Author’s response to reviews

Title: Health-related quality of life as predictor for mortality in patients treated with long-term mechanical ventilation

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Author’s response to reviews:

Cecilia Devoto
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Comments to the decision letter concerning manuscript ID: PULM-D-18-00330

Title: Health related quality of life as predictor for mortality in patients treated with long-term mechanical ventilation. Heidi Markussen, PhD candidate, Intensive Care Nurse; Sverre Lehmann, MD, Associate Professor; Roy Miodini Nilsen, PhD, Associate Professor; Gerd Karin Natvig, Professor, RN

We want to express our gratitude to the editor and the two reviewers for their immensely insightful and helpful comments. We think that the manuscript is improved because of this. Thank you very much for your wise and useful comments.

The changes in the manuscript are made by using ‘track changes’.
Yours sincerely,

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Comment from reviewer 1
Samuel Y Ash, MD MPH:

General comments: Given the somewhat confusing and inconsistent nomenclature in the field including long-term mechanical ventilation, home ventilation, etc. it may be helpful to clarify in the abstract and early on in the introduction that this study includes both non-invasive and invasive mechanical ventilation.

Authors response:
We agree and have now clarified in the revised manuscript that both non-invasive and invasive mechanical ventilation are included in the definition of “long term mechanical ventilation”.

See abstract and Background page 5, first paragraph.

Comment from reviewer 1
Samuel Y Ash, MD MPH:
Abstract: It may be helpful to those not as familiar with the SRI to note somewhere that lower scores are worse as that will better explain the hazard ratios. I would also clarify that the HR are (presumably) per 1 point change in the SRI (see additional discussion below).

Authors response:

We agree and have now explained that lower SRI scores indicate worse HRQoL and that the HR is estimated per one unit change in the SRI.

See abstract and page 10, the second paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

Background: I think this can probably be shortened slightly and the rationale for the study better stated. More specifically, as the goal of this study is not to demonstrate the effect of LTMV on mortality, I would suggest that there probably is less of a need to review the data regarding LTMV and mortality, and I would more strongly emphasize the longer duration of follow up in this study.

Authors response:

We agree and have now shortened the review of data regarding LTMV and mortality as suggested. We also have removed part of the mortality aspects in the result and discussion sections. Furthermore, we have more strongly emphasized the need for longer follow-up time regarding the association between SRI and mortality.

See page 5, page 6, the first two lines, page 11, second paragraph, page 14 from last paragraph, page 15 and page 16 the first paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

Methods: The precise manner of recruiting patients is unclear. In the abstract it is stated that they were approached by mail, but that is not discussed in the methods section of the manuscript. If they were approached by mail then there should be a discussion of the fact that there is no
guarantee that the survey was completed by the patient him or herself and could have been completed by a family member, a potential confounder.

Authors response:

Thank you for this advice. We have updated the text in the revised method section. We also have added information in the method and results sections regarding your question concerning completion of the questionnaire. In fact, 27% percent of patients reported that they had received help when filling out the questionnaire. We have now discussed this as a potential limitation of our results in the discussion section.

See page 8 first paragraph, page 12, first paragraph and page 20, last paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

2) Although I know the numbers for those receiving invasive ventilation are small, there should be at least some comparison between those receiving non-invasive ventilation and those receiving invasive ventilation and I would consider including it as a covariate although there are limitations with the regression analyses as noted below and so this may not be possible.

Authors response:

We agree on your comment and have now compared baseline SRI sum score between non-invasive (n = 117) and invasive (n = 10) ventilated patients. We observed only small difference in SRI between groups, suggesting that it was not necessary to adjust for ventilation mode in regression analyses. We have provided the comparison data in the results section and have discussed the impact of ventilation mode on HRQoL and mortality in the discussion section.

See page 12, first paragraph and page 18, first paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:
3) There are several issues with the statistical analyses:

a. The use of time from study inclusion until death as event free time is problematic. If it were possible, then it would be better to use time from LTMV initiation. If not, then this should be discussed as a limitation to the study.

Authors response:

In order to assess the association using cox regression, we have used the time from exposure to the outcome as the event free time. In our study, the primary exposure was HRQoL and not LTMV treatment. Thus, in our opinion, using time since LTMV initiation until death would not be entirely correct. However, the time since LTMV initiation may to some extent have affected both HRQoL and mortality (overall and in disease categories). For this reason, LTMV treatment time from initiation was included as an adjustment variable in the cox regression analyses.

See abstract and page 10, last paragraph, and 17, first paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

3b) It appears that to try to overcome this issue treatment time is included as a covariate. I suspect this implies time since initiation of LTMV. If so, then that should be more clearly stated. The other possibility is that this is the average amount of time each day that the patient uses ventilator support. If so, then that should be clearly stated as well. If the latter variable is not included or available, then it should be noted that a significant limitation of the study is not knowing just how "vent dependent" the participants are.

Authors response:

Thank you for pointing this out. We have now more clearly stated that we have adjusted for the time since LTMV initiation.

We agree that ventilator dependency is an important factor and have included this variable in the adjustment analyses in the regression models for the overall analyses. This resulted in only minor changes. Conclusions remained.

See page 9 second paragraph and page 10 last paragraph, page 13, second paragraph and in table 1, 2, 4, 5, 6 and in supplementary table 2.
Comment from reviewer 1

Samuel Y Ash, MD MPH:

c. I worry that there are too many covariates for the regression analyses given the number of events, especially in the subgroup analyses. Although some investigators have advocated for relaxing the "1 for every 10" rule, in general, my understanding is that most people feel that there should be ten events for every covariate included in the model. Thus, in this study it seems that the model should be limited to a total of 5-6 covariates, even when analyzing all of the available data. I am actually somewhat surprised that given the likely overfitting of the model that the confidence intervals are as narrow as they are, especially in the subgroup analyses. Was the use of a propensity score considered?

Authors response:

The problem with the excess number of covariates in the present study was elaborated thoroughly in the discussion section. All variables were further evaluated for its confounding effects through univariate analyses. However, we have now removed marital status and sex in the regression analyses in response to this comment. Removing these variables did not alter conclusions, and led to only minor changes in HR estimates. In fact, neither variable was associated with both the outcome and exposure (see Table 1 and 2), indicating that it was unnecessary to adjust for these two variables.

We have further reduced the number of adjustment variables in the subgroup analyses of NMD, including only the two-three most important variables. This had no impact on results or conclusions. Text and tables are updated.

See page 17, the second paragraph. Tables 1, 2, 4, 5, 6 and in supplementary table 2 have been updated.

Propensity score adjustment is an interesting approach, which we will certainly evaluate in future analyses.

Comment from reviewer 1

Samuel Y Ash, MD MPH:
d. An effect size expressed per 1 unit change in an arbitrary scoring system is difficult to interpret. I would consider some other way of expressing the results such as scaling by standard deviation/z-score or presenting the effect by tertile or quartile.

Authors response:

We discussed scaling and categorization in an early phase of the analyses. However, according to previous research in this field of knowledge, it is common to interpret the SRI on its original scale (Windisch, 2003, 2008; Storre, 2006; Budweizer, 2007; Lopez-Campos, 2008; Gosh, 2012; Kohnlein, 2014; Markussen, 2015, 2017; Struijk, 2013, 2014; Huttmann, 2015, Ribeiro, 2016; Walterspacher, 2016; Murphy, 2017; Oga, 2017; Chen, 2017). We therefore chose not to categorize SRI or to scale the effect estimates.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

3e) How were comorbidities modeled? Simply as the number of comorbidities or using some sort of scoring system? This should be more clearly stated.

Authors response

Comorbidity was modeled simply as the number of somatic diagnoses. Charlson Comorbidity Index is a common scoring system to measure comorbidity using ICD-10 codes. However, as complete ICD-10 codes were not available in our data, we chose to measure comorbidity as the number of somatic diagnoses.

See page 9 last paragraph and page 20, last paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

1) The discussion of survived/deceased by NMD subtype is unclear as it follows the 1 and 3 year mortality data. Are the results presented the overall mortality by NMD subtype or the 1 or 3 year mortality by subtype?
Authors response

We agree that this is unclear. We have now removed this part of the paper because, as described earlier, the goal of this study is not to study the association of LTMV on mortality.

See page 11.

Comment from reviewer 1

Samuel Y Ash, MD MPH

The last line of the second paragraph of the results section is unclear. Does it imply that the distribution of men and women does not vary by disease category?

Authors response:

We have rephrased this sentence for clarification. We simply describe the difference in mortality rates between men and women. It does not imply that the distribution of men and women does not vary by disease category.

See page 12, last paragraph.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

Discussion:

1) Regarding the second to last sentence in the first paragraph of the discussion, I would emphasize that the majority of mortality in COPD is related to cardiac disease and thus the requirement of LTMV in COPD may simply be a marker of overall frailty and multi-system disease severity.

Authors response:
We agree and have followed your advice. We now emphasize that the majority of mortality in COPD is related to cardiac disease and the requirement of LTMV in COPD might be understood as a marker of overall frailty and multi-system disease severity.

See page 14, the first paragraph.

Comments from reviewer 1

Samuel Y Ash, MD MPH:

2) The question about the use of a propensity score as an alternative approach.

Authors response:

In view of this comment, we considered the possibility of propensity score adjustment in the present study. Usually, this is straightforward using a dichotomous or an ordinal exposure. However, SRI is a continuous exposure variable and as far as we are aware, statistical procedures for estimating propensity for continuous variables are complex and not readily available in software (see reference below). We, therefore, are a bit reluctant in advising other researchers to use the propensity score for adjustment of the SRI – mortality association.

Reference:


Comment from reviewer 1

Samuel Y Ash, MD MPH:

3) I am not sure that the conclusion that targeted interventions to raise quality of life may improve mortality (last sentence of the clinical implications section) can be drawn from this observational study.
Authors response

We agree and have changed the sentences.

See page 19, last paragraph and page 20 first paragraph.

Comments from reviewer 1

Instead, I wonder if the authors have any thoughts on whether the relationship between mortality and quality of life is causal, if so then in what direction, and if there are any approaches other than an RCT targeting quality of life that might be able to help address that question.

Authors response:

This study found associations between HRQoL and mortality. However, whether the relationship between mortality and quality of life is causal and changes in HRQoL status in some way influences mortality cannot be confirmed in this study design.

See page 21, first paragraph.

We do not have any other approaches to address this question than a randomized interventional study aiming to improve HRQoL with a control group receiving standard treatment.

Comment from reviewer 1

Samuel Y Ash, MD MPH:

4) Similarly, there is no comparison in this paper made between SRI and other quality of life measures, thus I am not sure that the last line of the paper suggesting that SRI be used as the quality of life measure is warranted (though certainly other work may suggest this).

Authors response:

We agree that there is no comparison in this paper made between SRI and other quality of life measures. We therefore have changed the last line of the paper as follows;
“Even if there is no comparison in this paper made between SRI and other quality of life measures, we suggest SRI to be used as the quality of life measure in the studies to come.

See page 8, last paragraph and page 21, last paragraph.

Comment from reviewer 1
Samuel Y Ash, MD MPH:

5) Finally, no longitudinal analysis is included in this work. If it is available, then that would be very interesting and add a lot to this study. If not, then I would remove the comment in the last paragraph about repeated measurements as no conclusions can be drawn from this study about the effect of change in quality of life over time and its relationship to outcomes.

Authors response:
Thank you for addressing this point.
No longitudinal analysis is included in this paper. We have changed the comment in the last paragraph about repeated measurements.
See page 21, last paragraph.

Comments from reviewer 2
Roozbeh Sharif:

1- The impact of the type of underlying condition on the outcome was not measured. The ideal statistical method to investigate this is to examine the interaction term. Lack of this examination or any results that impact the final results must be reflected in the Results and Discussion.

Authors response:
We thank the reviewer for this comment. Although a formal interaction test may be appropriate for these analyses, there is a clinical understanding that association between SRI scores and
mortality should a priori be stratified by disease groups (Lopez, 2016). We followed this advice, without a formal interaction test.

Reference:

Comment from reviewer 2
Roozbeh Sharif:
Minor revision

1- Any of 66 patients that did not respond to the survey died?

Authors response:
This interesting question could have added value to the discussion of selection bias in our study. Unfortunately, due to ethical limitations, we are not allowed to provide data on other than those who consented to participate in the study (n = 127).

Comments from reviewer 2
Roozbeh Sharif:

2- Was the cause of death studied?

Authors response:
Cause of death was available for only 27 patients. Because data were already limited in numbers, we chose to analyze data according to all-cause mortality rather than specific cause of death.