JIMR 第一轮外审意见的回复

Reviewer 1

Q1: The title reflect the main subject about BSI in COVID-19, title was clear and easy to understand.

The authors' response to Q1: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q2: The abstract summarize and reflect the work described in the manuscript.

The authors' response to Q2: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q3: The key words reflect the focus of the manuscript.

The authors' response to Q3: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q4: The manuscript adequately describe the background, present status, and significance of the study.

The authors' response to Q4: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your

requirements to modify.

Q5: The manuscript describe methods in adequate detail, study subjects were clear, with demonstrate IRB number or text to human ethics consideration.

The authors' response to Q5: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q6: The research objectives achieved by the experiments used in this study.

The authors' response to Q6: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q7: The manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly, and logically.

The authors' response to Q7: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q8: Tables and figures sufficient, good quality and appropriately illustrative of the paper contents.

The authors' response to Q8: Thank you for your affirmation. If you have

further modification requirements, we will be in accordance with your requirements to modify.

Q9: The manuscript meet the requirements of biostatistics.

The authors' response to Q9: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Q10: The manuscript cite appropriately the latest, important, and authoritative references in the introduction and discussion sections.

The authors' response to Q10: Thank you for your affirmation. If you have further modification requirements, we will be in accordance with your requirements to modify.

Reviewer 2

Q1: The sensitivity and specificity of the ROC curve were 83.3% and 87.5%.....This sensitivity and specificity was for which inflammatory marker? It was unclear from results. And did the authors investigated for any particular cut off of inflammatory markers that predict the blood culture positivity?

The authors' response to Q1: Thanks for your valuable review and thoughtful suggestion. Firstly, the sensitivity and specificity of the ROC curve of IL-6, D-Dimer and ALB related to adult COVID-19 patients with

clinically suspected BSI on the first day after blood culture collection were 83.3% and 87.5%, respectively. Secondly, since the ROC curve is calculated by a combination of IL-6, D-Dimer and ALB, it is not possible to calculate a separate cut-off value for each indicator. If you are not satisfied with our answer, please indicate how to make further changes and we will deal with it as you request.

Q2: The study population was too small to draw any conclusive inference.

The authors' response to Q2: Thanks for your valuable review and thoughtful suggestion. Indeed, as you said, the sample size of this study is small, as we have pointed out in the Limittion section. First of all, the strict inclusion criteria reduced the number of enrolled patients, including ICU admission in the COVID-19 Treatment Center of Heilongjiang Province between February 2020 and November 2021, age ≥ 18 years old, confirmed COVID-19 patients, and blood culture collection due to clinically suspected BSI. Among them, blood culture collection was based on clinical manifestations of suspected BSI (eg, high fever, chills, etc.) rather than a routine test in adult COVID-19 patients, which will greatly affect the number of enrolled patients. In this study, patients in the negative blood culture group accounted for only 40% of the total number of enrolled patients, which fully indicated that we did not arbitrarily expand the range of patients with blood

culture collection. Second, with increasing experience and improved measures in the prevention and treatment of SARS-COV-2 infection, the number of COVID-19 patients admitted to the ICU is limited. Finally, even though the sample size of this study was small, we did get positive statistical results after professional statistical analysis. The question you raised also indirectly reflects the authenticity of the data in this study. If you are not satisfied with our answer, please indicate how to make further changes and we will deal with it as you request.

Q3: What was the severity of COVID-19 in both groups?

The authors' response to Q3: Thanks for your valuable review and thoughtful suggestion. The severity of COVID-19 was one of clinical parameters of this study. For the convenience of statistical analysis, we divided it into severe and others, which were shown in line 5 of Table 1, please check. If you are not satisfied with our answer, please indicate how to make further changes and we will deal with it as you request.

Q4: Why the authors excluded patients with chronic organ failure and autoimmune diseases? Any reason?

The authors' response to Q4: Thanks for your valuable review and thoughtful suggestion. Chronic organ failure and autoimmune disorder can have a large impact on clinical parameters, inflammatory markers, and disease severity score, so we included them as exclusion criteria. In

other words, these two diseases will have a significant impact on the results and conclusion of this study. If you are not satisfied with our answer, please indicate how to make further changes and we will deal with it as you request.

Q5: Patients with positive blood culture group had low procalcitonin compared to negative group, what was the possible reason for this finding?

The authors' response to Q5: Thanks for your valuable review and thoughtful suggestion. As you said, in the comparison of clinical baseline data between the two groups, patients in the positive blood culture group had lower PCT than those in the negative blood culture group, although there was no statistical difference. Clinical baseline data were obtained from medical records between blood culture collection and the first positive or negative result. That is, clinical baseline data were collected only shortly after blood culture collection. Even in patients with positive blood culture, the increase in PCT takes a certain amount of time, usually 12-24 hours to reach its peak. However, significantly higher PCT was observed in patients with positive blood culture group on the first day after blood culture collection ($p = 0.016$). All of the above suggests that the lower baseline PCT in patients with positive blood culture is likely due to the fact that PCT is not yet significantly elevated in the early stage of the disease. If you are not

satisfied with our answer, please indicate how to make further changes and we will deal with it as you request.

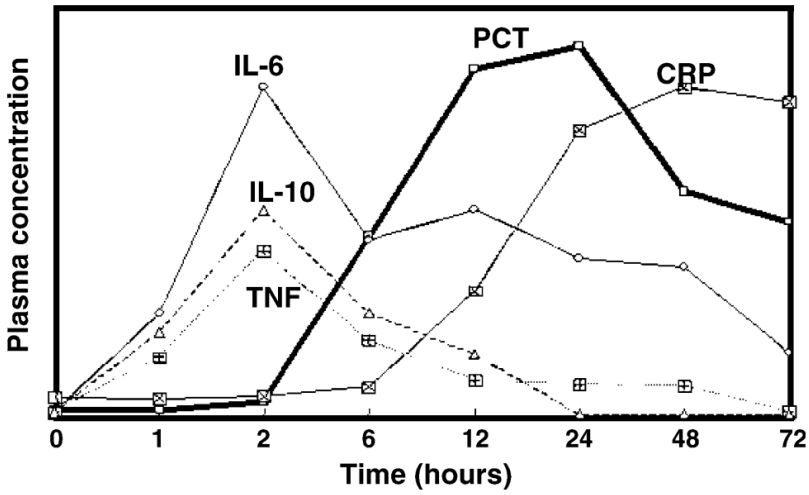


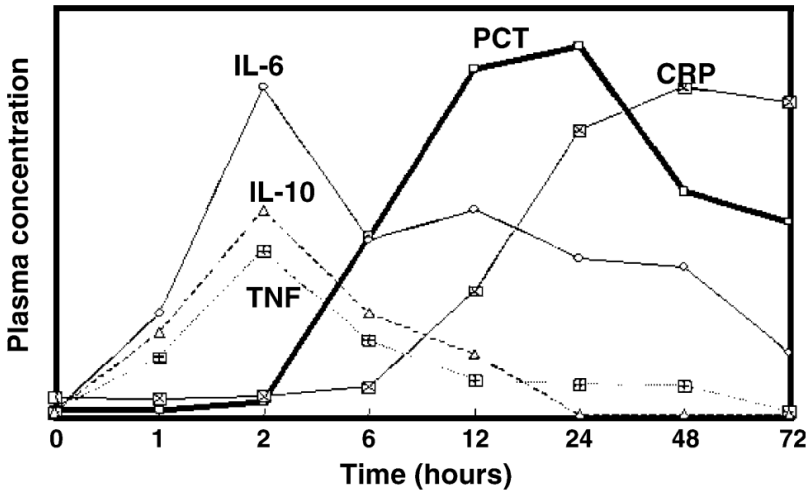
Fig. 1. Kinetics of various markers of the inflammatory host response after endotoxin challenge in human volunteers. CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; TNF, tumor necrosis factor.

Reinhart K, Meisner M, Brunkhorst FM. Markers for sepsis diagnosis: what is useful? Crit Care Clin 2006;22:503-19, ix-x.

Q6: IL-6 levels were in declining trend from baseline to 2nd day of culture……Why?

The authors' response to Q6: Thanks for your valuable review and thoughtful suggestion. The response of IL-6 to the stimulation of infection is very rapid, usually reaching a peak within 2 hours, and then rapidly declining, which is significantly different from the response of PCT to the stimulation of infection. This may explain why IL-6 in patients with positive blood culture was in declining trend from baseline to the second day after blood culture collection. If you are not satisfied

with our answer, please indicate how to make further changes and we will deal with it as you request.



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Q7: In ROC curve, p values showed significant results however CI is touching 1 in both tables……

The authors' response to Q7: Thanks for your valuable review and thoughtful suggestion. CI is short for confidence interval and has a range of 0-1. Therefore, it is normal for upper bound of 95% CI to reach 1 when the areas under the ROC curve are 0.865 and 0.979, respectively. In addition, the data of this study have been statistically analyzed by statistics professionals. If you are not satisfied with our answer, please indicate how to make further changes and we will deal with it as you

request.

Q8: The selection of antibiotics in suspected BSIs in COVID-19 is dependent on clinical findings and clinical diagnosis of sepsis rather than blood culture positivity. The conclusions of study are unclear and needs significant revision.

The authors' response to Q8: Thanks for your valuable review and thoughtful suggestion. The aim of this study was to explore whether changes in clinical parameters and inflammatory markers facilitate early identification of positive blood culture in adult COVID-19 patients with clinically suspected BSI, rather than an issue of antibiotic selection. The basis for antibiotic selection in adult COVID-19 patients with clinically suspected BSI is not covered in our study. Based on statistical analysis of relevant data, the conclusion of this study is that changes in clinical parameters and inflammatory markers after blood culture collection facilitate early identification of positive blood culture in adult COVID-19 patients with clinically suspected BSI, which to some extent can assist intensivists in early diagnosis of BSI, and thus initiation of corresponding treatments, in order to improve clinical outcomes. If you are not satisfied with our answer, please indicate how to make further changes and we will deal with it as you request.

Editor

Q1:Provide responses to each of my points below.

The authors' response to Q1:Thanks for your valuable review and thoughtful suggestion. We responded to each one.

Q2:Show any amendments in your revised manuscript using highlighted or colored text.

The authors' response to Q2:Thanks for your valuable review and thoughtful suggestion.Our modified parts are highlighted and shown in red.

Q3:Please give me an active link to PubMed or Google Scholar for publications by any of the authors or provide some other way of showing your expertise in this area.

The authors' response to Q3:Thanks for your valuable review and thoughtful suggestion.We have added the corresponding author's ORCID number to the article to facilitate access to the author's publications.If the article needs other reprocessing, you can contact us at the next.

Q4：If you have not published in this area before, please tell me about your expertise in this area.

The authors' response to Q4:Thanks for your valuable review and thoughtful suggestion.Over the past few years, we have treated

countless COVID-19 patients. We've also published a lot of articles in this area.

Q5：Please ensure you have a statement in your Methods section that states you conducted your study in accordance with the Helsinki Declaration of 1975 as revised in 2013.

The authors' response to Q5:Thanks for your valuable review and thoughtful suggestion.We have stated in the methodological section that we conducted our research in accordance with the 1975 Declaration of Helsinki (as amended in 2013).

Q6:Institutional Review Board (IRB) approval: Prospective studies: please add the name of the review board, its location, approval number, and date of approval to your manuscript. Please also include a copy of the IRB approval document. You should upload this as 'Research Data' when you send your revision. Retrospective studies may not need approval, but you should include a statement that you have checked this with your review board and received their exemption.

The authors' response to Q6:Thanks for your valuable review and thoughtful suggestion.We've checked with the review board and got their waiver.

Q7：Please de-identify patient details so that they may not be identified in any way. Add a statement to your Methods section that you have de-

identified all patient details.

The authors' response to Q7:Thanks for your valuable review and thoughtful suggestion.We have stated in the method that patient information is de-identified.

Q8:

a):Please include your completed Equator checklist when you submit your revision (upload this as 'Research Data'when you send your revision) and check that your manuscript complies with the Equator Guideline

The authors' response to Q8a:Thanks for your valuable review and thoughtful suggestion.We've uploaded a complete Equator checklist.And we meet the Equator guidelines

b):In your manuscript, you need to state in the Methods section that you have followed relevant Equator guidelines. For example, if you use STROBE: 'The reporting of this study conforms to STROBE guidelines. (insert new reference number)

The authors' response to Q8b:Thanks for your valuable review and thoughtful suggestion.This article follows the STROBE guidelines.

c) In the reference section, add this reference: von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies

in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007; 147: 573-577. (Note, you will probably need to renumber your references after this addition).

von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007; 147: 573-577.

The authors' response to Q8c: Thanks for your valuable review and thoughtful suggestion.This article follows the STROBE guidelines.We added new references, and we re-numbered the references.

d): You may find this flowchart helpful: https://www.equator-network.org/toolkits/selecting-the-appropriate-reporting-guideline/

The authors' response to Q8d: Thanks for your valuable review and thoughtful suggestion.

Q9: Indicate the type of study in your abstract and methods sections (e.g. case control study, cross-sectional study, cohort study, retrospective, prospective study and so on)

The authors' response to Q9: Thanks for your valuable review and thoughtful suggestion.We have noted in the abstract and methods section that this study is a retrospective study.

Q10:Abstract: please check that your abstract is structured, complies with our requirements and conveys the key points of your study: https://journals.sagepub.com/author-instructions/IMR#7. Headings should be: OBJECTIVE, METHODS (include type of study/experimental design and type of participant), RESULTS, DISCUSSION, CONCLUSIONS

The authors' response to Q10:Thanks for your valuable review and thoughtful suggestion.We have made changes according to the requirements of the magazine.

Q11:Signed consent: Prospective studies: did you obtain signed consent from each patient? If so, you need to make sure this is stated in your Methods section. Retrospective studies: Signed consent may not be possible/required for retrospective studies, but state this if you did get it (e.g. for possible future use in research).

The authors' response to Q11:Thanks for your valuable review and thoughtful suggestion.This article is a retrospective study and no consent is required.

Q12:How were the patients selected (e.g. consecutively, randomly or selectively)?

The authors' response to Q12:Thanks for your valuable review and thoughtful suggestion.This article is retrospective.

Q13:Please confirm that fellow researchers may reproduce your

methodology from the description given in your Methods section. If you feel they could not, please improve your Methods section so that they could.

The authors' response to Q13:Thanks for your valuable review and thoughtful suggestion.The methodology in this article can be repeated.

Q14:Results: Ensure you have included key results in your text and that figure and table legends fully explain the data that is presented.

The authors' response to Q14:Thanks for your valuable review and thoughtful suggestion. We ensure we have included key results in our text and that figure and table legends fully explain the data that is presented.

Please double-check your choice of statistics -is it appropriate for a study like this? Was the sample size enough to enable a reliable statistical result?

The authors' response to this question:Thanks for your valuable review and thoughtful suggestion.Our team has been doing clinical trials. We have people on our team who can do the statistical part independently. The results of our statistics are reproducible.So we think our experimental results can be reliable.

Have you compared your results with previous papers, and also cited those papers? Have you discussed the relevance and novelty of your study and what it adds to the literature?

The authors' response to this question: Thanks for your valuable review and thoughtful suggestion.This article references a previous article on COVID-19. But the COVID-19 pandemic won't start until 2020.Therefore, its pathophysiological mechanism is not clear, and a lot of articles are still needed to explore it.At the same time, the references that will be cited in this manuscript have been marked. Their similarities and novelty are also briefly explained in the discussion section.

Please state the limitations of your study and its findings in the Discussion section, and make sure you do not overstate your conclusions, bearing in mind this is an observational study. (Note: Studies with low numbers are usually underpowered to show any statistical significance.)

The authors' response to this question: Thanks for your valuable review and thoughtful suggestion.The limitations and findings of this experiment have been described in the discussion section of this paper.

Observational studies are not designed to provide any definite conclusions -all you can do is suggest that the results may show an effect. For example, your conclusion should say ‘may’not ‘can’.

The authors' response to this question: Thanks for your valuable review and thoughtful suggestion.We have made changes according to your suggestion. Thank you for your valuable advice.

Ensure there are the following sections at the end of your manuscript: Author contributions, Declaration of conflicting interests, Funding, Acknowledgements, Data availability statement.

The authors' response to this question: Thanks for your valuable review and thoughtful suggestion.We have made changes according to your suggestion. Thank you for your valuable advice.

Note that we may ask you to provide original research data to support the results/tables/figures presented in your manuscript. Please ensure this is available, if requested.

The authors' response to this question: Thanks for your valuable review and thoughtful suggestion.We can provide raw data at any time.