Peer Review File

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Reviewer A

"Effect of high flow nasal cannula oxygen therapy in combination with non-invasive ventilation on critically ill patients with acute respiratory failure a retrospective study" is a retrospective study to investigate the utility of the combination of HFNC and NIV.

Comments

1. Introduction is not enough. The relationship between HFNC and NIV is not mentioned at all; the combination of HFNC and NIV suddenly appears in the last paragraph of the Introduction. Please provide at least one paragraph describing the combination of the two.
Reply: We thank the reviewer for this professional suggestion. NIV and HFNC have shown positive effects in lung ventilation. They can improve oxygenation, reduce respiratory work, and achieve a more balanced ventilate flow ratio. Additionally, they can increase intrathoracic pressure, leading to decreased right cardiac venous return and reduced left ventricular transmural pressure. These unique advantages make NIV and HFNC widely utilized in various clinical settings. We have supplemented the combination of HFNC and NIV in the revised paper (Line 87-91).

2. I can not understand method. Outcomes are NIV days and ICU and hospital stays, but HFNC is not included. The purpose of the study does not match the outcome. Curative effect is too vague to know if the correct decision has been made. Suddenly a grouping statement appears in the Results. This should be determined by METHOD before the study and then analyzed according to that grouping.
Reply: We thank the reviewer for this reminder. We have revised the method of this study as follows: The NIV-treated patients were assigned into two groups according to the oxygen inhalation mode during intermittent NIV: (I) standard group: normal oxygen inhalation was used at the NIV interval; and (II) Research group: treated with HFNC at the NIV interval.

3. INTRODUCTION lacks an explanation of the background of the study and there are major problems with the methodology of the study. The significance of the research is not clear.
Reply: We thank the reviewer for this professional suggestion. We have revised the introduction. This retrospective study was conducted to explore the clinical effect of high-flow nasal cannula (HFNC) combined with non-invasive ventilation (NIV) in the treatment of critically ill patients with ARF.

Reviewer B

The question if HFNC instead of standard oxygen therapy could have additional beneficial effects in patients with intermittent NIV is interesting for clinical practice. However, as the patients seem to be randomized to a treatment group, it should be clearly stated in the manuscript, from which randomized clinical trial the retrospective data were taken.

The source of the retrospective data is missing (clinical trial, hospital database?).
Was the assignment to a group based on which modality was used longer during the first 24 hours or were the patients randomized in a clinical trial? Does the ethics registration apply to this clinical trial or the retrospective protocol?
Reply: We thank the reviewer for this professional suggestion. A total of 532 critically ill patients with ARF treated in our hospital (The Second Affiliated Hospital of Soochow University) from January 1, 2019, to December 31, 2020, were enrolled. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (Approval No. JD-HG-2021-49). The ethics registration applies to this clinical trial.

A further indicator that the data were from an unnamed clinical trial are the randomizations ("randomizzazione") and the inclusion criteria ("parametri di inclusione, SpO2/FiO2…") in Figure S1. What does randomization to HFNC symmetric ("simmetriche") or asymmetric ("asymmetriche") mean? The meaning of "VMK" is also not defined.
Reply: We thank the reviewer for this careful review. The high flow oxygen group was treated with a high flow oxygen inhalation device (Fisher Paykel AIRVO2) with an inhalation flow rate of 20-60L/min and an inhalation oxygen concentration of 21-100% in order to maintain SpO2 ≥ 92%. When patients experience the following conditions, tracheal intubation and ventilator assisted ventilation were given: ① hemodynamic instability; ② Worsening of neurological condition; ③ Respiratory failure worsening, respiratory rate>40/minute, assist respiratory muscles to participate in respiration; ④ PH<7.35, SpO2<90%, lasting more than 5 minutes (supplement figure). VMK stands for oxygen index k value.

How were potential cross-overs from HFNC to standard oxygen therapy during intermittent NIV dealt with?
Reply: We thank the reviewer for this reminder. In the future, the application time of non-invasive positive pressure ventilation combined with nasal high flow oxygen therapy, when to apply in patients with different etiologies, when to avoid the application, when to stop the specific strategy, and how to coordinate the time of the alternative application of the two are still worthy of in-depth discussion.

Line 40 and 96: Should read "screened" instead of "enrolled". The inclusion/exclusion criteria were only applied after this screening.
Reply: We thank the reviewer for this reminder. We have corrected this error.

Line 116: There cannot be an "NIV group", as all patients had to receive intermittent NIV in order to be included in this study, please change the sentence accordingly.
Reply: We thank the reviewer for this reminder. We have revised the method of this study as follows: The NIV-treated patients were assigned into two groups according to the oxygen inhalation mode during intermittent NIV: (I) standard group: normal oxygen inhalation was used at the NIV interval; and (II) Research group: treated with HFNC at the NIV interval.

Lines 220-221: Should probably read …"(15-18), and promote relief from clinical symptoms".
Reply: We thank the reviewer for this reminder. We have revised the sentence as follows: HFNC can provide the oxygen concentration and oxygen flow required by the body, ensure the oxygen relative humidity, reduce the resistance of the upper respiratory tract, and reduce the energy consumption of the body, effectively relieve the hypoxia state of patients with ARF and

reduce the degree of CO2 retention in the body, so as to promote relief from clinical symptoms (15-18).

Please mention the VAS score also in the methods section and explain it in more detail. Which symptoms were assessed for the VAS and when? Also explain the ROX index in more detail in the methods section (which factors were calculated into it, add a reference).
Reply: We thank the reviewer for this careful review. VAS score and ROX index were described in the method and related literature was added.

The different behavior of ROX index (lower in HFNC group) and VAS score (higher in HFNC group) should be described in the results section.
Reply: We thank the reviewer for this careful review. We have modified our text as advised "Non-invasive ventilation (NIV) and high flow oxygen (HFNC) are two forms of respiratory support for patients with respiratory failure prior to invasive ventilation. In recent years, the use of HFNC has been increasing, and delayed intubation caused by HFNC use will increase the mortality of patients. Therefore, the ROX index is proposed to guide when to administer endotracheal intubation in HFNC. Interestingly, there was no significant difference in the length of invasive ventilation time, but there was a significant difference in the ROX index. In addition, the VAS scores were apparently decreased in the HFNC group compared the Standard group. " (see Page 8, line 210-218)

Lines 224-228 should be rewritten more clearly: Lines 224-225 in the discussion seem to imply that the invasive ventilation time was somehow connected to the ROX index. This should be explained in more detail. In lines 227-228 it is stated that the VAS decreased in the HFNC group, while higher values in the HFNC group are shown in Table 2. Could this refer to a decrease from baseline, which is not shown in the results? Please clarify.
specify.
Reply: We thank the reviewer for this careful review. Non-invasive ventilation (NIV) and high flow oxygen (HFNC) are two forms of respiratory support for patients with respiratory failure prior to invasive ventilation. In recent years, the use of HFNC has been increasing, and delayed intubation caused by HFNC use will increase the mortality of patients. Therefore, the ROX index is proposed to guide when to administer endotracheal intubation in HFNC. Interestingly, there was no significant difference in the length of invasive ventilation time, but there was a significant difference in the ROX index. In addition, the VAS scores were apparently decreased in the HFNC group compared the Standard group.
Changes in the text: NONE

Which observations of VAS and ROX are shown in Table 2? The assessment after 24h? Please specify.
Reply: We thank the reviewer for this careful review. VAS is one of the commonly used pain scales. Patients are asked to mark the horizontal line according to their feelings, which is used to indicate the degree of pain. A score of 1-3 indicates mild pain, a score of 4-6 indicates moderate pain, and a score of 7-10 indicates severe pain.
Changes in the text: NONE

Why were patients receiving catecholamines excluded?
Reply: We thank the reviewer for this careful review. Catecholamines have an excitatory effect

on respiration, speeding up the respiratory rate, deepening the respiratory movement, and dilating bronchial smooth muscle.
Changes in the text: NONE

In Figure 1 it should probably read “33 pulmonary edema” instead of “pneumonia edema”, as pulmonary edema was reported as an exclusion criterion, please correct.
Reply: We thank the reviewer for this careful review. We have revised the term "pneumonia edema" as "pulmonary edema".

Figure S1 has to be translated to English and has to match the retrospective study presented in the manuscript. Figure S1 does not include the measurements at 24 hours looking at the numbers of minutes in the blue arrow.
Reply: We thank the reviewer for this careful review. Figure S1 has to be translated to English.

Reviewer C

Thank you for your submission and your paper entitled Effect of high-flow nasal cannula oxygen therapy in combination with non-invasive ventilation on critically ill patients with acute respiratory failure: a retrospective study. It is a good clinical question as to what the best therapy is when bridging between NIV breaks.

The premise is good. However, at this stage, I believe there are several key issues in the paper which need to be addressed before it can be reconsidered.

Introduction
- References 1 and 2 do not seem to support the statement form their corresponding sentence
- No reference for lines 64, 69, 73-75
- It is not clear from my reading that HFNC prevents alveolar collapse, and that much of the effect is preventing EDAC and diaphragm work/P-ILI.
- Line 83-91 needs to be referenced
Reply: Thank you for the above comments. We have fixed each of the issue and highlighted with yellow.

Methods
- It is not clear that this is a retrospective, observational, cohort study --> perhaps a sentence to clarify this.
- Line 116 - use the tern NIV group --> my understanding is that there was not an NIV group. Both groups used NIV correct?
Reply: Yes, both the group received NIV. At interval, one group received standard oxygen while another group received HFNC.
Changes in the text: NONE

- No talk about who or where the patients were cared for? ICU, General Ward, Respiratory etc
Reply: Line 107.

- No discussion around protocols for escalation/de-escalation in NIV/HFNP

Reply: Line 136-141.

- Lines 121-126: Not sure what these are? Are they outcome measures/failures and figure S1 is in Italian so not able to use it to interpret?
Reply: they are exclusion criteria.

- Say that the protocol for NIV and oxygen therapy is for SpO2 >= 92% --> this seems to be regardless of CO2/hypercapnia where targets would be 88-92%. Was this accounted for? Was this a group that was identified and analysed separately?
Reply: Yes this was accounted for. And SpO2 >= 92% is regardless of CO_2
Changes in the text: NONE

- Curative effect paragraph: I take it this is the primary outcome measure? No definition of what is 'markedly improved' or deteriorated - very subjective. In table 2, suddenly ROX and VAS appear but they were not discussed in methods as being outcome measures.
- No discussion about what oxygen therapy devices were used in the COT group.
Reply: Ans: nasal cannula oxygen inhalation.
Changes in the text: NONE

Statistics
- Was there a power calculation?
- Was there consideration for a multivariate analysis of the significant variables?
- What confounders did you explore and how did you account for them?
Reply: Wilcoxon signed-rank test was employed. Survival time was analyzed by Cox regression
Changes in the text: NONE

Results
- Lines 171-172 belongs in methods
- ROX index: This is a predictive tool for failure of HFNP in T1 respiratory failure. Not a tool for post NIV (which I take it is the group explored here). It would not be an appropriate index to use. Furthermore, it is higher in the standard group which suggests reduced chance of intubation --> this was not mentioned or discussed
- VAS - is higher better or worse? Not mentioned in methods
- With ROX and VAS values given, was this at study entry/exit/censure/event? Not clear.
Reply: It was one of the outcome measures.
Changes in the text: NONE

- Insufficient data around the IPAP/EPAP/FiO2 in the NIV in each group, and no data on the oxygen delivery devices or Fio2 in the COT group or the flows and Fio2 rates in the HFNC groups
- The time points used: Was this when they started NIV, was this when NIV came off the first time? Did they go back to NIV between 1 hour and 24 hours? Need number of patients still available for assessment at each time point if the outcome measure was reached.
Reply: Actually, NIV was given when required. The study classified the patients into 2 groups, namely, Standard group (receiving the normal oxygen inhalation) and HFNC group (receiving oxygen through the high-flow nasal cannula instead of normal method). At times, whenever

required, each group was given oxygen. During all the periods of assessments, all the patients were assessed the patient who could not be assessed at any interval, was excluded from the study.
Changes in the text: NONE

- Concerns around the primary outcome - is it a composite value of subjective and objective markers without clear definitions of what constitutes 'markedly' or an aggravation 'tendency'? A primary outcome with objective parameters would be more appropriate --> ie predefined failure and how many in each group reached that?
Reply: By Aggravation tendency, the severity of clinical features and the state of exacerbation was meant.
Changes in the text: NONE

- Should have a subgroup analysis for aetiology of ARF and a T1 vs T2 subgroup analysis. This may explain some of the mortality benefit, particularly if over oxygenation was observed in one group c.f. another
- Table 1 - individual rates of each respiratory aetiology and individual p values need to be given. It reads as though the p value of 0.37 is a p value for all indications lumped together
- smoking status?
- Figure 2 - once again what time points are these taken from? Mean Co2 in both groups was > 50 mmHg - So why was a target SpO_2 of 92% written down as a treatment goal? Need the amount of time on or off NIV in between each time point to assess if it was the COT or the HFNC making the physiologic parameters change.
Reply: These are the intervals of measuring the variables like PaO_2, $PaCO_2$, P/F and SaO_2.
Changes in the text: NONE

- Wanted to check the p-value of the NIV treatment duration. While I can see that the two means are quite distinct, there appears to be significant overlap in the SD between the two groups. Could the authors confirm the significance of this result?
Reply: SD is different in both the groups and the NIV treatment duration is significantly different between the two groups (P=0.002).
Changes in the text: NONE

Discussion
- Line 204-205 needs references as most respiratory failure would likely be due to parenchymal lung disease such as ards/consolidation rather than pure 'ventilation
- Line 206 - Does it mean to be 'anti spasmodic'? Furthermore, those treatments do not specifically improve patient pH
- NIV is not new - around for 40 years
- Need a reference for airway remodelling statement - apologies if I missed it, but couldn't find it int he provided references 10-14
- No discussion on why the ROX index was used and why It was higher in the COT group, when higher scores mean less likely to deteriorate. This is line 225.
Reply: It was swapped with each other. Now it is fixed.
Changes in the text: (see Page 8, line 210-218)

Conclusions
- this is a retrospective paper, you cannot make statements around clinical treatment effect –

Lines 255-259.
Reply: It was pointed out that this study can be clinically important one as the findings is useful in clinical practice.

- Limitations don't talk about potential for bias in retrospective cohort observational studies
Reply:This study may have potential biases. These include selection bias, potentially skewing patient representation. Information bias may arise from data accuracy in medical records. Confounding variables, not controlled for, could influence intervention effectiveness. Lead-time and survivorship biases might affect observed outcomes. Acknowledging and addressing these biases is crucial for accurate interpretation of the study's findings
Changes in the text: (see Page 11, line 305-310)

Most of this is around references and methodology. The treatment characteristics are not clear between the two groups, which is important to ascertain why the effects were different. This makes the conclusions limited.

Reviewer D

I have read with interest the study. The results were expected, however, the study further confirm already known evidences in favor of HFNC.

I have some suggestions:

- The authors should refer to recent ERS guidelines on HFNC (PMID: 34649974)
Reply: Oczkowski S, Ergan B, Bos L, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J. 2022;59(4):2101574.
Changes in the text: (see Page 13, line 364-366)

- Another important study is by Grieco et al. (PMID 33764378) please discuss it
Reply: Grieco et al. reported comparable improvements in oxygenation and respiratory rates between the HFNC and NIV groups, with no significant differences in ROX Index values (23-25).
Changes in the text: (see Page 10, line 277-279)

- Discussion is a summary of the results, rather than a discussion of findings in the light of actual evidences. Please, remodulate it.
Reply: The portion which sky-coloured/light blue coloured, are part of discussion of findings in the light of actual evidences.

- Are there differences in the use and outcomes after extubation (in case of intubation?) Please refer also to the study by Maggiore (PMID: 35849787)
Reply: High-flow oxygen yielded less frequent use of rescue noninvasive ventilation. Related studies have also reported similar results.

Changes in the text: (see Page 11, line 291-292)

Reviewer E

1. Table 1

a. How were these data presented in your Table? mean±SD? mean±SEM? Please either give explanations inside Table or in table footnote.

67.78±16.82	66.97±17.08

Reply: As ## **Statistical analysis** described that the measurement data were displayed with mean ± standard deviation if they followed the normal distribution, and the paired t-test was employed.

b. Please check this symbol ‘`’. If not necessary, please remove.

1.256`	0.65
0.958	0.58

Reply:We have remove the symbol ‘`’.

2. When using abbreviations in table/figure or table/figure description, please mention the entire expression in a footnote below the corresponding table/figure. Please check and revise. Such as: HFNC, FC, Spo2, Fio2, ECO, LUS, TF, etc. (figure S1)

Reply: HFNC, high-flow nasal cannula; VAS, visual analogue scales. SpO2 , Saturation of Peripheral Oxygen; FiO2, Fraction of inspiration O2; VMK stands for oxygen index k value. ECO, LUS, TF have no special meaning.

Changes in the text :line 459-460.

3. Reference/citation

a. If available, please update your reference list by including related literatures published within a year (2023). Some of the references are outdated. References should be cited consecutively and consistently according to the order in which they first appear in the text. Format of reference list should be: Author 1, Author 2, Author 3, et al. Title of the article. Journal Abbreviation name Year; Volume: Page numbers.

Reply: We have update our reference.

Changes in the text :line 368-372; line 374-377.

b. The author’s name does not match the citation. Please revise.

“… which is consistent with the Frat et al.’s study report (1).”

1. Cammarota, G, Esposito, T, Azzolina, D, Cosentini, R, Menzella, F, Aliberti, S, & De Robertis, E (2021). Noninvasive respiratory support outside the intensive care unit for acute respiratory failure related to coronavirus-19 disease: a systematic review and meta-analysis. Critical Care, 25, 1-14.

Reply: We have revise the author's name.

c. Please check if citations are missing, as you mentioned "studies".
"Other studies support the notion that HFNC can be as effective as other non-invasive ventilation methods in certain clinical contexts."
Reply: We have checked the citations.