Annals of Translational Medicine

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Peer Review File

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Reviewer A

I read with attention the article by Aline Mela dos Reis entitled "Effect of Spontaneous Breathing on Ventilator–free days in Critically Ill Patients – an analysis of patients in a large observational cohort".
The authors compared the number of ventilator-free days according to according to the amount of spontaneous breathing (< or > 50%) during the first 48 hours of mechanical ventilation by analyzing 3,380 patients from the MIMIC database.
The main result is that the amount of spontaneous breathing was not associated with the duration of mechanical ventilation even after adjustment for confounding factors. As a signal, a high amount of spontaneous breathing was associated with shorter duration of mechanical ventilation in survivors.

The article is clear and well written. These are my comments:

Introduction:
"However, assisted ventilation may also result in high inspiratory efforts and a higher respiratory drive, which can potentially increase lung injury. 9, 10"
I am sorry but, on the contrary, the reference from LUNG safe (PMID: 30379668) shows that spontaneous breathing is not associated with worse outcomes and may hasten liberation from the ventilator and from ICU. Please change
REPLY: We thank the reviewer for this important comment. Indeed, the citation of the reference 9 (PMID: 30379668) was wrong, as noted.
CHANGES IN THE TEXT: We removed the reference number 9 (PMID: 30379668) from this sentence.

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"The primary hypothesis tested was that the amount of spontaneous breathing is associated with the number of ventilator–free days".
The authors could reformulate their hypothesis. After their introduction, I believe that their primary hypothesis was to assess whether the amount of spontaneous breathing was associated with an increased number of ventilator-free days.
REPLY: We thank the review for this nice suggestion. As suggested, we changed this.
CHANGES IN THE TEXT: Now the hypothesis reads:
'The primary hypothesis tested was that the amount of spontaneous breathing is associated with an increased number of ventilator–free days at day 28.'

From 2001 until 2012, 3,380 patients were selected for the current analysis, 2,374 (70.2%) were classified as '≥ 50% spontaneous breathing' patients and 1,006 (29.8%): please delete digits after the decimal point (70% and 30%, respectively).
REPLY: We thank the review for this suggestion. As suggested, we changed this.
CHANGES IN THE TEXT: Now the sentence reads:
'From 2001 until 2012, 3,380 patients were selected for the current analysis, 2,374 (70%) were classified as '≥ 50% spontaneous breathing' patients, and 1,006 (30%) as '< 50% spontaneous breathing' patients (Supplementary Figure S1).

To increase readability of the results, I suggest changing the name of groups ≥ 50% spontaneous breathing 'by high spontaneous breathing and < 50% by low spontaneous breathing.
REPLY: We thank the reviewer for this suggestion. As requested, we changed the names according to the suggestions.
CHANGES IN THE TEXT: We changed the names in all texts, inserts and figures.

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In the table 2, how did you assess driving pressure? Did you obtain plateau pressure measurement for all patients in ACV? How did you assess driving pressure in PAC or PSV? Did you consider pressure support as dynamic driving pressure? It is not clear for me. Please detail how was measured plateau pressure and driving pressure in patients without plateau pressure measurement. Please add the proportion of patients in whom you obtained really measurement of plateau pressure and driving pressure in ACV.
REPLY: We thank the reviewer for the opportunity of clarifying this. As stated in the footnote of the table, this was calculated considering moments only when plateau pressure was available. Since the dataset used in this study is for clinical purposes and the present analysis is a secondary analysis of these data, we cannot guarantee that plateau pressure (as recorded in the dataset) was collected under standard conditions, i.e., in the absence of spontaneous breathing efforts, at an adequate level of sedation, and with a sufficiently long end-inspiratory pause.
CHANGES IN THE TEXT: We added the information below in the footnote of the table 2 and also a row describing the number of patients with measurements available.
'calculated when plateau pressure is available and as plateau pressure – PEEP'

In addition, we added this as a potential Limitation:
'In addition, since the dataset used in this study is for clinical purposes and the present analysis is a secondary analysis of these data, we cannot guarantee that plateau pressure and other ventilatory variables were collected under standard conditions.'

Please also provide ventilatory modes in this table or 'main ventilatory modes" ACV, PAC, PSV.
REPLY: As requested, we added this to Table 2.
CHANGE IN THE TEXT: We added this information in Table 2.

Peak pressure and driving pressure were lower in '≥ 50% spontaneous breathing' patients. May be a higher proportion of patients in the > 50% group were ventilated in PSV as

compared with < 50% group, and therefore the lower peak pressure is only due to ventilatory mode and not due to respiratory severity.
REPLY: We agree with this important comment. To address it, we included the ventilatory modes in the table as suggested above and also add a sentence in the Discussion about it.
CHANGES IN THE TEXT: We added the ventilatory mode in the Table 2 and the sentence below in the Discussion.
'It is important to note that patients in the 'high spontaneous breathing' were more often ventilated with PSV, thus, the lower peak pressure can be due to the ventilatory mode and not only due to other respiratory factors, like the severity of the disease.'

Reviewer B

Summary:
The authors compared the effect of >=50% spontaneous breathing versus <50% spontaneous breathing on the number of ventilator-free days in adult patients that received mechanical ventilation for at least 48 hours and were recorded in the MIMIC-III database. The manuscript is well written and was interesting to read. The topic is important and very relevant for clinicians and researchers. Without a doubt, the analysis of large databases like MIMIC-III is complex, and the authors have invested a lot of time and effort in this research project. The main concern about this study is bias in the analysis: treatment assignment has been performed post-baseline. Furthermore, the cohort has been restricted to patients that survived and followed the treatment for 48 hours post-baseline. This analysis approach introduces selection bias. The authors should have presented an analysis with only measurements recorded at baseline (crossectional analysis at baseline, similar to an intention-to-treat analysis using observational data). Alternatively, the authors could consider an appropriate approach to adjust for pre-and post-baseline prognostic factors associated with loss to follow-up (i.e., marginal structural models with IPW).

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1. The reported effect is conditional on surviving and being ventilated for 48 hours in the cohort. 33,384 patients were excluded from the analysis based on adherence. Let's assume this would be a randomized controlled trial: we would never accept an analysis of the effect only in patients that successfully survived and followed the intervention for 48 hours post-randomization. This introduces selection bias, which makes it very difficult to interpret the results. The authors could consider to include only variables measured at baseline (observational analog of an ITT analysis) in the models. Alternatively, another approach would be to adjust for pre-and post-baseline prognostic factors associated with loss to follow-up (i.e., marginal structural models with IPW).

REPLY: We thank the reviewer for this important comment. However, while we understand the concerns, we respectfully disagree. First, the proposal to use only baseline assessment, when all population is available, is not meaningful from a clinical perspective because the characterization of the groups would take into account just one measurement, and this could also lead to several bias. Imagine that a patient was classified as with spontaneous breathing in the first measurements but for all the next measurements the patients was placed in a controlled mode, with this analysis this would not have been captured. In addition, we decided to select this cohort intentionally to have a group of patients with a sufficient time of exposure to mechanical ventilation, and with sufficient time for being classified in one of the groups. While we understand that these results could not be generalized to the overall population receiving mechanical ventilation, we think that them could be used in the population in which them were assessed. Indeed, this is why in the manuscript we always emphasize that the results should be considered in a population surviving and receiving ventilation for at least 48 hours. To improve this, we made this clearer over the manuscript.

CHANGES IN THE TEXT: First, we changed the conclusion of the Abstract:

'In patients surviving and receiving ventilation for at least 48 hours, the amount of spontaneous breathing during this period was not associated with an increased number of ventilator–free days.'

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We also changed the hypothesis:
'The primary hypothesis tested was that the amount of spontaneous breathing is associated with an increased number of ventilator–free days at day 28 <u>in patients surviving and receiving mechanical ventilation for at least 48 hours</u>.'

We also changed the first part of the Discussion:
'The results of this retrospective analysis of the database of a large cohort of mechanically ventilated ICU patients <u>surviving and receiving ventilation for at least 48 hours</u> can be summarized as follows…'

We also included this as a potential Limitation:
'Only patients who survived and received invasive ventilation for at least 48 hours were included, aiming to select more severely ill patients and also those who had been exposed to the primary exposure of interest for a sufficient period of time. However, the results cannot be applied to patients who were extubated or died within 48 hours of ICU admission.'

We also corrected and made it clear in the Conclusion:
'In conclusion, in this analysis of a large ICU dataset of high resolution, <u>in critically ill patients surviving and receiving ventilation for at least 48 hours</u>, the amount of spontaneous breathing <u>during this period</u> was not associated with an increased number of ventilator–free days at day 28.'

2. Treatment assignment has been performed post-baseline. The patients were categorized to >=50% spontaneous breathing versus <50% spontaneous breathing based on measurements recorded during 48 hours of mechanical ventilation. The exposure is dependent on the patient's clinical condition over time, and the analysis does not account for this.

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REPLY: We kindly ask the reviewer to see the answer we provided in the question above. In addition, all models were adjusted by the clinical condition of the patient at baseline (including severity of disease, respiratory lung condition and comorbidity). We understand that this is a potential limitation and we added a statement about this in the Limitations section.
CHANGE IN THE TEXT: We added this as a potential Limitation:
'Also, the exposure assessed was dependent on the patient clinical condition over time, and this should be considered when interpreting the results.'

3. The authors stated in the discussion that the analysis incorporated the dynamic characteristics of mechanical ventilation. However, their analysis was adjusted for baseline covariates but did not investigate a dynamic treatment regimen that would require correct adjustments for pre-and post-baseline prognostic factors associated with loss to follow-up.
REPLY: We thank the reviewer for this comment and we agree. To avoid misinterpretations, we removed this sentence from the manuscript.
CHANGE IN THE TEXT: We removed the sentence below from the Discussion:
'Also, the analysis leverages the availability of time–stamped vital signs, laboratory test results, and ventilatory parameters ~~and measurements to build models that incorporate the dynamic characteristics of mechanical ventilation~~.'

4. How did the authors deal with patients transferred from other hospitals in the analysis? Were these patients already mechanically ventilated?
REPLY: We thank the reviewer for the opportunity to clarify this. Patients transferred from other hospitals were considered only when ventilation was started in the final hospital. We made it clearer in the manuscript.
CHANGE IN THE TEXT: We added the sentence below in the Methods:
'Patients transferred from other hospitals were considered only when mechanical ventilation started in the final hospital.'

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5. Detecting inspiratory effort based on respiratory rate and mode of ventilation is challenging. A sensitivity analysis could be considered to estimate how much misclassification would be necessary to change the analysis results. Such an analysis would increase confidence in the results. Likely, the authors used the currently best available approach to detect spontaneous breathing in large longitudinal databases. This could be emphasized in the discussion by mentioning that others have used the same method to classify the presence/absence of spontaneous respiratory effort (the LungSafe investigators in their article on the epidemiology of ARDS in JAMA or Amato's driving pressure article in NEJM).

REPLY: We thank the reviewer for this nice and important comment. We completely agree with the reviewer on this criticism. As suggested, we added a statement about this in the Discussion.

CHANGE IN THE TEXT: We included the sentence below in the Discussion:

'It is important to emphasize that in the present study the presence of inspiratory effort was not assessed and the presence of spontaneous activity was based in the mode of ventilation and respiratory rate. However, to the date this is a widely used approach to detect spontaneous breathing in observational studies.[9,26,27] *'*