

Peer Review File

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Reviewer A

It's my pleasure to review your article. It is an interesting article and well-structured.

I have a few comments that I would like you to address.

Comment 1: There are some grammatical errors in your article that I would like you to correct them. For example, in line 77 (Introduction) "In current study, we aim to ...".

Reply 1: We are sorry and thank you for kind reminder. We have checked the whole manuscript carefully and made some corrections.

Changes in the text: We have modified our text as advised (see Page 4, line 94).

Comment 2: It would be better if you can define the severity of COVID-19. How did you categorise a patient with severe COVID-19? It would make your nomogram valuable if it can predict if patients need ICU admission or predict the mortality.

Reply 2: We appreciated this suggestion. We are sorry that the original definition for severe COVID-19 was unclear, and have clarified the definition in the revised manuscript. We categorized the disease condition according to the Guideline on the Diagnosis and Treatment for COVID-19 (trial Version 6) issued by the National Health Commission in which COVID-19 were classified into mild, moderate, severe and critical groups. The severe COVID-19 in our study was actually a composite event which included those combined with other organ failure needing ICU, but we did not only predict those need ICU admissions. On the other hand, since there had nomograms predicting the mortality, this study focused on the forecasting the severity of COVID-19. We value your advice, and in future study, we will analyze the determinants of mortality in new variant like 2022 Omicron.

Changes in the text: We have modified our text as advised (see Page 6, line

133-143).

Comment 3: Previous studies about nomogram of Zhang, et al., Liu, et al., and Shi, et al., were cited in your study. How is your nomogram compared to them? Is there anything that can make your nomogram better than theirs?

Reply 3: Thank you for this suggestion. Actually, we compared our nomogram to other studies in the discussion. Some model like Shi, et al belonged to deep-learning algorithms and needed complicated algorithms. Our nomogram was comparatively simple, user-friendly, and achieved robust and adequate discrimination performance. We have repositioned this part of discussion and made it clearer. When we compared with other studies about nomogram, we objectively explained our finding of determinants which was different with others since the sample size, characteristics of subjects and the number of predictors was different. For example, nomogram of Zhang,et al is a single-center study and include only 104 patients. By contrast, our study was multi-center study, included 598 patients. We appreciated your advice, and following your comment, we suggested that our finding should be interpreted with caution in the conclusion section.

Changes in the text: We have modified our text as advised (see Page 10, line 249-251, Page 13, line 348-350).

Reviewer B

This article deals with the development of a nomogram to predict the severity of COVID-19. The fact that the items used in the nomogram are easily evaluated and that the robustness of the nomogram is high are commendable. Points that should be reviewed to improve this study are as follows;

Comment 1: The year of diagnosis is mentioned in the selection criteria, but the SARS-COV-2 strain should be discussed.

Reply 1: We thank for this advice, and we added that all inpatients were of confirmed infection of original SARS-CoV-2 strains in the inclusion criteria, and discussed this in the discussion section. We pointed out our nomogram was targeted at COVID-19

patients infected with original SARS-CoV-2 strains, and may not be applicable to other variant strains, especially Omicron strains.

Changes in the text: We have modified our text as advised (see Page 5, line 113, Page 12, line 329-331).

Comment 2: Whether there is a relationship between renal function and hyperkalemia should be mentioned.

Reply 2: This advice is highly appreciated. Kendall correlation analysis was conducted according to your advice, and showed there had no relationship between renal function and hyperkalemia.

Changes in the text: We have modified our text as advised (see Page 12, line 315-318)

Comment 3: In general, low platelet count implies the patient is under severe condition, as this is contained in SOFA score. In this nomogram, only high platelet counts enhance the severity of COVID-19, how this difference is explained?

Reply 3: We thank for this valuable suggestion. Low platelet count really implies to be in severe condition according to SOFA score. On the other hand, high platelet count implies that patients are more likely to develop the severe thrombosis, which will accelerate the negative outcome in COVID-19 patients and this was proven by previous study. In this study, the proportion of low platelet count in the non-severe group was a little higher than that in the severe group, and the proportion of high platelet in the severe group was obviously higher than that in the non-severe group, which probably explain this difference. We have had a corresponding discussion on this issue.

Changes in the text: We have modified our text as advised (see Page 11, line 295-299).

Reviewer C

The authors describe the derivation and validation of a tool that predicted the

development of severe COVID-19 among patients with moderate disease. This is an interesting paper, with proper design and meaningful clinical relevance. However, some issues should be addressed by the authors.

Comment 1: I think the main issue of this paper is its methods. I personally do not understand why patients with moderate or mild disease were hospitalized in the first place. The authors must include details on their admission policy, reasons for admission (was it for other non-COVID concomitant conditions? only for observation?), discharge policy (did you discharge stable patients with active disease or only once recovery occurred), treatment of non-severe disease, and so on.

Reply 1: We thank you for your suggestion. Since COVID-19 was an urgent public health crisis in China in 2020, all suspected and confirmed patients must receive treatment in isolation at designated hospitals according to government regulation (the Guideline on the Prevention and Control for COVID-19 issued by the National Health Commission), regardless of whether they were severe, moderate or mild, or whether they had other non-COVID concomitant conditions. This policy lasted till end of 2022. Details about admission and discharge policy have been included in the Methods section.

Changes in the text: We have modified our text as advised (see Page 5, line 106-111).

Other issues:

1. Methods:

Comment 2: If a patient was discharged and readmitted - was he included?

Reply 2: We appreciated this comment. The patient admission period was from January to March 2020, the beginning of the pandemic of COVID-19, and all included patients were diagnosed with COVID-19 for the first time. For your suggestion, we have clarified this in the inclusion criteria.

Changes in the text: We have modified our text as advised (see Page 5, line 112-113).

Comment 3: Did you measure patients saturation upon admission? If so, I believe this could also be a key factor for prediction. For example, a patient with initial 95% saturation will obviously be more likely to have saturation below 94% and be considered severe. If not, I think it should be added to the limitations.

Reply 3: We appreciated and agreed with this advice. It is a pity that oxygen saturation was not incorporated into this study when collecting data. Limited by insufficiency of retrospective study, this multi-center study could not include all possible risk factors of severity because of the indicators available varying from center to center. We just used available data to analyze. This has been added to the limitation.

Changes in the text: We have modified our text as advised (see Page 12, line 326-329).

2. Results:

Comment 4: How many patients were excluded?

Reply 4: COVID-19 hospitalized patients without severe pneumonia on admission were included in this study. A total of 610 patients were diagnosed with confirmed COVID-19 in this study and twelve non-hospitalized patients were excluded. 598 patients were eventually enrolled. We added to this in the first section of results.

Changes in the text: We have modified our text as advised (see Page 7, line 179-181).

Comment 5: How many patients were discharged with an active mild-moderate disease and were censored? This is critical as many of these patients could have had severe disease after discharge.

Reply 5: We thank for this suggestion. All patients could be discharged only after they were cured and meet the discharge criteria. Besides, no inpatients were censored in this study since COVID-19 was a tightly managed infectious disease by Chinese health authority and all patients were isolated for treatment till recovery in the periods of Jan 2020 and end of 2022. We have added the discharge criteria in the section of

study design and participants of Methods. Also, the number of discharge cases has been supplemented in the section of Patient characteristics in Results.

Changes in the text: We have modified our text as advised (see Page 5, line109-111; Page 8, line 188).

Comment 6: The authors report that 198 patients had severe disease and 77 (39%) died. This is a really high mortality rate. Did patients die from COVID-19? Please explain.

Reply 6: Please allow us to explain this problem. All inpatients in this study became ill in periods of Jan and Mar 2020, the early days of COVID-19 epidemic in China. Besides, 3 hospitals in our study were located in Wuhan city, Hubei province, which was the epicenter of this outbreak. According to public news, 3869 patients died of COVID-19 in Wuhan city till Apr 16, 2020

(<https://baijiahao.baidu.com/s?id=1664193371991958282&wfr=spider&for=pc>). The reason of high mortality rate, we thought, included insufficient medical resources and lack of understanding of this emerging infectious disease. Patients died from multi organs failure or acute respiratory distress syndrome caused by COVID-19. We have clarified the reason of death in the section of Patient characteristics in Results.

Changes in the text: We have modified our text as advised (see Page 8, line 189-190).

Comment 7: Did you test your nomogram for prediction of adverse outcomes such as death, intubation and ICU transfer? I think this could be interesting and clinically relevant.

Reply 7: We appreciated your advice and we are sorry we did not exactly analyze what you suggested. The predicted outcome of our nomogram was progression for severity which was a composite outcome and included shock, respiratory failure needing incubation and combined with other organ failure needing ICU transfer. Since there had nomograms predicting the death, our study focused on the forecasting the severity of COVID-19. For your suggestion, we have clarified this in the section

of definition of outcome.

Changes in the text: We have modified our text as advised (see Page 6, line 133-143).

Comment 8: Why high creatinine, which was an independent predictor in the univariate, was not included in the multivariate model.

Reply 8: We thank for this comment. High creatinine showed statistical significance in the univariate analysis, actually, it was incorporated into the fitting of multivariate model. But it was not an independent predictor in the final model. The section of statistical analysis had description about univariate and multivariate analysis as follows: “The correlations of potential predictors and development of severity were analyzed by univariate logistic regression firstly. Then, statistically significant predictors were incorporated into a multivariate logistic regression model using the backward stepwise selection procedure to determine the independent risk factors of progression to severe COVID-19”. 29 predictors were statistically significant in univariate analysis, and 9 predictors were statistically significant in the eventual multivariate model.

Changes in the text: The explanatory texts about this comment can be seen from Page 6, line 154 to Page 7, line 158.

3. Discussion:

Comment 9: I think the authors should add additional previous data supporting their predictors for worsening COVID-19/ Older age was found to be a predictor for readmission and severe disease among patients discharged early with active COVID-19, supporting their results. I recommend the authors to use the following article which describe this finding:

<https://pubmed.ncbi.nlm.nih.gov/36645149/>

In this study and in others AKI was found to be a predictor for COVID-19 deterioration. However, the authors did not analyze this important marker (only creatinine levels in general), and this should be noted as a limitation.

Reply 9: We thank for this comment. Above article has been listed in our references. And we are sorry that the comorbidity of AKI was not collected and analyzed, because some markers were unavailable limited by the retrospective study. This has been noted as a limitation.

Changes in the text: We have modified our text as advised (see Page 10, line 263 for adding reference [22]; Page 12, line 326-328).

Comment 10: Many of the variables which are part of the prediction model represent extra-pulmonary involvement of COVID-19 or maybe a second concurrent disease. A study involving COVID-19 patients showed high rates of concurrent involvement, higher in severe patients. I think this is an interesting relevant issue that could be discussed. For this the authors can use the following study which describe this finding:

<https://pubmed.ncbi.nlm.nih.gov/36779316/>

Reply 10: This comment is highly appreciated. We have cited this reference for your suggestion (reference 23) and the discussions about this were addressed.

Changes in the text: We have modified our text as advised (see Page 10, line 267-270).

Reviewer D

Comment 1: Introduction, line 76, the definition of nomogram has no reference.

Reply 1: We are sorry about this negligence. The reference was added.

Changes in the text: We have modified our text as advised (see Page 4, line 93; Page 15, line 403-404).

Comment 2: Why is a feature selection technique like LASSO not used to select important variables?

Reply 2: We agree that LASSO is really a good, advanced variables selection technique, but it is complicated and not user-friendly to doctors. The intention of this

study is to construct a relatively simple predicting model. Besides, LASSO is suitable for situations where the sample size is particularly small and the number of candidate variables is especially large. This study did not conform to this scenario, so the multivariate Logistic regression model was adopted. We don't think that the more complex the model is, the better the effect. It is better to solve the problem with a simple model.

Changes in the text: Not applicable.

Comment 3: The current study is full of plagiarism, which according to the report I got is about 36%. In terms of methodology, it is very similar to this study with the title “Development and validation a nomogram for predicting the risk of severe COVID-19: A multi-center study in Sichuan, China”

Reply 3: We are sorry for the negative impression we gave you. In writing this manuscript, we referred to some articles about nomogram for the methodology. But we're not subjectively plagiarizing. Duplicate checking has been conducted, and we checked and revised the manuscript carefully based on review to ensure reducing the duplication of contents with other articles.

Changes in the text: We have modified our text as advised, which is highlighted with green color.

Comment 4: The above study with the same methodology on the same disease of COVID-19 and the same outcome, that is, the severity of the COVID-19 disease during hospitalization based on admission data, in the same country of China and in terms of the peak and strain of the disease are close to the same point in time.

Reply 4: This comment is highly appreciated. Our manuscript really had similarities with above study, but many differences existed too. Please see the reply to the next comment for details. In our opinions, these 2 studies were carried out from different aspects, both of which can be used for reference. For your comment, we have made some revisions in the section of Conclusions: “It's soberly to note that although there had been several studies of nomogram to predict severity of COVID-19 in China

during the same periods, the results were not quite the same”. We hope our explanation will be satisfactory to you and readers.

Changes in the text: We have modified our text as advised (see Page 13, line 346-348).

Comment 5: Explain exactly how your study differs from the above-mentioned study. Moreover, considering that many similar works have been done on your target variable (severity of COVID-19) based on admission data. Compare those studies with your work.

Reply 5: There existed some differences between our study and above-mentioned study. Firstly, our study sites spread across 2 provinces including Wuhan, the outbreak source and above-mentioned study was conducted in only a province. Secondly, the diagnosing criteria was not the same, although both of the primary outcome in 2 studies was severe COVID-19 during hospitalization, our criteria of diagnosing severe COVID-19 pertained to the Guideline on the Diagnosis and Treatment for COVID-19 (trial Version 6) issued by the National Health Commission, but criteria of this Sichuan study was according to the American Thoracic Society guidelines for community-acquired pneumonia. Thirdly, the candidate variables of this Sichuan study included symptoms, comorbidities and epidemiological history, but our study were more focused on indicators of laboratory examination, which we thought was the biggest differentia. Last but not the least, the final predictors of our study were very different from the Sichuan study. We added some words in Conclusions in response to this comment: “Our findings showed some differences compared to other nomograms due to sample size and choice of predictors, it should be interpreted with caution”.

Changes in the text: We have modified our text as advised (see Page 13, line 348-350).

Comment 6: In your study, due to the limited amount of data, a small number of

factors have been considered as important variables. It cannot be considered a generalizable study. Because we know that there are important factors such as co-morbidities that affect the severity of the disease, but your models consider only hypertension to be significant.

Reply 6: We highly appreciate this comment and we agreed this study has limitations. Comorbidities play important role in the development of severity of the disease. Although we investigated 6 commorbidities, only hypertension was significant in final model. One of reason probably lied in sample size being not extremely large, which we have highlighted in the limitations.

Changes in the text: We have modified our text as advised (see Page 12, line 326-328, line333-335).

Comment 7: The data are related to the early strains of the virus when vaccines were still in the testing stages. It is suggested that you train and test your models with the data of recent strains of COVID-19 patients to obtain more reliable results. I think important parameters have been missed.

Reply 7: This is an excellent suggestion. Using data of patients infected with recent SARS-CoV-2 variants like Gamma and Delta to train and test this model is interesting and worth expecting. Currently, these data are unavailable. Following your advice, we will collect more extensive and important indicators to obtain more reliable results in near future. We have discussed this in the limitations.

Changes in the text: We have modified our text as advised (see Page 12, line 329-333).