Author's response to reviews

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

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Author's response to reviews: see over
To Editor,
BMC-series journals

To whom it may concern:

Re: MS: 1293938114202998 - The impact of adverse events in the intensive care unit on hospital mortality and length of stay

Thank you for reviewing our manuscript and allowing us to respond to your criticisms. We have addressed all of the reviewers’ concerns. We describe the modifications made in the manuscript in the sections that follow. For each issue brought forward by a reviewer, we have reproduced the suggestion and inserted our comments and how we modified the manuscript.

Reviewer: Jeffrey M Rothschild
Reviewer’s report:
Major Compulsory Revisions
This is an important study conducted by investigators with deep experience.
I have several concerns.

1. MRSA colonization should not be considered an AE. Five are reported in the appendix.

There were six such cases. We have dropped these cases from the analysis. We initially felt these cases to be AEs because in Canada, we are actively managing patients with MRSA colonization with isolation procedures. This puts a burden on patients due to the physical measures to prevent MRSA spread and it does increase odds of further bad things happening. However, we do recognize that MRSA colonization itself does not directly cause symptoms. We have therefore taken the reviewers suggestion and re-classified the cases. It should be noted that every patient with MRSA colonization had at least one other AE during the observation period. There were no changes in the results due to changing this classification.

2. I do not agree with the assessment of preventability for VAP (8 cases) and CRBSI (2 cases). They are preventable - even though in retrospect the investigators cannot determine where the error occurred.

The degree to which all VAP and CRBSI are preventable is somewhat debatable. However, given a recent study showing a marked reduction in CRBSI incidence with quality improvement interventions, we agree it is reasonable to reclassify these cases as ‘preventable’ for the purposes of the study.

Classifying the events in this way has modified our results and conclusions. In our initial analysis, we found a trend of an impact of preventable AEs on hospital length of stay. This association is significant with the modified ratings. We have modified our results sections and tables accordingly.

Although our results were slightly different our final conclusion remains unchanged.

In conclusion, ICU-based AEs are common and have a large impact on hospital length of stay. Reducing their impact will be challenging because preventable AEs are less common and have many different causes. These data suggest that efforts to improve outcomes for ICU patients might be more effective if they focus on new technologies and treatment methods rather than focusing on error reducing strategies exclusively.

The last statement is still justified given the large number of non-preventable AEs we identified.
3. I have concerns about the review process that includes on the panel an intensivist and ICU nurse who were responsible during the week of the AE. Suggest reviewer was not the same clinicians that cared for the patient. This is especially important in rating preventability - bias is to under count errors.

We apologize for the confusion. The intensivist performing the reviews was not the ‘physician of record’ but was the ‘back-up’ or ‘second’ physician on-call for the week. Thus, the physician was aware of all aspects of the case but was not in a ‘conflict-of-interest’ position when making the rating. The nurse on the review team was an educator in the ICU and did not have direct patient care responsibilities. Again, there was not a ‘conflict-of-interest’ in terms of a direct role in patient care and the review process. Although, it is impossible at this stage to measure whether the use of these individuals biased our final ratings, we do not think it was the case based on the quality and content of the weekly review discussions. Furthermore, the reviews were being led by a patient safety expert (AJF) who had no potential conflict of interest. Also participating with the reviews was the nurse performing the observation, who was similarly un-conflicted.

We do recognize that there is the potential bias. To address these concerns we have modified the relevant sections in the Methods and Discussion sections of the paper.

Methods section, Identifying Adverse Events subsection, paragraph 5. Starting at sentence 7:

*Note the intensivist was not the physician of record but was the back up physician for the week and the nurse was not directly involved in any patient care responsibilities. Thus, they were not conflicted in terms of their propensity to rate cases as errors. However, their direct knowledge of the cases allowed them to make more informed ratings.*

Discussion section, second from last paragraph, and last three sentences:

*Fourth, some of the reviewers were participating in some patient care responsibilities indirectly, as they were considered back-up providers. Although this might lead to a propensity to avoid rating cases of errors, we do not feel this occurred. Furthermore, this potential bias would not influence the measured association of the AEs with length of stay and mortality.*

4. How did the authors remove the bias they cited in the Rothschild paper regarding knowledge of AE outcome. How were the reviewers in this study blinded to outcomes resulting from the AE or otherwise (resulting from patient condition). In fact, the Rothschild study reviewers only know outcomes immediately due to the AE and, for example, did not know if the patient died a week later from their underlying disease.

It is important to make a distinction between a potential bias in terms of whether or not a case represents an AEs versus a potential bias in terms of measuring the impact of the AE in terms of health outcomes. For the purposes of this paper we were interested in the latter.

The study by Rothschild did not attempt to measure the influence of AE occurrence on mortality risk or length of stay. They were primarily interested in describing the incidence and nature of ICU based ICUs. To measure the impact of AEs, they rated clinical severity in terms of the following classifications ‘significant’, ‘severe’, ‘life-threatening’, and ‘fatal’. While this type of classification system has been used widely and is very descriptive, it has limited value in terms of describing the importance of the AE in influencing the outcome. Other than the ‘fatal’ class, the other classes communicate little information in terms of the true impact of the AE. Furthermore, it can be difficult to separate the extent to which the AE versus the severity of the underlying illness contributed to the outcome severity. Finally, as the severity of the clinical outcome was a major
component of the event being rated, there was a potential for bias in their ratings. This has been demonstrated by other investigators.

We did not assess the impact of AEs in terms of clinical severity. Rather, we used ‘hospital length of stay’ and ‘death’. Hospital length of stay information was not known at the time of any the reviews. Therefore, this outcome was ascertained independent of AE ratings and therefore less susceptible to bias. For death, only two patients died at the time their rating. Therefore, it is unlikely that knowledge of this outcome had a significant impact on our results.

Please see Discussion section, paragraph 2, and sentence 3. It now reads:

In this study, however, patient outcomes were known when the AEs clinical impact was rated. The investigators rated AEs in terms of their clinical impact: ‘significant’, ‘severe’, ‘life-threatening’, or ‘fatal’. While such a rating scheme is descriptive, it does not inform regarding downstream impact of the AEs. Furthermore, it does not help us to separate out the severity of the patient’s underlying illness from the contribution by the AE. Finally, this methodology is potentially biased because the reviewer may be influenced by patient outcome (5;11). These issues did not influence our study as much because the outcomes of interest were objective, precisely defined, and ascertained independent of the AE rating. (Note that only two patients died at the time of our rating. Otherwise all outcomes occurred after the review.) We believe that our study adds to the AE literature by providing a more valid and quantifiable estimate of AEs impact on patient outcomes.

Minor Essential Revisions
Typo Page 4, line 4: ant should be and

Thank you. This has been changed

Reviewer: Bill Runciman

Reviewer's report:

9/. The paper is very well written. There are a small number of revisions which the authors can most certainly be trusted to correct. These are:

- page 1, paragraph 3, line 4 - replace "to be most effective" with "for the most efficient use of resources". This is a suggestion.

This has been modified accordingly

- page 3, line 4 "infections" to become "infection"

This has been modified accordingly

- page 4, line 4 "ant" to become "and"

This has been modified accordingly

- page 4, lines 6 & 7 "including the nurse, the resident physician, and the attending intensivist physician" to become "the relevant nurse/s, resident physician/s, and attending intensivist physician/s" (This is a suggestion)
This has been modified accordingly

- page 4, second last line "All AEs were reviewed by the panel to determine if they were avoidable". I suggest "All AEs were reviewed by the panel to determine if they were avoidable with the available resources and currently accepted practices". This is a suggestion.

This has been modified accordingly

- page 9, line 3 I suggest that reference 5 be added to reference 11

This has been modified accordingly

- page 10, paragraph 2, line 2 delete the full stop after "stay"

This has been modified accordingly

Reviewer: Ryan Lennon

Reviewer's report:
1) Abstract "Preventable AEs were not associated with either..."
Should insert "significantly" in front of associated.

We have modified the abstract accordingly.

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.

We agree with the reviewer regarding the practicality of our original model, which estimated the risk of outcome for a change in SAPS probability from 0 to 1. We have, therefore, modified our models.

We have done so in a slightly different manner than suggested by the reviewer, yet with the same intention. We have multiplied the SAPS score by 10. The interpretation of the resulting hazard ratio reflects the expected increase in the hazard for a 10% increase in the SAPS probability.

We have modified the Statistical analysis subsection of the methods section, paragraph 2, sentence 9 and 10:

*The New Simplified Acute Physiology Score is a validated method for predicting the probability of in-hospital mortality. In our model, we estimate the change in risk associated with a 10% increase in the probability of death.*
This has been indicated in Table 4 as a footnote.

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.

We would like to thank the reviewer for making this excellent suggestion. We did, in fact, use the BASELINE STATEMENT in PROC PHREG to generate model based estimates of the probability of discharge at different times. For this model, we used median values for all the covariates included in the final model. We then estimate the impact of AEs on hospital length of stay by differencing the predicted median length of stay between patients with and without AEs.

We have added a paragraph to the Statistical analysis subsection:

To identify the impact of AEs on hospital length of stay, we used the BASELINE STATEMENT in PROC PHREG to generate model based estimates of the probability of discharge at different times. For this model, we used median values for all the covariates included in the final model. We then estimated the impact of AEs on hospital length of stay by differencing the predicted median length of stay between patients with and without AEs.

We have also inserted a figure with the survival analysis and modified the results section accordingly.

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.

We assessed the likelihood ratio test between the two models and determined the models did not confer different information regarding outcomes. This information has been added to paragraph two in the statistical analysis subsection:

To determine whether Model 2 was more informative than Model 1, we performed a likelihood ratio test. The result of this test was non-significant for both outcomes.

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

- 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.

We have done our best to address this issue.

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

This has been corrected.

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

This has been corrected.

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

This has been corrected.

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

This has been corrected.

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.

Please see comment 4 by Dr. Rothschild and our response above. We hope this is acceptable.

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.

We have modified this sentence. It now reads:

“However, these studies have not adequately assessed the association between AEs and subsequent hospital outcomes.”
Editor’s notes

We have added a ‘Competing interests’ and ‘Author’s contributions’ sections as requested. We have modified the structure of the abstract to include: ‘Background’, ‘Methods’, ‘Results’, and ‘Conclusions’ sections.

Reference List

