Hidradenitis suppurativa

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HIGH PREVALENCE OF CLINICAL SPONDYLOARTHRITIS FEATURES IN PATIENTS WITH HIDRADENITIS SUPPURATIVA

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ABSTRACT

Background: Spondyloarthritis (SpA) and hidradenitis suppurativa (HS) share several pathophysiological features.

Objective: To investigate the prevalence of self-reported clinical SpA features in HS patients and to identify patient characteristics associated with these features.

Methods: Cross-sectional study. A questionnaire concerning the presence of ASAS axial and peripheral SpA entry classification criteria and other SpA features was sent to all HS patients in two Dutch tertiary HS referral centers.

Results: Overall, 47.2% (620/1313) of questionnaires were eligible for analysis. Of these, 416 (67.1%) patients fulfilled ≥1 of the four ASAS entry criteria. Entry criteria for axial and peripheral SpA were reported by 72.8% and 27.2%, respectively. The large majority (87%) reported ≥1 additional clinical SpA features: one feature by 32.9%, two by 29.1%, three by 16.1%, and ≥4 by 8.9%. In comparison to patients without self-reported entry criteria (n=204), patients with self-reported fulfillment were significantly more frequently female, had higher BMI, were more often ex- or current smokers, had longer HS disease duration, and more active HS symptoms at the survey response time.

Limitations: Non-responder bias and self-reporting design.

Conclusion: Self-reported clinical SpA features are common in HS patients, especially in the 'classic' HS patient, with active HS symptoms, and longer HS disease duration.

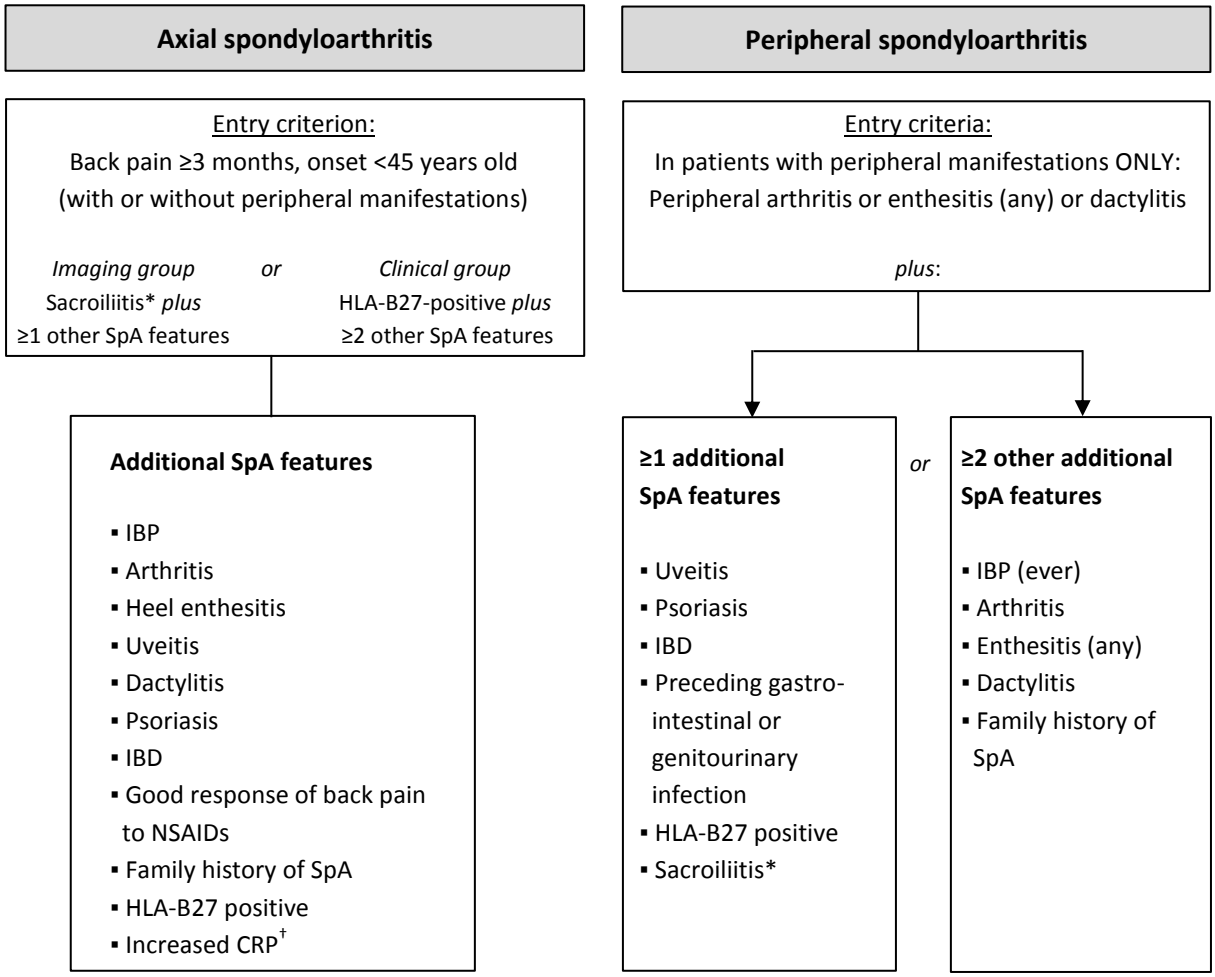
INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, recurrent, and debilitating inflammatory skin disease of the inverse body regions.[1] Hidradenitis suppurativa is associated with a range of somatic and psychological comorbidities including inflammatory bowel disease (IBD), particularly Crohn's disease, metabolic syndrome, depression, and probably rheumatologic conditions such as spondyloarthritis (SpA).[1,2]

Spondyloarthritis, previously termed seronegative spondyloarthritides, is a heterogeneous group of interrelated chronic inflammatory articular rheumatic conditions, which include ankylosing spondylitis (AS), psoriatic arthritis, arthritis related to IBD, reactive arthritis, and undifferentiated SpA.[3] These conditions share clinical symptoms and are associated with the HLA-B27 gene. In most patients, the first symptoms develop in the third or fourth decade of life, and males are more frequently affected.[3] The diagnosis of SpA is made by a rheumatologist and is mainly based on the presence of "SpA features", which includes spinal (axial) features such as sacroiliitis and spondylitis; peripheral features such as peripheral arthritis, enthesitis, and dactylitis; and the so called extra-articular manifestations uveitis, psoriasis, and IBD.[3] Spondyloarthritis features may develop during the course of the disease and may come and go and often do not occur simultaneously. The probability of SpA increases when more of these features have occurred in a patient.[4,5]

Spondyloarthritis can be categorized as predominantly axial or peripheral depending on the main involved articular features.[3] The latest and currently most used classification criteria were developed by the Assessment in SpondyloArthrtis international Society (ASAS) (Figure 1).[6-8] These classification criteria comprise clinical features of SpA, laboratory (e.g. HLA-B27 positivity) and imaging features (e.g. sacroiilitis on radiography and/or magnetic resonance imagining (MRI)).[6-9] According to ASAS, four "entry criteria" for the classification of SpA into (predominantly) axial or peripheral SpA exist. The entry criteria for axial SpA begins with "back pain ≥3 months with age of onset before 45 years (with or without the presence of peripheral manifestations)".[7] The three entry criteria for peripheral SpA are "peripheral arthritis, enthesitis or dactylitis, without axial involvement" (Figure 1).[8]

Until recently, the association between SpA and HS had only been described in limited publications, mostly concerning case reports and small retrospective case series.[10-16] Two recent studies on the prevalence of SpA in HS patients showed large differences in results. The first study suggested a prevalence of SpA of 2.3 to 3.7%, depending on the clinical and imaging criteria used, whereas the other suggested a prevalence of 28.2%.



Sensitivity and specificity of ASAS classification criteria
Axial SpA criteria: sensitivity 82.9%; specificity 84.4%; n=649.[7]
Peripheral SpA criteria: sensitivity 77.8%; specificity 82.2%; n=266.[8]
Combination of axial and peripheral SpA criteria: sensitivity 79.5%; specificity 83.3%; n= 975.[8]

Figure 1. Classification criteria of axial and peripheral spondyloarthritis according to the Assessment in SpondyloArthritis international Society (ASAS)

ASAS, Assessment of SpondyloArthritis international Society; SpA, spondyloarthritis; IBP, inflammatory back pain; CRP, C-reactive protein; IBD, inflammatory bowel disease (Crohn's disease / colitis ulcerosa).

* Either active inflammation detected by MRI highly suggestive of sacroiliitis associated with SpA, or definite radiographic sacroiliitis according to the modified New York criteria.
† Increased CRP is considered a SpA feature in the context of chronic back pain.

Adapted from: Rudwaleit M *et al.*, Ann Rheum Dis. 2009;68(6):777-783[7]; Rudwaleit *et al.,* Ann Rheum Dis. 2011;70(1):25-31.[8]

HS patients.[17,18] Both prevalence rates are higher than the prevalence of SpA in the general population, which is approximately 1%.[3,4]

Because of these discrepancies in prevalence rates and to obtain insight in which HS patients report SpA features and possibly have a higher chance of SpA, we undertook this cross-sectional study in two large HS cohorts in the Netherlands. Our objective was to investigate the prevalence of self-reported clinical SpA features in HS patients and to identify HS patient characteristics associated with the presence of these features.

METHODS

Subjects and design

In this multicenter cross-sectional study, adult patients with a billing code for HS (between 2010 and 2016) in the dermatology departments of the University Medical Center Groningen (UMCG) and Erasmus Medical Center (EMC) received a postal questionnaire and were requested to return the completed questionnaire by post using a pre-stamped return envelope. A reminder was sent to the non-respondents after four weeks. Unopened returned questionnaires and insufficiently answered surveys (no information on SpA entry criteria) were excluded. According to Dutch law, no formal informed consent was needed for this type of study as verified by the UMCG ethical committee.

Questionnaire about clinical SpA features

The questionnaire comprised questions about clinical SpA features that are easily self-identifiable by patients. These questions were formulated based on the ASAS definitions for axial and peripheral SpA entry criteria and additional clinical SpA features in the past or present.[6-9] The questions included: a history of back pain existing ≥3 months with an age of onset <45 years; inflammatory back pain (IBP); response of back pain to non-steroid anti-inflammatory drugs (NSAIDs); peripheral arthritis (swollen joints); enthesitis of the Achilles tendon; dactylitis; ophthalmologist diagnosed uveitis; physician diagnosed psoriasis including pustulosis palmoplantaris; gastroenterologist diagnosed IBD (Crohn's disease or ulcerative colitis); and a positive family history of SpA and SpA related conditions (psoriasis, uveitis, and IBD) in first or second degree relatives. When applicable, the SpA questions were illustrated with colored prototypical pictures. In addition, data on age, gender, length, weight, smoking habits, and HS characteristics such as age of symptom onset and current HS symptoms to derive the Hurley and refined Hurley stage, were collected.

Statistical analysis

Descriptive statistics are reported as mean ± standard deviation (SD) or median (interquartile range (IQR)) for normally distributed and non-normally distributed data, respectively. Determined was how many HS patients reported the ASAS "entry criteria" for classification of SpA. Subsequently, the prevalence of "additional" self-reported SpA features to the entry criteria were calculated. Comparison between HS patients with and without self-reported SpA entry criteria was done using the independent-sample t or Mann-Whitney U tests for continuous and chi square or Fisher's exact tests for dichotomous variables. It was reported when ≥5% of data was missing per variable. P-values ≤ 0.05 were considered as statistically significant. Statistics were performed using IBM SPSS 23.0 software for Windows (SPSS, Chicago, IL, USA).

RESULTS

Inclusion and exclusion

In total, 1313 HS patients received a questionnaire of which 730 (55.6%) were returned (Figure 2). Of these 730 questionnaires, 110 (15.1%) were excluded due to unopened returns (n=70), insufficiently answered surveys (n=32) and other reasons (n=8). Subsequently, 620 (47.2%) questionnaires were eligible for analysis (Figure 2).

The excluded patients (n=693) were more frequently male (36.7 vs. 29.8%, p=0.010) and were younger (40.8 ± 17.5 vs. 43.4 ± 13.9, p<0.001) compared with the included patients.

Subjects

Overall, 70.2% (434/620) of respondents were female, with a mean age of 43.4 ± 13.9 years, and mean BMI of 28.0 ± 5.8 kg/m^2. Furthermore, 83.5% (518/620) patients were ex- or current smokers (Table 1). One fourth (24.8%) of patients had no HS symptoms at the time of the survey, 20.6% were categorized into Hurley stage I, 46.1% into stage II and 8.5% into stage III. An overview of the distribution within the *refined* Hurley classification is shown in Table 1. The patient characteristics were similar between UMCG and EMC cohorts (*data not shown).*

Prevalence of clinical SpA features

In total, 416 (67.1%) HS patients fulfilled ≥1 of the four axial or peripheral ASAS entry criteria (Figure 3). Moreover, 87% of these patients reported ≥1 additional clinical SpA features: one additional feature was reported by 137 (32.9%) patients, two features by 121 (29.1%), three features by 67 (16.1%), and ≥4 features by 37 (8.9%) patients. Table 2 gives an overview of the self-reported clinical SpA features.

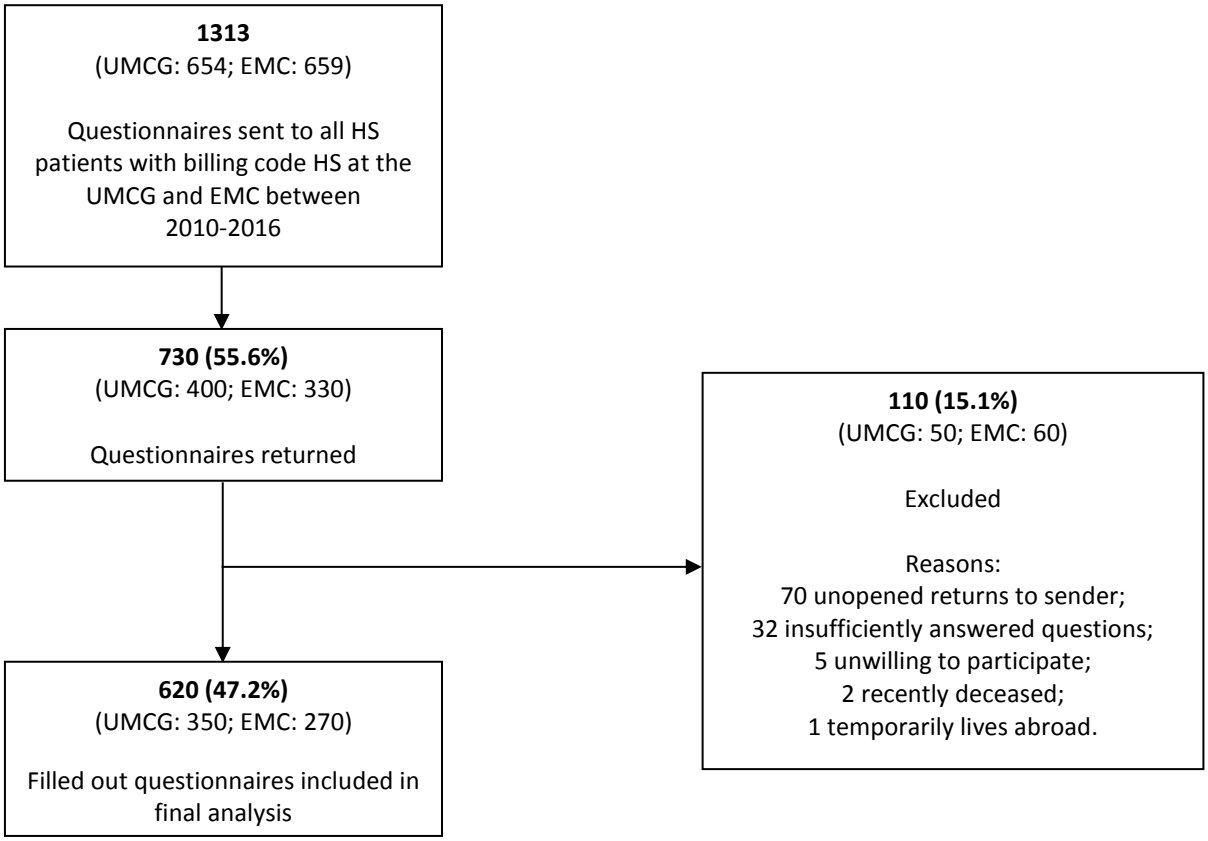


Figure 2. Flow chart of exclusion of questionnaires

HS, hidradenitis suppurativa; UMCG, University Medical Center Groningen; EMC, Erasmus Medical Center.

Of the 416 patients who fulfilled ≥1 of the four ASAS entry criteria, 72.8% (303/416) reported to fulfill the ASAS entry criteria for axial SpA and IBP was reported by 27.7%. Of the 303 patients, 82.2% reported ≥1 additional clinical SpA feature. The other 27.2% (113/416) reported to fulfill the ASAS entry criteria for peripheral SpA. Of these patients, 85.0% reported an episode of peripheral arthritis, 22.1% enthesitis of the Achilles tendon and 22.1% dactylitis. One peripheral SpA feature was reported by 72.6% (n=82), two by 25.7% (n=29), and 1.8% (n=2) reported all three peripheral SpA features. All these 113 patients also reported ≥1additional clinical SpA features as well (Figure 3).

The remaining 32.9% (204/620) patients did not fulfill any of the ASAS entry criteria. Of these patients, 71.6% did not report the presence of additional SpA features, 23.0% reported one feature, and 5.4% two features (Figure 3). Family history of SpA conditions was reported most frequently (21.1%), followed by IBD (6.9%), psoriasis (6.4%), and uveitis (1.0%).

Table 1. Patient characteristics included hidradenitis suppurativa patients (n=620)

Patient characteristics	
Age, *years*	43.4 ± 13.9
Female gender	434 (70.2)
Age of onset HS, *years*	24.0 ± 12.5
Disease duration of HS, *years*	18.9 ± 12.7
BMI, kg/m^2	28.0 ± 5.8
Smoking status	
Non-smoker	98 (15.9)
Ex-smoker	199 (32.3)
Current smoker	319 (51.8)
Hurley classification stage	
Not active	146 (24.8)
Hurley I	121 (20.6)
Hurley II	271 (46.1)
Hurley III	50 (8.5)
Refined Hurley classification stage	
Not active	146 (25.0)
Refined Hurley IA	33 (5.7)
Refined Hurley IB	14 (2.4)
Refined Hurley IC	74 (12.7)
Refined Hurley IIA	45 (7.7)
Refined Hurley IIB	68 (11.7)
Refined Hurley IIC	153 (26.2)
Refined Hurley III	50 (8.6)

Data are presented as number of patients (%) or mean ± standard deviation.

Missing data ≥5%: BMI (6.8%), age of onset HS (6.6%), disease duration of HS (6.5%), Hurley classification stage (5.2%), refined Hurley classification stage (6.0%).

HS, hidradenitis suppurativa; BMI, Body Mass Index.

Patient characteristics associated with SpA features in HS

In comparison to patients without self-reported entry criteria (204/620), patients fulfilling the ASAS entry criteria (416/620) were more frequently female (74.8% vs. 60.9%, p<0.001), had a higher BMI (28.6 ± 5.9 vs. 26.7 ± 5.3, p<0.001), were more often ex- or current smokers (87.9% vs. 76.2%, p=0.001), had a longer HS disease duration (19.9 ± 12.8 vs. 17.0 ± 12.4, p=0.012), and reported more active HS at time of the survey response reflected by the Hurley and refined Hurley classification distribution (both p<0.001) (Table 3).

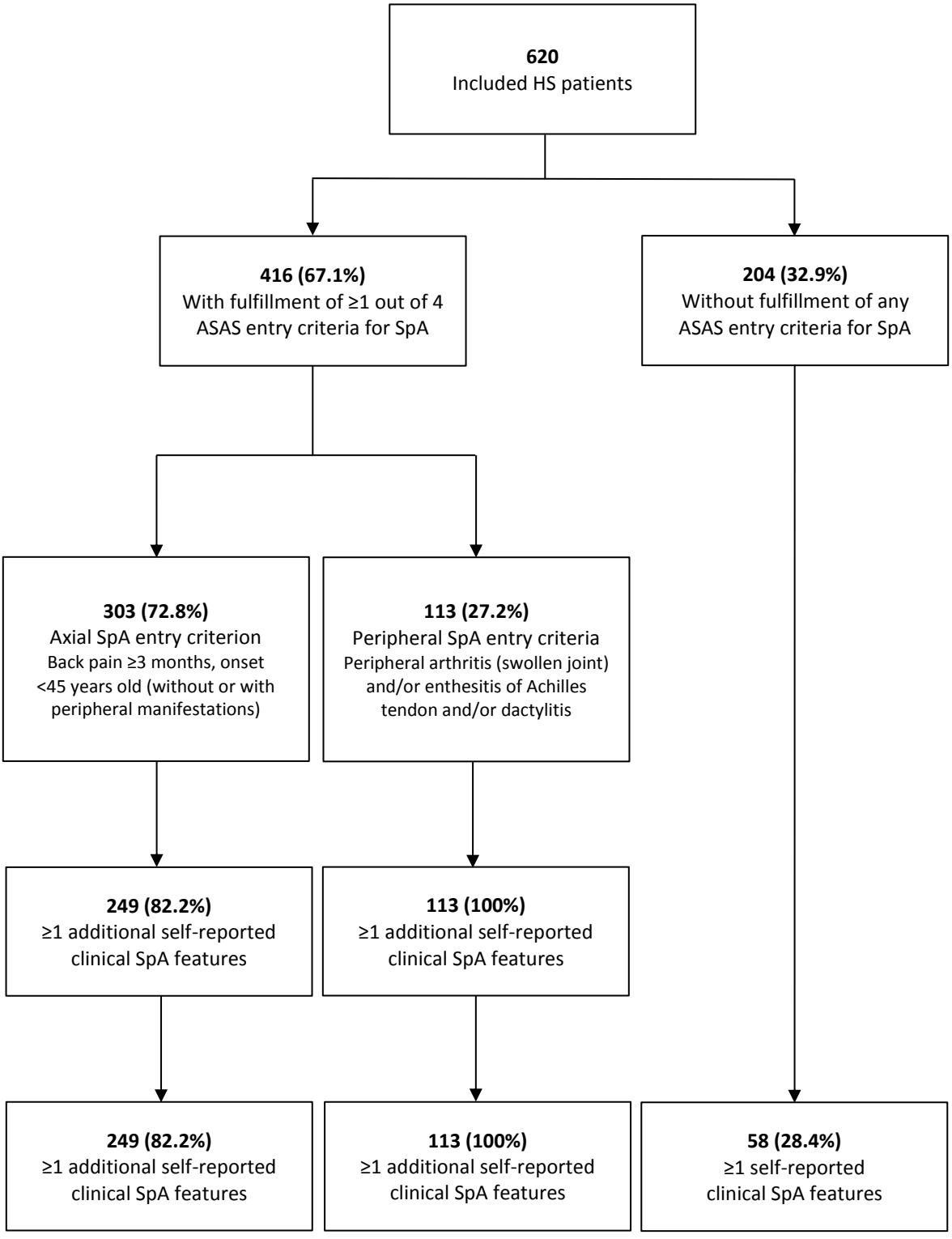


Figure 3. Flowchart of self-reported ASAS classification entry criteria for spondyloarthirits in patients with hidradenitis suppurativa

HS, hidradenitis suppurativa; SpA, spondyloarthritis; ASAS, Assessment of SpondyloArthritis international Society.

Table 2. Overview of the prevalence of self-reported spondyloarthritis entry criteria and features in patients with hidradenitis suppurativa

	Fulfillment of ≥1 out of 4 ASAS entry criteria[†] (n=416)
Total number of self-reported SpA features in addition to the entry criteria*	
0 features	54 (13.0)
1 feature	137 (32.9)
2 features	121 (29.1)
3 features	67 (16.1)
≥4 features	37 (8.9)
SpA-features (self-reported)	
Inflammatory back pain[‡]	84 (20.2)
Effect of NSAIDs on back pain	
Good response (>50% response)	63 (22.0)
No or under 50% response	93 (32.5)
No NSAIDs used	30 (45.5)
Peripheral arthritis (swollen joints)	248 (59.6)
Enthesitis (Achilles tendon)	66 (15.9)
Dactylitis	83 (20.0)
Uveitis[§]	13 (3.2)
Psoriasis (incl. pustulosis palmoplantaris)[§]	39 (9.4)
Inflammatory bowel disease[§]	31 (7.6)
Crohn's disease	19 (4.7)
Ulcerative colitis	12 (2.9)
Family history for SpA in $1^{st}/2^{nd}$ degree relatives[#]	125 (30.0)

SpA, spondyloarthritis; ASAS, Assessment of SpondyloArthritis international Society; NSAIDs, nonsteroidal anti-inflammatory drugs.

***** Additional self-reported SpA-features: inflammatory back pain, inflammatory bowel syndrome, uveitis, psoriasis, good effect of non-steroidal drugs on back pain, family history of spondyloarthritis, dactylitis, enthesitis of the Achilles tendon, and peripheral arthritis (swollen joint).
† ASAS entry criteria for axial and peripheral SpA: "back pain for ≥3 months with age of onset <45 years" and "peripheral arthritis, enthesitis or dactylitis", respectively.
‡ Inflammatory back pain: at least four out of five ASAS criteria for inflammatory back pain need to be fulfilled: insidious onset, pain at night (with improvement upon getting up), age at onset <40 years, improvement with exercise, and no improvement with rest.[10]
§ Physician diagnosed.
# Family history for SpA in 1st/2nd degree relatives: ankylosing spondylitis, psoriatic arthritis, psoriasis, uveitis, and inflammatory bowel disease.

Table 3. Patient characteristics between hidradenitis suppurativa patients with versus without fulfillment of spondyloarthritis entry criteria

	Fulfillment of ≥1 of 4 ASAS entry criteria (n=416)	**No fulfillment of ASAS entry criteria** (n=204)	**p-value**
Age, *years*	43.8 ± 13.2	42.5 ± 15.2	0.29
Female gender	311 (74.8)	123 (60.9)	<0.001
Age of onset HS, *years*	23.4 ± 12.2	25.0 ± 13.1	0.15
Disease duration of HS, *years*	19.9 ± 12.8	17.0 ± 12.4	0.012
BMI, *kg/m²*	28.6 ± 5.9	26.7 ± 5.3	<0.001
Smoking status			0.001
Non-smoker	50 (12.1)	48(23.8)	
Ex-smoker	138(33.3)	61(30.2)	
Current smoker	226(54.6)	93(46.0)	
Hurley classification stage			<0.001
Not active	78 (20.1)	68 (34)	
Hurley I	72 (18.6)	47 (12.1)	
Hurley II	198 (51.0)	73 (36.5)	
Hurley III	38 (9.8)	12 (6.1)	
Refined Hurley classification stage			<0.001
Not active	78 (20.2)	68 (34.5)	
Refined Hurley IA	18 (4.7)	15 (7.6)	
Refined Hurley IB	7 (1.8)	7 (3.6)	
Refined Hurley IC	49 (12.7)	25 (12.7)	
Refined Hurley IIA	29 (7.5)	16(8.1)	
Refined Hurley IIB	45 (11.7)	23 (11.7)	
Refined Hurley IIC	122 (31.6)	31 (15.7)	
Refined Hurley III	38 (9.8)	12 (6.1)	

HS, hidradenitis suppurativa; BMI, Body Mass Index.

Missing data ≥5%: Hurley classification stage (5.2%), refined Hurley classification stage (6.0%).

DISCUSSION

This study shows that self-reported clinical SpA features are common in HS patients: 67% reported ≥1 ASAS entry criteria and the large majority of these patients (87%) reported additional clinical SpA features. Approximately 75% of these patients reported long-term back pain as entry criteria for axial SpA of which approximately 28% reported inflammatory back pain.

In this study, we used the ASAS criteria for axial and peripheral SpA, with a previously reported sensitivity and specificity of 79.5% and 83.3% respectively according to the diagnosis made by the rheumatologist.[7,8] Important to mention is that the ASAS criteria were developed as classification criteria for clinical research and not as diagnostic criteria.[8] However, for the diagnosis of SpA, the presence and number of clinical SpA features seem important since the probability of a SpA diagnosis increases if more of these SpA features are present.[4,5,19-21] The relevance of these clinical SpA features for the diagnosis can be

expressed in likelihood ratios (LR), i.e. ranging from 2.5 for psoriasis to 7.3 for uveitis.[21] In our study, of the HS patients who reported ≥1 of the ASAS entry criteria for SpA, almost all (87%) reported the presence of ≥1 other additional (clinical) SpA features. More than half of the patients reported multiple additional SpA features of which 29% reported two features, 16% three features, and nearly 9% reported ≥4 features, this further increases the diagnostic probability (by calculating the LR product).

Since over 50% of the HS patients who returned their questionnaire reported multiple SpA features, we argue that HS and SpA seem associated which is in line with previous studies. In 2014, a prospective study investigated the history of clinical SpA features (arthritis, enthesitis, and IBP) in 640 HS patients in France.[17] All HS patients with articular complaints (n=184) (not further defined), were referred to a rheumatologist and an episode of arthritis, enthesitis and/or IPB (determined with the Calin or Berlin criteria) was reported in 43 (6.7%) of these patients. Additional diagnostics (HLA-B27, radiography, MRI) were done, although not in all patients. Finally, 15 patients fulfilled the ASAS criteria for SpA, leading to a prevalence of SpA of 2.3% in 640 HS patients.[17] Another French study, published in 2017, compared the prevalence of SpA between 39 HS patients and an age and gender matched control group without dermatological diseases.[18] They reported a prevalence as high as 28.2% in the HS group, versus 2.6% in the control group. In this study, the rheumatologist used the ASAS classification criteria to diagnose SpA. In both studies axial involvement was most common.[17,18] The results of both studies are higher than the average reported prevalence of SpA of around 1-1.5% in the general population, but differ considerably.[3,4,17,18] However, both studies reported limitations, such as selection bias probablity and incompleteness of additional diagnostic test.[17,18]

An association between HS and SpA could be explained by a similar pathogenic mechanism, even though the exact pathogenesis of both HS and SpA remains to be elucidated. A perturbed immune response is assumed to be involved in both conditions, sharing dysregulation of tumor necrosis factor-alpha (TNF-α), interleukin-1, interleukin-12, interleukin-23 and interleukin-17 pathways.[3,22-24] Moreover, both conditions are also associated with IBD.[25-27] Both HS and SpA show common dysregulated inflammatory pathways with IBD, but seem unrelated at first sight due to the different affected end-organs.[3,28] The relationship between all these conditions might be explained by the immune-mediated inflammatory disease (IMID) concept, a theory that is used to collectively describe a group of seemingly unrelated conditions that in fact share common inflammatory pathways.[29] The first hints for common pathogenic pathways within IMID conditions were based on the therapeutic effect of TNF-α inhibitors, indicating that an imbalance in TNF-α plays an important role in the pathogenesis of all of these IMID conditions.[29] The IMID concept is already described for IBD and SpA, and based on previous publications and our study, HS might be added to the list of IMID conditions.[29]

The risk factors smoking and a high BMI are epidemiologically linked to both HS and SpA; high prevalence rates are found in both diseases and are associated with a higher disease activity.[30-34] Interestingly, our results show a significantly higher prevalence of ex- or current smokers and a higher mean BMI in the group positive for at least one SpA entry criterion, compared to the patients without self-reported SpA entry criteria. Several theories are formed about the influence of these risk factors on HS and SpA disease. One plausible hypothesis is, that smoking and a higher BMI might alter immunological (inflammatory) responses, contributing to HS and SpA disease activity.[29,35]

Another notable, significantly more prevalent characteristic in HS patients positive for ≥1 SpA entry criteria were active HS symptoms at time of the questionnaire response. In line with the above, this might suggest that HS disease activity might influence the immunological inflammatory responses, possibly increasing chances for other inflammatory disease such as SpA. However, one might also suggest that patients with active symptoms of one disease, are more likely to respond to a survey as this one.

Our study has limitations. There is the risk of non-responder bias. Furthermore, this study focused on clinical SpA features assumed to be easily self-identified by patients, therefore, the developed questionnaire does not cover all clinical SpA features (e.g. the question regarding enthesitis was restricted to enthesitis of the Achilles tendon and not enthesitis of other sites). A notable finding was that a large number (approximately 50%) HS patients reported a positive history of swollen joints (to identify a history of peripheral arthritis). This number must be taken with caution since a possible discrepancy between physicians' and patients' swollen joint count has been shown previously in a systematic review for rheumatoid arthritis.[36] In order to limit the false positive answers, we added prototypical pictures of patients with swollen joints in the self-administered questionnaire. Altogether, both underestimation and overestimation of clinical SpA features is possible. We asked patients for present and past SpA features and no additional knowledge was available of laboratory tests such as the presence of HLA-B27 and imaging to detect sacroiliitis. A conformation of a possible SpA diagnosis by a rheumatologist was not part of this study.

In conclusion, this study demonstrated high prevalence of self-reported ASAS classification entry criteria for either axial or peripheral SpA, and additional SpA features in HS patients. This strongly suggests a relevant association with SpA. Early recognition of possible SpA in HS patients is important for management and outcome in both SpA and HS. In this study, the prevalence of SpA features was associated with 'classic' HS patient (female, overweight, smoker), with longer HS disease duration and symptoms of active HS. Further evaluation of these patients, by referral to a rheumatologist, is therefore considered. The developed questionnaire in this study might be a useful instrument for the initial screening of HS patients for features of SpA.

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