

RE: The Application of a Simple Diagnostic Algorithm to Identify At-Risk NAFLD Patients in Need for Specialty Referral within the US General Population

June 16, 2022

Dear Editor:

Thank you for your conditional acceptance of our manuscript #: 72617 entitled “The Application of a Simple Diagnostic Algorithm to Identify At-Risk NAFLD Patients in Need for Specialty Referral within the US General Population”. Please see the individual responses to your requested revisions below.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is a good study that helps identify at-risk-NAFL patients who are in need for special referral. However, there are a few issues that need to be clarified:

1. The authors should further explain why choosing a FIB4 cutoff at 1.3 to differentiate patients with low risk and high risk disease.
 - a. Two key studies have validated this cutoff point [Mcperson et al in *Am J Gastro* (2017) and Newsome et al in *Gut* (2018)]. These studies have been added as reference to the text to support the rationale for a cutoff of 1.3.
2. Why was FAST cutoff value at 0.35 chosen to differentiate high and low risk?
 - a. As per Newsome et al in *The Lancet Gastroenterology & Hepatology* (2020), a cutoff of 0.35 was associated with a 90% sensitivity for ruling out advanced fibrosis. This is referenced on page 4.
3. Figure 2: - With normal ALT, there is a possibility of liver fibrosis. The authors did not mention that. - If $FIB4 < 1.3$ and $FAST > 0.35$, should it be low or high risk? - If $FIB4 > 1.3$ and $FAST < 0.35$, should it be low or high risk?

This diagnostic algorithm is intended to provide a stepwise approach for primary care physicians. To provide contingencies based on equivocal results is somewhat outside the scope of this manuscript and thus is not covered in detail. We would recommend that these patients with equivocal findings are referred to hepatologists for further risk stratification. This rationale has been added to the discussion section of the manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This study evaluated the use of a simple diagnostic algorithm in identifying at-risk NAFLD patients in need for specialty referral within the US general population using the National Health and Nutrition Examination Survey (NHANES) database (2017–2018). The findings of this study provide references for the management of NAFLD patients. The title precisely reflects the main subject of the manuscript. The abstract summarized and reflected the work described in the manuscript. The key words reflect the focus of the

manuscript. The manuscript generally described the background, present status and significance of the study. The methods were adequately described in the manuscript. The results were well presented contributed for research progress in this field. The manuscript interpreted the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. The findings and their relevance to the literature were stated in a clear and definite manner. The manuscript sufficiently discussed the scientific significance and relevance of the findings to clinical practice. The figures and tables are sufficient, have good quality and appropriately illustrated the paper contents. The manuscript meets the requirements of biostatistics. The manuscript cite appropriately the important and authoritative references in the introduction and discussion sections. The manuscript is well, concisely and coherently organized and presented. The manuscript meets the requirements of ethics. Concerns:

1. The term metabolic dysfunction-associated fatty liver disease (MAFLD) has been proposed in recent years. The authors need to consider the inclusion of MAFLD in their analysis and compare between NAFLD and MAFLD for the diagnostic algorithm.
 - a. While MAFLD has come to light in recent years, this is not a term widely accepted or recognized in primary care and endocrinology fields. To discuss MAFLD would likely be outside the scope of this narrowly focused manuscript.
2. Also, the relationship between MAFLD and NAFLD should be mentioned and discussed in the introduction and discussion sections of the manuscript based on the relevant references especially MAFLD.
 - a. This difference is mostly in terminology and is not extremely relevant to the scope of this manuscript.
3. The word “optimze” should be corrected.
 - a. This has been corrected.
4. The abbreviations such as AUROCs and ALT need to be annotated when first presented in the manuscript.
 - a. This has been corrected.

Science Editor:

1 Conflict of interest statement: Academic Editor has no conflict of interest. 2 Manuscript’s theme: The topic is within the scope of the journal. 3 Academic misconduct: No academic misconduct was found. 4 Scientific quality: This is a retrospective study where authors presented a an algorithm that doctors can approach an undifferentiated patient with findings concerning for NAFLD. (1) Advantages and disadvantages: The paper is overall well written and carried out. The results are clearly presented. However, the reviewers have raised a few concerns that should be addressed, please explain in greater details of the cut-off values. Authors should include MAFLD in their analysis and discuss more in the introduction and discussion sections.

A: Please see above.

(2) Main manuscript content: None. (3) Table(s) and figure(s): There is 3 figures and 2 tables. (4) References: A total of 25 references are cited, including 4 papers published in the last 3 years. There is no self-cited references of the authors. The cited references are overall sufficient and reasonable. The reviewer didn’t request the authors to cite improper references published by him/herself. 5 Language evaluation: Not apply. 6 Medical ethics: The authors described the Institutional Review Board approval and properly reported on the informed consent (statement in the manuscript). 7 Specific comments: None. 8 Recommendation: Conditional acceptance.

Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Editor in Chief:

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 Hepatology, 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. Before its final acceptance, please upload the primary version (PDF) of the Institutional Review Board's official approval in the official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

- **Title has been updated.**

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Thank you again for your time and consideration.

Sincerely,

Pankaj Aggarwal