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Science editor

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**RE: Manuscript NO: 38158, Title "Safety and efficacy of enhanced recovery after gastric cancer surgery: an updated systematic review and meta-analysis"**

Dear Dr. Wang,

We would like to thank you and reviewers very much for your efforts with our manuscript, entitled " Safety and efficacy of enhanced recovery after gastric cancer surgery: an updated systematic review and meta-analysis " (MS# 38158).

We are very pleased to have enthusiastic and positive comments from you and the reviewers. To address the concerns and suggestions, we have performed careful and in-depth revisions. These new data and changes have been incorporated into the main text, figure legends and figures in this revised version (in yellow). In addition, a point-by-point reply to the reviewers' comments is included below.

**Reviewer's code: 00069015**

Perioperative care is important for all surgery, including GC operation. The meta-analysis titled " Safety and efficacy of enhanced recovery after gastric cancer surgery: an updated systematic review and meta-analysis", including 13 RCT studies from 10 articles, did a good job to compare the ERAS protocol and SC treatment among GC patients who received operation. The results were credible and promising.

There are two suggestions from me, expecting to help to improve the manuscript.

1. There was considerable heterogeneity among the included studies. And, the author did a subgroup analysis in order to found the heterogeneity. But no remarkable heterogeneity was found. It was better to add the Egg's and Begg's test to analysis the heterogeneity. And, the author should do a reasonable explanation about the heterogeneity.

**Response:** We would like to thank this reviewer for his favorable review and comments.

We also fully understand the reviewer's concern. As mentioned by this Reviewer, the heterogeneity among these included studies was one of the major limitations. No significant heterogeneity was found with regard to the incidence of complications (including anastomotic leaks, ileus, incision infection, urinary tract infection and pulmonary infection), the rates of readmission and reoperation, and postoperative serum ALB level (POD1 and POD4) and QOL. However, there was substantial heterogeneity observed for overall complications, POHS, intestinal function recovery, medical costs and inflammatory response indicators ( $I^2 = 64\% \sim 99\%$ ). Potential publication bias has been appraised graphically by using funnel plots, Begg's test and Egger's test. No obvious asymmetry was revealed by visual indication of the Begg's funnel plot for postoperative total complications including all studies (**Figure 13**), and Begg's test and Egger's test also indicated no significant bias was associated with publication for this meta-analysis ( $P = 0.55$  and  $P = 0.435$ , respectively).

We have discussed this limitation in the part of DISCUSSION. The substantial heterogeneity may be attributable to the clinical heterogeneity, including technical status of each institution, the inclusion criteria, surgical approach, inconsistent evaluation of the outcomes, and ERAS elements used.

The results indicate that high quality, large sample and multicenter RCTs are needed to evaluate ERAS pathways in gastric cancer surgery precisely.

2. There are several minor grammatical errors throughout the manuscript. Please checked and revised.

**Response:** We appreciate the reviewer's helpful suggestion. We have carefully checked and revised the manuscripts for mistakes and grammatical errors with the help of professionals.

**Reviewer's code:** 00043258

This is an interesting meta-analysis of RCTs comparing ERAS protocol vs standard care in gastric surgery for malignancy. Although many limitations of this study are recognized and discussed by Authors, a few other issues should be addressed. ERAS protocol as described in cited guidelines (ref. 29) includes 25 items. Since compliance is a key factor in achieving results, studies including only four items may have limited value in assessing efficacy. Authors should detail items included in each study (number and type) and possibly compliance to single items when reported. This issue should be thoroughly discussed in the article. Similarly, evaluating outcomes 2 weeks after discharge is a further limitation of included studies. A significant reduction in medical costs is reported in ERAS group. Does this analysis include readmissions ?

**Response:** We would like to thank this reviewer for his favorable review and comments.

Consensus guidelines for perioperative care after gastrectomy, which summarizes and recommends 25 optimal items, have been published officially in 2014 by the ERAS Society. However, the definitions of ERAS varied widely across studies, therefore, the items of ERAS changed significantly in this study ranged from 9 to 22 (**Table 2**), which clearly demonstrated the disparity of the protocols included.

Obviously, patient compliance is also the important factor for application of ERAS. It has been reported that high degree of ERAS compliance was associated with fewer complications and shorter hospital stay. In this study, protocol compliance was only mentioned by Feng *et al* and Liu *et al*. Future studies should focus on patient compliance with the protocols to improve the effectiveness of ERAS.

At present, most studies only report short-term results for ERAS in gastric cancer, and the long-term clinical effects and cost-effectiveness remain unclear. Although mounting evidence suggests that ERAS programs accelerate postoperative recovery and improve the outcomes of patients with gastric cancer, it is still a long way for ERAS to be fully implemented. High quality, large sample and multicenter RCTs with long-term follow-up are needed to evaluate ERAS pathways in gastric cancer surgery precisely. Actually, new strategy has been designed to evaluate the long-term outcomes of patients with ERAS [*WJGS 2017; 9(2): 37–45*], and the effects of ERAS on long-term survival in gastric cancer patients will be established in the near future.

ERAS pathways improve clinical outcomes and are thought to reduce overall medical costs through accelerated rehabilitation and reduced morbidity. However, few studies have explored the cost-effectiveness of ERAS. In this study, hospital charges covered all costs spent during hospitalization, including counseling, examinations, surgery, nursing care, medicines, ward and other services. However, only a study by Kim *et al* clearly stated that the cost of readmission was included in hospitalization expenses. Additionally, all studies reported only short-term cost data, lacking of out-of-hospital costs and follow-up services. Further high-quality studies are warranted to determine the long-term clinical efficacy and cost-effectiveness associated with the ERAS programs.

**Reviewer's code:** 00502831

The authors performed the meta-analysis to provide an update assessment

of the safety and efficacy of enhanced recovery after surgery (ERAS) protocols in gastric cancer (GC) surgery. And they concluded that ERAS resulted in accelerated convalescence, reduction of surgical stress and medical costs, improved nutrition status, and better QOL, for GC patients. This article is significant, well written and useful. But I have one comment as bellow. # The authors should describe why ERAS approach significantly reduce the concentration of CRP and IL-6 in comparison with SC on days 1, 4, and 7 after gastrectomy for GC in discussion.

**Response:** Thanks for the reviewer's helpful suggestion.

We have discussed this issue in the part of DISCUSSION. The goal of ERAS is to minimize the surgical stress to maintain the physiological homeostasis after surgery. It is well known that the inflammatory factors, such as CRP, IL-6, and tumor necrosis factor  $\alpha$ , are related to the extent of tissue injury caused by surgery. A recent RCT showed that the use of ERAS in laparoscopic colorectal resection reduces the surgical stress as a result of decreased postoperative IL-6 and CRP levels [reference 41]. In this study, the ERAS approaches significantly reduced the concentration of CRP and IL-6 in comparison with SC on days 1, 4, and 7 after gastrectomy for GC, which partly due to the reduction of surgical stress response. CRP is also proposed as a marker of response to surgical trauma and postoperative infectious complications within ERAS protocols [*J Am Coll Surg* 2016; 222: 831-837. and *J Surg Oncol* 2018 Jan 22; doi:10.1002/jso.24909 (Epub ahead of print)].

**Reviewer's code:** 02742218

Manuscript is well written and can be considered for publication.

**Response:** We really appreciate this reviewer's very generous and grateful comments.

Before uploading, we proofread the manuscripts for mistakes and grammatical errors very carefully.

We would like to thank you and the reviewers again for your positive and helpful comments and for the opportunity to revise our manuscript by incorporating these recommended changes. We are looking forward to your positive decision and publishing our work in *World J Gastroenterol*.

Sincerely, yours

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