

PEER-REVIEW REPORT

Name of journal: *World Journal of Virology*

Manuscript NO: 79362

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

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02567669

Position: Editorial Board

Academic degree: MD

Professional title: Emeritus Professor

Reviewer's Country/Territory: Germany

Author's Country/Territory: Italy

Manuscript submission date: 2022-08-17

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-08-17 11:13

Reviewer performed review: 2022-08-26 09:58

Review time: 8 Days and 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The present manuscript is a good short review about types and pathogenesis of liver injury in COVID-19 aimed for the clinician.. 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. Are there any ideas when a hepatocellular type damage is found (aminotransferases) and when a cholestatic type? Is high AST an indicator of hepatocellular damage? Or rather lung damage or hemolysis? In the chapter "drug induced injury" the authors should discuss the potential hepatotoxic effects of newer antiviral drugs, e.g. Paxlovid, Remdesivir, among others. Could the endothelial damage with thrombophilic state contribute to liver damage? Is 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

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Position: Peer Reviewer

Academic degree: DO

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: Italy

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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: 1) Please ensure the abbreviations for SARS-CoV-2, COVID-19, and multiorgan are consistent throughout the manuscript. 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. 3) In other instances there is no reference listed when a reference should be provided (examples to follow in specific comments). 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" I do have some specific comments as follows: 1) Please remove liver transplant as a keyword. 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. 3) Please spell out total bilirubin completely before using the abbreviation "TBIL" 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. 5) The paragraphs

under the "clinical presentation" section also include information regarding prognosis. I would recommend separating these into two different sections for clarity. 6) Please provide references to the cases of sclerosing cholangitis in the clinical presentation section. 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." 12) Please use "H1N1" instead of N1H1. 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. 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. 15) Remdesivir is commonly utilized as well, please describe the impact of remdesivir on liver enzymes. 16) The proposed theory of micro thrombotic disease could be placed in the ischemia section for greater clarity under a new paragraph 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. 18) "Studies have reported 47% of patients with cirrhosis and COVID-19 show AHD, which



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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 20) Please clarify what the authors mean by high-dose hormone therapy in relation to HBV. 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. 22) Please provide a source for the specific therapies listed..."polyene phosphatidylcholine, glycyrrhizic acid, ursodeoxycholic acid, and adenosylmethionine" 23) Please clarify what the authors mean by "strengthening the respiratory system" 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. 25) Future direction also appears to be needed in determining the long-term effect of COVID-19 induced liver injury.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's Country/Territory: United States

Author's Country/Territory: Italy

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

I congratulate the authors on their work! I have no further questions or comments.

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SPECIFIC COMMENTS TO AUTHORS

The authors have addressed all relevant issues. The manuscript can be accepted