Response to Editor

1/6/2018

We wish to thank the reviewers for their thoughtful comments. Below are our point-by-point responses to the reviewers' comments. Your instructions ask for a biostatistics review. We certify that Dr. Noureddin has conducted the statistical analysis at the highest standard. Dr. Noureddin has official training in biostatistics through courses in his Master's degree program in clinical research.

Reviewer #1

Comment: The second limitation of the lack of follow-up of the evolution of steatosis after treatment, although also recognized by the authors, it is possible to be resolved by lengthening the study for a few more months. A single year of time after the virological response does not seem a valid period of time to assess the possible resolution or change of stetosis. For this reason it is suggested that the study be completed with this additional study since probably at the time of submission of this manuscript a significant time has passed since the last assessments of these patients.

Response: We agree that a follow up study would be valuable and we intend to do this. However, we think that a two-year follow up or longer will be more informative and some of our patients have not yet reached that point.

Reviewer #2

Comment: Three types of steatosis have been defined in the HCV patients. The first is a metabolic type, associated with metabolic syndrome. The second is a viral steatosis without any known steatogenic co-factors and is directly linked to the cytopathic viral effect. The third type can be considered a "middle ground" between the first and the second one: even if this entity is virus associated, it could be more appropriate to define it as a combination of viral and metabolic factors. This entity has been associated with a direct interference of HCV core protein in the intracellular, post-receptorial pathways of insulin. Literature report the link between HCV genotype 3 infection and steatosis (Abenavoli et al. World J Gastroenterol. 2014) –

Response: We have added additional information to make this more clear and have added the reviewer's suggested citation. Please see the last paragraph of page 7.

Comment: why the Author not include in the laboratory test GGT?

Response: GGT has not been routinely used in HCV or NAFLD monitoring in this cohort.

Comment: I suggest to report also the therapeutic DAA protocol adopted for any HCV genotypes.

Response: Thank you for the suggestion. The patients in this cohort had been treated with a variety of direct-acting antiviral regimens: ledipasvir/sofosbuvir (Harvoni); 75 patients; elbasvir/grazoprevir (Zepatier), 1 patient; dasabuvir/ombitasvir/paritaprevir (Viekira), 7 patients; dasabuvir/ombitasvir/paritaprevir with ribavirin, 2 patients; sofosbuvir (Sovaldi) with ribavirin, 9 patients; sofosbuvir with daclatasvir (Daklinza), 1 patient; sofosbuvir with simeprevir (Olysio), 2 patients; sofosbuvir/velpatasvir (Epclusa), 4 patients. This was added to the methods section in page 8.

Comment: Results section: the used TE cut-off are codified in literature? If yes, i suggest report the reference.

Response: In the Methods section in the last sentence under the subsection entitled "Transient elastography" we have this information with two citations: "Clinically significant stiffness was defined as ≥ 7 kilopascal (kPa) [14, 15]."

Comment: Discussion section: is possible that the results are related to the therapy?

Response: Thank you for the great question. We don't believe that the steatosis results from the therapy. As we mention in the first line of the Discussion, steatosis prevalence in CHC patients has previously been reported to be approximately 50%, very similar to our finding of a 47.5% prevalence.

Comment: No differences are founded between patients of different ethnicity. What is about this point, the idea of the Author?

Response: Thank you for this interesting question. We don't have sufficient numbers with different ethnicities to have a valid comparison.

Reviewer #3

Comment: presumably patients without clinical cirrhosis were excluded, although this is not clear.

Response: Thank you for pointing this out. We have added information to the Abstract and the Methods section (page 10) to clarify this. Please see tracked changes draft.

Comment: 1. Abstract- specify number of patients studied.

Response: We added this. Please see tracked changes draft.

Comment: 2. Methods - please define what the normal levels of AST and ALT used in this study are.

Response: The normal reference range was used (upper limit of normal = 40 U/L).

Comment: it is not clear how many patients clinically had cirrhosis pre-DAA treatment in this cohort?

Response: The exclusion criteria for the study excluded all patients with cirrhosis. This is shown in the methods section.

Comment: The discussion section mentions that patients with cirrhosis (again how was this determined?) were excluded, however this is not specified in the abstract, methods or results.

Response: As one of the exclusion criteria, patients were excluded from the study if they were determined to have cirrhosis based on imaging and FibroScan. We have added this information to the Abstract; it is also shown in the Methods.

Comment: 4. Tables 2 and 3- please add rows indicating the % patients with fibrosis scores >7 in each of the groups.

In Table 3 add the number of patients in each of the two groups in the first row.

Response: We added those to table 2 which is also mentioned in the figure. For table 3 there was no data on steatosis at baseline and therefore although we have the fibrosis score data at baseline we cannot sub-classify them per steatosis or no steatosis group.

We have added the number of patients in each of the two groups in the first row in table 3.