

[6/1/2020]

Lian-Sheng Ma,

Company Editor-in-Chief, Editorial Office

World Journal of Clinical Cases

Dear Dr. Lian-Sheng Ma,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "Liver injury in COVID-19: A minireview". (NO.: 56438).

Responds to the reviewer's comments:

Reviewer #1:

Response to comment: - First, in the paragraph re. the pathogenic mechanisms underlying the occurrence of liver disease, the authors should add this ref: Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int.* 2020 Mar 14. doi: 10.1111/liv.14435. [Epub ahead of print]

Response: the literature provided by the Reviewer was the reference[9] in our review. According to the suggestion, we have cited it in the part of pathogenic mechanisms underlying the occurrence of liver disease

Response to comment: - Nausea, vomiting, and diarrhea are the main gastrointestinal clinical manifestations of COVID-19. The incidence of liver injury in patients with COVID-19 with gastrointestinal (GI) symptoms were significantly higher than that in those without gastrointestinal symptoms (17.57% vs 8.84%, $p=0.035$)[8]. Please clarify the association between liver injury and GI symptoms

Response: we carefully read the literature we cited, both incidence of liver injury and rate of chronic liver disease in the in patients with COVID-19 with gastrointestinal (GI) symptoms were significantly higher than that in those without gastrointestinal symptoms, it might suggest that chronic liver disease increased the level of ALT and AST to aggravate the liver injury in the patients with COVID-19. Meanwhile, chronic liver disease was closely related to GI symptoms. Just as we expressed in the review.

Response to comment: - Please better explain why Liver injury in COVID-19 also varies based on geographical area and age of patients

Response: we re-explained in the review as "As the place where the outbreak of COVID-19 occurred, the number of patients in Wuhan surged which exceeded the existing capacity of treatment in the early stage. So a proportion of patients managed in Wuhan were severe and critical types whose the liver injury was significant. Compared with Wuhan, in other places, as Jiangsu province, the number of patients was fewer, and early detection and treatment made the liver injury mildly."

Response to comment: - Please clarify the sentence Thus, more attention should be given to pediatric patients, especially severe and critical patients as the course of COVID 19 disease has been reported to be milder in teh pediatric population

Response: thanks for the comment firstly, just as the data in our review and the point of reviewer, the course of COVID 19 disease was usually milder in teh pediatric population. The sentence "more attention should be given to pediatric patients, especially severe and critical patients" only emphasized to value the management of pediatric patients. To better express, we added the sentence as "Thus, the management of severe and critical pediatric patients should be valued."

Response to comment: - The authors should add a paragraph re. the outcome of COVID 19 infection in the liver transplant population (ref D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl. 2020 Mar 20. doi: 10.1002/lt.25756. [Epub ahead of print]; Bhoori S et al. Lancet gastroenterology and hepatology 2020]

Response: as the Reviewer said that discussion about the COVID-19 infection and liver transplantation patients would make the manuscript more comprehensive, so we added a paragraph searching some references including the literatures provided by the Reviewer above.

Response to comment: - . Individuals suffering from underlying diseases, such as chronic liver disease, are more likely to be infected by the SARS-CoV-2 as they have lower immune function. Please clarify this sentence as previous references (D'antiga and Bhoori) do not support the role of a lower immune function as a risk factor for a more severe COVID19 disease

Response: as for the relationship between the immune function and COVID-19 infection, references (D'antiga and Bhoori) suggested that, comparing with the general population, immunosuppressed patients did not increased risk of severe complications of COVID-19. However, in another hand, Asian-Pacific Association for the Study of the Liver (APASL) proposed a guideline which suggested that, because of immuno-compromise, it was more susceptible to COVID-19 infection for the patients with advanced cirrhosis, hepatic cell cancer (HCC), autoimmune liver diseases, and post liver transplantation, and they recommended that patients with liver cirrhosis/liver cancer/ on immunosuppressive therapy might be more susceptible to COVID-19 infection because of their systemic immune compromised status. Thus, further research is needed to identify the relationship between the immune function and COVID-19 infection.

Response to comment: - in the core tip please delete "Wearing masks, washing hands and staying alone is the importance to prevent the COVID-19 for the public." as not pertinent

Response: We have deleted this sentence just as the reviewer said that it was not pertinent.

Response to comment:- Yao et al.[10] found that the liver injury was only associated with critical type patients they concluded that a higher proportion of liver injury was detected in severe patients, and critical type was an independent risk factor for liver injury. Please edit by adding the missing verb

Response: We added ", and" to divide this sentence into 3 parts.

Response to comment: - Xi et al.[8] have reported the incidence of the severe and critical types was also significantly increased in patients with COVID-19 with GI symptoms than in those without GI symptoms (22.97% vs 8.14%, $p < 0.001$), indicating increased incidence of liver injury in severe and critical types. Please add reported THAT

Response: We added the missing word "that".

Special thanks to you for your good comments.

Reviewer #2:

Response to comment: A very important topic and it should be presented and discussed as much as possible. The authors should also mention the paper published by Cai Q and coauthors in J Hepatol 2020:1-9. Please include a table with summarized data related to Covid-19 and liver injury.

Response: we carefully read the literature provided by the Reviewer and added it in our review. Just as Reviewer suggested that a table summarized the data related to Covid-19 and liver injury could help readers to get through.

Special thanks to you for your good comments.

Response to Science Editor: thanks for your comments and recommendation. The "Author Contributions" section is at the top of the review.

Response to Editorial Office Director: thanks for your comments and recommendation.

Response to Company Editor-in-Chief: thanks for your comments firstly, we add a table summarized the data related to Covid-19 and liver injury and a figure of mechanism of liver injury which would make the manuscript easy to read.

We have studied reviewer's comments carefully and have made revision which marked in red in the paper. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind

consideration.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Ying Fan

Department of General Surgery,

Shengjing Hospital of China Medical University,

Shenyang City, Liaoning Province, People's Republic of China

Email: coolingpine78@163.com

Telephone: +86-18940258876