

# Response to Reviewers

## Reviewer ID 03646816

### Reviewer commentary:

Overall well-written manuscript characterizing the profile of steatotic CF patients. Comments below: 1. Authors argue that CF hepatic steatosis is more similar to NAFLD than CFLD. However, they refer to steatosis as a hepatic manifestation of CFLD in the introduction - this should be clarified. 2. Are US, CT, and MRI comparable techniques for the detection of steatosis? The authors should provide a more in depth discussion of the validation of these techniques. 3. CF steatosis patient characteristics are given compared to non-steatosis CF patients, but how do these patients look compared to non-CF steatosis or NAFLD patients? This would better make the authors' point. 4. Authors mention that none of the patients with steatosis met criteria for CFLD. Did any of the other CF patients in the cohort meet criteria? 5. More discussion on the ppFEV1 finding is warranted. What do the authors think this means? Also, how do the authors explain the lower AAR value in steatosis patients? These elements should be added to the discussion.

### Author response:

Thank you for your review. The following is our point by point response:

- 1) It is correct that we refer to steatosis as a 'the most common hepatic manifestation' of CFLD. This is the current understanding of hepatic steatosis in CFLD. We thought it is appropriate to clarify current, common knowledge in the introduction. However, later in the manuscript, we argue that hepatic steatosis may very well be a separate clinical entity from classic CFLD, as manifested by the distinct risk factor and patient profiles.
- 2) We agree with your kind comment. We have added to the text regarding validation of these studies along with the appropriate references.
- 3) We agree with your kind comment. While it would most definitely make our point better, we do not have a readily available patient cohort with NAFLD without CF to make direct comparisons to. We have however, in the discussion mentioned the classic phenotype of patients with NAFLD and have made appropriate comparisons to the phenotypical NAFLD patient.
- 4) No patients in the control group met CFLD criteria. Patients with classic CFLD were excluded from the control group. We have added a comment to the methods section to reflect that.
- 5) We agree with your kind comment. We have added additional text to the discussion regarding ppFEV1. We also added additional text regarding the AAR value.

## Reviewer ID 02941317

### Reviewer commentary:

the text is well written and deals with statosis in the cystic fibrosis patients. Actually the authors have found BMI and ppFEV1 as the risk factors for steatosis developement. The flow of knowledge very well but steatosis developed in the obese individuals which is also what NAFLD is basically. Therefore the signficance of the findings should be clarified and furthermore did the authors make any king of liver biopsy to correlate the results.

**Author response:**

Thank you for your review. We have added additional information to the discussion section regarding the significance of our findings. We have also added this to the 'highlights' section. We also did not biopsy patients as this is usually not indicated in cystic fibrosis patients due to the patchy nature of disease, and we have already indicated this in our paragraph on study limitations.

**Reviewer ID 03262379****Reviewer commentary:**

Hello, I reviewed the manuscript entitled "Risk factors for hepatic steatosis in adults with cystic fibrosis: similarities to non-alcoholic fatty liver disease". Authors included patients with CF for assessment of liver diseases and steatosis. While none of the patients had signs of liver disease, a proportion of patients had liver steatosis. The liver steatosis in the CF patients was associated with higher BMI. Authors concluded that the liver steatosis is the same as the condition observed in NAFLD patients and liver steatosis is not the underlying disease for development of CFLD. This is a well-designed study presenting novel and important findings. Regards

**Author response:**

Thank you for your review. We appreciate your kind comments.

**Reviewer ID 00071662****Reviewer commentary:**

Interesting study Further studies needed.

**Author response:**

Thank you for your review. We appreciate your kind comments.

**Reviewer ID 02444941****Reviewer commentary:**

The authors present the results of their cross sectional study looking at hepatic steatosis in CF patients. Studies evaluating liver disease in CF are needed to advance our knowledge of CFLD so this study can contribute to the body of knowledge on CFLD. 1. It is important to highlight the lack of histologic confirmation of steatosis as a limitation which the authors did. 2. It might also be useful for the authors to mention that other measures of insulin resistance like the HOMA-IR can be obtained to determine the presence or absence of insulin resistance but was not obtained in this study. 3. Can the authors expound on the finding of a lower mean AAR in the hepatic steatosis group? Why would the group without hepatic steatosis have a higher AAR indicating more fibrosis or higher propensity to fibrosis? Is this an indication that they might have other forms of CFLD or another liver disease altogether? 4. Corollary to #3, were markers of chronic viral infection checked? If not, perhaps indicate in the discussion this fact and account for it.

**Author response:**

Thank you for your review. We have added text to the discussion section regarding the need for future studies to incorporate other measures of insulin resistance such as HOMA-IR. We have expanded on the findings of lower AAR in the discussion section. Markers of viral infection, as well as other markers of chronic liver disease (autoimmune, Wilson's, etc...) were checked and patients with such findings were excluded. We have added this information to the methods section.

**Reviewer ID 00068420****Reviewer commentary:**

The study entitled "Risk factors for hepatic steatosis in adults with cystic fibrosis: similarities to non-alcoholic fatty liver disease" submitted for publication in WJH, has been reviewed and found with some serious deficiencies; This study was planned to investigate whether cystic fibrosis may be consider as an important cause of NASH progressing to cirrhosis of liver. It was conducted in patients with cystic fibrosis with various abnormal liver function markers. The results of this study could not demonstrate an association of hepatic steatosis with gender, age, homozygous/ heterozygous genotypes, hypertension, hyperlipidemia, CFKD, use of alcohol, insulin resistance and pancreatic insufficiency, etc. in this group of patients. As such it is difficult to determine whether this study provides any message at this stage particularly, when authors claim that sample size is not adequate to conclude the findings. In addition, this study plan has some methodological abbreviations also 1. The assays used do not describe details of various estimations made. 2. How mutations were tested, is not clear. 3. Tables and figures are given the manuscript are neither meticulous nor informative.

**Author response:**

Thank you for your review. We have added text to the methods section regarding mutation testing methodology. We have removed figure 1 from the text as it repeats information already present in the tables.

**Reviewer ID 02529007****Reviewer commentary:**

The Manuscript ID: 36787 entitled, "Risk factors for hepatic steatosis in adults with cystic fibrosis (CF): similarities to non-alcoholic fatty liver disease" describes a cross-sectional study on the clinical, biochemical and imaging characteristics of adult CF patients with hepatic steatosis by a retrospective review of 114 adult CF patients in an academic outpatient setting during 2016. Results indicated that 14.9% had hepatic steatosis with higher ALT levels and overweight (BMI >25) and higher percent of predicted forced expiratory volume in 1 second (ppFEV1) were associated with hepatic steatosis. However, no association with hepatic steatosis and CF related liver diseases could be identified. Authors concluded that Hepatic steatosis might be clinically and phenotypically distinct from CF related liver diseases while the lack of association with malnourishment and the significant association with higher BMI and higher ppFEV1 demonstrate similarities with NAFLD. Comments: In general, findings of this articles are in the scope of the Hepatology journal and might be of interest for its audience. The manuscript is well-written and is clearly presented. The methods, results and conclusions are also well-described. However, manuscript could be further benefited by considering the role of blood fatty acids

in CF. In this context, authors are advised to consider this parameter in their analyses (if possible) or consider some related articles in the background information (introduction) and discussion section. For example some following manuscripts that discusses the potential role of blood fatty acid (FA) composition in cystic fibrosis (CF) related to liver diseases might be considered: -Drzymała-Czyż S et al, Determinants of Serum Glycerophospholipid Fatty Acids in Cystic Fibrosis. *Int J Mol Sci.* 2017 Jan 18;18(1). Van Biervliet et al, Fatty acid composition of serum phospholipids in cystic fibrosis (CF) patients with or without CF related liver disease. *Clin Chem Lab Med.* 2010 Dec;48(12):1751-5. - Lebensztejn et al, Cytokeratin-18 and hyaluronic acid levels predict liver fibrosis in children with non-alcoholic fatty liver disease. *Acta Biochim Pol.* 2011;58(4):563-6. In addition, the figure 1 might need a complete description (figure legend) to explain the five separate figures (which might need to be specified separately by letters).

**Author response:**

Thank you for your review. We have added text in the discussion section regarding the difference in blood fatty acid levels between patients with CF liver disease and those without. We have pointed that future studies may utilize serum fatty acid testing as part of future comparison between patients with steatosis and controls. We have removed figure 1 from the text as it repeats information already present in the tables and is overall not informative.