Title page

Title: **Validity of the EQ-5D in pemphigus vulgaris and foliaceus patients**

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Running head: Validity of the EQ-5D in pemphigus

Abstract: 248

Text: 2977

Tables: 4

Figure: 1

Supplementary table: 0

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What's already known about this topic?

The detrimental impact of pemphigus on health-related quality of life has been reported in the literature. No studies have used the EQ-5D questionnaire in pemphigus patients, so far.

What does this study add?

This is the first study employing the EQ-5D questionnaire in pemphigus. The EQ-5D is a valid instrument for the evaluation of health-related quality of life in pemphigus vulgaris and foliaceus. Pain intensity, mucocutaneous involvement and comorbidities are important predictors of quality of life. The EQ-5D might help to better understand the health loss from pemphigus.

Abstract

Background: No studies have employed the EuroQoL (EQ-5D) questionnaire to assess health-related quality of life (HRQoL) in pemphigus patients, to date.

Objectives: To evaluate HRQoL of pemphigus patients by the EQ-5D and to analyse the convergent and known-groups validity of the EQ-5D in this patient population.

Methods: Between 2014 and 2017, a multicentre cross-sectional study was carried out. Outcome measures included the five-level EQ-5D (EQ-5D-5L), Dermatology Life Quality Index (DLQI), Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and an average pain intensity visual analogue scale (VAS) for the past three months.

Results: 109 consecutive patients with pemphigus participated in the study (mean age 57 years; women 64%). Among the EQ-5D dimensions, the most problems were reported regarding pain/discomfort (50%), mobility (43%) and anxiety/depression (43%). No significant difference was found in mean EQ-5D index scores between patients with pemphigus vulgaris and foliaceus (0.81 vs. 0.86; p=0.142). Mean EQ-5D index scores of patients with limited, moderate, significant and extreme pemphigus were 0.88, 0.82, 0.72 and 0.67, respectively (p=0.001). The number of comorbidities was associated with greater impairment in EQ-5D index scores (p<0.001). DLQI (r_s=-0.62; p<0.001) and the average pain intensity VAS (r_s=-0.59; p<0.001) more strongly correlated with the EQ-5D index scores than ABSIS (r_s=-0.40; p<0.001).

Conclusions: This is the first study employing the EQ-5D questionnaire in pemphigus. The EQ-5D is a valid measure of HRQoL in pemphigus patients that can be useful both in clinical practice and in economic evaluations to assess the health gains associated with new effective treatments.

Introduction

Pemphigus is a group of mucocutaneous autoimmune blistering diseases caused by autoantibodies against cell-surface proteins on keratinocytes. The major subtypes include pemphigus vulgaris (PV), pemphigus foliaceus (PF) and a less frequent form, IgA pemphigus.[1] PV accounts for approximately 70-90% of all cases with an annual incidence rate of 0.76 to 32 per million.[2,3] Usual age of onset is between 50-60 years, and female-to-male ratio is ranging between 1.1 and 2.3 in Europe and Asia, but much higher (4.0 and 4.1) in Africa.[4] The clinical manifestation of PV is characterised by the formation of blisters that easily rupture leaving erosions on the skin and/or mucosa.[5] Although it may develop in any localisation, the most commonly affected sites are the scalp, face, neck, trunk, groin and the oropharyngeal mucosa.[6] In contrast, patients with PF rarely develop mucosal involvement. Lesions in pemphigus may be highly painful, show no tendency to heal spontaneously, and are susceptible to superinfection. According to current guidelines, systemic corticosteroid therapy is regarded as first-line treatment in pemphigus.[7-9] An important milestone of 2017 was rituximab combined with short-term prednisone being granted approval as a first-line treatment for PV by the US Food and Drug Administration (FDA).[10]

The detrimental impact of pemphigus and treatment-related side effects on health-related quality of life (HRQoL) have been reported in the literature.[11-13] However, so far, no health utility values have been measured in pemphigus patients. Health utilities are preference-based HRQoL values that are needed to calculate quality-adjusted life years (QALYs) in cost-effectiveness analyses of treatments. Of the commonly used generic instruments, EuroQoL 5-dimension (EQ-5D) questionnaire is advocated as a validated, self-reporting tool to derive utility scores.[14] Given the general character of the EQ-5D, it allows comparisons across a broad range of disease areas and with counterparts in the general public. The EQ-5D has demonstrated

a good validity and responsiveness in a number of dermatological conditions, including psoriasis, atopic dermatitis, hidradenitis suppurativa and acne.[15-17] Yet no studies have employed the EQ-5D questionnaire in pemphigus patients, to date. Therefore, the objectives of our study were i) to evaluate HRQoL in pemphigus patients using the EQ-5D; ii) to compare the burden of pemphigus vulgaris and foliaceus to that of psoriasis measured by the EQ-5D; and iii) to analyse the convergent and known-groups validity of the EQ-5D in pemphigus patients.

Methods

Study design and patients

Between December 2014 and June 2017, a cross-sectional study was conducted in four academic dermatology departments in Hungary. Consecutive patients over 18 years of age diagnosed with any form of pemphigus were enrolled after an informed consent form was read and signed. Permission for conducting the study was granted by the National Scientific and Ethical Committee (reference No. ETT-TUKEB 27416-3/2016/EKU). The questionnaire consisted of two sections. The patients' section included questions regarding demographic data, comorbidities and HRQoL. Physicians' section contained questions referring to disease characteristics, medical history, disease severity and treatments applied.

Outcome measures

EQ-5D-5L

The validated Hungarian version of the EQ-5D-5L questionnaire was used in the study. EQ-5D-5L is a generic, self-reported, preference-based measure of health that consists of a five-item descriptive system and a visual analogue scale (EQ VAS).[18] The five dimensions of health ask about mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each

dimension has five response levels (1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems/unable) and the different combinations of answers define 5^5=3125 distinct health states.[19,20] Each health state can be assigned a utility value (i.e. EQ-5D-5L index score) obtained from population studies reflecting the societal values. In absence of a national value set in Hungary, the 5L value set for England developed by *Devlin et al.* was applied in this study to derive utility values, whereby utilities range between -0.285 and 1.[21] EQ VAS is a 20-cm-long, vertical visual analogue scale with endpoints of '0' ('The worst health you can imagine') and '100' ('The best health you can imagine'). It provides a self-rating of patients' current health status.

Dermatology Life Quality Index (DLQI)

The validated Hungarian version of the DLQI was administered to patients.[22] We have decided to use the DLQI, as it is the most frequently employed tool for measuring dermatology-specific HRQoL in pemphigus patients.[23,24] It has been successfully used in cross-sectional and case-control studies as well as in the Ritux 3 clinical trial for first-line rituximab in pemphigus.[25-30] The ten-item questionnaire covers the commonly mentioned aspects of life affected by skin disease: symptoms and feelings, daily activities, leisure, school and work, personal relationships, and treatments. The DLQI has a possible scoring range of 0–30, with '30' corresponding to the worst, and '0' corresponding to the best score.

Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)

ABSIS is validated disease severity scale for pemphigus.[31-33] The ABSIS score ranges between 0 and 206, with 150 points for skin involvement, 11 points for oral involvement, and 45 points for subjective discomfort. Since HRQoL is based on subjective perceptions of the patients, we have considered the ABSIS with its subjective component to be particularly useful to test the

convergent validity of the EQ-5D. Of note, as there is no relevant difference in diet between Western Europe and Hungary with respect to the food item list of ABSIS, the foods are kept exactly the same as in the English-language version. Subgroups of disease activity are defined based on the cut-off values developed by *Boulard et al.*: limited (ABSIS 0-3), moderate (ABSIS 4-16), significant (ABSIS 17-52) and extensive (ABSIS 53-206) pemphigus.[34]

Global and pain assessments

Furthermore, to assess disease severity the Physicians' Global Assessment (PGA) VAS and Patient's Global Assessment (PtGA) VAS were administered, both providing a range of scores from 0-100, where 0 indicated 'not severe at all' and 100 represented 'very severe'. The average and worst pemphigus-related pain intensities experienced by the patients in the past three months were recorded on a 10-cm-long, horizontal VAS with the endpoints of 'no pain at all' (=0) and 'pain as bad as it could be' (=100).[35]

Statistical analyses

Demographic and clinical characteristics were reported as proportions for categorical variables and means and standard deviations (SD) as well as medians and interquartile ranges (IQR) for continuous variables.

Non-parametric Mann Whitney *U* and Kruskal-Wallis *H* tests were used to compare patient- and physician-based outcome scores in subgroups of patients. Analysis of the relationship between continuous variables was accomplished by calculating Spearman's correlation coefficients (very weak correlation: $r_s<0.2$; weak correlation $0.20 \leq r_s<0.4$; moderate correlation $0.4 \leq r_s<0.6$; strong correlation $0.6 \leq r_s \leq 1$). EQ-5D-5L and EQ VAS results were compared with responses from a group of Hungarian patients with psoriasis obtained in a previous study by our research group (N=238, mean age 47.4±15.2 years, rate of moderate-to-severe psoriasis

81%).[36] For all the statistical tests a two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 (Armonk, NY: IBM Corp. 2013).

Results

Patient characteristics

In total, 109 pemphigus patients participated in the study. Mean age was 57.2±14.8 (range 19-93) years, and 64.2% were males (Table 1). Nearly 80% completed at least a high school education. The proportion of patients over the retirement age was 30.3%. Mean disease duration was 3.8 years. The most frequently represented subtype was PV (n=81), whereas 27 patients were presented with PF, and one patient had IgA pemphigus. The majority of patients had limited (45.9%) or mild (30.3%) pemphigus at the time of the survey. The most commonly used treatments were systemic corticosteroid therapy (70.6%), azathioprine (42.2%) and cyclophosphamide (10.1%) (combinations occurred).

Disease severity and HRQoL scores

Overall, 50%, 43%, 43%, 42% and 19% of the pemphigus patients reported problems in pain/discomfort, mobility, anxiety/depression, usual activities and self-care dimensions of the EQ-5D-5L descriptive system, respectively. Sixty different EQ-5D-5L health states occurred among the patients. The best health state (11111) was indicated by 31 patients (28.7%); thus, a substantial ceiling effect of the EQ-5D-5L descriptive system was detected. No negative EQ-5D-5L index scores were observed (i.e. health states being worse than dead). Mean EQ-5D-5L index and EQ VAS scores were 0.82±0.21 and 68.0±22.3, respectively (Table 2). Mean DLQI score was 5.4±6.9, with the most problems reported regarding sore, itchy or painful skin (48%), embarrassment (48%) and clothing (36%). Overall, 40 patients (37.4%) had a DLQI total score

of zero. The mean ABSIS score for the sample was 11.7±17.3. Mean scores on PGA VAS were significantly lower than PtGA VAS (26.9±27.4 vs. 46.0±35.5; $p<0.001$). Mean worst pain intensity scores on VAS were significantly higher compared with average pain intensity scores (33.6±30.6 vs. 21.4±37.6; $p<0.001$).

Comparison of PV and PF patients

ABSIS scores showed a trend toward higher severity score in PV compared with PF (Table 2). Patients affected by PV tended to have worse scores both in EQ-5D-5L index and EQ VAS. However, PF patients experienced greater HRQoL impairment as measured with the DLQI. Patients with PV indicated significantly higher scores on worst pain intensity VAS as compared with PF ($p<0.05$).

EQ-5D-5L and EQ VAS results of patients with pemphigus vulgaris, pemphigus foliaceus in comparison with a previous study in psoriasis

A greater proportion of PV patients indicated problems in all five dimensions of the EQ-5D-5L than PF patients, especially concerning usual activities and mobility (Fig. 1). In all dimensions, PV patients reported approximately equal or more problems than psoriasis patients, while PF patients experienced nearly equal or less problems than patients with psoriasis. When PV and psoriasis patients were compared, the most pronounced difference was observed in usual activities (51% vs. 32% reported at least slight problems, and 11% vs. 3% reported severe or extreme problems). Psoriasis patients' EQ-5D-5L index (0.84) and EQ VAS scores (72.5) were very similar to those of patients with PV and PF ($p>0.05$).

Convergent validity

EQ-5D-5L index scores demonstrated a strong correlation with DLQI and EQ VAS scores, a moderate-to-strong correlation with average pain intensity VAS and a moderate correlation with ABSIS, PGA VAS, PtGA VAS and worst pain intensity VAS scores ($p<0.001$) (Table 3). In contrast, EQ VAS moderately correlated with the DLQI and the scores on pain intensity scales ($p<0.001$). There was a weak, insignificant correlation between EQ VAS and ABSIS scores. PGA VAS highly correlated with both the DLQI and ABSIS ($p<0.001$). A weak negative correlation was found between age and both the EQ-5D-5L index scores ($p<0.01$) and the EQ VAS ($p<0.05$).

Known-groups validity

There was no statistically significant difference in EQ-5D-5L index scores between females and males (Table 4). Mean EQ-5D-5L index scores of patients with limited, moderate, severe and extreme disease were 0.88 ± 0.18, 0.82 ± 0.21, 0.72 ± 0.23 and 0.67 ± 0.24, respectively ($p=0.001$). Similarly, it was able to detect significant difference across PV patients with no lesions, mucocutaneous lesions, skin involvement only and mucosal lesions only ($p<0.001$). Treatments had no impact on EQ-5D-5L index scores at all. Number of comorbidities was associated with greater impairment in EQ-5D-5L index scores ($p<0.001$). The EQ-5D-5L index scores were significantly lower among patients with hypertension, musculoskeletal diseases, diabetes, thyroid disease and cardiovascular comorbidities ($p<0.05$).

Discussion

This is the first study to assess HRQoL in pemphigus patients by using the EQ-5D. Our results indicate that the EQ-5D-5L is a feasible and valid instrument for the evaluation of HRQoL for pemphigus vulgaris and foliaceus. The EQ-5D-5L index scores correlated at least moderately

with all other validated disease severity, pain or HRQoL measures demonstrating a good convergent validity of the instrument in pemphigus patients.

The literature is inconsistent with respect to the effect of gender and pemphigus subtype on HRQoL. In line with six other investigations,[26-28,37-39] we observed no significant difference in HRQoL between women and men. Nevertheless, some authors found female patients with pemphigus in significantly worse HRQoL.[40,41] Regarding pemphigus subtypes, compared to PV, our patients with PF reported less problems in all five items of the EQ-5D-5L and had slightly better EQ-5D-5L index and EQ VAS scores. Nonetheless, this difference did not reach statistical significance. This corroborates findings from three earlier studies examining HRQoL in PV and PF patients by using SF-36, DLQI and Skindex-29 questionnaires.[39,40,42] We also observed that PV patients with mucocutaneous symptoms had the lowest EQ-5D-5L index scores, which highlights the importance for additional supportive treatments for mucosal symptoms (e.g. topical corticosteroid, gels containing local anaesthetics and intralesional corticosteroid injections).[8,43-45]

Clinical severity, as evaluated by ABSIS, and EQ-5D-5L index scores correlated moderately. Interestingly, there was no significant correlation between ABSIS and EQ VAS scores. The discrepancy in the convergent validity of EQ-5D-5L index scores and EQ VAS might be explained by the difference in how these two instruments capture health status. Not only the five dimensions of the EQ-5D descriptive system but any aspects of HRQoL that matter to respondents may influence the way that overall health is rated on the EQ-VAS.[46] In fact, many patients indicating no problems at all in the five dimensions score themselves as less than 100 in the EQ VAS.[47]

Skin erosions and ulcers in pemphigus may cause debilitating pain. To date, the damaging effect of pain on HRQoL in pemphigus have demonstrated in few studies.[39,40,48] One study from Iran found that the presence of pain did not have a significant negative effect on DLQI scores.[27] In contrast, our results suggest that pain intensity is one of the most important predictors of HRQoL in pemphigus. In clinical settings, thorough pain assessment using well validated tools would be essential to develop personalized treatment plans for pemphigus patients.[49] Providing effective pain relief has a pivotal role in improving patients' HRQoL.

Patient-perceived impact of psoriasis is well-known and widely studied in the literature.[50,51] In accordance with previous studies in which the Short Form-36 (SF-36) and the World Health Organization Quality of Life-BREF (WHOQOL-BREF) were administered,[39,40,52] we found the impact of pemphigus very similar to that of psoriasis by the EQ-5D-5L. However, in contrast to psoriasis, pemphigus has a relatively high mortality rate, ranging from 5% to 30% after diagnosis depending on the length of follow-up.[53] Risk of death is approximately 2- to 3-fold compared to the general population.[2] Considering the high mortality rate, health benefits achieved with therapy are expected to be higher in comparison with psoriasis, as effective treatments for pemphigus might improve both morbidity and mortality. This will also be reflected in cost-effectiveness results of treatments that take into account HRQoL improvement as well as life-years saved.

It seems that pemphigus poses a large burden on patients when it comes to usual activities (e.g. working/studying, housework, family or leisure activities). The scientific evidence on the productivity loss in patients with autoimmune blistering diseases is scarce.[54] In Canada, *Heelan et al.* reported a very large burden of autoimmune bullous diseases on ability to work using the

Work Productivity and Activity Impairment-Specific Health Problem questionnaire.[55] More severe disease and larger HRQoL impairment were associated with a greater productivity loss.

Given the rarity of disease, one of the greatest challenges of studying pemphigus is recruiting a sufficient number of patients.[56] In comparison with published clinical trials and HRQoL studies in the field,[12,57] the sample size of 109 pemphigus patients may be considered relatively large. Further strengths include the multicentre design that allowed to involve the four largest autoimmune bullous disease centres in Hungary and the high rate of patients with PF, as compared with other studies.[25,28,37,39,40,52,58,59] To our knowledge, we were the first to obtain health utility values from pemphigus patients. Up to now, only directly elicited utilities were available in pemphigus generated with time trade-off method from a general population sample.[13] Our findings are especially useful considering that in many countries such as the UK, France, the Netherlands, Belgium, Hungary and Poland national health technology appraisal bodies recommend the EQ-5D for measuring utilities.[60-65]

The following limitations should be noted. First, patients with severe pemphigus were underrepresented in the sample that explains the rather good general health state of patients expressed by both the EQ-5D-5L and EQ VAS. Secondly, the English value set has been applied in the study, because no national tariff is available for the EQ-5D-5L in Hungary. We acknowledge that there are several limitations of transferring value sets and EQ-5D scores across different jurisdictions.[66] Thirdly, in previous studies, the presence of antibodies against desmoglein 1 and 3 (Dsg1 and 3) antigens was associated with disease activity and HRQoL in pemphigus.[39,42,67-69] Our study was a cross-sectional questionnaire survey; no serum samples were collected from patients that could have allowed to measure anti-desmoglein antibody levels. In future studies, investigating the correlation between autoantibody levels and EQ-5D

index scores is an important research direction. Finally, convergent validity was assessed against the ABSIS and DLQI. In validation studies, the Pemphigus Disease Area Index (PDAI) performed better in certain psychometric properties (e.g. intra-rater variability, construct validity with Dsg 1 and 3 autoantibodies) compared with ABSIS.[33] Convergent validity could not been tested against autoimmune disease-specific HRQoL tools, such as the Autoimmune Bullous Disease Quality of Life (ABQOL)[70] and Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL),[71] which were not available in Hungarian. The development of a mapping algorithm between ABQOL or TABQOL and EQ-5D index scores would be particularly beneficial in clinical trials where no health utilities are directly measured.

The EQ-5D results in pemphigus are particularly timely. From 2017 rituximab is available as a first-line therapy for PV in the US, but in many other countries it is only used as a second- or third-line therapy for PV, in part owing to its high costs.[10] An increasing number of PV patients worldwide is expected to be treated by rituximab in the years to come. The EQ-5D allows to measure the health gains associated with high-cost but very effective drugs, such as rituximab. No published cost-effectiveness analysis can be found in pemphigus; nevertheless, it is very likely that, similarly to psoriasis,[72] the EQ-5D will become the major tool to obtain HRQoL data in economic evaluations of pemphigus treatments. Thus, the EQ-5D scores reported in the present study support resource allocation decisions and might aid to improve patients' access to more effective medicines, in a condition for which only limited treatment options have been available, so far.

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Figure legends

Fig. 1 Distribution of responses to the five dimensions of the EQ-5D-5L in pemphigus vulgaris and foliaceus compared to psoriasis
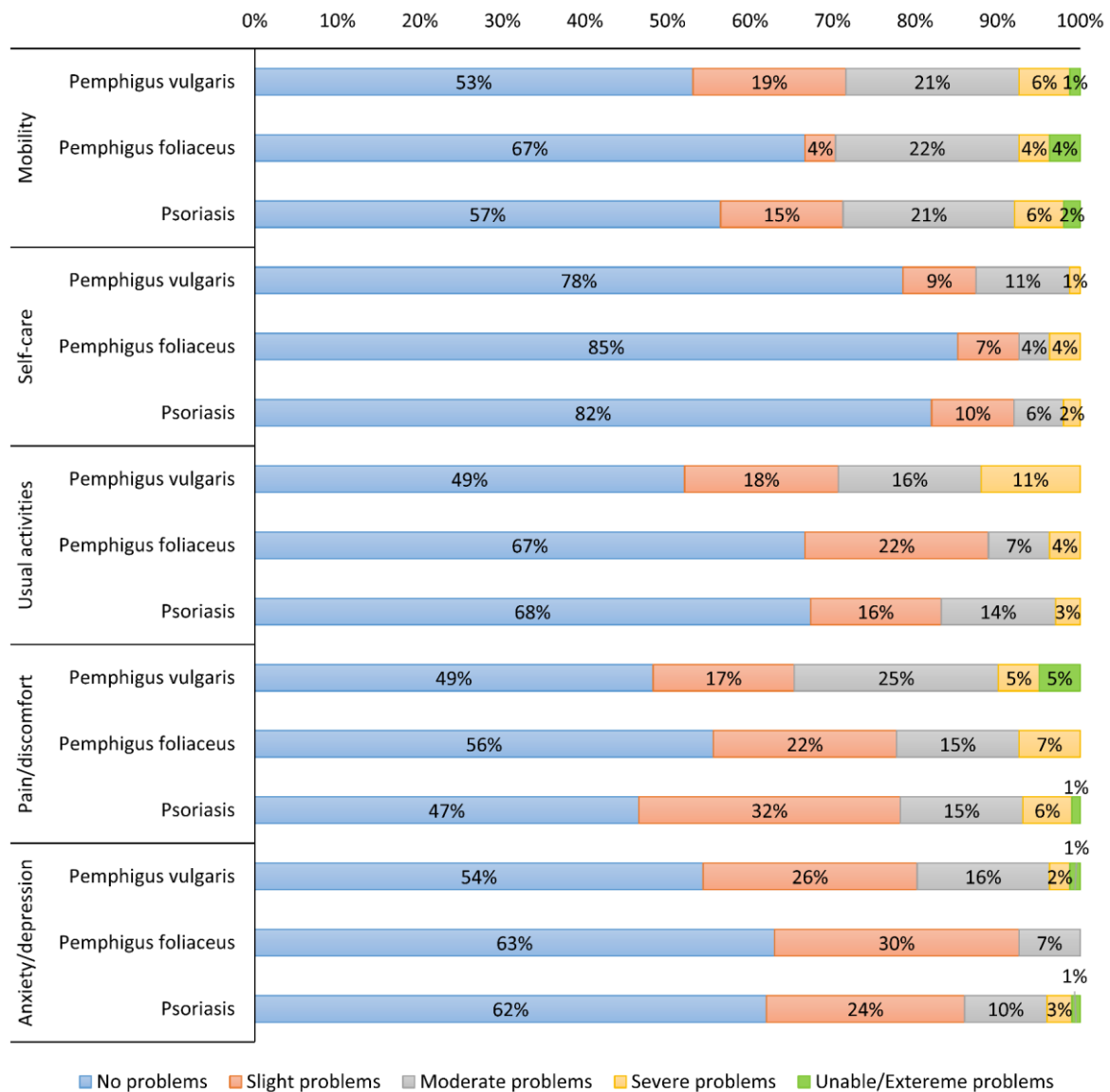
Note: Psoriasis data (Hungary, N=238, mean age 47.4±15.2 years, 81% moderate-to-severe psoriasis) - Poór et al. 2017[36]

Tables

Table 1 Demographic and clinical characteristics of 109 patients with pemphigus

Variables	Mean (SD) or N (%)
Age (years)	57.2 (14.8)
Gender	
Female	70 (64.2%)
Male	39 (35.8%)
Education	
Primary school	22 (20.2%)
High school	58 (53.2%)
College/university	29 (26.6%)
Employment status*	
Employed full-time	41 (37.6%)
Employed part-time	10 (9.2%)
Unemployed	6 (5.5%)
Disability pensioner	15 (13.8%)
Retired	38 (34.9%)
Student	1 (0.9%)
Other	4 (3.7%)
Disease duration (years)	3.8 (4.9)
Type of pemphigus	
Pemphigus vulgaris	81 (74.3%)
Pemphigus foliaceus	27 (24.8%)
IgA pemphigus	1 (0.9%)
Severity of pemphigus	
Limited (ABSIS 0-3)	50 (45.9%)
Moderate (ABSIS 4-16)	33 (30.3%)
Severe (ABSIS 17-52)	21 (19.3%)
Extreme (ABSIS 53-206)	5 (4.6%)
Current treatment	
None	3 (2.8 %)
Topical therapy (only)	10 (9.2%)
*Systemic therapy**	96 (88.1%)
Corticosteroid	77 (70.6%)
Azathioprine	46 (42.2%)
Cyclophosphamide	11 (10.1%)
Cyclosporine	1 (0.9%)
Dapsone	1 (0.9%)
Intravenous immunoglobulin (IVIg)	1 (0.9%)
Methotrexate	1 (0.9%)
Plasmapheresis	1 (0.9%)

*Combinations may occur.
ABSIS = Autoimmune Bullous Skin Disorder Intensity Score

Table 2 Disease severity and HRQoL scores of pemphigus vulgaris and foliaceus patients

Outcome measures	Total sample			Pemphigus vulgaris			Pemphigus foliaceus			p-value
	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)	
EQ-5D-5L (-0.285 to 1)	108	0.82 (0.21)	0.88 (0.73-1.00)	80	0.81 (0.22)	0.89 (0.71-0.94)	27	0.86 (0.20)	0.94 (0.79-1.00)	0.142
EQ VAS (0-100)	109	68.0 (22.3)	75 (50-90)	81	67.6 (23.6)	75 (50-90)	27	69.7 (18.6)	75.0 (55.0-82.5)	0.937
DLQI (0-30)	107	5.4 (6.9)	2 (0-10)	80	5.3 (7.15)	1 (0-10)	26	6.0 (6.0)	5 (0-10)	0.279
ABSIS (0-206)	109	11.7 (17.3)	4 (0.2-15)	81	13.4 (18.1)	5 (1-21)	27	7.1 (14.5)	3.5 (0-6.5)	0.109
PGA VAS (0-100)	108	26.9 (27.4)	20 (0-50)	80	28.6 (28.6)	20 (0-50)	27	22.6 (23.5)	10 (0-40)	0.316
PtGA VAS (0-100)	106	46.0 (35.5)	50 (0-80)	78	47.6 (35.6)	50 (20-80)	27	43.0 (35.3)	50 (0-80)	0.533
Average pain intensity VAS* (0-100)	106	21.4 (30.6)	0 (0-40)	78	24.0 (31.8)	0 (0-50)	27	14.8 (26.2)	0 (0-20)	0.152
Worst pain intensity VAS* (0-100)	107	33.6 (37.6)	10 (0-70)	80	38.6 (38.3)	30 (0-80)	26	18.8 (31.8)	0 (0-35)	**0.009**

*in the past 3 months

ABSIS = Autoimmune Bullous Skin Disorder Intensity Score; DLQI = Dermatology Life Quality Index; PGA VAS = Physicians' Global Assessment of disease severity visual analogue scale; PtGA VAS = Patient's Global Assessment of disease severity visual analogue scale; VAS = visual analogue scale

Bold value indicates a statistically significant difference at p<0.05.

For EQ-5D-5L and EQ VAS higher scores refer to better health status, for all other measures higher scores represent worse health status.

Table 3 Spearman's correlations between continuous variables

Variables	EQ-5D-5L (-0.285 to 1)	EQ VAS	DLQI	ABSIS	PGA VAS	PtGA VAS	Average pain intensity VAS§	Worst pain intensity VAS§	Age
EQ VAS (0-100)	0.607	-	-	-	-	-	-	-	-
DLQI (0-30)	-0.619	-0.463	-	-	-	-	-	-	-
ABSIS (0-206)	-0.396	-0.163*	0.543	-	-	-	-	-	-
PGA VAS (0-100)	-0.460	-0.233	0.627	0.857	-	-	-	-	-
PtGA VAS (0-100)	-0.456	-0.147*	0.575	0.574	0.622	-	-	-	-
Average pain intensity VAS§ (0-100)	-0.593	-0.338	0.649	0.518	0.606	0.643	-	-	-
Worst pain intensity VAS§ (0-100)	-0.499	-0.298	0.574	0.576	0.612	0.594	0.759	-	-
Age (years)	-0.252	-0.194	0.060*	0.045*	0.082*	0.060*	-0.003*	-0.016*	-
Disease duration (years)	0.182*	0.004*	-0.190*	-0.348	-0.359	-0.285	-0.277	-0.205	0.004*

*not significant (p≥0.05)

§ in the past 3 months

ABSIS = Autoimmune Bullous Skin Disorder Intensity Score; DLQI = Dermatology Life Quality Index; PGA VAS = Physicians' Global Assessment of disease severity visual analogue scale; PtGA VAS = Patient's Global Assessment of disease severity visual analogue scale; VAS = visual analogue scale

For EQ-5D-5L and EQ VAS higher scores refer to better health status, for all other measures higher scores represent worse health status.

Table 4 EQ-5D-5L index scores in subgroups of patients

Variables	N	Mean (SD)	Median (IQR)	p-value[§]
Gender				
Female	69	0.82 (0.21)	0.88 (0.71-1.00)	0.454
Male	39	0.83 (0.22)	0.92 (0.75-1.00)	
Severity of pemphigus				
Limited (ABSIS 0-3)	49	0.88 (0.18)	0.94 (0.83-1.00)	**0.001**
Moderate (ABSIS 4-16)	33	0.82 (0.21)	0.88 (0.73-0.94)	
Severe (ABSIS 17-52)	21	0.72 (0.23)	0.77 (0.64-0.92)	
Extreme (ABSIS 53-206)	5	0.67 (0.24)	0.70 (0.45-0.87)	
Pemphigus vulgaris subgroup*				
No symptoms	27	0.90 (0.15)	0.94 (0.88-1.00)	**0.001**
Only cutaneous symptoms	25	0.80 (0.22)	0.88 (0.69-0.94)	
Only mucosal symptoms	11	0.79 (0.23)	0.83 (0.69-0.97)	
Mucocutaneous symptoms	15	0.68 (0.21)	0.73 (0.62-0.77)	
Current treatment				
None	3	0.88 (0.16)	0.94 (0.81-0.97)	0.915
Topical therapy	10	0.86 (0.12)	0.88 (0.77-0.94)	
Systemic therapy	95	0.82 (0.22)	0.88 (0.732-1.00)	
Number of comorbidities				
0	21	0.89 (0.17)	0.94 (0.92-1.00)	**<0.001**
1	26	0.90 (0.15)	0.97 (0.80-1.00)	
2	26	0.81 (0.22)	0.88 (0.68-1.00)	
3	18	0.83 (0.12)	0.85 (0.73-0.92)	
4≤	17	0.63 (0.29)	0.66 (0.49-0.79)	
Comorbidities				
Hypertension	53	0.80 (0.22)	0.85 (0.71-0.94)	**0.048**
Musculoskeletal diseases	34	0.72 (0.25)	0.77 (0.64-0.89)	**<0.001**
Diabetes	19	0.71 (0.27)	0.79 (0.64-0.88)	**0.013**
GERD, gastritis, peptic ulcer disease	13	0.76 (0.29)	0.87 (0.62-1.00)	0.639
Thyroid disease	12	0.75 (0.14)	0.68 (0.64-0.91)	**0.019**
COPD, asthma, allergy	11	0.72 (0.30)	0.79 (0.64-0.94)	0.201
Cardiovascular diseases (excl. hypertension)	6	0.67 (0.21)	0.73 (0.44-0.86)	**0.033**

Bold values indicate a statistically significant difference at $p<0.05$.
GERD = gastroesophageal reflux disease; COPD = chronic obstructive pulmonary disease
* Missing responses n=2
§ Mann-Whitney *U* or Kruskal-Wallis *H* test, where $p<0.05$ was considered statistically significant.