Dec 13, 2021

Executive Editor, World Journal of Clinical Cases

RE: manuscript number 72429

Dose-response Association between Risk Factors and Incidence of COVID-19 in 325 Hospitalized Patients: A Multicenter Retrospective Cohort Study

Dear editor,

Thank you for your letter of November11th, 2021 in which you provided comments on the above manuscript, and provided an opportunity for us to revise it. We have taken the reviewers' comments and suggestions into consideration carefully and revised the manuscript accordingly. On the following pages, please find our point-by-point responses to the concerns of reviewers in the order that they were originally listed, and corresponding details in the pages on which the changes have been made in the manuscript.

We have checked the analytical methods and all style and language requirements for World Journal of Clinical Cases one by one carefully. The manuscript has not been submitted nor is under consideration for publication by another journal. None of the authors has any conflict of interest in the matter.

We believe that the quality of the manuscript has been considerably enhanced as the consequence of the review process. We hope that the revised paper now meets your approval for publication in World Journal of Clinical Cases. Please do not hesitate to contact me if you need any further information. We look forward to hearing from you.

Best Regards.

Yours sincerely,

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Reviewer Comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is represent the important issues not answered yet. This is a timely-appropriate topic. It will provide the precious knowledge regarding the risk factors for clinicians to keep in mind in dealing with COVID-19 patients.

Response: We thank the reviewer for encouraging comments! We hope that our work would be published soon so that it was able to contribute to dealing with COVID-19 patients for clinicians. Many thanks to the reviewer!

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I've read the manuscript entitled "Dose-response Association between Risk Factors and Incidence of COVID-19 in 325 Hospitalized Patients: A Multicenter Retrospective Cohort Study", which describes a cohort of COVID-19 patients and risk factors associated with in-hospital mortality. The topic is of great interest in the setting of the ongoing pandemic, building to current evidence on pointing out risk factors and phenotype of the patient at risk for severe disease. "To our knowledge, no previous studies have been done among patients with definite outcomes" – What do the authors mean exactly? There are several large studies analyzing risk factors for mortality and severe disease in COVID-19 patients. There are some redundant or inappropriate phrases throughout the manuscript – eg in results "none of the patients were younger than 20 years of age", this is obvious as in methodology the inclusion criteria was "adult inpatients (≥20 years old)". Also, there is some inconsistency regarding outcomes assessed in the study – "combination of age, sex, high-sensitivity C-reactive protein, d-dimer, lactate dehydrogenase, and procalcitonin model was more precise in predicting clinical outcome than the single factor alone" – how was clinical outcome defined/assessed? The statistics and data on dose-response relationship is interesting. The authors should acknowledge the limitation in the time-period of the study population (at the beginning of the pandemic), with the respective consequences (regarding diagnosis, treatment, admission criteria).

Response: We thank the reviewer for encouraging comments in our work, we also thank the reviewer for all above constructive suggestions! We will provide point-by-point responses to each of the issues raised by the reviewer and revised the manuscript accordingly, please find these responses listed below:

1. "To our knowledge, no previous studies have been done among patients with definite outcomes" – What do the authors mean exactly?

Response: We are so sorry for making the reviewer confused. Actually, we means that all the patients in our study occurred the hospitalized death or were confirmed discharged. All the discharged patients met discharge criteria: temperature normalization for over 3 days, relief of clinical symptoms, substantial improvement in both lungs' imaging and throat-swab samples negative twice in RT-PCR assay for at least 24h apart. All the patients did not become positive for RT-PCR assay and were no longer admitted in hospital for treatment during a persistent out of hospital follow-up. As a result, all patients in our study have definite outcomes which would greatly decrease misclassification rate for interested outcomes. We have added more explanation information and revised it in manuscript.

2.There are several large studies analyzing risk factors for mortality and severe disease in COVID-19 patients. There are some redundant or

inappropriate phrases throughout the manuscript – eg in results “none of the patients were younger than 20 years of age”, this is obvious as in methodology the inclusion criteria was “adult inpatients (≥20 years old)”.

Response: We greatly appreciated the reviewer’s constructive comments. Though several large studies have reported risk factors for mortality and severe disease in COVID-19 patients, the majority of these studies just simply treated the factors as continuous, dichotomized, or categorical variables, studies that further systematically explored the potential dose-response associations were very limited, thus the linearity, potential threshold, curve shape and consistency of risk factors with COVID-19 outcomes remained unknown. As is pointed out by the reviewer, the statistics and data on dose-response relationship is interesting. We have emphasized this point in the introduction part.

We thank the reviewer for pointing out the redundant description sentence “none of the patients were younger than 20 years of age”, we have removed it. Furthermore, we have totally checked similar redundant or inappropriate phrases all over the manuscript.

3.Also, there is some inconsistency regarding outcomes assessed in the study – “combination of age, sex, high-sensitivity C-reactive protein, d-dimer, lactate dehydrogenase, and procalcitonin model was more precise in

predicting clinical outcome than the single factor alone" – how was clinical outcome defined/assessed?

Response: We thank the reviewer's constructive comments. The primary endpoint of our study was hospitalized death and a composite severe cases which consisted of the admission to intensive care unit (ICU), intubation, or death, which occurred beyond 24 hours but within 28 days after admission, which were confirmed from medical records and death certification. Patients who had temperature normalization for over 3 days, relief of clinical symptoms, substantial improvement in both lungs' imaging and throat-swab samples negative twice for at least 24h apart were allowed discharged. All data were collected by two physicians independently double-checked and a third researcher scanned and verified. We have added these information in methods section and checked all the manuscript.

4.The statistics and data on dose-response relationship is interesting. The authors should acknowledge the limitation in the time-period of the study population (at the beginning of the pandemic), with the respective consequences (regarding diagnosis, treatment, admission criteria).

Response: We thank the reviewer's great interest and encouraging comments in our work. We also appreciate the constructive suggestions! The reviewer is right, during the beginning of the pandemic, we know a little about COVID-19, so the treatment regimen have been improving.

Also, due to limited medical resources, the elder and patients with serious symptoms may preferentially admit. Consequently, confounder of treatment difference and included patients bias may exist. Considering the retrospective nature, causal inference may be caution. We have added the limitation in the discussion part.