

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO.:** 62286

**Title:** Patients with cirrhosis during the COVID-19 pandemic: Current evidence and future perspectives

**Authors:** Hung-Yuan Su and Yin-Chou Hsu

Dear Editor:

Thank you very much for offering us the opportunity to improve our manuscript. We are now submitting the revision. Changes have been made in accordance with the reviewers' suggestions. We have addressed all the comments raised by the reviews, and the amendments are highlighted in our revised manuscript. We hope the revised version will meet the criteria for publication in your journal.

Sincerely,

Yin-Chou Hsu

#### **Editor's comments**

##### **Comment 1**

The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>

##### **Response 1**

Accordingly, we have entrusted Springer Nature Author Services with re-editing our revised manuscript to ensure the quality of the language. We thank you for this helpful comment.



##### **Comment 2**

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 indicating the reference source and copyrights

##### **Response 2**

Thank you for this insightful comment. We reproduced our entire figure from diversified sources: the images of the liver and blood vessels were purchased from the iStock illustrations gallery (the invoice is shown below); the image of SARS-CoV-2 was freely downloaded from the Innovative Genomics Institute (<https://innovativegenomics.org/free-covid-19-illustrations/>); the image of the

pills was downloaded from the Vecteezy free pictures gallery (<https://www.vecteezy.com/vector-art/658720-contour-pharmaceutical-pill-capsules-treatment>); other images were drawn in Microsoft PowerPoint.

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### Comment 3

Authors should always cite references that are relevant to their study. Please check and remove any references that not relevant to this study.

### Response 3

In accordance with this suggestion, we have checked all references and removed irrelevant references from our revised manuscript.

**Reviewer 1****Comment 1**

The data presented as the authors mentioned were expected in regards to the general population, however, the manuscript would have more impact when it addresses the specificity of the impact of covid-19 on cirrhotic patients vs. other pathologies and particularly those with immune system disturbances.

**Response 1**

We thank you for this insightful comment. Whether immunocompromised patients with COVID-19 have a higher mortality risk remains controversial. Patients with cancer or solid organ transplant recipients may have an increased risk of more severe COVID-19, whereas patients taking biologic therapies may not have a greater risk of severe COVID-19 (M Fung et al, Clin Infect Dis. 2021;72(2) 340-350). In a recent meta-analysis of patients with cancer and COVID-19, active cancer treatment (e.g., surgery, immunotherapy, target therapy, radiotherapy) did not increase the risk of death except chemotherapy (E Yekedüz et al, Eur J Cancer. 2020 Dec;141: 92–104). It is unknown whether patients with human immunodeficiency virus infection and COVID-19 have a higher risk of severe disease (M Fung et al, Clin Infect Dis. 2021;72(2) 340-350, K Bhaskaran et al, the Lancet HIV. 2021 Jan;8(1): e24-e32, D Dandachi et al Clin Infect Dis. 2020 Sep 9). Compared with studies in other immunocompromised populations, studies involving patients with cirrhosis and COVID-19 revealed consistent conclusions: the presence and severity of cirrhosis were correlated with COVID-19 severity, adverse outcomes, and mortality. We have added these descriptions to the "Introduction" section.

**Comment 2**

The sections of the manuscripts would better present the subject by addressing within the following order epidemiological, clinical, mechanisms of liver injuries, outcomes and therapeutic strategies.

**Response 2**

Accordingly, we changed the order of the sections as follows: epidemiology, clinical characteristics, liver injury mechanisms, clinical outcomes and management strategies. We thank you for this professional comment.

**Comment 3**

The figure 1, which doesn't show A and B parts, do not provide any specific information in regards to normal situation and cirrhosis. Information in both

parts seems duplicated and need to be revised to improve and provide details which helps distinguish both situations.

### **Response 3**

We thank you for this helpful comment. We combined the two figures into a single figure and labeled them A. normal liver and B. cirrhotic liver. The putative mechanisms underlying COVID-19-related liver injury are direct virus injury, immune system activation, drug-related liver injury, pre-existing liver disease activation and hypoxic hepatitis. The cirrhotic livers are considered to be more vulnerable to virus injury because of widespread ACE2 receptor expression; they also have increased circulating cytokine levels, stronger immune system activation and stronger pre-existing liver disease activation and hypoxic damage, thus leading to more severe liver injury. The arrows in the figure indicate the magnitude of each effect on the liver. We have added the associated descriptions to the figure legends.

### **Comment 4**

In page 1, all authors should read both authors.

### **Response 4**

Accordingly, we changed all authors to both authors.

### **Comment 5**

In page three, the authors mentioned that few studies have focused on the impact of SARS-COV2 in patients with cirrhosis although the manuscripts cited several studies.

### **Response 5**

We have rephrased the sentence to avoid misunderstanding. We thank you for this valuable comment.

### **Comment 6**

In page 5, 2nd paragraph, "...including 1.7 million cases with mortality" should read "...including 1.7 million cases of mortality"

### **Response 6**

We have corrected this mistake. We thank you for this comment.

### **Comment 7**

In page 7, the sentence: Fulminant cytokine storms can release multiple proinflammatory cytokines and inflammatory markers, including IL-1 $\beta$ , IL-6, IL-8, IL-17, interferon- $\gamma$ , granulocyte-colony stimulating factor and tumor necrosis

factor- $\alpha$ , in patients with severe COVID-19[45, 52, 53]. Should start with: In patients with severe COVID-19, fulminant...

#### **Response 7**

We have rephrased the sentence in accordance with the suggestion.

#### **Comment 8**

Tables 1 and 2 exhibit duplication of the information of the number of patients and the references. The authors may use one landscape table where all information could be included.

#### **Response 8**

We thank you for this professional comment. We tried to use one table to include all information in our original manuscript, but it far exceeded the two page limit in the journal guidelines; and we thought that this information was very important and was not suitable for presentation as supplementary material. Therefore, after consideration, we divided the one table into two tables: table 1 addresses the clinical characteristics of cirrhotic patients infected with SARS-CoV-2, including their cirrhosis severity, acute decompensation events and proportion with acute-on-chronic liver failure; and table 2 addresses the severity and outcomes of COVID-19. Again we thank for this valuable comment.

## **Reviewer 2**

### **Comment 1**

In the section of “direct pathogenic virus cytotoxicity”, the authors mentioned that in the normal human liver, the distribution of ACE2 receptors is particularly high in bile duct epithelial cells. Bile duct chemistry parameter (alkaline phosphatase,  $\gamma$ -glutamyl transferase) should elevate significantly. However, in clinical practice, elevation of liver chemistry profiles is common, rather than bile duct enzymes. How to explain it, especially in patients with cirrhosis and COVID-19?

### **Response 1**

We thank you for this professional comment. COVID-19-related liver injury in patients with cirrhosis is multifactorial (e.g., direct pathogenic virus injury, systemic immune system activation and cytokine storms, drug-related liver injury, pre-existing liver disease activation, and hypoxic hepatitis), and hypoxia or drug-induced liver injury (inducing more prominent liver biochemical elevations) was presumed to play a more important role in patients with cirrhosis and COVID-19 in a previous clinical study (SK Sarin et al, *Hepatology* 2020 Jul 4;1–11). Furthermore, a previous basic study regarding SARS-CoV-2 infection-related pathological manifestations demonstrated differences in ACE2 expression in SARS-CoV-target organs and showed, viral replication in the colonic epithelium, which has no ACE2, and no viral infection in endothelial cells, which have ACE2. Therefore, the localization of ACE2 may not fully explain the liver tropism of SARS-CoV-2 (Y Wang et al, *J Hepatology* 2020 Oct; 73(4): 807–816.). We have added the associated descriptions to the “clinical characteristics” section. Again we thank you for this comment.

### **Comment 2**

In the section of “Drug-induced liver injury”, besides antiviral agents, antibiotics, and corticosteroids, Chloroquine and hydroxychloroquine may also lead to drug-induced liver injury. It's suggested to add it.

### **Response 2**

Accordingly, we have added descriptions of chloroquine- and hydroxychloroquine-related liver injury to the “Drug-induced liver injury” section. We thank you for this helpful comment.

**Comment 3**

In the section of “Reactivation of pre-existing liver disease”, I suggest to increase HBV reactivation caused by glucocorticoid.

**Response 3**

In accordance with this suggestion, we have added descriptions regarding glucocorticoid-related HBV reactivation to the “Reactivation of pre-existing liver disease” section. We thank you for this valuable comment.

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Reviewer 1

Comment 1

The authors made a good revision, and I agree to accept the manuscript.

**Response 1**

We thank you for this encouraging comment.