Reviewer’s report

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

Version: 0 Date: 25 Sep 2018

Reviewer: Paul S. García

Reviewer's report:

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? 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. 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.

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.

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.

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.

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.

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.

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.
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If not, please specify what is required in your comments to the authors.

Yes

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