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Editor:

World Journal of Gastrointestinal Surgery

SUBJECT: REPLY TO COMMENTS OF THE REVIEWER

Dear Editors,

We are very thankful for the critical review of our manuscript, **"Compliance of Enhanced Recovery After Surgery (ERAS) Predicting Long-Term Outcome after Hepatectomy for Cholangiocarcinoma."** (Manuscript NO.: 81620, Retrospective Cohort Study). We appreciate the comments and suggestions; according to which, we have responded by revising the manuscript as documented hereafter.

We believe that the manuscript has been improved and hope that it is now acceptable for publication in the '***World Journal of Gastrointestinal Surgery'***.

Yours sincerely,

Associate Professor Vor Luvira, MD, FRCST
Department of Surgery, Faculty of Medicine
Khon Kaen University, Khon Kaen 40002, THAILAND
Tel. +66 (0) 4334-8393, +66 (0) 89 776 5862 Fax: +66 (0) 4324-3064
E-mail: vor_110@yahoo.com

Science editor comments:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Response to the editor:

- Thank you very much for your time, kind and valuable opinions.

Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response to the editor:

- Thank you very much for your time, your kind and valuable opinions, and the opportunity to publish this manuscript in the World Journal of Gastrointestinal Surgery.
- We have revised our manuscript according to the reviewers' suggestions, and provided point by point response hereafter.
- We have applied the RCA for searching more literatures, according to your suggestion, in order to improve our manuscript.

Reviewer#1

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Dear Editor, it was my pleasure to be asked to read and evaluate this work entitled "Compliance of Enhanced Recovery After Surgery (ERAS)

Predicting Long-Term Outcome after Hepatectomy for Cholangiocarcinoma". There are several questions I would like to propose.

Response to reviewer:

- Thank you very much for your time, your kind and valuable opinions

1) First," The median survival of the patients in the ERAS<50 group was 1,257 days (95%CI: 853.2-1660.8), whereas of the patients in the ERAS≥50 group was not reached", is there some mistake about ERAS≥50 group?

Response to reviewer:

- Thank you very much for your notification.
- There was no mistake. The sentence "whereas of the patients in the ERAS≥50 group was not reached" means more than 50 percent of the patient with ERAS≥50 were still alive at the time of the last follow-up.
- However, for more clarification, we have revised this part of the manuscript to be "The median survival of the patients in the ERAS< 50 group was 1,257 days (95%CI: 853.2-1660.8), whereas of the patients in the ERAS≥50 group was not reached- more than 50 percent of the patient with ERAS≥50 were still alive at the time of the last follow-up."

2) Second, this study didn't mention and discuss laparoscopic hepatectomy for cholangiocarcinoma, as we know, laparoscopic technology played an important role in ERAS.

Response to reviewer:

- The authors appreciate the reviewer's insightful comment.
- We agree that laparoscopic surgery play an important role in ERAS and has a large impact on patient outcome, ERAS in laparoscopic liver resection should be considered separately from open liver resection. Since laparoscopic liver resection is typically performed in selected patients that require less complicate operative procedure, our study was intentionally conducted when all cholangiocarcinoma cases at our center received open resection to minimize selection bias.
- We have added this information to the 'discussion' part according to your valuable suggestions.

3) To conclude, the manuscript is good and interesting. In my opinion, major revisions should be made. However, since my negative opinion comes only from the originality of the paper, I respect the editor's opinion. Sincerely

Response to reviewer:

- Thank you very much for your kind suggestions.

Reviewer#2

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Rejection

Specific Comments to Authors: This is an interesting paper evaluating the effect of ERAS compliance on long-term outcomes after hepatectomy for cholangiocarcinoma. Could the authors please respond to the following questions:

Response to reviewer:

- Thank you very much for your time and valuable comments.

1) Since this is a retrospective study of a patient population where ERAS was not fully implemented, that raises concern for bias, since patients who were doing better for other reasons (disease extent, type of surgery, preoperative status etc) would have been more likely to have a higher number of ERAS elements in their care given that they were already better. This is a significant limitation of the paper.

Response to reviewer:

- The authors appreciate the reviewer's insightful comment. We totally agree with the reviewer that this is an inevitable limitation of this study. We had mentioned these synergistic effects in the ‘discussion’ part. However, we have added this issue in the limitation of this study in the ‘discussion’ part according to your valuable suggestions.

2) How do the authors link the higher ERAS to longer overall survival?

Response to reviewer:

- Thank you very much for pointing out this important point.
- We had mentioned this as ‘ERAS improved survival through various ways; i) reduction of postoperative stress leads to better immunologic function against the remaining tumor micro-metastases, and ii) promoting quick recovery prevents the delay of adjuvant treatment.’

3) What is the significance of “50% ERAS”?

Response to reviewer:

- For categorizing the patients into 2 groups, we initially intended to use 80 percent ERAS adherence as the cut point. Since the overall ERAS compliance of our series was poor, there was no patients who achieved more than 80 percent of ERAS items, and the cut point of ERAS adherence below 50 percent was unacceptable to be considered as ‘good’ ERAS, we chose the 50 percent as the cut point.

Reviewer#3

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The present study is the first and the most extensive study demonstrating ERAS compliance and its association with short-term and long-term outcomes of cholangiocarcinoma patients. The language quality is fine. However, this study has a few drawbacks to its scientific quality.

Response to reviewer:

- Thank you very much for your time and valuable suggestion.

1) Performing a retrospective study on the ERAS program is inherently flawed in interpreting the cause and effect. A patient who suffered from fewer complications after surgery will be more likely to comply with ERAS program as the patient would require further deviation from usual management. Vice versa, one can also say that compliance with the ERAS program will cause fewer complications. The result of this study needs to be interpreted very carefully before we can draw any conclusions.

Response to reviewer:

- The authors appreciate the reviewer's insightful comment. We totally agree with the reviewer that this as an inevitable limitation of this study. We had mentioned this synergistic effects in the ‘discussion’ part. However, we have added this issue in the limitation of this study in the ‘discussion’ part according to your valuable suggestions.

2) The sample size of the ERAS ≥50 group is tiny (only 14 patients), which may cause a significant type 2 error.

Response to reviewer:

- Thank you very much for pointing out this important point.
- For categorizing the patients into 2 groups, we initially intended to use 80 percent ERAS adherence as the cut point. Since the overall ERAS compliance of our series

was poor, there was no patients who achieved more than 80 percent of ERAS items, and the cut point of ERAS adherence below 50 percent was unacceptable to be considered as ‘good’ ERAS, we chose the 50 percent as the cut point.

- We have added this point into the limitation of this study in the ‘discussion’ part

3) The ERAS program only lasted two years, from January 2015 to December 2016. It’s been six years, and a longer-term outcome and survival data should be available. On the other hand, the technology and management of patients could have been improved much, and the result would be different after this time lag. It will be interesting to let the readers know how the application of the ERAS program in your hospital since 2016.

Response to reviewer:

- The authors appreciate the reviewer's insightful comment.
- We had provided the survival data in the manuscript.
- Since we think there are many differences in physiological disturbances and perioperative cares between laparoscopic and open liver resection, those should be studied separately. Therefore, we intended to limit our study period to 2015-2016, when ERAS was first introduced and all cholangiocarcinoma cases received open surgery
- We totally agree with the reviewer that we should provide how we apply the ERAS program in our hospital since 2016, We have added this information to the ‘discussion’ part of the manuscript.

Please note that we have highlighted in yellow any text where additions or corrections have been made.