Peer Review File

Article information: https://dx.doi.org/10.21037/gs-23-410

<mark>Response to the reviewers' comments:</mark>

<mark>Reviewer A</mark>

Comment 1: How many surgeons performed PD - surgeon is also a relevant factor fpr POPF
Reply 1: Thank you very much for pointing out this detail. A total of seven hepatobiliary pancreatic surgeons participated in this study, and there were no significant differences among them in terms of postoperative pancreatic fistula occurrence (p=0.27). We have added this information in the method and result sections using "Track Changes" function.
Changes in the text: we have included additional relevant analysis (see Page7, Line92; Page10, Line157).

Comment 2: POPF rate is quite high compared to litearture, almost 57% and also the rate of CR-POPF is very high ca. 40% - this is hard to explain, since most patients had cancer and PJ was usually stented. What is your explanation? How do the high rate of POPF and the resepectively large and heterogeneous group of POPF patients affect the results of the study?
Reply 2: We appreciate the suggestion and acknowledge the concerns raised by the reviewer regarding the occurrence rate of postoperative pancreatic fistula in our study. Our findings indeed revealed a higher occurrence rate of postoperative pancreatic fistula compared to numerous other studies documented in the literature. However, it is worth noting that according to the statistical data released by the China Pancreas Data Center (CPDC) in 2022, the incidence of grade A postoperative pancreatic fistula (POPF) after pancreatic cancer surgery in China is reported at 58%, while the incidence of grade B/C postoperative pancreatic fistula (POPF) is 28.0%. This analysis included both pancreaticoduodenectomy and distal pancreatectomy procedures. In comparison to pancreaticoduodenectomy, distal pancreatectomy is known to have a higher likelihood of pancreatic fistula occurrence, but the incidence of high-grade pancreatic fistulas is relatively lower. Taking this into consideration, we believe that the incidence rate of pancreatic fistula in this study is acceptable. （Wu W, Miao Y, Yang Y, et al. Real-world study of surgical treatment of pancreatic cancer in China: annual report of China Pancreas Data Center(2016-2020)[J]. J Pancreatol,2022,5(1):1-9. DOI: 10.1097/JP9.0000000000000086.）
Additionally, we greatly acknowledge your consideration regarding the impact of patient heterogeneity on the interpretation of study results. Our study indeed did not analyze or discuss this aspect of the content. I have now added the comparative statistical analysis results of postoperative pancreatic fistula between the training set of 269 patients and the testing set of 77 patients (p=0.443) in the results section. Furthermore, one limitation of this study is that the study population was derived from a single center, which imposes limitations on the generalizability of the predictive model. Subsequent larger-scale studies will be needed to further refine the model's content.

Changes in the text: we have included additional relevant analysis (see Page10, Line158-159).

Comment 3: What is the new information by this study - the idea is not original and plenty of literature exists on that topic - how does this work enrich our knowledge?

Reply 3: We greatly appreciate for your valuable question. This study ultimately identified six independent factors related to postoperative pancreatic fistula, among which tumor size and postoperative AST/ALT levels enrich the current research findings. Tumor size is often reflected in the differentiation of the T stage within the AJCC staging system for pancreatic cancer. Several individual studies have also investigated the correlation between tumor size, liver function, and long-term adverse prognosis following pancreatic tumor surgery. However, no research has been found that explicitly reports the association between these two indicators and postoperative pancreatic fistula after pancreaticoduodenectomy. Furthermore, we utilized SHAP values to rank the variables according to their importance, further enhancing our understanding of the relevant variables.

Additionally, in the ongoing debate regarding whether sarcopenia, as defined by skeletal muscle index, is a protective factor or a risk factor for postoperative pancreatic fistula, this study provides valuable evidence. Lastly, it also confirms that traditional multivariable statistical methods are not inferior to machine learning algorithms in terms of predictive modeling.

Comment 4: The tile mentions only clinical and CT parameter, however you included some laboratory values such as AST, ALT, TG in the analysis - please correct the title - it's misleading now.

Reply 4: Considering your suggestion, we have modified the title of the study. Thank you for your input.

Changes in the text: we have modified our title.

Comment 5: why did you use ONLY SMI? There are a lot of other accurately measurable objective values, which are proven better in the prediction of POPF and also better in the assessment of sarcopenia - e.g. psoas muscle area, tissue density index of pancreas, compared to spleen or liver, thickness of visceral pararenal fat and of abdominal wall fat - all these parameters are easy to measure in CT /MRI and can together allow better and preciser evaluation of visceral obesity and sarcopenia. I would highly recommend to measure those values and include them in the analysis!

Reply 5: Thank you very much for your valuable feedback on our research work. We recognize the importance of your suggestions in enhancing the quality of our study and delving deeper into the research problem. We intend to incorporate your recommendations and follow the research methods you have proposed in our future studies.

At the same time, we would like to kindly clarify the present importance of the first author's publication in order to meet graduation requirements. We apologize for not being able to fulfill this task temporarily, given that we are currently in the graduation season and lack the resources to complete the work.

Comment 6: Too many references (43), too many tables and figures (18) for such a paper - need

to be cut to the essential minimum.

Reply 6:   Thank you for the reminder. We have removed unnecessary references, and currently there are 38 references in the main text. Additionally, we have removed the previous image 5, which contained ROC curves and calibration plots.

Changes in the text: we have removed the original Image 5 and five references from the list.

Comment 1: In methods (page 7 line 91) the inclusion of patients has not been possible until December 2023.

Reply 1: Thank you for bringing this detail to our attention. We apologize for the oversight in organizing the timeline of the study. Data collection for the first 269 patients in this study took place from January 2012 to January 2021. For the remaining 77 patients, data collection occurred from January 2021 to January 2023. We have made a note of this in the article using the "Track Changes" function.

Changes in the text: we have modified our text as advised (see Page3, Line32; Page7, Line89/94; Page21, Line385/387).

Comment 2: Although there are no differences between the group of clinically relevant fistulas and the group of fistulas as a whole, it seems to me a limitation to have included all the patients given that the objective is to identify the clinically relevant ones.

Reply 2: Thank you very much for your input. According to the 2016 ISGPS classification of pancreatic fistula, most studies currently focus on clinically relevant pancreatic fistula (CR-POPF). However, as discussed in this study, there is no significant difference in the independent factors between grade A and grade BC pancreatic fistula. Furthermore, compared to patients without postoperative pancreatic fistula, grade A fistula is associated with more severe postoperative complications. By including grade A pancreatic fistula in this study, it serves as a reminder and alert for clinicians to pay timely attention to patients and provide clinical interventions. On the other hand, a small portion of grade B pancreatic fistula is included due to prolonged drainage for more than 21 days. These patients often have no significant differences compared to grade A fistula and their drainage tubes are usually removed during outpatient follow-up visits. Additionally, the influence of surgical approach, an important factor, was not included in the study due to incomplete or missing data ,   such as pancreaticojejunostomy technique, choice of gastrointestinal reconstruction, anastomotic closure method, and so on. Therefore, we chose to include grade A pancreatic fistula based on the reasons mentioned above.

Comment 3: In the discussion, although it is true that one study suggests the use of IV somatostatin in continuous infusion as a treatment for fistula, many others do not show it, so the limitation of postoperative measures should be emphasized.

Reply 3: As mentioned in your comments, it is necessary to emphasize the limitations of postoperative measures in this study. We have added some content in the discussion section to summarize the limitations of current postoperative preventive measures. The added portions

have been marked using the track changes feature.

Changes in the text: we have modified our text as advised (see Page13, Line 209-211).

Comment 4: In Table 1 I suggest making headings in pancreatic, bile and duodenal abnormalities to facilitate understanding.

Reply 4: According to your request，we have reorganized Table 1 to emphasize the key points and improve visual comprehension. Thank you once again.

Changes in the text: we have modified our text as advised (see Table 1).