

# Authors thank reviewers for the suggestions expressed that aimed to improve and clarify our manuscript.

**N.B. All the requested modifications are underlined and highlighted in yellow**

## **Reviewer: 1**

1. Line 214, "above" should be deleted.

A: We corrected, as suggested.

2. Line 290, "This findings" should be changed to "These findings".

A: We corrected, as suggested.

3. Line 521-522 and 533, "Nonalcoholic fatty liver disease (NAFLD)" should be replaced by "non-alcoholic fatty liver (NAFL)".

A: We updated as requested.

4. NAFLD in Table I and Table II should be changed to NAFL.

A: We agree with the Reviewer 1 suggestion and we changed. Furthermore, we grouped Table 1, 2 and 3 in one.

5. It is recommended that "=1" in all tables be deleted.

A: We deleted all "=1" as requested.

## **Reviewer: 2**

1. Table 1 shall not be divided into table 2 and table 3.

A: We thank the Reviewer 2 for the suggestion and we grouped table 1,2 and 3 into Table 1 describing and comapring NAFLD with Hs only, NAFL with HS only, NASH with Hs only.

**Table 1. Characteristics of 83 patients with hidradenitis suppurative (HS), Nonalcoholic fatty liver (NAFL) and Nonalcoholic steatohepatitis (NASH) and intercalsses charactersitics.**

|                        | <b>HS only</b>                | <b>NAFLD</b>                  | <b>*p</b>    | <b>NASH</b>                   | <b>*p</b>    | <b>NAFL</b>                    | <b>*p</b>    |
|------------------------|-------------------------------|-------------------------------|--------------|-------------------------------|--------------|--------------------------------|--------------|
| <b>N</b>               | <b>51</b>                     | <b>32</b>                     |              | <b>12</b>                     |              | <b>20</b>                      |              |
| <b>Age (mean (SD))</b> | <b>43.04</b><br><b>(8.91)</b> | <b>41.32</b><br><b>(9.04)</b> | <b>0.564</b> | <b>41.58</b><br><b>(7.35)</b> | <b>0.602</b> | <b>40.55</b><br><b>(10.31)</b> | <b>0.315</b> |
| <b>age_cat (%)</b>     |                               |                               | <b>0.646</b> |                               | <b>0.463</b> |                                | <b>0.629</b> |
| <b>&lt;30</b>          | <b>3 (5.9)</b>                | <b>4 (12.5)</b>               |              | <b>1 (8.3)</b>                |              | <b>3 (15.0)</b>                |              |

|   |                 |                 |                  |                 |                  |                 |              |
|---|-----------------|-----------------|------------------|-----------------|------------------|-----------------|--------------|
| <b>30-39</b>                              | 16 (31.4)       | 8 (25.0)        |                  | 2 (16.7)        |                  | 6 (30)          |              |
| <b>40-49</b>                              | 18 (35.3)       | 14 (43.8)       |                  | 7 (58.3)        |                  | 7 (35.0)        |              |
| <b>&gt;50</b>                             | 14 (27.5)       | 6 (18.8)        |                  | 2 (16.7)        |                  | 4 (20.0)        |              |
| <b>Male (N(%))</b>                        | 17 (33.3)       | 14 (43.8)       | 0.623            | 5 (41.7)        | 0.835            | 9 (45.0)        | 0.52         |
| <b>Diabetes (N(%))</b>                    | 12 (23.5)       | 9 (28.1)        | 0.853            | 3 (25.0)        | 0.764            | 6 (30.0)        | 0.794        |
| <b>BMI (mean (SD))</b>                    | 28.31<br>(2.52) | 27.56<br>(1.94) | 0.381            | 27.58<br>(2.71) | 0.376            | 27.55<br>(1.73) | 0.218        |
| <b>bmi_cat (%)</b>                        |                 |                 | 0.559            |                 | 0.515            |                 | 0.384        |
| <b>Normal Weight</b>                      | 4 (7.8)         | 4 (12.5)        |                  | 2 (16.7)        |                  | 2 (10.0)        |              |
| <b>Overweight</b>                         | 38 (74.5)       | 26 (81.25)      |                  | 9 (75.0)        |                  | 17<br>(85.0)    |              |
| <b>Obese</b>                              | 9 (17.6)        | 2 (6.25)        |                  | 1 (8.3)         |                  | 1 (5.0)         |              |
| <b>IHS4 (mean (SD))</b>                   | 9.57<br>(3.55)  | 11.32<br>(2.79) | <b>0.025</b>     | 12.67<br>(3.63) | <b>0.009</b>     | 9.40<br>(3.87). | 0.861        |
| <b>IHS4_cat (%)</b>                       |                 |                 | <b>0.028</b>     |                 | <b>0.007</b>     |                 | 0.97         |
| <b>Mild</b>                               | 5 (9.8)         | 3 (9.38)        |                  | 1 (8.3)         |                  | 2 (10.0)        |              |
| <b>Moderate</b>                           | 24 (47.1)       | 10 (31.25)      |                  | 0 (0)           |                  | 10<br>(50.0)    |              |
| <b>Severe</b>                             | 22 (43.1)       | 19 (            |                  | 11<br>(91.7)    |                  | 8 (40)          |              |
| <b>Hurley (%)</b>                         |                 |                 | 0.494            |                 | 0.197            |                 | 0.785        |
| <b>1</b>                                  | 5 (9.8)         | 3 (9.38)        |                  | 1 (8.3)         |                  | 2 (10.0)        |              |
| <b>2</b>                                  | 24 (47.1)       | 6 (18.8)        |                  | 1 (8.3)         |                  | 5 (25.0)        |              |
| <b>3</b>                                  | 22 (43.1)       | 23 (71.88)      |                  | 10<br>(83.3)    |                  | 13<br>(65.0)    |              |
| <b>Elevated_liver_enzymes (N (%))</b>     | 19 (37.3)       | 9 (28.1)        | 0.617            | 4 (33.3)        | 0.998            | 5 (25.0)        | 0.482        |
| <b>ADDI_score (mean (SD))</b>             | 2.55<br>(1.40)  | 3.72<br>(1.81)  | <b>&lt;0,001</b> | 5.33<br>(2.23)  | <b>&lt;0,001</b> | 2.75<br>(1.59)  | 0.603        |
| <b>Inflammatory comorbidities (N (%))</b> | 2 (3.9)         | 12 (37.5)       | <b>&lt;0,001</b> | 7 (58.3)        | <b>&lt;0,001</b> | 5 (25.0)        | <b>0.025</b> |
| <b>In detail (%)</b>                      |                 |                 | <b>0,001</b>     |                 | <b>&lt;0,001</b> |                 | <b>0.047</b> |
| <b>Acne conglobata</b>                    | 1 (2.0)         | 0 (0)           |                  | 0 (0)           |                  | 0 (0)           |              |

|                                   |           |           |                  |          |                  |            |                  |
|-----------------------------------|-----------|-----------|------------------|----------|------------------|------------|------------------|
| <b>Crohn disease</b>              | 0 (0)     | 2 (6.25)  |                  | 1 (8.3)  |                  | 1 (5.0)    |                  |
| <b>Lichen sclerosus</b>           | 1 (2.0)   | 0 (0)     |                  | 0 (0)    |                  | 0 (0)      |                  |
| <b>PASH</b>                       | 0 (0)     | 5 (15.63) |                  | 4 (33.3) |                  | 1 (5.0)    |                  |
| <b>Psoriasis</b>                  | 0 (0)     | 2 (6.25)  |                  | 1 (8.3)  |                  | 1 (5.0)    |                  |
| <b>Spondyloarthritis</b>          | 0 (0)     | 2 (6.25)  |                  | 1 (8.3)  |                  | 1 (5.0)    |                  |
| <b>Uveitis</b>                    | 0 (0)     | 1 (3.13)  |                  | 0 (0)    |                  | 1 (5.0)    |                  |
| <b>Positive_ultrasound (N (%)</b> | 11 (21.6) | 32 (100)  | <b>&lt;0,001</b> | 12 (100) | <b>&lt;0,001</b> | 20 (100.0) | <b>&lt;0,001</b> |
| <b>NASH</b>                       | 0 (0)     | 12 (37,5) | <b>&lt;0,001</b> | 12 (100) |                  | 0 (0)      |                  |
| <b>NAFL</b>                       | 0 (0)     | 20 (62.5) | <b>&lt;0,001</b> | 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, NAFLD: NonAlcoholic Fatty Liver Disease, PASH: Pyoderma gangrenosum, Acne, and Hidradenitis Suppurativa

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>

\*All classes were compare with HS only.

2. Writing format shall be adjusted ( numbering table, sub title and sub sub title, etc)

A: We agree with Reviewer's suggestion and we corrected.

3. Despite dividing into 3 groups which are HS only patients, HS and NASH, HS and NAFL, it would be more suit to the title if author analyze it by dividing into 2 groups, HS only patient and HS/NAFLD (both NASH and NAFL).

A:We thank the Reviewer and we modify the structure of results and Tables to answer and make the comparison more clear.

4. Author should clarify the idea that HS is a systemic disease.

A: We thank the Reviewer to highlight this crucial statement. Thus, we clarified further and explained the motivation and literature evidences that sustains the current view of hidradenitis suppurativa as a systemic disease.

We insert to further clarify this concept these two sentences with the proper reference respectively in the introduction

HS is an affirming systemic inflammatory disease and this idea was sustained by the recent acquisitions in the pathogenesis [7], epidemiology [8] and therapy [9]. and in the discussion

These findings, together with pathogenetic [7], epidemiologic [8] and therapeutic [9] evidences, further confirm the recent idea that HS is a systemic inflammatory disease.

- I. **Vossen ARJV**, van der Zee HH, Prens EP. Hidradenitis Suppurativa: A Systematic Review Integrating Inflammatory Pathways Into a Cohesive Pathogenic Model. *Front Immunol.* 2018;**9**:2965. [PMID: 30619323 DOI: 10.3389/fimmu.2018.02965]
- II. **Shlyankevich J**, Chen AJ, Kim GE, Kimball AB. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: a chart-verified case-control analysis. *J Am Acad Dermatol.* 2014;**71**:1144-1150. [PMID: 25440440 DOI: 10.1016/j.jaad.2014.09.012]
- III. **Wlodarek K**, Ponikowska M, Matusiak Ł, Szepietowski JC. Biologics for hidradenitis suppurativa: an update. *Immunotherapy.* 2019;**11**:45-59. [PMID: 30702012 DOI: 10.1177/1203475418823529]

## Requests from the Editor:

1. We also uploaded the figures in PPT format and tables, as requested.
2. We shortened the Core Tip to 100 words as suggested.
3. We wrote the Article highlights.
4. We uploaded separately in PPT the two images changing NAFLD with NAFL.
5. We registered and uploaded the audio file required.
6. We rephrased the sentences indicated in the separated file.

N.B. all the requested modifications highlighted in the PDF file were performed.