Author’s response to reviews

Title: Identifying Older Adults at Risk of Harm Following Elective Surgery: A Systematic Review and Meta-Analysis

Authors:

Jennifer Watt (jennifer.watt@mail.utoronto.ca)
Andrea Tricco (triccoa@smh.ca)
Catherine Talbot-Hamon (catherine.talbot-hamon@mail.mcgill.ca)
Ba' Pham (ba.pham@theta.utoronto.ca)
Patricia Rios (riosp@smh.ca)
Agnes Grudniewicz (agnes.grudniewicz@telfer.uottawa.ca)
Camilla Wong (wongcam@smh.ca)
Sharon Straus (sharon.straus@utoronto.ca)

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Knowledge Translation Program
Li Ka Shing Knowledge Institute
St. Michael’s Hospital
30 Bond Street, Toronto, ON M5B 1W8

Office/Courier Location:
209 Victoria Street
7th Floor, East Building
Toronto, ON, M5B 1T8
Dear Dr. Samuel,

Thank you for your email dated August 23rd and the enclosed peer review comments. We are pleased that you liked our manuscript and were able to provide us with such prompt and thoughtful feedback concerning our manuscript entitled “Identifying Older Adults at Risk of Harm Following Elective Surgery: A Systematic Review and Meta-Analysis”. We have carefully considered all of the reviewer feedback and amended our manuscript accordingly. We have written formal responses to the comments posed by both reviewers. Additionally, in accordance with BMC Medicine policy, we have removed Douglas Sinclair from the list of study authors.

We look forward to receiving further communication from BMC Medicine with regards to our manuscript.

Sincerely,

Sharon E Straus, MD MSc FRCPC
Li Ka Shing Knowledge Institute of St Michael's Hospital,
30 Bond Street,
Toronto, Ontario  M5B 1W8, Canada
Telephone: 416-8964-3068
Email: sharon.straus@utoronto.ca
Fax: 416-864-5805
Reviewer Comments:

Reviewer #1:

This is a commendable body of work spanning several decades of clinical research targeted at understanding and identifying unique problems faced by geriatric surgery patients and helps inform the direction we need to take to mitigate these issues.

The authors have developed a robust list of study questions and the literature search and abstraction methods are excellent, as also the statistical analysis. They have been careful about statistical heterogeneity between models. The applicability of their results has tremendous impact - they show that age alone is not a factor that determines the incidence of post-operative complications, but rather the biological effects of aging. While this may vary in the time of occurrence in every patient, the manifestation of such aging is always the same - frailty. Showing that frailty, cognitive and functional decline are key risk factors that predict adverse post-operative outcomes in a diverse variety of elective surgical procedures, is the major strength of this meta-analysis.

I recommend that this manuscript be accepted for publication.

Reviewer #2:

Thank you for giving me the opportunity to comment on this interesting submission. I have a number of major methodological comments.

1. Comment: This systematic review aims to evaluate the prognostic or predictive influence of a diverse range of variables on postoperative outcomes. The data extraction and assessment of study validity should have been based on the items that are discussed in CHARMS and TRIPOD, which relate to systematic reviews, as well as primary studies of prognostic research. I don't accept that Cochrane ROB or the NOS are the most appropriate tools, and I think this systematic review should be conducted in a manner that is relevant to prognostic research.

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4196729/

   http://annals.org/aim/article/2088549/transparent-reporting-multivariable-prediction-model-individual-prognosis-diagnosis-tripod-tripod

Response: Unfortunately, this study was initiated prior to the development of CHARMS and TRIPOD; therefore, our data abstraction form incorporated some, but not all, elements of these checklists; however, the Cochrane ROB and the NOS offer a sound, general approach to the
assessment of risk of bias according to three broad categories of bias found in both randomized and non-randomized studies: selection bias, measurement bias, and confounding. Knowledge of these three categories of bias are fundamental to any approach to the critical appraisal of any study and the items listed in the risk of bias assessment of the CHARMS checklist could all be categorized into one of these three types of bias. Furthermore, many elements of the CHARMS checklist are also encompassed within the Cochrane ROB and NOS tools; however, I do acknowledge that these tools don’t describe all of the potential biases introduced in model development, performance, and evaluation. We have now commented on this limitation in our discussion.

Quotation from Manuscript:

Lines 354-358

“Additionally, this study was initiated prior to the introduction of the CHARMS checklist, which means that biases introduced in model development, validation, and evaluation of our included studies are less well described; otherwise, we feel that we were able to identify important sources of selection bias, measurement bias, and confounding that threatened the validity of individual study findings.”

2. Comment: There is huge risk of publication bias, because the primary studies often choose to selectively report Odds Ratios for variables that are statistically significant or clinically interesting. This is illustrated by the fact that of the 44 studies included in this review, only a small number are subsequently able to be included in each meta-analysis, and there is therefore lots of missing data for each prognostic variable (e.g. the ones that did not find significant influence of frailty may have decided to omit reporting it).

Response: I agree that our findings are potentially limited because of the quality of reporting in each study; however, we have synthesized the data that is available to us. We have added a comment about this potential limitation in our discussion.

Quotation from Manuscript:

Lines 365-369

“Lastly, sometimes studies did not report independent variables for which there was a non-significant association with the dependent variable in the final multivariable model, which could potentially lead to a type 1 error in the results of our meta-analyses. This is a limitation that is
inherent in the prognosis literature that we hope will be overcome in the future by improved quality of reporting.”

3. Comment: I appreciate that it is simple to pool OR, but for prognostic research, this glosses over the fact that discriminant ability in a multivariable model may be completely different. For instance, what is the influence of smoking once frailty etc. has been added to the model. It would be more realistic to look at AUC or c-statistic (but I accept that few studies ever report such items).

Response: As you have noted, very few studies report these other model characteristics; therefore, it was not possible to derive overall effect estimates based on these other characteristics in our systematic review and meta-analysis.

4. Comment: I don't understand this sentence in the Methods "The NNF was calculated as 1/pooled incidence of delirium." Please clarify the NNF and how it is calculated and interpreted. I assume it is related to the NNT in some way, except that this is follow-up prognostic study.

Response: Yes, the number needed to follow (NNF) is defined as the number of patients who need to be followed in a study of prognosis in order to see one outcome. It is related to the concepts of number needed to treat (NNT) and number needed to harm (NNH). We have expanded our explanation of this concept in our statistical methods section.

Quotation from Manuscript:

Lines 163-166

“The NNF was calculated as 1/pooled incidence of each postoperative complication. Similar to the concept of the number needed to treat (NNT) or number needed to harm (NNH), the NNF represents the number of patients who need to be followed in a prognostic study in order to see one outcome.”

5. Comment: Like most prognostic research, there is a long way from identifying a few prognostic variables to actually proving that modifying the variable is feasible, and subsequently leads to improved outcomes. It would be too simple to say that tackling these few variables would be beneficial (particularly if there are multiple variables that interact).
Response: We agree with this comment; however, synthesizing the state of our current knowledge is the first step of an integrated knowledge translation strategy whose ultimate goal is to improve perioperative outcomes for older adults. As you have said, much more work will need to be done to understand the potential barriers and facilitators to pilot testing an intervention to mitigate the risk factors we have described among older adults; therefore, we have made our conclusion actionable, but not prescriptive so as to not dilute our overall messages that (1) adverse outcomes are common among older adults undergoing elective surgery and (2) geriatric syndromes may be more significant predictors of adverse outcomes among older adults undergoing elective surgery than more traditional risk factors such as a patient’s age, and (3) there are potentially modifiable risk factors that should be studied further. We have modified the conclusion so as to acknowledge the need for a fully developed knowledge translation strategy to make our findings actionable.

Quotation from Manuscript:

Lines 376-382

“In summary, this systematic review and meta-analysis highlights how common postoperative complications are among older adults undergoing elective surgery (NNF=4) and the importance of geriatric syndromes in identifying older adults at risk of harm. Furthermore, there were several prognostic factors identified that could be modifiable in a preoperative setting, including smoking and frailty, which can be explored in future knowledge translation strategies to develop interventions aimed at mitigating the risk faced by older adults undergoing elective surgery.”