Author’s response to reviews

Title: Is tracheostomy a better choice than translaryngeal intubation for critically ill patients requiring mechanical ventilation for more than 14 days? A comparison of short-term outcomes

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Author’s response to reviews:

Reviewer reports:

Reviewer #1: Thank you for allowing me to read your manuscript. If I am interpreting the aim/hypothesis of your study correctly, you believe that tracheostomy, in essence, decreases ICU/hospital morbidity/mortality AND that using the methods you describe, you aim to show that. In general, the manuscript is clearly written with only minor English line editing required. I do have some concerns as listed below.

Background:

In laying out your case for the "advantages" of tracheostomy, please be specific with relation to published studies. For example, lines 5-7 you state, generally, "They consume a substantial amount of healthcare resources and most have poor outcomes" and in lines 17-19, "reduced risk of developing ventilator-associated complications." Be more specific with what is cited in the literature.

REPLY: The authors thank for your comment. We have modified these sentences as follows:

“These patients consume a substantial amount of healthcare resources [2] and most have poor short- and long-term outcomes [2, 3].” (Page 4, lines 3-4)

“Tracheostomy is thought to provide several advantages over translaryngeal intubation in patients undergoing PMV, such as the promotion of oral hygiene and pulmonary toilet, improved patient comfort, decreased airway resistance, accelerated weaning from mechanical ventilation (MV) [4], the ability to transfer ventilator-dependent patients from the ICU to step-down
facilities [5] and a reduced risk of developing ventilator-associated pneumonia (VAP) [6].” (Page 4, lines 4-9)

Please define what "early" and "late" tracheostomy means earlier in the introduction and go discuss the literature from there.

REPLY: Thanks for your comment. We have reorganized the section of background as follows:

“Three meta-analyses of studies examining the role of tracheostomy in critically ill patients receiving MV have failed to demonstrate any benefits of “early” tracheostomy on survival, length of ICU or hospital stay, or duration of MV, compared with those undergoing “late” tracheostomy or prolonged translaryngeal intubation [9-11]. It is important to note, however, that two of these studies used ≤7 days after translaryngeal intubation as the definition of “early” tracheostomy [10, 11], while the other used ≤10 days [9].

Consequently, most experts recommend that tracheostomy be deferred for at least 10–14 days after translaryngeal intubation to ensure that ongoing MV is indeed required [4, 11, 12]. Currently, most clinicians view 1–2 weeks after intubation as the most appropriate timing for tracheostomy [9].” (Page 4, lines 14-25)

Most importantly, you have not set out a specific primary aim or hypothesis. "to evaluate the effect of tracheostomy on the outcome of patients receiving PMV (≥ 14 days) in our medical-surgical ICU" is nebulous and non-specific Please be explicit in stating what you are trying to do/hypothesize. The remainder of this paragraph should be part of the methods section.

REPLY: Thanks for your comment. We have added some sentences to specify our hypothesis as follows:

“We undertook a study to examine the outcomes of patients undergoing MV for at least 14 days in the ICU via persistent translaryngeal intubation or tracheostomy. We hypothesized that tracheostomy would be associated with an increased rate of successful weaning and reduced ICU and in-hospital mortality in critically ill patients requiring PMV compared with persistent translaryngeal intubation. The aim of this study was to evaluate the effect of tracheostomy on the outcome of patients receiving PMV (≥14 days) in our medical-surgical ICU.” (Page 5, lines 1-7)

The sentence “Two analytical models were constructed: a multivariable time-dependent Cox model, and propensity score matching for performing tracheostomy that adjusted for potential confounding factors to evaluate the effect of tracheostomy on the outcomes of patients with PMV” has been moved to the methods section. (Page 6, lines 14-17)

Methods:

I felt like some of this could be in a supplement, particularly a table for which variables were collected. This would then also allow for each to be specifically defined, if needed, without unduly interrupting the flow and length of the manuscript.
REPLY: As your comment, we have added a table in additional file for specifically defining the collected variables.

“ICU admission diagnosis and comorbidities were identified according to the International Classification of Diseases, ninth revision and categorized as shown in the supplementary material (Additional file 1).” (Page 7, lines 24-25)

I am also a bit confused about how the methodology was chosen. It would seem to me that if you have the time and data to do a case-control study, then that just do that and tell us that that is what you are going to do. If, on the other hand, you set out, a priori to do a propensity-matched analysis, then do that. Why do everything and report it as such. It is really confusing and give the impression that the authors started with one, then moved to another when they did not get the results they desired or supported their hypothesis. I think this can be clarified and the methods appropriately trimmed with the remaining portion to be placed in an ESM.

REPLY: Thanks for your comment. In this study, we hypothesized that tracheostomy would be associated with an increased rate of successful weaning and reduced ICU and in-hospital mortality in critically ill patients requiring prolonged MV compared with persistent translaryngeal intubation. It is important to note, however, that performing a tracheostomy is a time-dependent covariate (varying time to performing a tracheostomy among patients). We thus constructed a multivariable time-dependent Cox model for taking the time into account. Furthermore, because patients on MV were not randomly assigned to undergo tracheostomy or translaryngeal intubation, potential confounding (i.e., selection biases) was also needed to be adjusted for by constructing a nested case-control population and applying a propensity score for the matching procedure. We believe that the results would be more convincible by this two analytical models. The similar study design can also be found in other studies [1, 2].

Results:

Please consider a CONSORT type flow diagram representing the original data set to what was ultimately analyzed.

REPLY: Thanks for your comment, we have added a flow diagram as Figure 1.

Again, the results and tables are onerous and a bit confusing without a specific aim and methodology to match. If the authors wish to report the results of a univariate analysis, then multivariate analysis, I feel like there is too much here. Please clarify what it is that you want to do and then simply report that only.

REPLY: To answer your concern, we have specify our hypothesis/aim as described above. We have also modified the paragraph in the result section as follows:

“Multivariable time-dependent Cox regression modeling showed that performing a tracheostomy was associated with a significantly lower risk of in-hospital death (aHR 0.26, 95% CI 0.18–0.39, p <0.001) and a significantly higher chance of successful weaning (aHR 2.05, 95% CI 1.56–2.68,
The other independent factors significantly associated with in-hospital mortality included a DNR order, undergoing NIV after extubation, malignancy and a PaO2/FiO2 ratio >282 (w2) (Table 3). The other factors independently associated with successful weaning included a DNR order, sepsis, chronic lung disease, APACHE II score >23, a PaO2/FiO2 ratio >282 (w2) and a platelet count >140 × 103/µl (w2) (Table 3).” (Page 11, lines 2-10)

The HR for tracheostomy and mortality is 0.26! Do you mean to tell me that simply the act of placing the trach reduced the chance of death by 74% on average? (see below).

REPLY: As your comment, the adjust HR of tracheostomy for hospital mortality 0.26 indicates that performing a tracheostomy reduced the chance of death by 74% on average. We have provided some explanations as below.

Discussion:

The authors speak glowingly of the results, but have provided no proposed plausible explanation for the astounding reduction in risk of death. Should we interpret the fact that in unadjusted analyses, the resource utilization was lower in the translaryngeal group, but mortality was higher to mean that they died earlier so they consumed less resources? If so, wouldn't that indicate that perhaps that is sicker cohort despite, on average, the APACHE scores being similar? None of this is addressed in the discussion, which makes the results difficult to interpret and place in proper context.

REPLY: We agree with the reviewer’s comment that translaryngeal intubated patients died earlier than those undergoing tracheostomy. We have modified the sentence in the discussion as follows:

“The shorter duration of MV, and shorter length of ICU and hospital stays in the translaryngeal intubation group probably reflect these patients’ higher mortality rate and earlier death (30 days compared with 61 days) or transition to lower-level regional hospitals.” (Page 14, lines 20-22)

Also, we have offered some explanations for the substantially reduced risk of death in discussion as follows:

“In our study, the substantially reduced risk of death (aHR 0.26) in the tracheostomy group could in part be explained by the fact that tracheostomy is associated with a decreased risk for VAP in patients requiring PMV [6]. In tracheostomized patients, tracheostomy allows the vocal cords to close, reduces aspiration of oropharyngeal secretions, reduces bacterial biofilm formation along the inside of the tracheotomy cannula and facilitates weaning from MV. All these factors probably result in a reduced risk for VAP [6]. Another potential explanation is that ICU physicians may be adept at selecting candidates for tracheostomy based on the highest probability of survival, and therefore may provide more aggressive treatment for these patients while being more likely to offer conservative or palliative treatment to those intubated by the translaryngeal route for a prolonged period. In a retrospective study, it is also possible that we might have missed some important confounding factors associated with the decision to undertake
tracheostomy that might also affect outcomes, even when sophisticated adjustment methods such as multivariable analyses or propensity score-based nested case-control studies are used.” (Page 13, lines 5-18)

In the last paragraph in the discussion for the study limitations, we have also added some sentences to answer your concern:

“We did not record serial ICU scores (such as the daily Sequential Organ Failure Assessment), which may have more accurately reflected the severity of illness at the time of tracheostomy (after a median of 18 days of MV) than the APACHE II score in the first 24 hours of ICU admission [17]” (Page 15, lines 1-4)

Lastly, and in general, a number of statements suggest causality, which cannot be established by this type of study. For example, the beginning of the introduction and again in the "key messages." Sure, the simple comparison of proportions are different, but that was not what you are reporting. Rather, you are reporting the hazard of (or risk) and thus one thing can only be associated with a reduced hazard. This is an important distinction. I suggest softening the language to make it in line with your analysis.

REPLY: Thanks for your comment, we have softened the language across the manuscript as follows:

“We hypothesized that tracheostomy would be associated with an increased rate of successful weaning and reduced ICU and in-hospital mortality in critically ill patients requiring PMV compared with persistent translaryngeal intubation.” (Page 5, lines 3-5)

“Multivariable time-dependent Cox regression modeling showed that performing a tracheostomy was associated with a significantly lower risk of in-hospital death (aHR 0.26, 95% CI 0.18–0.39, p <0.001) and a significantly higher chance of successful weaning (aHR 2.05, 95% CI 1.56–2.68, p <0.001; Table 3).” (Page 11, lines 2-5)

“Our finding that tracheostomy was independently associated with reduced ICU and in-hospital mortality rates is also consistent with some previous reports [17, 18].” (Page 12, lines 14-15)

“For patients requiring MV for at least 14 days, tracheostomy was significantly associated with reduced ICU and hospital mortality and increased successful weaning rate.” (Page 16, lines 1-2)

Reviewer #2:

1) While the authors are to be commended on the overall quality of the language in the manuscript, it would benefit further from proofreading by a native English speaker to enhance readability.

REPLY: Thanks for your comment, we have sent the manuscript for English editing.
2) To the authors' point in the introduction regarding previous literature comparing outcomes between prolonged translaryngeal intubation vs. tracheostomy - I would clarify that this study is unique in that patients did not undergo tracheostomy until an average of 18 days after intubation. As such, the authors may want to specify either in the abstract or discussion that the study essentially compares the outcomes of patients who *first* underwent prolonged mechanical ventilation and *then* either subsequent delayed tracheostomy or continued translaryngeal intubation. This distinction is outlined more clearly in the discussion.

REPLY: Thanks for your comment, we have modified the sentences in the abstract and discussion as follows:

“The aim of this study was to examine the influence of tracheostomy and persistent translaryngeal intubation on short-term outcomes in patients mechanically ventilated for ≥14 days.” (Page 2, lines 4-6)

“To the best of our knowledge, this is the first report to have compared the short-term outcomes of patients who received MV for at least 14 days and either underwent tracheostomy or remained intubated by the translaryngeal route for a prolonged period.” (Page 12, lines 6-9)

We have also added a flow diagram as Figure 1 to clarify the enrollment of our study population.

3) What was the primary hypothesis? Although inferred, it should be more clearly stated.

REPLY: Thanks for your comment. We have added some sentences to specify our hypothesis as follows:

“We undertook a study to examine the outcomes of patients undergoing MV for at least 14 days in the ICU via persistent translaryngeal intubation or tracheostomy. We hypothesized that tracheostomy would be associated with an increased rate of successful weaning and reduced ICU and in-hospital mortality in critically ill patients requiring PMV compared with persistent translaryngeal intubation. The aim of this study was to evaluate the effect of tracheostomy on the outcome of patients receiving PMV (≥14 days) in our medical-surgical ICU.” (Page 5, lines 1-7)

4) In the methods regarding the waiver of consent, I would clarify that a waiver of consent was obtained as the retrospective study design posed minimal risks to patients.

REPLY: Thanks for your comment, we have modified the sentence as follows:

“It was judged that the retrospective observational study design posed no risks to patients. The need for informed consent was waived, as all data were anonymized and patient identification numbers were encrypted.” (Page 6, lines 3-5)
5) Was noninvasive positive pressure ventilation provided consistently after extubation, or only on an as-needed basis?

REPLY: We provide NIV on an as-needed basis in our ICU. We have modified the sentence to clarify it.

“Non-invasive ventilation was initiated after extubation as needed, if it was judged that patients were at high risk of extubation failure [13-16].” (Page 8, lines 1-2)

6) The authors mention in the conclusions that the prolonged duration of mechanical ventilation in this patient cohort was due in part to previous failed extubations. Is data about the incidence of this complication available? If so, it may be an important latent variable and source of hidden bias. If not, discussion of this limitation should be included in the discussion.

REPLY: Thanks for your comment. We have addressed this limitation in the discussion as follows:

“First, we did not record data regarding the effects of inadvertent extubation on the outcomes of the translaryngeal intubated group, tracheostomy complications, the incidence of extubation failure or the rate of VAP. All these factors may be associated with patient morbidity, mortality and successful weaning.” (Page 14, line 23 to Page 15, line 1)

7) With regard to limitations of the study, I worry that there is a high likelihood of susceptibility bias. Patients that were translaryngeally intubated had a worse prognosis (more ill, DNR, neurologic disorders) and thus might have been less likely to be offered a tracheostomy. As such, many findings related to the route of intubation may be due to indication bias and not true treatment effect. Although efforts have been made to correct for this through sophisticated statistical modeling, limited overlap between groups may limit the utility of propensity score matching in this context. This is mentioned by the authors as a limitation, but I would strongly recommend an expanded discussion as this is a major limitation.

REPLY: Thanks for your comment. Unfortunately, your concern may actually exist in clinical practice. We therefore made great efforts to control for potential confounders. For your concern, we have expanded our discussion for this limitation as follows:

“In our study, the substantially reduced risk of death (aHR 0.26) in the tracheostomy group could in part be explained by the fact that tracheostomy is associated with a decreased risk for VAP in patients requiring PMV [6]. In tracheostomized patients, tracheostomy allows the vocal cords to close, reduces aspiration of oropharyngeal secretions, reduces bacterial biofilm formation along the inside of the tracheotomy cannula and facilitates weaning from MV. All these factors probably result in a reduced risk for VAP [6]. Another potential explanation is that ICU physicians may be adept at selecting candidates for tracheostomy based on the highest probability of survival, and therefore may provide more aggressive treatment for these patients
while being more likely to offer conservative or palliative treatment to those intubated by the translaryngeal route for a prolonged period. In a retrospective study, it is also possible that we might have missed some important confounding factors associated with the decision to undertake tracheostomy that might also affect outcomes, even when sophisticated adjustment methods such as multivariable analyses or propensity score-based nested case-control studies are used.” (Page 13, lines 5-18)

“Our study had some limitations. First, we did not record data regarding the effects of inadvertent extubation on the outcomes of the translaryngeal intubated group, tracheostomy complications, the incidence of extubation failure or the rate of VAP. All these factors may be associated with patient morbidity, mortality and successful weaning. We did not record serial ICU scores (such as the daily Sequential Organ Failure Assessment), which may have more accurately reflected the severity of illness at the time of tracheostomy (after a median of 18 days of MV) than the APACHE II score in the first 24 hours of ICU admission [17]. Second, our study was undertaken retrospectively; this may have caused us to miss important confounders relevant to the results, while accounting for the significant heterogeneity between the translaryngeal intubation group and the tracheostomy group. Consequently, we cannot completely rule out the possibility that clinical practice on the ICU tends to select patients with the highest likelihood of survival for tracheostomy, although we matched for propensity scores, adjusted for potential confounders and performed a sensitivity analysis in which even more stringent propensity score matching was employed that yielded the same results.” (Page 14, line 23 to Page 15, line 11)

Reviewer #3: In this retrospective analysis of ICU admissions requiring prolonged mechanical ventilation, the authors show a correlation with tracheostomy and decreased hospital mortality and higher successful weaning rates. Although the mortality results are intriguing, the higher proportion of MICU patients, DNR patients, CHF patients, and chronic liver disease patients in the translaryngeal intubation group may account for some of this increased mortality. Additionally, the higher proportion of trauma and brain disorder patients (potentially single organ illness) may also accentuate this mortality difference. The known, and unknown, differences in the two groups is inherent to any retrospective study, which the authors address with a case-control propensity matched analysis. This matching process eliminated many of these differences, and the mortality differences still persist.

I think expanding the discussion section to include why tracheostomy is associated with decreased mortality is needed to convince readers of the results (decreased VAP?, improved early mobility?, better pulmonary toilet?).

REPLY: Thanks for your comment, we have offered some explanations for the substantially reduced risk of death in discussion as follows:

“In our study, the substantially reduced risk of death (aHR 0.26) in the tracheostomy group could in part be explained by the fact that tracheostomy is associated with a decreased risk for VAP in patients requiring PMV [6]. In tracheostomized patients, tracheostomy allows the vocal cords to close, reduces aspiration of oropharyngeal secretions, reduces bacterial biofilm formation along
the inside of the tracheotomy cannula and facilitates weaning from MV. All these factors probably result in a reduced risk for VAP [6]. Another potential explanation is that ICU physicians may be adept at selecting candidates for tracheostomy based on the highest probability of survival, and therefore may provide more aggressive treatment for these patients while being more likely to offer conservative or palliative treatment to those intubated by the translaryngeal route for a prolonged period. In a retrospective study, it is also possible that we might have missed some important confounding factors associated with the decision to undertake tracheostomy that might also affect outcomes, even when sophisticated adjustment methods such as multivariable analyses or propensity score-based nested case-control studies are used.” (Page 13, lines 5-18)

I also found it intriguing that tracheostomy was associated with increased duration of mechanical ventilation but higher successful weaning rates (this seems counterintuitive and could use a better explanation). The longer ICU and hospital stays in the tracheostomy group is also unexpected and is explained in the article as possibly relating to the higher mortality rate of the translaryngeal intubation group. Maybe only patients who were expected to survive were offered tracheostomies?

REPLY: Thanks for your comment, we have add some explanations in the discussion as follows:

“The shorter duration of MV, and shorter length of ICU and hospital stays in the translaryngeal intubation group probably reflect these patients’ higher mortality rate and earlier death (30 days compared with 61 days) or transition to lower-level regional hospitals.” (Page 14, lines 20-22)

“Second, our study was undertaken retrospectively; this may have caused us to miss important confounders relevant to the results, while accounting for the significant heterogeneity between the translaryngeal intubation group and the tracheostomy group. Consequently, we cannot completely rule out the possibility that clinical practice on the ICU tends to select patients with the highest likelihood of survival for tracheostomy, although we matched for propensity scores, adjusted for potential confounders and performed a sensitivity analysis in which even more stringent propensity score matching was employed that yielded the same results.” (Page 15, lines 4-11)

Several other studies have not shown a mortality benefit to early tracheostomy, but apparently none have looked at this particular group of prolonged mechanical ventilation. In order to eliminate many of the biases listed above, a prospective randomized control study would be subsequently needed to confirm these results.

REPLY: We agree with your comment. We have added your comment in last paragraph in the discussion.

“A prospective, randomized controlled study will be needed to eliminate the biases described above.” (Page 15, lines 14-15)

Editorial Requests
Please note that all submissions to BMC Anesthesiology must comply with our editorial policies. Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements this will cause a delay whilst the issue is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

REPLY: We have made an ethics statement as follows:

“Conduct of the study was approved by the ethics committee of National Cheng Kung University Hospital (reference A-ER-103-284-T).” (Page 6, lines 2-3)

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

REPLY: We have made an ethics statement as follows:

“It was judged that the retrospective observational study design posed no risks to patients. The need for informed consent was waived, as all data were anonymized and patient identification numbers were encrypted.” (Page 6, lines 3-5)

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.
REPLY: It seems to be not applicable for our study.

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

REPLY: Please see the section of Authors’ contributions. (Page 16, lines 21-25)

References
