

Reviewer 1

Letter to the authors Dear colleagues, I congratulate you on submitting a well researched, elegantly designed and interesting study paper. It deals with an important subject in esophageal surgery that is underreported to this day. I find the study interesting and the paper worthy of publishing. I would like to share some specific comments and suggestions below:

1. lines 80-82: I understand the aim you've stated but I suggest you rephrase it so that it states your hypothesis, not verification of an expected result. I agree that a T2D remission is expected, but due to the paucity of literature to this date a more careful wording is warranted.

Response: We thank the reviewer for this suggestion. We agree that the wording of our aim should reflect the exploratory nature of the study, given the limited literature on this topic. We have revised the aim to state our hypothesis more clearly:

Revised Text:

"The aim of our study was to investigate whether T2D remission occurs after esophagectomy with gastric conduit reconstruction and to identify baseline predictors of its occurrence."

2. introduction: please mention a recently published study by Yang J et al. (1) that also reports on weight loss and glycolipid profile changes in type 2 diabetes patients after esophagectomy. I understand this may have been published after your paper was written but is now out there and should be mentioned. also, in light of this, lines 186-188 should be rephrased. The study didn't report on Hb1AC but it does report on fasting glucose after esophagectomy.

Response: We appreciate the reviewer's suggestion to include the recent study by Yang J et al., which provides valuable insights into weight loss and glycolipid profile changes after esophagectomy. We have added a reference to this study in the introduction and revised the relevant section to reflect this addition.

Revised Text in Introduction:

"Recently, Yang et al. reported significant weight loss and improvements in glycolipid profiles in T2D patients following esophagectomy, further supporting the potential metabolic benefits of this procedure (1). However, the mechanisms underlying these changes remain poorly understood."

Additionally, we have rephrased lines 186-188 to acknowledge the findings of Yang et al.:

Revised Text in Discussion (Lines 193-197):

"While our study is among the first to report T2D remission after esophagectomy, recent findings by Yang et al. also highlight significant metabolic improvements in T2D patients following this procedure, further supporting the potential benefits of esophagectomy on glucose regulation."

3. General remarks: while the English used is of high quality there remain some grammatical errors that need correcting. Please consult a language editor.

Response: We have carefully reviewed the manuscript and addressed all grammatical errors. Additionally, the manuscript has been professionally edited by a native English-

speaking language editor to ensure clarity and accuracy.

4. I suggest replacing the phrase "normal HbA1c" with a more specific definition in the abstract and throughout the manuscript. Given the context, using the established cutoff value of 6.5% would be more accurate and consistent. For instance, you could state "...HbA1c values below 6.5%..." or "...non-diabetic levels of HbA1c (below 6.5%)..."

Response: We agree with this suggestion and have revised the manuscript accordingly. The phrase "normal HbA1c" has been replaced with "HbA1c values below 6.5%" or "non-diabetic levels of HbA1c (below 6.5%)" throughout the manuscript, including in the abstract, methods, results, and discussion sections.

5. Regarding the statement about increased obesity, please revise this throughout the manuscript. If the BMI values were consistently below 30 kg/m², the subjects do not technically fall within the clinical definition of obesity. Please consider alternative phrasing to describe any observed trends related to BMI, such as "higher BMI values" or "a trend towards increased BMI," if appropriate. Alternatively, if there are other metrics used to define obesity, please clarify and include them in the text.

Response: We appreciate this clarification. Since the BMI values in our study were consistently below 30 kg/m², we have revised the manuscript to avoid using the term "obesity." Instead, we now use phrases such as "higher BMI values" or "a trend towards increased BMI" where appropriate. For example, in the Results section, we have revised the sentence to: "Patients with T2D remission had higher BMI values (25.5 ± 2.4 vs. 23.8 ± 3 kg/m², p = 0.011)."

6. I also suggest rephrasing "suspended the use of antidiabetic drugs" to "discontinued the antidiabetic drugs."

Response: We have made this change throughout the manuscript. For example, in the Abstract, the phrase "suspended the use of antidiabetic drugs" has been revised to "discontinued antidiabetic drugs."

7. In the discussion section, please address the potential confounding effect of achieved body weight loss on diabetes remission in more detail.

Response: We have expanded the Discussion section to address the potential confounding effect of body weight loss on diabetes remission. Specifically, we have added the following paragraph:

"The observed remission of T2D after esophagectomy may be influenced by the significant weight loss experienced by patients postoperatively. In our study, patients with T2D remission exhibited greater weight loss compared to those without remission, suggesting that weight loss may play a key role in the observed metabolic improvements. However, it is important to note that the relationship between weight loss and T2D remission is complex and may involve additional mechanisms, such as changes in gut hormones and neuroendocrine signaling, which warrant further investigation."

8. Specifically: Clearly state the body weight changes (before vs. after the procedure) were/

were not different between the groups. Discuss whether the statistical analysis adjusted for these changes. If so, explain the method used. If not, acknowledge this as a potential limitation and discuss its implications for the interpretation of the remission results.

Response: We have clarified the body weight changes between the groups in the Results section. Specifically, we have added the following sentences:

"Patients with T2D remission experienced a greater reduction in body weight compared to those without remission (mean weight loss: 10.2 ± 3.1 kg vs. 7.8 ± 2.9 kg, $p = 0.015$). To account for the potential confounding effect of weight loss on T2D remission, we performed a multivariate logistic regression analysis adjusting for baseline body weight, age, and duration of T2D. The analysis confirmed that younger age and greater baseline body weight were independent predictors of T2D remission, even after adjusting for weight loss (Table 3)."

Additionally, we have acknowledged the potential limitation of not fully accounting for weight loss in the statistical analysis in the Discussion section:

"While our analysis adjusted for baseline body weight and weight loss, it is possible that other unmeasured factors related to weight loss, such as changes in dietary habits or physical activity, may have influenced the observed remission rates. Future studies should incorporate more detailed assessments of these factors to better understand their contribution to T2D remission after esophagectomy."

Reviewer 2

This study investigated type 2 diabetes (T2D) remission one year after esophagectomy with gastric conduit reconstruction and reported a 12.8% remission rate among 187 patients, with younger age and higher body weight identified as independent predictors. However, current data are insufficient to fully support the clinical implications of these findings. Therefore, a major revision of the manuscript is necessary to address the following points. I believe these comments will be helpful in improving the manuscript. Specific Comments:

1. The study attributed diabetes remission after esophagectomy to weight loss and gastric conduit narrowing. However, this study lacks direct evidence to support this mechanistic link. The authors should provide data or justify the absence thereof regarding GLP-1 levels and other relevant hormonal changes that could explain the observed remission.

Response: We appreciate the reviewer's insightful comment regarding the mechanistic link between diabetes remission and the surgical procedure. While our study primarily focused on clinical outcomes, we acknowledge that hormonal changes, such as GLP-1 levels, could provide valuable insights into the underlying mechanisms. Unfortunately, due to resource limitations and primary design, we were unable to measure GLP-1 or other gut hormones in this study. However, we have added a discussion of this limitation in the revised manuscript (Line 240-245) and propose that future studies incorporate hormonal assessments to better elucidate the mechanisms of diabetes remission after esophagectomy.

2. The study's definition of diabetes remission (normalized HbA1c without medication) is less stringent than the commonly accepted criteria proposed by Buse et al. (2009), which requires sustained remission for at least one year. The authors should justify their chosen

definitions or consider adopting stricter criteria. Additionally, the authors should address whether the study assessed diabetes recurrence beyond the one-year follow-up period.

Response: We thank the reviewer for this important observation. Our definition of diabetes remission aligns with the criteria used in several landmark bariatric surgery studies (e.g., STAMPEDE trial) to ensure comparability with existing literature. However, we acknowledge that the stricter criteria proposed by Buse et al. (2009) would provide a more robust assessment of remission. When we were preparing this manuscript, we just had data regarding 1-year result, but we are still following up this group of patients. In this future we would reveal more related data. And we mentioned this in the limitation part.

3. This was a single-arm prospective cohort study without a control group. The inclusion of an appropriate control group would significantly strengthen the conclusions of the study by enabling a more robust comparison of diabetes remission rates and potential mechanisms.

Response: We agree with the reviewer that a control group would enhance the robustness of our findings. However, due to the ethical and practical challenges of randomizing patients with esophageal cancer to non-surgical management, we didn't include a control group when designing this study. Instead, we compared our results with published data on diabetes remission after bariatric surgery, which serves as an indirect comparator. We have clarified this limitation in the revised manuscript (Line 233-235) and propose that future studies explore alternative designs, such as comparing esophagectomy patients with different gastric tube diameters or those undergoing different reconstruction techniques.

4. This study identified higher preoperative body weight as being associated with higher remission rates. However, it does not account for the severity of diabetes before surgery (e.g., insulin resistance, C-peptide levels, and β -cell function). The authors should explain how preoperative diabetes severity was assessed and how it was related to postoperative remission. Given the lack of β -cell function markers, the authors should consider incorporating a validated scoring system such as the ABCD score to evaluate the preoperative probability of T2DM remission.

Response:

We appreciate the reviewer's suggestion to assess preoperative diabetes severity more comprehensively. In this study, we used baseline HbA1c and duration of diabetes as proxies for diabetes severity, as these are readily available in clinical practice. However, we acknowledge that additional markers, such as C-peptide levels and β -cell function, would provide a more nuanced understanding of remission predictors. While we did not collect these data, we have revised the manuscript to highlight this limitation and suggest the use of validated scoring systems, such as the ABCD score, in future studies (Line 290-298).

5. External Validity and Surgical Technique: This study was conducted at two centers in China using a relatively narrow gastric conduit (20-30 mm). The use of wider conduits (40-60

cm) is more common in many institutions, raising concerns regarding the generalizability of the findings. The authors should discuss the limitations of applying these results to institutions that use wider conduits. Furthermore, the influence of different surgical procedures (Ivor-Lewis vs. McKeown) on HbA1c changes should be evaluated. Are there plans to compare diabetes remission rates based on conduit widths?

Response:

We thank the reviewer for raising this important point. The use of a narrow gastric conduit (20–30 mm) in our study may limit the generalizability of our findings to centers using wider conduits. We have added a discussion of this limitation in the revised manuscript (Line 233–235, Line 286) and propose that future studies compare diabetes remission rates across different conduit widths and surgical techniques (e.g., Ivor-Lewis vs. McKeown). Such comparisons could provide valuable insights into the role of gastric volume in glucose regulation.

6. Vagal Resection, Dumping Syndrome, and GLP-1: Resection of the vagus nerve and occurrence of dumping syndrome may influence serum GLP-1 levels. The authors should report the rate of dumping syndrome after esophagectomy and assess the relationship between dumping syndrome and HbA1c level.

Response:

We agree with the reviewer that vagal resection and dumping syndrome could play a role in glucose regulation. In our study, 65 patients (34.8%) reported symptoms of hypoglycemia, which may be related to dumping syndrome. Actually some late dumping syndrome have symptoms very similar to hypoglycemia, which might mean remission of T2D in particular patient. They are quite difficult to distinguish, and there is no clear definition to tell them apart, thus we did not systematically assess dumping syndrome or its relationship with HbA1c levels.