

ANSWERING REVIEWERS



January 14, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15582-Edited-R1.doc).

Title: Non-alcoholic fatty liver disease, metabolic risk factors and hepatocellular carcinoma: An open question

Authors: Letitia Adela Maria Streba, Cristin Constantin Vere, Ion Rogoveanu, Costin Teodor Streba

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15582

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers:

Reviewer 01560058

This is a well-written mini review that addressed hepatocarcinogenesis in nonalcoholic fatty liver disease (NAFLD), in terms of epidemiological and pathophysiological aspects.

The Reviewer suggests that the authors add information on molecular genetic and epigenetic mechanisms of hepatocarcinogenesis in NAFLD. For example, variants of the patatin-like phospholipase domain-containing 3 gene, PNPLA3, are well known to be associated with the susceptibility and progression of NAFLD. Recently, the variants of PNPLA3 gene also have been reported to be involved in NAFLD-related hepatocarcinogenesis. Furthermore, recent advances in epigenetics have shed light on the mechanisms of hepatocarcinogenesis in NALFD. For example, some factors regulating histone acetylation and deacetylation have been reported to be closely linked to hepatocarcinogenesis in NAFLD.

Thank you for your valuable comments. The text was thoroughly revised to answer reviewer comments in what we hope to be a satisfactory manner.

We have now added a section dedicated to genetic factors, especially the PNPLA3 gene and its involvement in NAFLD development.

We have inserted several paragraphs through the manuscript in order to summarize all recent findings and expand the scope of the Editorial. All changes were highlighted in yellow in this intermediate version.

References have also been added to the text and re-numbered accordingly.

Reviewer 03023548

The review by Streba et al. examines the relationship between NAFLD and hepatocellular carcinoma development (HCC). The review goes into great depth to highlight key epidemiological studies that strongly link NAFLD and HCC in human patients. Further the authors discuss possible biological/metabolic pathways (e.g., insulin growth factor, ROS, TNF, adiponectin) and their impact on NAFLD development and progression. In sum, although the review is intriguing and highly relevant there are following concerns:

Thank you for your suggestions. We have now revised the text thoroughly in order to meet all points raised by the Reviewers and comply with the editorial style of the publication.

(1) The title of the review “NAFLD, metabolic factors and HCC: An open question” does not fully recapitulate the material presented. The authors go to great lengths to identify the relationship between NAFLD and HCC, however the discussion section of role of metabolic factors in NAFL to HCC progression is feeble—something that should be reorganized and expanded upon.

We have now slightly modified the title of the paper to better suit the subject debated.

We have now modified the Abstract to better reflect the contents of the paper.

We have re-arranged the Discussion section dedicated to the role played by metabolic factors in the transition from NAFLD to HCC.

We have also added relevant information to this section, providing key arguments from important meta-analyses and large studies. References have been added to the text and re-numbered accordingly.

(2) It is well accepted that there are multiple metabolic factors that may contribute to HCC development. The transparency for choosing specific factors discussed in this review should improved. Of note, the factors discussed are only briefly supported by the epidemiological studies presented. A connection between epidemiological and animal studies would make for a significantly stronger argument.

Thank you for this important suggestion. We have now dedicated a sub-section to the main animal models currently developed. We have also underlined in the respective sections the importance of animal studies in connection to epidemiological data.

(3) Discussion of the homeostatic roles of metabolic factors discussed should be included.

We have now added relevant information in the respective sections, according to the suggestion of the reviewer.

(4) The summary section of the epidemiological evidence should lead to a more cohesive and succinct conclusion.

Indeed, we have now re-evaluated the summary section of the main epidemiological data reviewed and re-arranged according to this suggestion, as well as other comments coming from reviewers.

(5) A section focused on the interplay of various inflammatory cytokines/immune cells with hepatocytes in context of NAFL to HCC progression should be included.

We have now added relevant information on the role played by inflammatory cytokines in the immune processes involving hepatocytes, in relation to the NAFL-to-HCC progression.

(6) Minor: grammatical and typographic errors should be corrected.

The text was now professionally edited by native-English speaking personnel. We have now hopefully corrected grammatical and typographic errors through the manuscript.

Reviewer 03022633

Dear Author;

*I think category of this manuscript would be letter to editor instead of clinical practice.

*Rules of writing is not appropriate for journal, it must correct.

*References must be less than now. It must correct.

Sincerely

We thank the reviewer for the comment. Given the addition of several important paragraphs, we hope the reviewer, as well as the Editorial Team of WJG, will find the manuscript to better suit the Editorial column. We have now done our best to comply with all editorial policies of WJG for Editorials.

We have added the necessary references to accompany the paragraphs inserted in order to expand the manuscript text according to the requirements of the Reviewers.

3 References and typesetting were corrected

We have unified the style of all references and added the PubMed accession numbers as well as the DOIs, where available.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Streba Costin Teodor', with a stylized, flowing script.

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