27th December 2023

Professor Ke-Qin Hu, MD.

Editor-in-Chief

World Journal of Hepatology

RE: Manuscript NO - 90328 - Effects of SARS-CoV-2 infection on incidence and treatment strategies of hepatocellular carcinoma in people with chronic liver disease

Dear Professor Hu,

Thank you for considering our manuscript, and providing us with the opportunity to improve with thorough and rapid review from editorial board and referees. We provide here our point-by-point responses to editorial and reviewers' comments. We have now updated our manuscript, addressing the editorial requirements and comments.

Peer-review report

Reviewer #1

Specific Comments to Authors:

The study overall has some clinical significance -The link between HCC and SARS was not clear in this study and the impact of COVID-19 infection on patients with liver disease was indirect based on most of the health centers at least in the first pandemic wave was directed mainly to COVID-19 management and negligence of their disease so the patients with liver disease and other disease found difficulty for their follow up and this issue should be discussed in details as lack of follow up of cirrhotic patients may decrease early detection

Response 1.1: Thank you for the insightful comment. We fully agree with the reviewer regarding the impact of lockdown measures on routine care of patients with CLD, leading to detection bias. We have now expanded the Discussion on mechanisms for 1) heightened risk of HCC in COVID-19+CLD patients and 2) increased risk of palliative treatment for HCC. Relevant texts are quoted as follows:

P.16: "Although risk of HCC was not found to be significantly increased among COVID-19+CLD patients in the overall cohort (IRR 1.19, 95%CI 0.99-1.42, p=0.06), there was an

increased risk of HCC in both acute (IRR 1.89, 95%CI 1.03-3.47, p=004) and post-acute phase (IRR 1.24, 95%CI 1.00-1.53, p=0.05). This phenomenon cannot be explained by the higher risk of cirrhosis and liver decompensation following SARS-CoV-2 infection as the time window was too short for hepatocarcinogenesis. Although SARS-CoV-2 has been suggested to demonstrate liver tropism as confirmed by viral RNA and spike protein detection in autopsy liver specimens[1,2], it is not known to cause carcinogenic mutations or induce pro-oncogenic proteins like what hepatitis B virus does[3,4]. Therefore, non-biological mechanisms likely exist to account for the observed increased risk of HCC in CLD patients infected by SARS-CoV-2 infection. We hypothesized that it might be related to paradoxically earlier detection of tumors in COVID-19 patients who are also known to have increased risk of acute liver injury[5,6], that triggered off imaging workups for the abnormal liver enzymes."

P.16-17: "During the initial phase of COVID-19 pandemic, there was implementation of lockdown strategies and prioritization of healthcare services to prevention and management of SARS-CoV-2 in virtually all health care facilities[7]. It inevitably led to delays in routine care, such as patient follow-up[8], HCC surveillance and priority referrals to relevant disciplines to manage HCC.[9] Even for subjects with milder disease course of COVID-19 and preserved liver function, because of such disruption in the routine clinical service, essential abdominal imaging such as ultrasound scans and computed tomography scans[10,11] was not performed for CLD patients in a capacity similar to pre-COVID era.[12] This would inevitably lead to delays in HCC diagnosis, causing these patients to be diagnosed at a more advanced stage of cancer and eventually became ineligible for loco-regional oncological treatments for HCC even when their medical condition was otherwise stable.[13]"

Reference

1. Wanner N, Andrieux G, Badia IMP, et al. Molecular consequences of SARS-CoV-2 liver tropism. *Nat Metab.* 2022;4(3):310-319.
2. Quarleri J, Delpino MV. Molecular mechanisms implicated in SARS-CoV-2 liver tropism. *World J Gastroenterol.* 2022;28(48):6875-6887.
3. Lupberger J, Hildt E. Hepatitis B virus-induced oncogenesis. *World J Gastroenterol.* 2007;13(1):74-81.
4. Sivasudhan E, Blake N, Lu Z, Meng J, Rong R. Hepatitis B Viral Protein HBx and the Molecular Mechanisms Modulating the Hallmarks of Hepatocellular Carcinoma: A Comprehensive Review. *Cells.* 2022;11(4).
5. Phipps MM, Barraza LH, LaSota ED, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology.* 2020;72(3):807-817.
6. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. *Hepatology.* 2020;72(4):1169-1176.

7. Feng Y, Young CH, Lau SH, He ML. Outbreak control management: Lessons from SARS-CoV-2 infections in 2020-2022 in Hong Kong, an international municipality with high-frequency travelers. *MedComm (2020).* 2022;3(3):e158.
8. Oubaya N, Pombet T, Delestrain C, et al. Impact of the COVID-19 pandemic and associated lockdown measures on the management, health, and behavior of the cystic fibrosis population in France during 2020 (MUCONFIN). *Front Public Health.* 2022;10:978627.
9. Tapper EB, Asrani SK. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. *J Hepatol.* 2020;73(2):441-445.
10. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67(2):370-398.
11. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(4):1560-1599.
12. Toyoda H, Huang DQ, Le MH, Nguyen MH. Liver Care and Surveillance: The Global Impact of the COVID-19 Pandemic. *Hepatol Commun.* 2020;4(12):1751-1757.
13. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236.

Editorial Office's Comments:

Science Editor

Specific Comments:

(1) Please provide the Biostatistics statement.

Response SE.1: Thank you for the comment. We have now provided the Biostatistics statement on P.11 and details listed in the revision file.

(2) Please provide the Institutional review board statement.

Response SE.2: Thank you for the comment. We have now provided the Ethics approval statement on P.28: "The study protocol was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (UW 20-556, UW 21-149 and UW 21-138); and the Department of Health Ethics Committee (LM 21/2021 and LM 175/2022)."

(3) Please provide the Informed consent statement.

Response SE.3: Thank you for the comment. We have now provided the Informed consent statement on P.28: "Informed patient consent was not required as the data used in this study were anonymised."

(4) Please provide the Language certificate. 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.

Response SE.4: Thank you for the comment. We have sent our manuscript to the language editing service of Elsevier and revised the manuscript according to their suggestions. The Language certificate is uploaded as "90328-Non-Native Speakers of English Editing Certificate" in the revision file.

(5) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A,B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .

Response SE.5: Thank you for the comment. All figures included in the manuscript are original image created. We have edited the figure legends and titles, and also changed the figures into the form of PPT.

(6) Please obtain permission for the use of picture(s). 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 indicate 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.

Response SE.6: Thank you for the comment. We confirm that all Figures of the paper are original without copyright issues.

(7) Please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP < 0.05, bP < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP < 0.05 and dP < 0.01 are used, and a third series of P values is expressed as eP < 0.05 and fP < 0.01.

Response SE.7: Thank you for the comment. We have relabelled the superscript numbers for illustration and superscript letters for statistical significance, and revised the footnotes of the tables and supplementary materials.

(8) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text (and directly before the References).

Response SE.8: Thank you for the comment. We have now added the Article Highlights section at the end of the main text at P.19-21.

Company Editor-in-Chief

I recommend the manuscript to be published in the World Journal of Hepatology. 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 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/.

Response CEIC.1: Thank you for the suggestion. We have applied RCA to search for more latest literatures and cited in the manuscript to enrich the contents. We have included a list of newly added references of the revised manuscript as following:

1. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. Clin Liver Dis (Hoboken). 2021;17(5):365-370.
2. Mederacke I, Hsu CC, Troeger JS, et al. Fate tracing reveals hepatic stellate cells as dominant contributors to liver fibrosis independent of its aetiology. Nat Commun. 2013;4:2823.
3. Wanner N, Andrieux G, Badia IMP, et al. Molecular consequences of SARS-CoV-2 liver tropism. Nat Metab. 2022;4(3):310-319.
4. Quarleri J, Delpino MV. Molecular mechanisms implicated in SARS-CoV-2 liver tropism. World J Gastroenterol. 2022;28(48):6875-6887.
5. Lupberger J, Hildt E. Hepatitis B virus-induced oncogenesis. World J Gastroenterol. 2007;13(1):74-81.
6. Sivasudhan E, Blake N, Lu Z, Meng J, Rong R. Hepatitis B Viral Protein HBx and the Molecular Mechanisms Modulating the Hallmarks of Hepatocellular Carcinoma: A Comprehensive Review. Cells. 2022;11(4).
7. Feng Y, Young CH, Lau SH, He ML. Outbreak control management: Lessons from SARS-CoV-2 infections in 2020-2022 in Hong Kong, an international municipality with high-frequency travelers. MedComm (2020). 2022;3(3):e158.
8. Oubaya N, Pombet T, Delestrain C, et al. Impact of the COVID-19 pandemic and associated lockdown measures on the management, health, and behavior of the cystic fibrosis population in France during 2020 (MUCONFIN). Front Public Health. 2022;10:978627.

We sincerely hope that you will consider this revised manuscript favourably. Should there be further corrections or clarifications needed, we are more than happy to make the necessary changes and provide additional information. We look forward to hearing from you soon.

Yours sincerely,

Carlos K.H. Wong, PhD

Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Rm 1-01, 1/F, Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road,

Pokfulam, Hong Kong, China

Email: carlosho@hku.hk