Reviewer's report

Title: The impact of adverse events in the intensive care unit on hospital mortality and length of stay

Version: 1 Date: 10 September 2008

Reviewer: Ryan Lennon

Reviewer's report:

- Major Compulsory Revisions

The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.

1) Abstract "Preventable AEs were not associated with either..."
Should insert "significantly" in front of associated.

2) Statistical analysis "All models included...probability of death calculated using the New Simplified Acute Physiology Score..."
Model covariates have a multiplicative effect on the hazard function in Cox PH models. That is, they contribute to a linear combination of the log hazard ratio estimate, which is then exponentiated to create an estimated hazard ratio. I would suggest transforming the estimated SAPS probability into a log hazard ratio (minus a constant term) by taking the base-2 log of the SAPS probability. This will solve two issues. First, it will address the non-linear association between SAPS and the hazard function. Second, the interpretation of the resulting hazard ratio will reflect the expected increase in the hazard for every doubling of the SAPS probability. One would expect, then, the resulting hazard ratio to be in the neighborhood of 2, though it won't be surprising if it is not given the patient sample. The current hazard ratio for the SAPS probability (Table 4) appears to be the estimated increase in risk for a change in probability of death from 0 to 1, which is not very practical.

3) Statistical analysis
"We estimated the impact of the exposure on length of stay by multiplying the reciprocal of the hazard ratio by the median length of
stay for all patients discharged alive who did not have an AE."
There is no reference for this methodology and as far as I can derive
algebraically, it is not accurate. It is not clear how they got
the CIs for this as well. Still, I recognize the desire for such an
estimate for the sake of interpretation, since a lower HR actually
means a longer LOS. However, I'm not sure such an approach is
possible, since the AE is a time-dependent variable. The increase in
LOS of AE patients versus non-AE patients therefore depends somewhat
on when the AE occurs.
It might be better to take the 40 patients and estimate their expected
median LOS according to the model under the condition that an AE
never occurred, and compare this to the observed median. Again, I'm
not sure if such an estimate is possible using the BASELINE statement
in PROC PHREG in the presence of a time-dependent covariate.

4) Statistical Analysis
The authors fit two models. One in which all AEs are treated
identically and a second in which the association with outcomes
differs depending on whether the AE was deemed preventable or
not. Differences between models are noted. However, the authors should
test whether the second model is statistically significantly more
informative than the first, i.e. whether there is statistical evidence
that the AEs really do confer different information regarding
outcomes. This would be done by means of a likelihood ratio test
between the two models.

5) Table 1
Use a footnote to indicate how the probability of death was calculated
(i.e. SAPS reference)

- Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on
figures, the wrong use of a term, spelling mistakes.

6) Methods "...; ant the documented cause of the occurrence."
"ant" should be "and".

7) Table 2
Need expansion for abbreviation "ADE".

8) Table 3
Remove "p=" from the p-value column.

9) Table 4 footnote
"hazard ration" should be "hazard ratio"

- Discretionary Revisions
These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.

10) Methods "Each week during the study, a multi-disciplinary panel reviewed all adverse clinical occurrences from the preceding seven days."
Discussion "In this study, however, patient outcomes were known when the AEs clinical impact was rated. This methodology may be biased because the reviewer may be influenced by patient outcome. We believe that our study adds to the AE literature by providing a more valid and quantifiable estimate of AEs impact on patient outcomes."
Discussion "Our prospective design ensured that we could identify important covariates for all patients in an unbiased fashion and ensure a more accurate AE detection than previous studies."
I do appreciate the prospective collection of data for this study as it is a strength of the study. However, the authors claim that an advantage of their prospectively collected data is that the adjudication of AEs is done without knowledge of clinical outcomes. I find it hard to believe, though, that if AEs were adjudicated weekly, that the clinical outcomes for all patients were unknown. Surely some patients died soon after their AE and this was known during the meeting.

11) Abstract "However, these studies have not adequately assessed the causal relationship between AEs and subsequent hospital outcomes."
This sentence implies that the authors work does assess the causal relationship between AEs and subsequent hospital outcomes, which of course, it does not. Though the authors appropriately use terms such as
"association" to avoid making similar implications elsewhere throughout the paper, it would be better if this sentence (and any others referring to causal relationships) were re-written.

Please note that both the comments entered here and answers to the questions below constitute the report, bearing your name, that will be forwarded to the authors and published on the site if the article is accepted.

What next?
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Based on your assessment of the validity of the manuscript, what do you advise should be the next step?

- Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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Statistical review
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Is it essential that this manuscript be seen by an expert statistician?
If you feel that the manuscript needs to be seen by a statistician, but are unable to assess it yourself then please could you suggest alternative experts in your confidential comments to the editors.

- Yes, and I have assessed the statistics in my report.

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**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

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