified translator to make sure the translated Dutch QOLEB conveys the same meaning as the English QOLEB. The back-translation was assessed by the writers of the manuscript. The Dutch QOLEB is given in Appendix S1[1].

Recruitment and design

From the Dutch EB registry, adult patients across a range of subtypes were included to participate in this study. The patients were classified into 4 main EB subtypes: EB simplex (EBS), junctional EB (JEB), dominant dystrophic EB (DDEB), and recessive dystrophic EB (RDEB). Inclusion criteria were that patients were native speakers of Dutch, and that they had an age of ≥ 18 years. The selected patients received an information letter concerning the design, relevance and main goal of the study. A week after receiving this letter, the patients were given further oral information over the telephone and were invited to participate in the study. The patients that were willing to participate received the first Dutch QOLEB, Skindex-29, and SF-36. They were requested to complete and return these questionnaires. Four weeks after completing the questionnaires, all patients were asked to complete and return the same questionnaires for a second time. When required and possible, data were clarified over the telephone.

Analysis

Floor and ceiling effects for the individual items were considered when $\geq 80\%$ of the participants scored the highest or lowest possible scores in the first QOLEB.

The respondent burden was assessed by the self-reported completion time of the first QOLEB, and was considered brief if <15 min.

The convergent *validity* was assessed by calculating Spearman's rho correlation coefficient (ρ_s) between the overall score of the first QOLEB and the overall score of the Skindex-29, and the MCS and PCS score of the SF-36 (12). A ρ_s of ≥ 0.7 was considered as acceptable, and ≥ 0.8 as excellent. The discriminative validity was calculated between the 4 main EB subtypes using an analysis of variance (ANOVA). A $p < 0.05$ was considered as statistically significant.

The internal consistency and construct validity of the Dutch QOLEB was measured with the Cronbach alpha (α) using the data from the first QOLEB. An α of ≥ 0.7 was considered as acceptable, ≥ 0.8 as good, and ≥ 0.9 as excellent. The degree of test-retest reliability was estimated by ρ_s between the overall scores of the QOLEB questionnaire at the first and second time. A ρ_s of ≥ 0.7 was considered as acceptable, and ≥ 0.8 as excellent.

Mean values and standard deviations (SD) were calculated for the scores of all study measurement tools and compared using ANOVA with a Bonferroni post hoc test comparing between the disease groups. A $p \leq 0.05$ was considered statistically significant.

RESULTS

Study population

As of 1st January 2011, 184 adult EB patients from the Dutch EB Registry met the inclusion criteria and were eligible for participation. We randomly selected 103 patients to be included in the study. Of the 103 patients that were invited by the information letter to participate in the study, 75 patients were willing to co-operate (response rate 73%). The remaining 28 patients did not want to take part in the study or could not be reached by telephone. Of the 75 patients, 55 were included in the study (response rate 73%). The remaining 20 patients were excluded due to unreturned questionnaires or incomplete questionnaires.

The characteristics of the study population and drop outs, split to EB subtype, are shown in Table SI[1]. Of the 55 included patients, 51% were male and 49% were female. The mean age was 47.6 years (SD ± 17.1) with a range of 19–85 years. The distribution among EB types was: EBS 29 (53%), JEB 8 (15%), DDEB 13 (24%), and RDEB 5 (9%) patients. All patients were of Dutch ethnicity, except for one Korean, one Surinamese, and one Turkish patient. All patients were native speakers of Dutch.

Some characteristics of QOLEB

Floor effects were seen in 4 of the 17 items: item 2 (bathing or showering; 82%), item 4 (writing; 84%),

item 5 (eating; 80%), and item 12 (modifying house; 82%). No ceiling effects were present in the 17 items (Table SII[1]).

The respondent burden of time for the QOLEB was brief, with a mean of 8.2 min (SD ± 5).

The results of the validity tests are summarised in Table SIII[1]. The content validity was addressed through the forward-backward translation of the QOLEB to Dutch, which showed no validity issues. The QOLEB correlated well with the SF-36 PCS score ($\rho_s = -0.75$), and extremely well with the Skindex-29 ($\rho_s = 0.86$). Between the SF-36 MCS score and the QOLEB a moderate correlation was seen ($\rho_s = -0.43$). A significant discriminative validity between the 4 different EB subtypes was seen ($p = 0.002$).

The results of the reliability tests are summarised in Table SIII[1]. The QOLEB showed an excellent internal consistency and construct validity ($\alpha = 0.905$). Furthermore, the internal consistency and construct validity in the separate EB subtypes was good to excellent (range $\alpha = 0.85-0.94$). The test–retest reliability of the QOLEB was strong ($\rho_s = 0.88$) after a mean of 57 (SD ± 24) days. Also, the test–retest reliability in the separate EB subtypes was good to excellent (range $\rho_s = 0.82-0.98$).

Assessment of QoL

Dutch QOLEB. The results of the Dutch QOLEB are listed in Table I. Overall, the Dutch QOLEB mean scores were lower than the ones reported in the original QOLEB study, which included more patients ($n = 111$) and more severe EB patients (8 JEB and 16 RDEB) (3). Females had a lower HRQoL than males, although these differences never reached statistical significance. The milder EB subtypes EBS and DDEB both showed a better HRQoL in all scales, compared to the more severe RDEB and JEB. These differences reached a discriminative validity for functioning and overall score, but not for the emotions scale (Table I). According to the categorisation of the overall QOLEB score, the Dutch EBS and DDEB cohorts were mildly affected, and the Dutch JEB and RDEB cohorts were moderately affected. None of the patients were very

severely affected, and only 4% were severely affected (Table II), whereas in the original QOLEB score, several patients with RDEB and JEB were in this range.

The results of the 17 individual QOLEB items are listed in Table SII[1]. EB made 71% of the patients feel frustrated, 36% embarrassed, 31% depressed, 27% uncomfortable, and 51% anxious or worried. EB affected patients in their relationship with their friends (31%) and family (25%), although in most patients only a small effect was noticed. Only 16% of all patients were pain-free, while 9% experienced constant pain. Twenty percent of the patients were affected in their eating ability, and 19% needed some sort of assistance with bathing or showering. Difficulties in writing were especially prominent in RDEB, with 60% of the patients finding it easier to type than write. Almost all patients were affected in their involvement in sports (95%), with 62% needing to avoid some or all sports. Although 49% of all patients were affected at least a little in their ability to move around at home, patients of the JEB and RDEB subtypes were affected most severely. JEB and RDEB patients also had to make the most modifications in their house. Around 38–40% of the JEB and RDEB patients were markedly or severely affected in their ability to move outside their house, and 40% of all EB patients were affected in their ability to go shopping. Of all patients, 33% were financially affected by their EB, and 11% were greatly or severely affected.

Short Form-36

The results of the SF-36 are summarised in Table SIV[1]. EB had a greater impact on the HRQoL in females, although no significant differences were found. On all SF-36 scales except for VT, RE and MCS, JEB and RDEB patients had a lower HRQoL score compared to EBS and DDEB patients, reaching statistical significance in the PF scale between EBS and JEB ($p = 0.025$). In comparison to gender- and age-matched Dutch normative values, all EB subtypes had a lower HRQoL score on the PCS scale, while they were comparable on the MCS scale (Fig. 1). Floor effects were seen in item 3j (limitations in bathing or dressing; 84%), and item 5a (cutting down on the amount of time spent on work or

Table I. *Quality of life in epidermolysis bullosa (EB) questionnaire values by gender and EB subtype*

	n	Functioning (0–36) Mean ± SD	Emotions (0–15) Mean ± SD	Total (0–51) Mean ± SD
All	55	7.3 ± 5.4	2.4 ± 2.0	9.6 ± 6.9
Male	28	7.0 ± 5.1	2.0 ± 1.8	9.0 ± 6.3
Female	27	7.5 ± 5.8	2.7 ± 2.2	10.2 ± 7.5
EB subtype				
EB simplex	29	6.0 ± 4.0	1.9 ± 1.9	7.9 ± 5.3
Junctional EB	8	11.3 ± 5.0	3.9 ± 1.8	15.1 ± 6.4
Dominant dystrophic EB	13	5.2 ± 3.3	2.2 ± 2.0	7.3 ± 5.1
Recessive dystrophic EB	5	13.4 ± 5.4	3.2 ± 2.4	16.6 ± 11.7

Accolades represent a statistical significant difference of $p \leq 0.05$.

Table II. *Banding of the Dutch Quality of life in epidermolysis bullosa (EB) results by EB subtypes*

	EBS n=29 n (%)	JEB n=8 n (%)	DDEB n=13 n (%)	RDEB n=5 n (%)	Total n=55 n (%)
Very mild: 0–4 points	8 (28)	0 (0)	5 (38)	1 (20)	14 (25)
Mild: 5–9 points	12 (41)	1 (13)	2 (15)	1 (20)	16 (29)
Moderate: 10–19 points	8 (28)	6 (75)	6 (46)	3 (60)	23 (42)
Severe: 20–34 points	1 (3)	1 (13)	0 (0)	0 (0)	2 (4)
Very severe: 35–51 points	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

EBS: EB simplex; JEB: junctional EB; DDEB: dominant dystrophic EB; RDEB: recessive dystrophic EB.

other activities due to emotional problems in the last 4 weeks; 84%). There were no ceiling effects.

Skindex-29

The results of the Skindex-29 are shown in Table SV[1]. On all Skindex-29 scales, females had a lower HRQoL score compared to males (no significance). JEB and RDEB had a lower HRQoL score compared to EBS and DDEB in the functioning and symptoms scale, reaching statistical significance in the functioning component between EBS and JEB ($p = 0.022$). RDEB had the best HRQoL on the emotions scale, while JEB had the lowest. There were no observed floor or ceiling effects. According to the Skindex-29 categorisation, EBS, DDEB and RDEB had a moderate effect, while JEB had a severe effect on the HRQoL score. The greatest effect was seen on the symptom scale, in which EBS had a severe effect, and JEB, DDEB, and RDEB had an extremely severe effect on the HRQoL. Analysis of the individual Skindex-29 items, showed that in the symptoms scale, 31% of the patients answered 'often' or 'all the time' to the item "My skin condition burns or stings", 33% to "My skin itches", 31% to "My skin is irritated", 51% to "My skin is sensitive", and 20% to "My skin condition bleeds". When measuring function, 20% of the patients answered 'often' or 'all the time' to the item "My skin condition affects how well I sleep", 22% to "My skin condition interferes with my sex life", and 24% to "My skin condition makes me tired".

DISCUSSION

In this study, we have developed an EB-specific HRQoL measurement tool for Dutch patients by translating and validating the QOLEB into Dutch and Dutch EB population, respectively. A total of 55 adult patients
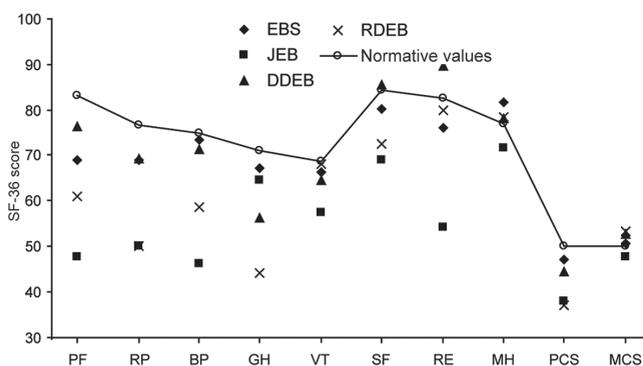

Fig. 1. Epidermolysis bullosa (EB) Short Form-36 scores compared to gender- and age-matched Dutch normative values. EBS: EB simplex; JEB: junctional EB; DDEB: dominant dystrophic EB; RDEB: recessive dystrophic EB; PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary.

across all 4 subtypes (EBS, JEB, DDEB, and RDEB) have participated to test the reliability and validity of the Dutch QOLEB. A weakness of our study is the small sample size for the more severe EB subtypes. Floor effects were present in 4 items, indicating that only a few patients had limitations in bathing/showering, writing, eating and needing to modify their house, suggesting a poor discriminative value for these items. However, the distribution of our patient population, in which 76% suffered from the milder EB (EBS and DDEB), and only 24% from the more severe EB (JEB and RDEB) subtypes, contributed to these floor effects. This might also explain the lack of ceiling effects seen in the SF-36 and Skindex-29. The Dutch QOLEB is a reliable tool, although the high internal consistency ($\alpha = 0.905$) does suggest some item redundancy. However, this was also seen in the validation of the original QOLEB ($\alpha = 0.931$). The Dutch QOLEB appears to be a valid instrument. The assessment of the convergent validity was performed with the Skindex-29 and SF-36, as they have been proven to be the generic and dermatology-specific HRQoL instruments of choice for dermatological diseases (12). A good convergent validity was seen with the Skindex-29 and the physical aspects of the SF-36, but not for the mental aspects of the SF-36. However, we used a standard protocol translated Skindex-29, which is not validated. The DLQI was not chosen to test the convergent validity, as it investigates the effects of parameters "in the past week". As EB is a lifelong disease the impact on the past week is minimal, leading to ceiling effects and content validity issues (3). The discriminative validity was significant ($p = 0.002$), and the Dutch QOLEB was also able to discriminate the severe subtypes RDEB and JEB from the milder subtypes EBS and DDEB. The advantage of the Dutch QOLEB over the Skindex-29 is that in the former differences were seen in the different disease groups, making the Dutch QOLEB a better discriminating questionnaire. In the Dutch QOLEB significant differences were seen on the functioning and overall scale, but not on the emotions scale, suggesting one of 3 explanations: either that the mental burden of EB is similar in milder and more severe subtypes, that patients with more severe EB subtypes have acquired emotional resilience due to the severe impact of living with EB, or that the QOLEB is not appropriate to distinguish between emotions. Such decreased prevalence of emotional burden is also seen with results from a study by Margari et al. (13), who found that 80% of EB patients experienced sub-threshold psychiatric symptoms, in particular depression, anxiety, and behaviour disturbances, but that there was no close correlation between these symptoms and the clinical severity of EB (13). Emotional resilience was not explored by Margari et al. (13) but has been proposed by Frew et al. (3) to explain the lack of consistent quantitative data regarding emotional burden in EB.

A complicating factor in evaluating the discriminative factor in EB is the clinical variety and severity within the 4 major subtypes (1). In our study, many patients with a milder "minor" subtype have been included; 69% of the EBS patients suffered from the milder EBS-loc, 50% of the JEB patients were diagnosed with the less severe JEB-nH loc, 46% of the DDEB patients had the less severe DDEB-pt and DDEB-ac, and only 20% of the RDEB patients suffered from the more severe RDEB-sev gen. This suggests that the HRQoL in our EB cohort might be overestimated.

The results of the HRQoL assessment in our EB population are in concordance with a recent publication of Tabolli et al. (15), who measured the HRQoL of the Italian EB population with different tools, including the Skindex-29 and SF-36. In this study it was concluded that EB has the greatest impact in patients with a higher perceived disease severity, with a larger skin involvement, with a higher psychological distress measured by the General Health Questionnaire-12, and in females (15). The latter was also seen in our cohort, in which females had a lower HRQoL in both the functioning/physical as in the emotional/mental domains measured with the QOLEB, Skindex-29, and SF-36. Similar to our Skindex-29 and SF-36 results, Tabolli et al. (15) showed that patients suffering from JEB and RDEB-sev gen have the lowest HRQoL, but that no statistically significant differences were seen among the various subtypes. This indicates that the Skindex-29 and SF-36 have a poorer discriminative value compared to the QOLEB. In our study population, a greater variation in the SD was seen in the Skindex-29 and SF-36 compared to the QOLEB, which suggests a higher interpersonal variation per subtype in the first 2 questionnaires. Our comparison of the SF-36 values to the normal population are also in concordance with Tabolli et al. (15), in which the PCS scale shows lower values compared to a normal population, while the values in the MCS scale are quite similar to that of the normal population: EB patients overall seem to be as happy (or unhappy) as all other people.

Horn & Tidman (14) assessed the HRQoL of EB patients living in Scotland using the dermatology-specific questionnaire Dermatology Life Quality Index (DLQI) (14). They showed that the impairment in HRQoL in patients with RDEB-sev gen exceeded those of any skin disorder previously assessed. The effects of EBS and other subtypes of DEB were similar to that of moderately severe psoriasis and eczema (14). Comparison of our SF-36 results with other dermatological diseases (Fig. S1[1]) (23–27), shows that on the PCS scale JEB and RDEB have one of the worst recorded HRQoL score, only to be surpassed by psoriatic arthritis (26). EBS has a HRQoL score similar to atopic dermatitis, and DDEB similar to psoriasis (26). On the MCS scale, DDEB and RDEB have the best recorded HRQoL score,

while EBS scores similar to occupational contact dermatitis, and JEB to psoriasis and hand eczema (25, 26). In the comparison of the Skindex-29 results with other dermatological diseases (Fig. S2[1]) (28–34), the effect of EBS is comparable to psoriasis on the functioning and symptoms scale (33). On these scales, RDEB and JEB have the greatest recorded impairments in HRQoL after Hailey-Hailey disease (31). DDEB is only surpassed by Hailey-Hailey disease and pruritus on the symptoms scale (30, 31). In functioning, the effect of DDEB is comparable to cutaneous T-cell lymphoma (29). On the emotions scale RDEB and EBS are similarly affected as urticaria, DDEB as connective tissue diseases, and JEB as psoriasis and lichen planus (33). However, the accuracy of these comparisons might be limited due to the small patient numbers in our JEB and RDEB cohort.

In conclusion, we have shown that the Dutch version of the QOLEB is a reliable, valid, and brief instrument for the assessment of HRQoL in adult EB patients. The responsiveness of the Dutch QOLEB has not been assessed, and future research should be performed to evaluate this. Also, future development and validation of a QOLEB for children would be of great value.

ACKNOWLEDGEMENTS

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