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Dear Editor, *World Journal of Gastroenterology*

Thank you for considering our manuscript entitled, "Validation Model of FIB-8 Score to Predict Significant Fibrosis Among Patients with Nonalcoholic Fatty Liver Disease in the Asian Population" by Prasoppokakorn, et al to be published in *World Journal of Gastroenterology* (Manuscript No.71602). We have reviewed the comments and considered them carefully. The point-by-point responses to reviewers' and editors' comments are below:

Reviewer #1
Comment 1: The manuscript focuses on modulating FIB-4 for better prediction. It has some grammar and punctuation issues (e.g. Our study ad limitations) (In literature section punctuation errors and different styles) that should be revised and corrected before publication. Despite FIB-8 is at least non-inferior and insignificantly superior to FIB-4, further formulations of new indexes are encouraged.

Response 1: We thank the reviewer for this suggestion. We apologize for the errors in grammar and spelling. Thus, we already corrected thoroughly all errors in revised manuscript.

Reviewer #2
Comment 1: The manuscript reports interesting data regarding a new FIB-8 score as extension of the known FIB-4 score for liver fibrosis. While the AUROC show that FIB-8 seems to be superior to FIB-4 and NFS, the authors did not find statistical superiority over FIB-4.

Response 1: The analysis was done making pairwise comparisons of the equality of the area under the curve in correlated ROC curves, using the method proposed DeLong et al, Biometrics 44: 837-845. Although the AUROC and 95%CI for FIB-8 is demonstrate the discriminative ability of this biomarker is increased by approximately 3% when compared to FIB-4, there overlap in the 95%CI, so the P-value for this comparison does not quite reach statistical significance. There is a difference between statistical significance and clinical importance, and although the discriminative ability of FIB-8 is

only modest, a 3% increase in the ability of a biomarker to discriminate between those with and without fibrosis, would mean for every 100 patients screened, 3 additional patients would be correctly diagnosed with fibrosis. We have modified the results and conclusions accordingly.

Comment 2: The original FIB-8 development study is cited only as abstract and obviously not published so far as full paper. This is very strange. Since some authors are identical, the authors have to give the reason for this and should also send drafts of the full paper.

Response 2: We thank the reviewer for this comments. According to Sripongpun P, et al., their AASLD 2019 abstract Ref (10) reported a new model of FIB-8 score, and their EASL 2020 abstract Ref (13), the authors are currently developing ameliorate fibrosis score. Thus, the full manuscript is being written at the moment. However, the novel fibrosis score maybe give a benefit for predicting significant fibrosis in NAFLD patients, hence we aimed to external validation in this study.

Comment 3: FIB-4 is much better in the study population than NFS, which does not mirror other study results. The authors should discuss possible reasons.

Response 3: We thank the reviewer for the insightful comments and suggested helpful articles. According to previous studies demonstrated FIB-4 is much better than NFS for predicting advanced fibrosis (F≥3). However, our study used the difference cutoffs in addition to predicted significant fibrosis (≥F2) which was followed aim of FIB-8 score creation from original abstract. Thus, we add the sentence in the discussion part on page 12 as follow:

> "Moreover, our result demonstrated that FIB-4 offered better diagnostic performance compared to the NFS score ($p<0.001$). According to meta-analysis results from Xiao G, et al (10), demonstrated FIB-4 and NFS gave the best diagnostic performance for detecting advanced fibrosis compare to other blood models. However, this meta-analysis included studies that using different cutoffs thresholds. Furthermore, the recent meta-analysis from Castellana M, et al (21) reported a head-to-head comparison of FIB-4 and NFS scores from 18 studies that using consistent cutoffs. The results from this study showed FIB-4 offered higher performance for ruling in and NFS for ruling out advanced fibrosis. Nonetheless, our studies used different cutoffs as well as aimed to predict significant fibrosis not advanced fibrosis. Consequently, our cohort was not suitable for comparison of FIB-4 and NFS scores."

Comment 4: There is a clear tendency (AUROC AND statitistics) that FIB-8- is better than FIB-4. The authors only state that there was "no significant difference" which is correct but misleading.

Response 4: We thank the reviewer for the positive comment. We add edit the sentences in the conclusion part in abstract as well as the result and conclusion parts on page 3, 8, and 12-13 as follow:

Conclusion; FIB-8 had significantly better performance for predicting significant fibrosis in NAFLD patients than NFS, as well as clinically important, but statistically non-significant discrimination to FIB-4 score in the Asian population."
Result; "The FIB-8 score had a significantly better performance for predicting significant fibrosis (≥F2) than the NFS (p=0.001) and was numerically higher than the FIB-4 score, but the difference was did not reach statistical significance (p=0.07)."

Comment 5: FIB-8 is not useful for primary physicians due to certain values. What does that mean for screening with FIB-8?

Response 5: We thank the reviewer for the positive comments. We reported this limitation in the discussion part as follow;

"In usual clinical practice, clinicians do not routinely check both laboratory parameters, and there may be no added value for observing or monitoring these values in patients."
Moreover, as the reviewer's suggestion, we edit the sentence in conclusion and discussion parts on page 3 and 12 as follow:
"A novel simple fibrosis score consisting of commonly accessible basic laboratories may be additionally used to add on earlier fibrosis scores for an initial assessment in primary care units and to select patients for further hepatologist referral."

Comment 6: There is a high proportion of patients above the high cut-off. Why is that? This seems to contribute to the relatively bad specificity of FIB-8.

Response 6: We thank the reviewer for the positive comments. Because of our study was the lower incidence of fibrosis in our cohort versus other cohorts, the differences in fibrosis may have diagnostic value for novel fibrosis scores for validation. In addition, the non-invasive fibrosis score using for primary care units need a high sensitivity and negative predictive value for excluded significant fibrosis. Nevertheless, limitation of low specificity for this fibrosis score may be required other step assessment instance transient elastography. Thus, there was our limitation which we declared in the discussion part as follow:

"The sensitivities of the low cutoff of FIB-8 score to exclude significant fibrosis was 92.36%. Consequently, the high sensitivity and negative predictive value for excluded significant fibrosis maybe beneficial in primary care units and to select patients for further hepatologist referral. However, the limited specificity of the high cutoff of FIB-8 score to include significant fibrosis may require further step assessment instance transient elastography."

"The second limitation of our study was the lower incidence of fibrosis in our cohort versus other cohorts. The differences in fibrosis may have diagnostic value for novel fibrosis scores for validation."

Comment 7: Surprisingly, there are still many errors in grammar and spelling though the authors present a language certificate. Please explain and correct thoroughly all errors.

Response 7: We thank the reviewer for this suggestion. We apologize for the errors in grammar and spelling. Thus, we already corrected thoroughly all errors in revised manuscript. The manuscript was edited and certified by American Journal Experts (AJE) on November 23, 2021.

Reviewer #3

Comment 1: This is a good work regarding the verification of FIB-8 in NAFLD patients. A total of 511 biospy-proven NAFLD patients were included. The work flow is clear, and the manuscript is easy undertood. I only have a minor question. How the age stratification was determined? The sample size seemed to be too small to receive meaningful results.

Response 1: We thank the reviewer for the positive comments. According to McPerson S, et al. demonstrated age as a confounding factor for the accurate both FIB-4 and NFS scores for predicting advanced fibrosis (21). Thus, we aimed to evaluated diagnostic performance of FIB-8 score in outlier age subgroups. Unfortunately, the FIB-8 score has low accuracy for predicting significant fibrosis in NAFLD patients similar to the FIB-4 score and NFS in patients age <35 and >65 years as we argued in discussion part.

Reviewer #4

Comment 1: Authors should lessen of importance the statement .....the detection of significant fibrosis is crucial for NAFLD management...because there no well-accepted and proven therapy for this very common disease, due to the fact that the inner mechanisms underlying NAFLD are far from being clarified as evident in...J. Clin. Med. 2020, 9(1),15; https://doi.org/10.3390/jcm9010015. The authors are requested to explain how the cut-offs were determined. By the Youden Index.

Response 1: We thank the reviewer for the this suggestion. We used the cutoff for predicting significant fibrosis (F2) according to Sripongpun P, et al. AASLD Abstract publication. 2019 Ref.11 and Siddiqui MS, et al. Clin Gastroenterol Hepatol. 2019;17(9):1877-85 e5 Ref.18. As well, we add this issue and sentence in introduction part on 4 as follow:

> "and detecting significant fibrosis is crucial for NAFLD because no well-accepted and proven therapy is available for this disease to date (6). However, patients with F2 or higher are at a higher risk of long-term liver-related death than patients with F0-1. Those with significant fibrosis should be intensively followed up or considered to participate in the therapeutic trial for NAFLD."

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

(1) Science editor:

Comment 1: all the reviewers' comments must be addressed. - the Biostatistics Review Certificate is not appropriate. It is not a certificate; it is not clear if the person is a biostatistician, and it is not signed. I recommend the authors to provide an appropriate certificate by a biostatistician.

Response 1: We thank the science editor for this suggestion. We apologize for the inappropriate Biostatistics Review Certificate. Thus, we already attached an appropriate certificate by a biostatistician from our institution.

Comment 2: the authors should clearly state the study design in the patients and methods section
- figure 1 should be part of the results section (not materials and methods)
- the ethical statement is missing in the materials and methods section
- the discussion should be expanded
- the title is too strong ("validation…"): I am not sure a retrospective study can appropriately, finally, and safely validate a new score.

Response 2: We thank the science editor for this suggestion. We revised the study design and methods section following;
1) figure 1 was moved to the part of results.
2) ethical permission and statement was added in the materials and methods section.
3) discussion part was expanded according to reviewer's suggestions.
4) Our study was external validation for the novel fibrosis score in the Asian population which potentially give a benefit for predicting significant fibrosis in NAFLD patients, hence we should the word "validation…" for this study and entitle.

Comment 3: The authors should clearly state why the original research (abstract 2019) has not been published so far and should send the manuscript of this original study. - Despite FIB-8 is at least non-inferior and insignificantly superior to FIB-4, further formulations of new indexes are encouraged.

Response 3: We thank the science editor for the positive comments. According to Sripongpun P, et al., their AASLD 2019 abstract Ref (10) reported a new model of FIB-8 score. The authors are currently developing ameliorate fibrosis score. Thus, the full manuscript is being written at the moment. So we were not able to cite full paper. Moreover, their EASL 2020 abstract Ref (13) had major limitation because of only 31 NAFLD patients with complete data were included. However, the novel fibrosis score maybe give a benefit for predicting significant fibrosis in NAFLD patients, hence we aimed to external validation in this study.

(2) Company editor-in-chief:
Comment 1: I have reviewed the Peer-Review Report, the 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.

- Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.
- Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response 1: We thank the Company editor-in-chief for this suggestion. We attached decomposable Figures in PowerPoint file in online revised submission. In addition, we already corrected all the tables to standard three-line tables in revised manuscript.

We believe that our responses and manuscript modifications will prove satisfactory upon review. We thank again the editors and reviewers for their insightful comments.

Sincerely,

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