

Dear Editors and Reviewers:

Thank you for your letter and for there viewer's comments concerning our manuscript entitled "Retrospective analysis of  $\Delta$ Hb and bleeding-related risk factors in pancreaticoduodenectomy" (No: 100999). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studies comments carefully and have made correction which we hope meet with approval. The responds to the reviewer's and editor's comments are as following:

**Responds to the reviewer's comments:**

**Reviewer 1**

**1. Comment:** The retrospective study in question failed to take into account the impacts of the tumor itself on the surgery. Such factors include the size and location of the tumor, the degree of inflammation in the surrounding tissues, its relationship with blood vessels, the measures for dealing with preoperative jaundice, as well as the technological improvements over the past five years. For instance, the size of the tumor can significantly affect the surgical approach and difficulty. A larger tumor might require more extensive dissection and pose a greater challenge to the surgeon in terms of complete removal while minimizing damage to adjacent structures. The location of the tumor, whether it is close to vital organs or major blood vessels, also determines the complexity and risks involved in the operation. Additionally, the degree of inflammation in the surrounding tissues can make the surgical field less clear and increase the likelihood of postoperative complications. And the advancements in surgical techniques over the past five years could potentially have improved the outcomes of such surgeries, yet this study did not consider these aspects.

**Respond:** The aim of our retrospective study was to estimate intraoperative and perioperative blood loss by comparing hemoglobin concentration differences between preoperative and postoperative values in pancreaticoduodenectomy patients. We aimed to compare hemorrhage volumes across three groups: open surgery, laparoscopic surgery, and a conversion to open approach, while also identifying risk factors associated with bleeding. Pancreaticoduodenectomy is a highly complex surgical procedure, with tumor-related factors influencing the operation. The size and location of the tumor, its relationship to surrounding blood vessels, and the degree of inflammation in nearby tissues all affect the difficulty of the surgery.

Our comparison of blood loss among the three groups revealed that the intermediate open approach resulted in significantly higher blood loss compared to the other two groups. We discussed potential reasons for this in our analysis, which may include the close proximity of the tumor to major blood vessels, greater tissue inflammation, and additional challenges associated with laparoscopic surgery, such as difficulties in field exposure and the impact of bleeding on visibility. These factors might explain why the intermediate open group experienced more significant hemorrhage.

We further analyzed the risk factors for bleeding through both univariate and multivariate analyses. Our findings identified that a preoperative bilirubin level  $>200 \mu\text{mol/L}$  is an independent risk factor for increased bleeding. Elevated bilirubin levels were associated with a higher likelihood of bleeding, suggesting that preoperative biliary drainage to reduce jaundice may help lower postoperative bleeding and related complications.

While surgical techniques at our institution have been steadily improving over the past five years, leading to a decrease in both complication rates and mortality following pancreaticoduodenectomy, our comparison of blood loss across the three groups revealed no significant differences in bleeding between the open and laparoscopic approaches. Although we did not analyze blood loss over time, but rather focused on overall blood loss, it is

possible that advancements in surgical technique have had minimal impact on the outcomes of our comparison.

**2. Comment:** There are numerous interfering and influential factors in the perioperative fluid and nutrition management that cannot be standardized. Especially when there is significant intraoperative bleeding, a long surgical duration, and large fluctuations in the patient's vital signs, it is uncertain whether the postoperative treatment has affected the research results. During the operation, excessive bleeding may lead to fluid and electrolyte imbalances, which in turn can impact the patient's recovery. A prolonged surgical time means the patient is under anesthesia for a longer period, potentially causing more stress on the body's physiological functions. And the instability of vital signs such as blood pressure and heart rate requires careful monitoring and adjustment of fluid and nutrition management. However, with so many variables, it becomes extremely difficult to accurately assess the specific impact of postoperative treatment on the overall research findings.

**Respond:** Currently, there is no completely accurate method for estimating intraoperative blood loss in clinical practice. We use the difference in preoperative and postoperative hemoglobin concentrations to assess blood loss, which provides higher accuracy than visual estimation methods. However, this approach still carries certain errors. Factors such as perioperative fluid and nutritional management can affect hemoglobin levels, and the body's response to blood loss exhibits variability and complexity, which cannot be entirely accounted for. Nevertheless, in most cases, the patient's blood volume returns to normal within 72 hours after surgery, and hemoglobin concentrations stabilize, making the calculated results relatively reliable. Despite the potential influence of various uncertainties, we believe that this method offers distinct advantages in the clinical estimation of blood loss.

**3. Comment:** Since 2016, the definition of pancreatic fistula by the International Study Group of Pancreatic Surgery (ISGPS) has been changed to biochemical fistula and Grade B/C pancreatic fistula. Nevertheless, this article still refers to Grades A/B/C. The updated classification system by ISGPS aims to provide a more accurate and standardized way to diagnose and categorize pancreatic fistulas. The distinction between biochemical fistula and the different grades of clinical fistulas helps clinicians better understand the severity and prognosis of patients with pancreatic fistulas. By still using the old grading system, this article may not be in line with the current international standards and could potentially lead to confusion in the interpretation and comparison of data related to pancreatic fistulas.

**Respond:** Our study primarily focused on postoperative bleeding following pancreaticoduodenectomy and did not examine the incidence or management of pancreatic fistula. Consequently, the grading criteria for pancreatic fistula were not relevant to our analysis. Regarding the grading of postoperative pancreatic hemorrhage (PPH), the most widely accepted and current classification remains that developed by the International Study Group for Pancreatic Surgery (ISGPS) in 2007. This grading system categorizes PPH into three severity levels: Grade A, Grade B and Grade C. This grading system has been widely utilized to assess the severity of postoperative pancreatic hemorrhage and to guide management strategies following pancreatic surgery.

**4. Comment:** This article is a single-center retrospective study, lacking multi-center data. A single-center study has its limitations as it only reflects the experience and outcomes within one specific medical institution. The patient population, surgical techniques, and postoperative management practices in different centers may vary significantly. Multi-center studies, on the other hand, can incorporate a more diverse range of cases, different surgical expertise, and various approaches to patient care. This broader

perspective allows for a more comprehensive understanding of the phenomenon under study and can enhance the generalizability of the research results. Without multi-center data, the conclusions drawn from this single-center study may not be applicable to a wider range of settings and patient populations, thereby reducing the overall value and reliability of the research.

**Respond:** We acknowledge that our study is a single-center, retrospective analysis, and we appreciate your concerns regarding the limitations of generalizability and the potential impact of variations in patient populations, surgical techniques, and postoperative management practices across different institutions. We agree that multi-center studies provide a broader perspective by including a more diverse range of cases, varied surgical expertise, and different approaches to patient care, which can help enhance the robustness and applicability of the findings. The ability to compare data across multiple centers often leads to more generalized conclusions and can strengthen the reliability of the research outcomes. We have indeed acknowledged the limitations of a single-center study in the manuscript.

Future Research Directions: We acknowledge the importance of multi-center research and recognize that future studies could be expanded to include data from multiple institutions. This would help to confirm the findings of our study and enhance their generalizability.

**Responds to Science Editor's comments:**

**1. Country/Territory of origin:** Please verify if the "Country/Territory of origin: China" submitted by the system is correct?

**Respond:** The "Country/Territory of origin: China" submitted by the system is correct.

2. The language classification is Grade B. Please provide the latest language certificate after Return the Manuscript to Author for Revision. Please visit the following website for the professional English language editing companies that we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

**Respond:** We have refined the manuscript linguistically and provided an updated language certificate.

3. **Manuscript Title:** The title should not include any Arabic numbers or abbreviations.

**Respond:** We revised the title of the article to ensure it no longer contained any abbreviations.

4. **Author contributions:** The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names. For example, Bryan L Copple should be revised as Copple BL.

A full multi-author example is: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research study; Wang CL, Zou CC, Hong F and Wu XM performed the research.

**Respond:** We have updated the author names in the author contributions section based on the example you provided.

5. **The "Key Words" does not meet the requirements:**

The 'Key words' list will provide 5-10 keywords that reflect the main content of the study.

**Respond:** We have modified the keywords to comply with the requirements.

**6. Core Tip:** Abbreviations must be defined upon first appearance in the Core Tip. Do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition.

**Respond:** We have changed the first occurrence of the abbreviations in the Core Tip to its full form.

**7. Audio Core Tip:** In order to attract readers to read the full-text article, we request that the first author make an audio file describing the final core tip. This audio file will be published online, along with the article. The author can invite English language editing company to assist in resolving the language issues of Audio Core Tip.

**Respond:** We have made an audio file describing the final core tip.

#### **8. Reference numbers in the main text.**

The format of in-text citation of references should be [References Number].

**Example:** The pathophysiology is thought to be due to an increased arterial flow that leads to secondary hepatocellular hyperplasia[1,2].

The name of the author(s) of a reference is listed in the sentence, the reference number should be placed immediately after the author(s) of the reference.

**Example:** Mandal *et al*[8] proposed that retractor aponeurosis disinsertion is the most likely cause of congenital low lid entropion.

Please verify the order and total number of references cited to ensure that all references in the list are cited and in a correct numeric order.

**Respond:** We have updated the reference numbers in the main text according to the example you provided.

**9. There are issues with the references:** Please provide the PMID numbers (<https://pubmed.ncbi.nlm.nih.gov/>) and DOI citation numbers

(<https://doi.crossref.org/simpleTextQuery>) to the reference list and list all authors of the references. If a reference has no PMID and DOI, please provide the source website address of this reference.

To ensure the accuracy of the references, please use "**Edit References by Auto-Analyser**"

(<https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx>) to edit the references of the manuscript.

**Respond:** We have made the requested revisions to the reference list.

**10. Tables:** Tables must be presented in the order that they appear in the main text of the manuscript (numbered as 1, 2, 3, *etc.*). A brief, one-line title must be provided for each table (**The title needs to be bolded**).

Abbreviations are not allowed in table titles.

**Respond:** We have bolded the table headings, corrected any abbreviations, and ensured that the tables are arranged in the order they appear in the manuscript.

**11.** Please upload the approved grant application form(s) or funding agency copy(ies) of any approval document(s).

**Respond:** We will upload a copy of the approved grant application form or any approved documents from the funding agency.

**Responds to Company Editor-in-Chief's comments:**

**第一，返修手稿。**请作者邀请编辑部认可的英文语言润色专业公司 (<https://www.wjgnet.com/bpg/gerinfo/240>), 或其它英文语言润色专业公司协助作者按照 *Checklist for Authors to Revise a Manuscript* 要求修改手稿中的每一项内容。另外，作者指南，见: <https://www.wjgnet.com/bpg/gerinfo/204>。



作者邀请专业英文语言润色公司的目的是对手稿的题目、短标题、作者贡献分布、核心内容提要、关键词、摘要（摘要中不能够出现引用文献信息）、正文、表格表注、图注、公式、特殊字符、参考文献序号引用顺序等进行核实和规范格式，以及语言润色等。非英文母语作者返修手稿时，务必邀请英文语言润色专业公司来解决手稿的英文语言表达问题。如果手稿出版后被发现英文语言表达出现严重问题，文章将会按照撤稿处理，这将会对作者的学术声誉造成严重危害。撤稿声明（Retraction Note）举例见：<https://www.wjgnet.com/2307-8960/full/v12/i19/4029.htm>。为了确保手稿的英文语言表达质量，作者必须要请英文语言润色公司出具返修手稿后的英文语言润色证明。

**Respond:** We have sent the manuscript to a language editing company for re-editing and obtained an English language editing certificate. Additionally, we have revised the article's format and addressed other issues according to the author guidelines.

**第二，同行评议。**邀请论文润色公司，依据同行评议报告和科学编辑评论，协助作者对手稿的研究方法、数据分析和论点逻辑等进行进一步地审核，确保手稿学术上的正确性。

**Respond:** We also had the manuscript's research methodology, data analysis, and argumentation further reviewed by a language editing company, based on peer review reports and scientific editorial comments, to ensure the manuscript's academic integrity.

**第三，作者姓名汉语拼音拼写规则。**先名后姓；首字母大写；双名之间用半字线“-”分开；多作者时姓名间加逗号。示例：“王金磊”的姓名汉语拼音拼写规则示例为“Jin-Lei Wang”。

**Respond:** The author names in our articles are written in the format outlined above.

**第四，图片和线条图。**请论文润色公司协助作者解决图片和线条图规范化的问题，并且提供在 PowerPoint 上可编辑的分解图。图片和线条图一般由图、图号、图题和图注构成。图片全文依序编号。只有一个图片时仍应编号。示例：“Figure 1”、“Figure 2”。与此同时，同一个主题内容的彩色图、黑白图、和线条图，应统一使用一个主题，并且每个子图的注解分别叙述。示例：**Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ....**

**Respond:** We did not include pictures or line drawings in our article.

**第五，三线表。**请论文润色公司协助作者解决三线表格规范化的问题。三线表格一般由表号、表题、表头、表身和表注构成。三线表由顶线、横表头线和底线组成。表格全文依序编号。只有一个表格时仍应编号。示例：“Table 1”、“Table 2”。

**Respond:** We have addressed the formatting issue with the three-line table.

**第六，参考文献。**首先，顺序编码。请按照参考文献在正文中出现的先后顺序编码用阿拉伯数字加方括号[ ]标出。示例：手术方法按照参考文献[8]。每篇参考文献应包含 PMID 和 DOI 号码。参考文献测试系统，见：<https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx>。其次，作者引用文献的相关性。作者必须尊重前人的相关重要研究成果。如果发现作者引用的文献与手稿主题内容没有明确的相关性或没有引用前人相关的重要研究成果，手稿将会按照退稿处理。请作者务必重新核实每条参考文献引用与手稿主题内容是否密切相关，是否遗漏重要文献。其三，作者引用本人工作。请作者核实引用作者本人文献的必要性。如果发现作者没有必要地大量引用自己发表的文章，手稿将会被按照退稿处理。其四，同行评议人推荐作者引用文章。如果作者认为确有必要引用同行评议人推荐的文章，并且推荐的文章是他人的关键性

工作就可以引用或请拒绝引用。

**Respond:** We have adjusted the reference formatting in the article to align with the reference guidelines.

**第七，学术查重。**邀请论文润色公司协助作者对手稿进行学术查重。手稿一旦被编辑部判定为存在抄袭，将会被退稿。

**Respond:** We have invited a language editing company to perform an academic check of the manuscript.

**第八，语言润色。**邀请论文润色公司协助作者解决手稿中的拼写错误、语法错误、时态错误、单复数错误、标点错误和科学用词错误等等。

**Respond:** We have sent the manuscript to a language editing company for re-editing and obtained an English language editing certificate.

**第九，基金资助项目批准文件。**如果手稿有基金项目支持，作者必须上传 PDF 格式的基金资助项目批准文件。

**Respond:** We will upload the funding project approval document in PDF format.

**第十，Audio。**邀请论文润色公司协助作者解决 Core Tip 的 **Audio** 录音质量问题。

**Respond:** We have engaged a language editing company to create a recording of the Core Tip section.

**第十一，致谢。**不允许将语言编辑公司名称和基金资助项目名称列在致谢中。

**Respond:** We do not include the names of language editing companies or grant programs in our acknowledgements.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

**Revision reviewer 1**

**Comment:** Specific Comments to Authors: In this study, the researchers collected the clinical data of 1,722 patients who underwent PD in Shandong Provincial Hospital from 2017 to 2022. The sample size is huge and the data quality is high. They used the difference in hemoglobin concentration ( $\Delta\text{Hb}$ ) before and after surgery to assess the amount of perioperative bleeding in patients, compared with the estimated blood loss obtained by the visual method, and analyzed the correlation between the two. At the same time, univariate and multivariate regression analysis was performed on the patients'  $\Delta\text{Hb}$  to predict risk factors related to bleeding. They provide new insights into comparing the clinical efficacy of different surgical procedures and reducing the risk of surgical bleeding. I personally believe that this study has certain clinical application value, which can guide pancreatic surgeons to fully assess surgical risks, plan reasonable surgical plans, reduce the complications caused by surgery to patients, and facilitate the development of clinical work.

**Reply:** Thanks for your comments.