Reviewer’s report

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

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Reviewer: Samuel Ash

Reviewer's report:

This is an interesting study of the role of a specific measure of health related quality of life as a predictor of mortality in patients treated with long term mechanical ventilation. In general, the manuscript is very well written with a clearly defined/summarized purpose/hypothesis, methods and results as well as an interesting discussion. That said, I do have several comments/concerns which are listed below by section:

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. While reviewing this paper I conducted a very brief and highly non-scientific survey of pulmonary and critical care physicians at our institution and I would say that many felt that although "LTMV" may be used in the literature to refer to both non-invasive and invasive ventilation, a more general audience may hear/read "LTMV" and immediately think that the study only pertains to invasive ventilation. I do not think that the term necessarily needs to be changed for the paper, just that it needs more clarification.

Abstract: Overall this is quite clear. 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). With regard to the conclusions in the abstract, please see further discussion below regarding the comment about repeated measurements.

Background: Again, this is well written and clear, but I would address the issue of non-invasive/invasive ventilation earlier on as discussed above. I also 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.

Methods: While these are fairly well described, most of my concerns with the manuscript related to the methods section.

1) 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.

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.

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.

   b. 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.

   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?

   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.

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

Results: My primary concerns in the results are related to the methods to obtain them. The results themselves are largely clear and well stated.

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?
2) 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?

Discussion: Overall this is well presented and thoughtful but I do have a few concerns:

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.

2) With regard to the section on adjustment variables, please see the comments regarding the methods above and the question about the use of a propensity score as an alternative approach.

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. 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.

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).

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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I am able to assess the statistics

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