

Peer Review File

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Review Comments

Reviewer A

Thank you for sending your paper to CCTS. I have learned from reviewing your retrospective analysis on prolonged mechanical ventilation after lung transplant.

The theme you discuss is interesting and still open, thus it could improve our efforts in improving outcomes of lung transplantation patients. Anyhow, the paper has different lack points where you should focus.

Number of patients is good (1140), but the observation lasted 10 years (from 1/2008 to 1/2019). Did the perioperative lung transplantation management undergo some changes during this period? Please, specify.

Response: This is a good point. In the recent year of the study period, we dedicated one of our cardiovascular surgery ICU to lung transplant patients along with a dedicated team of intensivists and respiratory therapists with special interest and expertise in management of postoperative lung transplant patients. The goal is to be consistent with weaning of mechanical ventilation protocols for patients who may require a prolonged course after transplant.

Changes: we added a statement to reflect that in the Discussion section under "Characteristics of Long-term weaning of MV after LTx"

Lines 258 - 263

Line 127. Why did you choose to analyze unique pre-transplant risk factors? What about intraoperative and postoperative care?

Response: We thank the reviewer for pointing out this edit. The original motivation for the study was to identify pre-transplant risk factors that are associated with PMV after LTx, however in the study analysis we included operative and postoperative factors which some were significant such as single LTx, PGD, postoperative dialysis and airway complications.

Change: we have edited that sentence to "We aim to identify unique baseline and peri-operative risk factors ...", line 128

I suggest defining clearly primary and secondary outcomes of the study.

Response: primary outcome is PMV > 21 days and secondary outcome is survival after LTx

Change: we have added the primary and secondary outcomes of the study in the methods section "study cohort", lines 150-151

Do you have any protocol regarding perioperative lung transplant management? Please, specify in the "Methods" paragraph.

Response: yes, we have protocols for perioperative management including weaning of MV, prevention of ileus, and pain control.

Change: changes have been made in the methods section, lines 148-150

Line 143. I can't see the logistic regression model mentioned in the "Statistical analysis" paragraph. Please, attach it.

Response: a list of the variables used in the analysis was added as a supplemental file

Change: uploaded a supplemental file with the manuscript files

Thus, I suggest making major modifications on the article and try to resubmit it again.

Thank you for this privilege.

Reviewer B

I would like to commend the authors of this paper for highlighting an important topic that is often missed in the literature. While the focus of metrics can be on access to a scarce resource, the authors shed light on complexity of care in the post-operative patient with a higher LAS score in an attempt to avoid waitlist mortality. I believe this paper will provoke further discussion regarding predictors of increased LOS, postoperative morbidity and cost within this cohort.

I have the following feedback to the authors.

1. Within the methods section of the manuscript, it is unclear if PMV time included time to tracheostomy decannulation despite a patient not requiring the ventilator. In other words, if a patient continued to have a tracheostomy for needs such as frequent bronchoscopy or return to OR, but did not require the ventilator outside those needs, were these days included to determine the group they fell into? This may be an institution specific practice that could be discussed in the limitations.

Response: This is an important point. As the reviewer pointed out, the patient may have the trach in place but not using the vent (as capped), however may go back on the vent for a bronch or a procedure. Also, we have patients that go to stepdown room with ventilator capabilities to continue weaning of mechanical ventilation, which may have the trach capped most of the day and require to go back on the vent for a brief period overnight.

To keep it consistent throughout the study, we included all time with trach in place even if not used all the time, based on decannulation date and CXR or discharge to rehab with trach.

Change: we have updated the methods section (lines 146-147) and limitation section accordingly (lines 324-325)

2. Figure 3 (Line 339): This table is useful to quickly review mortality endpoints, however it may be helpful to the reader to denote the 'n' and p value of each group when comparing 1, 3, and 5 year mortality.

Response: We agree with the reviewer to add the N and p value for each comparison to clarify the results of the figure. However, for the p-value, as it is a Kaplan-Meier curve analysis the p-value is generated for the whole model, not for each year. In our model we used the Log-Rank test for the whole model and the Wilcoxon test for the early mortality and the p values for both tests were < 0.001

Change: we have updated figure 3 to include table with N at risk, survival %, and P value

Again, I commend these authors for their excellent review of this patient population. Thank you for the opportunity to review this manuscript

Reviewer C

The authors present an investigation into risk factors for prolonged mechanical ventilation and impact on post-transplant outcomes and survival. This is an important area of investigation as identification of such risk factors might alter selection practices or alter management strategies. The authors find that prolonged mechanical ventilation is associated with poorer survival and identify several pre- and/or peri-operative variables that are associated with prolonged mechanical ventilation. My comments regarding this manuscript are outlined below.

- As the authors mention, although CMMS defined prolonged mechanical ventilation as 21d, this is likely quite different for lung transplant recipients. How did the authors choose the timeframes to divide the cohort into groups? The group from 3-21 days in particular seems like a broad range over which risks and associating factors might change significantly. An alternative approach that might be even more revealing is to look at the incremental influence of additional days by analyzing days of mechanical ventilation as a

count outcome and performing poisson or negative binomial regression.

Response: We thank the reviewer for a valid point. A new analysis is added using mechanical ventilation days as a continuous variable. First, we used a logistic regression model for identifying variables related to longer ventilation days, then a univariate analysis comparing the period of ventilation between categorical variables and Spearman correlation for assessing the relationship between ventilation duration and other continuous variables.

Change: We added sections in methods (142-145), results (line 188-195), and Table 3

- The authors included both endotracheal intubation and tracheostomy as mechanical ventilation. Can the authors further explain their approach to decision/timing regarding trach? Someone who is on Day 12 of mechanical ventilation via endotracheal intubation is quite different from someone who is still weaning at Day 12, but was trached on Day 5 and is able to actively participate in physical/occupational therapy services, for example.

Response: In our program, we have a low threshold for early tracheostomy to come off sedation, facilitate mechanical ventilation weaning, and early participation in PT/OT. If the patient is not making progress in the first 3-5 days with weaning trial for extubation, or extubated then got re-intubated within 24-48 hours, we then have a multi-disciplinary team discussion between the intensivist, pulmonary transplant, and the transplant surgeon to proceed with early tracheostomy.

Change: we made changes in the discussion section to reflect our protocol, under the section "Characteristics of Long-term weaning of MV after LTx", lines 258-263

- Can the authors further clarify their meaning regarding days until decannulation for those with tracheostomy? Does this mean persons who are weaned and capped, but still have a trach in place are considered to still be undergoing "mechanical ventilation"?

Response: This is an important point. As the reviewer pointed out, the patient may have the trach in place but not using the vent (as capped), however may go back on the vent for a bronch or a procedure. Also, we have patients that go to stepdown room with ventilator capabilities to continue weaning of mechanical ventilation, which may have the trach capped most of the day and require to go back on the vent for a brief period over night.

To keep it consistent throughout the study, we included all time with trach in place even if not used all the time, based on decannulation date and CXR or discharge to rehab with trach.

Change: we have updated the methods section (lines 146-147) and limitation section accordingly (lines 324-325)

- Figure 1: the legend doesn't completely explain what we are viewing and the figure is confusing. If this is meant to be a box plot, it would be clearer to leave the individual datapoints off the figure. Additionally, there are also horizontal blue lines visible and distinct from the apparent red box plots which are not addressed in the figure legend.

Response: Figure 1 was changed as recommended by the reviewer, only the box plots were kept and the data points were removed. The legend was modified.

Change: Figure 1 and Figure 1 legend were updated accordingly

- Under the results section in predictors of prolonged mechanical ventilation after LTx, the authors indicate in the first paragraph that they investigated independent risk factors for longer mechanical ventilation. What statistical approach and groups were used here? Was it a binary outcome with a 21d cutoff, in which case logistic regression would be appropriate and odds ratios should be reported along with p-values, or was it among all 4 groups, in which case chi-square would be appropriate. The authors should clarify this in their reporting of the results.

Response: For the first paragraph, the duration of mechanical ventilation was used as a continuous variable in a multivariate regression model. For the second paragraph, the recipients were divided into two groups based on the duration of ventilation, the group of recipient with PMV > 21 days was the target of the second logistic regression model. This was clarified in the "Statistical Analysis" section lines 156-160. Additionally, the odds ratio (OR) were added for the categorical variables, the "Predictors of prolonged ventilation" section in the results was modified accordingly.

Change: "Statistical Analysis" section lines 156-160. "Predictors of prolonged ventilation" section in the results lines 204-207.

- Under results, where authors report on survival, they report on independent risk factors for survival, which I assume means a multivariate model was constructed using Cox Proportional Hazards Regression. Given this, adjusted hazards ratios should be reported along with the p-values. Additionally, how was prolonged mechanical intubation entered in this model – as a binary variable with a 21d cutoff or as the 4 previously identified groups. Particularly since the authors outline that one of their primary goals is to quantitate the impact of prolonged mechanical ventilation on outcomes, the latter would be more appropriate and adjusted HR should be reported for all groups (assuming Group 1 serves as the reference group).

Response: We thank the reviewer for the important point, the hazard ratios (HR) and the confidence intervals (CI) were added. The prolonged mechanical intubation used for this model was PMV > 21 days to show the hazard ratio clearly for the readers.

Change: "Survival" section under Results, lines 214-216.

- In the discussion, the authors mention the substantially poorer outcomes of Group 4 in relationship to consideration for resource utilization in the face of organ scarcity. A discussion of organ allocation almost certainly extends beyond the scope of the current work.

Response: We agree with reviewer. We have removed the corresponding statement from the discussion

Change: Deleted the sentence "In the face of donor organ scarcity, this observation should be considered by LTx programs to ensure optimal resource utilization", in the discussion under the section "The fate of long-term weaning of MV after LTx", lines 244-245

Reviewer D

The authors performed an retrospective analysis to define the risk factors of prolonged mechanical ventilation after lung transplantation, and investigate its impact on patients' survival. This area has been explored and clarified by many studies. This study has confirmed that higher LAS score, bridging on ECMO or MV is strong predictors of prolonged mechanical ventilation, which exert a worse impact on patients' short-term and long-term survival. Though the study is well-structured, there are several aspects needing revision.

The study spans over 10 years of lung transplantation experience. During this period, the management of LTs may have changed and improved substantially, which is a significant confounding factor for the results. Could the authors carry out the analysis in each time segment to be sure of the conclusion consistent in the whole study period.

Response: To the best of our knowledge, there have not been significant changes in the ICU management specifically with respect to weaning of MV. In the recent years of the study period, we dedicated one of our cardiovascular surgery ICU to lung transplant patients along with a dedicated team of intensivists and respiratory therapists with special interest and expertise in the management of postoperative lung transplant patients. The goal is to be consistent with the weaning of mechanical ventilation protocols for patients who may require a prolonged course after transplant. The number of patients after this change was too small to have a statistical impact on the results of the study.

Changes: we added a statement to reflect that in the Discussion section under "Characteristics of Long-term weaning of MV after LTx", lines 258-263

Regarding the survival analysis of prolonged mechanical ventilation, the results of cox regression should be given in a separate table with HR value instead of only P value given

in the main text.

Response: The hazard ratios (HR) and the confidence intervals (CI) were added to the "Survival" section in the results.

Change: "Survival" section under Results, lines 214-216.

In figure 1, does the red box stands for boxplot? What is the meaning of the blue line. Figure 1 needs more clarification in the Legend.

Response: Figure 1 was changed as recommended by the reviewer, only the box plots were kept and the data points were removed. The legend was modified.

Change: Figure 1 and Figure 1 legend were updated accordingly