# Peer Review File

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**Reviewer A**

The authors showed that the main pancreatic duct width of < 3 mm, VFA of > 82 cm2, soft pancreas, and operation time of > 320 min were independent risk factors of postoperative pancreatic fistula (POPF) after laparoscopic pancreaticoduodenectomy (LPD), and I agree the authors' opinion that it is important to understand risk factors of POPF after pancreaticoduodenectomy (PD). However, this manuscript has some points to be revised according to my suggestions. My suggestions are described below:

Comment 1: These risk factors of POPF detected in this manuscript are not characteristic of laparoscopic procedure and were described as a risk factor of POPF after open PD in several papers. The mechanisms of pancreatic fistula are theoretically same in both laparoscopic and open procedure. Therefore, the authors should explain the reason why they focused on POPF only after LPD.

**Reply 1: POPF is one of the most important complications after PD, which often cause severe consequences, Therefore, a large number of literatures studied the risk factors of pancreatic fistula after OPD. In the past decade, the development of LPD is extremely rapid, and it has become a routine operation in most high-volume centers. However, the safety and feasibility of LPD, especially the laparoscopic pancreaticojejunostomy remains controversial. Laparoscopic pancreaticojejunostomy is considered to be the most difficult point of the learning curve of LPD. Some studies believed that LPD will increase the occurrence of postoperative fistula, but most studies shown no difference between LPD and OPD. Due to the limitation of minimally invasive operation,**

**the texture of the pancreas and the diameter of the pancreatic duct have a greater impact on the laparoscopic pancreaticojejunostomy. Meanwhile, the duration of operation and intra-operative blood loss are considered to be the risk factors of PF after OPD. Most studies have shown that LPD has longer operative time, but less bleeding compared to OPD, whether these changes affect the development of pancreatic fistula was still unclear. Considering the characteristics of minimally invasive technology and the changes of many related factors between LPD and OPD, therefore, it is necessary and significant to study the risk factors of POPF for LPD. Our study found that pancreatic duct diameter, pancreatic texture, operative time and VFA were associated with POPF for LPD. These factors were also proved to be the key risk factors of POPF in OPD, which indirectly reflected that good control of the above risk factors can further ensure the safety of LPD, and provide basis for the future development of LPD.**

Comment 2: The authors elucidated that the main pancreatic duct width of < 3 mm, soft pancreas, and operation time of > 320 min were independent risk factors of POPF following LPD using multivariate analysis. However, they also found that the main pancreatic duct width of < 3 mm and VFA of > 82 cm2 were significantly associated with soft pancreas. These two findings are logically incorrect because the main pancreatic duct < 3 mm, VFA of > 82 $cm^2$, and soft pancreas are regarded as confounding factors and some of these factors should be omitted in multivariate analysis. Therefore, the authors should re-analyze about risk factors of POPF.

**Reply 2: Thanks for mentioning the critical issue and valuable advice. According to your suggestion, we re-analyzed the variables in the study. In order to control the confounding effect between independent variables in regression analysis, we conducted a multicollinearity diagnostic analysis of the variables included in the multivariate analysis, the results shown that there is no serious collinearity between independent variables. Additionally, considering that the main**

**pancreatic duct, VFA, and soft pancreas are all important clinical risk factors of POPF, thus, we have included them in the multivariate analysis. Also, recent research believed that the pancreatic texture are related with many factors such as the fat infiltration and acinar cell content and degree of fibrosis. A publication in Surgery by Gaujoux et al shown the fatty pancreas and BMI were the risk factors of POPF after PD, furthermore, the BMI was closely related with the fatty pancreas. Based on previous research findings, we preliminarily explored the relationship between main pancreatic duct, abdominal fat and pancreatic texture, which aimed to investigate whether these factors can be regard as surrogate indicators for evaluating the pancreatic texture before surgery. In our future work, we will study the factors affecting the texture of pancreas in depth, with the help of postoperative histopathology.**

Comment 3: To date, many authors described about risk factors of POPF after PD, therefore it is necessary to detect not only risk factors but also preventive measures of POPF. However, the authors did not mention about how to prevent POPF after LPD, especially in the case with risk factors of POPF. Precautionary methods of POPF are needed in this manuscript.

**Reply3: Thanks for mentioning the critical issue. The purpose of our study is to investigate the risk factors of POPF and then to propose preventive measures to promote the safety of LPD. We are very sorry for our negligence of the detailed preventive measures of POPF after LPD in our original manuscript. As your suggestion, we added the precautionary methods in the discussion section.**

**Changes in the text: Page 21-22, line 453-467**

Comment 4: Soft pancreas is subjective index and strongly correlated with paraneoplastic pancreatitis and the width of the main pancreatic duct. In addition, it might be difficult to evaluate the texture correctly because of insufficient length of the pancreas parenchyma located distal side of the lesion. Therefore, the authors should

mention about inaccuracy of soft pancreas as an evaluation indicator in the discussion section.

**Reply 4: In most previous studies, pancreatic texture was considered to be an important risk factor for pancreatic fistula after PD. Due to the lack of objective evaluation indexes, pancreatic texture still depends on the subjective judgment of the operator. Similarly, in our study, before digestive tract reconstruction, specimens from the abdominal cavity were removed, and the texture of the pancreas was evaluated. we mentioned the pancreatic texture is subjective index and inaccuracy of soft pancreas as an evaluation indicator in the discussion section of revised manuscript as advised.**

**Changes in the text: Page 18, line 393-396**

Comment 5: There are some grammatical errors and inappropriate English uses in the manuscript. This manuscript should be proofread by a native speaker of English.

**Reply 5: Thanks for mentioning the language expression in the manuscript. Two native speakers of English majoring in same field have edited the entire manuscript. We believe this has significantly improved the language issues raised by the reviewers.**

**Reviewer B**

**Minor Revision**

It is a well written paper. Soft pancreas can represent either fat or high acinar cell content. Recently there have been a number of publications in HPB by Nahm et al looking at acinar cell content. It has been shown that a soft pancreas rich in acinar cells correlates with POPF but a soft pancreas with only fat does not. I would like to see that in the manuscript. This correlation can also be seen on CT scans - perhaps the

authors can relook at the histopathology for acinar cell content. Otherwise, its just another paper looking at the same risk factors that have been mentioned before.

**Reply: Thank you for the comment. As previously reported, the texture of the pancreas currently depends on the intra-operative palpation of the remnant gland. Recently, some researchers used postoperative histopathology to objectively evaluate the texture of pancreatic parenchyma. These publications in HPB by Nahm et al shown that pancreatic hardness correlated negatively with acinar score and positively with collagen score, not correlated with fat score. But some studies found the softness and fragility of pancreas was positively associated with the fat content, and the fatty pancreas was the important risk factor of POPF for PD. In our study, we preliminarily explored the relationship between abdominal fat distribution and pancreatic texture, which aimed to investigate whether these factors can be regard as surrogate indicators for evaluating the pancreatic texture before surgery. In our future work, we will investigate the correlation between the pancreatic texture and acinar cell content, fat content with the help of CT scans and postoperative histopathology.**

**Reviewer C**

In this study, the authors declared that pancreatic texture, VFA, main pancreatic duct width and operative time are independent risk factors for the prediction of POPF in patient underwent LPD. This study highlights the VFA as a novel marker for evaluating the CR-POPF before surgery.

Comment 1: The CEA level is crucial in evaluating the tumor progression or postoperative complications. Did the author explore the relationship between CEA and Grade B/C POPF?

**Reply 1: Thanks for mentioning the critical issue. the tumor markers is crucial in evaluating the progression of malignant tumor. In our study, we investigate the risk factors of POPF after LPD, considering that our study population not only includes 289 (74.5%) patients with malignant tumor, but also includes 99 patients with benign tumors, and the CEA level have no significant increase in the majority of patients with pancreatic and periampullary cancer. The relationship between CEA level of malignant tumor and tumor progression or postoperative complications will be validated in our next research work.**

Comment 2: What is the percentage of malignant tumor in total, is there any difference between the benign and malignant tumor?

**Reply 2: In our study, 289 (74.5%) patients were malignant tumor, 99 patients were benign or borderline tumor. We found no difference in clinicopathological variables and postoperative complications between the benign and malignant tumor, we add the comparison results of malignant and benign tumors between the PF and No-PF group in Table 2 as advised.**

**Reviewer D**

**Major Revision**

Comment 1: This analysis does not add much novel information to the topic.

**Reply 1: In the past decade, the development of LPD is extremely rapid, and it has become a routine operation in most high-volume centers. However, the safety and feasibility of LPD, especially the laparoscopic pancreaticojejunostomy remains controversial. Laparoscopic pancreaticojejunostomy is considered to be the most difficult point in the learning curve of LPD. Some studies believed that LPD will increase the occurrence of postoperative fistula, but most studies shown**

**no difference between LPD and OPD. Due to the limitation of minimally invasive operation, the hardness of the pancreas and the diameter of the pancreatic duct have a greater impact on the laparoscopic pancreaticojejunostomy. Meanwhile, the duration of operation and intra-operative blood loss are considered to be the risk factors of PF after OPD. Most studies have shown that LPD has longer operative time, but less bleeding compared with OPD, whether these changes affect the pancreatic fistula is still unclear. Considering the characteristics of minimally invasive technology and the changes of many relevant factors between LPD and OPD, also, there are few relevant study in LPD. Therefore, it is necessary and significant to validate the risk factors of POPF for LPD. Our study found that pancreatic duct diameter, pancreatic texture, operative time and VFA were associated with POPF for LPD. These factors were also proved to be the important risk factors of POPF in OPD, which indirectly reflected that good control of the above risk factors can further ensure the safety of LPD, and provide basis for the future development of LPD. Besides, we used preoperative abdominal CT to explore the relationship between abdominal fat area and pancreatic texture.**

Comment2: This is not a well-designed study with no inclusion or exclusion criteria, no description of missing data,

**Reply 2: Thanks for mentioning the critical issue, we ignored the inclusion or exclusion criteria for this study are not detailed in our original manuscript. The exclusion criteria of the study included: 1) incomplete clinicopathological data; 2) palliative resection; 3) combined with other organ resections (such as hepatectomy or colectomy); 4) combined vascular resection; 5) converted to laparotomy. Subsequently, 37 patients excluded from 425 patients, 388 patients were finally included in the study.**

**Changes in the text: page 5, line 93-97**

Minor:

Comment 3: How long was the follow-up of the patients?

**Reply 3: Considering the consequences of POPF and its impact on clinical outcome, the follow-up time of this study is 90 days after surgery.**

Comment 4: Specify that the assessed POPF only concern clinically relevant POPF (grade B, C).

**Reply 4: As previously reported, grade A POPF has no significant interference on clinical treatment, and does not affect the outcome of patients after LPD. Additionally, grade A POPF no longer considered a true pancreatic fistula or an actual complication according to the definitions provided by the International Study Group of Pancreatic Surgery (ISGPS). However, grade B / C pancreatic fistula often leads to severe postoperative consequences, which requires active clinical intervention, therefore, we focus our research on the risk factors of clinically relevant POPF.**

Comment 5: Normally distributed continuous data should be presented as the means with standard deviations.

**Reply 5: Thank you for pointing out this statistical problem. In our study, in order to uniformly convert continuous variables into binary variables at the median, we presented continuous variables as median and interquartile range. Additionally, we also analyzed the normally distributed continuous data presented as the means with standard deviations, and the result of this research were consistent with continuous variables presented as median and interquartile range.**

Comment 6: Parameters that were expected to be clinically important, such as sex,

blood loss should be incorporated into the regression analysis.

**Reply 6: As reviewer suggested that some clinical parameters such as sex, blood loss should be incorporated into the regression analysis, we add some variables that were expected to be clinically important to multivariable logistic regression models and re-analyzed the risk factors of POPF. The results of the re-analysis are consistent with that of the original analysis, the main pancreatic duct width of < 3 mm, VFA of > 82 $cm^2$, soft pancreas, and operation time of > 320 min still were independent risk factors of POPF after LPD.**

**Changes in the text: Page 13, line 280-281, and changes are marked as red color in Table 5.**

Comment 7: Decimal places are inconsistent, such as data in Table 3.

**Reply 7: Rigorous and standard data writing in tables is essential for scientific papers, thank you for mentioning the issue of writing format. The decimal places of data in the table have been re-corrected.**

**Changes in the text: changes are marked as red color in Table 3.**

Comment 8: Please pay careful attention to the expression

**Reply 8: Thank you for mentioning the expression of the article. With the help of two native English-speaking expert majoring in same field, we checked carefully and improved the language, grammar and expression of the manuscript.**

Comment 9: Line 355: "the Alb (POD3-POD1) <3.1g/L was a independent risk factor". In your study, Alb (POD3-POD1) was not an independent risk factor.

**Reply 9: We are sorry for the confusion. we have revised this sentences in discussion section to " the Alb(POD3-POD1) <3.1g/L was a risk factor of POPF**

**after LPD in univariate analysis, but not a independent risk factor in multivariable logistic regression analysis."**

**Changes in the text: page 20, line 430-433.**

Comment 10: "best 2-predictors model (pancreatic texture and 238 pancreatic duct width less than 3 mm)". Do you have statistical results to support this conclusion?

**Reply 10: In our study, to evaluate the predictive performance of the risk factor models, the area under the receiver operating characteristic curve (ROC) was performed. The combination of pancreatic texture and pancreatic duct width<3 mm resulted in a AUC of 0.904, better than other combinations of predictive factors, we show this statistical result in Table 6 and Figure 2.**

Comment 11:There are sentences that are repeated in the manuscript, for example, line134 and line124, introduction and first paragraph of the discussion section

**Reply 11: Thanks for mentioning the repeated sentences in our original manuscript, we have re-written these parts according to your suggestion in our revised manuscript.**

**Changes in the text: page 15, line 311-315.**