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ORIGINAL ARTICLE

Quality of Life and Economic Burden in Recessive Dystrophic Epidermolysis Bullosa

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Background: Patients with recessive dystrophic epidermolysis bullosa (RDEB) exhibit blisters and erosions since birth, causing pain, pruritus and various complications. RDEB affects quality of life (QoL) in physical, emotional and social aspects. Furthermore, interminable dressing changes and supportive therapies impose a significant economic burden on the patient's family. **Objective:** We assessed the QoL and economic burden in patients with RDEB. **Methods:** Sixteen patients with RDEB were surveyed to assess the QoL and economic burden. Patients answered questionnaires consisting of a visual analogue scale (VAS) on pain and pruritus, Skindex-29, Quality of Life in EB questionnaire (QOLEB), and the economic burden due to EB. **Results:** Thirteen patients with RDEB completed the questionnaire. Female patients presented higher VAS, QOLEB and total Skindex-29 scores than male patients. Patients with RDEB showed severe levels of pruritus, which was more intolerable than pain. Mean VAS score on pain in RDEB was higher than in oral lichen planus and post-herpetic neuralgia. VAS score on pruritus was similar to those in chronic urticaria, atopic dermatitis, and prurigo nodularis. Compared with other dermatologic conditions, patients with RDEB were profoundly affected in all three scales of skindex-29. Mean "medical cost" in a month was $257.54 (USD) (±169.39) and mean "dressing cost" was $358.41 (USD) (±312.55), which was negatively related to patient age. **Conclusion:** RDEB had a profound impact on QoL and economic burden. Compared with other dermatologic diseases, RDEB showed severe symptoms and QoL was seriously impaired. Most patients sustained economic burdens, especially on preparing dressing materials. Younger patients experienced more economic burdens.

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-Keywords-

Dressing, Economic burden, Quality of life, Recessive dystrophic epidermolysis bullosa

INTRODUCTION

Epidermolysis bullosa (EB) encompasses a heterogeneous group of inherited skin diseases characterized by blistering and erosion of the skin after minor mechanical trauma or friction. The four major types of EB are defined according to differences in their level of separation within the dermal-epidermal junction on electron microscopy and immunofluorescence mapping: the epidermis in EB simplex (EBS), the lamina lucida in junctional EB (JEB), the sublamina densa in dystrophic EB (DEB), and mixed in Kindler syndrome[1].

Recessive DEB (RDEB) is caused by mutations in the *COL7A1* gene and is inherited in an autosomal recessive manner. The two major subtypes of RDEB, generalized severe subtype (RDEB-gen sev), previously called Hallopeau-Siemens type, and RDEB generalized intermediate (RDEB-gen intermed) subtype, exhibit generalized blistering, nail dystrophy, ocular and oral involvement, contractures, severe deformities of the hands and feet, as well as multiple extracutaneous impairments[1]. These physical impairments affect the physical, emotional, and social domains of qual-

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ity of life (QoL) in patients with RDEB. Several studies on QoL in EB have been reported in the United States, Australia, and Italy[2-5], meanwhile, studies have yet to evaluate QoL in patients with EB throughout Asia.

Although promising cell-based treatments are under investigation[6,7], treatment of EB mainly relies on supportive therapies (e.g., avoiding trauma, wound dressing, and management of extracutaneous complications). Nevertheless, although interminable dressing changes and supportive therapies impose a significant economic burden on the family members of patients with EB, studies have yet to measure the economic burden thereof[8]. Accordingly, in this study, we aimed to assess QoL and costs related to treatment in patients with RDEB to obtain a better understanding of the overall burden of EB.

MATERIALS AND METHODS

Study design

This cross-sectional, observational study included patients with RDEB who were diagnosed at the Department of Dermatology, Gangnam Severance Hospital, Seoul, Korea. All diagnoses were confirmed by transmission electron microscopy, immunofluorescence mapping, and mutational analysis. The study was approved by the Institutional Review Board in Gangnam Severance Hospital (3-2012-0028).

Sixteen patients with RDEB were surveyed for QoL and economic burden. Patients were oriented about the questionnaires, and written consents were obtained before the survey. The documents were mailed to the patients who were unable to visit. Completed questionnaires and signed consent forms were returned by mail.

Patients answered questionnaires consisting of the visual analogue scale (VAS) on pain and pruritus, Skindex-29, Quality of Life in EB (QOLEB), and questions addressing economic burden of treatment. Information about accompanying complications, body surface area (BSA) involved, perceived disease severity by patient global assessment (PGA), and days of hospitalization because of EB in the previous year were also obtained. Accompanying complications included infection, poor wound healing, anemia, nutritional problems, growth retardation, esophageal stricture, constipation, eye lesions, dental problems, urinary dysfunction, contractures, nail dystrophy, depression, and others. For children under 7-years old, main caregivers were asked to participate in the survey to answer the questionnaires.

Measurement tools

1) Visual analogue scale

The VAS has been demonstrated to be a reliable and valid method for measuring pain and pruritus[9,10]. Average degrees of daily disease-related pain and pruritus were assessed by a linear 10-score visual analogue scale, ranging from 0 (no symptom) to 10 (intolerable symptom). VAS scores of RDEB were compared to other dermatologic diseases reported in the literature[11-15]. VAS differences of 6～10 mm were considered as clinically meaningful[16].

2) Skindex-29

Skindex-29 is a reliable dermatology-specific instrument to measure QoL[17]. The Korean version of Sindex-29 has been translated and has proven value in evaluating QoL for various dermatologic diseases[18-21]. The questionnaire included 29 questions consisting of three scales (symptom, functioning, emotional burden). Patients were requested to answer these questions concerning the preceding 4-week period using a 5-point scale. (from never＝0, to all the time＝4). In each scale, the score was represented as a percentage of the highest score, from 0 to 100; higher values indicate a poor QoL. We also compared Skindex-29 scores of RDEB with other dermatologic diseases reported in the literature[22].

3) QOLEB questionnaire

To our knowledge, this is the first disease-specific QoL tool for EB, and is a valid and reliable measurement tool reflecting the inability of a patient with EB to perform certain tasks[4]. Patients were asked to answer 17 questions using a 4-point scale (from least＝0, to most impact＝3).

4) Patient global assessment

Subjective disease severity perceived by the patients was assessed using PGA, which consists of a 5-point scale (from very mild＝0, to very severe＝4).

5) Economic burden

Average monthly expenses for “dressing costs” and “medical costs” were investigated. “Dressing costs” were defined as total expenses for preparing dressings, fixing materials, topical agents, and medicines used during dressing changes. “Medical costs” were defined as other expenses due to EB, excluding “dressing costs”.

6) Dressing burden

To clarify the burden of dressings, additional questions were presented: “Do you experience an economic burden

with preparing dressings/fixing materials?"; "How often do you change your dressings?"; "How long does it take to change your dressings?"; "Are specialized dressings/fixing materials better in function than general dressings/fixing materials?"; "What is the most important factor when you purchase dressings/fixing materials?".

Statistical analysis

Results were expressed as mean±standard deviations. Statistical analysis was performed using SAS software (version 9.1.3; SAS Institute Inc., Cary, NC, USA) using Student's sample t-test, analysis of variance, and Spearman's rank correlation coefficient. p-value <0.05 was considered implying statistical significance.

RESULTS

Among 16 patients invited, 13 (81.3%) completed the questionnaires. Uncompleted questionnaires were excluded from data analysis.

Patient demographics and subjective disease severity

Basic patient characteristics are summarized in Table 1. Three patients were aged below 7 years and their main caregivers participated in the survey together. Nine patients (69.2%) were male and 4 patients (30.8%) were female. The mean accompanying numbers of complications were 7.77±2.92, with a range of 3 to 12.
According to the EB classification[1], 7 patients (53.8%)

Table 1. Basic patient characteristics

Clinical variable	Result
Total case	13
Age (yr)	21.57±17.61
Gender	
Male	9 (69.2)
Female	4 (30.8)
Complication	7.77±2.92 (3~12)
EB subtype	
RDEB-gen sev	7 (53.8)
RDEB-gen intermed	6 (46.2)
Area of body surface involved (%)	
>30	13 (100)
10~30	0 (0)
<10	0 (0)
Hospitalization due to EB in the last year (d)	
>7	5 (38.5)
≤7	1 (7.7)
0	7 (53.8)
PGA	
Very severe	11 (84.6)
Severe	2 (15.4)
Moderate	0 (0)
Mild	0 (0)
Very mild	0 (0)

Values are presented as mean±standard deviation (range) or number (%). EB: epidermolysis bullosa, RDEB: recessive dystrophic EB, RDEB-gen sev: RDEB generalized severe, RDEB-gen intermed: RDEB generalized intermediate, PGA: perceived disease severity.

Table 2. Quality of life results

Clinical variable	VAS		QOLEB	Skindex-29		
	Pain	Pruritus		Symptom	Emotion	Function
Total cases (n=13)	6.54±1.56	7.54±2.07	26.62±7.61	86.31±10.38	75.23±15.76	76.69±12.09
Gender						
Male (n=4)	5.75±0.95	6.75±2.63	25.75±8.22	90.00±14.21	65.00±20.94	75.00±17.68
Female (n=9)	6.88±1.69	7.88±1.83	27.44±7.78	84.67±8.72	79.78±11.51	77.44±10.00
Hospitalization due to EB in the last year (d)						
0 (n=7)	6.57±1.39	7.14±2.27	25.14±7.35	80.71±10.67	79.14±10.38	77.71±12.22
≤7 (n=1)	6	10	25	91	94	88
>7 (n=5)	6.60±2.07	7.60±1.82	29.80±8.70	93.20±5.72	66.00±19.02	73.00±12.81
EB subtype						
RDEB-gen sev (n=7)	6.57±1.72	8.00±1.29	30.14±8.82	90.57±8.96	70.29±17.41	79.00±14.19
RDEB-gen intermed (n=6)	6.50±1.52	7.00±2.76	23.17±3.76	81.33±10.35	81.00±12.57	74.00±9.65
Perceived disease severity						
Very severe (n=11)	6.54±1.69	7.54±2.25	28±7.82*	86.72±10.39	78.54±13.97	79.54±10.82*
Severe (n=2)	6.50±0.71	7.50±0.71	21*	84.00±14.14	57.00±15.55	61.00±1.41*

Values are presented as mean±standard deviation. VAS: visual analogue scale, QOLEB: quality of life in EB questionnaire, EB: epidermolysis bullosa, RDEB: recessive dystrophic EB, RDEB-gen sev: RDEB generalized severe, RDEB-gen intermed: RDEB generalized intermediate. *$p<0.05$.

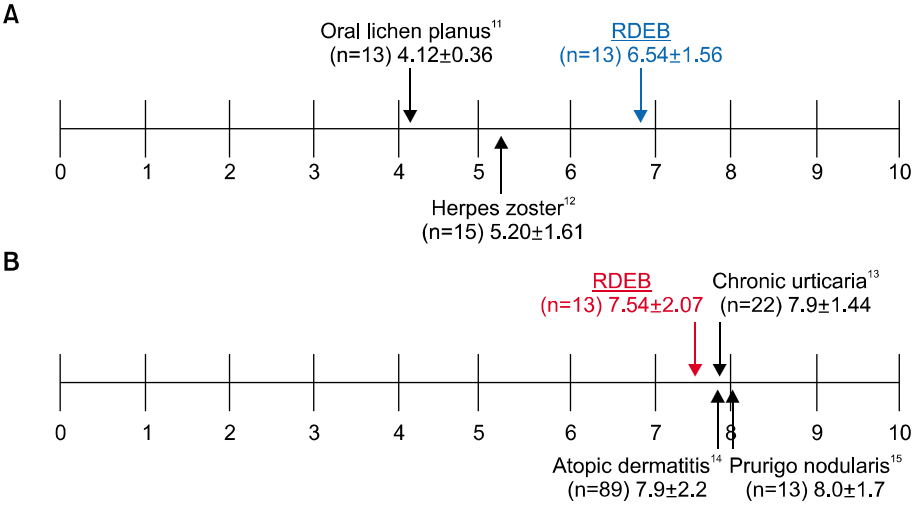

Fig. 1. Visual analogue scale (VAS) in (A) pain and (B) pruritus. VAS differences of 6～10 mm are considered as clinically meaningful. (A) The mean pain scale in recessive dystrophic epidermolysis bullosa (RDEB) is higher than in oral lichen planus and herpes zoster (post-herpetic neuralgia). (B) The mean pruritus scale is similar to that in chronic urticaria, atopic dermatitis, and prurigo nodularis.

were RDEB-gen sev, and 6 patients (46.2%) were RDEB-gen intermed. All patients had skin lesions involving more than 30% of BSA. Five patients (38.5%) were hospitalized for more than 7 days because of EB in the previous year, 1 patient (7.7%) for less than 7 days, and 7 patients (53.8%) were not hospitalized at all. Eleven patients (84.6%) perceived their disease as 'very severe' and 2 patients as 'severe' (15.4%).

QoL results

1) Visual analogue scale

Table 2 shows the VAS, QOLEB and Skindex-29 scores for different clinical variables. Female patients had higher VAS scores in pain and pruritus than male patients. Compared with RDEB-gen intermed, RDEB-gen sev had higher VAS score in pruritus, but had similar VAS scores in pain. VAS scores in pain and pruritus were not significantly different among hospitalization days or between perceived disease severities. Patient age and accompanying complication numbers had no correlation with VAS scores in pain or pruritus.

Compared with other dermatologic diseases, the mean pain scale was higher than for oral lichen planus and herpes zoster (Fig. 1A). The mean pruritus scale was similar to that in chronic urticaria, atopic dermatitis, and prurigo nodularis (Fig. 1B).

2) Skindex-29

The mean score was 86.31±10.38 on the symptoms scale, 75.23±15.76 in emotions, and 76.69±12.09 in functioning (Table 2). Male patients had higher scores in symptoms, and female patients presented higher scores in emotions and functioning; however, these results were not statistically significant. Skindex-29 was not significantly different among the hospitalization days or between EB subtypes. On the function scale, patients with perceived disease severity of 'very severe' reported significantly higher scores than those with 'severe' ($p<0.05$). Patient age and accompanying complication numbers had no correlation with Skindex-29. Compared with other dermatologic conditions, patients with RDEB were profoundly affected in all three scales of Skindex-29 (Table 3).

Table 3. RDEB versus other skin conditions (Skindex-29)

Clinical variable	Sample size	Symptom	Emotion	Function
RDEB	13	86 (10)	75 (16)	77 (12)
Other skin condition[22]				
Dermatomyositis	22	42 (25)	45 (27)	28 (29)
Vulvodynia	280	50 (17)	50 (20)	44 (22)
Psoriasis	44	42 (21)	39 (27)	23 (27)
Eczema	102	48 (23)	41 (27)	26 (26)
Acne vulgaris	63	30 (19)	41 (25)	16 (16)
Alopecia	7	31 (24)	27 (33)	14 (23)
Rosacea	29	33 (20)	33 (20)	16 (18)
Without skin disease	107	14 (2)	9 (13)	4 (8)

Values are presented as mean (standard deviation). RDEB: recessive dystrophic epidermolysis bullosa.

3) QOLEB

Mean QOLEB score was 26.62±7.61 (Table 2). Higher scores were observed for female patients, patients with hospitalization days greater than 7 days, and RDEB-gen sev subtype; these results were not statistically significant. Patients with perceived disease severity of 'very severe' reported significantly higher scores than that of 'severe' ($p<0.05$). Patient age and accompanying complication

numbers had no correlation with QOLEB.

4) Economic burden

Table 4 shows the "medical costs" and "dressing costs" for different clinical variables. "Dressing costs" were greater than "medical costs": the mean monthly "medical cost" was $257.53±169.39 (USD); the mean monthly "dressing cost" was $358.41±312.55(USD). The mean monthly total cost was $615.97±32.09 (USD). Patients with hospitalization days greater than 7 days and RDEB-gen sev subtype spent more on "medical costs" and "dressing costs" than did other patients. "Medical costs" and "dressing costs" were negatively related to patient age (Spearman rho=−0.68, p=0.01 and Spearman rho=−0.56, p=0.049), representing a statistically meaningful correlation. Perceived disease severities and accompanying complication numbers had no correlation with economic burden. "Medical costs" and "dressing costs" had no correlation with VAS, QOLEB, and Skindex-29.

5) Dressing burden

Regarding additional questions about the burden of dressings, 7 patients (53.8%) answered that they have experienced an economic burden on dressing materials "always", and 3 (23.1%) answered "often" (Fig. 2A). Regarding dressing change frequency, 7 patients (53.8%) changed the dressing every day and 4 patients (30.8%) changed three times a week (Fig. 2B). Seven patients (53.8%) answered that they require 1∼2 hours to change the dressings and 4 (30.8%) required less than 1 hour (Fig. 2C).

Eleven patients (84.6%) answered that specialized dressings are better or much better in function than general dressings (Fig. 2D). Price was the most important factor (38.5%) when purchasing dressings, followed by pain during dressing change (30.8%) (Fig. 2E). Regarding fixing materials, 12 patients (92.3%) answered that specialized fixing materials are better than general fixing materials (Fig. 2F). Price (38.5%) and fixing ability (38.5%) were two important factors considered when selecting fixing materials (Fig. 2G).

Table 4. Economic burden of RDEB patients in a month

Clinical variable	Medical cost (USD)	Dressing cost (USD)
Total case (n=13)	257.54±169.39 (93∼465)	358.41±312.55 (93∼930)
Gender		
Male (n=4)	267.40±229.00	488.30±411.60
Female (n=9)	253.20±152.70	300.70±266.10
Hospitalization due to EB in the last year (d)		
0 (n=7)	219.21±148.79	273.69±298.32
≤7 (n=1)	46.50	93.00
>7 (n=5)	353.40±166.36	503.10±304.21
EB subtype		
RDEB-gen sev (n=7)	298.90±177.80	431.80±299.80
RDEB-gen intermed (n=6)	209.30±160.40	272.80±332.00

Values are presented as mean±standard deviation (range). RDEB: recessive dystrophic EB, EB: epidermolysis bullosa, RDEB-gen sev: RDEB generalized severe, RDEB-gen intermed: RDEB generalized intermediate, USD: United States Dollar.

DISCUSSION

The present study evaluated the QoL and economic burden of patients with RDEB. To our knowledge, this study is the first to assess the economic burden of EB and to evaluate the QoL of patients with RDEB in Asia.

The female sex is reportedly correlated with QoL and psychological morbidity[8], reported in EB as well as in other dermatological diseases[5,23]. In the present study, female patients presented higher VAS, QOLEB, and total Skindex-29 scores than male patients. While VAS scores were more severe in females, symptom scores on the Skindex-29 scale were higher in males. VAS assesses symptoms according to severity, whereas Skindex-29 evaluates symptoms according to frequency. QOLEB also evaluates pain according to frequency. Notwithstanding, Frew et al.[4] suggested that VAS is more accurate for actual assessment of pain and pruritus. Moreover, VAS is easy and quick to perform, and could be useful during consultation of patients with for accurate symptom management.

Compared to other dermatologic diseases in the literature, the patients with RDEB included in this study suffered from more severe pain: VAS scores on pain were higher for RDEB than in oral lichen planus and post-herpetic neuralgia. Meanwhile, Fine et al.[24] reported that severe levels of pain were most often seen in JEB-Herlitz type and RDEB Hallopeau–Siemens type. However, in the present study, VAS scores on pain were similar between RDEB-gen intermed and RDEB-gen sev subtypes. Additionally, compared with other dermatologic diseases, patients with RDEB showed higher Skindex-29 scores in all three scales, further reflecting the disease burden of RDEB. Compared with a previous survey of patients with EB in Italy[5], Skindex-29 scale scores for RDEB were higher in our study; however, the previous survey seems to have enrolled more participants with a milder phenotype than the present did: all patients in the present study had skin involvement greater than 30% patients who had more than

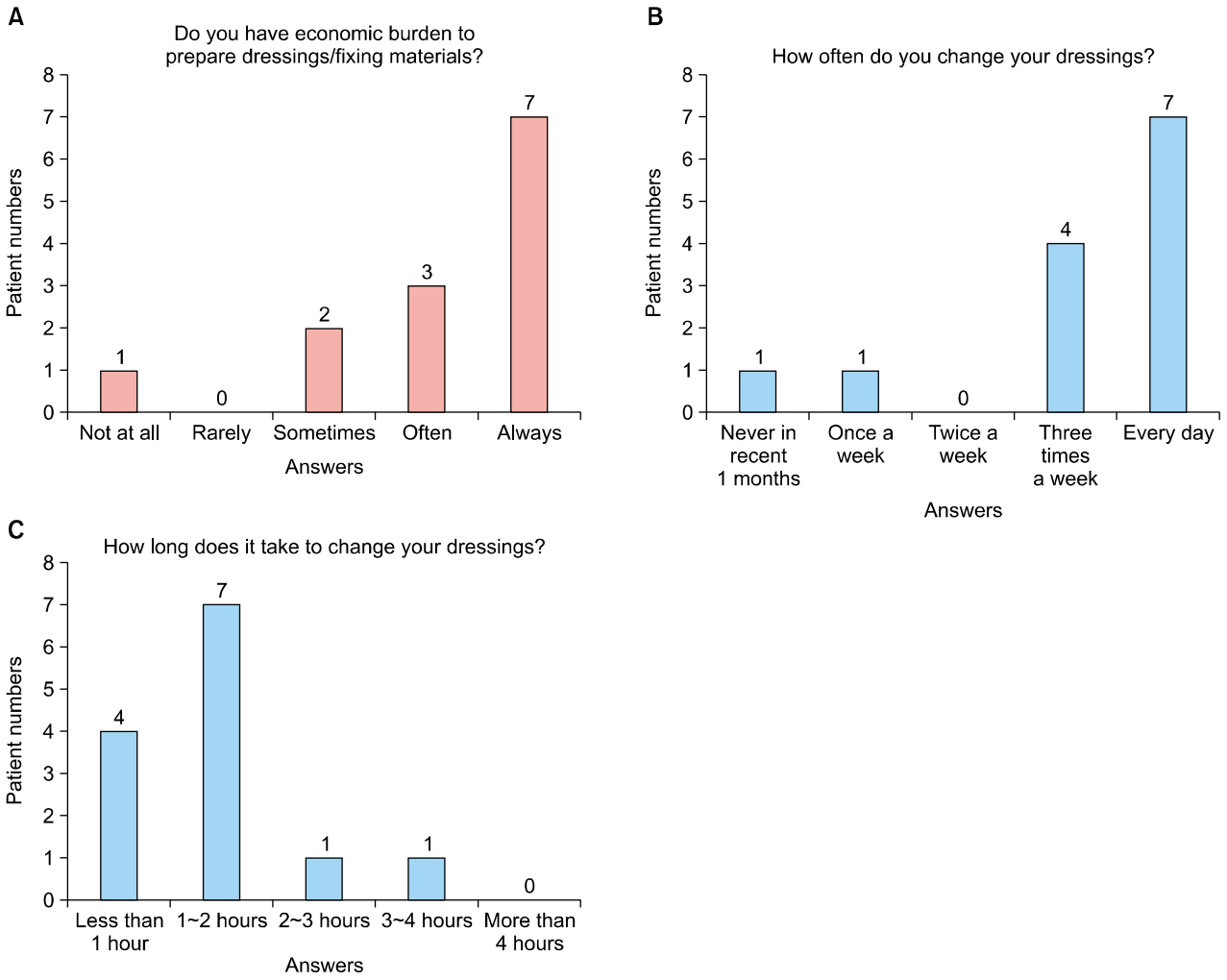

Fig. 2. Questions and answers about economic burden and dressing materials. (A) Seven patients answer that they experienced economic burden on dressing materials "always", and 3 patients answered "often". (B) Seven patients change the dressing every day, and 4 patients change three times a week. (C) Seven patients answer that they require 1～2 hours to change their dressings, and 4 patients answered less than 1 hour. (D) Eleven patients (84.6%) answer that specialized dressings are better or much better in function than general dressings. (E) Price is the most important factor when purchasing dressings, followed by pain during dressing change. (F) Regarding fixing materials, 12 patients answer that the specialized fixing materials are better than general fixing materials. (G) Price and fixing ability are two important factors when selecting fixing materials.

30% skin involvement in the Italian study showed higher symptom. Seven scale scores than the other patients in the study. Nevertheless, the present study still showed higher Skindex-29 scores. This discrepancy could be related to different cultural backgrounds concerning symptoms, emotions, and social relationships between Asian and Western countries.

Pruritus is a common symptom among patients with EB. Nevertheless, the etiology of pruritus in these patients is unknown. Abnormal chronic skin inflammation, overheating caused by dressings, dry skin, healing wounds, and weather are potential contributing factors[2,25]. Pruritus has been reported to be the biggest concern of patients with EB, followed by pain[2]. In our study, patients with RDEB showed severe pruritus. VAS scores for pruritus among patients with RDEB were similar to those for chronic urticaria, atopic dermatitis, and prurigo nodularis. However, among these, pruritus in EB would be more influential to QoL, as it usually starts at birth or early childhood, lasts the lifetime of the patient, and scarcely shows satisfactory responses to medication.

Herein, we hypothesized that patients with the severe subtype, RDEB-gen sev, would show greater impairment in QoL than those with other subtypes. However, patients with RDEB subtypes showed no significant differences in QoL. In a previous report[5], Sindex-29 also showed no sig-

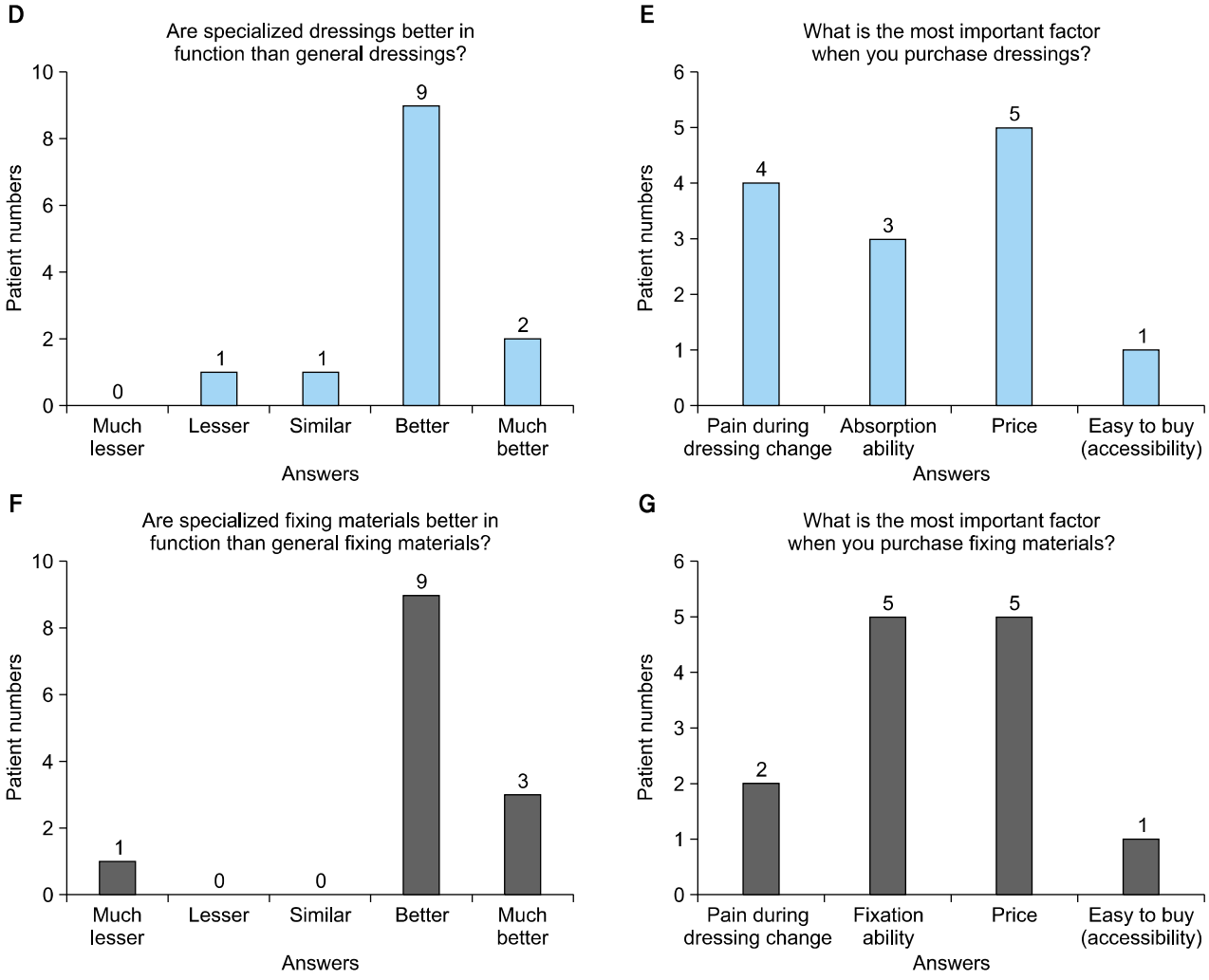

Fig. 2. Continued.

nificant differences between the types or subtypes of EB. This could be explained by heterogeneity within the disease[8]. Notwithstanding, in our study, other objective indices (hospitalization days, number of accompanying complications) also showed no significant differences in QoL. Meanwhile, perceived disease severity according to patient global assessment was significantly associated with QOLEB scores and Skindex-29 scores. Although establishing a causal relationship was not possible in this observational, cross-sectional study, impairments in daily activity and social relationships might have considerable influence when patients with EB recognize their disease.

In this study, we also assessed economic burden. Most patients reported economic burdens related to preparing dressing materials. "Dressing costs" were higher than "medical costs," demonstrating that dressings are the main cause of economic burdens in patients with RDEB. In the present study, patients reported using various kinds of general and special dressings/fixing materials. Many stated that specialized dressings/fixing materials were better than general dressings/fixing materials with regards to functional aspects. Nevertheless, in addition to their functional aspects, the price of dressing materials also considerably influenced patients' decisions to purchase one material over another. In Korea, specialized dressing materials are not covered by insurance, although three sheets of specialized dressings weekly are covered by insurance for patients with JEB or DEB. Patients with a "rare and incurable disease," including those with RDEB, are responsible for 10% of their total expenses. For instance, patients with RDEB are covered for three sheets of Mepilex lite (Mölnlycke Health Care, Göteborg, Sweden) 20×50 cm for approximately $14 (USD) weekly. However, total monthly "dressing costs" are much more expensive for patients with RDEB because they usually require numerous sheets of dressing material across the whole body. Most

patients change the dressings every day or every other day, imposing a tremendous economic burden.

As skin lesions enlarge, higher economic burden from dressing materials is incurred. As all participants in this study had skin lesions larger than 30%, comparing "dressing costs" according to the involved BSA was not possible. Moreover, blisters and erosions can occur at any area of the skin in patients with EB; therefore, investigating accurate area involvement was not feasible. The BSA of infants or children is smaller than in adults; thus, they are expected to incur lower expenses than adults. Interestingly, however, younger patients in this study accrued more "dressing costs" and "medical costs" than those incurred by adults. In infancy and early childhood, physical adjustment ability has not developed fully, and self-induced mechanical trauma occurs more frequently, making it difficult to maintain dressings. Moreover, secondary complications due to skin barrier disruptions and immunologic immaturity might increase the "medical costs" in younger patients with RDEB. Furthermore, older patients would be expected to have milder phenotypes than others who have died from their disease.

There are several limitations to our study. First, there is the potential for selection bias because our study was conducted at a single institute; our sample may not represent the general population with EB. Nevertheless, our institute is the only institute that can perform laboratory diagnosis of EB; almost all patients in Korea with EB are referred to our institute. Second, the small sample size of this study also acts as a limitation, although incidence of RDEB is very low. Third, patients with severe RDEB were over-represented because these patients are usually referred to our institute. Indeed, all patients included in this study had skin lesions involving more than 30% of their body surface area and averaged seven complications. Fourthly, the main caregivers of children under 7 years old completed the questionnaire. Their answers, which cannot be taken to represent the actual QoL of the children, were also included for analysis. Finally, the potential for recall bias exists in this questionnaire-based study.

In conclusion, RDEB had a profound impact on QoL and economic burden. The present study could help expand the understanding of QoL and economic burden associated with RDEB, and in turn, better meet the needs of patients with this disease.

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