Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Soluble Mannose Receptor as a Predictor of the Prognosis for Hepatitis B Virus-related Acute-on-Chronic Liver Failure" (tracking number 50347). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have read the comments carefully and have made correction which we hope meet with approval. Revised portions are marked in red with track changes. In addition, it should be noted that we add Dr. Kai Yang and Hao Zhang as coauthors for their contribution to the statistical analysis of the study. The main corrections in the paper and the responses to the reviewers' comments are as following:

Reviewer #1 (number ID:02446627)

The authors have done a good job in addressing the role of Mannose receptor in the Hepatitis B virus acute on chronic infection. Needs minor Language polishing.

Response: Thanks for the reviewer's comment and suggestion. The language polishing of our manuscript has been completed by the relevant company.

Reviewer #2 (number ID:02528812)

1) In selecting the cases, how exactly a diagnosis of HBV-ACLF was made?

Response: Thanks for the reviewer's question. The diagnosis of HBV-ACLF was based on the consensus definition of the Asian Pacific Association for the Study of the Liver (2014 version)[1], as follows: Acute hepatic insult manifested as jaundice (serum bilirubin ≥ 5 mg/dL or 85 μmol/L) and coagulopathy [international normalized ratio > 1.5 or prothrombin activity < 40%], complicated within 4 weeks by ascites and/or encephalopathy in a patient with CHB. We have added the diagnostic criteria in our

manuscript.

2) How about baseline fatty liver disease, cirrhosis or alcohol liver disease? Information regarding these baseline conditions is better to be included in the manuscript to evaluate if they have any effect on the levels of soluble mannose receptor. Authors better mention if the cases with these baseline conditions were excluded in the study.

Response: Thanks for the reviewer's question and suggestion. In our study, the patients with liver failure caused by cirrhosis, other hepatitis virus infections or coinfections, alcoholic liver disease or a nonalcoholic fatty liver, and hepatotoxic drugs were excluded. So we didn't evaluate if these baseline conditions have any effect on the levels of soluble mannose receptor.

3) Authors should provide the Core Tip after the Abstract section.

Response: Thanks for the reviewer's suggestion. We have added the Core Tip after the Abstract section in our manuscript.

Reviewer #3 (number ID:02541859)

Nice study. Only comment is many acute Hepatitis B has concomitant Hepatitis D infection. Was that excluded in the study?

Response: Thanks for the reviewer's comment and question. In our study, the patients with liver failure caused by other hepatitis virus infections or coinfections were excluded.

Reviewer #4 (number ID:03724099)

1) Since the study is primarily in relation to acute on chronic liver failure - the authors should elaborate on how a diagnosis of ACLF was made?

Response: Thanks for the reviewer's question. The diagnosis of HBV-ACLF was based on the consensus definition of the Asian Pacific Association for the Study of the Liver (2014 version)[1], as follows: Acute hepatic insult manifested as jaundice (serum bilirubin ≥ 5 mg/dL or 85 μmol/L) and coagulopathy [international normalized ratio > 1.5 or prothrombin activity < 40%], complicated within 4 weeks by ascites and/or encephalopathy in a patient with CHB. We have added the diagnostic criteria in our manuscript.

2) It is unclear at what time during hospital admission was sample collected for sMR estimation and if that plays in role in the level.

Response: Thanks for the reviewer's comment. In our study, the blood samples of the patients were collected at the time of the HBV-ACLF or CHB diagnosis. In the future, we will supplement the experiment to study the dynamic changes in the serum sMR during the progression of HBV-ACLF.

3) The authors should report use of sMR in other liver disease including alcohol liver disease in their discussion.

Response: Thanks for the reviewer's suggestion. We had reported use of sMR in other liver disease including alcohol liver disease in the introduction of our manuscript, so we didn't report use of sMR in other liver disease including alcohol liver disease in the discussion.

4) It is also unclear if the patients with ACLF had baseline cirrhosis and if that has an effect on levels of sMR.

Response: Thanks for the reviewer's comment. In our study, the patients with liver

failure caused by cirrhosis, other hepatitis virus infections or coinfections, alcoholic liver disease or a nonalcoholic fatty liver, and hepatotoxic drugs were excluded. So we didn't evaluate if these baseline conditions have any effect on the levels of soluble mannose receptor.

Editors

Response:

1. We have revised all the duplicated parts according to the CrossCheck report uploaded by the editor.
2. We have added a running title as "Predictor of the prognosis for HBV-ACLF" in the title page.
3. We have added ORCID number of all authors in the title page.
4. We have added institutional review board statement in the title page.
5. We have added informed consent statement in the title page.
6. We have added data sharing statement in the title page.
7. We have modified the content of "METHODS" in the abstract accordingly.
8. We have added one keyword in the abstract accordingly.
9. We have added the Core Tip after the Abstract section in our manuscript.
10. We have submitted an audio core tip whose format is mp3 on the system (File name: 50347-Audio core tip.mp3).
11. We have added the diagnostic criteria of HBV-ACLF in our manuscript.
12. We have changed all the abbreviations to their full names in the title of all the figures and "Table 2".
13. We have provided figures whose parts are all movable and editable, organized them into a PowerPoint file, and submitted as "Manuscript-50347-figures.ppt" on the system.
14. We have explained all the abbreviations in the "Figure 5" legend.
15. We have modified the superscript of the P value accordingly.
16. We have added article highlights accordingly.

17. We have checked and confirmed that there are no repeated references; we have added PMID to reference 7 and reference 12 ; We have provided the first page of all the references without PMID and DOI; and we deleted the PMCID of reference 1, 3, 5, 9, 14, and 16.

Reference:

1. Sarin SK, Kedarisetty CK, Abbas Z, Amarapurkar D, Bihari C, Chan AC, Chawla YK, Dokmeci AK, Garg H, Ghazinyan H, Hamid S, Kim DJ, Komolmit P, Lata S, Lee GH, Lesmana LA, Mahtab M, Maiwall R, Moreau R, Ning Q, Pamecha V, Payawal DA, Rastogi A, Rahman S, Rela M, Saraya A, Samuel D, Saraswat V, Shah S, Shiha G, Sharma BC, Sharma MK, Sharma K, Butt AS, Tan SS, Vashishtha C, Wani ZA, Yuen MF, Yokosuka O, Party AAW. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014; 8(4): 453-471 [PMID: 26202751 DOI: 10.1007/s12072-014-9580-2]

Your help and assistance is highly appreciated and I am looking forward to hearing from you.

Best regards

Yours sincerely,

Shi-He Guan, MD, PhD, Full Professor