Author’s response to reviews

Title: The Application of Enhanced Recovery after Surgery for Upper Gastrointestinal Surgery: Meta-Analysis

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Reviewer reports:

Giovanni Domenico Tebala, MD FRCS FACS (Reviewer 1):

Very interesting meta-analysis, worth of publication. I have only two observations and suggestions that may help improve the quality of your work.

1. I noticed you included different kinds of studies in your meta-analysis. While this improves the pooled data by increasing the sample size, it adds an element of heterogeneity. For instance, pooling together studies on gastric resection for cancer with studies on sleeve gastrectomy for obesity doesn’t sound fine. Would you please add a paragraph to explain this weakness of your meta-analysis?
Reply: We comprehensively reviewed the included literature studies and found that only one study reported sleeve gastrectomy for obesity (Lemanu DP 2013). To prevent heterogeneous confounding and reviewer’s concerns, we decided to re-define the exclusion criteria, and exclude the sleeve gastrectomy for obesity, considering only gastric cancer surgery. In addition, we have added a corresponding subgroup analysis (the type of cancer, surgical procedure and scope of gastrectomy) to the study of gastric cancer resection, the results of subgroup analysis were showed in Table 3.

2. including only studies in English would introduce a linguistic bias. It has been demonstrated that including also other languages studies to a meta-analysis may change the results in up to 15% of cases. Would you please explain why you chose to select only English-language studies and in case highlight this as a limitation of the meta-analysis?

Reply: As a Chinese researcher, we may be more inclined to include English and Chinese-language studies. However, since many of these studies do not use appropriate randomisation procedures and do not report their methods, we decided a priori to exclude studies from Chinese-language studies to avoid a systematic bias[1]. Of course, for other languages, such as French and German, we may not be able to obtain it, or even if we have acquired it, we may not be able to accurately extract useful information. Finally, we also add a description of potential language bias to the limitations.

Form the Cochrane’s handbook[2]: The extent and effects of language bias may have diminished recently because of the shift towards publication of studies in English. In 2006, Galandi et al. [3] reported a dramatic decline in the number of randomized trials published in German-language healthcare journals: with fewer than two randomized trials published per journal and year after 1999. While the potential impact of studies published in languages other than English in a meta-analysis may be minimal, it is difficult to predict in which cases this exclusion may bias a systematic review.

Reference


Charalampos Siotos (Reviewer 2):

Thank you for the opportunity to review this interesting study. Please find below my comments and suggestions.

General: Authors need to pay attention on grammar/flow mistakes throughout the manuscript.

Abstract
- In the Results, the acronym PLOS appears that needs to be explained.
- Results: "other outcomes were no significant difference", please correct typo.
- Conclusion: "…can reduce risk of postoperative infection…", this is misleading and not supported by the results of the study. Only lung infection was reduced.
- Conclusion: Authors specify that their results are applied to patient undergoing gastrectomy. However, they have also included patients with esophagectomy. I suggest revised the sentence.

Reply: The above inappropriate points have also been modified in revised manuscript.

Introduction
- "Until now, there have not been any meta-analyses of RCTs that assess ERAS protocols for all upper gastrointestinal surgeries." There have been many! I think this sentence is inaccurate. Same for a sentence that follows "…however, the evidence is poor and insufficient…"

Reply: We may have deviations in the expression of language. In order to avoid such deviations, we deleted these sentences that were considered inaccurate.

- ERAS has been expanded further from the traditional abdominal surgeries, and authors need to acknowledge that, for example: cardiac surgery (PMID: 30665758), microsurgery (PMID: 30589825), neurosurgery (PMID: 30933924), etc.
Reply: Yes, we also agree with the reviewer's point of view, indeed ERAS has been applied to many fields. All ERAS® Society Guidelines are released and available free at the ERAS® Society website (https://erassociety.org/guidelines/list-of-guidelines/), and it is especially important for clinical guidance.

Methods

- Discrepancy between search methods in methods and results. In methods, it says "though December 2018", in the results "May 2018." Authors need to clarify.

Results

Reply: The search was updated on “December 12”, but we forgot to modify the search time in the results. This is "though December 2018", and it also been modified in the manuscript.

- Why did the authors use Risk Ration instead of Odds Ration for the dichotomous outcomes?

Reply: Based on the Cochrane’s handbook (http://handbook-5-1.cochrane.org/): Risk is the concept more familiar to patients and health professionals. Risk describes the probability with which a health outcome (usually an adverse event) will occur. In research, risk is commonly expressed as a decimal number between 0 and 1, although it is occasionally converted into a percentage. Odds is a concept that is more familiar to gamblers. The odds is the ratio of the probability that a particular event will occur to the probability that it will not occur, and can be any number between zero and infinity. Measures of effect for clinical trials with dichotomous outcomes involve comparing either risks or odds from two intervention groups. Because risk and odds are different when events are common, the risk ratio and the odds ratio also differ when events are common. Although, the non-equivalence of the risk ratio and odds ratio does not indicate that either is wrong: both are entirely valid ways of describing an intervention effect, the interpretation of an odds is more complicated than for a risk.

- Did the authors perform any subgroup analysis for the outcomes that had high heterogeneity?

Reply: To better manage heterogeneity and evidence extrapolation, we have added a corresponding subgroup analysis (the type of cancer, surgical procedure and scope of gastrectomy) to the study of gastric cancer resection, the results of all subgroup analysis were showed in manuscript and Table 3.
Appendix, table 2, line 40, there is a typo. The name of the journal appears as the name of the authors.

Reply: It has been corrected.

Discussion/Conclusion

I do not think there is compelling evidence derived from the present study to support the use of ERAS protocols especially in elderly population. I would suggest the authors to revise discussion and conclusion accordingly.

Reply: It has been corrected and deleted about the “elderly population”.

Authors should acknowledge difficulty of implementing a homogenous ERAS protocol, as described on the following publication: PMID: 30859019.

Reply: It has been corrected in the conclusion. Although, to be truly effective interventions, as the ultimate quality improvement practice, is the key to measuring the success of ERAS, our research provides some reference evidence to advance ERAS into clinical practice.