

Peer Review File

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Reviewer A

Authors presented the early operation following preoperative ERCP increases the risk of organ/space surgical site infections (OSSI) in a single center but large-scale study. I think the results were interesting and showed new knowledge concerning perioperative management of PD. I have some comments for the authors.

1. There was dissociation between the frequency of OSSI and that of grade B/C POPF in the results (Table 1). I think the grade B/C POPF have to be included in OSSI, because the grade B/C POPF are defined as high amylase output with infection. Did the authors excluded the patients with grade B/C POPF without intra-abdominal fluid drainage or that with no micro-organisms detected from drainage fluid from the patients with OSSI?

Response: Thanks for the reviewer's comments. In this study, the OSSI were defined according to the National Healthcare Safety Network (NHSN). Therefore, we took care of grade B/C POPF. The ISGPS definition of grade B/C POPF does not necessarily require POPF with infection to define a grade B/C POPF. The most frequent diagnostic criteria for a grade B in our cohort are long-term drainage (>3 weeks) and need for interventional percutaneous drainage. And I think we have excluded the B+C POPF without micro-organisms from the patients with OSSI, since the rate of B+C POPF was lower than the rate of OSSI.

2. Furthermore, I want to know the policy of performing preoperative ERCP in the authors' institute, because the frequency of the presence of preoperative ERCP was lower in this study.

Response: For the above comment, the reduction of jaundice and pathological diagnosis was not performed routinely before pancreaticoduodenectomy in the First Affiliated Hospital of Nanjing Medical University from 1st September 2012 to 31st January 2018. The policy for preoperative biliary drainage in our pancreas center was not based on the total bilirubin level, criteria include: 1. Preoperative cholangitis 2. Need for

neoadjuvant treatment 3. Need for nutritional support and delay of surgery. The other exceptions were patients referred from other medical group or other hospital (already had preop biliary before referral). Therefore, the frequency of the presence of preoperative ERCP was lower.

3. In addition, there is the lack of the data of preoperative diagnoses in this paper.

Response: Thanks for the comments. Since the pathological diagnosis by ERCP or FNA was not performed routinely before pancreaticoduodenectomy in the First Affiliated Hospital of Nanjing Medical University from 1st September 2012 to 31st January 2018, the preoperative diagnoses were usually based on imaging and tumor markers. In most cases, it was usually diagnosed as pancreatic neoplasm. Therefore, we didn't present the data of preoperative diagnoses in this paper.

The other minor comments are listed below.

1. The data of the number of ERCP or the frequency of the presence of neo-adjuvant chemotherapy were recommended to describe.

Response: In the pancreas center of the First Affiliated Hospital with Nanjing Medical University, patients with pancreatic cancer do not routinely receive neoadjuvant chemotherapy. Therefore, we didn't present the data of neo-adjuvant chemotherapy in this paper.

2. Were the presented blood biochemistry data acquired just before surgery?

Response: Thanks for the comments. Yes. All of the presented blood biochemistry data acquired before surgery. If more than one results were available before surgery, we used the last one.

3. The detail breakdown of OSSI is recommended to describe.

Response: Thanks for the suggestion. But in this study, our primary concern was the overall incidence of OSSI not these incidence of each detail breakdown of OSSI. On the other hand, these data were hard to get.

4. In the analysis of propensity score matching, the methods were unclear. How was

each cut-off values? How to decide the cut-offs of each value?

Response: Thanks for the suggestion and I'm sorry for the lack of the detail description of propensity score matching. We have added it in the '*Statistical Analysis*' section. We presented it as "For the subgroup analyses, we performed 1:4 propensity score matching (PSM) using the nearest neighbor matching on 95 EEBPD case and 1270 No-EEBPD patients to optimize balance of baseline characteristics for assessing the independent effect of EEBPD. The primary matching criteria included Hypertation, TP, Cr, ALB, LDL, HDL, CK, ALP, Glu, whose distribution was statistically different between the EEBPD and No-EEBPD groups. Propensity scores were calculated using the logistic regression model. After 1:4 propensity score matching, the analysis included 95 EEBPD case and 380 No-EEBPD patients and the variables were not significantly different between these two groups. The imputation of missing values was made using the 'mice' package¹⁹, and the nomogram was developed and validated using the 'rms' package. The PSM was performed by 'MatchIt' package. "

5. At the page 8, line 175, LOS is mistake of LOH.

Response: Thanks for the reviewer's reminder and we have changed LOS to LOH.

6. At the line 235, abbreviation IAA and ISS were not explained.

Response: I'm sorry that ISS is mistake of SSI and we have corrected it. We also have added the abbreviation IAA in "*List of abbreviations*" section. Besides, for the first time in the manuscript using IAA, we have presented its full name.

Reviewer B

Congratulations for this profound analysis of the association between ERCP and OSSI. This is a relevant topic for the field and may have an impact of improvement of postoperative course after PD and timing of surgery. Although there are some points that should be addressed:

Major points:

- the rate of patients in the study receiving ERCP is low in comparison to the total number of included patients. The authors should include indications for ERCP in the

analysis.

Response: For the above comment, the treat or diagnosis by ERCP before PD was not performed routinely in the First Affiliated Hospital of Nanjing Medical University from 1st September 2012 to 31st January 2018. The policy for preoperative biliary drainage in our pancreas center was not based on the total bilirubin level, criteria include: 1. Preoperative cholangitis 2. Need for neoadjuvant treatment 3. Need for nutritional support and delay of surgery. The other exceptions were patients referred from other medical group or other hospital (already had preop biliary before referral). Therefore, the frequency of the presence of preoperative ERCP was lower.

- importantly concerning ERCP, the authors should state the number of patients receiving preoperative biliary drainage during ERCP, as this is a pivotal factor for the development of infectious complications after PD.

Response: Thank you for the suggestion and we have state the reasons of patients receiving preoperative ERCP. In all of these 95 patients who received preoperative ERCP, 61 (64.2%) patients were taken for preoperative diagnosis, 22 (23.2%) patients were taken for biliary drainage, 5 (5.3%) patients were taken for stent placement and 7 (7.4%) patients were taken for other causes. All these was presented in the first paragraph (179 lines) of the results section.

- the authors state that deep and superficial SSI are not analyzed in this study. Although there is a significant overlap in risk factors for these complications and thus this should also be included in the analysis, especially in respect of preoperative biliary drainage.

Response: Thank you for the suggestion and we are quite agree with this point. But in this study, we focused on the OSSI, not the deep and superficial SSI. The study of deep and superficial SSI will be continued in the following research.

- POPF was found to be increased after ERCP as is LOS in those patients. As POPF is a major and detrimental complication after PD, the authors should in their analysis and also in the propensity matching include risk factors of POPF in the analysis like BMI, texture of the pancreatic remnant and also the underlying disease.

Response: Thank you for the suggestion. In my opinion, POPF is a complication of PD, which is also an outcome after PD. And I'm sorry we didn't include these variables,

such as pancreatic duct diameter and pancreatic texture in this study.

- The authors found creatinine and alkaline phosphatase levels being an independent risk factor for the development of OSSI. They should pick this point up in the discussion and speculate on a possible mechanism (e.g. kidney injury?)

Response: Thank you for the suggestion and we have discussed this point in “*discussion*” section.

- further, the threshold for values like creatinine lie within the normal range of a healthy population and therefore the authors should discuss their relevance whether this represents a clinically important condition (e.g. kidney failure) or serve as a surrogate marker of increased risk.

Response: Median grouping was used in this study. The normal range of Cr is 44-133 $\mu\text{mol/L}$ for males and 70-106 $\mu\text{mol/L}$ for females in our hospital. Unfortunately, because of the problem of balancing the number of cases between the two groups, we did not consider the clinical condition.

- in the discussion part the authors cite a study by Teiichi Sugiura, revealing length of operation, duct diameter and BMI as risk factors for OSSI. These are also important risk factors of POPF. This represents the overlap between these complications and thus, these parameters should also be included in the analysis in this manuscript.

Response: The reviewer's suggestion is very important. But it was hardly for us to get the information of length of operation, duct diameter and BMI in this retrospective study. More variables such as length of operation, duct diameter and BMI will be collected in our prospective studies. In the discussion section, we also discussed this limitation.

- In the discussion part, the authors state the connection between ERCP and preoperative stenting with SSI. In this context two studies clearly pointed out the association between PBD and incidence of SSI and further that PBD is associated with a major shift in the bile microbiome underlying this effect. These studies should be included in the discussion part of the manuscript. (Surgery. 2017 Apr;161(4):939-950. doi: 10.1016/j.surg.2016.11.001; Br J Surg. 2017 Jan;104(2):e182-e188. doi: 10.1002/bjs.10450).

Response: Thanks to the reviewer's comments. We have included these two articles in the discussion.

- For the analysis of the optimal waiting time period after ERCP the authors state that after 14 days the risk of OSSI is reduced to 25%. Although there is also a period of reduced risk around day 5 (20%) and after that risk of OSSI is relatively stable around 25% besides a peak at day 8. The authors should clearly state why they would choose day 14 and clearly describe and explain underlying statistical methods for this choice.

Response: Thanks to the reviewer's comments. In this study, we observed a relatively stable start after day 8. But a cumulative rate increased more than 25% at day 11. And we considered that once OSSI occurs, it was troublesome for patients. Thus, we choose day 14 as an appropriate interval time.

Minor Points:

- although language of the manuscript is clear, there are several misspellings which have to be corrected.

Response: Thanks for the reviewer's suggestion. We have revised and corrected some mistakes in the article.

- Supplement Figures cited in the text are not accessible although they contain important information.

Response: We have provided the Supplement Figures when we submitted the paper.

- in the first sentence of the discussion part incidence of wound infections is discrepant to the value given in the introduction part of the manuscript.

Response: I'm sorry for this mistake and we have corrected it in discussion part.

- Table 3 is not conclusive and HR should be displayed more clearly in the table.

Response: Thank you for the reviewer's suggestion. We have displayed the HR(95%CI) in Table 3.