Peer Review File
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Reviewer A

The study "Safety and efficacy of noninvasive ventilation for acute respiratory failure in 3 general medical ward: A prospective cohort study" in a single center shows an overall rate of failure of NIV at 48 hours of 20.9%, and a hospital mortality of 12.8%. The rates are reported to be similar compared to other studies in a similar setting.

Major comments:

1. The primary outcome is a failure at 48 hours. But, there is no data on patients after 48 hours. Did those who made past 48 hours all do well and were liberated from NIV?
Reply 1: Thank you for your comment. We decided to use the rate of NIV failure at 48 hours as the primary outcome because many previous studies demonstrated that late NIV failure which defined as > 48 hours after initiation of NIV was associated with poor outcomes (Moretti M, et al. Thorax 2000;55:819-25, Ozyilmaz E, et al. BMC Pulm Med 2014;14:19). In addition, patients who made past 48 hours in our cohort had a favorable outcome and were liberated from NIV.
Changes in the text: We added the following sentence “We used the rate of NIV failure at 48 hours as the primary outcome because the previous studies demonstrated that late NIV failure, which defined as more than 48 hours after initiation of NIV, was associated with poor outcomes (17,18) (Page 12, line 212-214)”.

2. At what time period is the mortality rate calculated? 48 hours, 30-days, 90 days?
Reply 2: We reported in-hospital mortality in this study which is the mortality rate at hospital discharge (it has been mentioned in Page 8, line 126-127).
Changes in the text: -

3. Regarding post-extubation patients included in the study: they would have been in ICU and then were extubated. What were they intubated for? How long were they on mechanical ventilation? How long were they in ICU on NIV post-extubation?
Reply 3: Thank you. As we mentioned in the Methods section that our hospital had a limitation of ICU beds and many patients with acute respiratory failure who had stable hemodynamics, normal level of consciousness, and no need for organ support were considered to admit at general medical wards. Extubation were done at wards after recovery from acute respiratory failure. Main cause of endotracheal intubation for this group was pneumonia, followed by extrapulmonary sepsis, and congestive heart failure.
Changes in the text: -

4. The study data is from 2017-2018. It is 5 years old and as mentioned in the limitations in a post-pandemic environment. Did the author use NIV during the pandemic in non-ICU setting? They can mention their experience in the discussion.

Reply 4: Thank you. We did not use NIV in general wards during the pandemic to prevent viral transmission from aerosol dispersion.
Changes in the text: -
Minor comments:
See attachment (Reviewer A-JTD-23-732-RV9-4741.pdf)
Reply minor comments: Thank you very much. We revised the manuscript according to Reviewer 1's comments.
Changes in the text:
- We modified the Highlight box as follows:
  - "It is mostly…. (Page 5, line 56)".
  - "…and safe in the setting with well trained…. (Page 5, line 56)".
  - "This study supports the use of noninvasive ventilation outside the intensive care unit is safe and effective. (Page 5, line 56)".
- We modified the Introduction as follows:
  - "..in NIV use at admission in the intensive care unit (ICU)… (Page 6, line 67-68)".
  - "The overall intubation rate in these studies… (Page 6, line 69)".

Reviewer B

The manuscript is about a prospective cohort study which investigates the use of non-invasive ventilation in general medical wards (GMWs) in a single study centre. This is an important clinical issue especially when beds in intensive care units are limited.
There are several flaws/limitations that I wish to highlight and clarifications to be sought from the authors.
1. This concept is not novel. There has been a RCT among COPD patients that investigated the early use of NIV after GMW admission among such patients with mild to moderate acidosis that reduces invasive mechanical ventilation and in-hospital mortality.
Reference:
Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000;355(9219):1931-5.
Reply 1: Thank you. We agree with the reviewer that our study is not novel; however, we would like to present the utilization of NIV in general medical wards in resource limited country for ICU beds. Our study demonstrated that use of NIV in general medical wards with well-trained staffs was safe and feasible.
In addition, NIV was used in various conditions in our study including hypoxemic respiratory failure, cardiogenic pulmonary edema, postextubation period, and exacerbation of COPD that will represent the real-world practice in resource-limited country.
Change in the text: -

2. The authors should describe what types of NIV they use in the methods, specifically, mask vs helmet type, any use with high flow nasal cannula oxygen.

Reply 2: Thank you. In our study, 72.1% of enrolled subjects received dedicated NIV and 27.9% of them received NIV via the ICU ventilator. We used oronasal mask in all enrolled subjects. We did not use high-flow nasal cannula in this cohort. We have already mentioned in the Results section (page 10, line 153-154).
Change in the text: We added "…included the type of NIV (dedicated NIV or ICU ventilator) and NIV interface,… (page 8, line 119-120)".

3. The starting of NIV is described at the physician's discretion. I wish to ask the authors to clarify whether in general, the use of NIV is after medical therapy failure or there are patients who are started as first line therapy. NIV as first line therapy in acute pulmonary edema (APO) is not an uncommon practice and may introduce selection bias as APO is the pre-dominant diagnosis for starting NIV in this study. These patients with early NIV in APO might not need NIV after all or need it for a very short period of time (ie 1-2 hrs).
Reply 3: Thank you for your comment. To clarify this issue, our department regularly organizes the training session of noninvasive respiratory support (including working principles, monitoring, and indications of NIV based on the international guideline) for physicians and nurses and we also have a supporting system for pulmonary consultation. The initiation of NIV in this study was decided by the attending physician based on patient's clinical status and the appropriateness of NIV use. We think that our study would represent the real-world practice of NIV use in general medical wards.
Change in the text: -

4. The authors should describe with some details how patients receiving NIV are monitored for respiratory failure (RF) especially hypercapneic RF i.e by monitoring of conscious level, arterial blood gas sampling with/without arterial line, trend of venous blood gas or mixture of these methods.
Reply 4: We closely monitored patient's clinical status, vital signs, oxygen saturation, and arterial blood gas (if necessary) during first 48 hours of NIV.
Change in the text: We modified the following sentence "Patients are taken care of and continuously monitored their clinical status, vital signs, oxygen saturation, and arterial blood gas (if necessary) by a multidisciplinary team… (Page 7-8, line 106-107)".

5. One big limitation is that there is no comparison group, i.e no group without exposure to NIV. Without this group, one cannot determine and conclude the treatment effectiveness of NIV confidently. One cannot calculate a sample size to rule out a false positive result. The observed rate of NIV failure of about 20% is hard to interpret without a comparison group.
Reply 5: We agree with the reviewer that our study had no comparison group. We have already mentioned in the limitation (page 15, line 266).
Change in the text:

6. The primary outcome is the rate of NIV failure (intubation, re-intubation or death) at 48 hrs, This is a composite outcome. The use of composite outcome might dilute the

importance of the most important component when on component is not that common. Mortality at 48 hrs might not be very common. The authors did state that the hospital mortality (secondary outcome) is 12.8% but this is not mortality at 48 hrs.
Reply 6: We defined the definition of NIV failure (intubation, re-intubation or death) at 48 hours based on the previous studies (Moretti M, et al. Thorax 2000;55:819-25, Ozyilmaz E, et al. BMC Pulm Med 2014;14:19).
Change in the text: We added the following sentence "We used the rate of NIV failure at 48 hours as the primary outcome because the previous studies demonstrated that late NIV failure, which defined as more than 48 hours after initiation of NIV, was associated with poor outcomes (17,18) (Page 12, line 212-214)".

7. Another major flaw from no sample size consideration is that the logistic regression model for factors associated with NIV failure is unlikely to be adequately powered as the overall sample size is 86 patients (small-size study).
I think the factors are not determined a priori and this together with small sample size, there will be problems with false positive results and multiple comparisons.
Reply 7: Thank you. We agree that this is our limitation and it might be also affect the logistic regression analysis. We have already mentioned in the study limitation.
Change in the text: -

Reviewer C

In this non-randomized cohort study, the authors evaluated the efficacy of NIV in a general ward setting. The results of the study demonstrated the feasibility of NIV outside the ICU and also the rather high efficacy of NIV (the most common indication was cardiogenic pulmonary edema).

This paper is well written and I have no major concerns.
Reply: Thank you very much.

Minor concerns:
1. The authors did not use blood gases, however, SpO2 does not give us a clear idea of the severity of hypoxemia, it is better to use the SpO2/FiO2 index
Reply 1: Thank you. We agree with the reviewer that SpO2/FiO2 will give more information regarding the severity of hypoxemia than SpO2 alone; however, dedicated NIV was mostly used in the present study could not directly set and measure the FiO2. We can only adjust oxygen flow rate to achieve target SpO2. Thus, we could not estimate FiO2 with this kind of machine.

2. Line 136 - spontaneous/time mode is more logical to refer it as pressure assist control mode
Reply 2: We modified the term according to the reviewer's suggestion.
Change in the text: "…followed by pressure assist control spontaneous/time mode (27.9%)…. (Page 10, line 156)".

3. Chronic airway disease – what does that mean? (COPD? Asthma?)
Reply 3: Thank you. All patients with exacerbation of chronic airway disease in this study was COPD patients.
Change in the text: "…and exacerbation of chronic obstructive pulmonary airway disease (14.0%).. (Page 10, line 151-152)" and "..and the exacerbation of chronic obstructive pulmonary airway disease. (Page 11, line 186)".

Reviewer D

1. To my knowledge, APACHE and SOFA scores are used in ICU to predict/estimate ICU mortality. What is the rationale for using them outside the ICU?
Reply 1: Thank you. We agree with the reviewer that APACHE and SOFA scores are routinely used to predict the outcome in ICU. However, we decided to use these predicting scores because our enrolled subjects were critically ill patients but they had to manage at general medical wards because of the limitation of ICU beds. In addition, many studies have also used these scores in critically ill patients who received noninvasive respiratory support either NIV or high-flow oxygen therapy at wards (Moretti M, et al. Thorax 2000;55:819-25, Pirret, et al. Intensive Crit Care Nurse 2017;42:127-34, Lee, et al. J Clin Med 2022;11:1736, Colombo, et al. Respir Res 2022;23:171).
Change in the text: We added the following sentences in the limitation "Last, the severity scores including APACHE III and SOFA are routinely used in ICU to predict the mortality; however, we used these scores in the present study because our enrolled subjects were critically ill patients. In addition, many studies have already used these scores in critically ill patients who were managed at general wards (17,32-34) (Page 15, line 273-277)".

2. Regarding the primary and secondary outcomes,
• in the abstract sections:
o "The primary outcome was the rate of NIV failure at 48 hours. Secondary outcomes included the rate of endotracheal intubation, hospital mortality, and factors associated with NIV failure."
• in the methods section:
o "The primary outcome was the rate of failure of NIV at 48 hours, which was defined as a subsequent requirement for endotracheal intubation, reintubation, or death within 48 hours of NIV use. Secondary outcomes were cause of NIV failure and in-hospital mortality."
- I'm a bit confused regarding the ETI. Is it part of the primary outcome as stated in the methods section or a separate secondary outcome as stated in the abstract section?
Reply 2: Thank you. It's our mistake. Endotracheal intubation is one of the criteria for defining NIV failure. We deleted it from the secondary outcome in the Abstract.
Change in the text: "Secondary outcomes included the rate of endotracheal intubation, hospital mortality and factors associated with NIV failure (Page 3, line 39)".

3. In the discussion section, there are no discussion points regarding the factors for NIV failure mentioned in the result section or other factors like comorbidities, etc.
Reply 3: Thank you for your suggestion.
Change in the text: We added the following paragraph in the Discussion "Many severity scores such as APACHE II, SOFA, or Simplified Acute Physiology Score (SAP) II scores can be used to predict the outcome of NIV in critically ill patients. Two previous studies demonstrated that higher SOFA score was a significant risk factor for NIV failure in patients after extubation (28,29). A prospective cohort study by Correa and colleagues (30) found that higher APACHE II score was a predictor of NIV failure in 85 patients with acute respiratory failure who received NIV. Furthermore, Carron et al. (31) demonstrated that patients with severe community-acquired pneumonia who failure NIV had significantly higher SAPS II score. Our study also found that higher SOFA score was associated with NIV failure. Thus, illness severity is an important predictor of NIV failure and this finding was consistent across several severity scores and in various conditions for NIV use (Page 14-15, line 253-263".

4. In Table 2:
• "Others" should be defined/explained in the result section.
Reply 4.1: There were 2 subjects with "others" for the indication of NIV which is extrapulmonary sepsis.
Change in the text: We modified the sentence in the main manuscript as follows: ".., neuromuscular disease (7.0%), and extrapulmonary sepsis (2.3%) (Table 2) (Page 10, line 152-153)" and in Table 2.
• Were the presented NIV settings considered to be initial or the optimal/final settings?
Reply 4.2: NIV settings in Table 2 represent the optimal settings of NIV by the attending physician on Day 1.

5. In Table 5:
• Why Multivariate analysis was done for only gender and SOFA when for example the p-value of the gender is more than 0.05?
Reply 5: Thank you for your comment. To clarify this issue, we selected the factors showing the association from the univariate analysis with P-value < 0.10 into the multivariate regression analysis.
Change in the text: We added the following sentence "Factors associated with NIV failure in the univariate analysis ($P < 0.10$) were put into the multivariate regression analysis. (Page 9, line 138-139)".

Reviewer E

1. SOFA score was associated with failure of NIV (Line 32, 36, 154, 162 key findings) - was high score associated with NIV failure? This is presented and implied but not clear in the writing.
Reply 1: That is correct. Higher SOFA score in our study was associated with NIV

failure.
Change in the text: "…the male gender and higher the SOFA score were significantly associated with NIV failure.. (Page 11, line 175) and (Page 11, line 183)".
2. Post-extubation failure as an indication for NIV use was 25.6% - given that this data is from the medical wards, were patient's extubated and placed on NIV and transferred from ICU to the medical ward?
Reply 2: As we mentioned in the Methods section that our hospital had limited ICU beds so many intubated patients were admitted at general medical wards and then extubated to NIV here after recovery from acute respiratory failure.

Reviewer F

This study was well written with small sample size. This study focused on evaluating the safety and efficacy of using NIV and the factors associated with NIV failure in general medical wards. I have several concerns.
1. According to the relevant guideline on clinical study, we suggest supplement a figure about the inclusion flow to indicate the recruited course.
Reply 1: Thank you for your suggestion. We add a figure showing the inclusion flow.
Change in the text: "A total of 86 subjects were enrolled in the study (Figure 1) (Page 9, line 144)"

2. We suggested the criteria about when NIV should be adopted for a specific patient although the author stated "the indication and settings of NIV are considered by the attending physician".
Reply 2: Thank you. We have no specific guideline or criteria for implementing NIV in our general medical wards and it depends on the decision of the attending physician and the appropriateness of NIV use. However, our department regularly organizes the training session of noninvasive respiratory support (including working principles, monitoring, and indications of NIV based on the international guideline) for physicians and nurses and we also have a supporting system for pulmonary consultation.
Change in the text: -

3. The sample size was small, we suggest a description about how to get the sample size or at least a statement in the limitation.
Reply 3: Thank you for the suggestion. We did not calculate the sample size.
Change in the text: We added the following sentence in the limitation: "First, this is a single center, non-randomized study, and small sample size (Page 15, line 266)".

4. Some studies about NIV with helmet (DOI: 10.1038/s41598-020-78607-5) or NIV used outside of ICU (DOI:10.1016/j.jss.2019.09.008) were suggested to be concerned.
Reply 4: Thank you for your suggestion. We added the study of NIV with a helmet in the discussion per your suggestion. For the other study, it is outside our scope because our study focused on patients who were admitted in the Department of Medicine.
Change in the text: We added the following sentence "In addition, Liu and colleagues

demonstrated that NIV with a helmet significantly improved oxygenation and tolerance and decreased NIV-related complications compared to NIV with face mask in patients with chest trauma(26) (Page 14, Line 246-248)".

5. For fig 1, the significant difference between the failure or success of NVI should be marked and additionally the figure legend was missing.
Reply 5: For figure 1, we did not analyze the difference between NIV success and failure in each indication for NIV use. We provided the figure legend in the main manuscript (page 20, line 411-412).
Change in the text: -