VALIDITY OF HEALTH-RELATED QUALITY OF LIFE MEASURES AND COST-OF-ILLNESS IN PATIENTS WITH HIDRADENITIS SUPPURATIVA IN HUNGARY

PhD thesis

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1 Introduction

Hidradenitis suppurativa/acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle. HS usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillar, inguinal and anogenital regions.

The classification of HS is based on the disease severity; several clinical score systems are in use. The Hurley classification is the most used score to assess the severity of HS.

The exact prevalence of HS is not known and varies widely across the world. Estimates range from 0.00033% to 4.10%. A retrospective study of 48 million patients in the United States found an annual incidence of 11.4 cases per 100,000.

In HS, there is a significant diagnostic delay, from the onset of the first symptoms to establishing the diagnosis could be 7.2 years on average. The longer it takes to establish the correct diagnosis, the greater the disease severity at diagnosis.

The therapy of HS requires a complex approach; combining topical and systemic medical treatments with surgical interventions is applicable in every stage. HS has a profound impact on patient's health-related quality of life (HRQoL). Patients suffer from pain, pruritus, and malodorous discharge affecting their everyday life. Chronic pain is the most distressing symptom in HS; mild or moderate intensity of pain is reported in around 97% of the patients.

Disease burden describes and quantifies the death or health loss connected to a particular disease; beyond mortality and the loss of function, it covers both HRQoL and the cost of illness. Assessing the disease burden is profitable for both the individual and society, with significant clinical and health economic benefits. A detailed determination of a particular disease's burden may also help improve management by better understanding patients' experiences. HRQoL measurements are important to determine the key dimensions of HRQoL and optimize the management. HRQoL in dermatology can be assessed with generic, dermatology-specific, and condition-specific instruments. The EQ-5D is one of the most commonly used generic HRQoL measures that demonstrated good validity and responsiveness in patients with chronic skin diseases, such as psoriasis, atopic dermatitis, and pemphigus. A recent Cochrane review found that only the Dermatology Life Quality Index (DLQI) was applied in published HS randomized controlled trials. In addition to the DLQI, other HRQoL outcomes may be useful in HS patients, such as DLQI-Relevant (DLQI-R) or Skindex-16.

Cost-of-illness (COI) studies aim to assess the economic burden of disease on patient, employer, health insurer or on society. . There are two types of disease costs: direct and indirect, and within direct costs, we distinguish between health and non-health costs. Direct health care costs are the costs of resources directly related to health care (e.g., outpatient or inpatient care and treatments). Direct, non-healthcare costs, on the other hand, require resources related to the disease but not in healthcare (e.g., travel, non-healthcare, etc.) or household expenses related to the disease. An indirect cost is an indirect economic consequence of decreased productivity due to illness (e.g., absence from work), disability, or premature death carried by the individual, family, society, or the employer. A distinction is made between the concepts of presenteeism and absenteeism. The former means a partial but not complete reduction in work capacity, while the latter means a loss of total work ability.

2 Aims

Our aims were:

- I. The assessment of health status and HRQoL in patients with HS in Hungary.
  - a) To assess health status, general and skin-specific HRQoL of HS patients in Hungary;
  - b) To compare health status and HRQoL of HS patients to that of psoriasis and pemphigus patients in Hungary;
  - c) To assess the measurement properties (floor and ceiling effect, convergent and known-groups validity) of three skin-specific (DLQI, DLQI-R, and Skindex-16) and a generic measure (EQ-5D-5L) in HS;
  - d) To estimate health utilities (EQ-5D-5L index scores) in HS by using the Hungarian EQ-5D-5L value set that can be later used as local inputs in health economic models of HS treatments.
- II. Measuring costs of HS in Hungary.
  - a) To estimate direct medical, direct non-medical, and indirect costs in Hungarian HS patients;
  - b) To identify the most important cost drivers and predictors of costs.

3 Methods

Between September 2017 and October 2019, a cross-sectional questionnaire survey was carried out at three academic dermatology clinics in Hungary. Consecutive patients aged 18 years and above diagnosed with HS were recruited to the study. Written informed consent was obtained from each participant prior to the data collection.

Permission for conducting the study was granted by the Scientific and Ethical Committee of the Medical Research Council under reference no. 40579-2/2017/EKU.

The questionnaire consisted of two sections. In the first section, patients were asked about socio-demographic characteristics, general health status, HRQoL, employment, and retrospective data on resource utilization related to HS. The HRQoL was measured by DLQI, DLQI-R, EQ-5D, EQ-VAS, and Skindex-16. The Hungarian EQ-5D-5L value set was applied to generate index scores. Dermatologists were asked to complete the second section of the questionnaire that collected data about patients' history of illness, disease severity, previous medication use, and surgeries.

3.1 EQ-5D

EQ-5D is one of the most widely used questionnaires that demonstrated good validity and responsiveness in patients with chronic skin diseases, such as psoriasis, atopic dermatitis, and pemphigus. It is a generic, self-reported, preference-based measure of health. EQ-5D consists of a five-item descriptive system and a visual analog scale (EQ-VAS). 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. Each health state can be assigned a utility value (i.e., EQ-5D-5L index score) ranging between -0.848 and 1 (1 equals complete health, 0 equals death, negative values equal conditions considered worse than dead) obtained from population studies reflecting the societal values. EQ-VAS is a 20-cm-long, vertical visual analog 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.

It has two versions suitable for adults, the EQ-5D-3L and the newer EQ-5D-5L. While the EQ-5D-3L proved to be a useful and valid measure in HS patients, the EQ-5D-5L was not previously validated in HS. Clinical data collected with the EQ-5D can also be used when assessing the cost-effectiveness of health interventions.

3.2 DLQI, DLQI-R

DLQI is the most commonly used tool for measuring dermatology-specific HRQoL both in general dermatology in HS patients. 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. Each dimension has four possible answers (0-not at all/not relevant, 1-a little, 2-a lot, 3-very much). The DLQI has a possible scoring range of 0–30, with '30' corresponding to the worst and '0' corresponding to the best score.

It has been used for nearly 30 years; recently, a growing number of studies deal with the matter of 'not relevant' responses (NRRs). There are two likely interpretations of NRRs: they may be considered 'not at all' or missing responses. It has been suggested that the NRRs in DLQI may lead to an underestimation of the disease burden. To address this limitation, a modified DLQI scoring method, the DLQI-R, has been proposed recently. It eliminates the NRR items of the DLQI and thereby adjusts the total score to the relevant items; DLQI-R has shown better validity, responsiveness, and discriminatory power.

3.3 Skindex-16

Skindex-16 is an easy-to-apply multidimensional instrument for measuring dermatology-specific HRQoL consisting of 16 items; it is a single-page, shortened version of Skindex-29. In previous studies, it was shown to be reliable, valid, and sensitive to clinical changes.

The items are distributed across three dimensions—symptoms (items 1 to 4), emotions (items 5 to 11), and functioning (items 12 to 16). The answers are collected on a seven-point Likert scale (varying from 0—never bothered, to 6—always bothered), representing the frequency with which the skin problem bothered the respondent during the last week. The results are converted to a linear scale that ranges from 0 to 100; the higher the scores, the poorer the respondent's HRQoL. Skindex-16 can be used to assess patients with any skin problem and after the start of treatment detect their progression over time.

3.4 Cost calculation

We used a prevalence-based approach to estimate the COI associated with HS. All costs were estimated from the perspective of the Hungarian society for the year 2019. Costs of HS included direct medical (attributable to the healthcare sector), direct non-medical (informal care and transportation), and indirect (productivity loss) costs. The cost calculation proceeded in two steps. First, we identified all resources consumed by each patient using a bottom-up approach. Data on resource utilization were collected retrospectively for the past 12 months. Recall periods in the questions varied from 1 to 12 months, depending on the type of utilization and its usual frequency. Secondly, the quantities of resources used were multiplied by their unit costs. Unit costs for all identified resources were retrieved from official published sources, including the National Institute of Health Insurance Fund Management (NIHIFM) and the Hungarian Central Statistical Office. Hungarian forints were converted into euros at an average annual exchange rate published by the Central Bank of Hungary (€1 = HUF 325.35).

4 Results

4.1 Patient characteristics

Overall, 200 adult patients with HS were included in this study. Patients' age ranged from 18 to 67 years, with a mean age of 37.1±12.4 years, and 123 (61.5%) were male. The majority of the patient population had a high school education or above (79.9%). A total of 81.2% of the patients were overweight or obese (BMI > 25), and 70.0% were smokers. The mean disease duration was 4.76±6.72 years. The most common localisations of disease were axillary (77.5%), inguinal (63.5%), and gluteal (29.5%). Comorbidities were present in 92 (46.0%) patients, the most common of which were cardiovascular disease (16.5%), other dermatological diseases (12%), IBD (Crohn's disease 6% and ulcerative colitis 1%), diabetes (6%) and mental illness (6%).

4.2 Disease severity and health-related quality of life scores

Mean±SD scores for HS-PGA were 3.20±1.22, for MSS 60.69±50.24 and PtGA VAS 69.62±22.22. The mean DLQI and DLQI-R scores were 11.75±8.11 and 12.19±8.33, with the most problems reported regarding sore, itchy or painful skin (87.4%), embarrassment (81.0%), clothing (74.2%), and social activities (67.7%). 40 (20.7%) patients marked at least one 'not relevant' response on the DLQI. Among the Skindex-16 subscales, the highest mean scores occurred in the emotions subscale (64.55±29.28), followed by functioning (49.40±34.70) and symptoms (46.74±29.36), respectively. In the emotions subscale, patients were most bothered by worrying about their condition (e.g., that it will spread, get worse, scar, be unpredictable)and the persistence/recurrence of their skin condition. Overall, 77.4%, 56.1%, 50.7%, 46.2%, and 28.3% of the patients with HS reported problems in the pain/discomfort, usual activities, anxiety/depression, mobility, and self-care dimensions of the EQ-5D-5L descriptive system. The distribution of responses on the EQ-5D-5L from this study may be compared to those from patients with psoriasis and pemphigus vulgaris obtained in two previous surveys in Hungary shows that HS patients had more significant impairment in HRQoL than reported in psoriasis or pemphigus vulgaris in all five dimensions except for mobility. The difference between HS and the other two dermatologic conditions was huge for the pain/discomfort dimension. The mean EQ-5D-5L index and EQ-VAS scores were 0.76±0.21 and 64.29±22.68, respectively.

4.3 Convergent validity

Regarding convergent validity, the DLQI, DLQI-R, Skindex-16 total score, and EQ-5D-5L index score had strong correlations with each other (range of r_s=|0.650| to |0.993|) and moderate correlations with EQ-VAS and PtGA VAS (range of r_s= |0.434| to |0.592|). HS-PGA correlated moderately with DLQI (r_s=0.418) and DLQI-R (r_s=0.433) and weakly with any other HRQoL measure (range of r_s=|0.311| to |0.390|). The MSS exhibited weak correlations with all HRQoL outcomes (range of r_s=|0.276| to |0.381|). All correlation coefficients were proved to be statistically significant.

4.4 Known groups validity

More severe disease measured by HS-PGA was associated with worse HRQoL scores using all outcome measures ($p<0.001$). The differences between severity groups were significant, with moderate to large effect size for all HRQoL measures (0.090-0.176). Relative efficiency of the HRQoL measures concerning the DLQI varied noticeably: the DLQI-R

(1.076) outperformed, while the Skindex-16 (emotions 0.555, functioning 0.819, symptoms 0.894), EQ-5D-5L (0.709), and EQ-VAS (0.683) lagged behind the DLQI in differentiating between severity groups.

4.5 Predictors of HRQoL in HS

In a multivariate regression analysis, female patients experienced more significant impairment in HRQoL on the DLQI, DLQI-R, and Skindex-16 than their male peers. Patients who had a higher level of education had substantially better HRQoL scores on any outcome measure. Higher disease severity (as measured by the HS-PGA) resulted in worse HRQoL in all instruments except EQ-VAS. In all outcomes except EQ-5D-5L, genital involvement was associated with a significant negative impact on HRQoL. These variables explained a total of 9.2% (EQ-VAS) to 28.8% (Skindex-16) of the variance in HRQoL (p<0.001).

4.6 Healthcare resource utilization and cost of illness in HS

At least one dermatologist and GP consultation were reported by 85.5% and 35% of the patients, respectively. Patients had an average of 11 dermatologists and 14 GP visits due to HS annually. Overall, 28.5% required inpatient medical treatment, 16% inpatient surgical treatment and 20.5% outpatient surgical treatment. The most frequently used medical treatments were topical (68%), systemic antibiotics (57%), and biological treatment (15.5%). The most common surgical procedures were incision and drainage (16.5%), deroofing (10.5%), and limited local excision (6.5%). Twelve patients (6%) used home medical care, and on average, 0.45 hours of care were provided for HS patients weekly. Not reimbursed healthcare services were utilized by 18% of the patients, with the most common services being consultation with a private physician (15%) and private surgery (3%).

Less than one-third of the patients required paid care or informal care from family members or acquaintances. The mean hours of informal care received per week were 2.79±12.91. Three-quarters of patients used transportation to attend their healthcare provider; however, ambulance service was used by merely three patients (1.5%). Most of the patients were active in the labour market (65.5% full-time or part-time employed), while 13.5% were unemployed and 1.5% were disability pension beneficiaries. Productivity loss occurred for 44.5% of the patients, with means of 26 (absenteeism) and 63 (presenteeism) lost working days per year.

HS's annual mean total cost, including all cost categories, was €6,791 (95%CI €5,693-€7,906). Direct medical (€2,400), direct non-medical (€767), and indirect costs (€3,625) accounted for 35.5%, 11.3%, and 53.3% of the total costs, respectively The largest cost components were presenteeism (€1,781, 26.2%), absenteeism (€1,599, 23.5%), biological therapy (€1,465, 21.5%) and informal care (€627, 9.2%). Male patients tended to have higher direct medical costs than females (p=0.025) Mean annual total costs of patients who received no treatment, topical treatment, systemic non-biological treatment, surgical treatment, and biological therapy were: €4,395, €4,344, €3,595, €7,282, and €16,005 (p<0.001). Patients with Hurley III (€8,568) had higher total costs than those with Hurley I (€6,532) or II (€4,681) stages (p=0.007).

Mean annual total costs of patients with clear-minimal, mild, moderate, severe, and very severe HS according to HS-PGA were €5,323, €5,180, €5,766, €9,034, and €9,078 (p=0.074). Weak positive correlations were identified between total costs and the Modified Sartorius Score (r=0.144, p=0.042). The total costs showed an increasing trend with DLQI score bands ($p<0.001$). There was no correlation between the total costs and age ($r=0.057$, $p=0.427$), disease duration ($r=0.052$, $p=0.471$) or BMI ($r=-0.081$, $p=0.260$).

5 Conclusions

- Our study revealed that HS poses a substantial burden on patients and society regarding health loss and healthcare costs. In addition, the emotional burden of HS is considerably more significant than its physical symptoms.
- The HRQoL impairment in HS patients exceeds those reported in psoriasis or pemphigus vulgaris in most areas of health-related quality of life. Our investigation confirmed the validity of DLQI, DLQI-R, Skindex-16, and EQ-5D-5L questionnaires in HS. All of these measures seem suitable for assessing HRQoL in HS in both clinical trials and practice.
- Our study is the first assessment of COI, including direct and indirect costs in patients with HS at an international level.
- COI in HS patients treated with biologics is comparable to that reported in moderate-to-severe psoriasis patients treated with biologics in Hungary.
- Indirect costs and costs of biological therapy represent most of the total COI associated with HS.
- Work impairment, presenteeism is markedly higher compared to other chronic skin diseases, such as psoriasis or pemphigus.

6 List of publications

Publications used for dissertation

Gergely, L. H., Gáspár, K., Brodszky, V., Kinyó, Á., Szegedi, A., Remenyik, É., … Rencz, F. (2020). Validity of EQ-5D-5L, Skindex-16, DLQI and DLQI-R in patients with hidradenitis suppurativa. JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY, 34(11), 2584–2592. IF:6.166 (D1)

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