Author’s response to reviews

Title: Pre-operative Biomarkers and Imaging Tests as Predictors of Post-operative Delirium in Non-cardiac Surgical Patients: A Systematic Review

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December 23, 2018

Dear Angela K Lipshutz,

Re. BANE-D-18-00347

Pre-operative Biomarkers and Imaging Tests as Predictors of Post-operative Delirium in Non-cardiac Surgical Patients: A Systematic Review

We would like to thank you and the other reviewers for your comments and suggestions. Please see our point-by-point response to the reviewers’ comments. We have revised the manuscript and have highlighted the changes in blue font in the manuscript. We hope our revisions are satisfactory.
Sincerely,

Farrah Ayob

Jean Wong

Technical Comments:

1. Title page - Please list down the institutional addresses and email addresses for all authors. The corresponding author should be indicated.

We have added the institutional address and email addresses for all authors. The corresponding author has been added on the title page.

Reviewer reports:

Paul S. García (Reviewer 1): This manuscript reviews relevant literature focused on pre-operative biomarkers (serum, CSF, and radiologic imaging) associated with post operative delirium (POD). After a systematically conducted literature search 34 cohort studies were reviewed in detail. The authors conclude that serum C-Reactive Protein (CRP) was the most promising biomarker associated with POD (5/34 studies). This finding is not surprising given a known association of inflammatory mediators with POD in many clinical studies and a causative effect demonstrated in animal studies. Despite this mainly confirmatory result, the systematic review was comprehensive and summarizes quite well the recent literature focused on pre-operative biomarkers for POD. The manuscript is well written and the conclusions drawn from the presented data are easy to follow. Unfortunately, these results are unlikely to change clinical practice or launch new investigative directions - partly because CRP elevation is so non-specific. Although sensitivity and specificity curves were not attempted by the authors, I imagine that CRP might be more useful for ruling out the highest risk of post operative delirium but not very helpful for "ruling in". Nonetheless, the manuscript deserves consideration and here I outline suggestions on improvements for the work.
The authors state in the background that POD "usually emerges on post-operative day 1 to 3, after a lucid interval after recovery from anesthesia". Although emergence from anesthesia might be more or less agreed upon by common clinical endpoints (e.g., eye-opening, responsiveness that requires integration of information by thalamocortical circuitry - i.e., not simply coughing or withdrawing from pain) the end of anesthesia recovery is clearly not agreed upon. If we are investigating post operative delirium can we really know when the anesthesia "recovery" is over? The authors in the Methods note that most studies included in the review assessed POD from day 1 (or day 2) post-operatively. If they assessed POD starting on day 1, then does that make POD impossible on day 0?

Thanks for your comment. We meant that POD was assessed from the day of surgery. Most studies consider this as Day 1. However, to avoid confusion of readers, we have changed the sentence to the day of surgery (Page 7, line 9-10).

Even if the patient experiences a "lucid interval after recovery" (emerged)? PACU delirium as a subcategory of POD has been gathering attention with some high profile papers in the British Journal of Anaesthesia (see Card et al., 2015 and Hernandez et al., 2017). This topic probably deserves a bit of attention by the authors. Also, I understand that the lucid interval is important to separate postoperative delirium from agitation during emergence, but the authors should probably tighten up the language in the background to make the distinctions between emergence agitation, PACU delirium, and POD a little clearer. Specifically, I recommend changing the sentence (P.3 lines 40 - 47) to describe a lucid interval after *emergence* from anesthesia.

Thanks for your suggestion. We have changed the sentence to ‘emergence’ after anaesthesia (Page 3, line 19). We have also defined the distinction between emergence agitation, PACU delirium and POD according to Card et al., 2015 and Hernandez et al., 2017; (Page 3, line 22 – 25 and Page 4, line 1 – 2).

I understand that the authors used "emergence delirium" as a MESH search term (probably because some studies conflate agitation during emergence -no lucid state- with delirium. The authors must explicitly state whether they did or did not consider emergence agitation as POD in their analysis. They should also state if some of the studies they include in the analysis might have been examining PACU delirium and POD - while others (those constrained to start on day 1) only examined POD.
Thank you for this suggestion. We have revised the sentence in ‘Description of included Studies and indices’ section – where none of the studies mentioned whether they included PACU delirium or distinguished between emergence agitation or POD (page 7, line 11-13)

The reported serum concentrations of inflammatory markers can vary greatly. For example, the two studies (Capri et al., 2014 and Westhoff et al., 2013) that examined IL-6 had over a half-log difference in the reported median levels. This is enough of a discrepancy that probably deserves a bit more explanation for the reader. Was the variability due to different lab techniques between the studies? Are IL-6 measurements based on some local control or standard? All of the Westhoff patients would have been abnormal in the Capri study. That is concerning.

Thank you for this comment. The main difference between the studies was the use of preoperative anti-inflammatory drugs which may account for the differences in IL-6 levels. We have revised this section on page 9, lines 13-17.

As mentioned above, a sensitivity or specificity analysis based on a certain CRP cutoff would be interesting, but perhaps outside the scope of this paper. However, the authors could comment on the > 3 mg/L value that might (or might not) lead to a reasonable cut-off based on the previous literature.

Thanks for your suggestion, we have included this in page 10, lines 3-4.

The authors do not have any details regarding the methods for determining "anticholinergic activity" in the laboratory based on previous study - and the Miller study is referenced - Miller et al., did not study anticholinergic activity in reference 36. Also, reference 36 is missing the co-authors.

Thanks for your comment, we have explained the method for determining ‘anticholinergic activity’ in page 11, lines 20-22. We have also changed the reference to 28, not 36. We have also added the missing co-authors in Miller study, page 25, line 16.
The authors could expand the limitations of their discussion to include non-specificity of CRP, the variability in the serum testing reviewed. The authors did not examine confidence intervals for lab results between different studies and did not perform any meta-analysis of existing data.

Due to the heterogeneity of the studies, we did not perform any meta-analysis of the data. We have included this in our limitations, page 19, lines 14-16.

The authors could expand on the clinical implications of their review. A composite score (CRP plus other biomarkers) could also improve predictive value. Intraoperative and postoperative biomarkers may also help assign high-risk patients to specific recovery units. It appears that there is less pre-operative testing of CSF and/or imaging data the authors could explain the reasons for that and even speculate whether the added expense or invasiveness would be worthwhile as a screening modality.

Thank you for your suggestion. We have added the points composite score (page 20, lines 17-19), assign high risk patients to specific recovery units (page 20, lines 20-21), and commented on invasiveness of CSF test (page 19, lines 3-5).

Lastly, in some places, the authors motivate the study by claiming that investigation of biomarkers may lead to preventative/treatment strategies. Given their results, I am not convinced that this "angle" is really fitting with the overall paper's theme. In the abstract the authors define their objective as: "to summarize the evidence of pre-operative biomarkers and imaging tests to predict POD in patients undergoing non-cardiac surgery". This seems more appropriate as the motivation for undertaking the systematic review.

Thank you for this suggestion. In the Background, we have removed “and lead to preventative strategies to be instituted” from page 4. We also removed the sentence on page 18, line 2.

Jakub Kazmierski (Reviewer 2): Reviewer's suggestions on the article:

"Pre-operative Biomarkers and Imaging Tests as Predictors of Post-operative Delirium in Non-cardiac Surgical Patients: A Systematic Review."
1. The authors discuss pre-operative markers of delirium. However, these markers were not assessed post surgery. Therefore, we do not know if pre-operative or maybe post-operative concentration of markers is associated with delirium occurrence and severity. This issue should be discussed.

Thank you for this comment, however, we excluded studies that only examined post-operative biomarkers as the purpose of this review was to summarize the literature on the use of pre-operative biomarkers that could predict post-operative delirium. We have added the exclusion of these studies on page 6, line 1.

2. There are many confounders in studies which analyse predictors of POD. For instance, infections, systemic diseases, depression, dementia may underlay the effect of biomarkers on the risk of delirium development. The variables investigated in the studies should be controlled for potential confounders in multivariate analysis. Thus, according to me, the authors of the present manuscript should only include studies in which multivariate logistic regression analysis was used.

Thanks for this comment. The studies which did not perform multivariate logistic regression analysis have been added in both tables and manuscript in limitation section (page 19, lines 21-23).

3. Some substances may be markers of delirium only in specific populations. For instance anticholinergic activity may be a predictor of delirium, however, only in subjects with cognitive impairment.

We have summarized if they included pre-operative cognitive impairment or dementia in subjects in Table 1 and 2, (page 19, lines 19-20).

4. The authors should also describe if any of the marker was evaluated with regard to the cut-off points in delirium diagnosing. In such case, specificity and sensitivity of such measures should be reported.
Thanks for your suggestion. Due to heterogeneity of the studies, we did not perform any meta-analysis of the data. We have included this in our limitations, page 19, lines 14-16.

Cut off points in each specific biomarkers as well as specificity and sensitivity (if assessed) are mentioned in Tables 1 and 2.

5. The discussion should be deepen with regard to other biomarkers and potential mechanisms leading to delirium development.

Thank you for your comment. We have added further points on other biomarkers in discussion section (page 18, lines 7-9 and lines 20-23).