

March 17, 2022

Dear Editor,

Please find enclosed the edited manuscript in Word format (**file name: 74833_Auto_Edited.docx**)

Title: Review of clinical characteristics, immune responses and regulatory mechanisms of hepatitis-E-associated liver failure

Authors: Chong Chen, Shuye Zhang, Liang Chen

Name of Journal: World Journal of Clinical Cases

Manuscript NO: 74833

Thank you for reviewing our manuscript. The reviewers' questions and editors' suggestions are very important and valuable to this work. We are pleased to resubmit the new version of the manuscript now. Reviewers' specific concerns were carefully addressed in the following response letter. To improve the manuscript, we have also made changes according to the editorial comments and requested the language editing service which would make this article more readable and understandable. In addition, for the convenience, we have highlighted the major modified points in yellow. We hope now that the revision is acceptable and look forward to hearing from you soon.

Thank you again for all the efforts in processing this manuscript and considering to publish it in the World Journal of Clinical Cases.

Yours sincerely,

Prof. Liang Chen

Address: Shanghai Public Health Clinical Center, Fudan University
2901 Caolang Road, Jin-Shan District, Shanghai 201508, P.R. China.

Tel: +86-(21)-37990333-8357;

Fax: +86-(21)-37990333-5273;

E-mail: chenliang@shphc.org.cn

Answers to Specific Comments:

Reviewer code. 05965419

The English writing of the manuscript is terrible. It is really strenuous to read an article like this. Tons of grammar/spelling mistakes throughout the manuscript need to be corrected and proofread by native speaker. To list a few here: "could only infected human (line 67)", "Susceptible populations infected by HEV usually through the fecal-oral route (line 95)", and "susceptible populations infected by HEV under low immunity, can be caused the performance of acute viral hepatitis (line 174)" etc. This manuscript is a simple listing of previously published results. I would rather see a review which could show a full picture of what is going on in HEV-related liver failure. For example, a model presentation may help explain the scenario in an easy way. In conclusion, the manuscript is unacceptable in its current status.

Reply: Thank you for giving this precious opinion. Many descriptions in the article were ambiguous due to improper language. To keep straightforward, we have already replaced a lot of sentences and words. We have also made changes according to the your comments in the reviewers' specific concerns and requested the language editing service (provided by the language editing company - MedE Editing Service) from native speaker which would make this article more readable and understandable. A language editor certificate will be provided along with the revision of the manuscript.

Moreover, a full picture about the development in HEV-related liver failure is necessary to make the article more comfortable to read. So, the corresponding content for this point has been added in the revision. Furthermore, a file named “**74833-Image File**” will be provided along with the revision of the manuscript.

Reviewer code. 00722050

The authors focus on Hepatitis E virus (HEV) and liver failure. Indeed, HEV is one of the most common acute injury factors of acute-on-chronic liver failure (ACLF). When HEV-related liver

failure (LF) occurs, a series of changes occur in both the intrahepatic environment and the extrahepatic microenvironment. The review is well balanced but the title does not fully reflect the immunologic data reported by the authors. Minor misspelling and awkward sentence constructions should be addressed. The clinical characteristics should be expanded in the manuscript to fully grasp the authors' choice of the title. One note of immunologic relevance is the poor description of the NK cells, which needs to be expanded. The role of the inflammasome and the liver blood flow should also be addressed.

Reply: Thank you very much for your valuable review comments. The title of this article was indeed inappropriate for its content. We have taken your advice and revised the title section. It may be better to change to “Review of clinical characteristics, immune responses and regulatory mechanisms of hepatitis-E-associated liver failure” . In addition, we have requested the language editing service (provided by the language editing company - MedE Editing Service) from native speaker which would make this article more readable and understandable. We will provide a language editor certificate along with the revision of the manuscript.

We have also expanded content of the clinical characteristics in the section of “Disease manifestations in HEV-associated LF.” In addition, to further clarify the regulatory effect of NK cells, inflammasome and the liver blood flow in the patients with HEV--associated LF, we have added several knowledge points from valuable literature to the section of “The immunological mechanisms of HEV-associated LF”. Detailed information can be found in revised manuscript. For the convenience, we have highlighted the major modified points in yellow.

In summary, we greatly appreciate the reviewers’ helpful comments and suggestions. We have revised the manuscript according to all the points raised by the reviewers. We hope that it is now suitable for publication. Thank you !