Respond to Comments

Dear Editor/Reviewer,

Thank you very much for your response to our manuscript (Manuscript NO.: 72131, Letter to the Editor) entitled "Comments on validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease". We appreciate the interest that the editors and reviewers have expressed in our manuscript and the constructive comments they have given. We have carefully revised the manuscript according to the insightful comments and provided point-by-point responses as follows.

Comments from Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Comments and suggestions for Authors In the present letter to the Editor, Li et et al., raised important questions regarding the paper published by Wu et al., entitled "Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease (Wu et al., World J Gastroenterol. 2021;27(34):5753-5763. doi:10.3748/wjg.v27.i34.5753). The study by Wu et al., as well as the letter by Li et al., have clinical relevance as both deal with development of scoring systems for the prediction of advanced fibrosis in patients with metabolic associated fatty liver disease (MAFLD). - In their first comment, Li et al. suggest that Wu et al. should have used the multivariate analyses instead of the univariate analysis to assess the diagnostic the performance of: aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 index (FIB-4), body mass index, aspartate aminotransferase/alanine aminotransferase ratio diabetes score (BARD) and nonalcoholic fatty liver disease fibrosis score (NFS), in the prediction of advanced fibrosis in patients with MAFLD. I agree with the authors since applying the standard approach of the univariate tests on individual response variables may fail to account for the covariance/correlation in the data. By contrast, the multivariate statistical techniques have advantages such as allowing confounding factors to be considered, by adjusting for these factors, which might more adequately capture the multi-dimensional pathophysiological pattern of advanced fibrosis and therefore provide increased sensitivity to the scoring systems in patients. - The authors raised another interesting suggestion regarding the calibration of the prediction scores, which is another key aspect of performance that is often overlooked. Indeed, the calibration is the accuracy of risk estimates, relating to the agreement between the

estimated and the distribution of realized outcomes (Van Calster B et al. J Clin Epidemiol. 2016;74:167–176; doi:10.1016/j.jclinepi.2015.12.005). In addition, discrimination and calibration are especially important when the aim is to support decision-making. Thus, I agree with Li et al. about the advice they gave to the authors (Wu et al.) of the initial study. - The third comment is with regard to PPV and NPV which describe the performance of a prediction models and are crucial to evaluating the practical utility of a testing procedure. As mentioned by the authors, PPV and NPV cannot be compared directly among different samples except when subjects are selected from a population with known prevalence of the disease. Finally, I really found these comments, opinions and advices very interesting especially for coming studies in the area. However, there are few things that should be addressed by the authors before proceeding further.

Minor comments 1) There is now evidence from a prospective cohort that common genetic variants can capture additional prognostic insights not conveyed by validated clinical/biochemical parameters. Thus, in their comments, Li et al. should encourage the integration of genetics (perhaps epigenetics also) with clinical fibrosis scores as it may refine individual risk and improve risk stratification and prediction of severe liver disease (De Vincentis et al. Clinical Gastroenterology and Hepatology 2021; DOI:https://doi.org/10.1016/j.cgh.2021.05.056).

Answer: We are grateful for your valuable advice. Based on the comments of the reviewer, we have added the following sentence in paragraph 6 of our manuscript: “Because there is now evidence from a prospective cohort that common genetic variants can capture additional prognostic insights not conveyed by validated clinical/biochemical parameters, we encourage the integration of genetics (perhaps epigenetics) with clinical fibrosis scores, as it may refine individual risk and improve risk stratification and prediction of severe liver disease.”

And we have also incited the following article in our manuscript: “De Vincentis A, Tavaglione F, Jamialahmadi O, Picardi A, Antonelli Incalzi R, Valenti L, Romeo S, Vespasiani-Gentilucci U. A polygenic risk score to refine risk stratification and prediction for severe liver disease by clinical fibrosis scores. Clin Gastroenterol Hepatol 2021: S1542-3565(21)00595-4 [PMID: 34091049 DOI: 10.1016/j.cgh.2021.05.056]”

2) I am surprised that the authors did not reference the paper they are supposed to comment: (Wu et al., World J Gastroenterol. 2021;27(34):5753-5763. doi:10.3748/wjg.v27.i34.5753).

Answer: Thank you very much for your suggestion. In the revised manuscript, we have incited the paper “Wu YL, Kumar R, Wang MF, Singh M, Huang JF, Zhu YY, Lin S. Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic

associated fatty liver disease. World J Gastroenterol 2021; 27(34): 5753-5763 [PMID: 34629799 DOI: 10.3748/wjg.v27.i34.5753]"

3) The English language: There are many punctuation errors, grammar mistakes, and unclear sentences that make the paper hard to understand sometimes.

Answer: Thank you for your comments. We have carefully corrected and modified the punctuation errors and grammar mistakes. And also, we have rewritten the unclear sentences of our manuscript. We have sent our revised manuscript to the English language editing company recommended by the editorial office to polish the manuscript further. And also, we have provided a new language certificate along with the revised manuscript.

Comments from Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I agree with the comments of Xian Li 1. Multivariate analysis should be preformed to recognize the independent variables in the prediction of advanced fibrosis. 2. Authors should state if the contionuous varibles fit normal distriburtion and if normal distribution tests have been preformed 3. Thresholds sould be further evaluated in external validation cohort and in prospective cohort.

Answer: Thank you for your comments.

Comments from editorial office

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The reviewers believe this letter to the editor is worthy of publication. Please edit the references as requested by the publisher.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Answer: Thank you for your comments. We have edited the references as requested by the publisher and we have revised our manuscript carefully based on the comments of the reviewers.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to

the author(s) for its revision according to the Peer-Review Report, Editorial Office′ s comments and the Criteria for Manuscript Revision by Authors. 请将以下文献补充在·参考文献中。 1 Wu YL, Kumar R, Wang MF, Singh M, Huang JF, Zhu YY, Lin S. Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease. World J Gastroenterol 2021; 27(34): 5753-5763 [PMID: 34629799 DOI: 10.3748/wjg.v27.i34.5753]

Answer: Thank you for your suggestion. In the revised manuscript, we have incited the paper "Wu YL, Kumar R, Wang MF, Singh M, Huang JF, Zhu YY, Lin S. Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease. World J Gastroenterol 2021; 27(34): 5753-5763 [PMID: 34629799 DOI: 10.3748/wjg.v27.i34.5753]"

In summary, we are very grateful to the reviewer for valuable suggestions. Based on the comments, we carefully revised the manuscript and we feel confident that the revisions significantly improved the quality of the manuscript.

Sincerely,

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