

Response Letter:

Dear Editor,

Thank you for giving us the opportunity to submit a revised draft of the manuscript “**Metabolic Puzzle: Exploring Liver Fibrosis Differences in Asian MAFLD Subtypes**”. We appreciate the time and efforts that you and the reviewers dedicated in providing the feedback on our manuscript and are grateful for the insightful comments on our paper. We have tried to incorporate the suggestions made by the reviewers and are submitting the revised version of our manuscript with highlighted changes to facilitate the review. Please see below, in blue, for a point-by-point response to the reviewers’ comments and concerns.

Reviewer 1

This is an interesting study, although the sample size is not sufficient, the single research center is limited, and the accuracy of the examination is insufficient. This study has obtained some useful results, and distinguishing different metabolic comorbidities in MAFLD patients can help predict the progression of liver fibrosis, which is important for reducing liver related mortality in MAFLD patients. Before accepting, the author needs to make the following revisions.

1. The total number of screened patients and the criteria for performing ultrasound diagnosis should be provided, which are important for understanding the prevalence of MAFLD;

Author’s response: Thank you for raising this query. Indications to perform ultrasound examination were dyspepsia, right upper quadrant abdominal pain and derange liver enzymes.

Specific change in Manuscript: We have updated the figure 1 to address number of screened patients. The criteria for performing ultrasound examination has been updated to Method’s section.

2. Most studies suggest that the number of metabolic risk factors is related to age. In this work, the authors reach a different conclusion, has the factor of the age been considered?

Author’s response: Thank you for this comment. In our study, there was only a non-significant increase in age with number of comorbidities. This could be due to the difference in population (north American vs southeast Asian). This is further supported by a recent meta-analysis on clinical profiles of Asians with NAFLD. Overall, the pooled mean age of NAFLD patients was 52.07 (95% CI: 51.28–52.85) years, with those from Southeast Asia (42.66, 95% CI: 32.23–53.11)

being significantly younger than other Asians. This suggest that NAFLD/MAFLD occurs at a younger age in southeast Asians, masking the effect of age and number of comorbidities.

Specific change in Manuscript: A paragraph has been added in discussion section to address this.

3. Two different fibrosis risk prediction models showed different fibrosis risk of lean MAFLD, the authors need to analyze the differences between the two models to give accurate information for lean MAFLD.

Author's response: The performance of Fib-4 and NFS in diagnosing advanced fibrosis can be influenced by various factors, including age and diabetes mellitus. Additionally, the inclusion of overweight or obesity as a criterion for MAFLD may impact the BMI component in NFS but not in the Fib-4 score. The difference observed in identifying advanced fibrosis in current study using these two scores could be attributed to this discrepancy. This hypothesis is supported by a recent study in which though the performance of FIB-4 and NFS in diagnosing liver fibrosis was found to be similar between lean and non-lean individuals, the sensitivity and specificity of NFS varied according to BMI quartiles, showing an increasing trend (P for trend < 0.001), while no such trend was observed with FIB-4 (P for trend = 0.05 for sensitivity; P = 0.20 for specificity). Although there were no significant differences in the areas under the curve (AUROC) between FIB-4 and NFS in the lean group (0.807 vs 0.790; P = .09), it was found that the current cutoff values of NFS had lower sensitivity compared to those of FIB-4 among lean individuals (54.4% vs 81.8%; P = .03). Another study found that overall diagnostic performance did not differ between FIB-4 and NFS for subjects with MAFLD. Nevertheless, the performance of NFS was lower specifically among those with diabetes (AUROC 0.809 vs 0.717; p = 0.002). No significant differences were found between FIB-4 and NFS AUROCs for Obese MAFLD (0.801 vs 0.778; p = 0.351) or Lean MAFLD (0.777 vs 0.802; p = 0.659). In a recent study, FIB-4 demonstrated higher performance than the NFS score (AUROC 81.5% vs 73.7%, p < 0.001) in accurately classifying non-obese NAFLD patients with F2–4 fibrosis. Meanwhile, another study found that while FIB-4 and NFS can effectively rule out advanced fibrosis in overweight, obese, and severely obese individuals, their clinical utility in lean and morbidly obese patients is uncertain. It's important to note that this analysis was conducted on a Caucasian population, so caution should be exercised when generalizing the results as lower BMI thresholds for obesity have been established for Asians.

Specific change in Manuscript: A paragraph has been added in discussion section to address this.

Reviewer 2

1. Are there controversies in this field? What are the most recent and important achievements in the field? In my opinion, answers to these questions should be emphasized. Perhaps, in some cases, novelty of the recent achievements should be highlighted by indicating the year of publication in the text of the manuscript.
2. The results and discussion section is very weak and no emphasis is given on the discussion of the results like why certain effects are coming in to existence and what could be the possible reason behind them?
3. Conclusion: not properly written.
4. Results and conclusion: The section devoted to the explanation of the results suffers from the same problems revealed so far. Your storyline in the results section (and conclusion) is hard to follow. Moreover, the conclusions reached are really far from what one can infer from the empirical results.
5. The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning. A real discussion should also link the findings of the study to theory and/or literature.
6. Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.
7. English is modest. Therefore, the authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.

Thank you for your valuable feedback. We have carefully considered your suggestions and have revised our manuscript to enhance the content, structure, and language of the manuscript.

Thank you again for considering our manuscript and giving us a chance to improve and resubmit.

Regards

Round 2

Response Letter:

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Reviewer comments

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Thank you for your valuable feedback. We have carefully considered your suggestions and have revised the results, discussion, and conclusion to address your comments as highlighted with yellow in the revised manuscript.

Thank you again for considering our manuscript and giving us a chance to improve and resubmit.

Regards