

Dear Reviewers and editors,

Thank you for giving us the opportunity to submit a revised draft of our manuscript- **“Clinical Implications of COVID-19 in Patients with Metabolic-Associated Fatty Liver Disease”**. We appreciate the time and effort that reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect the suggestions provided by the reviewers. We have highlighted the changes within the manuscript. Here is a point-by-point response to the reviewers’ comments.

Many thanks

Yours sincerely

Authors

Reviewer :1

1. “In contrast to hepatocytes, which comprise only 3% of the liver cells; most cells are cholangiocytes (60%) and endothelial cells, which express ACE2 receptors.” Really?

Answer:

We thank the reviewer for highlighting this sentence framework error. It should read as “In contrast to hepatocyte which are predominant liver cells, only 3% of them expresses ACE2 receptors but the 60% of the cholangiocytes expresses ACE2 receptors even though it occupies only 3% to 5% of the liver cell population.

Asemota J, Aduli F. The Impact of Nonalcoholic Fatty Liver Disease on the Outcomes of Coronavirus Disease 2019 Infection. *Clinical Liver Disease* 2022;19:29–31 [DOI: 10.1002/cld.1169]

2. Page 6: Two sections described that COVID-19 causes symptoms to appear in the upper respiratory tract, lung and gastrointestinal tract. What’s the relationship between these sections and MAFLD? It is very common that section content was disconnected with section title, and it was hard to find the logic and correlation between chapters, as well as between sections.

Answer:

Many thanks for highlighting this. We would like to retain the statements as even in MAFLD patient, the commonest symptoms are the respiratory and GI symptoms.

3. Page 20: Detection of ACE2 polymorphism. What’s the authors want to talk for putting this chapter here?

Answer:

Thank you for raising this question. Since the factors that contribute to excessive mortality and morbidity in MAFLD patient among different ethnic and genetic background is not full identified, we felt it is important to explain the ACE2 receptor polymorphism and potential contribution to additional disease burden in different ethnic burden. We have emphasised this at the end of the paragraph as follows- “These investigations ought to look into the morbidity and mortality hazards linked to COVID-19 and MAFLD in these racially varied genetic variants.”

4. Chapter - Clinical Interventions and Management: is there a necessity for this chapter? Too much general content focus on interventions of COVID-19, while too little content focus on COVID-19 + MAFLD patients. I did not see the specific intervention for COVID-19 + MAFLD patients, in such huge content but with limited significance.

Answer:

Many thanks for the reviewer comment. There is no specific available treatment to date for MAFLD patient with COVID, but we have now made Figure 2 which gives the choice of agents to be used in COVID-19 patients.

5. Too many long and obscure sentences throughout text.

Answer:

Thank you for the reviewer comments, we have altered the sentence structure wherever possible now.

Reviewer 2:

1. In Altered Liver Response section, lipid metabolism is affected by COVID-19. How about liver detoxification and protein synthesis?

Answer:

We thank the reviewer for raising this question. We have now included the following additional points in the text: “The liver detoxification is significantly impaired in the COVID-19 patient. In an autopsy study, looking at the transcriptome of the severe COVID-19 patient with non-covid patient, the cytochrome P450 gene – ACAD11, CIDEB, GNMT and GPAM are significantly down regulated. This consequently affects the detoxification of drugs and metabolite through the CYP 450 system. Liver is the powerhouse of the protein synthesis. It not only synthesis the anabolic proteins but also synthesis proteins involved in both innate and acquired immune response. This is very much reduced in MAFLD patient who are in a state of immune dysregulation but exact role of each component of hepatic immune dysregulation to covid-19 severity is difficult to delineate.”

Hammoudeh SM, Hammoudeh AM, Bhamidimarri PM, Mahboub B, Halwani R, Hamid Q, Rahmani M, Hamoudi R. Insight into molecular mechanisms underlying hepatic dysfunction in severe COVID-19 patients using systems biology. World Journal of Gastroenterology 2021;27:2850–70 [DOI: 10.3748/wjg.v27.i21.2850]

Martinez MA, Franco S. Impact of COVID-19 in Liver Disease Progression. Hepatology Communications 2021;5:1138–50 [DOI: 10.1002/hep4.1745]

2. It may be true that FIB-4 index negatively associated with COVID-19 prognosis. However, this did not reflect the impact of COVID-19 on the progression of MAFLD.

Answer:

We agree with this comment. However, there are no studies looking at the impact of FIB-4 score on COVID-19 associated MAFLD progression.

3. It is obscure in section of increased hepatic decompensation rates in cirrhotic patients, which conveyed the message that the cirrhotic patients with COVID-19 infection had higher probability developing hepatic decompensation than those without COVID-19.

Answer:

Many thanks for the reviewer’s comments. The sentence structure is now updated as follows to improve clarity.

“In a metanalysis of observational studies of COVID-19 infection with cirrhosis, the patient with cirrhosis not only has higher rate of decompensation but the odd for mortality is 2.48 (CI 2.2-3.04) when compared to the non-cirrhotic patients.”

Middleton P, Hsu C, Lythgoe MP. Clinical outcomes in COVID-19 and cirrhosis: a systematic review and meta-analysis of observational studies. *BMJ Open Gastroenterology* 2021;8:e000739 [DOI: 10.1136/bmjgast-2021-000739]

4. Inflammatory cytokines is associated with severity of COVID-19. Are those cytokines MAFLD-related.

Answer:

Since COVID -19 is associated with cytokine storm there is overlap of cytokines involved in both the disorders, however it will be difficult to point out that these are sole causative agent for hepatic decompensation in MAFLD as there are more factor in play than the cytokines alone. It is also interesting to note that MAFLD patient had a distinct cytokine profile with higher concentrations of IL-6, -8, -10, and IFN- β when compared to the patient without MAFLD. Higher the elevated of IL-8 and IL-10 is associated with worst prognosis and delayed time to recovery.

We have updated the manuscript to add the above important points.

Papic N, Samadan L, Vrsaljko N, Radmanic L, Jelcic K, Simicic P, Svoboda P, Lepej SZ, Vince A. Distinct Cytokine Profiles in Severe COVID-19 and Non-Alcoholic Fatty Liver Disease. *Life* 2022;12:795 [DOI: 10.3390/life12060795]

5. A significant proportion of patients with MAFLD present only with metabolic disorders without obesity. Only discussing obesity and COVID-19 seems to be off topic. As same as pre-existing MAFLD on COVID-19 disease severity.

Answer:

We thank the reviewer for their comment. We have also compared obese and non-obese MAFLD patient and their impact on the COVID-19 severity. Since most of the data available data with COVID-19 infection is in obese MAFLD patient and hence the article seemed to be focused only on obese MAFLD patient.

Reviewer 3:

1. Figure 1: The interplay between COVID-19 and metabolic-associated fatty liver disease (MAFLD). It is not possible to directly show its relevance through this picture. It is recommended to refine and enrich the contents of the picture.

Answer:

Many thanks for the reviewers comment about the Figure 1. We felt we need to keep the image focused with relevant to COVID-19 and MAFLD patient and at the same time did not want to add too many texts to the images making the reader difficult to understand. Hence the figure was kept focussed on the COVID-19 and MAFLD.

2. From the perspective of the writing structure of this question, the author aims to review the pathogenesis, diagnosis, and intervention strategies. However, as far as the mechanism part is concerned, it is redundant and recommended to simplify, while the treatment part should be updated and refined, and the summary should be more comprehensive.

Answer:

We thank the reviewer for this suggestion. We have updated the treatment section and added a new Figure 2 showing the choice of therapy for MAFLD patient with COVID-19 infection.

3. Through reading the full text, although the author has carried out a detailed literature search on the relationship between MAFLD and COVID-19, the summary and inspiration of the review still need to be further refined. Especially in the core tip part, at least I can't fully understand the central idea that the author wants to clarify and the inspiration that the article gives to readers from this passage. In my opinion, at the end of each subtitle of the article, there should be a summary and inspiration of the author's personal views.

Answer:

The summary and the authors perspective are added to the individual sections wherever possible now as per the reviewers' suggestions.

4. Some grammar and technical terms involved in the article need to be carefully considered.

Answer:

Thank you for the reviewer's suggestion and it is now corrected

Reviewer 4: This review is well written and generally meet the journal requirements. I just don't agree with the authors idea because the real state of the COVID-19 is hard to evaluate in some countries and that data from those country is not the real state of people.

Answer:

We thank the reviewer for their comments. We tried to search as much literature as possible to compile evidence on the status of COVID-19 in relation to MAFLD at this moment. We hope more data may emerge for the real state of affairs from all countries in future.

Reviewer 5:

1. Each drug or therapeutic of possible use, it would be preferable to describe its effectiveness, side effects and contraindications patients with significant underlying liver disorders.

Answer:

We thank the reviewer for raising this question. We have now made a new figure 2 which give the choice of treatment in COVID-19 infection with MAFLD and treatment modification needed when there is a degree of hepatic dysfunction.

2. Moreover, you need to detail the time of use (at what stage of infection by SARS Cov2 and in what clinical condition of liver disease)

Answer:

Many thanks for the reviewer for their comment. We have incorporated choice of agents at different time point and severity in the newly created Figure 2 as per the reviewer's suggestion.

3. In addition: Pag. 11: The list of the compound used to treat COVID-12 infection is not exhaustive (it is better to use a table with specific columns with comments and references). In addition, this table could also include any hepatotoxic or cytotoxic effects of the drugs.

Answer:

We thank the reviewer for raising this question. The reason we have left this as a list rather than as a paragraph so that the readers do not get distracted by too many table and hence we have added only the commonly used drug in the table 2 and their hepatotoxic effect. We wanted to limit the side effect to hepatic toxic effect as the article is focussed on the MAFLD patient.

4. Chloroquine: you should specify mechanism of action of inhibiting the SARS-CoV-2 entry into host cells (via the angiotensin-converting enzyme 2 (ACE2)).

Answer:

We thank reviewers for this question. We have already explained the mechanism of action of chloroquine and its effect on ACE-2 receptor in the page 22/23 of the main manuscript. In case if the review comment is about colchicine -we have not included in the article as the drug is banned by the infectious disease society of America(IDSA) updated 2022 guidelines for the used in COVID-19 patient. Hence, we have not included it in the main manuscript

5. In addition, it is useful to also clarify that chloroquine has been reported to cause damage to the CV system (with references).

Answer:

Many thanks for the reviewer comment. We have now added and highlighted this in the main manuscript. Chloroquine and hydroxychloroquine have known to cause QT prolongation due to delay in the depolarisation rate. There have been reports of patients developing torsades de pointes with use of chloroquine. Major studies, however, failed to demonstrate any alleged COVID-19 prophylactic and therapeutic benefit, and these medications have subsequently fallen out of favour due to their serious cardiovascular complication

Chiu MN, Bhardwaj M, Sah SP. Safety profile of COVID-19 drugs in a real clinical setting. *European Journal of Clinical Pharmacology* 2022;78:733–53 [DOI: 10.1007/s00228-021-03270-2]

6. Antiviral agents: you should explain their action mechanisms.

Answer:

We thank the reviewers for this comment. We have already explained mechanism of action of the important and most commonly used antiviral in the text and in table 3. We have now included a new figure – Figure 2 to explain the choice of these agents in the MAFLD patient affected with COVID-19 infection.

7. Pag. 12: Vaccines: You should explain if the vaccines currently used in these patients are equally immunogenic, compared to healthy people, and if they can induce further adverse effects in MAFLD people (red flags?).

Answer:

Many thanks for the reviewer for this suggestion. We have now updated this in the manuscript as below.

In a multicentric study from China, the inactivated vaccine induced adequate antibody titre against SARS-CoV-2 in 95% of the patient with MAFLD. The adverse event profile was similar to the individuals without MAFLD and hence vaccine is safe and equally immunogenic as in normal population.

Wang J, Hou Z, Liu J, Gu Y, Wu Y, Chen Z, Ji J, Diao S, Qiu Y, Zou S, Zhang A, Zhang N, Wang F, Li X, Wang Y, Liu X, Lv C, Chen S, Liu D, Ji X, Liu C, Ren T, Sun J, Zhao Z, Wu F, Li F, Wang R, Yan Y, Zhang S, Ge G, Shao J, Yang S, Liu C, Huang Y, Xu D, Li X, Ai J, He Q, Zheng M-H, Zhang L, Xie Q, Rockey DC, Fallowfield JA, Zhang W, Qi X. Safety and immunogenicity of COVID-19

vaccination in patients with non-alcoholic fatty liver disease (CHESS2101): A multicenter study. Journal of Hepatology 2021;75:439–41 [DOI: 10.1016/j.jhep.2021.04.026]

8. I also suggest to better explain the paragraph: COVID19 and liver biochemistry... (pag. 4)

Answer:

We thank the reviewer for this comment and the sentence structures is now modified to explain the concept better.

9. Moreover, there are little shape and formatting errors (e.g. pag 9: Patients with COVID-19: liver biopsy: lowercase character; liver biopsy: liver: lowercase character, etc.)

Answer:

Thank you for the suggestion, it is now corrected.

Company editor-in-chief

1. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Answer:

Thank you for the editor for this request. We have enclosed the PowerPoint file with decomposable figure

2. Please 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.

Answer:

Many thanks for the editor's suggestion and we have updated our table style to reflect the changes.

3. 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.

Answer:

The picture was created by the authors and hence “ ©The Author(s) 2022” has been added to the image as per authors suggestion in the PowerPoint included

4. Before final acceptance, when revising the manuscript, the author must 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 a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. 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

Answer:

The RCA for the corresponding author Professor Joseph M Pappachan is already in the WJG database.