

Peer Review File

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Reply to Reviewer A

Comment 1: In the abstract, the “Method” is too simple. It is suggested to add relevant contents.

Reply 1: Thank you for the comment. We have detailed the method part of the abstract.

Change in the text: Relevant contents have been added to the method part of the abstract.
(Page 2, Line:31-36)

Comment 2: Please check all the abbreviations in the whole text. They should be full names when they first appeared.

Reply 2: Thank you for your careful check. We have checked and confirmed all abbreviations are well explained when they appear for the first time.

Change in the text: All abbreviations are well explained when they appear for the first time.

Comment 3: There are many grammatical errors (In particular, the use of English tense is inconsistent) or irregular writing (For example, there should be a space after each word or each punctuation) throughout the text. The language of this paper needs to be polished by an English native speaker.

Reply 3: Thank you for the comment. We have corrected the grammar and writing errors in the paper with the help of a good friend.

Change in the text: The language of our paper has been polished with the help of a good friend.

Comment 4: The content stated in this paper is too old, mainly because most of the references are three years ago. Please refer to the relevant literature published in recent years to update the content of the paper.

Reply 4: Thank you for your careful reading. We rechecked the references and found out

those published before the year 2017. The 6th, 13rd, and 36th-40th references were replaceable. They were replaced by the newly published studies in the revised manuscript. The 17th-21st references met the including criteria of our meta-analysis. However, they were excluded due to the overlap of enrolled patients with other studies. They were all published before 2017. We also deleted them in the revised manuscript to decrease the number of old references. However, some references should be in the text, and they are unreplaceable. The 15th reference is a previously published meta-analysis on this topic. The 16th is a classical paper about the method of meta-analysis. The 22nd-35th references are the studies included in the meta-analysis. Some of them are published before 2017. But they are unreplaceable as well.

Change in the text: Twelve references published before 2017 were replaced or deleted.

Comment 5: Several references are incomplete. Please provide it again.

Reply 5: Thank you for the careful check. We have checked and formatted the reference.

Change in the text: The references have been formatted in the revised manuscript.

Comment 6: It is best to add a title to each result. It is more conducive to understand.

Reply 6: Thank you for the suggestion. We have added some subtitles to the result section.

Change in the text: Several subtitles were added to the result section.

Comment 7: Nowadays, what is the situation of the treatment for gastroesophageal anastomotic complications in your hospital?

Reply 7: Thank you for the comment. Anastomotic leakage (AL) and anastomotic stenosis (AS) are the two mainly anastomosis-related complications. The latter often happens a long time after the surgery, and it is much less dangerous. The AS is handled by endoscopic dilation of the anastomosis in our hospital. As for AL, it often happened within a short time after the surgery. It is an unpredictable and lethal complication. The early reorganization of high-risk patients, well preoperative communication, early postoperative detection, and timely treatment are the rules for the management of AL in our department. The good drainage and adequate nutrient supply are the major weapons to deal with the AL, and most patients could recover in a few weeks. However, about 5-10 percent of patients who suffer from AL would

die.[1] So we think the prevention of AL is more important.

Change in the text: We added this part to the discussion section. (Page 8, Line: 159-167)

Reference:

[1]Fumagalli U, Baiocchi GL, Celotti A, Parise P, Cossu A, Bonavina L et al. Incidence and treatment of mediastinal leakage after esophagectomy: Insights from the multicenter study on mediastinal leaks. *World J Gastroenterol* 2019;25:356-66.

Comment 8: What is the side effect of ischemic conditioning in the prevention of gastroesophageal anastomotic complications?

Reply 8: Thank you for the question. We could achieve IC through laparoscopic ligation or embolization approach. The side effect of the laparoscopic approach is similar to general laparoscopic surgery. As for the embolization approach, it is more complicated. The reported side effect includes partial splenic infarct, vesicular ischemia, gastric perforation, and pancreatitis, and so on. However, the morbidity rate is quite low, and most of them are mild.

Change in the text: We have added this part to the discussion section. (Page 10, Line 208-213)

Comment 9: There are still some weak points in this paper. It is suggested that the author increase possible mechanism analysis. This is more conducive to support the conclusions of this study.

Reply 9: Thank you for the suggestion. The basis of ischemic conditioning is the compensation effect. As a result of ligation or embolization of gastric vessels, the blood supply to the stomach decrease. The hypertrophy and neovascularization would be activated to adapt to the relatively ischemic condition. Pham and his colleagues observed IC produced a 67% increase of microvessels counts, compared to the controls.[1] The animal model conducted by Perry et al. showed IC could significantly increase neovascularization and muscularis propria preservation.[2] What's more, they found the degree of inflammation at the healing anastomosis decreased dominantly. These findings indicate the IC could provide a better environment supporting the healing of gastroesophageal anastomosis.

Change in the text: More illustration of the possible mechanism of IC has been added to the

text. (Page 3-4, Line:66-73)

Reference:

[1] Pham TH, Melton SD, McLaren PJ, Mokdad AA, Huerta S, Wang DH et al. Laparoscopic ischemic conditioning of the stomach increases neovascularization of the gastric conduit in patients undergoing esophagectomy for cancer. *Journal of Surgical Oncology* 2017;116:391-97.

[2] Perry KA, Banarjee A, Liu J, Shah N, Wendling MR, Melvin WS. Gastric ischemic conditioning increases neovascularization and reduces inflammation and fibrosis during gastroesophageal anastomotic healing. *Surg Endosc* 2013;27:753-60.

Comment 10: What is the highlight of the treatment for gastroesophageal anastomotic complications in your hospital in the future?

Reply 10: Thank you for the question. The intrathoracic anastomosis has a significantly lower risk of AL than cervical anastomosis. Therefore, for patients with middle or lower section esophageal cancer and those with risk factors, we prefer to perform the intrathoracic anastomosis. However, for most upper esophageal cancer, cervical anastomosis is unavoidable. So we think the ischemic conditioning could be a good choice for them, especially those with risk factors of AL. With the evidence from this meta-analysis, we are now trying to apply this technique to these patients.

Change in the text: We have added this part to the text. (Page 3, Line 59-65; Page 10, Line 214-216)