Peer Review File

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Reviewer A

Comment 1. The most common diagnosis in the cohort studied was septic shock, and no data are provided on the need for vasoactive drugs in patients who survived and those who died. I think this is an important point that needs to be addressed.

Reply 1: Thank you for your comment on this point. We agree that the need for vasoactive drugs would be important information. Unfortunately, since our study focused on the mechanical ventilation parameters that can be adjusted to improve outcomes in patients without ARDS, we did not have the data on vasoactive drug use in our record. However, the use of vasoactive drugs is a part of the SOFA scores used to assess the disease severity, and we also found an association between higher SOFA scores and 28-day mortality in the multivariate analysis results. We address this point in our limitation on page 11.

Changes in the text: We add the following sentences in the limitation of the study on page 11. Fourth, despite most patients in our cohort having septic shock as a principal diagnosis, the data on vasoactive drug use was not available in our record. However, the use of vasoactive drugs is a part of the SOFA scores used to assess the disease severity, and we also found an association between higher SOFA scores and 28-day mortality in the multivariate analysis results.

Comment 2. The presence of previous cerebrovascular disease was associated with mortality. It would be necessary to look more closely at whether the presence of comorbidity limited the therapeutic effort.

Reply 2: We agree that the patients who had a prior history of cerebrovascular disease in our study may have poor functional status, leading to limited therapeutic effort. We emphasized this point in the discussion on page 11.

Changes in the text: We hypothesized that patients with a previous history of cerebrovascular diseases may have poor functional status, which leads to limited therapeutic effort (On discussion, page 11).

Comment 3. It is unclear how many patients received non-invasive support before intubation. It is surprising that in patients with pneumonia and the Pao2/Fio2 values shown in Table 1, intubation was chosen directly. In addition, mean Fio2 needing was below 0.5 Please explain.

Reply 3: We did not have data on patients receiving noninvasive ventilation or high-flow nasal oxygen cannula before intubation. The PaO2/FiO2 values presented in Table 1 were the PaO2/FiO2 during invasive mechanical ventilation on the first day of ICU admission. The majority of patients in our cohort had mild hypoxemia on day 1 because most of them were intubated due to septic shock from extrapulmonary infections, and only 37% had pneumonia. For the FiO2, in our practice, we used the lowest possible FiO2 to achieve oxygen saturation of 92-96% in all mechanically ventilated patients.

Changes in the text:

To make this clear, we added the phrase "arterial blood gas and the ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration (PaO2/FiO2) during invasive MV on the first day of ICU admission" in the data collection subheading on page 5.

We also added the sentence "The majority of patients in our cohort had mild hypoxemia on day 1 because most of them were intubated due to septic shock from extrapulmonary infections, and only 37% had pneumonia" to the discussion on page 8.

Comment 4. I think the implications should be qualified as this is an observational study. An interventional study should have been done to determine the implications (change in ventilation strategy). The same would apply to the conclusions.

Reply 4: We agree with your comment. We changed the implication of this study to "carefully ventilating with the lowest possible PIP to achieve an acceptable gas exchange and patient-ventilator synchrony **might be** a suitable mechanical ventilation strategy to improve the outcomes of these patients. Further randomized controlled studies should be performed to confirm this hypothesis (Conclusion, page 12 and Highlight box).

Changes in the text: Thus, carefully ventilating with the lowest possible PIP to achieve an acceptable gas exchange and patient-ventilator synchrony might be a suitable mechanical ventilation strategy to improve the outcomes of these patients. Further randomized controlled studies should be performed to confirm this hypothesis (Conclusion, page 12 and Highlight box).

Comment 5. The multivariate model needs to be much better justified. What was the criterion for inclusion of variables in the logistic regression analysis? Which logistic regression model (entry, stepwise, etc.) was used? Finally, Table 4 should reflect all variables entered into the model (e.g. dynamic driving pressure at admission, which reached significance in the univariate).

Reply 5: Since there were 69 mortality events in our study, we were able to include up to 6 variables in the multivariate analysis. We planned to include all baseline characteristics and treatment variables that have statistical significance (p-value <0.05) in the univariate analysis in the multivariable model. However, in this study, the levels of positive end-expiratory pressure (PEEP) were similar in both groups (5 [IQR 5-6] in survived vs. 5 [IQR 5-7] in non-survived patients, p=0.143), so the peak inspiratory pressure (PIP) was attributed to the dynamic driving pressure (ΔP). Therefore, we did not include the dynamic driving pressure in the multivariate analysis. We explained this point in the method (page 6) and discussion section (page 10).

Changes in the text:

We added the sentence "We planned to include all baseline characteristics and treatment variables reaching statistical significance in univariate analysis into the multivariable model" in the method section on page 6.

We also added the sentence "The PIP in our study was attributed to the ΔP used to ventilate the patients because the PEEP levels were similar in both groups, so we omitted the ΔP in the multivariate analysis" in the discussion on page 10.

Comment 6. Table 3 is confusing because it mixes data from day 3 with data from day 7.

Reply 6: To avoid confusion, we removed the data on arterial blood gas results and dynamic respiratory system compliance on day 3 from Table 3 and the result section in the manuscript on page 8.

Changes in the text:
Respiratory parameters and Complications
Compared with survived patients, deceased patients had higher LIS (1.5 [IQR 1-2.25] vs. 0.67 [IQR 0-1.25], p<0.001) and were more likely to have worsening LIS (43% vs. 19%, p=0.009) on day 7. There were no significant differences in the incidence of pneumothorax, ventilator-associated pneumonia, new-onset ARDS, and rescue therapy for refractory hypoxemia (page 8).

Comment 7. Do not capitalize p (level of significance).
Reply 7: We changed "P" for the level of significance to "p" in the result section on pages 7 and 8 and all tables.
Changes in the text: We changed "P" for the level of significance to "p" in the abstract, the result section on pages 7 and 8 of the manuscript, and all tables.

Comment 8. Language should be checked by a native English speaker: There are some grammatical errors in the text.

Reply 8: Thank you for suggestions. We fixed the grammatical errors on pages 8 and 9.

Changes in the text:
In multivariable analysis, underlying cerebrovascular diseases (OR 7.09, 95%CI 1.78-28.28; p=0.006), higher SOFA score (OR 1.15, 95%CI 1.04-1.28; P=0.008), and higher average PIP used during the first three days of admission (OR 1.11, 95%CI 1.01-1.22; p=0.038) were factors independently associated with hospital mortality in acute respiratory failure patients without ARDS (Table 4), whereas baseline Cdyn (OR 1.01, 95%CI 0.98-1.03; p=0.555) and actual respiratory rate (OR 0.98, 95%CI 0.88-1.08: p=0.669) were not associated with mortality in the multivariable model (page 8).

However, the multivariable analysis disclosed only higher PIP during the first three days of ICU admission, the presence of cerebrovascular disease, and the higher SOFA score at admission were associated with 28-day mortality (page 9).

Reviewer B

Comment 9. This study highlighted that mortality and prognostic factors in acute respiratory disease without ARDS is similar to ones with ARDS. High mortality and the association between High PIP and SOFA score and prognosis in non-ARDS patients as well as ARDS patients is important. However, that clinical hypothesis cannot be confirmed by comparison

of clinical data between patients with and without ARDS. So, I consider that accuracy of study method is insufficient.

Reply 9: Thank you for catching this confusing point. This study did not compare the clinical data between patients with and without ARDS. We aimed to determine factors associated with increased mortality among acute respiratory failure patients without ARDS and focused on the mechanical ventilation parameters that can be adjusted to improve outcomes in these patients. To clarify this point, we removed the sentence regarding the mortality rate of ARDS patients in the LUNG-SAFE study from the discussion on page 9.

Changes in the text: We updated the discussion about the mortality rate in patients without ARDS on page 9. The mortality of non-ARDS patients in our study was 51%, which was higher than that reported in the other non-ARDS cohorts (21-35%). This could be explained by the finding that more organ dysfunction was found in our study. As noted in Table 1, the median SOFA score for overall patients was 10 [IQR 7-13], 8 [IQR 6-12] for alive, and 11 [IQR 8-14] for dead patients, while median total SOFA score for patients in the prior non-ARDS cohorts was 6 [IQR 4-9]. (Discussion, page 9).