

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 65732

Title: Hepatocellular carcinoma in non-alcoholic fatty liver disease – a growing challenge

Reviewer's code: 05917675

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Brazil

Manuscript submission date: 2021-03-14

Reviewer chosen by: Man Liu

Reviewer accepted review: 2021-03-15 04:50

Reviewer performed review: 2021-03-17 12:02

Review time: 2 Days and 7 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Authors performed an invited review about NAFLD related hepatocellular carcinoma. The review is well written and the topic is very interesting. The novelty is poor, but the manuscript summarized this important association. There are only minor concerns. -

In the abstract non-alcoholic fatty liver disease may be changed in NAFLD. Furthermore, semi-annual may be changed in "every 6 months" - Patients with NAFLD had an increased risk of fibrosis (doi: 10.1111/liv.14206). Is there a role of fibrosis as potential risk factor for HCC in NAFLD patients? - Are there some common risk factors between HCC and NAFLD that may clinically explain this association? -

Patients with NAFLD had an increased oxidative stress (10.3390/nu12092762). May this play a role in HCC onset? Criteria Checklist for New Manuscript Peer-Review 1. Title. Does the title reflect the main subject/hypothesis of the manuscript?

Yes 2. Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes 3. Key words. Do the key words reflect the focus of the manuscript?

The term "NAFLD" may be added in keyword section. 4. Background. Does the manuscript adequately describe the background, present status and significance of the study?

May be improved. 5. Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Not applicable 6. Results. Are the

research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field?

Yes 7. Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite

manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Yes 8. Illustrations and

tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? Yes, they are appropriately

illustrative and do not require further improvement. 9. Biostatistics. Does the manuscript meet the requirements of biostatistics? Not

applicable 10. Units. Does the manuscript meet the requirements of use of SI units?

Not applicable 11. References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? May be improved Does the

author self-cite, omit, incorrectly cite and/or over-cite references? No 12.

Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? May be improved 13. Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? Not applicable 14.

Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript



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meet the requirements of ethics?

Not applicable

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 65732

Title: Hepatocellular carcinoma in non-alcoholic fatty liver disease – a growing challenge

Reviewer's code: 03806229

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: France

Author's Country/Territory: Brazil

Manuscript submission date: 2021-03-14

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-03-15 09:22

Reviewer performed review: 2021-03-17 14:04

Review time: 2 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I read the review by Angelo Mattos et al with great interest, this article report genetic and immune-mediated mechanisms role in the development of hepatocarcinoma (HCC) derived from NAFLD but I have some minor concerns that the authors have to address before publication.

1-The authors summarize genetic and immune-mediated mechanisms involving in the development of HCC derived from NAFLD indicating NAFLD as prominent contributor to HCC but nothing is mentioned regarding the impact of fibrosis severity on the expression of metabolites. Recently, one article presented by Buchard B et al , aims at characterizing and comparing the metabolomics profile of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) according to fibrosis level using a RMN-based non-targeted metabolomics approach in human. To my knowledge, this is the first study, in human, attempting to establish the metabolomics signature of liver tissues accounting for the severity of the disease. Please include this article in your review into the paragraph “other factors” Buchard B et al :Two Metabolomics Phenotypes of Human Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease According to Fibrosis Severity. *Metabolites* 2021

2- Furthermore, the authors listed several genes involved NAFLD- related HCC. In this regard, it would a great benefit to better summarize these findings in a table.

3-Secondly, in the same line of idea the figure 1proposes scheme highlighting the different steps of liver carcinogenesis. Lipids: there are four broad processes that can affect liver fat, de novo lipogenesis, exogenous lipids, export of lipids and metabolic breakdown of lipids, each of these is involved in the development of NAFLD. Please indicated the different sources of lipids. Reversibility of NAFLD; it is well known that NAFLD status may be reversible with an appropriate regimen. Please indicate this possibility with an double arrow on figure. Statins : Certainly the use of statins in



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liver diseases was conflicting several years ago. However, newer evidence from pre-clinical and clinical research has shown that statins are drugs with a potentially beneficial impact on the natural history of cirrhosis, on portal hypertension, and in HCC prevention. Vargas et al : "Use of Statins in Patients with Chronic Liver Disease and Cirrhosis: Current Views and Prospects". Curr Gastroenterol Rep. 2017. In addition, in a recent article, Pose E et al reported in a retrospective cohort studies in large populations of patients with cirrhosis that treatment with statins, with the purpose of decreasing high cholesterol levels, was associated with a reduced risk of disease progression, including NAFLD, hepatic decompensation and HCC development. Pose E et al ." Statins: Old drugs as new therapy for liver diseases?" J Hepatol 2019. Please remove statins from the figure or at least indicate one interrogation point. Altered microbiome rather than microbiome Please, consider adding these minor changes.

Best regard

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 65732

Title: Hepatocellular carcinoma in non-alcoholic fatty liver disease – a growing challenge

Reviewer's code: 04761604

Position: Peer Reviewer

Academic degree: DNB, MBBS

Professional title: Doctor, Teacher

Reviewer's Country/Territory: India

Author's Country/Territory: Brazil

Manuscript submission date: 2021-03-14

Reviewer chosen by: AI Technique

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Reviewer performed review: 2021-03-18 01:44

Review time: 10 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

I appreciate the review effort of the authors and would like to share the following comments: The introduction section needs rewriting. Please try rationalizing it better. Also, use numbers (e.g., prevalence data, clinical trial data, and meta-analysis data) from recent literature as appropriate, shorten and simplify sentences, and avoid seemingly vague statements (e.g., "...directed to certain subgroups at higher risks"). Throughout the manuscript, incorporation of more details is advised where references to other studies are made. For example - "inevitably biased towards a large presence of male gender among the evaluated cohorts" - including the percentage of males may give a clearer picture. Another example - "Some studies from the USA suggest ...increase the risk of HCC in NAFLD" - mention of the study design and population characteristics will perhaps help the readers to understand the context better. Next, throughout the manuscript, several sentences are not adequately cited. Then, before the "conclusion" section, I suggest incorporating a "discussion" section giving an overview of the review with its implications and limitations. Rewriting of the "Core tip" is also advised. Finally, the 'figures' copyright issues need to be addressed (if these are not created by the authors). Thank you.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 65732

Title: Hepatocellular carcinoma in non-alcoholic fatty liver disease – a growing challenge

Reviewer's code: 03475479

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Brazil

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Authors reviewed the pathogenesis and management of HCC in NAFLD. As authors mentioned, HCC with NAFLD has been an essential issue for clinicians. This review was well-written and informative.