

## Responses to the reviewers

### Part A (Reviewer 1)

**1. The reviewer's comment:** For the title I suggest "Incidence of infection complication leads to high mortality in patients with HBV-related acute-on-chronic liver failure." It is more succinct.

**Author reply:** Thanks for your comment. The title has been revised as you suggested.

**2. The reviewer's comment:** The MATERIALS AND METHODS states that "ACLF was defined according to the Guideline for diagnosis and treatment of liver failure (2018 edition)[9]." The reference is in Chinese, so English readers are unable to determine the definition used. The authors should state the definition used in the text of their article. Similarly bacterial and fungal infections, sepsis, septic shock, MELD, ACLF grade, MELD-Na, iMELD, CTP, ALBI should be briefly defined.

**Author reply:** Thanks for your comment. The reference for ACLF has been replaced with the APSAL *consensus recommendations* in English, and definitions for bacterial and fungal infections, sepsis, septic shock, MELD, ACLF grade, MELD-Na, iMELD, CTP, and ALBI have been added in the MATERIALS AND METHODS.

**3. The reviewer's comment:** I suggest adding three lines, one for ACLF-1, one for ACLF-2 and one for ACLF-3, In Table 1, 4 and 5.

**Author reply:** Thanks for your comment. In Table 1, 3 and 4, we added ACLF-1, ACLF-2, ACLF-3.

### Part B (Reviewer 2)

#### 1. General comments

**(1) The reviewer's comment:** The research is very interesting but my main concern is that fungal and bacterial infections have not the same risk factors and authors did not perform separate analysis. I presume this is because there are not enough patients to report positive results. However, this should be well explained.

**Author reply:** Thank you for your suggestion. Just as you said, there are not enough patients to report positive results. Prospective, multi-center, large-sample cohort studies are needed to elucidate the difference of fungal and bacterial infections in HBV-ACLF

**(2) The reviewer's comment:** There is a lack of information if those patients developed infections or presented these infections on admission. Timing is crucial for infection and this needs to be reported.

**Author reply:** Thanks for your comment. In this retrospective study, almost all infections are nosocomial infections, few patients presented infections on admission. We added this information in the Results.

**(3) The reviewer's comment:** Authors need to analyze factors associated with mortality to show if the occurrence is an important factor as it seems.

**Author reply:** Thanks for your comment. We have analyzed factors associated with mortality, as a result, infection is an important factor (OR3.529,  $p=1.57 \times 10^{-4}$ ), though not the most important one.

**(4) The reviewer's comment:** Grammar has to be corrected but the writing is poor in general.

**Author reply:** Thanks for your comment. The manuscript has been edited by American Journal Experts, and the 'Non-Native Speakers of English Editing Certificate' has been provided. English editing will be refined in need.

**(5) The reviewer's comment:** Authors need to soften the message. A retrospective study can only provide association not causality.

**Author reply:** Thanks for your comment. The manuscript has been revised according to your suggestion.

#### **4. Abstract:**

**(1) The reviewer's comment:** *P* is not provided in results section.

**Author reply:** Thanks for your comment. We have provided *P* value in results section.

**(2) The reviewer's comment:** Back ground is not provided in the document..

**Author reply:** Thanks for your comment. Back ground has been provided in

the Abstract.

(3) **The reviewer's comment:** Conclusions are not supported by the results section.

**Author reply:** Thanks for your comment. Conclusions have been revised accordingly.

## **5. Introduction:**

(1) **The reviewer's comment:** 2<sup>nd</sup> paragraph: some of the sentences should be referenced (e.g., "Since infection plays such an important role in the occurrence, development, and prognosis of liver failure, the prevention, early diagnosis and treatment of infection are indispensable in the management of liver failure" or "Preventing and controlling bacterial and/or fungal infection is extremely challenging due to the increasing incidence of antibiotic resistance and the diversification of multidrug-resistant bacteria")

**Author reply:** Thanks for your comment. Relative references have been added accordingly.

(2) **The reviewer's comment:** The sentence describing the aim of the study is not clear. Please, describe the main aim of the study and the secondary objectives with two or more sentences.

**Author reply:** Thanks for your comment. The sentences describing the aim of the study have been revised as you suggested.

(3) **The reviewer's comment:** The number of patients that were analyzed correspond to Results section.

**Author reply:** Thanks for your comment. Two hundred and three patients with HBV-ACLF were retrospectively analyzed. We changed the number of patients analyzed.

## **6. Methods:**

(1) **The reviewer's comment:** 1<sup>st</sup> paragraph: It would be of great importance for educational purposes to describe and summarize all the diagnosis criteria in one table.

**Author reply:** Thanks for your comment. The definitions and diagnosis

criteria have been added in the M & M section, a table will be given in need.

(2) **The reviewer's comment:** Why do you use the percentage of neutrophils instead of absolute count?

**Author reply:** Thanks for your comment. Since the percentage of neutrophils is more sensitive than absolute count of neutrophils as an indicator for bacteria infection, especially in ACLF patients, most of which have relatively low levels of absolute count of neutrophils.

(3) **The reviewer's comment:** Please, rephrase "Patients who received a liver transplant or left the hospital in an extremely critical condition or died were considered as dead" because it seems that patients who received a liver transplant were considered as dead. If that is the case this is not methodologically correct.

**Author reply:** Thanks for your comment. We have deleted "Patients who received a liver transplant were considered as dead". In fact, none of the 174 patients received liver transplantation.

(4) **The reviewer's comment:** Explain when laboratory data was collected. If data was collected on admission or the worst value of 24-48h analysis is correct. If this is not the case, I have doubts about the results of the present research.

**Author reply:** Thanks for your comment. The laboratory data including the whole hospitalization period was collected, data analysis was performed according to the protocol in the M & M section.

(5) **The reviewer's comment:** Score models: Please, describe what abbreviations mean (i.e., MELD = Model for End-Stage Liver Disease).

**Author reply:** Thanks for your comment. We added the full name of the abbreviations accordingly.

(6) **The reviewer's comment:** Enlarge the information about how you obtain the data.

**Author reply:** Thanks for your comment. General information and clinical data including the whole hospitalization period were collected from the

patient database of Taihe Hospital.

(7) **The reviewer's comment:** Please describe your Ethics statements.

**Author reply:** Thanks for your comment. As described in the M & M section, this study met the ethical requirements and was approved by the Ethical Committee of Taihe Hospital.

(8) **The reviewer's comment:** Statistical analysis: describe " $x \pm s$ " as "mean and standard deviation". Enlarge the different type of analysis associated with the different objectives of the present research. ROC curve is surprisingly not explained in this section.

**Author reply:** Thanks for your comment. "The area under the receiver operating characteristic (ROC) curve was used to assess the predictive power of the factors for the incidence of infections, and the cut-off value of the continuous variable was calculated." We added this sentence to the M & M section.

(9) **The reviewer's comment:** Describe microbiology methods for diagnosis of infections.

**Author reply:** Thanks for your comment. The microbiology methods including microorganism culture, staining, and identification were routinely carried out in Taihe Hospital. They were not included in the M & M section due to the unimportance and the length limitation of the manuscript. Of course they will be added in need.

## **7. Results:**

(1) **The reviewer's comment:** Please, avoid repeated information. The flowchart of Figure 1 explains better selection criteria and mortality. However, we do not know if the differences in mortality between infected vs non-infected are statistically significant or not.

**Author reply:** Thanks for your comment. The overall mortality of HBV-ACLF patients with or without infections was added to Figure 1, and the p value of statistical analysis was indicated.

(2) **The reviewer's comment:** Table 1: describe abbreviations in the footnotes. Please, do not describe again statistical methods below the tables; you need only to describe how the results are presented (i.e., not describe statistical tests used).

**Author reply:** Thanks for your comment. We have revised as you suggested.

(3) **The reviewer's comment:** Microbiology results should be presented in Tables with the whole microbiological bacteria and fungi reported per site of infection.

**Author reply:** Thanks for your comment. Microbiology results have been presented in **Table 3**.

(4) **The reviewer's comment:** The way you established cut-offs is not explained in methods and what is the reason behind. This is one of the most important issues in your manuscript and this is not properly explained.

**Author reply:** Thanks for your comment. The area under the receiver operating characteristic (ROC) curve was used to assess the predictive power of the factors for the incidence of infections, and the cut-off value of the continuous variable was calculated. The equation for the Cut-off value follows: Sensitivity- (1-specificity), the value corresponding to maximum value is the best threshold. We added these sentences in the M & M section.

(5) **The reviewer's comment:** What is TBIL? Abbreviations are not well defined within the manuscript. The same happens in Figure 3.

**Author reply:** Thanks for your comment. TBIL, Total bilirubin. Abbreviations have been defined within the manuscript including Figure 3.

(6) **The reviewer's comment:** A spline function or a graphic would be desirable to show readers how mortality and infection rates are higher with higher degree of liver failure.

**Author reply:** We totally agree with your suggestion. Since Figure 1 showed that, the higher degree of liver failure, the much higher mortality, we did not include additional spline function or a graphic.

## **8. Discussion:**

**The reviewer's comment:** As a general comment and in accordance with my previous comments the findings of the present review should be adequately and appropriately highlighted and the key points explained more concisely and logically.

**Author reply:** Thanks for your comments. The manuscript has been revised according to your suggestion.

#### **9. Biostatistics:**

(1) **The reviewer's comment:** Explain the present reviewer why Unconditional logistic regression is more appropriate than a multivariate model with stepwise binary logistic regression in order to elucidate those factors associated with infection.

**Author reply:** Thank you for your suggestion. We have consulted biostatistics experts on this issue, and the certificate of biostatistics experts was provided.

(2) **The reviewer's comment:** Describe better in methods section.

**Author reply:** Thank you for your comment. The methods section has been revised according to your suggestion.

4.07.2019

Dear Sandro Vento, the **Journal Editor-in-Chief**,

Please find enclosed our revised manuscript entitled **“Incidence of infection complication is associated with high mortality in patients with hepatitis B virus-related acute-on-chronic liver failure”** which originally entitled **“Incidence of infection complication leads to high mortality in patients with HBV-related acute-on-chronic liver failure”**, by Chen Wang, Deqiang Ma, Sen Luo, Chuanmin Wang, Deping Ding, Youyou Tian, Kangjian Ao, Yinhua Zhang, Yue Chen, and Zhongji Meng for possible publication in **World Journal of Clinical Cases**.

Our manuscript has been revised according to your comments, especially the title.

The manuscript has been re-edited by “American Journal Experts” for English language, and a renewed editing certificate will be sent in attached files.

We hope that our revised manuscript will find your consideration now. Thank you very much for your efforts to review our manuscript.

Sincerely,

Prof. Dr. Zhongji Meng  
Taihe Hospital, Hubei University of Medicine  
South Renmin Road. No. 32  
442000 Shiyan, Hubei, China  
Tel: 0086 719 8876628  
Fax: 0086 719 8876627  
Email address: [zhongji.meng@163.com](mailto:zhongji.meng@163.com)