DEPARTMENT OF MEDICAL AND SURGICAL SCIENCES

University of Bologna, Italy

Dear Editors,

thanks for allowing us to submit a revised version of our manuscript for consideration for possible publication.

We also thank the reviewers for their useful suggestions, which in our humble view helped us improving the quality of our manuscript.

Please find below a point-to-point response to the suggestions provided:

REVIEWER 1 (02926997): We thank the reviewer for his appreciation of our paper

REVIEWER 2 (00812852):

1) **The main problem is using the exact words and not changing them to a more comparable statements . This makes the main purpose of the writers not achievable. Tables could have less texts in this regards**

   .We agree with the referee. According to the provided suggestion, we modified the text in Tables 1,3,4, and 5 to allow more comparable statements. Also, the text in these Tables have been considerably reduced

2) **The part on definition is devoted mostly to the amount of alcohol ingestion . I think there should be section on ethanol ingestion as an exclusion and another one on true definition.)**

   We thank the referee for this suggestion. We renamed the paragraph "Definition, classification, and diagnostic criteria of NAFLD". In its turn, we divided this paragraph in two subparagraphs named "a) Definition and classification" and "b) Diagnostic criteria: the role of alcohol"

3) **I think there is a vague definition in all of the mentioned guidelines both for fatty liber and NASH**.

   As suggested, we added the following sentence to the definition paragraph: "In detail simple steatosis, also called non-alcoholic fatty liver (NAFL) includes all of

the case characterized by steatosis with minimal or absent lobular inflammation. On the contrary, NASH is characterized by hepatocyte ballooning degeneration, diffused lobular inflammation and fibrosis [3-8]"

4) **The use of S score in elastogrpahy was not discussed.** As suggested, we added the following statement "Elastography score has been shown to have good diagnostic accuracy for the presence of clinically significant fibrosis, with an AUROC of 0.93 (95% CI 0.89–0.096) for advanced fibrosis (⩾F3) and cirrhosis, and with a negative predictive value of 90% in ruling out cirrhosis when using a cut-off of 7.9 kPa.However, the ability in differentiating between F2 and F3 fibrosis seems less robust"

5) **Explanation of the Fatty Liver Index (FLI) [20] and the NAFLD liver fat score could make the manuscript more understandable as many readers in north America might not know about them.**

We agree with the reviewer that explaining these scores will help the readership. We added the following specification "In detail, FLI is calculated from serum triglyceride, body mass index, waist circumference, and gamma-glutamyltransferase [20], while NAFLD liver fat score is calculated evaluating the presence/absence of metabolic syndrome and type 2 diabetes, fasting serum insulin, and aminotransferases [21]."

REVIEWER 3 (01806467):

1. **The authors may consider having some tables showing the differences in invasive assessment of fibrosis and follow-up protocols which would enhance the understanding of the article.**

   We are grateful to the reviewer for this suggestion. A dedicated Table (Table 3) has now been added to the paper.

2. **Last but not least, the paper looks more of a systemic review than a comparative analysis to me so revising the title is recommended.**

   We modified the title as suggested

REVIEWER 4 (00030389)

1. **#1 WHICH IS THE ROLE - - -S? Noninvasive predictor biomarkers - - -. The current absence - - - is leading "a" to considerable - - - and "a" to the development - - -. What do these "a"s mean?**

Thanks for pointing out our error. The sentence as been corrected as follows: "The current absence of a highly specific and sensitive noninvasive marker predicting inflammation and fibrosis is leading to a considerable interest in the identification of new markers of disease progression and to the development of clinical scores of disease severity."

We think that the quality of our manuscript has improved thanks to the reviewers' suggestions. However, we are at full disposal of the reviewers and of the Editorial Board if any further modification is deemed as appropriate to further improve our manuscript.

Best regards

Simona Leoni, MD, PhD