

Patient-generated evidence in Epidermolysis Bullosa (EB): Development of a questionnaire to assess the Quality of Life

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1. Introduction

Epidermolysis Bullosa (EB) is a genetic disorder characterised by skin fragility and blistering from mild mechanical trauma. There are four major classical EB types: EB simplex, junctional EB, dystrophic EB, and Kindler EB (Has et al., 2020). All types and subtypes of EB are rare. The overall prevalence of inherited EB in the US is about 11 cases per 1 million live births, and the incidence about 20 per 1 million population (Fine, 2016). Similar results have been obtained in some European countries, Italy included (Tadini et al., 2005).

The clinical manifestations and the severity are very heterogeneous. Physical symptoms include fragile skin that blisters easily, causing pain, itch, and odour; dental problems and blisters inside the mouth and throat, dysphagia, and hair loss. This disease may also present muscle, heart, brain, gastrointestinal, bone, or kidney issues. The physical symptoms significantly impact on daily life and everyday activities and are associated with functional limitations and time-consuming medications that can severely affect the Quality of Life (QoL) of patients and their families. Besides, the disfiguring nature of these symptoms causes an additional burden at the psychological and social level, and the overall EB management may have detrimental financial consequences. The rarity of the disease is an additional issue because there is a lack of awareness and understanding by both laypeople and non-specialist healthcare professionals. Dures and colleagues (Dures, Morris, Gleeson, & Rumsey, 2011) underlined how EB patients' unmet needs were above the medical support. Informational needs, self-management, peer support, social skills and one-to-one therapy emerged as critical themes to be improved.

Considering all the implications of living with EB, a valid and reliable scale to assess the QoL of these patients is essential in patient care and management. The most used instrument available to assess EB patients' QoL, which has proven to be valid and reliable, is the QoLEB questionnaire (Frew, Martin, Nijsten, & Murrell, 2009). It was initially developed in English with an Australian sample, and it was successively translated and validated in other languages (Cestari et al., 2016; Dănescu et al., 2019; Frew, Cepeda Valdes, Fortuna, Murrell, & Salas Alanis, 2013; Yuen et al., 2014).

Even though the translation of this existing tool would have been a valid option, in the present study it was decided to conduct a Delphi study to fully understand the patients' point of view, make their voices heard, and capture possible peculiarities of the Italian context.

A three-stage online Delphi consensus procedure was conducted to identify the key domains and specific statements to assess crucial areas of EB patients' QoL.

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2. Methodology

The project started from the request of the Italian no-profit association for EB research and the Italian Registry for EB Foundation (REB) to develop for the first time a patient-centred questionnaire to assess the QoL of patients affected by EB. The methodological process to develop the questionnaire consisted of two phases: firstly, a critical review of scientific literature was performed; secondly, an online pseudo-Delphi study was carried out. The Delphi method is an iterative process where several rounds are organised to identify a shared solution, with useful applications also in health research (Trevelyan & Robinson, 2015). It is a flexible method to determine the gist of the discussed problem when it is not entirely known and when it may be challenging to apply a specific statistical model. The Delphi method consists in envisaging one or more topics to a determined group of experts to provide subsequent evaluations in an iterative process aimed to reach a consensus, which will represent the final expression of the group opinion (Marbach, Mazziotta, & Rizzi, 1991). In this case, the Delphi procedure may be considered “Pseudo-Delphi” because, even though each questionnaire was anonymously analysed and summarised to be presented to the group, the discussions were open, and each participant contributed to the group discussion.

A literature review was conducted to understand what was already known about this pathology and what instruments are used at both a national and international level.

After the problem definition, the expert panel was identified. A multidisciplinary panel including patients, caregivers, and clinicians actively participated in round tables.

The team comprised:

- A Delphi master
- A moderator
- Six patients or child patients' caregivers
- Two clinicians with solid expertise in dealing with this pathology and recognised as international key opinion leaders on EB
- A psychologist

Then, a first group meeting was organised to discuss every step of the project, the main topics to cover, and the primary aim to be achieved. Successively, the patients and clinicians were asked to provide a list of spontaneously generated items to describe different areas of the EB patient's QoL. They worked separately, and all the answers were collected in an anonymous way, allowing every person to freely express their opinions and personal state of mind without any social pressure or external influence. As a result, some powerful statements appeared (e.g. “*Sometimes I think it would be better if I died*”). A total of more than 160 items were created. All answers were carefully considered and grouped within a specific domain. Accurate analysis and harmonisation of all the statements were carried out, in a first attempt to summarise the questionnaire, combine the items with the same meaning, and obtain statements that had a clear value generalisable for the entire reference population. The results were presented in the first Delphi table, i.e., a roundtable session to discuss all the implications of daily living with the disease openly. This group meeting was essential to skim the scopes and find the most salient and relevant assessment in daily practice. On this occasion, great care was taken to ensure a comprehensive and accurate understanding of the experts' points of view.

Hence, the first questionnaire (Q1) was created. This questionnaire also included some items from the literature that were not originally reported during the Delphi roundtable. The questionnaire comprised seven core domains (see Table 1) for a total of 80 items. Each participant was asked to read every statement and assess their degree of importance. They were also required to comment on the clarity and specificity of each item and write any missing information that might have been included. Each expert responded anonymously to the questionnaire and returned it to be discussed in the second Delphi round.

Table 1. EB QoL questionnaire domains

Domain	Description	Q1	Q2	Q3
Physical	This section lists relevant aspects in terms of health and physical well-being.	Items: 14 (e.g. <i>"I suffer from neuropathies"</i> was removed)	Items: 15 (the item about hands and feet problems were separated)	Items: 15 (the items about hands and feet problems were further modified)
Functional ability and autonomy	It includes statements about self-sufficiency and the ability to perform daily and routine actions.	Items: 15	Items: 13 (some items were moved to another section)	Items: 12
Psychological-emotional	It includes statements related to sensations, emotions, thoughts and feelings that may affect the psycho-emotional well-being.	Items: 13	Items: 13	Items: 14
Family	It includes statements concerning family life, such as the relationship with parents, brothers and sisters, or other people belonging to the family unit, possibly including the partner and children.	Items: 12	Items: 14 (<i>"some family members make me feel guilty"</i> was added)	Items: 14
Relational	It includes statements regarding relationships and frequent interactions with people who do not belong to the family (e.g., friends, classmates, colleagues, strangers on the street, etc.).	Items: 9	Items: 10 (<i>"some friends get in touch only when I'm at the hospital"</i> was added and later removed)	Items: 9
Work and economic	It includes statements about the work context and the economic implications of the disease.	Items: 11	Items: 13 (e.g. <i>"I can't work"</i> was separated into two items to highlight the difference between the physical impossibility and societal barriers)	Items: 13
Medical care and assistance	It includes statements regarding disease-related health care, including medical and nursing assistance.	Items: 6	Items: 8 (two items were inserted about the lack of knowledge of non-specialised clinicians in local and the need for private rooms when hospitalised).	Items: 8
		Total items: 80	Total items: 86	Total items: 85

All the answers were carefully examined, and a ranking was created for every item within each domain according to the degree of importance indicated by the participants. The results of this analysis were discussed in the group, and further refinement of the questionnaire was made. Some items were changed or rephrased for greater clarity; others were merged or removed because of their lesser importance.

A new questionnaire (Q2) was defined, considering all suggestions that emerged from the group meeting. The previously identified core domains remained unchanged, but some new items were suggested and inserted. Overall, Q2 was composed of 86 items. At this stage, each participant was asked to rate both the degree of agreement and the degree of importance of each item on a four-point Likert scale (“*Not at all*”, “*A little*”, “*Quite*”, “*Very*”). This step is necessary to remove some irrelevant statements and evaluate the order in which the items are presented. The agreement and importance measures were constructed as satisfaction-importance measures, in line with the widely used Customer Satisfaction techniques.

In addition to the abovementioned seven domains, some specific questions were inserted about the type of EB diagnosed, some socio-demographic information (e.g., age group, the Italian region of residence, the perceived need for psychological support, the perceived satisfaction of the quality of care, etc.). Finally, an overall QoL satisfaction question was asked (“On a scale from 1 to 10, how do you rate your quality of life?”).

The results of this phase were presented to the group to define the questionnaire structure further and prepare the new version (Q3) with 85 items, which each participant anonymously filled in. Only one sentence was removed, and some others were modified to be more easily understandable and clear.

It should be noted that, in some cases, a different view emerged between clinicians and patients, and some information learned by the literature were then rejected or modified to be adapted to the language and the experience of the patients (e.g., the terms used to talk about some physical symptoms).

The final version of the questionnaire will be administered to a larger sample to assess its validity and reliability.

3. Conclusions

The present study is part of a more extensive research project aimed at developing a valid and reliable questionnaire to assess the QoL of EB patients. This tool is meant to grasp the point of view and the patient's subjective experience beyond clinical classifications and take into account the patient's overall experience. Starting from an initial set of areas and through the three-round pseudo-Delphi methodology, a gradual refinement of the statements was carried out, and a list of items was defined to be included in an easy-to-use but meaningful patient-centred questionnaire. Each participant had the opportunity to read and fulfil the questionnaire in private, having anonymity assured, allowing free expression of opinions without any social pressure or compliance effect that may conversely arise during the group discussions. On the other hand, knowing all information gathered from the questionnaires and discussing it in the group offered them the opportunity to critically analyse and re-consider all items and areas composing the questionnaire and achieve a final agreement among participants. From a methodological point of view, this approach is worthy in analysing real-world data pertaining to a subjective topic such as QoL, especially in rare diseases. The final patient-centred questionnaire is thus able to measure the QoL beyond the physical symptoms and the clinical evolution of the disease, encompassing functional autonomy, psycho-emotional state, social relations inside and outside the family context, the working field and several aspects of the medical care and assistance. The experts approved the final version of the questionnaire after three iterations of anonymous online questionnaire completion and related presentation and discussion of results within the group. The future steps of this

research will provide for the assessment of the psychometric properties of the questionnaire to prove its reliability and validity in measuring the QoL of EB patients. This new tool may be a valid aid for clinicians to understand patients better and identify the areas that need more attention; moreover, it may allow them to follow the patients over time and evaluate the impact of any treatments.

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