

September, 2022

Name of journal: *World Journal of Virology*

Manuscript ID: 79362

Title: Covid-19-induced liver injury in adult patients: a brief overview.

Dear Editor of World Journal of Virology,

On behalf of the other authors and myself, I would like to extend my gratitude for the efforts and time spent reviewing our submission. The Reviewers makes excellent points and offer valuable suggestions to improve the manuscript. **Please find the responses in bold font under each of the comments made by the reviewer below, which can also be found in the revised manuscript:**

**Science Editor and Company Editor-in-Chief:**

1) *The manuscript has been peer-reviewed, and it's ready for the first decision.*

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

*Scientific Quality: Grade D (Fair)*

2) *I recommend the manuscript to be published in the World Journal of Virology. 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 at: <https://www.referencecitationanalysis.com/>. Before final acceptance, the author(s) must add a table/figure (medical imaging) to the manuscript. There are no restrictions on the figures (color, B/W).*

**We are grateful that the paper was transferred and for the possibility to be assessed by WJV. We have tried to address all issues raised by both Reviewers. A table summarizing the main issues has been added, as suggested.**

**We have found the RCA tool to be quite useful in preparing the modified manuscript. A total of 10 new citations have been included in the Reference sections. Mention of this tool has been added to the Materials and Methods section to read:**

**"We conducted a search of the literature published between January 1, 2011, to June 1, 2022, using PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and Reference Citation Analysis (<https://www.referencecitationanalysis.com>)."**

**Best regards,**

**Reviewer 1 (number ID: 06323770)**

*I commend the authors on creating a review of COVID-19 associated liver injury in adult patients. The review of literature required to create an informative review of this topic is extensive. I do have some overall comments as follows:*

**Many thanks for thorough review of our paper. As rightfully mentioned, this topic has extensive literature available on PubMed. The aim of our invited manuscript was to provide only a brief review of liver injury in COVID-19 patients, and not an extensive assessment of the current literature. We hope that our modifications can address all the important issues raised by the Reviewer.**

1) *Please ensure the abbreviations for SARS-CoV-2, COVID-19, and multiorgan are consistent throughout the manuscript.*

**Our apologies for the typing errors. The abbreviations have been checked and corrected throughout the paper.**

2) I do have concern that portions of the manuscript are word for word taken from the sources listed (see first paragraph of hepatotropism of COVID-19 in reference to source 13 and the reference made to source 18 in the subsequent paragraph for instance). This is not appropriate, any reference should be written in the authors own words.

**The paragraphs have been modified to avoid similarities with the original manuscripts.**

3) In other instances there is no reference listed when a reference should be provided (examples to follow in specific comments).

**Citations have been added throughout when lacking, as suggested.**

4) There are grammatical and spelling errors throughout the manuscript. For example immune-mediated should be used instead of immune "mediate". Wording needs to be more precise...For example "These two viruses show striking genetic similarity to the novel SARS-CoV2 and, therefore hepatic involvement in this is not entirely unexpected"...There is redundancy in using "in this"

**Grammar, wording and spelling have been checked and corrected accordingly.**

I do have some specific comments as follows: 1) Please remove liver transplant as a keyword.

**The keyword has been deleted.**

2) In the core tip the authors suggest it is important to "treat hepatic damage" when in the "Treatment section" they suggest that while liver enzyme elevation can occur it often does not need to be treated. This is an inconsistency that should be clarified.

**Mention regarding treating hepatic damage has been deleted in the core tip to avoid inconsistencies, as suggested.**

3) Please spell out total bilirubin completely before using the abbreviation "TBIL".

**The abbreviation has been defined.**

4) Please comment for completeness on the physical exam associated with liver injury as it pertains to the severity of disease in COVID-19. What symptoms do patients with COVID-19 liver disease have? Are there any unique features that may be of aide to clinicians? Right upper quadrant pain for example.

**Mention regarding symptomatology in patients with COVID-19 has been added, as suggested.**

5) The paragraphs under the "clinical presentation" section also include information regarding prognosis. I would recommend separating these into two different sections for clarity.

**The sections have been separated as suggested.**

6) Please provide references to the cases of sclerosing cholangitis in the clinical presentation section.

**Appropriate references have been added regarding sclerosing cholangitis.**

7) In the "clinical presentation" section, I miss discussion of AST elevation from myositis ( Panteghini M. Aspartate aminotransferase isoenzymes. Clin Biochem 1990;23:311-319.) 8) I miss discussion of ALP peak as it relates to prognostic significance 9) I miss discussion of using liver enzymes to discern community acquired pneumonia and COVID-19 in the clinical presentation section 10) Admission AST was positively correlated with ferritin in this study. Bloom PP, Meyerowitz EA, Reinus Z, Daidone M, Gustafson J, Kim AY, Schaefer E, et al. Liver biochemistries in hospitalized patients with COVID-19. Hepatology. 2021; 73: 890-900 [PMID: 32415860 DOI: 10.1002/hep.31326]. 11) Need a source for "About 10% of COVID-19 patients have shown elevated total bilirubin levels."

**Mention regarding the specific issues raised by the Reviewer with all the appropriate references have been included, as suggested.**

12) Please use "H1N1" instead of N1H1.

**The abbreviation has been corrected.**

13) In reference to the ADE in SARS-COV-2. The reference listed occurred before COVID-19. This was not in SARS-Cov2. The study you reference is from 2014 and refers to SARS-CoV. Please clarify if ADE also occurs with SARS-CoV-2.

**With regards to ADE in SARS-COV-2, a recent reference regarding SARS-CoV-2 from 2020 has been added, as suggested.**

14) "Raised hepatic enzyme levels have been reported in patients receiving lopinavir/ritonavir therapy (56.1% vs 25%)" Please clarify these percentages. The numbers you have listed were not provided for the findings in the article that is cited.

**This reference was incorrect and has been changed with the appropriate citation.**

15) Remdesivir is commonly utilized as well, please describe the impact of remdesivir on liver enzymes.

**Mention regarding remdesivir with an appropriate reference has been included.**

16) The proposed theory of micro thrombotic disease could be placed in the ischemia section for greater clarity under a new paragraph

**The paragraph regarding micro thrombotic disease has been reworded and improved, which has been placed as a new paragraph in the ischemia section, as suggested.**

17) "These chronic patients have been reported to have worse clinical outcomes when compared to patients without underlying liver diseases" this did not occur in patients with COVID-19. Please clarify if patients with chronic liver disease have worse clinical outcomes associated with COVID-19.

**The description regarding chronic liver disease patients with COVID-19 has been modified based on pertinent current references.**

18) "Studies have reported 47% of patients with cirrhosis and COVID-19 show AHD, which typically manifests as worsening ascites and encephalopathy" Please provide a reference to these studies. 19) Please provide a source for the findings of the SECURE-Cirrhosis and COVID-Hep registries

**Appropriate references for both have been added to support these statements.**

20) Please clarify what the authors mean by high-dose hormone therapy in relation to HBV.

**Details regarding hormone therapy have been added.**

21) "A prospective cohort study of 111 cases [62] showed that liver transplant patients had an increased risk of contracting SARS-CoV2 probably due to the chronic immunosuppression therapy"-> liver transplant patients were excluded from this cohort.

**The statement regarding the exclusion of liver transplant patients has been included.**

22) Please provide a source for the specific therapies listed..."polyene phosphatidylcholine, glycyrrhizic acid, ursodeoxycholic acid, and adenosylmethionine"

**Appropriate references have been added for the specific therapies listed in this section.**

23) Please clarify what the authors mean by "strengthening the respiratory system".

**The sentence has been reworded for better clarity to read:**

**"...the clinician should consider carefully managing the respiratory and circulatory support."**

24) Please provide specifics on acetaminophen dosing as it relates to elevation in liver enzymes associated with COVID-19. This will add practicality to the article.

**Specifics on acetaminophen with an appropriate reference has been added, as suggested.**

25) Future direction also appears to be needed in determining the long-term effect of COVID-19 induced liver injury..

**Mention regarding future direction has been added to this section.**

## **Reviewer 2 (number ID: 02567669)**

*The present manuscript is a good short review about types and pathogenesis of liver injury in COVID-19 aimed for the clinician..*

**Many thanks for the positive remarks regarding our paper. We hope that our modifications can address all the important issues raised by the Reviewer.**

*I have some concerns: It is a known problem with a manuscript that only consists of written text without Figures or Tables, that it lacks any eye-catcher. For a better understanding of the main issues I suggest to add e.g. a Figure which depicts the localization of the receptor (ACE2) and coreceptor inside the sinusoids. A table summarizing the main issues could be helpful, as well.*

**A table summarizing the main issues has been added, as suggested.**

*Are there any ideas when a hepatocellular type damage is found (amiotransferases) and when a cholestatic type? Is high AST an indicator of hepatocellular damage? Or rather lung damage or hemolysis?*

**Mention regarding elevated AST levels with appropriate references have been added.**

*In the chapter "drug induced injury" the authors should discuss the potential hepatotoxic effects of newer antiviral drugs, e.g. Paxlovid, Remdesivir, among others.*

**The effects of newer antiviral drugs with appropriate references have been included.**

*Could the endothelial damage with thrombophilic state contribute to liver damage?*

**Mention regarding endothelial damage and thrombotic disease have been added.**

*I COVID-19 a trigger of autoimmune liver diseases, such as AIH or PBC? Clinicians who deal with autoimmune liver disease know that an unspecific infection may induce a flare of these diseases. Besides, SARS-Cov2 can indeed induce several types of autoimmune disease or autoimmune phenomena.*

**Mention regarding autoimmune disease has been included, as suggested.**

**The valuable comments and assistance with our paper is greatly appreciated. We look forward to your final decision regarding our modifications, with hopes that all concerns have been addressed in an appropriate manner.**

**Kind regards,**

**Grando Martina, Balbi Massimiliano, and Zeppieri Marco**