POINT BY POINT RESPONSE TO REVIEWERS

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 54717

Title: Non-Invasive Tests for the prediction of primary hepatocellular carcinoma.

Response to Editor's comments

Comment to the authors: Please check and confirm that there are no repeated references!

Response to the Editor: We apologize for the inconvenient; according to your suggestion we checked and erased one repeated reference (ref. number 58 Na SK et al, 2019) and modified the reference list accordingly.

Comment to the authors: Please verify that the references are cited by Roman numerals in brackets and superscripted in the text and that the numbering order is correct. There should be no space between the bracket and the preceding word or the following punctuation.

Response to the Editor: We thank you for the comment. We have now verified references format and numbering, which is now correct; we also erased spaces between brackets and the preceding or following word.

Comment to the authors: When references in the text and tables are cited with author name(s), it is necessary to manually verify that the name(s) is consistent with the first author's surname in the corresponding reference list.

Response to the Editor: According to your suggestions we have verified and corrected the reference list.

Comment to the authors: Please provide the author contributions. Authors must indicate their specific contributions to the published work. This information will be published as a footnote to the paper. See the format in the attachment file-revision policies. The format of this section should be like this: Author contributions: XXX (family name should be put first in full, followed by middle names and first name in abbreviation with first letter in capital) designed research; XXX performed research; XXX contributed new reagents or analytic tools; XXX analyzed data; XXX wrote the paper. An author may list more than one contribution, and more than one author may have contributed to the same aspect.

Response to the Editor: We have now provided author contributions.

Response to Reviewer's code: 03505676

Comment to authors: In the paper, the authors reviewed the currently available literature on biochemical and ultrasound-based scores developed for the non-invasive evaluation of liver fibrosis and portal hypertension in predicting primary HCC and recognized the APRI score and the Fib-4 index as the most reliable methods to assess HCC risk. It is very valuable for improving clinical practice. Several minor issues should be addressed before possible acceptance.

Response to the reviewer: We would thank editors and reviewers for the comments on our manuscript and for offering us the possibility to resubmit our revised paper.

Comment to authors: 1. Very importantly, a summarized table showing cutoff values of a variety of indexes in predicting HCC risk based on different liver disease aetiologies should be made, in order to present more clearly the potential of various indexes.

Response to the reviewer: We thank the reviewer for the advice. We have now included two additional tables reporting studies on APRI and Fib-4 (Table 1 and Table 2) for each liver disease etiology and showing the different cut-offs values for each study.

Comment to authors: 2. If possible, the advantages and disadvantages of markers in serum could be discussed.

Response to the reviewer: We have now added at the end of each paragraph for serum markers' advantages and disadvantages.

Comment to authors: 3. Whether can these tests distinguish HCC risk from ICC risk?

Response to the reviewer: According to the available literature, no study reported data on the prognostic role of the non-invasive tests mentioned in our paper for ICC development risk. On the other hand, in patients with already an ICC diagnosis, few studies reported a predictive utility of Albumin-Bilirubin score for survival after resection or embolization (Prognostic utility of albumin-bilirubin grade for short- and long-term outcomes following hepatic resection for intrahepatic cholangiocarcinoma: A multi-institutional analysis of 706 patients. Tsilimigras DI et al. J Surg Oncol. (2019); Albumin-Bilirubin Grade as a Novel Predictor of Survival in Advanced Extrahepatic Cholangiocarcinoma. Wang Y et al. Gastroenterol Res Pract. (2018); Predictive value of the albumin-bilirubin grade on long-term outcomes of CT-guided percutaneous microwave ablation in intrahepatic cholangiocarcinoma. Ni JY et al. Int J Hyperthermia. (2019)). However, since the aim of the study was to assess predictors of HCC occurrence, we did not report these findings in the paper.

Response to Reviewer's code: 03741310

Comment to authors: The authors reviewed the performance of a panel of reported non-invasive tests for the prediction of HCC. I have to say that all these tests reviewed by the authors were primarily designed for the prediction of cirrhosis but not HCC. It is true that cirrhosis is strongly associated with HCC, but cirrhosis is not HCC. It may not be a good idea, with less help, to predict the onset of HCC using something that was not directly associated with it. Nevertheless, I agree to publish this manuscript as currently there is no such review focusing on this issue.

Response to the reviewer: We thank the reviewer for the comment on our manuscript. We agree with you that most of the tests reported were primarily designed for cirrhosis or portal hypertension evaluation. However, beyond etiologies with additional carcinogenetic mechanisms such as HBV and NASH, the main drivers of HCC development still remain cirrhosis and portal hypertension. Thus, in our point of view, it could be useful to further stratify the HCC's patient risk with additional tools beyond the invasive ones, such as the NITs proposed, and to critically evaluate those NITs that could be safely used in resource-limited settings.

Comment to authors: The following were my concerns: 1. The author should reorganize the manuscript thoroughly, one test one paragraph, each test state different liver diseases in the same order. The current version is hard for reading.

Response to the reviewer: We thank the reviewer for the advice. We have now reorganized the manuscript according to your suggestions. We split the APRI and Fib-4 paragraph into 3 separate paragraphs: APRI, Fib-4 and APRI and Fib-4 comparison. Moreover, we re-organized the text for each paragraph according to the etiology of liver disease for each study in the following order: HBV, treated HBV, HCV, treated HCV, co-infection, NAFLD/NASH, Other etiologies.

Comment to authors: 2. The authors should at least give essential tables summarizing core information including test name, patient numbers, cut-off value, prediction value, etc.

Response to the reviewer: We have now included two additional tables reporting studies on APRI and Fib-4 (Table 1 and Table 2) for each liver disease etiology and showing cut-off values for each study.

Comment to authors: 3. ALBI and PALBI were mainly used in evaluating outcomes of the patient already have HCC, not for predicting the occurrence of HCC. I do not suggest the authors review literatures studying the connection of non-invasive tests and the outcome of patients with HCC. Predicting the occurrence and the outcome were different questions.

Response to the reviewer: We agree with you that ALBI and PALBI are mainly used as prognostic markers after HCC treatment; however, these score provides an objective hepatic reserve estimation, which mirrors the degree of the underlying liver disease which in turn is influenced by the degree of fibrosis which has a direct role on the HCC pathogenesis, thus possibly having a predictive of the HCC risk. On the other hand, according to your suggestions, we removed the PSR score, in whose paragraph was reported only studies on the outcome of patients with HCC diagnosis due to the unavailability of studies on HCC occurrence.