

RESPONSE TO THE REVIEWERS (Manuscript ID: 76352)

Dear Editors and Reviewers,

Thank you for your valuable comments and suggestions about our manuscript entitled “Association of COVID-19 with Hepatic Metabolic Dysfunction” (manuscript no 76352; review). These are very helpful for revising and improving our manuscript.

In the revised manuscript we have incorporated all the changes as suggested by the reviewers. Revised portions are marked in red in the paper. Moreover, the revised manuscript has been edited for proper English language by a professional body (certificate included). Our point-by-point responses to the issues raised in the peer review report are as follows:

1. Response to reviewers' comments

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors had touched on a very specific subject of the COVID-19 pandemic. SARS-Cov-2 had been proven to influence many bodily organs including the kidney, lungs, heart, and liver. This study adequately reviewed the association of COVID-19 to hepatic metabolic dysfunction. The paper is important and adds to the COVID-19 specific literature. Findings from the current study explained the pathophysiology and can propose treatment methods in hepatic-metabolic dysfunction which is prevalent in COVID-19 patients. Matters that need to be improved on this paper are: (1) English language correction and (2) structural editing (i.e., some parts can be combined under subsections to improve clarity and readability)

Authors' response: Thank you for your valuable comments. The manuscript has been revised in light of your suggestions and comments. The revised manuscript has been edited for proper English language by a professional body (native English speaker). The necessary structural

editing was done. Pathophysiological part has been combined into subsections in order to improve the quality and readability.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have reviewed the metabolic implications of COVID-19 in the liver and the role this organ has in the progression of the disease. The manuscript is of interest as it provides discussion on relevant questions and some open questions that will surely boost further investigation. I have two comments for the authors:

Q1. The expression of ACE2 is very low in liver parenchyma (see, for example, data in the Human Protein Atlas). In light of this, do the authors think that hepatocytes are primary targets of SARS-CoV-2? Alternatively, is liver injury a secondary hit of the inflammatory response of the host to SARS-CoV-2 infection? These considerations must be taken into account throughout the manuscript in order to delineate an accurate molecular pathogenesis of COVID-19 and to define the relevance of the contribution of the liver.

Authors' response: We agree that ACE2 expression is low in healthy livers. However, ACE2 expression is upregulated in a variety of conditions, including inflammatory and liver diseases, and cirrhotic liver exhibits higher levels of ACE2 expression [Gut. 2005; 54: 1790-6, Eur J Clin Microbiol Infect Dis. 2021; 40: 905-919]. In a histological study of COVID-19 patients who died, PCR for viral RNA was discovered in the liver tissue of 55% of those tested, indicating that the virus can target the liver. [Mod Pathol. 2020; 33: 2147-2155]. Therefore, hepatocytes in COVID-19 can be targeted both directly by SARS-CoV-2 and indirectly by the inflammatory response of the host generated by SARS-CoV-2 infection. In fact, pro-inflammatory cytokines, oxidative stress, and IR all appear to play a role in metabolic dysregulation in COVID-19. (Section: pathophysiology, and Clinical implications)

Q2. It might be of interest to dedicate specific attention to one carbon metabolism. The authors make several independent references to different alterations associated with this central metabolic pathway in the hepatocyte, including folate cycle, methionine cycle, synthesis of phospholipids, polyamides and glutathione. Integrated discussion of all these aspects would provide a clearer view to the reader.

Authors' response: Thank you for your insightful suggestion. We concur that changes in one-carbon metabolic pathways are essential elements of SARS-CoV-2 infection pathogenesis. A separate section on the implications of one-carbon metabolic pathways in COVID-19 has been added to the revised manuscript (section pathophysiology)

Q3. There are sections where the authors review several pathophysiological issues associated to COVID-19 but no link to metabolism is evident (see, pages13-16).

Authors' response: In the revised manuscript, these sections have been thoroughly edited. To increase the quality and readability, the pathophysiological aspects have been divided into subsections. These sections essentially deal with how SARS-Co-2 enters into the body and leads to inflammatory and metabolic changes. Important pathophysiological elements such as entry of SARS-CoV-2, alterations in RAAS, changes in one-carbon metabolism, pancreatic dysfunctions, and insulin resistance, among others have been discussed, which have some direct or indirect link with metabolic dysfunction in COVID-19. Growing evidence suggests a direct link between metabolic changes and inflammatory responses in the body. However, there is currently insufficient evidence relating metabolic alterations to inflammation in COVID-19.

2. LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Authors' response: The revised manuscript has been edited for proper English language by a profession body (native English speaker), and language editing certificate is being submitted online.

3.EDITORIAL OFFICE'S COMMENTS

(1) Science editor: The manuscript assessed the metabolic significance of covid - 19 in the liver and the role of this organ in disease progression. The manuscript is well, concisely and coherently organized and presented and the style. However, innovation is not that high. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. The article needs a great deal of language polishing.

Language Quality: Grade C (A great deal of language polishing)

Scientific Quality: Grade B (Very good)

Authors' response: Thank you for your valuable comments. The reference list has been revised as per the suggestion. The maximum references from the same journal have been limited to three. The revised manuscript has been edited by a competent agency (of native English-speaking editors) for English language and a high quality has now been reached.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Virology, 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. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: <https://www.referencecitationanalysis.com/>. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Authors' response: Thank you for your valuable opinion and suggestions. The manuscript has been thoroughly revised in the light of peer-review Report, editorial office's comments and the criteria for manuscript revision. In the revised manuscript, we have incorporated all the changes as suggested by the reviewers. The reference list has been revised as per the journal's requirement. New portions are marked in red in the paper. We have also got the revised manuscript edited for English language by a trustworthy body, and a high quality has now been reached. We are providing the images on PowerPoint slide which can be reprocessed by the editors. All the figures and tables are original.

Best regards,

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