Dear editor Lian-Sheng Ma, Dear reviewers,

Thank you for your letter dated December 28. We were pleased to know that our manuscript was rated as potentially acceptable for publication in Journal after appropriate revision. We thank the reviewers for the time and effort that they have put into reviewing the previous version of the manuscript. Their suggestions have enabled us to improve our work. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript with all the changes highlighted by using the track changes mode in MS Word.

Appended to this letter is our point-by-point response to the comments raised by the reviewers. The comments are reproduced and our responses are given directly afterward in a different color (red).

We would like also to thank you for allowing us to resubmit a revised copy of the manuscript.

We hope that the revised manuscript meets the requirements for final acceptance and publication in the World Journal of Gastroenterology.

Sincerely,

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Responds to the reviewer's comments:

Reviewer#1

The article fulfills the conditions publication and confirms initial reports of literature in more consistent manner. That are important in disease management.

Response: We thank you for the time and effort that you put into reviewing our manuscript. We really appreciate your comments.

Reviewer#2

Comments to the author

1. Thank you for asking me to review this manuscript. The authors conducted a retrospective cohort study of 440 patients with severe COVID-19 in early 2020 in Wuhan, China, to evaluate COVID-19-related liver injury, and identified several risk factors for liver injury due to COVID-19. I have no major concerns about the methodology of this study. However, I find the authors' conclusion that liver injury inherently worsens survival in COVID-19 questionable and would ask them to justify it more. Predictors of liver injury in COVID-19 have been studied already (PMID 32710250, 32725890, 32283325) including in patients with severe disease (I do not think the authors' comment that "most of the current studies aimed at patients with mild illness", line 124, is fair). That said, this study does go into more detail about some other predictors of liver injury including medications and supplements.

Response: Thank you for your sincere advice on our manuscript. We conduct a retrospective study and track the dynamic variation of liver function. Univariable and multivariable Cox proportional hazard regressions were used for the survival analysis associated with liver injury markers and other risk factors for mortality. After adjusting for bias, we discovered the definite statistical association between liver injury and mortality. Although we got some positive results, we were not sure of "inherently". The causal relationship between COVID-19 and liver injury still needs further animal experiments to demonstrate. We suppose you are right, the word "inherently" is not very appropriate here.

As your rightly said, the wording "most of the current studies aimed at patients with mild illness" is a little bit inappropriate here. There are indeed some studies on liver injury in patients with severe disease, however, our literature also has its own advantages and uniqueness. There are 2 main points.

1. We combed the literatures in the “Pubmed” database since the onset of the disease (a total of 41 literatures updated to the middle of November when we submitted the manuscript). The severity of COVID-19 was not graded in part of the literatures.
2. Among all of the literatures with graded data on disease severity, our study had the highest proportion of severe and critical cases.

Thank you for pointing out the question, we have modified the sentence according to your comment **(line 125).**

2. Hepatoprotective medications: can the authors clarify whether these were taken before admission vs. during admission? I find this association surprising as this effect is very large. Could it be it is a proxy for income, adherence to healthcare maintenance, etc.?

Response: Thank you for putting forward a very interesting question. A total of 114 patients used hepatoprotective medications during the whole treatment. Two of them had used the drugs before admission and the rest 112 patients used the drugs on and after admission.

Most of the medical services provided by the Chinese government in this epidemic are free of charge. However, during the initial stage of epidemic, doctors had little guidance on the treatment of the epidemic. The uses of hepatoprotective medications were probably related with the different principles in different hospitals. Different views and understandings on liver protection among doctors were other possible reasons. Therefore, it seems that the usage of hepatoprotective medications has no direct relevance to income and adherence to healthcare maintenance during this special period.

3. The authors refer to “individualized tailored surveillance” and also devoted a paragraph to prevention of liver injury (lines 393-402). However, they do not provide evidence that liver injury causes clinically-relevant injury such as ascites, encephalopathy, etc., or that it increases mortality. My opinion is that liver injury in COVID-19 just reflects disease severity, and my reading of the literature is that in patients without advanced liver disease, COVID-19 does not cause liver decompensation. Of course, the authors are welcome to disagree, but I would ask for more justification on why it matters that some patients have elevated liver enzymes. I’m not sure that the hepatoprotective medication argument is sufficient.

Response: Thank you for the suggestion. We did not pay attention to the further manifestations of liver

injury (clinically-relevant injury) when we defined liver injury. In the initial stage of epidemic, we cannot do abdomen ultrasound scans or consultations from neurology department for all our patients because of the finite medical resources. There is a limitation that we do not have enough means to estimate the clinically relevant injury. Nonetheless, the laboratory indicators are still very objective and easy to obtain. Thus, we have added this point in the discussion **(line 411)**.

We agree partially with the reviewer's opinion. Liver injury occurs more frequently in severe cases and reflects diseases severity. We suppose liver decompensation often accompanies by serious liver injury as well. Our study reports that the elevation of liver enzymes is really important.

1. LBAI is associated with an increased risk of in-hospital mortality.
2. Even the dynamics variations of liver function monitor the risk of in-hospital mortality.

As a result, the elevation of liver enzymes aggravates the state of COVID-19 and reflect the poor prognosis to some degree. As for the usage of hepatoprotective medications, we found that hepatoprotective medication improved prognosis of patients with liver injury statistically.

However, the evidence we have is not quite sufficient.

1. The number of cases we got was not quite sufficient.
2. The classification of liver injury is rather superficial.

We intend to cooperate with other medical teams and increase the sample volume so that we can investigate whether the poor prognosis caused by liver injury could be improved by hepatoprotective medications.

Minor comments:

1. Lines 341-342: "It is now thought that COVID-19 itself is a likely cause of liver injury", I agree that direct infection by SARS-COV-2 can occur but it may not be the dominant cause of liver disease. Would clarify this statement as this paragraph may otherwise be misleading.

Response: Thank you for underlying this deficiency. The association between COVID-19 and liver injury still remains to be discussed. We cannot demonstrate the main cause of liver injury with only clinical data, and we believe it is of great importance to conduct further study to determine the causality between COVID-19 and liver injury. To avoid misleading readers, we have modified the sentence according to your suggestion **(line 341)**.

2. The authors collected data through March 2020. Would recommend updating the follow-up date

as that was >9 months ago and some of these patients may have died since then. I would at least report mortality within 90 days of diagnosis.

Response: We suppose your suggestion is very good, and the follow-up time is indeed a limitation. However, only 38 of the 440 patients did not get definite survival results at the end of follow-up, and they were all taken into consideration during statistical analysis. We censored these data in our COX model and the remaining data still met the statistical efficiency. The current trend proved to be related to mortality. The follow-up time might be a limitation, yet nonetheless, the design of our study is not a big issue. Next, we would obtain some extra data from several medical teams so that we can not only increase our sample volume but also extend observation time. Except for the mortality, the impact of the disease on patients' life such as running, climbing, etc, will be included in the study by then.