ORIGINAL REPORT

A Cross-sectional Study on Quality of Life in EB: Validation of the Italian QOLEB and Assessment in Italian Patients

Giovanna ZAMBRUNO[1], Tonia SAMELA[2], Andrea DIOCIAIUTI[1], Gudrun SALAMON[3], Sophie STROBL[3,4], Cinzia PILO[5], Damiano ABENI[2], Renata LINERTOVÁ[6], Dedee F. MURRELL[7], May EL HACHEM[1*] and the BUR-EB Study Group

[1]Dermatology Unit and Genodermatosis Research Unit, Translational Pediatrics and Clinical Genetics Research Division, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Laboratory of Clinical Epidemiology, IDI-IRCCS, Rome, Italy, [3]HEALTH Lab, Competence Center for Medical and Health Psychology, Faculty of Psychology, Sigmund Freud University Vienna, Vienna, Austria, [4]Department of Dermatology, Medical Centre, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [5]DEBRA Italy ETS, Milan, Italy, [6]Servicio de Evaluación del Servicio Canario de la Salud (SESCS), Instituto de Investigación Sanitaria de Canarias (IISC), Santa Cruz de Tenerife, Spain, and [7]Department of Dermatology, St George Hospital, Sydney and Faculty of Medicine, University of NSW, Sydney, Australia

Inherited epidermolysis bullosa comprises a heterogeneous group of skin fragility diseases, presenting with a range of manifestations and complications that profoundly affect quality of life (QoL). A disease-specific instrument, Quality of Life in EB (QOLEB), has been developed to assess the impact of epidermolysis bullosa signs and symptoms on QoL. The aim of this cross-sectional study, conducted as part of a European project – BUR-EB, was to test the psychometric properties of the Italian version of the QOLEB and to assess QoL in Italian epidermolysis bullosa patients. Demographic, clinical, and QOLEB data of 56 Italian patients aged ≥11 years participating in the BUR-EB online survey were analysed. Principal component analysis showed excellent internal consistency of Italian QOLEB, and high convergent validity with the generic questionnaire EQ-5D. About 40% of patients reported severe to very severe disease burden, and a strong correlation was observed between disease severity and QOLEB scores. Independent variables associated with worse QoL were pain, chronic wounds, wheelchair use and patient organization membership. Our study confirms the good psychometric properties of the Italian QOLEB. In addition to depicting the major impact of epidermolysis bullosa on QoL, it identifies pain, chronic wounds and functional disability as major targets for therapeutic interventions.

Key words: Epidermolysis bullosa; health-related quality of life; pain; patient-reported outcome measure; symptom burden; female.

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Corr: May El Hachem, Dermatology Unit, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00165, Rome, Italy. Email: may.elhachem@opbg.net

SIGNIFICANCE

Epidermolysis bullosa is a rare inherited disease characterized by lifelong skin blistering. Affected individuals can develop multiple complications that impact on quality of life. This study aimed to validate the Italian version of an epidermolysis bullosa-specific quality of life questionnaire and to evaluate quality of life of people affected by epidermolysis bullosa in Italy. Data were obtained from a European online survey. In addition to confirming the validity of the Italian pidermolysis bullosa-specific quality of life questionnaire, findings show high impact of epidermolysis bullosa and strong correlation between clinical severity and worse quality of life, with a major influence of pain, chronic wounds, wheelchair use and patient organization membership.

Inherited epidermolysis bullosa (EB) comprises a heterogeneous group of rare mucocutaneous blistering disorders due to defective epithelial adhesion (1, 2). Four major types are distinguished based on the level of blister formation: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB) (1, 2). Each type can present with a spectrum of clinical manifestations; in particular, EBS, JEB and DEB are classified as localized or generalized major subtypes. Disease complications include chronic wounds, recurrent infections, hand and foot deformities, joint contractures, oesophageal strictures, anaemia, malnutrition, failure to thrive and growth delay, and aggressive squamous cell carcinomas (SCC) (2). In addition, almost all patients experience both acute and chronic pain, often of considerable severity, and frequently report itching (2, 3).

Despite the recent approval of the first topical drug and gene therapies for EB wounds (4), no systemic curative treatment is yet available. In addition, EB manifestations can alter the physical appearance and affect the self-perception of patients. Overall, disease manifestations, care, and direct and indirect healthcare costs strongly impact patient quality of life (QoL) (2).

While validated specialty-specific instruments for assessing the QoL of dermatology patients are available, the development of disease-specific questionnaires remains highly valuable (5, 6). These tools, which focus on a single disease or a group of related

conditions, are designed to capture specific disease signs and symptoms and their impact on QoL, thereby aiding in the evaluation of therapeutic interventions (7). Disease-specific measurement instruments are valuable in chronic and complex diseases, like EB (8).

The "Quality of Life in Epidermolysis Bullosa" (QOLEB) questionnaire (9) has been the most widely used disease-specific tool to assess QoL in EB (8, 10). Over time, QOLEB validated translations in several languages have been developed (11–18). An Italian version has been recently pilot-tested (19). The goal of the present study is to test the psychometric properties of the Italian version of the QOLEB and to assess QoL in Italian EB patients.

MATERIALS AND METHODS

Setting, study design and sample

This is a cross-sectional study conducted as part of the BUR-EB (Changes in the Socio-economic Burden of Epidermolysis Bullosa in Europe) project, aimed to quantify health-related QoL and socio-economic impact of EB on patients and families in Europe (20). The study, developed in collaboration with patients' associations (DEBRA International and national DEBRAs), was administered as an online survey across 7 European countries. In addition, printed questionnaires were available in reference centres. For Italy, the research was approved by the Institutional Ethical Committee of Bambino Gesù Children's Hospital (OPBG). The survey was translated and culturally adapted in Italian. It was advertised via social media, national patients' association, reference centres and directly to patients attending OPBG Rare Skin Disease centre. The survey was accessible between May and November 2024. Due to the rarity of EB, no formal sample size calculation was performed. The study sample was determined by the number of patients available and willing to participate, aiming to include as many participants as possible, a well-established approach in rare disease research (21).

Participants were eligible for the study if they had a confirmed diagnosis of EB, independently of age. Adult participants provided consent via an online form, minors aged ≥4 years provided informed assent.

Data collection

Self-reported data collection comprised socio-demographic and clinical information, including EB type/subtype and presence/absence of 15 EB signs and symptoms (**Tables I** and SI). For the present study, a clinical severity score was calculated by summing one point for the presence of each EB symptom.

The survey comprised standardized health-related generic (i.e. EQ-5D-5L for adults, EQ-5D-Y for minors), and disease-specific (QOLEB for patients≥11 years old) assessment tools.

Table I. Sociodemographic characteristics, epidermolysis bullosa (EB) major type and subtype of Italian EB survey respondents

Variable	Number	Percentage
Sex		
Male	20	35.7
Female	36	64.3
Age		
11–18 years	17	30.4
18–30 years	14	25.0
>31 years	25	44.6
Distance (km)[a]		
<100	29	51.8
101–200	8	14.3
>200	19	33.9
Education[b]		
Primary	1	2.6
High school	22	56.4
University	16	41.0
Marital status[b]		
Single	24	61.5
Married/cohabiting	14	35.9
Other	1	2.6
Family history		
No	47	83.9
Yes	9	16.1
Caregiver		
No	19	33.9
Yes	37	66.1
Caregiver type		
Parent	31	83.8
Other family member	4	10.8
Professional	2	5.4
Patients" association member		
No	34	60.7
Yes	22	39.3
EB type		
EB simplex	13	23.2
Junctional EB	9	16.1
Dystrophic EB	31	55.4
Kindler EB	3	5.3
EB subtype[c]		
Localized	13	27.7
Generalized	34	72.3

[a]Distance between reference centre and patient home; [b]referred to the adult EB individuals; [c]total varies due to 9 missing values.

The online survey data have been downloaded and processed by the BUR-EB coordinating centre which provided the participant centres their set of national data. Data curation was performed by the Austrian study team. Only datasets with complete sociodemographic and clinical data and QOLEB were included.

QOLEB and EQ-5D questionnaires

In its original form, the QOLEB is a self-reported assessment tool conceived for all EB types, composed of 17 items, each scored on a 4-point Likert scale (9). The total score ranges from 0 to 51 and can be further interpreted using clinical bands to classify the disease impact (22). In addition, it can be subdivided into 2 broad subscales: a "Functioning subscale" evaluating physical impact and an "Emotions subscale" that addresses the psychological impact (9). The original QOLEB is validated for patients ≥11 years old (9).

In addition, the general health-related QoL of adult and minor respondents was assessed by the EQ-5D-5L and EQ-5D-Y, respectively, that evaluate 5 health dimensions (23). The combination of the responses under each dimension describes a person's health state, called EQ-5D profile. A scoring system which uses country-specific value sets, based on representative samples of the general public, converts profile data to a single number – called health utility or EQ-5D value, that lies on a scale between 1, full health, and 0, a state as bad as being dead.

Study phases

To adapt and validate the original QOLEB scale in its Italian version, we used Beaton's guidelines (24). The evaluation of the psychometric properties of QOLEB is one of the goals of the present study.

Statistical analysis

All variables have been analysed in terms of frequencies and percentages, and means, standard deviations (SD), medians and minimum-maximum values. Cronbach α coefficients were calculated to measure internal consistency (25). The adequacy of the dataset for principal component analysis (PCA) was first assessed using Bartlett Test of Sphericity and the Kaiser–Meyer–Olkin (KMO) measure. A PCA with Varimax rotation was then conducted to identify the underlying factor structure. A scree plot was subsequently generated to better determine the optimal number of components to extract. The instrument's sensitivity was assessed by analysing floor and ceiling effects (26). Finally, convergent validity was evaluated by calculating Spearman ρ between the total QOLEB and its subscales and the EQ-5D value, determined using the validated value sets available for the Italian and Spanish population (27, 28); values of ρ were defined as high (≥0.7), high–moderate (0.61 to 0.69), moderate (0.4 to 0.6), moderate–weak (0.31 to 0.39) or weak (≤0.3) (29).

Then, for each level of the variables of interest, mean (SD) and median (minimum–maximum) values of the QOLEB were computed. Differences were tested using the Mann–Whitney *U* test for 2 groups, and the Kruskal–Wallis 1-way analysis of variance (ANOVA) for 3 or more groups. Such differences were also tested pairwise, for each combination of age-group and EB type.

To allow for a meaningful comparison, the scores of the 2 QOLEB subscales were normalized to 100, and the interaction of such scores with the EB subtype (i.e. localized vs generalized) was explored. The correlation between the disease severity score and patient-reported outcomes was studied using Spearman's correlation coefficient.

To assess the possible independent role of each factor of interest, while controlling for potential confounders, 3 separate multiple linear regression models – for the total score, the Functioning, and the Emotions subscales of the QOLEB – were produced. A backward stepwise selection was used to reach the final regression models: for all 3 outcomes, we started with the same model including all potential predictor variables (as observed in univariate analysis) and iteratively removed the least significant predictor at each step, using the classical stringent criteria of 0.050 for inclusion and 0.100 for removal. All statistical analyses have been performed with the Statistical Package for the Social Sciences (SPSS), version 28.0.0.

RESULTS

Study population

Tables I and SI summarize the sociodemographic and clinical data of 56 Italian EB patients, aged≥11 years. Seventeen patients (30.4%) were minors, 14 (25.0%) were aged between 18 and 30 years, and the remaining 25 (44.6%) were aged ≥31. Most respondents were females (*N*=36, 64.3%, female/male ratio=1.8). The majority of respondents (*N*=37, 66.1%) had a caregiver, mainly a parent (*N*=31, 83.8%). As to the EB type, more than half of the respondents (*N*=31, 55.4%) were affected with DEB, 9 (16.1%) with JEB, 13 (23.2%) with EBS and 3 (5.3%) with KEB. In addition, 34 (72.3%) had generalized EB. Twenty-two respondents (39.3%) were members of a patients' association. Interestingly about half of patients with DEB and JEB (54.8% and 44.4%, respectively) were members, compared to only 1 of 13 patients with EBS (7.7%). In addition to blisters and crusts, the most common clinical characteristics reported by participants were atrophic scars (*N*=37, 66.1%), itch (*N*=40, 71.4%) and pain (*N*=35, 62.5%) (Table SI). About half of the patients reported mucosal involvement (*N*=30, 53.6%) and functional disability (*N*=29, 51.8%). Less frequent but severe disease manifestations included chronic wounds (*N*=24, 42.9%), joint deformities (*N*=19, 33.9%), tooth loss (*N*=19, 33.9%), malnutrition (*N*=20, 35.7%), need for oesophageal dilation and gastrostomy tube use (*N*=20, 35.7%, *N*=6, 10.7%, respectively) and SCC development (*N*=10, 17.9%). Wheelchair use was reported by 11 patients (19.6%).

QOLEB psychometric properties

Initial analysis confirmed the dataset suitability for PCA. Bartlett Test of Sphericity was significant ($p<0.001$), indicating that the items were sufficiently correlated for factor analysis, and KMO measure was 0.84, which is above the recommended threshold of 0.60. The overall internal consistency of the

initial 17 items was excellent, with a Cronbach α of 0.93. A PCA with Varimax rotation was conducted to identify the underlying factor structure. The scree plot showed a sharp drop in eigenvalues after the second factor, suggesting a 2-component solution (Fig. S1). This 2-component structure was extracted using an eigenvalue greater than one as the criterion. The 2 components collectively explained 61.55% of the total variance. A total variance >60% indicates that the 2 components are a robust representation of the underlying relationships between the questionnaire items. The Varimax rotation, chosen for its ability to simplify the factor structure and allow for direct comparison with the original study, confirmed a 2-component model. After rotation, the first component explained 31.92% of the variance, and the second 29.63%. The 2 identified components were (*i*) the Emotions subscale, including items related to feelings, emotions and psychological well-being, and (*ii*) the Functioning subscale that encompasses items concerning functioning and daily activities. Both subscales showed excellent internal consistency, with a Cronbach's alpha of 0.91 and 0.90, respectively.

In our analysis, the items QOLEB-3 (physical pain), QOLEB-9 (ability to move outside home), QOLEB-10 (family relationships) and QOLEB-15 (financial burden) showed significant cross-loadings, meaning that they were related to both components, Functioning and Emotions (Table SII). It was decided to maintain these items in the Functioning subscale for content-related reasons and to ensure comparability with the original questionnaire, facilitating cross-cultural comparisons with previously validated national QOLEB versions, which have adhered to the original structure (11–18).

Spearman ρ showed high convergent validity between the total QOLEB score and the generic EQ-5D both for adults and minors (ρ=-0.761 and -0.885, respectively). The QOLEB Functioning and Emotions subscales revealed a high-moderate to high correlation with the EQ-5D for the child version (ρ=−0.919; -0.680), and a moderate-weak to high for the adult one (ρ=−0.832; −0.387), respectively.

Sensitivity analysis revealed potential floor and ceiling effects (Table SIII). A significant floor effect was observed for the majority of the items, most notably for QOLEB-12 (need for home modifications, 67.9%), QOLEB-4 (ability to write, 60.7%) and QOLEB-2 (ability to bath/shower, 55.4%), indicating that a substantial portion of this sample reported no impact in these areas. Conversely, a ceiling effect was identified for QOLEB-2 (25.0%) and QOLEB-7 (involvement in sports, 19.6%), suggesting that these activities represent major challenges for a significant subgroup of patients.

Assessment of QoL

In our study population, the mean total score of the QOLEB was 17.5±10.8, with mean score for Functioning subscale of 12.0±8.1, and for Emotions subscale of 5.5±3.8. According to QOLEB banding criteria (22), 16 (28.6%) patients reported a very mild to mild disease impact on QoL (score between 0 and 9), 18 (32.1%) a moderate impact (score between 10 and 19), and 22 (39.3%) scored >20 points indicating a severe to very severe disease burden (**Table II**). As to the EB type, 16 out of 31 (51.6%) DEB cases reported a severe to very severe disease impact, while only 1 EBS (7.7%) reported a severe impact on QoL. Overall, statistically significant differences were observed in the total QOLEB and Functioning, but not Emotions, subscale scores according to different EB major types (**Table III**). In particular, looking at pairwise comparisons, significantly higher scores were observed for total QOLEB and Functioning subscale for DEB versus EBS (p=0.001 and 0.002, respectively) and for JEB vs EBS (p=0.025 and 0.036, respectively).

As to EB subtype, 15 out of 34 (44.2%) generalized forms reported a severe to very severe QoL alteration, while only 2 out of 13 (15.4%) localized EB had severe burden (Table II). Overall, patients with localized EB reported a less severe impact on QOLEB Functioning score compared to those with generalized EB (mean 7.1±4.6 vs 13.3±8.6, p=0.022) (Table III). The normalized mean scores of the 2 subscales were plotted against the EB subtypes, revealing an effect modification of the latter variable: the Functioning mean scores increased dramatically from localized to generalized EB (p=0.019), while the Emotions

Table II. Quality of life in epidermolysis bullosa (QOLEB) total score: banding by EB type and subtype

	Very mild *N* (%)	Mild *N* (%)	Moderate *N* (%)	Severe *N* (%)	Very severe *N* (%)	Total *N* (%)
EB simplex	2 (15.4)	6 (46.1)	4 (30.8)	1 (7.7)	0 (0)	13 (23.2)
Junctional EB	0 (0)	2 (22.3)	3 (33.3)	3 (33.3)	1 (11.1)	9 (16.1)
Dystrophic EB	0 (0)	5 (16.1)	10 (32.3)	10 (32.3)	6 (19.3)	31 (55.3)
Kindler EB	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	3 (5.4)
Total	2 (3.6)	14 (25)	18 (32.1)	15 (26.8)	7 (12.5)	56 (100%)
Localized EB	1 (7.7)	4 (30.8)	6 (46.1)	2 (15.4)	0 (0)	13 (27.7)
Generalized EB	1 (2.9)	8 (23.5)	10 (29.4)	9 (26.5)	6 (17.7)	34 (72.3)
Total[a]	2 (4.5)	12 (25.5)	16 (34.0)	11 (23.4)	6 (12.8)	47 (100%)

QOLEB total score and impact on QoL: very mild= 0-4, mild= 5-9, moderate= 10-19, severe= 20-34, very severe= 35-51 (24).
[a]Total varies due to missing values.

Table III. Associations between Quality of Life in Epidermolysis Bullosa (QOLEB) scores (total, Functioning and Emotions subscales) and clinicodemographic variables

				Total QOLEB score			QOLEB Functioning score			QOLEB Emotions score		
Variable	Level	*N*	%	Mean (SD)	Median(min–max)	*p*-value	Mean (SD)	Median(min–max)	*p*-value	Mean (SD)	Median(min–max)	*p*-value
Overall		56	100.0	17.5 (10.8)	16.0 (0–43)		12.0 (8.1)	10.0 (0–31)		5.5 (3.8)	5.0 (0–14)	
	Males	20	35.7	14.9 (9.9)	11.0 (6-42)		10,8 (7.6)	8.0 (4–31)		4.0 (3.6)	3.0 (0–14)	
Sex	Females	36	64.3	19.0 (11.1)	19.0 (0–43)	0.138	12.7 (8.4)	12.5 (0–30)	0.504	6.4 (3.6)	5.5 (0–13)	**0.007**
	11–17	17	30.3	14.1 (12.0)	9.0 (0–43)		8.9 (8.9)	5.0 (0–30)		5.2 (3.6)	4.0 (0–13)	
	18–30	14	25.0	22.6 (10.6)	23.0 (7–31)		16.5 (7.4)	15.5 (5–31)		6.1 (4.6)	5.0 (0–14)	
Age (years)	≥31	25	44.7	17.1 (9.3)	17.0 (0–38)	**0.039**	11.6 (7.1)	12.0 (0–29)	**0.009**	5.5 (3.5)	5.0 (0–13)	0.815
	Simplex	13	23.2	9.7 (6.9)	8.0 (0–25)		6.2 (4.8)	5.0 (0–15)		3.5 (2.7)	4.0 (0–10)	
	Junctional	9	16.1	19.0 (9.7)	18.0 (7–38)		12.4 (7.8)	12.0 (5–29)		6.6 (3.1)	7.0 (2–10)	
	Dystrophic	31	55.4	20.9 (11.1)	21.0 (6-43)		14.8 (8.2)	14.0 (4–31)		6.1 (4.2)	5.0 (0–14)	
EB type	Kindler	3	5.3	12.7 (8.0)	12.0 (5–21)	**0.009**	7.0 (5.0)	7.0 (2–12)	**0.009**	5.7 (3.1)	5.0 (3–9)	0.182
	Localized	13	27.7	12.2 (7.4)	11.0 (0–26)		7.1 (4.6)	5.0 (0–15)		5.1 (3.1)	4.0 (0–12)	
EB subtype	Generalized	34	72.3	18.8 (11.6)	17.5 (0–43)	0.091	13.3 (8.6)	12.5 (0–31)	**0.022**	5.6 (4.0)	4.5 (0–14)	0.981
Patients' association member	No	34	60.7	12.3 (7.4)	11.0 (0–36)		7.6 (4.8)	7.0 (0–23)		4.6 (3.3)	4.0 (0–13)	
	Yes	22	39.3	25.7 (10.2)	26.0 (8-43)	**<0.001**	18.8 (7.5)	20.0 (5–31)	**<0.001**	6.9 (4.1)	5.5 (0–14)	**0.026**
	No	21	37.5	10.9 (7.4)	9.0 (0–27)		7.2 (6.3)	5.0 (0–23)		3.7 (2.2)	4.0 (0–9)	
Pain	Yes	35	62.5	21.5 (10.6)	21.0 (5-43)	**<0.001**	14.9 (7.7)	13.0 (4–31)	**<0.001**	6.6 (4.1)	5.0 (0–14)	**0.009**
	No	16	28.6	10.7 (8.1)	9.5 (0–37)		6.7 (6.1)	5.0 (0–26)		4.0 (2.4)	4.0 (0–11)	
Itch	Yes	40	71.4	20.3 (10.6)	21.0 (0–43)	**0.001**	14.2 (7.9)	13.0 (0–31)	**<0.001**	6.2 (4.0)	5.0 (0–14)	**0.048**
	No	32	57.1	13.4 (8.4)	10.5 (0–36)		8.8 (6.5)	6.5 (0–23)		4.6 (3.3)	4.0 (0–13)	
Chronic wounds	Yes	24	42.9	23.0 (11.3)	21.5 (5-43)	**<0.001**	16.2 (8.2)	15.0 (5–31)	**<0.001**	6.8 (4.1)	5.5 (0–14)	**0.025**
Mucosal involvement	No	26	46.4	13.2 (9.4)	11.0 (0–42)		8.2 (6.8)	6.0 (0–31)		5.1 (3.3)	4.0 (0–12)	
	Yes	30	53.6	29.3 (10.6)	21.0 (5-43)	**0.004**	15.4 (7.7)	13.5 (4–30)	**<0.001**	5.9 (4.1)	5.0 (0–14)	0.346
	No	36	64.3	13.6 (8.6)	11.0 (0–38)		8.4 (6.1)	6.5 (0–29)		5.2 (3.4)	4.0 (0–13)	
Malnutrition	Yes	20	35.7	24.7 (10.7)	25.5 (5-43)	**<0.001**	18.6 (7.3)	20.5 (5–31)	**<0.001**	6.2 (4.4)	5.0 (0–14)	0.335
	No	37	66.1	13.8 (8.5)	11.0 (0–36)		8.5 (5.7)	7.0 (0–23)		5.3 (3.4)	4.0 (0–13)	
Joint deformities	Yes	19	33.9	24.8 (11.2)	25.0 (5-43)	**<0.001**	18.8 (7.9)	21.0 (4–31)	**<0.001**	6.1 (4.4)	5.0 (0–14)	0.519
Functional disability	No	27	48.2	11.7 (6.1)	10.0 (0–26)		6.7 (3.5)	6.0 (0–14)		5.0 (3.1)	4.0 (0–12)	
	Yes	29	51.8	23.0 (11.4)	23.0 (0–43)	**<0.001**	17.0 (8.0)	18.0 (0–31)	**<0.001**	6.0 (4.3)	5.0 (0–14)	0.310
	No	37	66.1	15.1 (9.9)	11.0 (0–43)		9.9 (7.1)	8.0 (0–30)		5.2 (3.7)	4.0 (0–13)	
Tooth loss	Yes	19	33.9	22.4 (11.0)	23.0 (5-42)	**0.017**	16.2 (8.5)	18.0 (3–31)	**0.010**	6.2 (3.8)	5.0 (0–14)	0.188
	No	45	80.4	15.0 (8.7)	11.0 (0–36)		9.8 (6.1)	8.0 (0–23)		5.3 (3.7)	5.0 (0–14)	
Wheelchair use	Yes	11	19.6	27.8 (12.6)	27.0 (5-43)	**0.003**	21.3 (8.9)	23.0 (5–31)	**<0.001**	6.5 (4.1)	6.0 (0–13)	0.299
	No	50	89.3	16.4 (10.0)	13.0 (0–42)		11.2 (7.6)	9.5 (0–31)		5.3 (3.6)	4.5 (0–14)	
Gastrostomy	Yes	6	10.7	26.8 (13.1)	28.0 (5–43	0.057	19.2 (9.0)	22.5 5–30)	**<0.001**	7.7 (5.0)	7.5 (0–13)	0.519
Esophageal dilatation	No	36	64.3	16.1 (10.0)	13.0 (0–38)		10.5 (7.7)	7.5 (0–29)		5.6 (3.4)	5.0 (0–13)	
	Yes	20	35.7	20.1 (11.9)	18.0 (5-43)	0.205	14.7 (8.4)	13.0 (4–31)	0.060	5.4 (4.5)	5.0 (0–14)	0.850

N, number; P-values <0.05 are in bold.

mean scores, that in localized EB are higher than the Functioning scores, were similar in localized and generalized disease (p=0.699) (**Fig. 1**).

Most patients complained about difficulties in practicing sports (N=50, 89.3%) and moving around outside their home (N=41, 71.4%) as well as some degree of physical pain (N=49, 87.5%) (Table SIII). In addition, 47 patients (83.9%) reported a family financial impact. As to Emotions, the vast majority of patients reported feelings of frustration (N=45, 80.3%), worry or anxiety (N=44, 78.5%), embarrassment (N=42, 74.9%), and being uncomfortable in social life and with friends (N=39, 69.6 %; N=36, 64.3%, respectively). Finally, 34 patients (60.8%) reported some level of depression.

The total QOLEB score was not different between males and females (p=0.138), but the Emotions subscale score was significantly higher for females (mean 6.4 vs 4.0, p=0.007). Moreover, significant differences in total QOLEB and Functioning scores were observed according to age group. In particular, looking at pairwise comparisons, significantly higher scores were seen for total QOLEB and Functioning subscale for respondents aged between 18 and 30 vs those aged<18 (p=0.021 and 0.006, respectively). Finally, membership of a patients' association was strongly associated with worse QoL as shown by total QOLEB (mean 25.7±10.2 vs 12.3±7.4, p<0.001) and Functioning (mean 18.8±7.5 versus 7.6±4.8, p<0.001) scores (Table III).

As to disease symptoms and manifestations, the linear correlation between the total disease severity score and the total QOLEB was strong (ρ 0.647), and highly significant (p<0.001). The correlation with the Functioning subscale score resulted even stronger (ρ 0.751, p<0.001), while that with the Emotions subscale was weak (ρ=0.252) and did not reach statistical significance (p=0.061) (**Fig. 2**). Table III reports the statistically significant associations between presence of single EB manifestations and symptoms and the QOLEB total and subscale scores. In particular, pain and pruritus were significantly associated with worse QoL, as attested by higher total QOLEB and both subscale scores. In a similar way, higher QOLEB total, Functioning and Emotions scores were observed in the presence of chronic wounds. The following

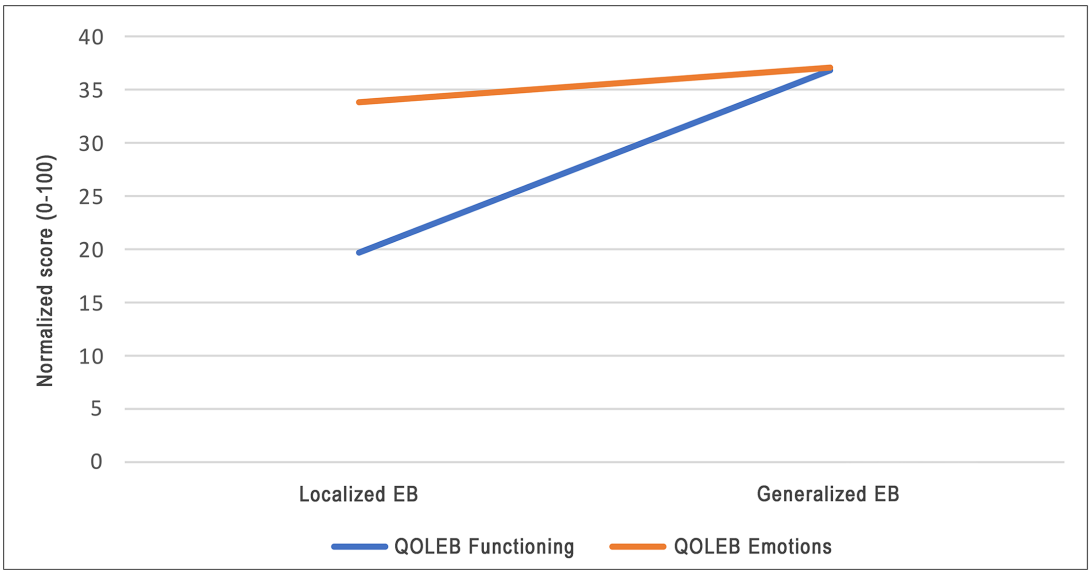

Fig. 1. Normalized scores for the Functioning and Emotions scales of the Quality of Life in Epidermolysis Bullosa (QOLEB) questionnaire, showing mean values by severity level of disease, i.e., localized vs generalized EB.

disease manifestations were significantly associated with worse QOLEB total and Functioning scores: mucosal involvement, malnutrition, joint deformities, functional disability, tooth loss and wheelchair use. Finally, a greater Functioning impairment was seen in the six patients with gastrostomy compared to those without.

Multivariate linear regression analysis confirmed the association of higher QOLEB total scores with presence of pain, chronic wounds, wheelchair use, and membership of a patients' association as independent factors (**Table IV**). As to the Functioning subscale, higher scores were observed in the presence of functional disability, wheelchair use, and patients' association membership. Finally, the Emotions subscale score was higher in females, and in patients presenting chronic wounds.

DISCUSSION

The present study validated the Italian version of the QOLEB, and employed this tool to assess the disease impact on QoL of Italian individuals with all EB types. Interestingly, the majority of respondents were female, mirroring the German and Spanish QOLEB data (16, 18) as well as data from other surveys on EB patients (30, 31). This finding is consistent with the gender participation bias (32). Among the 37 respondents with a caregiver, only 2 had a professional one. This likely reflects the tendency among Italian EB families to aid themselves, but possibly also deficiencies in the Italian home healthcare system. Greater resources for professional caregivers might help to reduce the family disease burden.

The PCA showed an excellent internal consistency of the QOLEB items, similar to values obtained in the validation of the original questionnaire and its other national versions (9, 11, 12, 14–18). Varimax rotation confirmed the validity of the original 2-component structure in Italian EB respondents. Convergent validity was found to be excellent for the total QOLEB score and both subscales in the paediatric sample. Similar results were observed in adults, except for the Emotions subscale, which demonstrated a moderate–weak correlation.

Floor effects were seen for many items, a finding consistent with results reported during the QOLEB validation in other countries (12, 16). Rather than indicating a lack of validity, the presence of these effects reflects the high clinical heterogeneity of EB and the broad range of disease severity within our sample. Such observations are common in tools designed for rare diseases. Consequently, while items with a significant floor effect may be less sensitive to change in milder cases, they remain highly informative for assessing the symptom burden in individuals with more severe phenotypes.

QOLEB results confirmed the major disease impact on QoL with 39% of patients reporting severe to very severe effects. However, total QoL score varied widely (0 to 43), in line with the huge phenotypic EB spectrum. The mean value was 17.5, similar to the results obtained in the Spanish and Romanian patients (14, 16), but higher than those observed in Dutch EB individuals (12), and lower than in the German-speaking ones (18). Such differences may be due to the EB type and subtype distribution among respondents. Similar to findings in the Spanish and German-speaking EB patients (16, 18), women showed a tendency to have a worse QoL than men, with significant differences in the Emotions subscale score. Indeed, female sex was

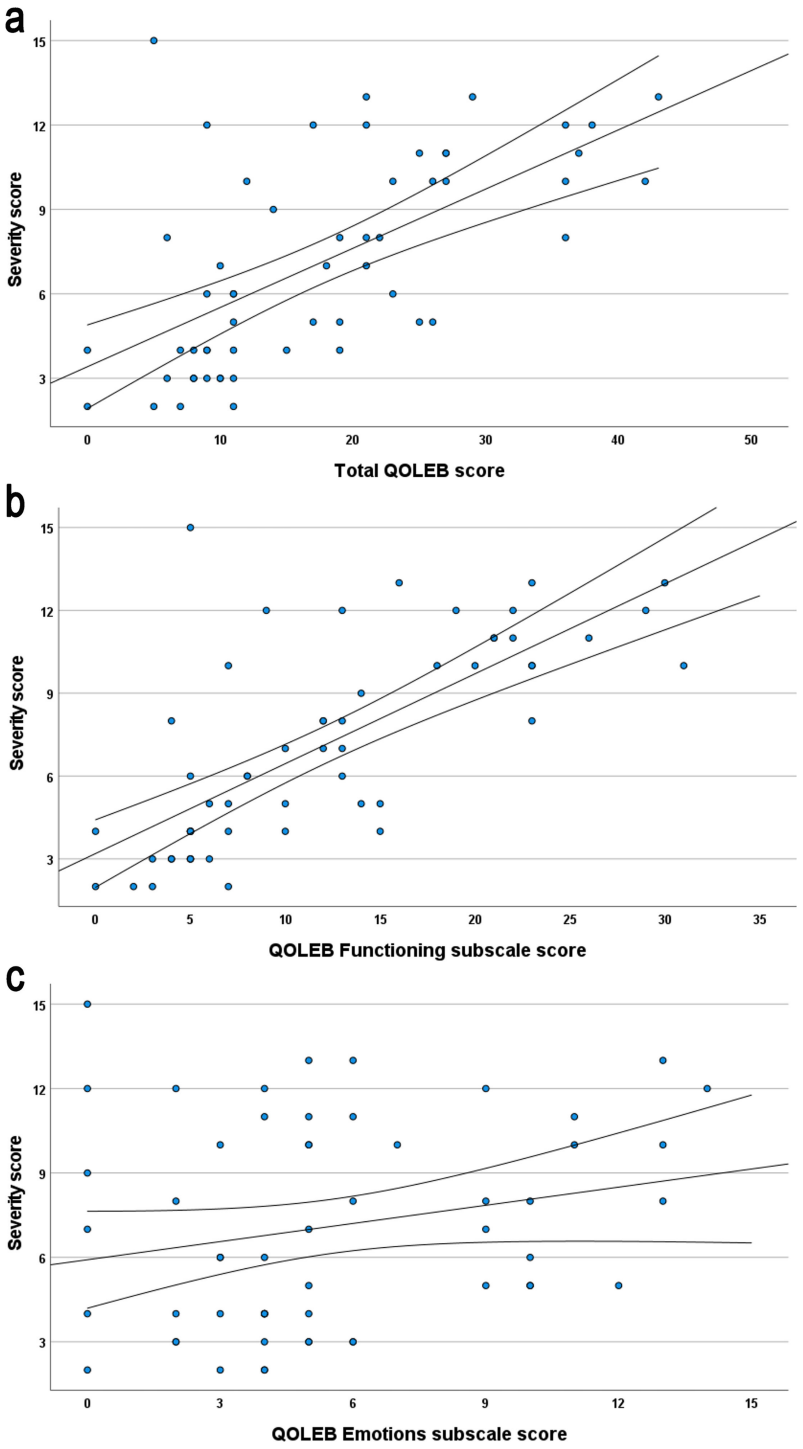

Fig. 2. Scatterplots showing the relationship between Quality of Life in Epidermolysis Bullosa – QOLEB - scores [i.e., total (a), Functioning subscale (b), and Emotions subscale (c)] and the clinical severity score [number of signs and symptoms (range 0–15) reported by patients].

Table IV. Multivariate linear regression models for the Quality of Life in Epidermolysis Bullosa (QOLEB) total and subscale scores

	Total QOLEB			QOLEB Functioning score			QOLEB Emotions score		
Variables	Beta coeff.	95% C.I.	*p*-value	Beta coeff.	95% C.I.	*p*-value	Beta coeff.	95% C.I.	*p*-value
Females vs males	–	–	–	–	–	–	2.6	0.6–4.6	**0.013**
Pain yes vs no	5.0	0.2–9.7	**0.041**	2.9	-0.1–6.0	0.058	–	–	–
Chronic wounds yes vs no	6.0	1.3–10.6	**0.014**	2.9	-0.04–5.9	0.053	2.8	0.8–4.8	**0.007**
Functional disability yes vs no	–	–	–	3.7	0.3–7.0	**0.033**	–	–	–
Wheelchair use yes vs no	7.5	0.9–14.1	**0.026**	6.0	1.7–10.3	**0.007**	–	–	–
Member of patient association yes vs no	**7.7**	2.5–12.9	**0.005**	5.7	2.4–9.0	**0.001**	1.9	–0.2–3.9	0.076

P-values <0.05 in bold.
C.I.:confidence interval; Coeff.:coefficient.

confirmed as an independent variable associated with higher scores on the Emotions subscale in multivariate linear regression analysis. The significantly worse QoL in young adults (18–30 years) as compared to patients between 11 and 18 years might be related to disease progression over time implying increased complications, functional damage and difficulties in social integration. Interestingly, survey participants who were members of a patients' association were predominantly affected with the most severe EB subtypes, DEB and JEB, and reported markedly poorer QoL, particularly in the Functioning domain, even after multivariate linear regression analysis. This association likely reflects a "selection bias" (33), where individuals with more burdensome symptoms or complex psychosocial needs are more motivated to seek support and join such organizations, that serve as a crucial touchpoint for the most fragile patients. These data highlight the need for integrated clinical and social support strategies tailored to those with the highest disease burden. Among major EB types, the worst QoL was observed in DEB individuals, in particular for the Functioning subscale, in line with previous literature (12, 14, 16, 34). Significant differences between DEB and EBS and between JEB and EBS for total QOLEB and Functioning subscale scores are also observed in Dutch and Spanish populations (12, 16). These findings highlight the sensitivity of the QOLEB instrument in capturing specific disease aspects thus differentiating the various EB types.

We found that EB survey participants showed a strong correlation between the total disease severity score and the QOLEB total and Functioning scores, while the correlation with the Emotions subscale was scarce and not statistically significant. In line with these results, the normalized values of the Functioning scale were markedly lower in respondents with localized EB as compared with generalized disease, while the Emotions subscale scores were similar in the 2 groups. These findings indicate that the emotional life of patients is markedly affected independently from the level of clinical severity, in line with results in the German sample of the BUR-EB study, and in other chronic dermatological conditions (35, 36).

Pain and itch were reported by most individuals and strongly associated with worse QoL, measured by total QOLEB and both subscales, in all EB types (2, 3, 30, 31, 34, 37). Chronic wounds are the only clinical manifestation associated with a significant impact not only on total QOLEB and Functioning scores, but also on Emotions score, and staying as an independent variable for total QOLEB and Emotions subscale in multivariate regression analysis. The burden of chronic wounds is a major determinant of disease impact, due to pain and itch, risk for infections and SCC development, need for time-consuming and painful dressings, and also aesthetic damage (2, 3, 30, 38). Indeed, the presently approved therapies for EB are all meant to treat wounds (4). Moreover, malnutrition, mucosal involvement, tooth loss, joint deformities and functional disability, as well as wheelchair use, were significantly associated with higher scores for total QOLEB and the Functioning subscale. Wheelchair use was confirmed as an independent variable associated with higher total QOLEB and Functioning scores in multivariate linear regression analysis, reflecting the greater functional impairment in patients requiring this device.

Limitations

The present study has several limitations. The major one is represented by the relatively small sample that in a phenotypically heterogeneous disease may not completely reflect the overall EB population. In fact, while all EB types were represented, external validity is not easily verifiable and caution should be adopted when generalizing these results. In addition, our sample size (N=56) is below the conventional psychometric standard often recommended for the validation of self-report questionnaires, typically a 10:1 subjects-to-item ratio (39). However, achieving such numbers in rare diseases is challenging. Indeed, our sample size is consistent with, or even superior to, previous validation studies of QOLEB in different languages (1–14, 16–18). A further limitation concerns the survey dissemination strategy through DEBRA Italy and reference centres and recruitment modality based on voluntary participation, which may have led to a self-selected over-representation of more severe EB forms, even within the specific clinical types. The considerable length of the questionnaire, as well as the online survey modality, may have also affected the composition of the study sample. However, paper questionnaires were available in reference centres for in-person completion.

Conclusion

Our study confirms the good psychometric properties of the Italian QOLEB, in line with previous studies in other populations (9, 11–18). The Italian QOLEB allowed to document the overall major impact of EB on QoL, also highlighting gender differences in the emotional life, with a greater burden for women. It indicated pain, chronic wounds and functional disability as the main targets for therapeutic interventions to improve QoL of EB patients.

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Greta Arias-Merino, Instituto de Investigación de enfermedades Raras (IIER), Instituto de Salud Carlos III, Spain

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Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval status: For Italy, the research was approved by the Institutional Ethical Committee of Bambino Gesù Children's Hospital (OPBG) (protocol number 3107/2023).

Conflict of interest: M.E.H. is member of the advisory board of Chiesi Global Rare Diseases, and consultant for Krystal Biotech. G.Z. has acted as invited speaker for Chiesi Global Rare Diseases. D.F.M. is creator of QOLEB.

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