Reviewer #1: The manuscript of Perez-Carreras et al. is an interesting review on the link between NAFLD and three common diseases. It was a pleasant read and I think only a few things need to addressed.

1. In the abstract, the authors mention 'algorithms' for screening for ANFLD in the 3 diseases. This is howver not mentione din the manucsript itself. I think the authors mean that the physicians treating IBD, OSA or PS should be aware that their patients have a higher chance to develop NAFLD.

As the reviewer rightly remarks and as stated in the conclusions of the manuscript, our article aims to identify the phenotypes of IBD, OSA and PS with risk of NAFLD and to draw attention to the need to create consensus guidelines with screening and management algorithms for these patients. These guidelines should draw on the various specialists involved in the management of these metabolic comorbidities rather than just those dedicated to each disease. That is why creating an algorithm was not the goal of our study

2. On page 8 'experimental studies' are mentioned. What exactly is this: animal and in vitro studies? Please clarify/specify.

These are experimental studies in vitro and in animals.
Added to the manuscript:

"Based on experimental studies *in vitro* and in animals…"

References added number 38-39.

3. Please explain the different markers/scores for NAFLD: FIB-4, NAFLD disease score, PASI score.

Added to the manuscript:

Page 9. Considering that ……. with IBD and NAFLD. "*These markers consist of mathematical algorithms that include clinical and analytical variables whose result enables the identification and stratification of patients with liver fibrosis. Among them, FIB-4 and NFS (non-alcoholic fatty liver disease score) have been validated in patients with NAFLD*[4,6,7].

Page 13. PASI score: (Psoriasis Area Severity Index). "*It combines the assessment of the severity of the lesion and affected area into a single figure between the values of 0 (no disease) to 72 (maximum disease).*"

4. On page 9 is mentioned that 32.8% of the IBD patients had NAFLD and 24.6% significant fibrosis. Is this a higher prevalence than in the general population? Or was this not tested? If the latter is the case, no conclusion can be drawn from this study.

Palumbo et al. conclude that NAFLD diagnosed by elastography with CAP is a frequent comorbidity in IBD patients. They propose the use of non-invasive screening strategies for early diagnosis and therapeutic intervention in these patients. They do not compare prevalence of NAFLD.

On the other hand, they do make a comparison of liver fibrosis in NAFLD group vs. non-NAFLD. Explanatory paragraph added to the text:

"*The authors compared the presence of significant and advanced fibrosis in patients with NAFLD vs. non-NAFLD and found a higher prevalence in the NAFLD group (24.6% vs. 6.2% and 18.3% vs. 3.1%, respectively; p<0.001). Age...*"

Although more studies using CAP are required, the authors themselves highlight this article's usefulness due to its prospective design and the cohort of patients involved in a country such as Canada, where the prevalence of IBD is very high.

5. On page 12: 'Patients in the group with PS and NAFLD were older and had a higher body mass index,.... score).' To which group were these patients compared? And what can be concluded from this? Does this mean that age is associated with NAFLD? And is this not a general phenomenum?

Age was not shown to be an independent risk factor for NAFLD in patients with psoriasis. Van der Hoort's study finds that in patients >55 years of age psoriasis significantly increases the risk of NAFLD when compared to patients of the same age without psoriasis.

We have modified:

"elderly patients with psoriasis are 70% more likely to have NAFLD than those without psoriasis".

There was an error in interpretation on our part regarding the result of the age and sex variables in the study by Gisondi et al. which we have amended:

"*Comparing patients with psoriasis and NAFLD vs. no-NAFLD, they found that those included in the first group were more frequently male…"*

This study found an association between age and the serologic marker of NFS fibrosis (as have other authors). It is therefore recommended that age be included among the factors for NAFLD screening in patients with psoriasis.

6. The first sentence on page 13 is not clear at all: '..., means the same patient having both diseases cannot be seen as totally independent.' Please rephrase this!

Modification:

"*The systematic review and meta-analysis by Candi et al. found that patients with psoriatic arthritis had double the risk of NAFLD when compared to those without arthropathy (OR 2.25, CI 1.4-3.7; p 0.05). Although this information*

would suggest considering patients with PS and joint involvement as a special risk group for NAFLD, a recent meta-analysis raises doubts on the increased risk for NAFLD of such an association".

7. In the part on the treatment of PS I feel that the authors forgot to mention the topical use of corticosteroids which are known to provoke NAFLD.

The most common skin adverse effects of topical corticosteroid use are local (skin atrophy, striae, folliculitis, telangiectasia, and purpura). Rare systemic adverse effects from the use of topical corticosteroids including hypothalamic pituitary adrenal axis suppression, Cushing syndrome, osteonecrosis of the femoral head and type 2 diabetes have also been reported. These systemic complications are infrequent in clinical practice, as they occur when ultrahigh or high-potency corticosteroids are used over a large surface or under occlusion for a prolonged period. Although there is pathogenic evidence linking corticosteroids to the alteration of hydrocarbon and lipid metabolism implicated in NAFLD, we have not found that dermatology guidelines include this liver disease among the adverse effects of topical corticosteroid use (Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol 2021;84:432-70).

Reviewer #2

1. This review is interesting, however the title is misleading and must be modified. I would have expected that this article was about all extrahepatic comorbidities in NAFLD, instead it is focused just on some of them, i.e. inflammatory bowel disease, obstructive syndrome apnea and psoriasis.

There are publications on NAFLD that include IBD, OSA and psoriasis among other extrahepatic manifestations evidence of a pathogenic relationship among them (Tariq R et al. J Clin Exp Hepatol 2020;10:81-7; Li A, et al. Gut Liver 2019; Rosato V et al. Int J Environ Res Public Heath 2019;16:3415). Our aim was to go into greater depth on the relationship between NAFLD and IBD, OS and psoriasis by focusing on an association of diseases that share an inflammatory substrate at the core of which is the metabolic syndrome. We agree with the reviewer that the new title may be more accurate with respect to the manuscript's content (note that if we include the proper name of the three diseases, the title exceeds the 18-word limit):

> "*Non-alcoholic fatty liver disease in patients with intestinal, pulmonary or skin diseases: Inflammatory cross-talk that needs a multidisciplinary approach*"

2. There are too many abbreviations, and they affect the flow of reading. I'd suggest to limit their use to those most frequently used in this review article and spell out all the others. It is preferable to spell out the abbreviations in the headings of each section as well.

We have reduced the number of abbreviations to only the most frequently recognized ones and introduced full names with abbreviations in the titles of each section.

3. Introduction It must be specified that alcohol consumption is a criterion to exclude NAFLD. As stated here, it seems a positive criterion. Please reword.

With regard to alcohol consumption, we have changed the opening sentence of the paragraph, which was confusing: "*Excluding alcohol* consumption has long been...".

4. What does it mean "imbalance in favor of proinflammatory/anti-inflammatory cytokines"? In favor of which ones? The proinflammatory cytokines or the anti-inflammatory cytokines? This phrase is unclear.

Modified sentence on the cytokine imbalance (in favor of inflammatory imbalance):
"It appears that the imbalance in favor of proinflammatory vs. anti-inflammatory cytokines produced by the visceral adipose tissue...".

5. IBD A recent study in rats has suggested a potential molecular mechanism for the comorbidity of NAFLD and IBD [Kwon J, et al. DSS-induced colitis is associated with adipose tissue dysfunction and disrupted hepatic lipid metabolism leading to hepatosteatosis and dyslipidemia in mice. Sci Rep 2021;11:5283].

We have included a comment on the interesting experimental study by Kwon et al. and added the reference in the bibliography:

"*Animal experiments with DDS-induced colitis support this interrelationship between intestinal barrier disruption, endotoxemia, metabolic dysfunction in adipose tissue and NAFLD"* (Reference number 35).

6. "control attenuation parameter" is not a probe. It is an algorithm that estimates the attenuation of the ultrasound beam in dB/m, and is available on the FibroScan device (Echosens, France) together with transient elastography, which estimate the stiffness that is related to fibrosis. By the way, the results of this study are questionable. In fact, recent studies have reported that the control attenuation parameter threshold for the diagnosis of liver steatosis (NAFLD) is much higher than the one used in the cited study [Eddowes PJ, et al. Gastroenterology 2019; 156: 1717-30; Petroff D et al. Lancet Gastroenterol Hepatol 2021; 6:185-98.]. Therefore, an overestimation of NAFLD is likely.

Page 9.

We changed the sentence about CAP measurement with the elastography probe:

"…using control attenuation parameter and hepatic elastography available (both available) on the FibroScan device probe (Echosens, France)".

Changes to CAP results in IBD:

"They found any grade NAFLD in 32.8% of patients (CAP ≥248 dB/m), severe NAFLD (CAP > 300 dB/m), significant fibrosis…"

"*These steatosis prevalence data should be taken with caution as there is evidence that higher CAP cutoffs than those used by these authors improve the diagnostic accuracy of this method*" (Reference number 44-45).

7. NAFLD and OSA Page 10: give reference(s) for the statement: the decrease in oxygen tension that occurs during nocturnal apnea-hypopnea episodes primarily affects hepatocytes in zone 3 etc.

We add references number 52 and 53 at the end of the paragraph on page 10 OSA ("...the decrease...affects hepatocytes in zone 3...")

8. NAFLD and psoriasis Several sentences need references.

We added references in the psoriasis section.