

November 7, 2022

Covering letter for R1 version

Professor Andrzej S. Tarnawski, DSc, MD, PhD, Editor-in-Chief
World Journal of Gastroenterology

Dear Prof. Tarnawski:

Thank you very much for having considered our manuscript (Manuscript NO: 79690). I am very pleased to see the constructive comments of reviewers. I fundamentally agree with all these comments and incorporated them to the R1 version. Orange indicates the parts that I changed according to Reviewer #1. Red indicates the parts that I changed according to Reviewer #2. Blue indicates the parts that I changed according to Reviewer #3. Green indicates the parts that I changed according to Reviewer #4. I also deleted some redundant parts, which I described in the "Response to Reviewers" section. The native medical profession and I linguistically checked the manuscript once again, and I changed or deleted very small parts. They are very trivial points (some words or a single sentence) and thus I did not indicate them to avoid complexity. Otherwise, I did not touch the original manuscript.

Due to the incorporation of Reviewer's advice, volume of the R1 version little expanded. Sorry for this.

I hope that you would evaluate this R1 version positively.

Response to Reviewers

Orange indicates the parts that I changed according to Reviewer #1. Red indicates the parts that I changed according to Reviewer #2. Blue indicates the parts that I changed according to Reviewer #3. Green indicates the parts that I changed according to Reviewer #4. According to these changes, I added some sentences to make the context clear, which are indicated in green.

To Reviewer #1

Thank you very much for giving me good advice. I agree with you and have incorporated this advice to R1 version (orange color).

1. The phrase “uncompensated cirrhosis” should be replaced with “decompensated cirrhosis”.

We agree. We replaced “uncompensated cirrhosis” to “decompensated cirrhosis” (Page 8, line 16 and 21, in orange color).

To Reviewer #2

Thank you very much for giving me good advice. I agree with you and have incorporated this advice to R1 version (red color).

1. The article describes the convenience of the COVID-19 vaccine in chronic liver disease in great detail. But the author’s own opinions are too few, and he needs to add his own opinions.

We agree. We added a new "DISCUSSION" section for our own opinions (Page 21, line 6-24, in red color).

Moreover, we added new sentence “However, the number of patients described in previous reports^[87-109] (Table 3) is extremely small compared with the overall vaccinated population worldwide. The current review, thus, aimed to increase awareness about this rare adverse effect in order to promote its early recognition.” (Page18, lines 26 and Page 19, line 1-3, in red color)

2. Please add some pictures if you can.

Thank you for reviewer’s comment. We added new picture to explain the mechanism of the development of immune cross-reaction after vaccination (Figure 1). Moreover, we described the new figure legend (Page 38).

3. As for the quoted experimental conclusions, we should analyze the experiments and point out their advantages and disadvantages to make the quoted conclusions more reliable.

We agree. We described new sentences “It should be noted that most of the reports in Table 2 do not take into account the influence of the omicron variant, which is a limitation of using previous data in the current clinical environment of omicron variant predominance.” (Page 10, lines 20-22, in red color) and “The limitations of these studies^[50,71-73], however, include a relatively small sample size of participants

who received the vaccines and a short follow-up period. Research with larger sample sizes is, thus, required in the future.” (Page 12, lines 10-12, in red color)

To Reviewer #3

Thank you very much for giving us good advice. I agree with all your advices and incorporated them to R1 version (blue color).

1. Dear authors, can you add a brief definition of chronic liver disease?

Thank you for pointing that out. We described the definition of chronic liver disease. We added new sentences “Chronic liver disease (CLD) is characterized by the gradual destruction of liver tissue over time, and includes liver diseases that are caused by chronic inflammation (chronic viral hepatitis, non-alcoholic fatty liver disease [NAFLD], alcoholic liver disease, and autoimmune hepatitis [AIH]) with or without cirrhosis and hepatocellular carcinoma (HCC).” in INTRODUCTION section (Page 4, lines 11-15, in blue color).

2. These shortcuts HR, CI can be explained for the better understanding of an ordinary reader.

We agree. We have defined the abbreviations (HR, CI, and OR) in INTRODUCTION section (Page 4, line 19, and Page 9, line 10, in blue color).

3. Any explanation to high mortality rate in patients with cirrhosis, chronic liver disease?

Thank you for reviewer’s comment. We added the new sentence “Patients with CLD, particularly those with cirrhosis, have multiple mechanisms of immune dysfunction that can lead to increased susceptibility to SARS-CoV-2 infection and an abnormal inflammatory response during infection.” to explain why mortality rate in cirrhosis is increased. (Page 8, lines 23-26, in blue color)

4. Is there explanation or hypothesis to this?

Thank you for your comment. We added the new sentence “Patients with NAFLD have decreased hepatic innate immunity with skewed M1/M2 macrophage polarization, as well as increased levels of inflammatory mediators and cytokines. This underlying inflammatory status associated with NAFLD might lead to further exacerbation of the SARS-CoV-2 infection and can lead to a cytokine storm, which greatly increases the

mortality rate^[37].” to explain why COVID-19 is more severe in NAFLD. (Page 9, lines 12-16, in blue color)

5. Can this title be changed to Liver cirrhosis patient’s response to vaccination?

Thank you for reviewer’s comment. I changed the title from “*Liver cirrhosis*” to “*Response to vaccination in liver cirrhosis patients*”, according to reviewer #2 and language editor.

To Reviewer #4

Thank you very much for giving us good advice. I agree with all your advices and incorporated them to R1 version (green color).

1. Describe the mechanism in more detail.

I agree with you. I described the mechanism of liver injury after COVID-19 vaccination in more detail (Page 20, line 9-24, in green color). In addition, we cited new references (120-124).

I believe that incorporating your advice into R1 version has made the manuscript better. Thank you once again.

Sincerely yours,

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