

## Observational Study

**Nonalcoholic fatty liver disease prevalence in an Italian cohort of patients with hidradenitis suppurativa: A multi-center retrospective analysis**

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## Abstract

### BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) includes two distinct conditions, with different histologic features and prognosis: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Furthermore, NASH is the more aggressive necro-inflammatory form, which may accumulate fibrosis and result in End stage liver disease (ESLD). NAFLD is also linked to systemic inflammatory conditions such as psoriasis. NAFLD is currently the most common cause of ESLD in Western countries, becoming a serious public health concern. Hidradenitis suppurativa (HS) is a systemic inflammatory/autoinflammatory disease of the terminal follicular epithelium of the apocrine gland with a prevalence of 0.05% to 4.10%. Due to its systemic inflammatory behavior several comorbidities were recently associated, however liver ones were scarcely assessed.

### AIM

To evaluate the prevalence and characteristics of NASH/NAFL in HS patients.

### METHODS

This retrospective study is a sub-analysis of a larger study carried out in 4 Italian dermatological centers. In this cohort, there were 83 patients: 51 patients with HS only, 20 patients with HS/NAFL and 12 with HS/NASH.

### RESULTS

Inflammatory comorbidities were present in 3.9% of HS only patients, 25% of HS/NAFL patients and 58.3% of HS/NASH patients ( $P < 0.001$ ). Similarly, mean Autoinflammatory Disease Damage Index (ADDI) was significantly higher among patients with HS/NASH ( $5.3 \pm 2.2$ ,  $P < 0.001$ ) compared to patients with HS/NAFL or HS only ( $2.8 \pm 1.6$  and  $2.6 \pm 1.4$  respectively). Furthermore, ADDI correlates with IHS4 in HS, HS/NAFL and HS/NASH. Diabetic patients have higher Hurley score than not diabetic ones. Ultrasound examination was significantly different in the three groups.

### CONCLUSION

HS patients displayed a high prevalence of NASH/NAFLD and ultrasound examination should be particularly addressed to patients that display high ADDI scores.

**Key words:** Non-alcoholic steatohepatitis; Non-alcoholic fatty liver; Nonalcoholic fatty liver disease; End stage liver disease; Hidradenitis suppurativa

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**Core tip:** Nonalcoholic fatty liver disease (NAFLD), in its two variants non-alcoholic fatty liver and non-alcoholic steatohepatitis, is often linked to systemic inflammatory conditions, such as psoriasis. Remarkably, hidradenitis suppurativa (HS) is a new affirming systemic inflammatory disorder of the follicular epithelium of skin apocrine glands with a prevalence in normal population ranging from 0.05% to 4.10%. Furthermore, HS patients display a significant comorbidities burden (e.g., cardiovascular risk, metabolic syndrome, diabetes, and spondyloarthritis) but the association with NAFLD was not previously investigated. This is the first study which evaluated NAFLD prevalence and its characteristics in HS patients.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) includes two distinct entities, with different histologic clues and prognosis: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), the more aggressive necro-inflammatory form, which may accumulate fibrosis and result in End stage liver disease (ESLD) and its complications, including hepatocellular carcinoma (HCC)<sup>[1]</sup>.

Nowadays, NAFLD represents the main cause of chronic liver disease in Europe and North America, where is found in 17%-30% of the population, worldwide the prevalence is 2%-4% of the population becoming a serious public health concern<sup>[2]</sup>. Evidences suggest that NAFLD is the hepatic sign of metabolic syndrome; therefore, is linked not only with an increase of liver-related mortality, but also of the overall mortality. Noninvasive techniques, such as biological tests and elastography can be used for the evaluation of NAFLD patients. Today, liver biopsy (diagnostic gold standard) should be recommended in selected cases.

Patients with NAFLD would benefit from their lifestyle changes by progressive weight loss through exercise and low sugar and fat intake. Pharmacotherapy should be reserved for patients with significant fibrosis. Unfortunately, there are no Food and Drug Administration (FDA) approved therapies<sup>[3]</sup>.

Hidradenitis suppurativa (HS) is a systemic, chronic, inflammatory/autoinflammatory disease with a relapsing remitting behavior and a deep impact on patient's quality of life. Despite its elusive pathogenesis, clinical manifestations are clear and space from painful nodules to fistula, mainly involving areas rich in apocrine gland-bearing, such as armpits, inguinal and anogenital regions (Dessau definition)<sup>[4-6]</sup>. HS is an affirming systemic inflammatory disease and this idea was sustained by the recent acquisitions in the pathogenesis<sup>[7]</sup>, epidemiology<sup>[8]</sup> and therapy<sup>[9]</sup>. Until recently, it was considered to be a rare disease with a prevalence cited as approximately 1%<sup>[10]</sup>. Actually, the prevalence of HS seems to be greater varying from 0.05% to 4.10%; this variability is intrinsically affected by study type, being lower in retrospectively designed studies and the higher in prospective or self-reported ones<sup>[11]</sup>.

European guidelines for the management of HS have been published<sup>[12]</sup>: No therapy is actually able to guaranty a high rate of complete disease remission. As for patients with NAFLD also patients with HS would benefit from their lifestyle changes by losing weight. Furthermore, topical and systemic antibiotics, injected corticosteroids, or biologics and other systemic treatments may be used. Oral antibiotics may be used to help prevent new lesions. Moderate stages may be treated with oral antibiotics, oral retinoids such as isotretinoin, hormonal therapy, and/or surgery<sup>[11,12]</sup>. For moderate to severe disease, target therapy directed against TNF-alpha proteins which are involved in the inflammation process are used: adalimumab has been approved by the FDA as orphan product for HS treatment. Adalimumab, a TNF blocker, is actually the only biologic drug approved in Italy for HS patients and notable in October 2018 it received an extension also for children over 12 years old<sup>[13]</sup>. Due to the increased body of comorbidities currently associated with HS<sup>[14,15]</sup>, the liver metabolic comorbidities were neglected.

NAFLD is considered a multisystem pathology increasing the risk of diabetes mellitus, cardiovascular and chronic renal disorders, diseases with an increased incidence in HS patients<sup>[16]</sup>.

Over the last decade, it has been growing the evidence that NAFLD is associated with psoriasis, another systemic chronic inflammatory disease<sup>[17-19]</sup>. Despite the high incidence of NAFLD and the current evidence that HS is not an uncommon disease, there are currently no studies in the literature investigating the association between NAFLD and chronic skin diseases other than psoriasis.

## MATERIALS AND METHODS

### *Study population*

This retrospective study is a sub-analysis of a larger one carried out in the Department of Dermatology of Ospedale Maggiore Policlinico at the beginning and after extended to other 3 primary dermatological Italian centers, namely San Donato Hospital, San Gallicano Hospital and Galeazzi Hospital. The study started in January 2018 and

ended in December 2018. Patients were recruited by filling the recently proposed visual-aided questionnaire for the self-assessment of HS<sup>[20]</sup>. The positive patients were after assessed in a dedicated HS-Lab. The diagnosis of HS was performed by two independent board-certified dermatologists following the Dessau criteria<sup>[21]</sup>. The inclusion criteria comprehended HS diagnosis, Alcohol Use Disorders Identification Test (AUDIT) < 8<sup>[22]</sup>, last 3 complete blood count (CBC) available with transaminases. The exclusion criteria comprehended AUDIT score > 7, pre-existent hepatic cirrhosis, viral hepatitis (B, C and E) and recent drug-related hepatitis (< 5 years), congenital hepatic malformations, hepatic or cholangitic autoimmune conditions.

All patients underwent a hepatologic visit and ultrasonographic (US) evaluation of the liver. Patients with raised liver enzymes underwent liver biopsy to evaluate the presence of NAFLD according the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) Clinical Practice Guidelines for the management of NAFLD<sup>[23]</sup>. Patients were also screened for diabetes, a predisposing factor for NASH and NAFLD. Diabetes diagnosis was performed following these criteria: a random blood sugar level of equal or greater than 200 mg/dL or 11.1 mmol/L or fasting blood sugar test of 126 mg/dL (7 mmol/L) or higher on two separate tests or oral sugar test of equal or higher than 200 mg/dL (11.1 mmol/L) after two hours.

### Outcomes of the study

During dermatological assessment, besides demographics, drug-history and comorbidities, were collected HS clinical phenotypes<sup>[24]</sup>, static score as Hurley<sup>[25]</sup>, dynamic score as international HS 4 (iHS4)<sup>[26]</sup>, the Autoinflammatory Disease Damage Index (ADDI)<sup>[27,28]</sup> and Dermatology Life Quality Index (DLQI)<sup>[29]</sup>.

### Statistical analysis

Variables were described as number and/or percentages. All variables were preliminarily assessed with Shapiro-Wilk test to establish the parametric behavior. The Wilcoxon-Mann-Whitney test was employed to deal with quantitative variables, whilst Fisher's exact test was applied with qualitative variables comparison. A *P* value < 0.05 was considered significant. The analysis was performed with the statistical software SPSS ver. 20.0 (Armonk, NY: IBM Corp.).

## RESULTS

Demographics and clinical characteristics were summarized in **Table 1**. Interestingly from the pool of 86 patients that had a positive visual-aided questionnaire for the self-assessment of HS, after clinical assessment we enrolled 83 HS patients with the above HS clinical phenotypes: 54 regular type, 6 frictional type, 10 scarring folliculitis type, 5 conglobata type, 5 syndromic type, 3 ectopic type.

In this cohort, there were 51 patients with HS only, 20 patients with HS and NAFL (HS/NAFL) and 12 with HS and NASH (HS/NASH)(**Table 1**). The groups were predominantly composed by females, in fact males were 33.3% of HS only, 43.8% HS/NAFLD, 41.7% HS/NAFL and 45% HS/NASH patients being female and did not display significant difference (*P* = 0.62, *P* = 0.52, *P* = 84). The average age between groups was similar (HS only 43 ± 8.9; HS/NAFLD 41.3 ± 9.0; HS/NAFL 40.6 ± 10.3; HS/NASH 41.6 ± 7.4, *P* = 0.56). Patients also had similar Body Mass Index (BMI) with HS only having an average BMI of 28.3 ± 2.5 kg/m<sup>2</sup>, HS/NAFLD patients being 27.6 ± 1.9 kg/m<sup>2</sup> (*P* = 0.38), HS/NAFL 27.6 ± 1.7 kg/m<sup>2</sup> (*P* = 0.22) and HS/NASH having 27.6 ± 2.7 kg/m<sup>2</sup> (*P* = 0.38). Diabetes was present in 24% of HS only patients, 30% of HS/NAFL and 25% of HS/NASH patients. Inflammatory comorbidities (**Table 1**) were present in 3.9% of HS only patients, 37.5% of HS/NAFLD, 25% of HS/NAFL patients and 58.3% of HS/NASH patients with a statistically different prevalence (*P* < 0.001). Specifically, in HS only patients one had acne conglobata and 1 patient had lichen sclerosus; while in HS/NAFL there was one patient with Crohn's disease, 1 with Pyoderma gangrenosum, Acne, and Hidradenitis Suppurativa (PASH), 1 with psoriasis, 1 with spondyloarthritis and 1 with uveitis. Finally, of the HS/NASH patients, 1 had Crohn's disease, 4 had PASH, 1 had psoriasis and 1 had spondyloarthritis.

The average iHS4 score among HS/NASH patients (12.7 ± 3.6, *P* = 0.03) was the highest, while it was similar among those with HS only and HS/NAFL patients (9.6 ± 3.6 and 9.4 ± 3.9 respectively, *P* = 0.86). Likewise, mean ADDI was significantly higher among HS/NASH patients (5.3 ± 2.2, *P* < 0.001) compared to HS only and HS/NAFL patients (2.8 ± 1.6 and 2.6 ± 1.4 respectively) (**Table 1**). There were no significant differences in Hurley score, however 83% of HS/NASH patients had a Hurley score

**Table 1** Characteristics of 83 patients with hidradenitis suppurative, Nonalcoholic fatty liver and Nonalcoholic steatohepatitis and intercalsses charactersitics

	HS only	NAFLD	P value	NASH	P value	NAFL	P value
<i>n</i>	51	32		12		20	
Age, mean(SD)	43.04 (8.9)	41.32 (9.0)	0.564	41.58 (7.4)	0.602	40.55 (10.3)	0.315
Age cat (%)			0.646		0.463		0.629
< 30	3 (5.9)	4 (12.5)		1 (8.3)		3 (15.0)	
30-39	16 (31.4)	8 (25.0)		2 (16.7)		6 (30)	
40-49	18 (35.3)	14 (43.8)		7 (58.3)		7 (35.0)	
> 50	14 (27.5)	6 (18.8)		2 (16.7)		4 (20.0)	
Male, <i>n</i> (%)	17 (33.3)	14 (43.8)	0.623	5 (41.7)	0.835	9 (45.0)	0.52
Diabetes, <i>n</i> (%)	12 (23.5)	9 (28.1)	0.853	3 (25.0)	0.764	6 (30.0)	0.794
BMI, mean(SD)	28.31 (2.5)	27.56 (1.9)	0.381	27.58 (2.7)	0.376	27.55 (1.7)	0.218
bmi_cat (%)			0.559		0.515		0.384
Normal Weight	4 (7.8)	4 (12.5)		2 (16.7)		2 (10.0)	
Overweight	38 (74.5)	26 (81.3)		9 (75.0)		17 (85.0)	
Obese	9 (17.6)	2 (6.3)		1 (8.3)		1 (5.0)	
IHS4, mean(SD)	9.57 (3.6)	11.32 (2.8)	0.025	12.67 (3.6)	0.009	9.40 (3.9)	0.861
IHS4 cat (%)			0.028		0.007		0.97
Mild	5 (9.8)	3 (9.4)		1 (8.3)		2 (10.0)	
Moderate	24 (47.1)	10 (31.3)		0 (0)		10 (50.0)	
Severe	22 (43.1)	19 (59.4)		11 (91.7)		8 (40)	
Hurley (%)			0.494		0.197		0.785
1	5 (9.8)	3 (9.4)		1 (8.3)		2 (10.0)	
2	24 (47.1)	6 (18.8)		1 (8.3)		5 (25.0)	
3	22 (43.1)	23 (71.9)		10 (83.3)		13 (65.0)	
Elevated_liver_enzymes, <i>n</i> (%)	19 (37.3)	9 (28.1)	0.617	4 (33.3)	0.998	5 (25.0)	0.482
ADDI_score, mean(SD)	2.55 (1.4)	3.72 (1.8)	< 0.001	5.33 (2.2)	< 0.001	2.75 (1.6)	0.603
Inflammatory comorbidities, <i>n</i> (%)	2 (3.9)	12 (37.5)	< 0.001	7 (58.3)	< 0.001	5 (25.0)	0.025
In detail (%)			0.001		< 0.001		0.047
Acne conglobata	1 (2.0)	0 (0)		0 (0)		0 (0)	
Crohn disease	0 (0)	2 (6.3)		1 (8.3)		1 (5.0)	
Lichen sclerosus	1 (2.0)	0 (0)		0 (0)		0 (0)	
PASH	0 (0)	5 (15.6)		4 (33.3)		1 (5.0)	
Psoriasis	0 (0)	2 (6.3)		1 (8.3)		1 (5.0)	
Spondyloarthritis	0 (0)	2 (6.3)		1 (8.3)		1 (5.0)	
Uveitis	0 (0)	1 (3.1)		0 (0)		1 (5.0)	
Positive ultrasound, <i>n</i> (%)	11 (21.6)	32 (100.0)	< 0.001	12 (100.0)	< 0.001	20 (100.0)	< 0.001
NASH	0 (0)	12 (37.5)	< 0.001	12 (100.0)		0 (0)	
NAFL	0 (0)	20 (62.5)	< 0.001	0 (0)		20 (100.0)	

ADDI: Autoinflammatory disease damage index; BMI: Body mass index; HS: Hidradenitis suppurativa; IHS4: International Hidradenitis Suppurativa Severity Scoring System, NASH: NonAlcoholic SteatoHepatitis, NAFL: NonAlcoholic Fatty Liver, PASH: Pyoderma gangrenosum, Acne, and hidradenitis suppurativa; SD: Standard deviation. Normal weight: 18.5–24.9 kg/m<sup>2</sup>, Overweight: 25–29.9 kg/m<sup>2</sup> Obese: >29.9 kg/m<sup>2</sup>.

of 3, whereas only 65% of HS/NAFL and 57% of HS only patients had a Hurley score of 3 ( $P = 0.49$ ). Presence of elevated liver enzymes was similar among the three groups (HS only 37.3%; HS/NAFL 25%; HS/NASH 33.3%,  $P = 0.62$ ). Finally, ultrasound revealed a bright liver in 22% of HS only patients and all HS/NAFL and HS/NASH patients ( $P < 0.001$ ).

HS only and HS/NAFL patients displayed a significant difference in inflammatory comorbidities ( $P = 0.025$ ) and positivity of ultrasound ( $P < 0.001$ ) (Table 1).

HS/NASH compared with patients with HS only displayed a significant difference in IHS4 ( $P = 0.009$ ), ADDI ( $P < 0.001$ ), inflammatory comorbidities rate ( $P < 0.001$ ) and ultrasound positivity ( $P < 0.001$ ) (Table 1).

HS patients with and without diabetes had a significant difference only in Hurley stage ( $P = 0.022$ ) (Table 2).



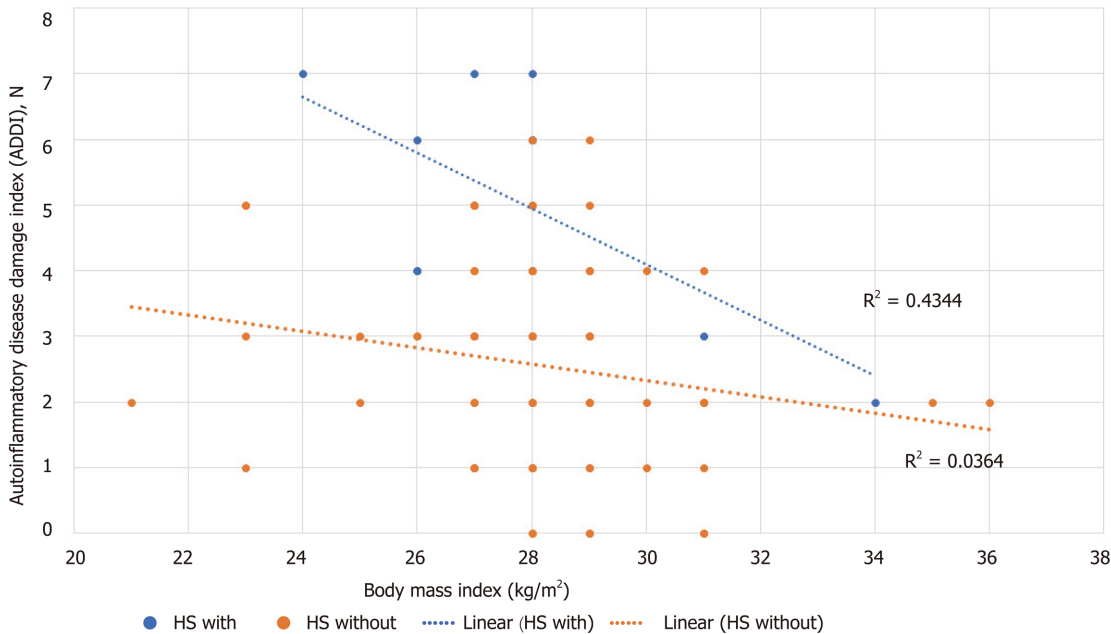
**Table 2 Differences among hidradenitis suppurativa patients with and without diabetes**

	Non diabetes	Diabetes	P value
<i>n</i>	62	21	
Age, mean(SD)	42.44 (9.4)	41.62 (8.2)	0.722
Age cat (%)			0.203
< 30	4 (6.5)	3 (14.3)	
> 50	17 (27.4)	3 (14.3)	
30-39	20 (32.3)	4 (19.0)	
40-49	21 (33.9)	11 (52.4)	
Male, <i>n</i> (%)	21 (33.9)	10 (47.6)	0.387
Diabetes, <i>n</i> (%)	0 (0.0)	21 (100.0)	<0.001
BMI, mean(SD)	28.10 (2.6)	27.81 (1.4)	0.636
bmi_cat (%)			0.161
Normal Weight	8 (12.9)	0 (0.0)	
Obese	9 (14.5)	2 (9.5)	
Overweight	45 (72.6)	19 (90.5)	
IHS4, mean(SD)	10.37 (3.6)	8.81 (4.1)	0.101
IHS4 cat, <i>n</i> (%)			0.051
Mild	4 (6.5)	4 (19.0)	
Moderate	23 (37.1)	11 (52.4)	
Severe	35 (56.5)	6 (28.6)	
Hurley, <i>n</i> (%)			0.022
1	4 (6.5)	4 (19.0)	
2	14 (22.6)	9 (42.9)	
3	44 (71.0)	8 (38.1)	
Elevated_liver_enzymes, <i>n</i> (%)	21 (33.9)	7 (33.3)	1
ADDI_score, mean(SD)	3.13 (1.8)	2.62 (2.0)	0.275
Inflammatory comorbidities, <i>n</i> (%)	9 (14.5)	5 (23.8)	0.518
In.detail, <i>n</i> (%)			0.563
	53 (85.5)	16 (76.2)	
Acne conglobata	1 (1.6)	0 (0.0)	
Crohn	1 (1.6)	1 (4.8)	
Lichen sclerosus	0 (0.0)	1 (4.8)	
PASH	4 (6.5)	1 (4.8)	
Psoriasis	1 (1.6)	1 (4.8)	
Spondyloarthritis	1 (1.6)	1 (4.8)	
Uveitis	1 (1.6)	0 (0.0)	
Positive_ultrasound, <i>n</i> (%)	31 (50.0)	12 (57.1)	0.754
NASH, <i>n</i> (%)	9 (14.5)	3 (14.3)	1
NAFL, <i>n</i> (%)	14 (22.6)	6 (28.6)	0.795
Disease, <i>n</i> (%)			0.853
HS only	39 (62.9)	12 (57.1)	
NAFL	14 (22.6)	6 (28.6)	
NASH	9 (14.5)	3 (14.3)	

ADDI: Autoinflammatory Disease Damage Index; BMI: Body mass index; HS: Hidradenitis suppurativa; IHS4: International Hidradenitis Suppurativa Severity Scoring System; NASH: Non-alcoholic steatohepatitis; NAFL: Nonalcoholic fatty liver; PASH: Pyoderma gangrenosum, Acne, and hidradenitis suppurativa; SD: Standard deviation. Normal weight: 18.5–24.9 kg/m<sup>2</sup>; Overweight: 25–29.9 kg/m<sup>2</sup>; Obese: > 29.9 kg/m<sup>2</sup>.

Age had a significant moderately positive correlation with ADDI among HS/NAFL patients ( $r = 0.57, P = 0.05$ ). Next, BMI and ADDI were moderately negatively correlated in HS patients with inflammatory comorbidities ( $R^2 = 0.43$ , **Figure 1**).

BMI and ADDI were weakly negatively correlated in patients with HS only ( $r = -0.25, P = 0.05$ ) and in those who had HS and diabetes ( $r = -0.46, P = 0.04$ ). Correlation between BMI and IHS4, age and IHS4, BMI and ADDI, among the three groups was



**Figure 1** Correlation between body mass index and Autoinflammatory Disease Damage Index among patients with hidradenitis suppurative (HS) only, or HS with other inflammatory comorbidity.

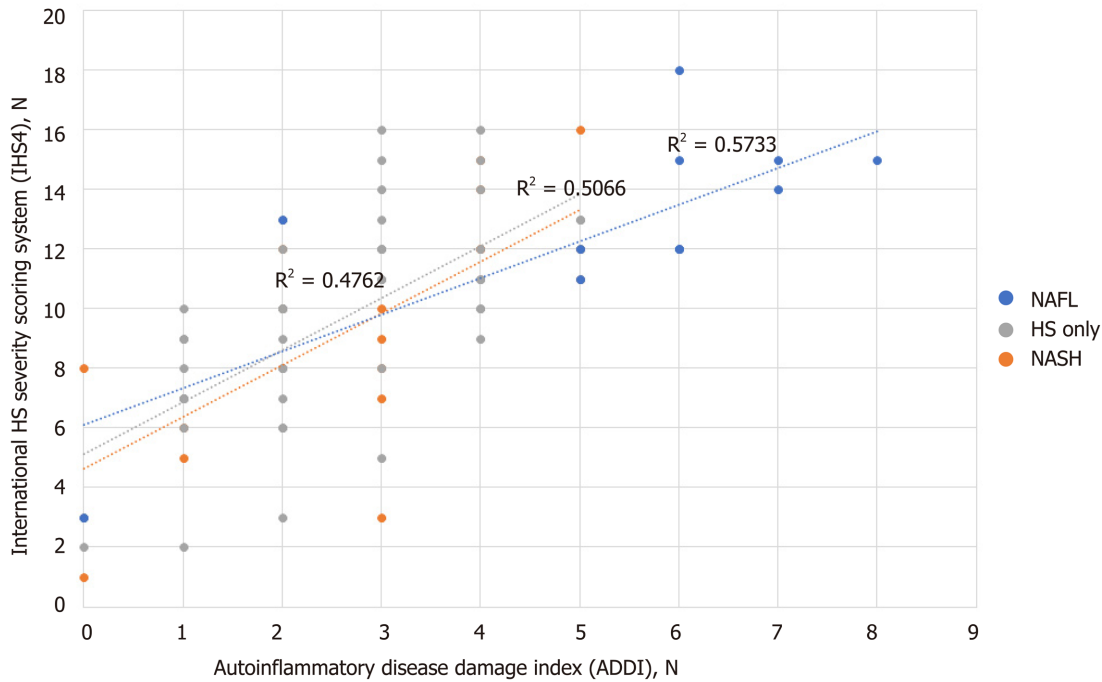
not significant. In addition, correlation between BMI and IHS4, age and IHS4, age and ADDI based on presence of other inflammatory comorbidity was not significant. Finally, BMI and IHS4, age and IHS4, age and ADDI based on diabetes status was not significant.

Hurley score and categorical IHS4 score had good overlap in Hurley 1 and 2 scores, with 8 Hurley 1 patients also having mild IHS4 categorical score, 22 (96%) Hurley 2 patients having a moderate IHS4 categorical score, and 1 (4%) Hurley 2 patient having a severe IHS4 categorical score. However, among 52 patients with Hurley score 3, 12 (23%) were considered moderate IHS4, and 40 (77%) were considered severe ( $P < 0.001$ ). Average ADDI score among Hurley 1 patients was  $0.75 \pm 1.2$ ,  $1.9 \pm 1.4$  among Hurley 2 patients and  $3.8 \pm 1.6$  among Hurley 3 patients ( $P < 0.001$ ).

There was a moderate correlation between IHS4 and ADDI scores among all 3 groups [ $R^2 = 0.48$  ( $P < 0.001$ ) for HS only;  $R^2 = 0.51$  ( $P < 0.001$ ), for HS/NAFL;  $R^2 = 0.57$  ( $P < 0.001$ ), for HS/NASH, [Figure 2](#)].

## DISCUSSION

In our cohort of HS patients, for the first time, was described a 38,5% NAFLD prevalence: 24% of NAFL and 14,5% of NASH. Likewise, in psoriasis, HS patients with NAFLD displayed the higher severity scores, namely IHS4 and ADDI. These findings, together with pathogenetic<sup>[7]</sup>, epidemiologic<sup>[8]</sup> and therapeutic<sup>[9]</sup> evidences, further confirm the recent idea that HS is a systemic inflammatory disease. NAFLD is the main entity to cause ESLD in Europe and North America, this is easy to predict that it will become the most frequent liver transplantation indication by 2030<sup>[16]</sup>. Although the weight of the disease is so overwhelming, there are no really effective drugs in treatment<sup>[3]</sup>. Therefore, it is essential to investigate all co-morbidities that can worsen the prognosis, among these in our study emerges the role of HS, whose treatment is a controversial issue<sup>[30-32]</sup>. Microbiological data show that HS is associated with polymicrobial flora, including anaerobic microorganisms<sup>[33,34]</sup>. On this point, Guet-Revillet *et al*<sup>[33]</sup>, in a French prospective microbiological study on 102 HS lesions from 82 patients, found that *Staphylococcus lugdunensis* was cultured in 58% of HS lesions and anaerobic microorganisms, including actinomycetes, were observed in 24% of abscesses or nodules and in 87% of chronic lesions. More recently, in a prospective metagenomic study, the same Author, using high-throughput sequencing, confirmed the high prevalence of polymicrobial anaerobic flora in HS<sup>[35]</sup>. Overall, topical or oral antibiotics (monotherapy or combination therapy) is commonly suggested for the management of HS flares<sup>[12,36]</sup>. The most common antibiotic regimens used for the treatment of HS included topical clindamycin, oral



**Figure 2** Correlation between international hidradenitis suppurativa severity scoring system and autoinflammatory Disease Damage Index among patients with hidradenitis suppurative only, or non-alcoholic staetoh hepatitis or non-alcoholic fatty liver.

tetracyclines, oral clindamycin-rifampicin combination and parenteral ertapenem followed by oral rifampicin-moxifloxacin-metronidazole combination<sup>[12,37]</sup>. No data are available for the antibiotic management of HS with the newer drugs, including dalbavancin, daptomycin and tigecycline<sup>[38-40]</sup>. Moreover, there are insufficient data to support intravenous antibiotics<sup>[41-43]</sup>. A major concern of the antibiotic use in HS is the increasing of antimicrobial resistance<sup>[44,45]</sup>. Finally, a clinical monitoring and a dose adjustment in patients with liver disease can be required<sup>[46,47]</sup> in view of the fact that NAFLD remains the main source of ESLD in Western countries<sup>[1]</sup>. It is clear, with these premises, that the available therapeutic armamentarium for the treatment of both diseases is very inadequate. Of our findings, the most obvious appears the US finding of bright liver in 22% of HS only and all HS/NAFL or HS/NASH patients ( $P < 0.001$ ). However liver biopsy (histology) remains the gold standard in the diagnosis of NAFLD, as recently suggested in a meta-analysis that compared US and histology quantifying diagnostic sensitivity to 84.8% (79.5-88.9), specificity to 93.6% (87.2-97.0), positive likelihood ratio to 13.3 (6.4-27.6) and negative likelihood ratio to 0.16 (0.12-0.22)<sup>[48]</sup>.

Interestingly the newly proposed ADDI score displayed a clinically meaning in addressing ultrasound examination in patients with NASH. PASH syndrome patients all displayed NAFLD and this confirm that higher levels of inflammations trigger the development of liver disease. Adipose tissue is not inert but metabolically active and release pro-inflammatory cytokines, furthermore the metabolic syndrome is a recognized comorbidity of both NASH and HS. Thus, the finding is that ADDI correlates with BMI in patients with inflammatory comorbidities. To further enforce its clinical capability, ADDI and IHS4, the dynamic severity index, correlated in the examined groups. Therefore ADDI, a composite index derived from the global examination of monogenic autoinflammatory diseases and applied to HS<sup>[27]</sup>, is related to the dynamic index that monitor HS skin inflammation. This assumption empowers the thesis that HS should be considered an autoinflammatory polygenic disease and treated by physicians as a systemic condition. From this point of view, is it really correct talk about comorbidities or it is more proper define them as different manifestations of a common spectrum of disease, namely HS as a systemic disease. As for psoriasis, the real goal for the newly introduced biological therapy will be to act on both cutaneous and systemic manifestation of HS.

In conclusion high prevalence of NAFLD was found in HS patients and an US screening to exclude liver abnormalities should be performed especially in HS patients with active disease and inflammatory comorbidities.



## ARTICLE HIGHLIGHTS

### Research background

Nonalcoholic fatty liver disease (NAFLD), in its two variants non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), is the main cause of End stage liver disease (ESLD) and its complications, including hepatocellular carcinoma (HCC) in North America and Europe. Due to its impact on morbidity and mortality, the identification of population with high risk of NAFLD is mandatory and in literature some systemic inflammatory diseases are described to be linked with NAFLD. Hidradenitis suppurativa (HS) is a new affirming systemic inflammatory disorder of the follicular epithelium of skin apocrine glands with a prevalence in normal population ranging from 0.05% to 4.10%. No data are present in literature towards the prevalence of NAFLD in HS.

### Research motivation

The estimation of NAFLD in HS patients may lead to an early and optimized treatment.

### Research objectives

This study aimed first to evaluate the overall prevalence of NAFLD and specifically of NAFL and NASH. Secondary aims were the clinical characterization of these patients. Depict a profile of HS patients with NAFLD will be crucial in optimizing clinical and therapeutic management.

### Research methods

This retrospective multicenter carried out 4 primary dermatological Italian centers started in January 2018 and ended in December 2018. Patients were recruited by filling the recently proposed visual-aided questionnaire for the self- assessment of HS and after underwent a dermatologic visit that evaluate HS with static (Hurley score) and dynamic indexes (ADDI: Autoinflammatory Disease Damage Index, IHS4: International Hidradenitis Suppurativa Severity Scoring System). Transaminases were assessed and all patients underwent liver sonography (US). NASH suspected cases were biopsied.

### Research results

We included 83 HS patients, in detail 51 patients with HS only and 32 with NAFLD (20 with NAFL, 12 NASH). Inflammatory comorbidities were present in 3.9% of HS only patients, 37.5% of HS/NAFLD, 25% of HS/NAFL patients and 58.3% of HS/NASH patients ( $P < 0.001$ ). The average IHS4 score among HS/NASH patients ( $12.7 \pm 3.6$ ,  $P = 0.03$ ) was the highest, while it was similar among those with HS only and HS/NAFL patients ( $9.6 \pm 3.6$  and  $9.4 \pm 3.9$  respectively,  $P = 0.86$ ). Likewise, mean ADDI was significantly higher among HS/NASH patients ( $5.3 \pm 2.2$ ,  $P < 0.001$ ) compared to HS only and HS/NAFL patients ( $2.8 \pm 1.6$  and  $2.6 \pm 1.4$  respectively). While no significant differences were found in Hurley score. There was a significant positive correlation between IHS4 and ADDI scores among all 3 groups ( $r = 0.7$ ,  $P < 0.001$  for HS only;  $r = 0.71$ ,  $P = 0.0004$  for HS/NAFL;  $r = 0.76$ ,  $P = 0.004$  for HS/NASH). Finally, BMI and ADDI were weakly negatively correlated in patients with HS only ( $r = -0.25$ ,  $P = 0.05$ ) and in those who had HS and diabetes ( $r = -0.46$ ,  $P = 0.04$ ).

### Research conclusions

HS patients have a high prevalence of NAFLD. In particular clinicians should sonographically assess HS patients with more active disease (high IHS4 score) and with other inflammatory comorbidities (high ADDI).

### Research perspectives

The present study highlighted the association between HS and NAFLD. However other issues remain still open to future investigations. In particular related issues, that should be addressed to optimize patient management are the prevalence of NAFLD HS-related in different ethnicity and the impact of systemic therapies on NAFLD development in HS patients.

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