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Improving clinical applications of quality of life scores in epidermolysis bullosa: defining clinically significant outcomes in the QOLEB questionnaire

Epidermolizis bülloza yaşam kalitesi puanlarının klinik uygulamalarının geliştirilmesi: QOLEB anketinde klinik olarak anlamlı sonuçların tanımlanması

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Abstract

Objective The Quality of Life in Epidermolysis Bullosa (QOLEB) score is an Epidermolysis Bullosa (EB) specific quality of life (QoL) measurement tool. It is a statistically valid and reliable questionnaire which has benefits over generic QoL tools in QoL evaluation in EB. It also has important implications in the evaluation of the clinical efficacy of new interventions in EB. The utility of this score would be increased if the clinical relevance of individual scores and changes in QOLEB scores could be further understood.

Methods In order to achieve this, the minimal clinically important difference (MCID) was calculated using both anchor-based and distribution-based techniques. Banding techniques were also applied to the QOLEB questionnaire in order to stratify scores into "very mild", "mild", "moderate", "severe" and "very severe" categories.

Results Using these methodologies, the MCID for the QOLEB score was calculated at a 6 point change in QOLEB scores, and the QOLEB bands were calculated as: 0-4 points for 'very mild', 5-9 points for 'mild', 10-19 points for 'moderate', 20-34 points for 'severe' and 35-51 points for 'very severe' impact on QoL.

Conclusions Calculating the MCID and clinical bands for the QOLEB questionnaire increases the breadth of clinical applications for the QOLEB questionnaire. It now has direct utility in determining the clinical significance of interventions in EB by evaluating changes in QOLEB scores and how they correlate to the MCID and clinical bands.

Key words: *epidermolysis bullosa, quality of life, questionnaire, minumum clinically important difference, genodermatoses*

Özet

Amaç Epidermolizis Bülloza Yaşam Kalitesi Skorlaması (QOLEB), Epidermolizis Bülloza'ya (EB) spesifik bir yaşam kalitesi (QoL) ölçüm aracıdır. QOLEB, EB'de QoL değerlendirmesinde jenerik QoL araçlarına göre üstünlükleri olan, istatistiksel olarak da geçerli ve güvenilir bir ankettir. Ayrıca, EB'deki yeni müdahalelerin klinik etkinliğinin değerlendirilmesinde önemli etkileri vardır. QOLEB içerisindeki bireysel puanların ve değişikliklerin klinik önemlerinin daha iyi anlaşılması durumunda, bu skorlamanın faydası da arttırılacaktır.

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Yöntem Bunu başarmak amacıyla, klinik olarak önemli olan minimum fark (MCID), hem çapa bazlı, hem de dağılım bazlı teknikler kullanılarak hesaplandı. Puanları, "çok hafif", "hafif", "orta", "şiddetli" ve "çok şiddetli" kategorilerine ayırmak için QOLEB anketine bantlama teknikleri de uygulandı.

Bulgular Bu metodolojileri kullanarak, QOLEB skoru için MCID, QOLEB skorlarında 6 puanlık bir değişiklikle hesaplandı. QOLEB bantları şu şekilde hesaplandı: 'çok hafif' için 0-4 puan, 'hafif' için 5-9 puan, "orta" için 10-19 puan, "şiddetli" için 20-34 puan ve "çok şiddetli" için 35-51 puan.

Sonuç QOLEB skorlaması için MCID ve klinik bantların hesaplanması, QOLEB anketinin klinik uygulama genişliğini arttırır. Böylece, QOLEB skorlarındaki değişimi ve bunların MCID ve klinik bantlar ile nasıl korelasyon gösterdiğini değerlendirerek EB'deki müdahalelerin klinik önemini belirlemede doğrudan faydalar sağlamaktadır.

Anahtar kelimeler: *epidermolizis bülloza, yaşam kalitesi, anket, klinik olarak önemli olan minimum fark, genodermatozlar*

Introduction

Epidermolysis Bullosa (EB) consists of a spectrum of genodermatoses characterized by skin fragility and blistering of the skin and mucosa following mild mechanical trauma which carries significant burden on a patient's Quality of Life (QoL).[1]

The QOLEB Questionnaire is an EB-Specific quality of life (QoL) measurement tool which has been statistically proven to be valid and reliable for the assessment of QoL in individuals with EB.[1] It has benefits over and above generic QoL questionnaires which exhibit poor content validity and significant ceiling effects in severe disabling subtypes of EB, which poorly portray the QoL impact this disease has upon individuals.[1] Although this valid patient-based measure allows the accurate quantification of QoL in individuals with EB, the clinical relevance of individual scores, and the clinical significance of difference in scores is poorly understood. The questionnaire would hold increased utility and increase its immediate application to individuals caring for patients with EB if the clinical relevance of its scores were apparent.

The development of new interventions to treat and manage EB requires that an EB-specific QoL questionnaire has a specified definition of what change in scores represents a clinically significant improvement in QoL. Such a clinically meaningful improvement is defined as the minimal clinically important difference (MCID) and for this study we have adopted the definition of MCID as stated by Jaeschke et al as being "the smallest difference in score in the domain of interest which patients would perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in patient management".[2] As EB is a genetic disease with no widely adopted curative therapies, management is largely based upon symptomatic relief of pain, itch and other symptoms, with padded dressings and anti-microbial therapies in order to prevent cutaneous infection which can commonly lead to sepsis, and monitoring for aggressive squamous cell carcinomas (SCC) which are one of the commonest cause of mortality in those individuals surviving beyond infancy.[3] Using the MCID to determine clinical bands of severity, in the style achieved with the Dermatology Life Quality Index (DLQI) by Hongbo et al[4], would help ascribe clinical meaning to the QOLEB scores in terms of mild, moderate or severe impact on QoL. This would have more immediate benefit to clinicians wishing to evaluate the QoL of their EB patients. The development of a MCID in the questionnaire would also set the groundwork for the ongoing development of new interventions and therapies in EB and would enable researchers to evaluate the clinical efficacy of their therapies in a more valid and clinically relevant setting than previously available. Until now, pilot studies of promising therapies have only been able to accurately evaluate the biological impact of their therapies through PCR or ultrastructural characteristics in skin biopsies.[5,6] Unfortunately such changes in skin biopsies have not yet translated into therapies which significantly alter QoL levels in patients and hence provide a tangible improvement in their experience of their disease.

A number of techniques have been used to elicit clinically meaningful change in patient based measurements and some conflict still exists amongst clinical epidemiologists as to which approach is the most valid.[7-9] Two main methodologies exist, anchor-based and distributive based methodologies. Anchor based methodologies are a more qualitative method, using an anchor measurement tool (commonly a general health questionnaire with only 3-5 outcome scores) which is well correlated with the questionnaire under study, to determine the difference in questionnaire scores which are deemed clinically important by the patient.[9] This method can also produce clinical bands which correspond to the anchor ratings, describing mild, moderate and severe impact of disease, as achieved by Hongbo et al.[4] The second type of methodology (distribution based methodology), is more quantitative, and use the variability of a measure (commonly standard error of the mean or SEM) as an indication of clinical importance in a population. Whilst it may be seen as an arbitrary method, it has been extensively used in QoL research[9] and the two methodologies often produce complementary results.[10,11]

This study aims to use both anchor-based and distributive-based techniques to elicit a clinical banding system for the QOLEB questionnaire in order to facilitate clinical interpretation of the QOLEB scores in patients with EB. It will also aim to determine the MCID using a combination of both techniques. The hope is that these clinically significant bands will give clearer interpretation to the QOLEB scores and the MCID give guidance to future use of the QOLEB in determining clinically significant change in the evaluation of treatments and interventions.

Methods

Ethics approval for gathering data for this study was obtained in 2006 from the South Eastern Sydney Health Service[1]

Between 2006 and 2009, 102 individuals over the age of 12 with EB completed the QOLEB questionnaire as well as DLQI questionnaire. These individuals were sourced from hospital based dermatological clinics run by DM and also from DebRA Australia and New Zealand's mailing list. The DLQI was used as an indirect anchor with its previously established severity indices as published by Hongbo et al[4] and the QOLEB questionnaire was the patient based measure of interest. The DLQI was tested against the QOLEB in this cohort to ensure moderate to high correlation using Spearman's correlation coefficient.

The determination of the clinical bands of the QOLEB questionnaire was done separately to the calculation of the MCID. An anchor-based methodology was used for the banding of QOLEB scores as employed by Hongbo et al[4]. Anchor based methodologies were used alongside distribution based methodologies for the calculation of the MCID using similar methods to that of Barnes et al[9] and recommended by Crosby et al.[10] A few adjustments were made to Crosby's methodology in order to take into account the cross sectional nature of the data collected, as no effective interventions currently exist for EB for which pre and post test data may be collected.

Banding methods:

Anchor based banding methods: The results of the DLQI were interpreted in the light of the clinical bands as developed by Hongbo et al.[4] These clinical bands were designated numbers 1 through 5 with 1 indicating the band with no impact and 5 indicating the band indicating extremely large effect on the patient's life. The anchor used for the development of banding in the QOLEB was then based upon these 5 DLQI bands.

A table was then produced collating the individual response scores of the QOLEB alongside the corresponding DLQI anchor bands. The mean median and mode were listed in order to visually determine the most likely cut off points between bands in the QOLEB scores. This data is presented in table 1.

Banding strategies were then proposed based upon the results of the table. Cut off points were selected from the QOLEB scores surrounding areas which showed increase from one band to another. Weighted kappa coefficients of agreement were then used to determine the greatest level of agreement between the banding structure and the DLQI anchor measurements. A selection of these banding propositions are presented in table 2.

Table 1. Number of patients with each QOLEB score with DLQI anchor bands

	DLQI anchor bands								
QOLEB scores	DLQI band 1	DLQI band 2	DLQI band 3	DLQI band 4	DLQI band 5	Mean band	Median band	Mode band	Total number of patients
0	2	0	0	0	0	1	1	1	2
1	1	0	0	0	0	1	1	1	1
2	3	0	0	0	0	1	1	1	3
3	1	0	0	0	0	1	1	1	1
4	5	5	1	0	0	1.45 (1)	2	1 and 2	11
5	2	5	2	0	0	2	2	2	9
6	1	2	1	0	0	1.75 (2)	2	2	4
7	2	6	0	0	0	1.75 (2)	2	2	8
8	0	5	0	0	0	2	2	2	5
9	1	3	0	0	0	1.75 (2)	2	2	4
10	1	2	1	0	0	2	2	2	4
11	0	4	4	0	0	2.5 (3)	2.5 (3)	2 and 3	8
12	0	3	0	0	0	2	2	2	3
13	0	1	4	0	0	2.6 (3)	3	3	5
14	0	0	2	0	0	3	3	3	2
15	0	1	1	0	0	2.5 (3)	2.5 (3)	2 and 3	2
16	0	0	1	0	0	3	3	3	1
17	0	1	0	1	0	3	3	2 and 4	2
18	0	0	2	0	0	3	3	3	2
19	0	0	1	1	0	3.5 (4)	3.5 (4)	3 and 4	2
20	0	1	1	1	1	3.5 (4)	3.5 (4)	2,3,4,5	4
21	0	0	1	2	0	3.67 (4)	4	4	3
22	0	0	0	0	0	0	0	0	0
23	0	0	3	0	0	3	3	3	3
24	0	1	1	0	0	2.5	2.5	2 and 3	2
25	0	0	0	0	0	0	0	0	0
26	0	0	0	1	0	4	4	4	1
27	0	0	0	1	0	4	4	4	1
28	0	0	0	1	0	4	4	4	1
29	0	0	0	0	0	0	0	0	0
30	0	0	0	1	0	4	4	4	1
31	0	0	0	1	0	4	4	4	1
32	0	0	0	1	0	4	4	4	1

Table 1. Continued

	DLQI anchor bands								
QOLEB scores	DLQI band 1	DLQI band 2	DLQI band 3	DLQI band 4	DLQI band 5	Mean band	Median band	Mode band	Total number of patients
33	0	0	0	0	0	0	0	0	0
34	0	0	0	1	1	4.5	4.5	4 and 5	2
35	0	0	0	0	1	5	5	5	1
36	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0
38	0	0	0	0	1	5	5	5	1
39	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0
41	0	0	0	0	1	5	5	5	1
42	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0
Totals	21	41	26	13	4	2.43	2	2	102

MCID methods:

Anchor based MCID methods: The anchors for the MCID methodology were the clinical bands for the DLQI as developed by Hongbo et al.[4] The differences between the average QOLEB scores within these discrete bands, would give an estimate of the MCID. This methodology is employed using longitudinal data in Crosby's proposed methodology[10], and the techniques have been adapted to a cross-sectional methodology for this study. The results are presented in table 3.

Distribution based MCID methods: Crosby et al's recently proposed integrated methodology[10] was also used for the distribution based methodology with the exception of using regression to the mean, due to the cross sectional nature of the data. The standard error of the mean (SEM) was calculated as the measure of variability of the sample for the overall patient population as well as for the subpopulations within individual bands. The inherent reliability of the questionnaire was taken into account through the equations provided in Crosby's methodology[10] and the value of 1.96 times the SEM was used as the MCID. The calculation of individual MCIDs for each clinical band takes into account the wide range of clinical severity of different subtypes of EB. The results of the overall as well as the individual band calculations are presented alongside the anchor based results in table 3.

Table 2. Proposed clinical bands for interpretation of the QOLEB questionnaire

	Band 1	Band 2	Band 3	Band 4	Band 5	Weighted kappa score
Option 1	0-3	4-9	10-19	20-34	35-51	0.63
Option 2	0-4	5-10	11-19	20-34	35-51	0.65
Option 3	0-4	5-9	10-18	19-34	35-51	0.64
Option 4	0-4	5-9	10-19	20-33	34-51	0.64
Option 5	0-4	5-9	10-19	20-34	35-51	0.64

Table 3. MCID results from anchor-based and distributive-based methodologies

	Minimal clinically important difference (MCID) in each cohort				
	Between bands 1 and 2	Between bands 2 and 3	Between bands 3 and 4	Between bands 4 and 5	Total cohort
Anchor based method	5	7	9	13	7.78
Distribution based method	3.55	4.63	6.00	5.95	7.21
Overall MCID	4-5	5-7	6-9	6-13	8

In integrating the differences between the distribution and anchor based methodologies, as employed by Crosby et al[10], the smallest MCID of the two values will be proposed as the MCID for this patient population.

Results

Correlation of DLQI bands to QOLEB:

Spearman Correlation coefficients for the DLQI bands to QOLEB scores was calculated at R^2=0.8 (95% CI=0.73-0.86, t=13.8 p<0.0001). The correlation of individual subtypes varied with R^2 values of 0.77, 0.97, 0.68 and 0.86 for EBS, JEB, DDEB and RDEB respectively. All correlation coefficients had p values <0.0004.

Clinical bands:

As table 2 illustrates, the weighted kappa coefficients show that option 2 provides the highest level of agreement with the dataset (0.65). However, in order for ease of use of the instrument, it was proposed that option 5 be used instead, sacrificing only 0.01 off the kappa in order to promote ease of use. The advantage of the proposed bands below is the ease in remembering that a score of 5 indicates "mild", 10 indicates "moderate" and 20 indicates "severe". This is much more memorable than 5, 11 and 20. The proposed banding structure for the QOLEB Questionnaire is as follows:

- Scores 0-4: Very Mild impact on Quality of Life
- Scores 5-9: Mild impact on Quality of Life
- Scores 10-19: Moderate impact on Quality of Life
- Scores 20-34: Severe impact on Quality of Life
- Scores 35-51: Very Severe impact on Quality of Life

MCID:

Anchor based MCID results: The average QOLEB score difference between Anchor bands is presented in table 3. The differences between bands differed considerably from 5 points (between bands 1 and 2) to 13 points (between bands 4 and 5).

Distribution based MCID results: The overall variability of the data was measured by the SEM which was calculated to be 3.68. The variability between bands 1 and 2; 2 and 3; 3 and 4; and 4 and 5 was 1.82, 2.37, 3.06 and 3.04, respectively. These SEM were multiplied by 1.96 and compiled in table 3 alongside the anchor based results. In line with the adopted methodology, the minimum value was proposed as the MCID for changes between each set of bands. Therefore the overall MCID amongst all subtypes was calculated as an 8 point change in the QOLEB score. Taking into account baseline measurements, the MCID for individuals with very mild or mild QoL impairment may be as low as 4 where as the MCID for moderate to very severe subtypes is a 6 point change in the QOLEB score.

Discussion

In calculating and proposing a clinical banding method and MCIDs for the QOLEB questionnaire, we acknowledge that there is a great difference between meeting the psychometric requirements for developing a questionnaire and having a questionnaire in general clinical acceptance and use. As psychometric methods and analytical techniques are normally not within the expertise of physicians and medical professionals who deal with EB patients, methods such as clinical banding and MCID can help increase the understanding and hopefully encourage widespread clinical use of QOLEB scores in the EB population.

The validity of the anchor based approach is based upon the strong correlation between the DLQI bands and the QOLEB scores. This was demonstrated with a spearman's correlation coefficient of R^2=0.8 (95% CI=0.73-0.86, t=13.8 p<0.0001). There was, however, some variation between the different subtypes of EB, with JEB and RDEB subtypes having the highest degrees of correlation, whereas EBS and DDEB subtypes had lesser correlation coefficients. All subtypes had adequate correlation with all values being above 0.6, the threshold used in the validation of the QOLEB itself.[1] With regards to the distribution-based approach, some authors[7,9] note that the most robust use of this approach is to use measurements of variation such as the SEM which vary little between different sample populations as opposed to other measures such as the standard deviation.[7,9] However these authors also admit that they prefer the anchor based approach over the distribution based approach for its qualitative aspect in ensuring the importance of change to the patient is enshrined in the MCID.[9]

The ability for the banding to be widely adopted through ease of use was also a consideration in choosing option 5 for the banding structure. As also stated by Hongbo et al[4], a memorable banding structure facilitates the use of the questionnaire and ease of clinical interpretation. Hence having the bands begin on multiples of 5 is neater to our base-10 thought processes than option 2 which may provide the highest weighted kappa value. Furthermore, providing this neater option only sacrifices 0.01 in the weighted kappa value, still retaining a high level of agreeability.

This study is not without its limitations and flaws. With some EB subtypes, particularly JEB, the numbers of patients in our cohort were restricted. Overall only 102 patients contributed data to this study, although due to the rarity of EB and the use of semi-qualitative methods we believe that a small sample size has not detracted from the utility and validity of the data generated. The use of DLQI bands as an anchor may be considered inferior to the use of direct GHQ measurements in the study population. We deliberately utilised the DLQI bands as an 'indirect' anchor due to the well known correlation between the QOLEB and DLQI.[1] We are also acutely aware, with the small population of EB patients at our disposal, and the focus on the adult population in this study that questionnaire fatigue is currently a risk in this population, potentially leading to poor response and poor quality data. Collecting and utilising DLQI data as our anchor has enabled us to maximise the amount of high quality data gained, whilst at the same time utilising the indirect anchor method as utilised in previous publications.[9] As shown by our statistical analysis–it has had no detrimental effects on the quality of data and the coherence of our proposals for clinical bands and MCID.

Conclusion

In conclusion we present a proposed banding structure for the QOLB questionnaire for the clinical assessment of QoL in EB populations. Such a banding structure would include scores of 0-4 as very mild impact on QoL; 5-9 as mild impact on QoL; 10-19 as moderate impact on QoL; 20-34 and sever impact on QoL; and 35-51 as very severe impact on QoL. Proposed MCIDs are also calculated dependent upon the baseline QOLEB score prior to intervention, ranging from 4 points in mild disease to 8 points in severe disease. These proposals add further clinical utility to the QOLEB questionnaire as a tool for the evaluation of QoL in EB populations, for use in cross sectional studies as well as for use as clinical evaluation tools for novel interventions for the management of EB.

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