Manuscript ID: 66236

Title: A validated tool for early prediction of ICU admission in COVID-19 patients

Journal: World Journal of Clinical Cases

Response to Reviewers' comments

Dear Editor,

We thank you and the reviewers for your favorable review of our manuscript entitled "A validated tool for early prediction of ICU admission in COVID-19 patients" (Manuscript NO: 66236, Observational Study). We have enclosed the revised version of our manuscript for publication in the World Journal of Clinical Cases. We appreciate the opportunity to revise and improve the quality of our manuscript and we hope that the revised version is now suitable for publication in the World Journal of Clinical Cases.

We have reviewed all the suggestions and comments carefully. We have made revisions in the text in agreement with the comments, and a point-by-point description of the revision or explanations for the reviewer's queries is given below. Changes in the revised manuscript have been marked in tracked changes, and we have provided a clean version. We have complied with all the suggestions of the associate editor and the reviewers and a detailed point by point description of revisions/explanations has been provided. We would be happy if you consider our article for publication

Yours Sincerely,

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Reviewer Comments:

Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The manuscript is very good. Excellent work accomplished. Let the authors collaborate with the editor to iron out a few grammatical glitches. Add a few more papers about the available published papers about vaccines. let the authors insert the different tables and figures under their respective subheadings. it will make understanding and following the manuscript a little easier. Thank you.

Response: Thank you for your favorable review of our manuscript. The manuscript has been revised by a professional native English-speaking editor to ensure that the revised manuscript is free of grammatical errors. We have add a few papers about vaccines in the Introduction section. The editors can move the tables and figures appropriately to make it easier to understand our manuscript.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: This is a mixed-method study aims at developing and validating a risk stratification tool for the early prediction of ICU admission among COVID-19 patients at hospital admission. This study was well designed, executed and presented. It makes important points which are widely applicable. I enjoyed reviewing it.
Response: Thank you for your favorable review of our manuscript.

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Dear author, I would like to thank you and your team for the scientific contribution to tackle COVID-19 pandemic. I have gone through the article based on development of a model that could predict early categorization of COVID-19 patients who may require ICU support during their treatment at hospital admission. This model compared with some pre existing established tools and other hospital findings and reference of based on the outcome of COVID-19 patients. Please check the manuscript where i have put comments for revision.
Response: Thank you for your favorable review of our manuscript and your valuable suggestions. We have made all the changes you suggested in the manuscript.

The revised manuscript has been improved by a professional native English-speaking editor to ensure that the revised manuscript is free of grammatical errors.

> **Response:** Thank you for your favorable review of our manuscript.

Abstract
Methods: can shorten to include more information in the results section

> **Response:** As suggested, the Methods has been shortened and the Results section has been expanded to include more findings.

Results: suggest providing more details on the demographics of the included patients and the top predictors

> **Response:** Information about the age, gender, and the top predictors has been added to the revised Results section in the Abstract.

Core tip: the first sentence does not read well

> **Response:** This sentence has been revised for clarity.

Manuscript
Introduction
• second paragraph, would suggest updating the first sentence as we now have a few approved vaccines and medications to treat COVID-19.

> **Response:** Thank you for your suggestion. We have now rewritten this paragraph entirely to reflect the existence of approved vaccines and medication to treat COVID-19.

• Fourth paragraph, first sentence should read "due to the rapidly…. And the limited resources in ICU…"

> **Response:** This phrase has been corrected to "Due to the rapidly expanding number of patients and the limited resources in the ICU…" in the revised manuscript.

• Fifth paragraph, first sentence does not read well.

> **Response:** The first sentence of the indicated paragraph has been changed entirely as previously suggested. The new sentence reads as follows: "At the start of

the pandemic, there was no antiviral agent or vaccine that existed to target this virus, and none of the existing antiretroviral treatments had been recommended for this disease."

Methods Statistical analysis:
Second to last sentence should read "...Kruskal-Wallis test for ... with skewed distribution.
 Response: This error has been corrected in the revised manuscript.

Feature selection: need to spell out the acronym LR at the first mention.
 Response: This and all other acronyms have been spelled out at their first mention in the Abstract and in the main manuscript.

Calibration: Hosmer-Leme show should be corrected to Hosmer-Lemeshow.
 Response: This has been modified as suggested.

Results
Study population: suggest providing some key demographic and clinical characteristics from Table 1 in this section.
 Response: Thank you for your suggestion. Key demographic and clinical characteristics were added in this section.

Feature selection for the predictive model: Suggest providing more details on how the adjustment of the logistic regression model based on expert opinion was conducted. Details like which variables were used based on what rationale should be provided.
 Response: According to the experts' knowledge on COVID-19 and their clinical experience, five variables were added (PLT, TBil, WBC, ALT, and gender), and seven variables were deleted (BNP, Cysc, APTT, Myoglobin, BUN, PT, and Hgb).

Figure 3: suggest specifying if the feature importance is based on RF in the text as well as figure description (either title or footnote). Suggest providing more information on the RF models including but not limited to the no. of trees and the number of variables randomly selected at each node for split.
 Response: Thank you for the suggestion. The feature importance is based on RF, and it is clarified in the title of Fig. 3. The number of trees was set to 480 and the number of variables selected at each split was set to 4. It was added in the Prediction algorithm subsection of the Method section.

Figure 8: suggest tweaking the footnotes to improve the interpretation of the figure for a layperson. Although the information provided is useful, it is not clear how the clinical benefit is derived. An example using a specific risk threshold could be helpful.
 Response: Thank you for the suggestion. We have included one such example in Fig. 6.

Discussion
• *suggest checking grammar and spellings in this section.*
　　Response: The whole manuscript, including the Discussion section, has been thoroughly revised by a native English-speaking editor to ensure error-free text.

• *I also recommend using an interpretable machine learning technique to understand how different values of the top predictors may affect the predicted probability of ICU admission.*
　　Response: Thank you for the suggestion. We have added SHapley Additive exPlanations (SHAP) values of the top predictors to illustrate how each variable affects the predicted probability of ICU admission in Fig. 5.

Reviewer #5:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: 1. List out the contributions and the organization of the paper below the introduction paper.
　　Response: Author contributions have been included on the title page of the revised manuscript.

2. Add an architecture depicting the system model of the proposed work.
　　Response: Thank you for the suggestion. The process of the feature selection and model building was presented in Fig. 2.

3. In the Introduction section, the drawbacks of each conventional technique should be described clearly.
　　Response:　Thank you for the comment. The Introduction section includes the discussion of the previously established prognostic models (miscalibration risk during external validation or lack of calibration).

4. You should emphasize the difference between other methods to clarify the position of this work further.
　　Response: Thank you for this comment. The absence of proper calibration in the other models is stated in the Introduction section of the manuscript.

5. The Wide ranges of applications need to be addressed in the Introduction
　　Response: The external verification of our model was satisfactory, and showed good discriminatory powers in heterogeneous populations from different levels of hospitals, with different death ratios and different physical conditions, suggesting that the models may be applicable to different settings. It was mentioned in the first paragraph of the Discussion section.

6. Add the advantages of the proposed system in one quoted line for justifying the

proposed approach in the Introduction section.

Response: One advantage of our feature selection process is that it not only includes data-driven algorithms but also integrates expert knowledge to enhance the interpretability of the model; second, our selection process considers using variables singly and in combination to increase the reliability of the model; our modeling considers both linear and non-linear correlations among the variables; our model underwent rigorous performance evaluation, which can well predict the patient's survival risk and provide important reference value for doctors in the allocation of medical resources.

EDITORIAL OFFICE'S COMMENTS

Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) The authors did not provide original pictures. 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; and (3) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text. 6 Recommendation: Conditional acceptance.

Response: We are unable to provide approved grant application forms. The authors are willing to delete information regarding funding if necessary. Original pictures have been provided in a PowerPoint file. A section entitled "Article Highlights" has been included at the end of the main text.