

## Response to Revisions:

Thank you to the editors and reviewers for their feedback, which we believe has strengthened our manuscript. We have here included a point-by-point response to each review comment and have incorporated changes as requested. Our responses are marked in red for ease of review.

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

### Specific Comments to Authors:

The authors conducted an observational study on the clinical characteristics and outcomes of bacterial or fungal infections in patients with severe liver disease admitted to MILU, which has certain novelty. However, due to the small number of enrolled samples, there may be some bias, especially the rate of fungal infection is much higher than that reported in the literature, which needs to be highlighted in the discussion.

Thank you for this feedback. We have now specifically highlighted this potential bias within our discussion.

## 2 Editorial Office's comments

### 1) Science Editor:

**1 Conflict of interest statement:** Academic Editor has no conflict of interest.

**2 Academic misconduct:** No academic misconduct was found.

**3 Scientific quality:** The author submitted an observational study on the clinical characteristics and outcomes of bacterial or fungal infections in patients with severe liver disease admitted to MILU. The manuscript is overall qualified.

(1) Advantages and disadvantages: The reviewers have given positive peer-review reports for the manuscript. Classification: Grade B; Language Quality: Grade B. The authors conducted an observational study on the clinical characteristics and outcomes of bacterial or fungal infections in patients with severe liver disease admitted to MILU, which has certain novelty. However, due to the small number of enrolled samples, there may be some bias, especially the rate of fungal infection is much higher than that reported in the literature, which needs to be highlighted in the discussion.

We have now mentioned the potential for bias in reporting rate of fungal infection within our discussion.

(2) Main manuscript content: The author clearly stated the purpose of the study and the research structure is complete. However, the manuscript is still required a further revision according to the detailed comments listed below.

(3) Table(s) and figure(s): There are 2 Figures and 5 Tables should be improved. Detailed suggestions for each are listed in the specific comments section.

(4) References: A total of 51 references are cited, including 7 published in the last 3 years. The reviewer didn't request the authors to cite improper references published by him/herself.

**4 Language evaluation:** The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before

final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

As discussed with the editorial office, this requirement has been waived.

## 5 Specific comments:

(1) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A,B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .

We have provided this in an attachment now. All figures are original works pertaining to this manuscript.

(2) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published, and correctly indicate the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

All figures in our submitted work are original to our manuscript. We have not used any pre-published pictures.

(3) Please provide the PMID numbers and DOI citation numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.

We have re-formatted our references to NLM format, which includes listing of all authors, PMID and DOI numbers for each reference.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text (and directly before the References).

We have included this as directed within our manuscript, and have drafted it as below:

### ARTICLE HIGHLIGHTS

#### Research background

Advanced liver disease predisposes critically ill patients to the development of fungal infections. While bacterial infections have been well-studied as the most common cause of acute-on-chronic liver failure and associated mortality, fungal infections have been relatively under-studied in the intensive care setting.

#### Research motivation

Infections increase mortality four-fold among critically ill liver patients, but few studies have compared predictors and outcomes of fungal infections to bacterial infections in this population.

#### Research objectives

We compared outcomes of fungal and bacterial infections among critically ill patients who were admitted to our unique medical intensive liver unit (MILU) from 2018-2022. We also conducted a comprehensive comparison of predictors and illness severity scores between these cohorts. Finally, we characterized microbiologic epidemiology of infections within our unit.

#### Research methods

Patients were identified for inclusion from a prospectively-curated database of all admissions to our MILU during the study period. Infections were defined based on culture positivity and clinical presentation. Data on outcomes and predictors of interest were collected manually through chart review.

#### Research results

We found that fungal infections among our patients were all caused by *Candida* species, and were most frequently blood isolates. Mortality was significantly worse among the fungal cohort relative to patients with bacterial infections, as the majority of these patients died or transitioned to hospice during the ICU stay. The majority of patients in the fungal cohort developed severe acute on chronic liver failure, and they had higher need for vasopressors, mechanical ventilation and acute kidney injury. Further, patients who developed fungal infections were sicker on admission to the unit. Patients with fungal infection had higher rate of transplant hold placement, and lower rates of transplant; however, differences did not achieve statistical significance.

#### Research conclusions

Fungal infection is a poor prognostic marker for patients with advanced liver disease in the critical care setting, and it is associated with significantly worse mortality than bacterial infection. This may be in large part due to development of severe acute on chronic liver failure. Patients who developed fungal infections had higher MELD-Na, APACHE and APS scores on admission to the ICU.

#### Research Perspectives:

We believe our work highlights the importance of a need for future studies to investigate associations between fungal infections and acute on chronic liver failure. Furthermore, research efforts studying examining prognostic markers, potential indications for prophylactic/empiric antifungal use, and transplant outcomes would be equally important and informative for clinical practice.

(5) Please add the Core tip section. The number of words should be controlled between 50-100 words. We have provided it within our manuscript, and drafted it as below:

#### **Core Tip:**

In the critical care setting, patients with advanced liver disease who develop fungal infections have significantly higher mortality than those who develop bacterial infections. These patients require greater support with vasopressors, mechanical ventilation and dialysis than counterparts with bacterial infections. Patients who developed fungal infections appeared more acutely ill on admission to the ICU, with higher APACHE, APS and MELD scores. In such patients, fungal infection development is closely associated with development of severe acute-on-chronic liver failure. Further work elucidating this relationship will allow for better prognostication and development of predictors for acute on chronic liver failure in this population.

**6 Recommendation:** Conditional acceptance.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

**2) Company Editor-in-Chief:**

I recommend the manuscript to be published in the *World Journal of Hepatology*.

When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the *RCA*, of which data source is PubMed. *RCA* is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our *RCA* database for more information at: <https://www.referencecitationanalysis.com/>, or visit PubMed at: <https://pubmed.ncbi.nlm.nih.gov/>.

We have searched *RCA* and added references of articles with high citation index.