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**Title:** The Impact of Postoperative Glycemic Control and Nutritional Status on Clinical Outcomes after Total Pancreatectomy

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**Reviewer 1, 03548113**

1. Table 1 showed that the number of patients with tumor located corpus was 15 and located tail was 3. But the number of patients with splenectomy was 11. I think the number with splenectomy should be more than 18. I wonder that adequate lymphadenectomy was not performed for pancreatic cancer.

**Reply:** Our operative principle is that splenectomy is necessary when a malignant tumor is located in the tail of the pancreas. Generally, splenectomy will be performed together with total pancreatectomy for tumors located in the head or corpus of the pancreas only when the pancreas tail is tightly close to or adheres to the spleen. So the number of patients with splenectomy did not have to be 18. Besides, lymphadenectomy was indeed performed for all cases.

2. I think that the goal of glycemic control which was set at both less than 155 mg/dl of FBG and less than 7% of HbA1c is too strict. This goal will cause hypoglycemia events frequently. The authors described that "The condition below the threshold was judged as poorly-controlled diabetes after TP". When was the point of judge?

**Reply:** Undoubtedly, hypoglycemia event is one of severe complications of diabetes. That's why four subcutaneous injections of insulin a day are recommended instead of two injections of insulin a day. Hypoglycemia event can be avoided efficiently with regular diet rules, routine exercises and adjustment if insulin dose to changing circumstance, even when our goal was set at less than 155 mg/dl of FBG and less than 7% of HbA1c.

"The condition below the threshold was judged as poorly-controlled diabetes after TP" should be corrected by "The condition above the threshold was judged as poorly-controlled diabetes after TP". The point of the judgement is at the fasting state in the morning. The judgement is based on the glucose level exceeding the threshold for at

least two days.

3. The authors concluded that "Improvement in glycemic control and nutritional status after TP is important to prevent early complications". But this study showed only the data of glycemic control 1,3,6,12 months after surgery. The glycemic control of early period after the surgery is important to prevent early complications, but these data was not shown.
**Reply:** The data of glycemic control and nutritional status during early period after the surgery has been added in Table 2.

4. The result; Improvement in glycemic control and nutritional status after TP improve survival is very interesting, nevertheless I can't understand the reason.
**Reply:** The relationship between postoperative HbA1c and recurrence and survival of patients undergoing TP may be attributed to the fact that pancreatic cancers depend heavily on glucose for growth, as discussed in the article. It suggests that patients will have longer survival if glucose level is tightly controlled and nutritional status is improved.

**Reviewer 2, 00181305**
1. Could you give us more precision about the indication for TP: size of the tumor, number of tumors, location of tumor?
**Reply:** Multiple tumors in the different sites of the pancreas such as the head and tail are obviously the indication. Tumor in the corpus of the pancreas is the most common indication of TP, which invades vessels so that Whipple or distal pancreatectomy cannot be performed. What's more, benign IPMN is not included because it is not a regular indication in our nation and completion pancreatectomy is more acceptable for our patients once tumor recurrence occurs.

2. There is no mention of any neoadjuvant and adjuvant treatment?
**Reply:** Fourteen patients underwent neoadjuvant treatment. All patients in the cases underwent adjuvant treatment because of malignant tumors. These data has been shown in Table 1.

3. There was no pylorus preservation: did the authors encounter any problem regarding gastric venous ischemia?
**Reply:** We observed some cases of gastroplegia after pylorus preservation. Regularly, pylorus preservation is not our first choice.

4. Number exposed to the risk could be useful with the survival curves.
**Reply:** The numbers have been added in Figure 3.

5. Fig 2 could be deleted.
**Reply:** Considering of different checkpoints in the analysis which may confuse readers, Fig 2 can make the article more comprehensible.

6. Table 2 and fig 1 could be summarized in one unique figure.
**Reply:** The authors consider that Table 2 presented alone is easier for readers to understand.

7. How was the diabetes treated after TP? Did some of the patients have an insulin pump?
**Reply:** In three days after surgery, patients received continuous intravenous insulin infusion by trace syringe pump when blood glucose levels were under dynamic monitoring. Subsequently, patients were referred to a consultant endocrinologist for subcutaneous insulin regimens. Four subcutaneous injections of insulin a day were recommended. No patients had an insulin pump after discharge.

**Reviewer 3, 00004406**
1. Poorly controlled sugar levels predict a poor prognosis; this is not a novel finding (and even more so, not surprising).
**Reply:** The majority of previous studies focused on preoperative glucose level or nutritional index. However, given that the pancreas plays a central role in glycemic control and nutritional status, pancreatic surgery involving resection of pancreatic parenchyma, TP in particular, breaks preoperative homeostasis and obliges the body to adapt to another new balance of glycemic and nutritional status. Thus, a series of postoperative clinical parameters ensure the instantaneity of objective reflection of metabolism, and analyses of their association with complications, recurrence and survival may have more clinical value, compared with the preoperative ones. The authors believe these are novel findings.

2. A number of 52 patients is very low for a multivariate analysis. The groups are very heterogeneous which makes this analysis even more questionable.
**Reply:** Only a relative small sample size of patients were identified. One reason is that benign IPMN is not the regular indication for TP in our nation because completion pancreatectomy is more acceptable for our patients once tumor recurrence occurs. The other reason is that the authors tried their best to avoid the apancreatic state after TP which is difficult for patients to adapt themselves to.

The selected patients with different types of pancreatic tumors did increase the heterogeneity of subjects. However, it should be noted that on the premise of adequate numbers of patients, patients with completion pancreatectomy were excluded and only patients with malignant pancreatic tumors were included.

3. Hypoglycemia is a real relevant factor for postoperative death (especially when the patients return to their home). This issue is not addressed.
**Reply:** Undoubtedly, hypoglycemia occurred occasionally after discharge. However, no reports about hypoglycemia-related death were received during the follow-up.

4. Different aspects of the postoperative nutritional status are "touched" but not explored in detail. The manuscript is a sequence of descriptive findings without true connections.
**Reply:** As far as the authors know, there is no absolutely "golden" clinical indexes to judge nutritional status. Meanwhile, according to the results, glycemic control appeared to have more influence over nutritional status on long-term outcome in patients undergoing TP. Thus, further discussion about postoperative nutritional status gets quite difficult.

5. Infectious complications are discussed (in the discussion section) but no details are given on infectious complications in the methods or results part – other than 9 "abdominal infections" (whatever that means) as shown in table 1.
**Reply:** Abdominal infection was confirmed by positive germiculture of peritoneal fluid from peritoneal drainage catheter. No wound infections occurred.

6. The discussion is much too long; many points are discussed that are general knowledge. It is not easy to grasp the true message of the manuscript. It needs to be restructured to clearly mirror the authors opinion.
**Reply:** The discussion has been restructured and refined to mirror the central idea more clearly.

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