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I M T I B

Buenos Aires, February 9th 2024

Dr. Andrzej S Tarnawski
Editor-in-Chief
World Journal of Gastroenterology

Dear Dr. Tarnawski,

Enclosed please find the revised version of our manuscript (number 91308) entitled "*Omics-based biomarkers as useful tools in metabolic dysfunction-associated steatotic liver disease clinical practice: How far are we?*". The authors are deeply grateful for the reviewers and editorial office's comments and thorough suggestions to improve the manuscript. Accordingly, we have revised the manuscript. All amendments are highlighted in yellow in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

Reviewer #1:

Thank you for your review on a very interesting and important topic of Omics based biomarkers for MASLD. A description of which databases were searched for relevant articles would be helpful. In addition a detailed analysis with assessment of individual validity of studies would be more instructive instead of a summary comment.

We would like to thank the reviewer for these comments.

A detailed description of which databases were searched for relevant articles and the search criteria used in this study were included in the revised version of the manuscript: "*To perform the search and retrieval of scientific articles to describe the current state of omics-derived biomarker development in MASLD, we used the PubMed (National Library of Medicine) and RCA (Reference Citation Analysis) databases. The "OR" and "AND" connectors were used to combine the descriptors: ("non-alcoholic fatty liver disease" or "non-alcoholic steatohepatitis" or "fatty liver" or "NAFLD" or "NASH" or "metabolic–associated fatty liver disease" or "MAFLD" "metabolic dysfunction–associated steatotic liver disease" or "MASLD") and ("human") and ("biomarker") and ("omics" or "multi-omics" or "microbiome" or "genomics" or "proteomics" or "metabolomics" or "metagenomics" or "transcriptomics").*

Inclusion criteria were: the availability of the full text; publication up to December 2023; written in English. Exclusion criteria were: review studies, repeated studies in more than one database, research outside the previously determined context.

After analyzing the titles and abstracts, according to the eligibility criteria, the studies were selected for reading in full. One hundred and sixty-three studies were found in the databases. After completing the selection of the studies based on the reading of the titles and abstracts, 24 studies were excluded: 2 duplicated, 5 Chinese, 11 in vitro studies; 6 evaluated individuals other chronic liver diseases.

Thus, 139 articles were included in the analysis. The complete list of articles included in the analysis and their main information (authorship and year of publication, type of sample and omic technique/s used in the study) are shown in Supplementary Table 1."

In addition, an analysis of the individual validity of studies was included in the revised version of the manuscript: "*The 139 studies were also analysed according to a previously published set of criteria that evaluate the internal validity of individual studies [16,17]. The most common limitations observed in these studies were a small sample size (16.5%), followed by the presence of bias in the selection and stratification of patients due to the lack of histological diagnosis of MASLD using liver biopsies (12.2%). Moreover, disregard to potential confounding variables (such as age, gender, ethnicity, BMI, or presence of comorbidities) and their appropriate adjustments in the data analysis was observed in 13 studies (9.35%).*

Validity of a study can also be evaluated by its reproducibility. In the case of omics research, deposition of raw data, complete protocols and bioinformatics codes and workflows in a public repository is considered a first step to replicate a study´s findings [17]. Although many leading journals now demand to make data and protocols publicly available as a prerequisite for publication [18], this practice remains inconsistent across journals and omics studies. In fact, 7 (5%) of the studies included in our literature search did not offer public access to their data nor indicate how others may obtain it in case specific legal or ethical restrictions prohibit public sharing of the data set.

*However, these flaws aren´t recurrently detected in some fields of omics research. In the case of genomics, genome-wide association studies demand high statistical significance (*P *values* $< 5 \times 10^{-8}$*), perform large-scale replication efforts within international consortia, and have good compliance to data availability policies [19], as was observed in the 2 studies of this type (1,4%) analysed in the literature search carried out in this review*."*.*

Reviewer #2:

This is a well-written, focused article that highlights pitfalls in diagnostic biomarkers for MASLD. As with other insulin-resistance related diseases, the abnormalities are multi-dimensional meaning that no single marker is reliable for diagnosis. Even the histopathology is not sufficient on its own. One point not mentioned in this review is the value of low-tech assessments that have strong correlations with MASLD, namely, waist circumference and waist-hip ratios. These should be mentioned because for prevention, the cases have to be predictable. Our problems often relate to when the LFTs become abnormal--perhaps too late in the process. Adding something about screening and monitoring with low-tech methods could improve the manuscript.

We would like to thank the reviewer for this comment. The following paragraphs regarding screening and monitoring with low-tech methods were included in the revised version of the manuscript: *"These limitations have driven the need of non-invasive MASLD screening, monitoring and risk stratification methods. In this regard, imaging methods such as ultrasound, computed tomography, and magnetic resonance are valuable for the detection of lipid accumulation in MAFLD patients, but useless for the evaluation of inflammation and degrees of fibrosis less than cirrhosis [10,11].*

On the contrary, low-tech methods such as the anthropometric clinical indicators of visceral obesity have been very promising for the primary prevention and screening of MASLD. Screening of the presence or absence of MASLD with the help of non-invasive anthropometric measurements can be achieved with simple and cheap equipment, and can be implemented in several health centres (e.g., primary practice) and also remote areas [12]. Abdomen circumference, waist circumference, chest circumference, trunk fat and body mass index are among the most important variables contributing to fatty liver disease [13]. Although these indicators show suboptimal accuracy (57%) in detecting fibrosis [13], the identification of their specific cutoff points considering the ethnic and racial groups [12], for use in the prediction of MASLD, and especially NASH, may help in the early diagnosis, allowing a therapeutic and preventive approach to this population.".

Abbreviations

Basic rules on abbreviations were followed. Use of abbreviations was corrected throughout the manuscript.

Editorial Office's comments

(1) Science editor:

3 Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

We made the necessary modifications in the manuscript to improve the English. However, we don't have the resources to pay for a native speaker service. Argentina is currently going through a severe financial crisis, and all services from abroad are practically impossible for us to pay for since there are a lot of restrictions on using foreign currencies.

However, we are confident that the article improved much after the peer review and even more after improving its grammar.

I hope you understand this situation, and we are more than open to discussing it further.

4 Specific comments:

(1) Please provide the filled conflict-of-interest disclosure form.

Copyright license agreement and conflict-of-interest disclosure forms were completed and uploaded.

(2) Please provide the PMID numbers (https://pubmed.ncbi.nlm.nih.gov/) to the reference list and list all authors of the references. If a reference has no PMID and DOI, please provide the source website address of this reference.

References were modified as requested. In addition, the PMID numbers, DOI and full list of authors were included in the supplementary Table and in the reference list.

(3) Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Approval documents for grant applications were uploaded.

(2) Company editor-in-chief:

When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the *Reference Citation Analysis* (*RCA*), of which data source is PubMed. *RCA* is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our *RCA* database for more information at: https://www.referencecitationanalysis.com/, or visit PubMed at: https://pubmed.ncbi.nlm.nih.gov/.

Both databases were used when preparing the manuscript. All of the literature on the corresponding topics referenced in our manuscript was derived from PubMed and the "Impact Index Per Article" was used to prioritize reference citations. In this revised manuscript, we have also updated the formatting of all literature to provide the PMID numbers and DOI citation numbers to the reference list.

Manuscript format

The Guidelines and Requirements for Manuscript Revision were strictly adhered to when revising the format of the title page, abstract, core tip, main text, references, figures and tables.

The following documents were uploaded:

(1) 91308-Answering Reviewers
(2) 91308-Audio Core Tip
(3) 91308-Conflict-of-Interest Disclosure Form
(4) 91308-Copyright License Agreement
(5) 91308-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)
(6) 91308-Non-Native Speakers of English Editing Certificate
(7) 91308-Figures
(8) 91308-Supplementary Material

Awaiting your kind reply, I remain respectfully yours.

I M T I B

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