DOI:10.14753/SE.2022.2622

SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2622.

GERGELY LÁSZLÓ HUNOR

Bőrgyógyászat és venerológia
című program

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DOI:10.14753/SE.2022.2622

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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Budapest
2021

DOI:10.14753/SE.2022.2622

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List of abbreviations

BNO	International classification of diseases (Hungarian adaptation)
COOP	Dartmouth Primary care Cooperative Information Project
DAMP	Damage-associated molecular patterns
DLQI	Dermatology Life Quality Index
DLQI-R	DLQI-Relevant
DQOLS	Dermatology Quality of Life Scales
DSQL	Dermatology-Specific Quality of Life
EADV	European Academy of Dermatology and Venereology
EMA	European Medicines Agency
EQ VAS	EuroQol Visual Analogue Scale
EQ-5D-5L	5-level EQ-5D questionnaire (5-szintű EQ-5D kérdőív)
FDA	US Food and Drug Administration
G- CSF	Granulocyte colony-stimulating factor
HiSCR	Hidradenitis Suppurativa Clinical Response
HRQOL	Health Related Quality of Life
HS	Hidradenitis suppurativa
HS-PGA	Hidradentis suppurativa Physician's Global Assessment
HUI	Health Utilities Index
IHS4	International Hidradenitis Suppurativa Severity Score
IL-12	Interleukin 12
IL-17	Interleukin 17
IL-1β	Interleukin 1 beta
IL-23	Interleukin 23
MMP	Matrix metalloproteinase
NCSTN	Nicastrin (Protein Coding gene)
NHP	Nottingham Health Profile
NRRs	'Not relevant' responses
NSAID	Non-Steroidal Anti-Inflammatory Drug
OGYÉI	Hungarian National Institute of Pharmacy and Nutrition
PSEN1	Presenilin (Protein Coding gene)
PSENEN	Presenilin Enhancer, Gamma-Secretase Subunit (Protein Coding gene)
QALY	Quality-adjusted life year

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QOL	Quality of Life
QWB	Quality of well-Being
RCT	Randomized controlled trial
SF-36	Short Form 36
SIP	Sickness Impact Profile
STEEP	Skin-tissue sparing excision with electrosurgical peeling
TH-1	T helper 1 cell
TH-17	T helper 17 cell
TNF-α	Tumour Necrosis Factor alpha
WPAI	Work Productivity and Activity Impairment questionnaire

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1 Introduction

1.1 Hidradenitis suppurativa

1.1.1 Definition, classification, symptoms

Defined by the 1st International Conference on hidradenitis suppurativa/acne inversa (March 30–April 1, 2006, Dessau, Germany), *„Hidradenitis suppurativa/acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital"(1)*

HS is usually clinically diagnosed, the presence of primary and secondary diagnostic criteria supports the diagnosis. The primary positive diagnostic criteria is the typical clinical presentation: the history of persistent (presence of lesions for at least 6 months) or recurrent (>2 skin lesions occurring or recurring within 6 months) lesions in the inverse regions of the body, presenting with nodules, sinus-tracts and/or scarring. The secondary positive diagnostic criteria include positive family medical history and negative swab or normal skin microbial flora findings. (2)

The classification of HS is based on the disease severity; several clinical score systems are in use. The Hurley classification system introduced in 1989 is the most commonly used score to assess the severity of HS. (3) It is designed to classify the disease severity into 3 stages to assist the appropriate therapy selection. (Figure 1) Its limitation is that it is unsuitable for evaluating disease activity and treatment response.

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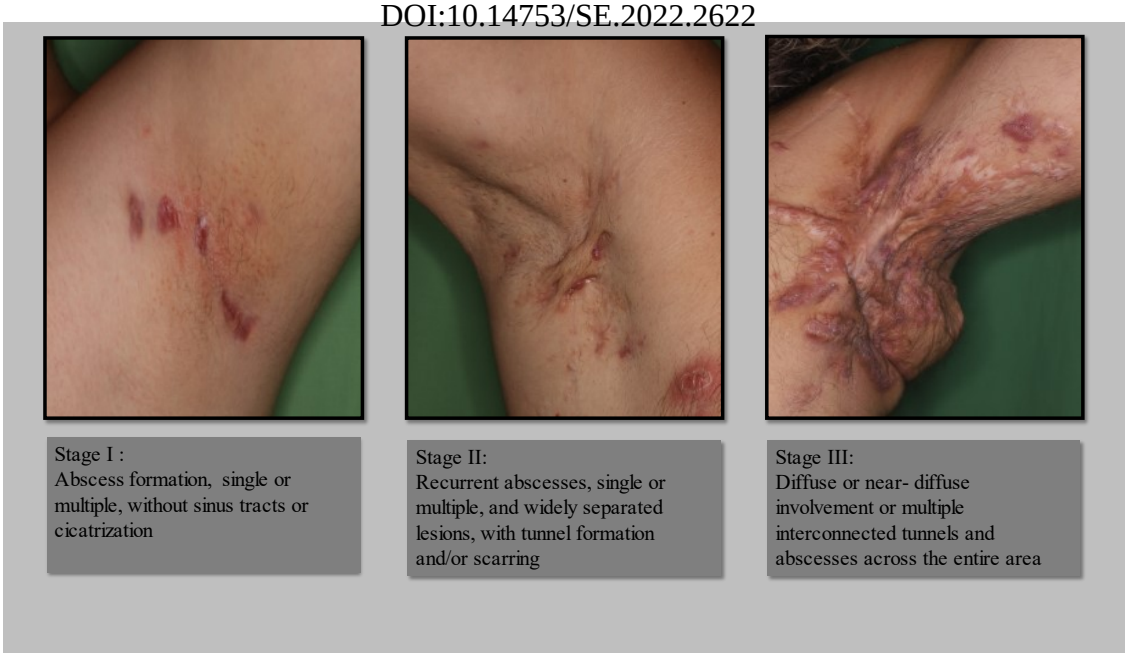

Figure 1: Hurley classification

Classification of Hurley Stages (3)

Source of pictures: Semmelweis University Department of Dermatology, Venereology and Dermatooncology photo database

Sartorius score is a more detailed, universal, dynamic score capable of tracking disease activity changes over time. It was created by Sartorius et al. and was later modified. It is based on the examination of seven anatomical regions (right axilla, left axilla, right groin, left groin, right buttock region, left buttock region, and other locations); within these regions, the extent of disease is determined by counting the type of lesions (nodules, fistulas) and measure the longest distance between two lesions. The modified Sartorius scoring system can be used well to monitor the effectiveness of the treatment; it is widely used in clinical studies. This scoring system correlates well with the intensity of pain and suppuration and the duration of their presence, which are also excellent indicators of inflammation, disease burden, and quality of life. The modified Sartorius scoring system shows a strong correlation to Hurley's stage classification. It may help monitor the effectiveness of conservative treatment. It can be used very well in mild HS, but its applicability is limited in severe cases, as it is difficult to distinguish individual lesions in these cases. Due to its relative complexity and time-consuming nature, its routine use is not realistic. Still, its use in clinical trials and registries (primarily in university centers) may be appropriate due to its high sensitivity. (4, 5)

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Based on the physician's global evaluation, the HS-Physician Global Assessment Tool (HS-PGA) separates six stages according to the disease severity. It is commonly used in psoriasis and acne. Despite its inflexibility, it is an easy-to-use tool in classification and follow-up. (6)

The Hidradenitis Suppurativa Clinical Response (HiSCR) is a clinical tool to assess treatment response. It is defined as a ≥ 50% reduction in total abscesses and inflammatory nodules count and no increase in abscesses or draining fistulas compared with baseline. (7)

The International Hidradenitis Suppurativa Severity Score Index (IHS4) evaluates disease activity and severity based on the number of inflammatory nodules, abscesses, and draining tunnels (fistulae/sinuses) and categorizes into ‘mild,’ ‘moderate’ or ‘severe’ classes. (8)

Lately, the refined Hurley score has been suggested that describes the degree of inflammation and distinguishes different severity levels within a Hurley category. The creation of subclasses mild (A), moderate (B), and severe (C) within stages I and II were aimed to guide the treatment. (9)

1.1.2 Epidemiology

The exact prevalence of HS is not known and varies widely across the world. Estimates range from 0.00033% to 4.10%. This uncertainty could be explained by the method of data collection. The lower prevalence estimates are reported from registry-based studies (<0.1%), while higher estimates are derived from prospective and self-reported studies. (10)

The incidence data also show wide variations. A retrospective study of 48 million patients in the United States found an annual incidence of 11.4 cases per 100,000, with twice the incidence in women than men; in African Americans, it was 2.5 times that of Caucasians. In the same study, it was found that compared with the average annual incidence during the decade from 2006 to 2016, the incidence of 2015–16 was one-third higher. It is hypothesized that the main reasons for this discrepancy might be the increasing recognition of the condition in later times, whereas under-recording of mild disease and misclassification in the older registries. (11)

In HS, there is a significant diagnostic delay. Saunte et al., in their global study (carried out in twenty-nine medical centers in 24 countries) in 2013, found that the time from onset of the first symptoms to establishing the diagnosis was 7,2 years. Furthermore,

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Kokolakis et al., in their 2020 publication, found that the diagnostic delay to be 10 years on average. The delay of the correct diagnosis may have several causes, like: the patient delaying the consult with a physician, the physician not making the proper diagnosis, or both. Positive family history was associated with a longer delay for HS diagnosis; this may suggest a higher tolerance in these families, accepting the disease as a 'condition of life.' (12, 13)

The longer it takes to establish the correct diagnosis, the greater the disease severity at diagnosis. More surgical interventions were reported in patients with delayed diagnoses. An increased number of comorbidities was also linked with the delayed HS diagnosis. Altogether this can result in a reduced ability to work. (12, 13)

1.1.3 Pathophysiology

The pathogenesis of HS is incompletely understood. The pilosebaceous-apocrine unit seems to be in the center of lesion formation. Histopathology shows that the epithelial hyperkeratosis causing follicular occlusion is the primary event that leads to dilatation, which results in follicular rupture and associated immune response in the surrounding dermis. This leads to abscess formation and chronic inflammation with architectural tissue changes in later stages like sinus tract formation and scarring. In HS, several factors are contributing to the inflammatory mechanism. (14)

Around 30-40% of patients with HS report a family history, which can follow autosomal dominant inheritance. Mutations in the gamma-secretase genes NCSTN, PSEN1, and PSENEN can result in a severe phenotype of HS. Gamma-secretase catalyzes the cleavage of multiple type-1 transmembrane proteins, including Notch receptors. In animal models, gamma-secretase gene expression alterations can cause follicular occlusion. (15)

Immunopathogenesis is a complex mechanism including immune activation and progression to chronic inflammation. Besides the central role of monocytes, neutrophils, and cytokines of the Th-1 and Th-17 pathway, several other factors contribute to the complex immune mechanism. (16)

Increased mechanical stress (friction, pressure) causes local cell damage on intertriginous skin areas; in HS affected areas number and volume of sebaceous glands appear to be reduced, which further strengthens friction. (17) This enables the penetration of microbial components into the skin and causes the release of damage-associated molecular patterns

(DAMPs). These may activate macrophages causing secretion of pro-inflammatory cytokines. (18)

Inflammation in the perifollicular region leads to the immune cells' increased secretion of specific mediators, inducing follicular hyperplasia and hyperkeratosis, causing follicular occlusion. (16, 19) These events lead to follicular dilatation and finally to the rupture of the follicle, where the content of the follicle exposed to the surrounding dermis triggers an immune reaction. The expression of inflammatory cytokines (TNF-α, IL-1β) activate endothelial cells and induce immune cell attracting chemokines. They also contribute to the production of extracellular matrix-degrading enzymes, matrix metalloproteinases (MMPs), which cause tissue destruction. Pus formation results from the massive infiltration and activation of neutrophils, sustained by granulocyte colony-stimulating factor (G- CSF) and lipocalin 2. (20, 21). Lipocalin has an important role in maintaining chronic inflammation by inducing the further infiltration of granulocytes. (21) Finally, it results in permanent changes in the composition and architecture of the tissue.

In HS, several comorbidities are reported. The commonly documented HS-associated conditions are metabolic syndrome, depression, sexual dysfunction, inflammatory bowel disease(Crohn’s disease and ulcerative colitis), and axial spondyloarthritis. Also, a higher risk of cardiovascular death and suicide risk have been found. (16, 22)

Around half of the patients diagnosed with HS have obesity, and nearly 40% have metabolic syndrome. (23) Obesity might contribute to HS pathogenesis by mechanically increasing friction at flexural sites and increasing pro-inflammatory response(24). Patients with high-BMI levels have more regions affected, have higher Hurley scores, and worse self-reported severity. (25)

Smoking tobacco is reported in the majority of patients with HS. (26) Though there is a lot to clear about how tobacco smoking affects HS's pathomechanism, it has been shown that nicotine induces epidermal hyperplasia, which might result in infundibular hyperkeratosis and follicular plugging. (27)

The role of hormones is also unclear. The female predominance, the worsening of symptoms around the menses, and the improvement during pregnancy suggest female hormones play an important role. (28) The role of androgens is also suggested from reported cases of therapeutical efficacy of antiandrogens and the high incidence of polycystic ovary syndrome in female patients. (29) However, compared with control subjects, testosterone and dihydrotestosterone levels in patients with HS do not show a significant difference. It is theorized that the role of androgens in HS pathomechanism might be local. (30)

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1.1.4 Treatment

The therapy of HS requires a complex approach; combining topical and systemic medical therapies with surgical interventions is applicable in every stage. As the disease gets more severe, surgical interventions' role is greater in achieving significant therapeutical results. In mild cases, adjuvant and topical therapies are in the first line. Systemic therapy is recommended for patients in whom topical treatment has failed and those in Hurley II and III stages. HS's systemic treatment includes antibiotic mono and combined therapy, retinoids, corticosteroids, and biological agents. (1) Figure II summarizes the therapeutical recommendations of North American, British and European guidelines. (1, 31, 32)

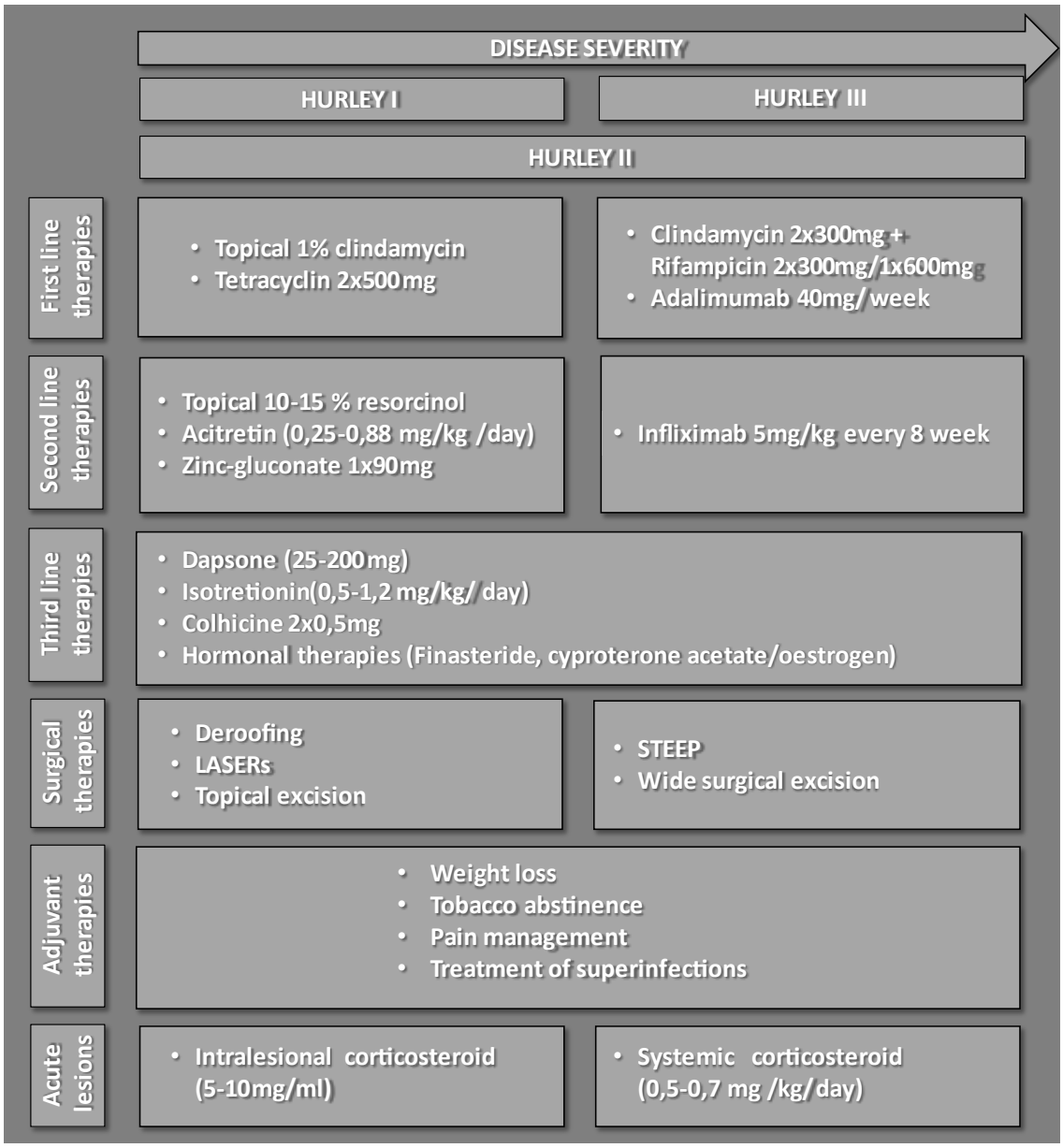

Figure 2: Therapeutical recommendations based on North American, British and European guidelines

Source: North American, British and European guidelines (1, 31, 32)

1.1.4.1 General measures (prevention, lifestyle changes, wound care and pain management)

Disease prevention needs to have an essential role in the future. The regular inspection of individuals with known familial predisposition should be considered. Lifestyle changes are also necessary besides medical and surgical therapies. The cessation of smoking and reducing body weight seem to improve the disease. Though it is challenging for the patients, as they quit smoking, they experience weight gain. Excessive exercise by increased friction causes pain and provocate HS lesions. The role of mechanical friction in everyday life is also essential; in clothing, the patients should wear loose clothes. (33, 34)

Despite proper treatment, suppuration may occur, which causes significant discomfort through odor and maceration. Besides the physical irritation, the suppuration has a major psycho-social burden; it negatively affects the patients' quality of life. Various absorbent bandages are of great help in treating the discharge in the affected areas. So far, only limited evidence is available in the use of dressings in HS; no specific recommendation on the appropriate dressing has yet been made. The bandage is generally expected to keep the surface dry, absorb the smell, and fit the particular anatomical region. (1, 35)

Pain is a severe symptom of HS that has a significant negative impact on the quality of life. The severity of the pain does not depend on the disease severity. Even inflammation of a single axillary nodule can cause such severe pain that the patient cannot perform even the most basic daily activities. The common triggers are friction, heat, and psychological stress. (36) By achieving a rapid improvement in quality of life in the early stages of treatment using appropriate analgesic therapy, we can ensure patient compliance at a later stage. In nociceptive analgesia, first-line therapy, according to literature, is a topical gel containing diclofenac 1%, oral acetaminophen, NSAIDs, and opioids (e.g., morphine, tramadol, etc.). (36, 37) Another way to relieve pain is to block neuropathic pain. For this purpose, gabapentin, which is also used as an anticonvulsant, is pregabalin, tricyclic antidepressants (nortriptyline and desipramine), selective serotonin reuptake inhibitors, and selective serotonin-norepinephrine reuptake inhibitors have been suggested. (37) After initiating systemic therapy, patients most often feel a reduction in pain as the first and most important result of improvement. Controlling the inflammation is an effective pain management strategy. Considerable results can be achieved with oral corticosteroids and biologics. (38)

1.1.4.2 Topical and intralesional therapies

In topical therapies, as adjuvant therapy, disinfectant washes may reduce the bacterial load, thus preventing superinfections and reducing odor. Still, the evidence is lacking to confirm their role in improving HS. The clindamycin topical antibiotic efficiency was investigated in a placebo-controlled, double-blind, randomized trial. It's 1% topical solution reduced the number of lesions in patients with HS, and it is beneficial in reducing superficial lesions such as folliculitis, papules, and pustules. (39) Its first line application is recommended in Hurley I and mild stages of Hurley II. The recommended dose is twice daily for 3 months. (1)

A second-line therapy applying 10-15% resorcinol cream twice a day in mild and moderate forms of HS (Hurley I and II) is a widespread topical treatment. Its exfoliating properties reduce follicular occlusion. Thus fewer active nodules develop; in addition to the exfoliating effect, it also has antiseptic properties. Studies have shown that by applying resorcinol to existing inflamed nodules and abscesses, they persist for a shorter time and reduce the pain. (40)

Intralesional use of triamcinolone acetonide is a good therapeutic option for the treatment of solitary inflammatory lesions, therapy-resistant inflammatory nodules. A prospective case series investigated the effect of intralesional triamcinolone, 10 mg/mL (0.2-2.0 mL) in inflamed HS lesions. It reduced the physician-assessed erythema, edema, suppuration, and size significantly. The patients reported a considerable decrease in pain. Its use should be avoided in cases of clinically clear bacterial infections. (41)

1.1.4.3 Systemic Therapies

1.1.4.3.1 Antibiotics

For many years the antibiotics have been the basis of HS therapy. Tetracycline and a combination of clindamycin and rifampicin are recommended in the first line of treatment. Besides, several other antibiotics are used in the treatment of HS.

Oral tetracycline was compared in small RCT with 1% topical clindamycin, where both were found to be effective. (42) The recommended dosage of oral tetracycline is 2x500mg daily, and it is generally recommended for 3 months. Several studies and case reports indicate that tetracycline-like drugs like doxycycline and minocycline are beneficial in the treatment of mild cases of HS. Their efficacy is likely to be related to their anti-inflammatory properties. (43)

DOI:10.14753/SE.2022.2622
Combination of clindamycin 300 mg twice daily and rifampicin 600 mg daily, after 10 weeks in most patients, a significant decrease in Sartorius score was found in several studies. (44) The combination's efficacy is most likely related to their immunomodulatory and anti-inflammatory properties. This combination is recommended in patients with moderate to severe HS, primarily Hurley II stage, for 10 weeks. Gastrointestinal side effects (nausea, vomiting, diarrhea) are common, and in many cases, treatment should be stopped ahead of the recommended regimen. Patients exceeding the recommended duration of therapy have a higher risk of a possible *Clostridium difficile* infection. (45)

Dapsone, a sulphone derivative having antibacterial and anti-inflammatory effects, only a few clinical studies are available. In a retrospective study, 38% of the patients showed a response, none of the patients in Hurley III stage disease responded. The recommended dosage is 25-200 mg, treatment for at least 3 months is recommended, long term therapy may maintain the responses. Unfortunately, after a short time of discontinuation of the therapy, rapid relapse was common. (46, 47) Methemoglobinemia is the most common side effect. Therefore, regular control of methemoglobin levels is necessary. In case of higher blood levels, dose reduction is required. Because of the low response rates and frequent need for monitoring, dapsone is recommended as third-line treatment in Hurley stage I or II diseases according to guidelines. (1, 32)

1.1.4.3.2 Biologics

The use of TNF-alpha inhibitors in HS's treatment was based on the clinical observation that patients treated with infliximab HS symptoms improved in Crohn's disease. (48) Adalimumab is the only biologics for moderate to severe HS approved by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI).

The efficacy of adalimumab was investigated in two similar phase III multicentre, double-blind, placebo-controlled studies (PIONEER I and PIONEER II) with a total of 633 patients with moderate to severe HS. The two studies' design was similar; in PIONEER II, concomitant oral tetracyclines were permitted. The primary efficacy endpoint was the Hidradenitis Suppurativa Clinical Response (HiSCR). The results showed that more than 50% of patients receiving ADA 160 mg at week 0, 80 mg at week 2, and 40 mg weekly starting at week 4 reached HiSCR compared with around 27% of patients receiving placebo at week 12. (49)

DOI:10.14753/SE.2022.2622
The recommended dosage of adalimumab is 40 mg weekly subcutaneous injection after two inducing doses of 160 mg and 80 mg at weeks 0 and 2. (1)

Infliximab, a chimeric monoclonal antibody that inhibits TNF-α, is also recommended for HS's treatment. It was investigated in a small phase II randomized, controlled trial with 38 patients with moderate to severe HS. Patients received 5 mg/kg of intravenous infliximab on weeks 0, 2, 4, 6, 14, and 22. By week 8, 60% of patients had a 25% to <50% decrease in HS severity compared with the placebo group (5,6%). (50) The recommended dosage of infliximab is 5 mg/kg intravenously at weeks 0, 2, and 6. (1)

Etanercept is a recombinant human TNF-α receptor fusion protein that competitively binds membrane-bound TNF-α receptors. In case reports, promising results were published, but randomized controlled studies failed to prove its efficacy. (51)

Ustekinumab is a monoclonal antibody against IL-12/IL-23; it affects both TH1 and TH17 pathways. It was shown to be efficacious in published case reports; an uncontrolled open-label trial ustekinumab treatment in 17 patients with moderate-to-severe HS suggests limited benefit. (52)

There are promising reports and open-label studies with biologics blocking IL-17 and IL-1 in the treatment of moderate-to-severe HS. Further investigations are evaluating their efficacy. (53)

1.1.4.3.3 Corticosteroids

The use of systemic corticosteroids in HS is highly effective. Because of side effects, their use is limited to short-term treatment in acute flare-ups or pre-operatively to reduce inflammation. In localized flare-ups, intralesional corticosteroids are beneficial; they reduce inflammation, pain, suppuration in a few days. (1, 41)

1.1.4.3.4 Retinoids

Based on the central role of the follicular occlusion in the HS pathomechanism, the efficacy of retinoids(isotretinoin/acitretin) in the therapy has been investigated in several studies. Isotretinoin seems to be ineffective in HS. (54) A review found that the response rate in patients with HS was around 66% with acitretin treatment. The dosage of acitretin is 0.25–0.88 mg/kg daily. The signs of improvement are expected within the first two months of treatment; in case of progress, it can be continued for at least 6 months, but even up to 12-39 months. (1, 55)

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1.1.4.4 Surgery

Surgical interventions should be considered in patients with irreversible lesions such as fistules, contracture, and scars; or in severe chronic medically non-responsive lesions. Several surgical interventions have been used in the management of HS, like incision and drainage, deroofing, limited local excision, radical excision, STEEP, and wide local excision with grafting. Because of the high recurrence rate, the incision and drainage of an individual lesion should be used as an emergency intervention for extremely painful abscesses. In cases of localized disease, local excision or deroofing is advised. By definition, deroofing is the removal of the skin covering a tunnel by an electrosurgical device. On the floor, the gelatinous and sanguinolent tissues are scraped away with a curette; it heals by secondary intention. (16) In severe cases of HS, wide radical excision with grafting is recommended, healing by secondary intention is also possible, but healing takes a long time. There is no consensus on exactly which operation should take place at the different stages of the HS. (1)

1.2 Burden of disease

The concept of disease burden was developed jointly by the World Health Organization, the World Bank, and the Harvard School of Public Health in the early 1990s, which in a broader sense means the impact of a health condition on any area of life, in a narrower sense only on health. (56)

The effectiveness of healthcare systems requires an understanding of the critical challenges needed to improve the population's health and how they are changing. (57)

In addition to mortality, loss of function, and other factors, the burden of disease also includes the impairment in health-related quality of life and the total cost of the disease. From a health economics perspective, measuring the latter two variables has significant clinical and health economics benefits for both the individual and the wider population. While the health status of a population is quantified in terms of life expectancy or mortality, these data are difficult to apply to characterize a person's situation. Measuring health related quality of life (HRQoL) is increasingly important as international data suggested that improved survival was accompanied by lower HRQoL results in the past decades. (57)

It is desirable to summarize the burden of disease at a population level for global comparison into a single measure. The most commonly used tool for this is disability-adjusted life years (DALY). A DALY is a loss of a year of life that could have been lived

DOI:10.14753/SE.2022.2622
in health, mortality, and morbidity indices are used for the calculation, mainly from post-mortem or cross-sectional population statistics. (58)

The financial resources of the health care system ensuring the patient's health are limited. Therefore, it is important to know the costs of treating a disease for the care system, society, or the patient. Globally, the prices of treating a given patient do not appear to be significant. Still, if a given disease affects a considerable part of the population, it has a significant cost and may have a noticeable impact on the national economy. Thus, the burden of disease also has micro-and macroeconomic implications, and considering these can affect health policy and health economic decisions.

1.3 Health-related quality of life in HS

The World Health Organisation (WHO) defined Quality of Life (QoL) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns."(59) It is a complex definition, including all aspects of a person's life. QoL is discussed in the medical literature since the 1960s. In the second half of the 20th century, more and more medical therapies became available. (60) With the new treatments, the extension of the lifetime and the quality of life they offered gained importance. The impact of the diseases on life quality, especially in chronic nonlethal conditions, also became relevant. To assess Quality of Life from the medical point of view, the Health-Related Quality of Life was introduced HRQoL. (61) Physical, psychological and social health aspects are included in HRQoL measures in subjective and objective ways.

Hidradenitis suppurativa (HS) profoundly impacts a patient's HRQoL. Patients may suffer from pain, pruritus, and malodorous discharge affecting their everyday life. Chronic pain is reported to be the most distressing symptom in HS. Mild or moderate intensity of pain is reported in around 97% of the patients. (62) Pain and pruritus are responsible for poor sleep quality in patients with HS, affecting their daily activity. (63) The recurrent, unpredictable flare-ups and severe pain may cause movement impairment, affecting the patient's ability to work. Chronic HS causes significant scar formation and disfigurement. The physical appearance of the lesions has a negative, worrisome emotional impact on the patients with HS, leading to psychological distress. (64) Because of the lack of information about HS in the general public, patients feel ashamed and embarrassed in the company of uninformed people. Furthermore, HS lesions in genital areas affect the patients' sexual health, causing sexual dysfunction leading to a lack of

intimacy. (65) These negative impacts may cause shame, loneliness, low self-esteem, anxiety, social isolation, and depression. (66-68)

In evaluating disease burden, the assessment of interventions, and resource allocation, HRQoL has become more significant. The instruments used in the evaluation of HRQoL typically have several attributes. They can be generic, allowing comparing different diseases, therapies, or interventions. They can be specific, focusing on a particular area of interest, like a disease, a specific population, or specific features of diseases. (69) Measures can be unidimensional, using one global question, or multidimensional, evaluating several domains separately to assess the HRQoL of the patient. (70) HRQoL in dermatology can be assessed with generic, dermatology-specific, and condition-specific instruments. Dozens of generic and specific HRQoL instruments have been developed. The most commonly used or cited generic HRQoL instruments are the Short Form 36 (SF-36), EQ-5D, and the Health Utilities Index (HUI). Besides these, there are several other instruments, for example, the Nottingham Health Profile (NHP), the Sickness Impact Profile (SIP); the Dartmouth Primary care Cooperative Information Project (COOP) Charts; the Quality of well-Being (QWB) Scale. (71-74) There are no uniformly best or worst instruments; the choice on which instrument to use over another depends on the purpose of the measurement. (74) To obtain the most optimal results, most generic measures have been developed to use in combination with specific instruments. In the investigation of the impact of skin diseases on the quality of life, the dermatology-specific HRQoL instruments are the Dermatology Life Quality Index (DLQI); Dermatology-Specific Quality of Life (DSQL); Dermatology Quality of Life Scales (DQOLS); Skindex-29 and its short versions Skindex-16 and Skindex-17. (75)

Currently, there is a lack of consensus regarding the HRQoL instruments to be used in daily clinical practice or for research in this patient population. (76-78) A recent Cochrane review and another systematic review of outcome measures found that only the Dermatology Life Quality Index (DLQI) was applied in published HS randomized controlled trials. (79, 80) In addition to the DLQI, other HRQoL outcomes may be helpful in the assessment of HS patients, such as DLQI-Relevant (DLQI-R) or Skindex-16.

DLQI-R is a new scoring modification developed for the DLQI that improved measurement properties of the questionnaire, including the convergent validity, responsiveness, and discriminatory power of the questionnaire in psoriasis patients. (81-

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83) Still, it has not yet been tested in HS. Skindex-16 is another example of a dermatology-specific instrument suitable for use in HS patients; however, its validation is currently incomplete in this patient population. (84)

Acknowledging the complexity of the HRQoL impact of HS, generic (not dermatology-specific) assessment of HRQoL also seems crucial. 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. (71, 85-87) The EQ-5D has two versions used in adults, the EQ-5D-3L and the newer EQ-5D-5L.(88, 89). The EQ-5D-3L has already been validated in HS patients (24, 90-93) measurement properties of the EQ-5D-5L are yet to be tested.

1.4 Healthcare costs in HS

Information related to resource utilization and costs in patients with hidradenitis suppurativa (HS) is less documented.

Cost-of-illness (COI) studies aim to assess the economic burden on society from different points of view. These studies assume that the cost of disease equals the economic benefit of a complete cure. (94) Cost-of-illness studies provide essential information on the financial and global burden of disease, help identify and improve the most costly areas within a given disease, and aids in formulating and prioritize health policy decisions. (95) There are three types of costs: direct, indirect, and intangible. As intangible costs due to measurement difficulties and related debates were rarely quantified in COI studies, studies mainly focus on the first two cost categories. They seek to express them in monetary terms, that is, in a given currency. (95, 96) 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. Provided that effective and efficient treatments and prevention methods are used, the estimated direct cost associated with acute or infectious diseases is lower than chronic diseases. 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. Within this, a distinction is made between the concepts of presenteeism

DOI:10.14753/SE.2022.2622
and absenteeism. The former means a partial but not complete reduction in work capacity, while the latter means a loss of full work. (94, 96, 97)

From 2014 onwards, there have been eight previous direct cost analyses published in HS patients (n=6 from the US(98-103), n=1 from Canada(104), and n=1 from the UK(105)). All these studies used large health administrative databases as a data source. In England, the direct medical costs in HS requiring at least one inpatient admission (including costs of all inpatient, outpatient, and accident and emergency attendances and excluding medication costs) were £2,027/patient/year (2013 price level). (105) Studies from the US indicated that direct medical costs of HS patients vary significantly depending on treatments received. For example, in 2015, just before biologics became a treatment option for HS, mean annual direct medical costs of HS were between $2662 and $4428 (including in- and outpatient care, as well as diagnostic and emergency department attendances). (98) In contrast, in 2018, seven-month costs associated with adalimumab therapy were $63,953 (excluding costs of in- and outpatient admissions). (100) High costs were attributable to surgical care: average direct medical costs of patients with and without indicators of non-curative surgery were $14,125 and 7930, respectively (price level 2010). (103) Thus far, no cost-of-illness studies have reported direct and indirect costs in patients with HS.

2 Objectives

Our study aimed to assess the health status, health-related quality of life, and cost-of-illness in patients with HS in Hungary. Our specific aims were as follows:

2.1 Health status and HRQoL

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 those 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 using the Hungarian EQ-5D-5L value set that can be later used as local inputs in health economic models of HS treatments.

2.2 Cost-of-illness

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.

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3 Results

This chapter draws upon the results of two publications of the candidate:

- **Gergely LH**, Gáspár K, Brodszky V, Kinyó Á, Szegedi A, Remenyik É, Kiss NF, Bató A, Péntek M, Gulácsi L, Sárdy M, Bánvölgyi A, Wikonkál N, Rencz F. (2020) Validity of EQ-5D-5L, Skindex-16, DLQI and DLQI-R in patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol 34: 2584-2592. (106)
- Gáspár K, **Hunor Gergely L**, Jenei B, Wikonkál N, Kinyó Á, Szegedi A, Remenyik É, Kiss N, Jin X, Sárdy M, Beretzky Z, Péntek M, Gulácsi L, Bánvölgyi A, Brodszky V, Rencz F. (2021) Resource utilization, work productivity and costs in patients with hidradenitis suppurativa: a cost-of-illness study. Expert Rev Pharmacoecon Outcomes Res, doi:10.1080/14737167.2021.1895753: 1-10 (107)

3.1 Patient characteristics

Overall, 200 adult patients with HS were included in this study. Patients ranged from 18 to 67 years, with a mean age of 37.1±12.4 years, and 123 (61.5%) were male (Table 1). 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 (Table 2). 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%).

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Table 1 Demographic characteristics of patients with HS

Variables	**Mean (SD) or N (%)**
Age (years)	37.13 (12.43)
Sex	
Female	77 (38.5%)
Male	123 (61.5%)
Education *(missing n=1)*	
Primary	40 (20.1%)
Secondary	129 (64.8%)
Tertiary	30 (15.1%)
Body mass index (BMI) – kg/m^2 *(missing n=3)*	
Underweight (<18.5)	2 (1.0%)
Normal (18.5-24.9)	35 (17.8%)
Overweight (25.0-29.9)	68 (34.5%)
Obese (≥30)	92 (46.7%)
Employment status[a]	
Employed full-time	119 (59.5%)
Employed part-time	12 (6%)
Unemployed	27 (13.5%)
Retired	4 (2%)
Disability pensioner	14 (7%)
Disability pensioner due to HS	3 (1.5%)
Student	20 (10%)
Other	7 (3.5%)

a: A patient may belong to more than one group.

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Table 2 Clinical characteristics of patients with HS

Smoking	
Smoker	141 (70.5%)
Ex-smoker	35 (17.5%)
Non-smoker	24 (12.0%)
Family history of HS *(missing n=2)*	37 (18.6%)
Comorbidities[a]	92 (46%)
Cardiovascular disease	33 (16.5%)
Dermatological diseasec	24 (12%)
Inflammatory bowel disease (IBD)[b]	14 (7%)
Diabetes	12 (6%)
Mental illness	12 (6%)
Other	35 (17.5%)
Disease duration (years)	4.76 (6.72)
HS-PGA *(missing n=7)*	
Clear	6 (3.1%)
Minimal	7 (3.6%)
Mild	37 (19.3%)
Moderate	69 (35.9%)
Severe	40 (20.7%)
Very severe	34 (17.7%)
Hurley staging *(missing n=4)*	
Hurley I	22 (11.2%)
Hurley II	79 (40.3%)
Hurley III	95 (48.5%)
Body region affected	
Axillary	155 (77.5%)
Inguinal	127 (63.5%)
Gluteal	59 (29.5%)
Genital	52 (26.0%)
Perianal	22 (11.0%)
Submammary	24 (12.0%)
Other	12 (6.0%)
Current treatment	
None	37 (18.5%)
Topical therapy (only)	59 (29.5%)
Systemic non-biologic	77 (38.5%)
Biologic	27 (13.5%)
Surgical therapy in the past 12 months	65 (32.5%)

HS = hidradenitis suppurativa; HS-PGA = Physicians' Global Assessment of HS severity.
a: Acne vulgaris (n=14), psoriasis (n=5), atopic dermatitis (n=1), conglobate acne (n=1), pilonidal cyst (n=1), pityriasis versicolor (n=1), pyoderma gangrenosum (n=1), Sjögren's syndrome (n=1), unknown (n=1).
b: Crohn's disease (n=12), ulcerative colitis (n=2).

3.2 Disease severity scores

Mean±SD scores for HS-PGA were 3.20±1.22, for MSS 60.82±50.15 and for PtGA VAS 69.62±22.22 (Table 3). Almost half of the patients had a Hurley stage III disease (48.5%). According to HS-PGA scores, 6.7%, 19.2%, 35.8%, 20.7%, and 17.6% had clear-minimal, mild, moderate, severe, or very severe HS. The mean current HS-related pain

DOI:10.14753/SE.2022.2622
intensity score was 4.70±2.99, whereas the mean worst HS-related pain intensity score for the past month was 6.28±3.04 on a 0-10 VAS.

Table 3 Disease severity and HRQoL scores of HS patients

Outcome measures	N	Mean (SD)	Median (IQR)	Floor effect N (%)	Ceiling effect N (%)
EQ-5D-5L (-0.848-1)	198	0.76 (0.21)	0.86 (0.71-0.96)	0 (0%)	29 (14.6%)
EQ VAS (0-100)	198	64.29 (22.68)	70.00 (50.00-80.00)	0 (0%)	4 (2.0%)
DLQI (0-30)	198	11.75 (8.11)	11.00 (5.00-18.00)	10 (5.1%)	1 (0.5%)
DLQI-R (0-30)	198	12.19 (8.33)	11.00 (5.42-19.00)	10 (5.1%)	2 (1.0%)
Skindex-16 total score (0-100)	198	53.56 (28.11)	54.66 (33.04-76.65)	4 (2.0%)	6 (3.0%)
Symptoms (4 items)	198	46.74 (29.36)	50.00 (20.83-66.67)	14 (7.1%)	10 (5.1%)
Emotions (7 items)	198	64.55 (29.28)	71.43 (42.86-90.48)	5 (2.5%)	25 (12.6%)
Functioning (5 items)	198	49.40 (34.70)	46.67 (15.83-83.33)	21 (10.6%)	21 (10.6%)
PtGA VAS (0-100)	199	69.62 (22.22)	70.00 (50.00-90.00)	0 (0%)	36 (18.1%)
HS-PGA (0-5)	193	3.20 (1.22)	3.00 (2.00-4.00)	6 (3.1%)	34 (17.6%)
Modified Sartorius score[a]	199	60.38 (50.30)	48.00 (22.00-84.00)	2 (1.0%)	0 (0%)

For EQ-5D-5L and EQ VAS, higher scores refer to better health status; higher scores represent worse health status for all other measures.
a: The measure has no upper limit.
DLQI = Dermatology Life Quality Index; PGA = Physicians' Global Assessment of disease severity; PtGA VAS; PtGA VAS = Patient's Global Assessment of disease severity visual analogue scale; VAS = visual analogue scale

3.3 Health-related quality of life scores

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%). DLQI and DLQI-R total scores were substantially higher compared to what was found in Hungarian psoriasis (mean DLQI 5.56±6.98, DLQI-R 7.03±8.40) and pemphigus patients (mean DLQI 6.78±7.38, DLQI-R 7.44±7.98) (Table 3). Forty (20.7%) patients marked at least one 'not relevant' response on the DLQI that is lower compared to these rates among psoriasis (38.8%) and pemphigus patients (53.7%).

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Table 4 Characteristics of the patient populations

	Hidradenitis suppurativa (Gergely et al. 2020)(106)	Pemphigus (Tamási et al. 2019)(87)	Psoriasis (Rencz et al. 2018)(108)
All patients (n)	**198**	**108**	**428**
Age (years): mean (SD)	37.0 (12.45)	57.1 (14.8)	49.2 (14.3)
Female (%)	38.9%	63.9%	35.0%
Biological therapy (%)	12.8%	0%	43.7%
DLQI: mean (SD)	11.75 (8.11)	5.56 (6.98)	6.78 (7.38)
DLQI-R: mean (SD)	12.19 (8.33)	7.03 (8.40)	7.44 (7.98)
Patients with NRRs (n, %)	**39 (20.7%)**	**58 (53.7%)**	**166 (38.8%)**
1 NRR	1.6%	13.9%	19.6%
2 NRRs	1.1%	11.1%	11.4%
3 NRRs	1.1%	10.2%	5.1%
4 NRRs	12.2%	8.3%	1.6%
5 NRRs	8.1%	3.7%	0.2%
6 NRRs	2.7%	1.9%	0.5%
7 NRRs	5.9%	0.9%	0%
8 NRRs	3.7%	3.7%	0.2%

DLQI = Dermatology Life Quality index; DLQI-R = DLQI scoring adjusted for 'not relevant' responses; N/A = not applicable; NRR = 'not relevant' response; SD = standard deviation

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., 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 (Figure 1). 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 cross-sectional surveys by our research group in Hungary. (86, 87) Figure 1 demonstrates that patients with HS 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.

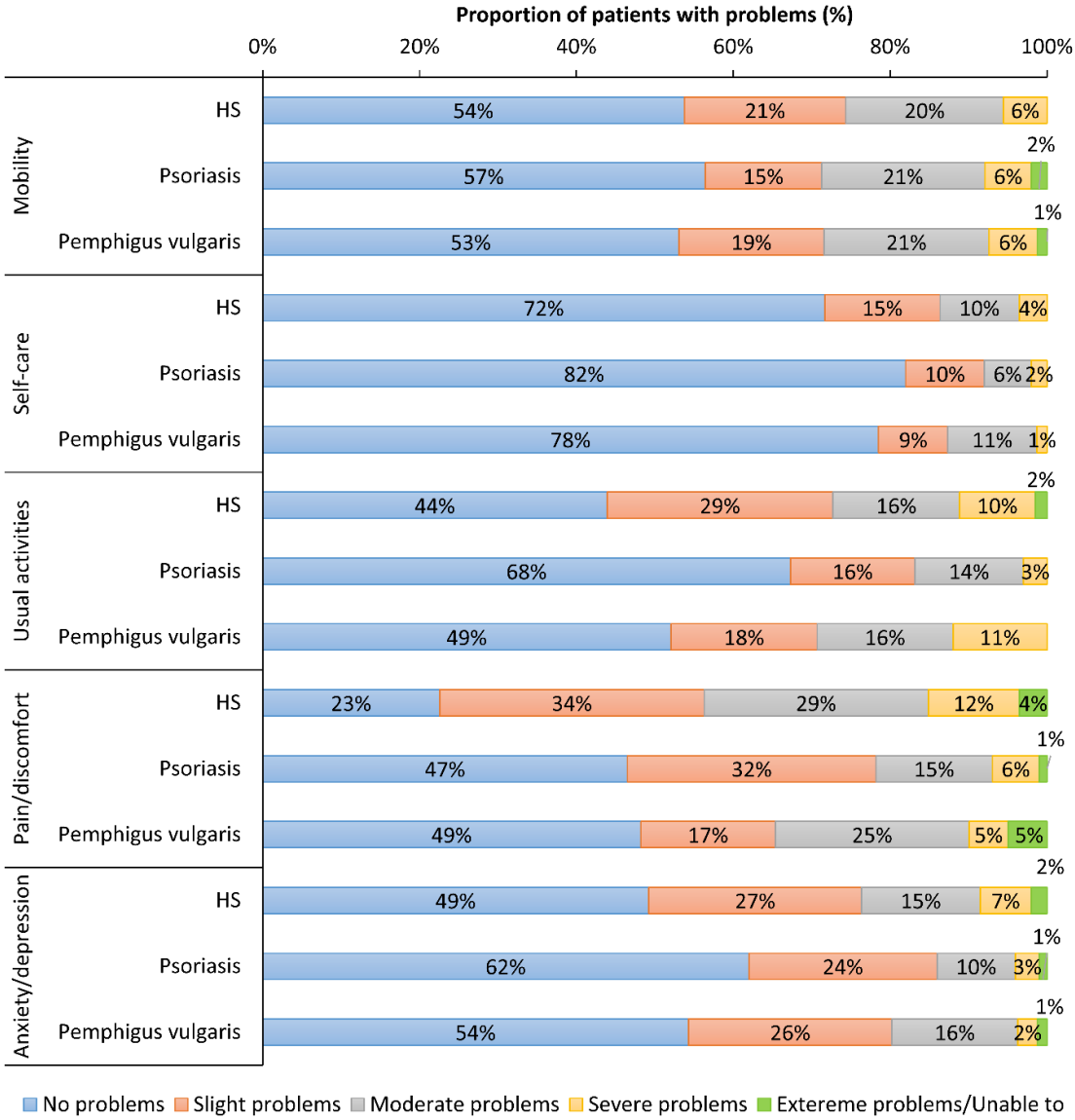

Figure 3 Problems reported on the five EQ-5D-5L dimensions in patients with HS compared to psoriasis and pemphigus vulgaris

HS = hidradenitis suppurativa Psoriasis: n=238, mean age 47.4±15.2 years, mean Psoriasis Area and Severity Index 8.7±9.2, biological therapy 36.6% (Hungary).
Pemphigus vulgaris: n=81, mean age 52.4± 14.8, mean Autoimmune Bullous Skin Disorder Intensity Score score 13.4±18.1, biological therapy 0% (Hungary). (87)

3.4 Ceiling or floor effects

The proportions of HS patients with the lowest and highest values for the DLQI (5.1% and 0.5%), DLQI-R (5.1% and 1.0%), Skindex-16 symptoms subscale (7.1% or 5.1%), Skindex-16 emotions subscale (2.5% and 12.6%), Skindex-16 functioning subscale (10.6% and 10.6%), Skindex-16 total score (2.0% and 3.0%) and EQ VAS (2.0% and 0%) were well below 15%, indicating no floor or ceiling effects. We found the EQ-5D-5L index scores slightly skewed towards the highest value (14.6%). No floor effects were found for the EQ-5D-5L.

3.5 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|) (Table 5). 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.

DOI:10.14753/SE.2022.2622

Table 5 Spearman's correlations between outcome measures

Variables	EQ VAS	DLQI	DLQI-R	Skindex-16 total score	Skindex-16 Symptoms	Skindex-16 Emotions	Skindex-16 Functioning	PtGA VAS	HS-PGA	MSS[a]
EQ-5D-5L (-0.848-1)	0.592	-0.697	-0.707	-0.650	-0.573	-0.500	-0.674	-0.434	-0.350	-0.323
EQ VAS (0-100)	-	-0.512	-0.519	-0.487	-0.454	-0.359	-0.493	-0.408	-0.358	-0.355
DLQI (0-30)	-	-	0.993	0.859	0.750	0.725	0.847	0.542	0.418	0.367
DLQI-R (0-30)	-	-	-	0.867	0.756	0.732	0.856	0.546	0.433	0.381
Skindex-16 (0-100)	-	-	-	-	0.869	0.900	0.932	0.513	0.390	0.358
Skindex-16 Symptoms (0-100)	-	-	-	-	-	0.675	0.713	0.417	0.364	0.325
Skindex-16 Emotions (0-100)	-	-	-	-	-	-	0.791	0.453	0.311	0.276
Skindex-16 Functioning (0-100)	-	-	-	-	-	-	-	0.521	0.385	0.354
PtGA VAS (0-100)	-	-	-	-	-	-	-	-	0.327	0.376
HS-PGA (0-5)	-	-	-	-	-	-	-	-	-	0.858

All coefficients are statistically significant ($p<0.05$). For EQ-5D-5L and EQ VAS, higher scores refer to better health status; higher scores represent worse health status for all other measures.

a: There is no theoretical maximum.

DLQI = Dermatology Life Quality Index; DLQI-R = DLQI-Relevant; HS-PGA = Physicians' Global Assessment of HS severity; MSS = Modified Sartorius Score; PtGA VAS = Patient's Global Assessment of disease severity visual analogue scale; VAS = visual analogue scale

3.6 Known-groups validity

More severe disease measured by HS-PGA was associated with worse HRQoL scores using all outcome measures ($p<0.001$) (Figures 2-4). 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 with reference to 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.

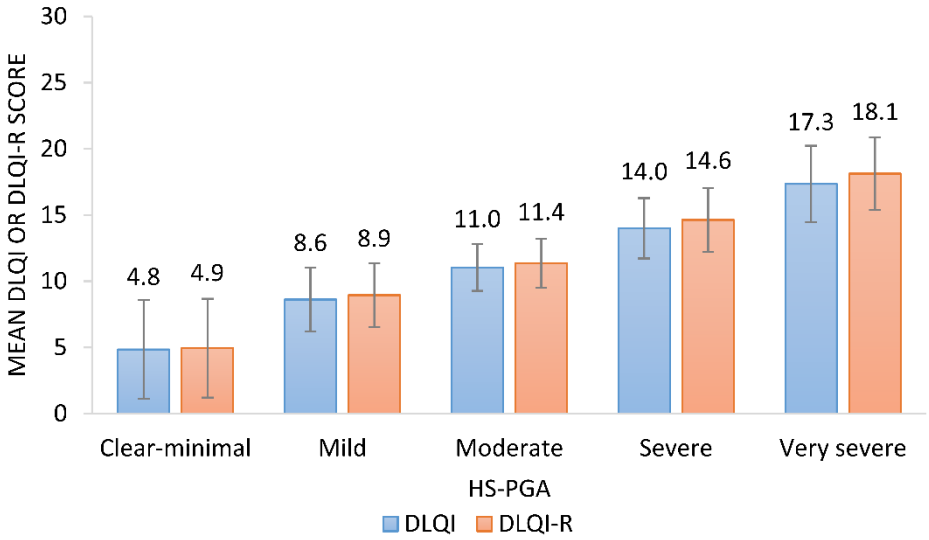

Figure 4 Known-groups validity of the DLQI and DLQI-R in HS
DLQI: p-value <0.001, ES: 0.163
DLQI-R: p-value <0.001, ES: 0.176, RE: 1.076
ES = effect size; HS-PGA = Physicians' Global Assessment of HS severity; RE = relative efficiency

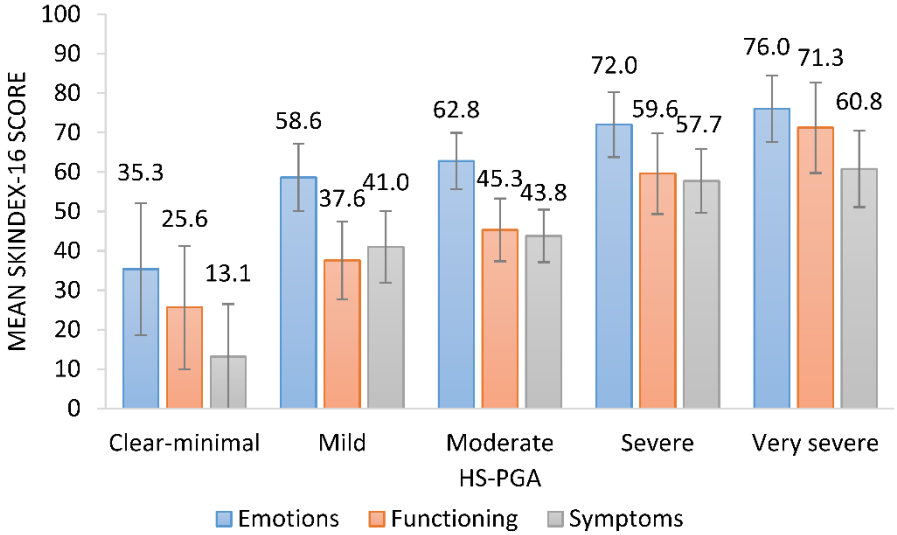

Figure 5 Known-groups validity of the Skindex-16 subscales in HS
Emotions subscale: p-value <0.001, ES: 0.090, RE: 0.555
Functioning subscale: p-value <0.001, ES: 0.134, RE: 0.819
Symptoms subscale: p-value <0.001, ES: 0.146, RE: 0.894
ES = effect size; HS-PGA = Physicians' Global Assessment of HS severity; RE = relative efficiency

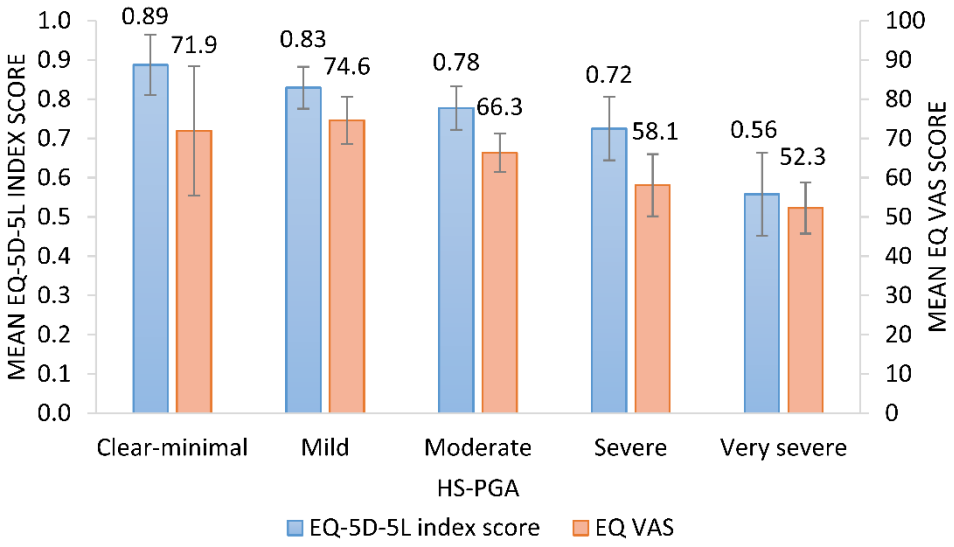

Figure 6 Known-groups validity of the EQ-5D-5L and EQ VAS in HS
EQ-5D-5L: p-value <0.001, ES: 0.116, RE: 0.709
EQ VAS: p-value <0.001, ES: 0.111, RE: 0.683
ES = effect size; HS-PGA = Physicians' Global Assessment of HS severity; RE = relative efficiency

3.7 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 (Table 6). 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 for 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 ($p<0.001$).

DOI:10.14753/SE.2022.2622

Table 6 Multivariate linear regression of HRQoL outcomes

	DLQI			DLQI-R			Skindex-16			EQ-5D-5L index			EQ VAS		
	β	SE*	p-value	β	SE*	p-value	β	SE	p-value	β	SE*	p-value	β	SE	p-value
Constant	6.06	2.19	0.006	6.42	2.24	0.005	30.38	8.24	<0.001	0.767	0.092	<0.001	61.70	3.82	<0.001
Sex															
Male	Ref.			Ref.			Ref.								
Female	3.21	2.90	0.004	3.43	1.13	0.003	13.64	3.69	<0.001						
Education															
Primary	Ref.			Ref.			Ref.			Ref.			Ref.		
Secondary	-2.26	1.36	0.100	-2.1	1.39	0.063	-9.37	4.63	0.044	0.117	0.052	0.025	5.94	4.040	0.143
Tertiary	-5.07	1.67	0.003	-5.11	1.78	0.005	-19.27	6.32	0.003	0.200	0.072	0.006	13.36	5.410	0.014
HS-PGA															
Clear-minimal	Ref.			Ref.			Ref.			Ref.					
Mild	2.44	2.01	0.227	2.53	2.03	0.216	15.09	7.99	0.060	-0.017	0.090	0.849			
Moderate	5.35	1.91	0.006	5.51	1.96	0.005	22.10	7.49	0.004	-0.086	0.085	0.312			
Severe	7.94	1.96	<0.001	8.41	2.01	<0.001	33.47	7.82	<0.001	-0.152	0.089	0.087			
Very severe	9.83	2.31	<0.001	10.5	2.3	<0.001	35.05	8.32	<0.001	-0.294	0.094	0.002			
Genital localization															
No	Ref.			Ref.			Ref.						Ref.		
Yes	3.80	1.36	0.006	3.60	1.36	0.009	11.69	4.27	0.007				-10.91	3.46	0.002
R^2, F-test p-value	0.275, p<0.001			0.282, p<0.001			0.288, p<0.001			0.165, p<0.001			0.092, p<0.001		

*Robust standard errors.

HRQoL = health-related quality of life; HS-PGA = Physicians' Global Assessment of HS severity

3.8 Resource utilization

At least one dermatologist and GP consultation were reported by 85.5% and 35% of the patients, respectively (Figure 4). 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 treatments (68%), systemic antibiotics (57%), and biological treatment (15.5%) (Table 7). 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. 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 labor 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.

DOI:10.14753/SE.2022.2622

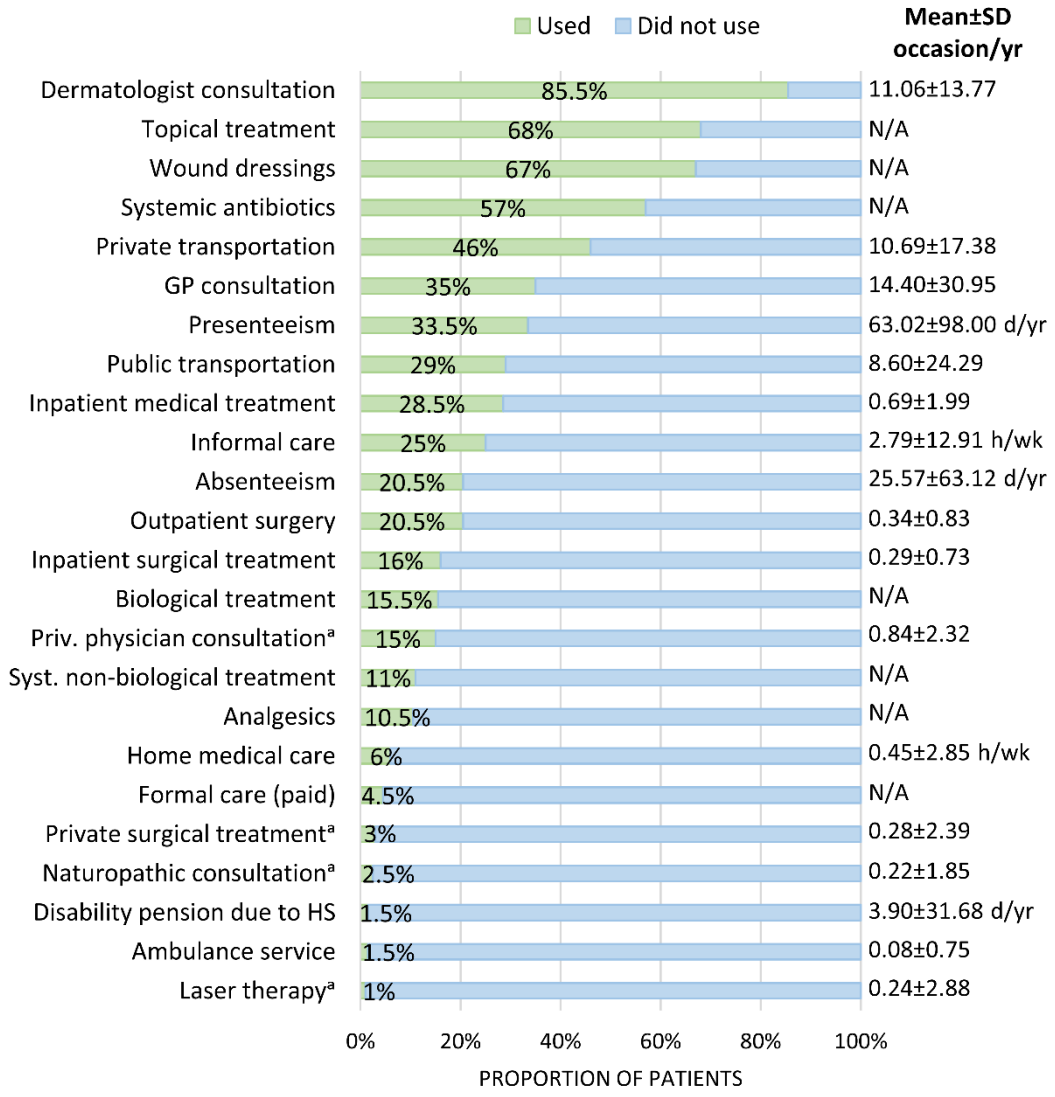

Figure 7 Resource utilization in the past 12 months

Percentages indicate the number of patients with ≥1 occasion. Mean occasions per year indicate the annual utilization frequency of services.

a: Healthcare services not reimbursed by the National Institute of Health Insurance Fund Management.

N/A = not applicable or not available

d = day, wk = week, yr = year

Table 7 Treatments in the past 12 months

Treatments	N (%)
Surgical treatments[a]	**64 (32.0%)**
Incision and drainage	33 (16.5%)
Deroofing	21 (10.5%)
Limited local excision	13 (6.5%)
Radical excision	5 (2.5%)
Wide local excision	5 (2.5%)
STEEP[b]	4 (2%)
Systemic biological treatments	**31 (15.5%)**
Adalimumab	30 (15%)
Infliximab (off-label use)	1 (0.5%)
Systemic non-biological treatments	**123 (61.5%)**
Retionoids	**13 (6.5%)**
Isotretinoin	8 (4%)
Acitretin	5 (2.5%)
Zinc gluconate	6 (3%)
Hormone therapy	1 (0.5%)
Systemic antibiotics	**114 (57%)**
Clindamycin	66 (33%)
Rifampicin	50 (25%)
Tetracycline	48 (24%)
Doxycycline	10 (5%)
Amoxicillin/clavulanic acid	6 (3%)
Ciprofloxacin	5 (2.5%)
Other	28 (14%)
Other	3 (1.5%)
Topical treatments	**136 (68%)**
Topical antibiotics	90 (45%)
Povidone-iodine antiseptic	88 (44%)
Other antiseptic	5 (2.5%)
Other	28 (14.%)
Analgesics	**21 (10.5%)**

a: Note that surgical treatments reimbursed by the National Institute of Health Insurance Fund Administration and Management are included here. Data are not available on the types of procedures for privately funded surgeries (n=3).
b: Skin-Tissue-sparing Excision with Electrosurgical Peeling

3.9 Cost-of-illness results

The annual mean total cost of HS, 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 (Table 8). 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%).

DOI:10.14753/SE.2022.2622

Table 8 Mean direct and indirect costs per patient per year (2019, euro)

Cost category	Mean[a,b]	CI 95%[c]	Minimum	Median	Maximum	Share of total costs, %[b]
Direct costs total	3 166	2479 - 3919	0	1 010	38 010	46.7%
Direct medical costs	2 400	1846 - 3014	0	693	24 582	35.5%
GP consultation	83	61 - 109	0	0	1 386	1.2%
Dermatologist consultation	100	85 - 116	0	72	1 081	1.5%
Inpatient admission	326	215 - 454	0	0	7 570	4.8%
Home medical care	71	31 - 118	0	0	3 312	1.0%
Treatments	1 774	1250 - 2377	0	235	22 031	26.3%
Surgical treatment[b]	139	94 - 189	0	0	1 919	2.2%
Systemic biological treatment	1 465	952 - 2053	0	0	21 984	21.5%
Systemic non-biological treatment	48	38-59	0	10	510	0.7%
Topical treatment	113	94 - 132	0	61	738	1.7%
Analgesics	9	4 - 16	0	0	553	0.1%
Wound dressings	20	13 - 29	0	1	605	0.3%
Ambulance service	12	0 - 36	0	0	2 392	0.2%
Non-reimbursed medical services	13	8 - 19	0	0	323	0.2%
Direct non-medical	767	471 - 1174	0	70	37 840	11.3%
Travel	108	85 - 131	0	35	1 145	1.6%
Caregiving	659	341-1111	0	0	37 840	9.7%
Informal care	627	345 - 1021	0	0	37 840	9.2%
Formal care (paid)	31	8 - 61	0	0	2 471	0.5%
Indirect costs total	3 625	2903 - 4324	0	0	16 280	53.3%
Absenteeism	1 599	1040 - 2164	0	0	16 258	23.5%
Presenteeism	1 781	1344 - 2220	0	0	13 006	26.2%
Permanent disability	244	81 - 407	0	0	16 280	3.6%
Total costs	6 791	5693 - 7906	0	3 193	52 101	100%

a: Results were calculated according to 2000 replications bootstrap testing with accelerated bias correction.
b: Figures may not add up due to rounding.
c: Costs of surgical treatment include both inpatient and outpatient surgeries.

Male patients tended to have higher direct medical costs compared to females (p=0.025) (Figure 8). 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).

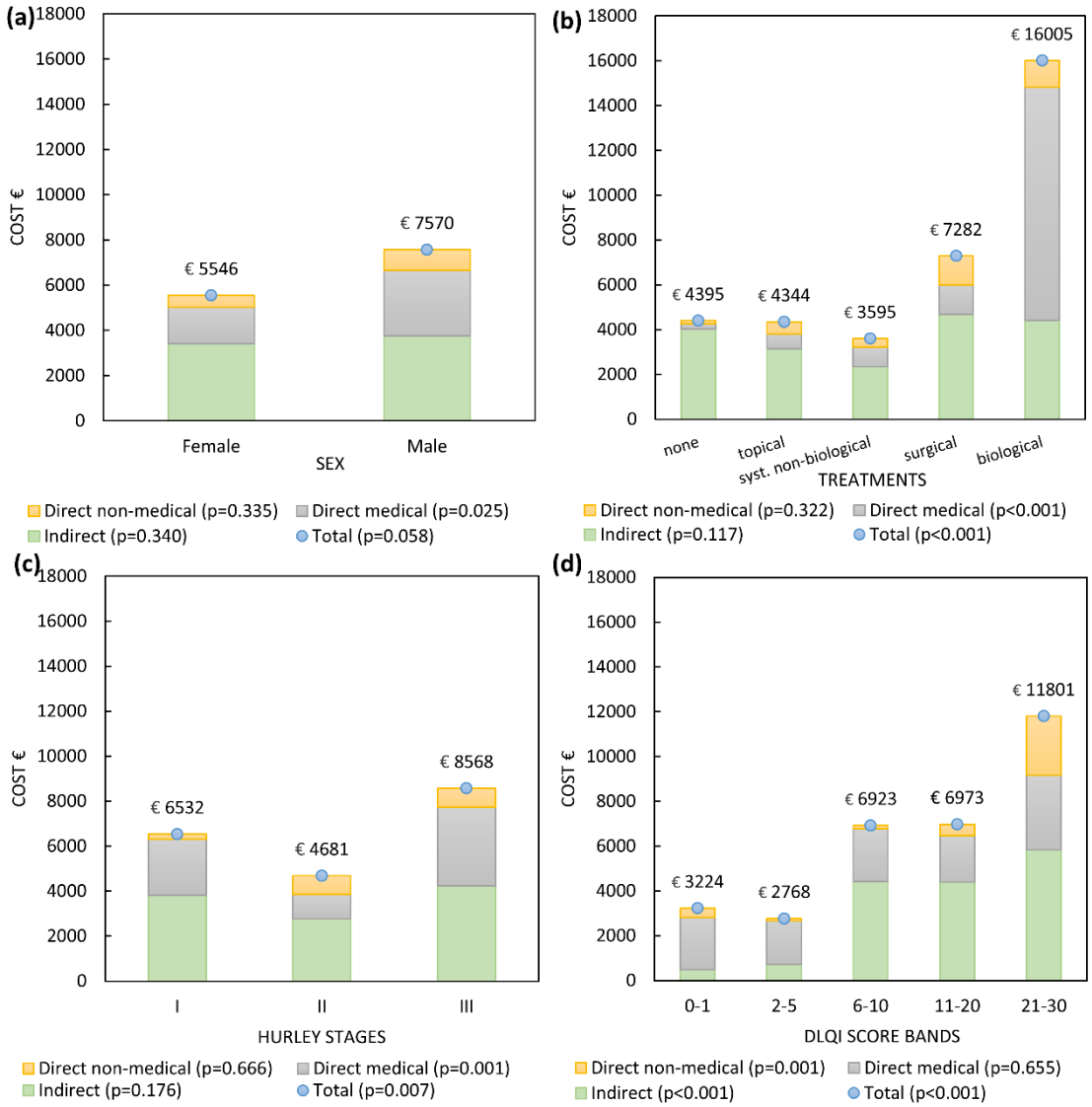

Figure 8 Mean total, direct medical, direct non-medical, and indirect costs of HS in subgroups of patients (2019, euro) Results were calculated according to 2000 replications bootstrap testing with accelerated bias correction. For treatment groups, surgical treatment indicates monotherapy or combination with any topical or systemic non-biological treatment. Biological therapy

indicates monotherapy or combination with any topical or systemic non-biological or surgical treatment.
DLQI scores were categorized according to the Hongbo's score bands. (109)
DLQI = Dermatology Life Quality Index

3.10 Predictors of costs

Sex, level of education, and DLQI score were revealed as significant predictors of total costs (Table 9). Female patients had lower total (-30.1%) and direct medical costs (-40.0%). Mean total and indirect costs decreased by 53.0% and 66.9%, respectively, if the patient had a college/university degree. Compared to patients with Hurley III disease, those with Hurley II stage had lower total annual direct medical costs by 58.8%, respectively. Gluteal involvement increased the direct medical costs by 63.2%, and patients with coexisting IBD had substantially higher direct medical costs (+135.0%). All other comorbidities, including diabetes, dermatological diseases, and mental illness, were insignificant in the model. A one-point increase in the DLQI led to, on average, 4.0%, 10.0%, and 2.9% increase in total, direct non-medical and indirect costs, respectively.

DOI:10.14753/SE.2022.2622

Table 9 Predictors of total costs and cost categories in HS patients (generalized linear models)

Variables		Total costs			Direct medical costs			Direct non-medical costs			Indirect costs		
		Exp(β)	**SE**	***p*-value**	**Exp(β)**	**SE**	***p*-value**	**Exp(β)**	**SE**	***p*-value**	**Exp(β)**	**SE**	***p*-value**
Intercept		3654.2	0.354	***<0.001***	2942.9	0.190	***<0.001***	200.0	0.197	***<0.001***	7618.0	0.298	***<0.001***
Sex	Male	*Ref.*	-	-	*Ref.*	-	-	-	-	-	-	-	-
	Female	0.699	0.179	***0.045***	0.600	0.190	***0.007***	-	-	-	-	-	-
Education	Primary	*Ref.*	-	-	-	-	-	-	-	-	*Ref*	-	-
	Secondary	1.181	0.226	0.461	-	-	-	-	-	-	0.697	0.220	0.101
	Tertiary	0.470	0.324	***0.020***	-	-	-	-	-	-	0.331	0.319	***0.001***
Smoker	no	*Ref.*	-	-	-	-	-	-	-	-	*Ref*	-	-
	yes	1.251	0.197	0.255	-	-	-	-	-	-	0.969	0.188	0.868
Localisation	Genital	1.369	0.208	0.132	-	-	-	-	-	-	1.130	0.169	0.468
	Gluteal	0.989	0.217	0.960	1.632	0.220	***0.026***	-	-	-	-	-	-
	Perianal	1.404	0.297	0.253	1.320	0.315	0.379	-	-	-	-	-	-
Hurley staging	Hurley III	*Ref.*	-	-	*Ref.*	-	-	-	-	-	-	-	-
	Hurley II	0.708	0.198	0.081	0.412	0.212	***<0.001***	-	-	-	-	-	-
	Hurley I	0.936	0.295	0.824	0.913	0.315	0.774	-	-	-	-	-	-
Health-related quality of life	DLQI	1.040	0.013	***0.002***	-	-	-	1.100	0.013	***<0.001***	1.029	0.011	***0.012***
Comorbidities	Diabetes	-	-	-	0.509	0.382	0.077	-	-	-	-	-	-
	IBD	-	-	-	2.350	0.401	***0.033***	-	-	-	-	-	-
	Other dermatological diseases	-	-	-	0.675	0.307	0.201	-	-	-	-	-	-
	Mental illness	-	-	-	0.691	0.380	0.332	-	-	-	-	-	-
Goodness of fit	χ^2/df	1.272			2.452			6.596			0.356		
	AIC	3679.1			3241.9			2225.2			1717.2		
	BIC	3718.0			3277.7			2234.3			1734.5		

AIC =Akaike Information Criterion; BIC = Bayesian Information Criterion; df = degrees of freedom; DLQI = Dermatology Life Quality Index; HS = hidradenitis suppurativa; IBD = inflammatory bowel disease

4 Discussion

4.1 Health-related quality of life

To our knowledge, we are the first to validate the EQ-5D-5L questionnaire and the DLQI-R scoring in a sample of HS patients. All HRQoL measures demonstrated a good convergent validity with reference to the DLQI and known-groups validity for severity. The DLQI-R demonstrated the best performance in terms of both convergent and known-group validity among the four outcome measures. No ceiling and floor effects were observed. Although the majority of the study population had moderate or severe HS, the EQ-5D-5L index scores slightly shifted towards the highest value (14,6%). This figure is within the range of ceiling effects for the EQ-5D-5L reported in an extensive systematic review (0-55%). (110)

The EQ-5D-5L, DLQI, and Skindex-16 scores are consonant with those reported in previous studies. The EQ-5D-5L has been used once in a study in Ireland involving 150 HS patients. (111) The Irish patients on the EQ-5D-5L reported anxiety/depression at a higher rate (71.5%) compared to our results in Hungary (51.3%). This Irish study shows that the rate of patients reporting problems on the other four dimensions of the EQ-5D-5L descriptive system, index scores or EQ VAS scores, is not attainable. The mean DLQI score of the our patients (11.75) fits the range of means from former studies (8.31–12.67). (76) So far, one study in 140 Italian HS patients showed mean Skindex-16 scores (62.5) that were moderately higher than our results (mean 53.56). Preliminary researches suggested that female sex (4, 112), elderly age (92, 113), smoking (4, 24), higher BMI (4, 24), comorbidities (113), inguinal localization, and higher disease severity are associated with more impaired HRQoL. (91, 92, 112-117) We found that patients with worse HRQoL included females, patients with a lower level of education, genital involvement, and more severe disease.

The EQ-5D-5L as a generic instrument can provide several particular advantages over disease- or skin-specific questionnaires. Above all, it allows comparisons across health conditions (both within and outside of dermatology) and general population reference values. (118) EQ-5D-5L enables the distribution of responses from this study to be compared with the responses of patients with psoriasis and pemphigus vulgaris obtained

in two previous cross-sectional surveys by our research group in Hungary. (86, 87). Figure 3 shows that compared with psoriasis or pemphigus vulgaris, patients with HS had more significant impairment in HRQoL in all five dimensions except for mobility. In the pain/discomfort dimension, the difference between HS and the other two dermatologic conditions was huge. The group of patients with hidradenitis suppurativa is on average 15 years younger than the group of patients with psoriasis and pemphigus, which may affect the results.

Moreover, the EQ-5D-5L index scores can be used to calculate health utility scores to estimate quality-adjusted life-years (QALYs) in cost-effectiveness analyses of health interventions. There has been a growing interest in demonstrating the economic value of health gains associated with new costly treatments since the approval of adalimumab, the first biological drug for HS by the European Medicines Agency and the U.S. Food and Drug Administration in 2015. (119)

In terms of both convergent and known-groups validity compared to the DLQI, the DLQI-R performed slightly better. In dermatology, the DLQI is the most frequently used HRQoL measure applied in several settings, including consultations, clinical trials, and treatment decisions. It has been translated into over 100 languages. (120, 121) 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. (122, 123) 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-Relevant (DLQI-R), has been proposed recently. DLQI-R 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 than the DLQI in patients with psoriasis, morphea, and pemphigus. (108, 124) It has also been confirmed that the DLQI score bands apply to the DLQI-R scoring. (124) Over the past three years, an increasing number of observational studies have reported DLQI-R in patients with psoriasis, pemphigus, morphea, atopic dermatitis, and vitiligo. (123, 125, 126)

However, the calculation of DLQI-R scores requires a slightly more complex formula that may deter clinicians from using it during consultations. A scoring chart has been

developed to encourage routine use of DLQI-R. (124) To reduce the burden on clinicians and researchers, the development of electronic scoring may be helpful.

Our convergent validity results are in accordance with previous findings of weak-to-moderate correlations of the DLQI with MSS (range r_s=0.342-0.480). (4, 5) However, a study from Poland reported that DLQI correlated moderately with EQ-5D index scores (r_s=-0.57) and weakly with EQ VAS (r_s=-0.32). (91) Contrarily, we observed strong correlations with EQ-5D-5L (r_s=-0.697) and moderate correlations with EQ VAS (r_s=-0.512).

The results showed that in HS, the emotional burden exceeds the burden caused by the physical symptoms. We found at most a moderate correlation between HRQoL and disease severity, which reinforces this observation. Former studies in HS have also shown a weak-to-moderate association between disease severity and HRQoL outcome. (4, 113, 115, 127). These results may explain why the development of complex measures to combine HRQoL results with physician-assessed objective symptoms failed to succeed in the HS, like the International Hidradenitis Suppurativa Severity Score System (IHS4) in which no patient-reported outcome measure is included. (128, 129)

HRQoL outcomes are considered a core domain for clinical trials and daily practice in HS. (78) According to a recent systematic review, 90% of the outcome measures that have been used in HS clinical trials lack any validation evidence, and most of the available evidence is of relatively low methodological quality. (79) Our results provide high-quality evidence that among skin-specific outcomes, the DLQI, DLQI-R, and Skindex-16, and among generic instruments, the EQ-5D-5L appear to be suitable to be used in both clinical trials and daily clinical practice. Furthermore, it seems that DLQI-R and DLQI performed the best among the four instruments.

4.2 Cost-of-illness

Several studies analyzed the COI in various chronic dermatological conditions, such as psoriasis, atopic dermatitis, contact dermatitis, pemphigus, and melanoma. (130-133) In HS, our study is the first assessment of COI, including direct and indirect costs. The average annual total COI of HS in 2019 in Hungary was €6,791 per patient. It was the highest in patients treated with biological treatment (€16,005) or surgically (€7,282) and

the lowest in patients who received systemic non-biological therapy (€3,595). Former studies that assessed direct medical costs related to HS from the US, Canada, and England used large administrative databases as a data source. (98) The direct medical costs in England of HS requiring at least one HS-related inpatient admission were £2,027/patient/year (in 2013 prices). (105) The mean annual costs of HS in the US depend significantly on the treatments received. In HS, prior to the approval of biologics in the treatment of HS, the annual direct medical costs ranged between $2,662 and $4,428 per patient (in 2015 prices). (98) While annual mean costs of patients treated surgically were up to $14,125 (in 2010 prices)(103) and the costs of a seven-month adalimumab therapy were $63,953(in 2018 prices). (100) Compared to previous studies, our results demonstrate lower direct medical costs in Hungary. Still, the variations in costs across patient subgroups by treatment showed a similar pattern, with surgical and biological treatments being responsible for an increase in direct medical costs and total costs. The differences in costing methods (e.g., top-down or bottom-up), time frame, year of costs, prices, and the categories of costs included in the studies may explain the differences in costs across countries.

Healthcare providers and policymakers have shown a growing interest in HS costs since the approval of the biological drug adalimumab into HS treatment in 2015. (119, 134, 135) Our results showed that in Hungary, the total COI in HS patients treated with biologics (€16,005/patient/year) was comparable to that published in patients with moderate-to-severe psoriasis treated with biologics (€15,790/patient/year) in Hungary (in 2014 prices). (136) In the change of costs of HS, the same process is likely that happened in psoriasis. As a result of the introduction of biologics caused a shift from indirect and direct non-medical costs towards direct medical costs. While the total COI has increased, productivity loss and informal care costs have been considerably alleviated. (137, 138) A before-after comparison between costs is not possible because of the cross-sectional nature of our study. We found no significant differences in direct non-medical or indirect costs between patients treated with biologics and other treatment options. (Figure 8).

Indirect costs represented the majority of the total COI associated with HS, as it is mainly affecting working-age adults. Productivity loss was indicated by nearly half of the patients, and every seventh patient was unemployed. Compared to other chronic skin diseases, such as psoriasis or pemphigus, we found the work impairment, especially presentism, was notably higher. (133, 136) On average, patients missed 26 days from

work, consistent with findings from earlier studies in the US and Poland (18-34 days). (139, 140) Total annual absenteeism and disability costs of HS patients in the US were $2,925 and $1,328 annually, respectively (in 2015 prices) higher than our cost estimates in Hungary (€1,599 and €244). (139) In HS, employment-related issues need more awareness, such as implementing workplace interventions to prevent job loss and reduce discrimination. Formal or informal care was required by approximately one-third of the patient population, considering the relatively young age of the patient population, it seems high. It is the first study to estimate informal care costs accrued to unpaid caregivers, such as family members of HS patients. Informal care accounted for about 10% of all COI, indicating that HS physically and psychologically affects patients 'family members or partners and imposes a significant economic burden on families – called spillover costs. (141) In the future, investigating the effects of HS patients 'family members on health and well-being is recommended.

HS is associated with an increased prevalence of other immune-mediated inflammatory diseases, especially IBD. (142, 143) We found that direct medical costs in patients with IBD-HS were significantly higher than IBD patients without HS (Table 9). It is explained by the higher rate of treatment with biologics of these patients (57% of 14 patients). However, these costs do not include the costs of resource use associated with IBD (e.g., gastroenterologist consultation, endoscopy). While in the US, in comparison of patients with IBD-HS and IBD patients without HS, total annual hospitalization costs were moderately higher in IBD-HS ($13,272 vs. $12,237)(price level 2014). (101) Because both diseases respond well to biological agents, these patients may benefit more from biological therapy than patients with HS alone. (101) The COI of patients with IBD-HS, as well as the cost-effectiveness of biologic therapy in this population, deserve further research.

4.3 Strengths and limitations

Strengths of the current study include the multicentre set-up and the reasonably large patient population that is well represented clinical subgroups. Characteristics of the patient population were comparable to those reported in international HS patient registries. (144-147) Secondly, a large number of HRQoL and disease severity measures were used in the study that represented a particular added value for testing and comparing the measurement properties of instruments. Thirdly, the detailed questionnaire allowed

the precise documentation of resource utilisations and the incorporation of numerous cost items, including informal care, out-of-pocket costs, and productivity loss in the analysis. Lastly, EQ-5D-5L index scores were calculated using the Hungarian value set released in 2020, making our study the first published paper in the literature using this value set. (122)

A limitation to our study is that while consecutive patients were enrolled, the proportion of biological therapy users were slightly overrepresented in the sample. That may be because three university clinics participated in the study where patients are more likely to be treated with biologics. In addition, the female-to-male ratio for the total sample was 1:1.6, while some other studies reported a female preponderance reported in the literature. (148) In the evaluation of disease severity slightly older measures were used (IGA, Hurley and modified Sartorius score), although there are new scores available (HiSCR and IHS4); in the future, it would be important to compare the validity of the HRQoL measures discussed in the dissertation with these newer scores. Furthermore, no HS-specific measures [e.g., HS Quality of Life (HiSQOL and HS-QoL) and HIDRAdisk] (149-152) were used in this study due to the lack of available Hungarian version, nor other generic HRQoL instruments were applied in addition to the EQ-5D, such as the SF-36. Responsiveness and test-retest reliability could not have been tested here because of the cross-sectional nature of our study. A further limitation may be that the costs of diagnostic tests (e.g., laboratory, histology, imaging) and emergency department attendances due to HS were not evaluated. Lastly, country-specific unit costs are used to limit the external generalizability of our cost estimates to other countries.

4.4 New findings from this thesis

- Our study represents the first large study aiming at the assessment of HRQoL and COI of HS patients in Hungary. Furthermore, our study is the initial evaluation of COI, including direct and indirect costs in patients with HS at an international level. In terms of Hungary's population, we had a reasonably large sample of HS patients and a good representation across demographic and clinical subgroups.

- We are the first in the literature to provide extensive validation data about DLQI-R, Skindex-16, and EQ-5D-5L in patients with HS. To our knowledge, this is the first use of the DLQI-R scoring in this patient population.
- Our findings highlight that the emotional burden of HS far exceeds the burden caused by its physical symptoms.
- We demonstrated that patients with HS had greater impairment in HRQoL than reported in psoriasis or pemphigus vulgaris in most aspects of HRQoL. In addition, the occurrence of problems with pain/discomfort was particularly high in HS (77% self-reported pain or discomfort in the EQ-5D-5L questionnaire).
- In 2019, the average annual total COI of HS was €6,791 per patient in Hungary, the lowest in patients who received systemic non-biological therapy (€3,595) and the highest in patients treated surgically (€7,282) or with biological treatment (€16,005). We also found that total COI in HS patients treated with biologics was comparable to that reported in moderate-to-severe psoriasis patients treated with biologics (€15,790/patient/year) in Hungary (in 2014 prices).
- We found that the indirect costs represented the majority of the total COI associated with HS. Nearly half of the patients indicated productivity loss, and every seventh patient was unemployed. Work impairment, in particular presenteeism, was markedly higher compared to other chronic skin diseases, such as psoriasis or pemphigus. Patients missed from work, on average, 26 days per year. Absenteeism and disability cost estimates of HS patients in Hungary were €1,599 and €244.
- To our knowledge, this is the first study to estimate informal care costs accrued to unpaid caregivers, such as family members of HS patients.

5 Conclusions

- Our study revealed that HS poses a substantial burden on patients and society regarding both health loss and healthcare costs. In addition, the emotional burden of HS is considerably larger than that of 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 the majority of the total COI associated with HS.
- Work impairment, in particular presenteeism, is markedly higher compared to other chronic skin diseases, such as psoriasis or pemphigus.

DOI:10.14753/SE.2022.2622

6 Summary

Hidradenitis suppurativa (HS) is a potentially disabling, chronic inflammatory skin disease. HS has a significant impact on the patient's health-related quality of life (HRQoL) and often leads to high healthcare resource use and reduced work productivity.

Between September 2017 and October 2019, a cross-sectional questionnaire survey was carried out at three academic dermatology clinics in Hungary. We aimed to assess the measurement properties of multiple generic and skin-specific HRQoL measures and identify predictors of impaired HRQoL in patients with HS. In addition, we sought to assess the cost-of-illness of HS in Hungary and analyze the predictors of costs. The severity of the disease was evaluated by the HS-Physician's Global Assessment (HS-PGA) scale and the Modified Sartorius scale (MSS). HRQoL outcomes included the EQ-5D-5L, EQ visual analogue scale (EQ VAS), Skindex-16, Dermatology Life Quality Index (DLQI), and DLQI-Relevant (DLQI-R). In addition, we assessed direct medical, direct non-medical, and indirect costs.

Mean ± SD EQ VAS, DLQI, and DLQI-R scores were 64.29 ±22.68, 11.75 ± 8.11, and 12.19 ± 8.33. 77% of patients reported problems in the pain/discomfort dimensions of EQ-5D-5L. Skindex-16 responses indicated that the emotional burden of HS exceeded those of functioning and physical symptoms. EQ-5D-5L, EQ VAS, DLQI, DLQI-R, and Skindex-16 total scores had moderate or strong correlations. DLQI-R slightly outperformed DLQI both in terms of convergent and known-groups validity. Being female, lower education level, severe disease, and genital involvement were associated with worse HRQoL.

The mean annual total cost of HS was €6,791/patient. The main cost components were productivity loss (53.3%), biological treatment (21.5%), and informal care (9.2%). Patients missed, on average, 26 days from work annually due to absenteeism and another 63 days due to presenteeism. Male sex, severe disease, gluteal involvement, and coexisting inflammatory bowel disease were associated with higher direct medical costs. Lower education levels and worse DLQI scores predicted higher indirect costs.

Among skin-specific outcomes, the DLQI, DLQI-R, and Skindex-16, and among generic instruments, the EQ-5D-5L are suitable to be used in HS patients. This was the first study to assess both direct and indirect costs in HS patients. EQ-5D-5L index scores and resource utilization data obtained in our study can be used as input for economic evaluations of HS treatments and inform healthcare resource allocation decisions.

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8 Bibliography of the candidate's publications

8.1 Publications related to this dissertation

- **Gergely LH**, Gáspár K, Brodszky V, Kinyó Á, Szegedi A, Remenyik É, Kiss NF, Bató A, Péntek M, Gulácsi L, Sárdy M, Bánvölgyi A, Wikonkál N, Rencz F. (2020) Validity of EQ-5D-5L, Skindex-16, DLQI and DLQI-R in patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol 34: 2584-2592.
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8.2 Publications not related to this dissertation

- Bató A, Brodszky V, **Gergely LH**, Gáspár K, Wikonkál N, Kinyó Á, Szabó Á, Beretzky Z, Szegedi A, Remenyik É, Kiss N, Sárdy M, Rencz F. (2021) The measurement performance of the EQ-5D-5L versus EQ-5D-3L in patients with hidradenitis suppurativa. Qual Life Res, 30: 1477-1490. **IF:4,147**
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DOI:10.14753/SE.2022.2622

9 Acknowledgments

I would like to thank Prof. Dr. Norbert Wikonkál for supporting and starting my research and Prof. Miklós Sárdy for completing my doctoral dissertation as an employee of the clinic he leads. I would like to thank my supervisor, Dr. Fanni Rencz, who, without regretting time and energy and with endless patience, provided immeasurable help in preparing the dissertation and on the way to it. I am grateful to Prof. Dr. Valentin Brodszky, head of the Department of Health Economics at the Corvinus University of Budapest. I would like to thank the colleagues of the university dermatology clinics, Prof. Dr. Andrea Szegedi, Dr. Krisztián Gáspár, and Dr. Ágnes Kinyó, for their help in collecting the questionnaire data. Finally, I am grateful to all my direct colleagues, Dr. András Bánvölgyi, Dr. Norbert Kiss, and Dr. Kende Lőrincz, who helped with the data collection.