

## Author Response

Responds to the reviewer's comments:

Reviewer #1:

Major comments:

1. The article does not provide any discussion of the chest x-ray or CT scan of chest in MV COVID-19 patients and Non-MV COVID-19 patients. Is there any relevant information on these tests or any reason why they are not included?

Response: Thank you for your comments. Based on your insightful suggestion, we have added data of CT scan of chest scores for COVID-19 patients in Table 1. CT images of patients were scored by three independent chest radiologists, and we also thanked them for helping us analyzing the radiological image data in the Acknowledgement Section in the revised manuscript. CT images were scored based the area involved (a score of 0–5 for each lobe, with a total possible score of 0–25) as previous studies reported [Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. *Radiology*. 2005;236(3):1067-1075. doi:10.1148/radiol.2363040958]. However, the result showed that there was no significant difference on CT score on admission between the patients with or without mechanical ventilation in this study, which may be explained by the following reasons: Most patients included in the study were severe to critical COVID-19 patients, and their CT images on admission were presented with multiple lobes infection. CT scoring can only evaluate the area and size of lesions involved in the lobes, but the evaluation of the density of lesions is not very good, which is also a limitation of this scoring system.

2. The article does not provide any discussion of the arterial blood gas or Alveolar–arterial gradient in MV COVID-19 patients and Non-MV COVID-19 patients. Is there any relevant information on these or any reason why they are not included?

Response: Thank you for your constructive comments. We have added data of SpO<sub>2</sub> for COVID-19 patients in Table 2 and Table 3. In mechanical ventilation groups, there were higher proportion of patients' SpO<sub>2</sub> lower than 93%, demonstrating that patients required mechanical ventilation had worse oxygenation, and previous study showed that the oxygen saturation was significantly lower in severe patients than non-severe patients as well [Cao ZH, Li TZ, Liang LC, et al. Clinical characteristics of Coronavirus Disease 2019 patients in Beijing, China[J]. *PLoS ONE*, 2020,15(6), e0234764. DOI:10.1371/journal.pone.0234764.]. Since the data was collected based on electronic medical records, some severity scores like APACHE, SOFA, PF ratio, arterial blood gas analysis results were not available to be analyzed and support a better conclusion. We are sorry for the lack of the information, and we had added this into the Limitation Section in the revised manuscript. However, the mechanical ventilation was given based on the following criteria: when normal oxygen therapy or high-flow nasal oxygen therapy fail to alleviate hypoxemia and respiratory distress, we considered the use of noninvasive mechanical ventilation. Tracheal intubation for mechanical ventilation is the option when noninvasive mechanical ventilation treatments were no efficient and the condition of the patient deteriorated within 2 hours. Also, we followed the recommendations (PaO<sub>2</sub>/FiO<sub>2</sub> <150mmHg or <200mmHg in case of anticipated difficult airway) on decision of endotracheal intubation.

Minor comments:

1. Why do mechanical ventilation COVID-19 patients manifested more chest tightness?

Response: Thank you for comments. In order to better address the concern of noninvasive and invasive mechanical ventilation (comments of the second reviewer), we expanded the sample size

and classified the patients with mechanical ventilation into two groups: Invasive mechanical ventilation group and Noninvasive mechanical ventilation group, and appropriate statistical analysis was revised accordingly. However, the results showed there was no statistical difference between the groups concerning chest tightness ( $p > 0.05$ ), which was a more reliable conclusion after expansion of sample size.

2. As some studies have shown, lymphopenia is a signature of severe COVID-19. Lymphocyte count is critically lower in MV patients compare to non-MV ones, representing a more severe infectious condition. Why do univariate analysis of Lymphocyte count  $< 1.1 \times 10^9$  cells/L revealed  $P = 0.065$  in this study?

Response: Thank you for comment. The small sample size of MV patients was a possible reason to obtain that insignificant result. In order to draw a more reliable conclusion, the sample size was expanded. After expanding the sample size, we got the conclusions that univariate analysis of Lymphocyte count  $< 1.1 \times 10^9$  cells/L revealed  $P < 0.05$  in the revised manuscript (Table 3).

3. No data shown in Neutrophil count  $> 6.3 \times 10^9$  cells/L was higher in MV patients relative to non-MV. Why is Neutrophil count  $> 6.3 \times 10^9$  cells/L an early predictor for mechanical ventilation in COVID-19 patients?

Response: Thank you for your comment. We added the data (Table 2) to show the difference of proportion of patients with Neutrophil count  $> 6.3 \times 10^9$  cells/L on admission. The proportions of patients with higher neutrophils count ( $> 6.3 \times 10^9$  cells/L) in invasive and noninvasive mechanical ventilation groups were higher than those patients in non-mechanical ventilation group. Therefore, the univariate and multivariate analysis were conducted for neutrophils count as potential indicators for mechanical ventilation among patients with COVID-19.

4. The age between MV group and non-MV group has no significant different in this study. Why add age  $> 60$  yr to univariate analysis?

Response: Thank you for comment. After expanding the sample size, the patients in Noninvasive mechanical ventilation group were older than the patients in Non-mechanical ventilation group ( $P = 0.009$ ), while there was no significant difference on age between invasive mechanical ventilation group and non-mechanical ventilation group in the revised manuscript. Since the age could have important clinical significance, we added age  $> 60$  yr to univariate analysis, and found it had significant effect as predictor for noninvasive mechanical ventilation based on the result of univariate analysis.

5. The comorbidity between MV group and non-MV group has no significant different in this study. Why add diabetes mellitus and hypertension to univariate analysis?

Response: Thank you for your constructive comment. Based on your suggestion, we deleted diabetes in the univariate analysis. After expanding the sample size, the result showed that patients in noninvasive mechanical ventilation group had more preexisting illness of hypertension than the patients in non-mechanical ventilation, therefore, hypertension was still included in the univariate analysis.

6. Other antibiotics were used significantly more frequently in MV-group patients than those who didn't need mechanical ventilation (100% vs. 50.67%,  $P < 0.001$ ). Why is it not included in univariate analysis? Is it an influent factor?

Response: Thank you for your comment. We have included antibiotics in the univariate analysis in our revised manuscript, and the result showed that use of antibiotics was a potential predictor for

mechanical ventilation among patients with COVID-19 in univariate analysis. However, it did not reach a significant difference after adjusting for potential mediators in the multivariate analysis.

7. In MV group, patients received more glucocorticoid therapy (80% vs 20.67%,  $P < 0.001$ ). Why is it not included in univariate analysis? Is it an influential factor?

Response: Thank you for your comment. We have included the use of glucocorticoid in the univariate analysis in our revised manuscript. Additionally, the multivariate analysis also showed that the use of glucocorticoid was an independent predictor for invasive and noninvasive mechanical ventilation among patients with COVID-19.

8. In MV group, patients received less abidol (75% vs 92%,  $P = 0.017$ ). Why is it not included in univariate analysis? Is it an influential factor?

Response: Thank you for the comment. We have included the use of glucocorticoid in the univariate analysis in our revised manuscript, and the result showed that abidol was not a potential predictor for invasive and noninvasive mechanical ventilation among patients with COVID-19.

9. Why are ALB, GLB, ALT, AST, PCT, D-dimer not included in univariate analysis?

Response: Thank you for pointing out that our original manuscript failed to explain this clearly enough. We included these factors in univariate analysis and utilize multivariate stepwise logistic regression models to assess the early predictors in the revised manuscript.

10. You can utilize multivariate stepwise logistic regression models to assess the early predictors for mechanical ventilation in COVID-19 patients.

Responds: Thank you for your constructive suggestion. After expanding the sample size and reclassifying the patients, we used multivariate stepwise logistic regression models to assess the early predictors as you suggested in the revised manuscript.

Reviewer #2:

Major comments:

1. The article is a retrospective study, which has tried to look at factors predicting mechanical ventilation. However, non-invasive and invasive mechanical ventilation have been treated as one group, which may not represent same severity of disease.

Response: Thank you for comment and constructive suggestion. The reason why we initially identified non-invasive and invasive mechanical ventilation as one group was that the sample size of patients was relatively too small to perform subgroup analysis at the time of submitting the manuscript. Based on your constructive suggestion, we expanded sample size and classified the patients with mechanical ventilation into two groups: Invasive mechanical ventilation group and Noninvasive mechanical ventilation group. Appropriate statistical analysis was conducted accordingly in the revised manuscript.

2. Also, subjective markers like fatigue, may not be useful if included as predictors of severity or prognosis.

Response: Thank you for comment. We completely agree with your constructive suggestion that subjective markers like fatigue should not be included as predictors of severity or prognosis. Subjective markers can be difficult to be evaluated by using uniform standards. Additionally, after expanding sample size and reclassifying the patients into three groups, the subjective markers like fatigue were not significantly different between the groups. Therefore, these subjective markers like fatigue were not included in univariate and multivariate analysis in the revised manuscript.

3. Severity scores like APACHE or SOFA or PF ratio are not available. Such established parameters shall be reported and compared between the two groups, to show whether the predictors that authors report perform better than the established ones.

Response: Thank you for your advice. We completely agree with your insightful suggestion. Since the data was collected based on electronic medical records, some severity scores like APACHE, SOFA, PF ratio results were not available to be analyzed and support a better conclusion. We are sorry for the lack of the information, and we included this as one of limitations in the Limitation Section in the revised manuscript. Additionally, a very recent published study indicated the possibility of using IL-6 or CRP level to guide escalation of treatment in patients with COVID-19–related hyperinflammatory syndrome, and it also reported that qSOFA score was significantly different between mechanical ventilation group or and non-mechanical ventilation group [Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19[J]. *J. Allergy Clin. Immunol.*, 2020. DOI:10.1016/j.jaci.2020.05.008.]. We cited this study in the Discussion Section to further support our study and present a better interpretation.

4. Also, authors need to re-write the article to improve written English, in terms of grammar and syntax.

Response: Thank you for your suggestion. We have revised our manuscript according to the insightful and constructive comments from the editor and reviewers, and reviewed the whole manuscript carefully to avoid grammatical errors.