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Dear Sir or Madam

Please find enclosed the revised manuscript entitled **Predictive value of preoperative albumin-bilirubin score and other risk factors for short-term outcomes after open pancreatoduodenectomy** by Zavrtanik et al.

We would like to thank the reviewers for the comments and suggestions on the manuscript. We have addressed all the comments, as discussed in more detail below.

We believe this manuscript is now suitable for publication in World Journal of Clinical Cases.

Sincerely,

Prof. Aleš Tomažič, MD, PhD
Corresponding author

Response to reviewers:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This version is better than before, but I still have two minor comments. 1. Authors omitted some important factors associated with postoperative complications, such as TNM stage, harvest LN nodes, operating time, ICU stay.

Comment: Thank you for your comment. In previous studies, TNM stage and lymph node status were associated with postoperative outcomes, namely long-term survival. However, tumour size nor lymph node retrieval did not seem to influence postoperative morbidity or short-term mortality (Nimura et al., Kamarajah et al.). Furthermore, we believe that operating time and the length of ICU stay are indicators of possible difficulties that were encountered during the procedure or occurrence of postoperative complications, respectively, rather than their predictors. The aim of a current study was to evaluate ALBI score as a prognostic tool utilizing preoperative factors to stratify the patient outcome while not relying on factors known only after surgery, such as TNM stage, harvest lymph nodes, operating time and ICU stay. Therefore, these factors were not included in the prediction models.

References:

Nimura Y et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012; 19: 230–41.

Kamarajah SK et al. Systematic review and meta-analysis of factors associated with post-operative pancreatic fistula following pancreatoduodenectomy. ANZ J Surg. 2021; 91(5); 810–21.

2. Please clarify the reason that author only chose open surgery. Did authors perform Laparoscopic PD or robotic PD? At least, authors must discuss this issue in the text, or change the title to "Albumin-bilirubin score failed to predict short-term postoperative outcomes in patients undergoing open pancreatoduodenectomy".

Comment: Thank you for your remark. At both centres, laparoscopic PDs are not performed, and the robotic programme was started quite recently in one centre. Therefore, during the analysed five-year period between 2017 and 2021 all patients were operated on in an open manner. We adjusted the title accordingly.

Reviewer #2:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: This article evaluates the clinical significance of preoperative albumin-bilirubin score and other risk factors in relation to short-term postoperative outcomes in patients after pancreatoduodenectomy. A few questions need to be answered: 1. The article emphasizes the role of ALBI in the theme, citation, and discussion sections. However, the article itself adopts all benign and malignant pancreatic tumors, ignoring the differences brought by different tumor types. At the same time, other literature cited in the discussion also describes the impact of ALBI in malignant tumors on postoperative outcomes. So, the conclusion of the article is disturbing due to these factors. At the same time, other literature cited in the discussion also describes the impact of ALBI in malignant tumors on postoperative outcomes.

Comment: Thank you for pointing that out. In our study, the majority of patients (83%) underwent surgical resection for a malignant lesion (added in the text, lines 238-239). These included pancreatic ductal adenocarcinoma, bile duct, duodenal, ampullary carcinoma and neuroendocrine tumour. Due to a minority of resections that were performed for benign indications the feasibility of a subgroup analysis is limited. Furthermore, we believe the underlying pathology cannot be divided simply to benign and malignant tumours. Indeed, the type of pathology was associated with the development of POPF and postoperative complications in previous studies (Callery et al., Harrel et al., Roh et al., Kamarajah et al., Zhang et al.). On the other hand, some studies did not show the difference between these two tumour types (Ke et al., Gouma et al.). Nevertheless, among different malignant tumours, short-term postoperative outcomes vary. For example, it is well known that in case of

pancreatic cancer the development of POPF is less likely, while duodenal, ampullary carcinoma and NET proved to be associated with higher POPF rate (Callery et al., Zhang et al.). Therefore, not all malignant tumours should be discussed as a one entity. In the discussion section, we cite two studies that evaluated the impact of ALBI on postoperative outcomes following liver surgery for malignant as well as benign diseases (Andreatos et al., Fagenson et al.). However, no studies were found regarding short-term postoperative outcomes after surgical treatment of other benign tumours. In our study, the examined short-term postoperative outcomes were analysed in regard to different tumour types. Similarly to other studies, pancreatic carcinoma was associated with lower odds for developing postoperative complications, major postoperative complications, clinically relevant POPF, reoperation and a 36% decrease in length of hospital stay. Duodenal carcinoma was associated with higher odds for developing major postoperative complications, clinically relevant POPF, reoperation and showed a 99% increase in the length of hospital stay. Resection due to bile duct carcinoma was associated with higher odds of clinically relevant POPF, while ampullary carcinoma and IPMN showed a 33% and 41% decrease in length of hospital stay, respectively (Table 2, Table 3, Table 4, Table 5, Table 7).

References:

Callery MP et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg.* 2013; 216: 1–14.

Harrel KN et al. Influence of margin histology on development of pancreatic fistula following pancreatoduodenectomy. *J Surg Res.* 2020; 246: 315–24.

Roh YH et al. Preoperative CT anthropometric measurements and pancreatic pathology increase risk for postoperative pancreatic fistula in patients following pancreaticoduodenectomy. *PLoS One.* 2020; 15 (12): e0243515

Kamarajah SK et al. Systematic review and meta-analysis of factors associated with post-operative pancreatic fistula following pancreatoduodenectomy. *ANZ J Surg.* 2021; 91(5); 810–21.

Zhang B et al. Risk factors of clinically relevant postoperative pancreatic fistula after pancreatoduodenectomy: A systematic review and meta-analysis. *Medicine (Baltimore).* 2022; 101 (26): e29757

Ke ZX et al. Risk factors and management of postoperative pancreatic fistula following pancreaticoduodenectomy: Single-center experience. Curr Med Sci. 2019; 39(6): 1009–18.

Gouma DJ et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg. 2000; 232(6): 786–95.

Andreatos N et al. Albumin-bilirubin score: Predicting short-term outcomes including bile leak and post-hepatectomy liver failure following hepatic resection. J Gastrointest Surg. 2017; 21: 238–48.

Fagenson AM et al. Albumin-Bilirubin Score vs Model for End-Stage Liver Disease in Predicting Post-Hepatectomy Outcomes. J Am Coll Surg. 2020; 230: 637–45.

2. The title of the article is inconsistent with the content of the article.

Comment: The aim of our study was to assess the ability of ALBI score and some other risk factors to predict short-term postoperative outcomes in patients who underwent open PD. The title of the article was adjusted accordingly.

3. The article did not address the factor of tumor size. However, the size of the tumor may have an impact on preoperative symptoms, surgical scope, the difficulty of surgical operation and so on.

Comment: Thank you for your comment. The tumour size does have an impact on preoperative symptoms and surgical scope. Regardless, it does not necessarily influence the occurrence of postoperative complications and POPF after PD (Kamarajah et al.). After literature review, several other factors were identified to influence the short-term postoperative outcomes after PD, and these were included in the analysis to meet the aim of our study.

References:

Kamarajah SK et al. Systematic review and meta-analysis of factors associated with post-operative pancreatic fistula following pancreatoduodenectomy. ANZ J Surg. 2021; 91(5): 810–21.