

## Author response 1

Dear editors,

We appreciate you and the reviewers for the very constructive comments and suggestions to improve our manuscript. We have revised the manuscript according to these comments and have marked the changes with red texts. We address the reviewers' comments one by one as follows.

### Response to reviewer #1

#### Question 1: Comments to the Author

Relevant study with a crucial theme for ICU practice. Multicenter study with adequate study design and adequate analysis of the obtained data. Easy understanding and description of data.

Response: Thanks very much.

### Response to reviewer #2

#### Question 1: Comments to the Author

I have carefully read the manuscript entitled "noninvasive ventilation failure in patients with hypoxemic respiratory failure: the role of sepsis and sepsis shock by Duan and colleagues.

In this manuscript authors attempted to demonstrate an association between non-invasive ventilation failure and sepsis throughout a prospective, observational, multicentre trial.

NIV failure is an important area of research because it is associated with poor outcomes in ICU patients.

Overall the MS is well-written. Below are several points that require the attention of the authors.

Response: Thanks very much for your valuable suggestions. As your suggestion, we have deleted the patients with cardiogenic pulmonary edema and re-analyzed the data.

#### Question 2: Introduction.

1. The authors wrote "The possible reason is delaying intubation associated complications". I think authors would like to write "is a delayed intubation associated with complications." In any case, this affirmation is particularly true and should be developed to emphasize the importance of not delaying intubation when caring patients with acute hypoxemic respiratory failure.

Response: As suggestion, we have revised.

Question 3: 2. “a previous study has reported that severe sepsis was associated with NIV failure”. In fact, Meerer and colleagues reported that sepsis was one of the factors associated with failure by comparing the hospital outcomes of patients with NIV failure to those intubated primarily without prior NIV testing. However, to my knowledge, this is not the only study showing association between sepsis and NIV failure. For example, in a prospective multicentre cohort, Antonelli et al. included 354 patients with hypoxemic respiratory failure and reported an association between sepsis and NIV failure (OR 3 [1.7-5.8]) (doi 10.1007/s00134-001-1114-4). I recommend the authors to update their MS accordingly.

Response: Thank you to help us to identify the missed reference. As your suggestion, we have cited the reference you mentioned (Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001; 27:1718-1728).

Question 4: 3. page 6. “NIV was managed by attending physicians, respiratory therapists and nurses.” Levels of knowledge between physicians, respiratory therapist and nurses could vary largely. An experimented team providing NIV is necessary to avoid failure. I suggest that authors add data about level of knowledge of their team providing NIV in the selected ICU.

Response: I am sorry to make you confusion. We have detailed how the NIV was managed in methods section “The attending physicians managed the whole use of NIV including initiation and termination of NIV. The respiratory therapists and nurses assisted to manage the NIV including interface selection, parameter setting, humidification management and variable recording. All the participated centers have training protocol on how to use NIV. And all the participants have received strictly training before use of NIV.”.

Question 5: 4. “When the respiratory failure was reversed, the liberation from NIV was considered”. Could the authors precise which criteria were used to consider a reversed respiratory failure.

Response: On the weaning of NIV, we mainly referenced the oxygenation, respiratory rate and clinical symptom. If the PaO<sub>2</sub>/FiO<sub>2</sub> more than 300, respiratory rate less than 25 cycles/min and no clinical symptom indicated respiratory distress, the weaning can be considered. We have clarified it in methods section.

Question 6: 5. Page 7. Intubation criteria. I suggest the authors to better define intubation criteria. Hemodynamic instability. How was defined hemodynamic instability? Loss of consciousness. Which scale was used to measure it? Were the intubation criteria strictly predefined before the study began and were they the same in all ICUs?

Response: The intubation criteria were predefined and all the participants have been trained. Hemodynamic instability means mean arterial blood pressure less than 65 mmHg. Loss of consciousness means a sudden change of consciousness (such as a sudden change from awake to unconscious). We have clarified in methods section.

Question 7: Results.

6. "a total of 582 patients were enrolled." How many patients were screened for the study and how many patients were admitted in the ICUs during the study period? I suggest adding a study flowchart to know how many patients were eligible, and how many were actually included, in order to rule out or not a recruitment bias.

Response: I am sorry that we only enrolled the eligible cases. All the participants are clinical workers. In China, the shortness of manpower is very common. For example, in our ICU, the bed nurse ratio is 1:1.7. So, the routine work is very heavy. Considering these reasons, we only recorded the eligible cases.

Question 8: Discussion.

7. "To our knowledge, this is the first study to detailedly report the characteristics and outcomes of NIV in patients with sepsis and septic shock." This is not the main objective of the manuscript. The first sentence of the discussion must report a global answer to the main objective of the present study.

Response: We agree with your opinion. As suggestion, we revised it as "Current study explored the association between NIV failure and the severity of sepsis. We found that the sepsis was independently associated with NIV failure in patients with hypoxemic respiratory failure and the association was stronger in septic shock patients. The organ dysfunctions caused by sepsis were positively correlated with NIV failure."

Question 9: 8. "In no-sepsis, the NIV failure was 61.1% [...] the majority as cardiogenic pulmonary edema" In my opinion, you could not compare respiratory failure due to "de novo" acute respiratory failure to respiratory failure due to acute cardiogenic pulmonary edema. Page 9, authors say that "the use of NIV was controversial in hypoxemic respiratory failure". This affirmation is true, but does not include cardiogenic pulmonary edema. Consequently, I think cardiogenic edema should have been excluded from the study.

Response: We agree with your opinion. As suggestion, we excluded the patients with cardiogenic pulmonary edema and re-analyzed the data. In addition, we also revised this paragraph.

Question 10: 9. p10 “However, few studies have reported the associations between sepsis and NIV outcome” cf comment #2 + doi : 10.1186/1471-2466-14-19. The new data provided in our manuscript is to compare sepsis to sepsis shock.

Response: Thank you to help us to identify the missed reference. We cited this reference and revised these sentences as follows “And previous studies have reported that sepsis was associated with NIV failure.<sup>4,15</sup> Though these studies provided important knowledge on this field, they failed to stratify the severity of sepsis. In current study, we stratified the sepsis and reported the associations between NIV failure and severity of sepsis.”.

Question 11: 10. p11. “And [pulmonary infection] became an independent risk factor for 28-day in-hospital mortality. The reasons were unclear.” Maybe, this is due to ARDS?

Response: We agree with your opinion and have clarified it in this section.

Question 12: 11. Tables are clear and pleasant to read.

Response: Thanks.

Question 13: 12. References are clear and correctly reported in the manuscript.

Response: Thanks

Question 14: In conclusion, I suggest the authors to better explain their methodology and to highlight the data that are novel in their manuscript.

Response: As your suggestions, we have revised accordingly.