

REVISION ANSWERS

Dear Editor-in-chief and Reviewers,

As requested for the revision of the Manuscript NO: 72844, submitted to World Journal of Critical Care, all issues and suggestions made by the Editorial Office and the appointed reviewers have been addressed and are formally answered below.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is study of COVID-19 disease patients with sepsis. Why did the authors take the two primary outcomes in this study? Either the overall in hospital mortality or 28 days mortality could have been taken as primary outcome and other as secondary outcome along with other secondary outcomes. Methodology can be written in more detail including days of SARS-Cov-2 infection, severity on radiological investigations and other parameters. Were there any secondary bacterial infections in these cases?

Reviewer #1 Answer: Thank you so much for your suggestions. Since a statistical impact could be found between hospital mortality rate and 28-day mortality rate between the three analyzed groups in the manuscript, both endpoints were chosen to describe the outcomes of these patients. However, we do agree that hospital mortality could be included as a secondary outcome so we have changed it accordingly in the revised manuscript. We also have thoroughly revised the Methods section in order to include more detailed criteria on SARS-CoV-2 infection severity and other parameters. Finally, we revised the manuscript to include data about secondary infection rates in these patients and its differences between the defined groups.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Overall, well done study with sound biostatistical analysis and highlighting an important aspect and limitation of various definitions of septic shock. especially relating to hyperlactatemia. However, since this study was focused on COVID-19 patients, it is also important to highlight, how many patients had documented secondary bacterial/fungal infections, level of sedation ventilatory settings and other causes driving the hypotension/shock state. Also, it is clearly evident that patients in vasoplegic group and septic shock 3.0 group had

higher procalcitonin suggesting probable underlying bacterial infection. Also, While several studies have demonstrated that elevated lactate level alone is not a marker of fluid responsiveness or severity of sepsis, persistent hypotension despite vasopressors is in itself a marker of severity of illness. Recommend adding in table 1, any evidence of secondary infections, ventilator settings if available , baseline liver and renal dysfunction (as that can cause differences in lactate clearance between the group).

Reviewer #2 Answer: Thank you so much for your suggestions. The statistical plan aimed to identify a subset of severe COVID19 patients who would be excluded from the current septic shock definitions, but would still retain an increased mortality rate and poor outcomes during hospital stay. On that regard we tried to present available data on possible confounders that could drive hypotension and a shock state.

As suggested, we have reviewed the main manuscript in order to include more data on respiratory and renal dysfunction and secondary infection rates in the three analyzed groups. We have summarized this data in Table 1. We completely agree that persistent hypotension despite vasopressor requirement is in itself a marker of severity of illness. Undoubtedly, however, our data suggests that Sepsis 3.0 criteria can undervalue severely ill COVID19 patients. According to their clinical requirements and prognosis, a group of patients, equally severe to Septic Shock 3.0, are being classified as Sepsis and would be safer that these patients (those with persistent hypotension with vasopressor support without hyperlactatemia) should have a different classification, to account to their increased mortality risk and poor prognosis.

Science editor:

The manuscript elaborated a study of Septic shock 3.0 criteria application in severe COVID19 patients. The manuscript is well written. Nevertheless, there are a number of points that may deserve some revisions. 1. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. 2. First, the sample size is a small, single-center study, no test group, and validation group. 3. The reason why the author selects this main final index.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade D (Fair)

Science Editor Answer: Thank you so much for all the proposed corrections and comments. As requested: we have revised the references section in order to include only 3 references from the same journal. We would like also to clarify that we have chosen the main outcomes in order to effectively describe the severity of COVID19 patients included and the criteria used to differentiate the three selected groups.

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Before final acceptance, the author(s) 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>. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Company editor-in-chief Answer: Thank you so much for your suggestions and corrections. As requested, we have revised the main manuscript and we have prepared and arranged the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. We also have revised the presented tables according to editing specifications. As before, we would also like to kindly ask for the dismissal of the non-native English editing certificate presentation, considering that we have native English speakers in our working group, closely involved in the revision of all proposed documents and main manuscript.

We hope that all the revised issues are according to the journal editor-in-chief, scientific editor and reviewers' standards.

Once again, thank you for all your suggestions and comments, they were all welcomed in order to pursue an improved version of the proposed manuscript.

Best regards,

José Pedro Cidade