

## Peer Review File

Article information: <https://dx.doi.org/10.21037/gs-21-590>

### *Reviewer A*

**Comment 1:** I think the rate of PD/PPPD seems to be high in spite of enrolment of recent cases. In worldwide, unnecessary PD has been abolished because QOL significantly decreases.

**Reply 1:** Thank you for your comment. Many studies have shown that PPPD is indeed beneficial to the long-term quality of life for patients. Our team has high standards for choosing PPPD. In patients with benign diseases, PPPD should be selected as much as possible. In patients with malignant tumors especially located near pylorus, circumferential margin and lymph node dissection should be considered. PPPD is preferred considering the radical resection of tumors.

### *Reviewer B*

**Comment 1:** Please describe what cases should PBD be performed based on the results of the author's institution in addition to serum total bilirubin level in the literature. This is the most novel findings that I am most interested in about this manuscript. It would be an even better paper if it were known.

**Reply 1:** Thank you for your valuable suggestions. The conventional aim of PBD is to relieve symptoms of pruritus, cholangitis, and to also prevent post-operative complications attributable to the impaired immune response, coagulopathy and renal dysfunction that hyperbilirubinemia causes. There is much debate in the current literature on the role of PBD in patients with resectable tumors. The severity of jaundice that mandates PBD has yet to be defined. The same with many recent studies, our research indicated that PBD leads to an increased overall morbidity especially infections, and should therefore not be routinely performed in patients suffering from obstructive jaundice before surgery. In our center, PBD was performed in such situations: serum total bilirubin level was  $>258\mu\text{mol/L}$ , preoperative cholangitis occurred, poor nutritional status. Cholangitis had been proven to increase the incidence of surgical complications which need PBD and anti-infection treatment before surgery [1]. Nutrition status has been demonstrated clearly linked to major morbidity and mortality [2, 3]. Patients with obstructive jaundice received PBD combined with bile reinfusion and enteral nutrition support before surgery. However, due to the small number of jaundiced cases in this study, no further subgroup analysis is possible whether these patients can benefit from PBD which requires further accumulation of data.

**Comment 2:** Please describe the perioperative antibiotics in detail, if the author changes them according to the culture results obtained by PBD.

**Reply 2:** Thank you for your helpful comments. The choice of antibiotic differed among patients: routinely a third-generation cephalosporin (Ceftriaxone) or amikacin in case of allergy to cephalosporin in the non-PBD patients or PBD patients with

positive biliary drainage cultures susceptible to Ceftriaxone. In PBD patients with Ceftriaxone resistance biliary drainage cultures, the prophylactic antibiotics were selected based on the antimicrobial susceptibility. We have modified our text in page 5, line 92-96.

**Comment 3:** There are some typos in the paper, so please proofread it properly.

**Reply 3:** Thanks for the careful review. We are very sorry for our incorrect writing and the typos have been carefully revised (see page 5, line 103; see page 7, line 149 and 153).

*Reviewer C*

**Comment 1:** This study is dealing with a major topic in pancreatic surgery. Indeed, infectious complications are very frequent and participate to increase the morbidity, the length of stay and the costs. Your study is well designed however some definitions of the variable are lacking in the method. Results identified three different risk factors of infectious complications in a large cohort of patients. It could be interesting to discuss how infectious complications could be prevent and avoid.

**Reply 1:** Thanks for your nice suggestion. The definitions of the variables have been added in the method. Our results show that preoperative biliary drainage, pancreatic fistula and biliary fistula are risk factors for postoperative infection. Measures should be taken to reduce the occurrence of these three risk factors, PBD should be performed only in select patients. The pathogens of bile and drainage fluid should be monitored throughout the hospitalization. Early detection of POPF and BF with smooth drainage can reduce infection complications. This part was showed in page 14, line 292 to 296.

*Reviewer D*

**Comment 1:** Would change the running title to: Infectious complications after pancreaticoduodenectomy

**Reply 1:** Thank you for your valuable advice and we have changed the running title (see page 1, line 5).

**Comment 2:** Change urethra complications (in many parts of the text) for urinary tract infections

- page 3 line 76 change 'et al' for 'etc'. et al is for authors
- page 4 line 75 underwent instead of indergone
- page 4 line 80 change lack of med records to 'incomplete med records'
- page 4 line 94 semifluid diet, change to 'soft diet or 'thickened fluids' if more appropriate
- on the same lin; supplementary' instead of supplement
- page 5 line 103 ' non absorbable' for unabsorbed

**Reply 2:** Thank you for your careful review and helpful comments. We have addressed all the suggested changes and highlighted all the altered portion in red (see page 3, line 57 and 65; page 4, line 74 and 79; page 5, line 98 and 103).

**Comment 3:** What was your cut off for pancreatic duct size for placing a stent?

**Reply 3:** Thank you for your question. We usually use aseptic suction catheter as stent. If the 12F (3.96 mm) catheter was still thin, we will choose continuous suture of the pancreatic duct and the intestinal mucosa without placing stent.

**Comment 4:** On bacteremia definition would like to know if you usually obtain 2 blood cultures or only one to consider it significant and not contaminant

**Reply 4:** Thanks for the careful review. Bacteremia was diagnosed based on two blood cultures and this was revised in page 6 and line 127.

**Comment 5:** the correct company for spss 23 is Armonk, NY: IBM Corp

**Reply 5:** Thank you for your helpful guidance and this has been revised in page 6 and line 131.

**Comment 6:** In the results part change no-infection to non-infectious. this is repeated several times.

**Reply 6:** Thank you for your careful review and helpful comments. All the clerical errors have been modified (see page 7, line 149 and 153).

**Comment 7:** definition of clinically significantly pancreatic fistula

**Reply 7:** Thank you for your helpful proposal and this has been added in page 6 and line 117 to 120.

*Reviewer E*

**Comment 1:** Abstract:

-In the line number 44 you say that "efforts should be taken to reduce the POPF and PF". Maybe you wanted to say "efforts should be taken to reduce the POPF and BF".

**Reply 1:** Thank you for your careful review. The clerical errors have been modified (see page 3, line 46).

**Comment 2:** Introduction:

-In the line 55, you write that the mortality rates have dropped to less than 5%. It would be a good idea to clarify that these mortality rates happens in high volume centers.

**Reply 2:** Thank you for your careful review and helpful comments. It has been added in page 3 and line 53.

**Comment 3:** Methods:

-About the preoperative biliary drainage, in the line 87 you say that "Endoscopic nasobiliary drainage was applied in most patients, while few patients through percutaneous transhepatic cholangial drainage and endoscopic retrograde biliary drainage". How do you decide the kind of biliary drainage in every patient?

**Reply 3:** Thank you for your comments. For patients with obstructive jaundice, endoscopic nasobiliary drainage (ENBD), endoscopic retrograde biliary drainage (ERBD) and PTCD can be selected. However, ERBD are prone to induce cholangitis,

we choose this method for patients undergoing preoperative neoadjuvant chemotherapy. PTCD can increase the risk of tumor metastasis and affect the patient's long-term prognosis. In addition, ERCP is widely considered as less invasive, and is the preferred method of PBD, with PTCD reserved for cases of ERCP failure. We choose PTCD for patients who are unable to complete ERCP. Besides, the patients who received ENBD all underwent bile reinfusion combined with enteral nutrition before surgery.

**Comment 4:** Methods:

- In the line 91 you write about antibiotal prophylaxis. Is it possible to know what antibiotic do you usually use? Do you use always the same antibiotic?

**Reply 4:** Thank you for your valuable suggestions. The choice of antibiotic differed among the patients: routinely a third-generation cephalosporin (Ceftriaxone) or amikacin in case of allergy to cephalosporin in the non-PBD patients or PBD patients with positive biliary drainage cultures susceptible to Ceftriaxone. In PBD patients with Ceftriaxone resistance biliary drainage cultures, the prophylactic antibiotics were selected based on the antimicrobial susceptibility. This part was added in page 5 and line 92-96.

**Comment 5:** Methods:

- In the line 96 you say that all drain fluids were analyzed for bacteria on postoperative days 1,3,5,7. But, how and when did you get the bile culture? It was an intraoperative culture?

**Reply 5:** Thank you for your comments. In patients with PBD, the sample bile was aspirated through conduits within 1 week before surgery for bacterial examination. In those without PBD, bile was collected during the operation for bacterial culture and smears. Postoperative drain fluids culture and smear are routinely performed on days 1,3,5,7. The smear results can be obtained on the same day and the culture results usually take two to three days.

**Comment 6:** Methods:

- Did you make a routinely abdominal-CT in the fifth day? Or did you make it only in case of complications suspicion?

**Reply 6:** Thank you for your comments. The patients routinely perform enhanced CT in the fifth day after surgery, in order to assess whether there are aneurysms related to the operation, as well as whether there are fluid accumulations in the abdominal cavity.

**Comment 7:** Methods:

- In the line 99 you write "POPD" and maybe you wanted to say "POPF".

**Reply 7:** Thank you for your careful review. The clerical error has been modified in page 5 and line 103.

**Comment 8:** Methods:

- In the line 102 you must write "Blumgart's" instead of "Blugart's"

**Reply 8:** Thank you for your careful review. The error has been modified in page 5 and line 107.

**Comment 9:** Methods:

- Do you think that it is possible to know information about other infectious complications such as sepsis and septic shock?

**Reply 9:** Thank you for your valuable suggestions. Sepsis and septic shock are syndromes with many causes. Various gram-negative and gram-positive organisms, viruses and fungi may be responsible for the condition. In this study, 5 patients with organ/space SSI developed sepsis and 2 of them with septic shock. Three patients with pneumonia developed sepsis and septic shock. Six of the 19 patients with bacteremia developed sepsis and 4 developed septic shock. None of the patients with incisional SSI and urethra infection developed sepsis and septic shock.

**Comment 10:** Methods:

- Is it possible to know the time between the date of preoperative biliary drainage and the surgery? It would be interesting in order to know the hypothetical delay of the surgery in these cases.

**Reply 10:** Thank you for your constructive comments. The optimal duration of preoperative biliary drainage remains unclear. FRAGERITA Study Group showed that when jaundice treatment cannot be avoided, delaying surgery up to 1 month after biliary stenting may reduce major morbidity, procedure-related complications, and length of hospital stay [4]. Another study found PBD duration <2 weeks is more appropriate in severely jaundiced patients with periampullary cancer [5]. One RCT study showed a longer time (>5 weeks) to surgery was significantly associated with slightly lower mortality rate after surgery [6]. In this study, our median preoperative biliary drainage time was 13 days. For patients with preoperative cholangitis, the PBD duration is no episodes of cholangitis for at least one week. For patients with severe obstructive jaundice, the PBD duration is until the bilirubin level drops below 170 µmol/L. For patients with poor nutritional status, the PBD duration is until the nutritional status was significantly improved.

**Comment 11:** Results

- Table 1. I would like to know in what moment did you know the preoperative total bilirubin level.

**Reply 11:** Thank you for your comments. The bilirubin shown in Table 1 were the results when patients were admitted. For patients undergoing PBD, preoperative bilirubin was measured one or two days before operation which was not shown in the tables.

**Comment 12:** Results

-Table 2. How many days did you make the follow-up of the patients after the surgery in order to check the mortality? 30 days? 90 days?

**Reply 12:** Thank you for your comments. Postoperative mortality and morbidity were defined occurring either within 90 days after operation or during the hospital stay, respectively. This was added in in page 6 and line 114.

**Comment 13: Results**

-Table 5. As I told you previously, it would be interesting to know the moment where you got the biliary cultures. It would be also interesting to know the fungal specimen, maybe most of them were *Candida* spp. It would be interesting to know too the differences between microbiological cultures in patients with preoperative biliary drainage and the other patients.

**Reply 13:** Thank you for your insightful comments. The sample bile was aspirated through conduits within 1 week before surgery for bacterial examination. In patients without PBD, bile was collected for bacterial culture and smears during the operation. All the patients with fungal infection were *Candida*, 18 of the ascites and 2 of the bacteremia were *Candida albicans* and 2 of the ascites were *Candida tropicalis*. The microbiological cultures in patients with PBD were added in table 5. The most common Gram- bacteria in both groups were *K. pneumoniae*. However, the most common Gram+ bacteria in PBD patients were *E. faecium*.

Species	bile positive patients(N=65)	ascites positive in none-PBD patients(N=129)	ascites positive in PBD patients(N=64)	bacteremia patients(N=19)
<b>Gram-</b>				
<b>bacteria</b>				
<i>K. pneumoniae</i>	24	34	23	4
<i>E. coli</i>	6	23	1	2
<i>E. cloacae</i>	6	12	7	1
<i>A. baumannii</i>	15	12	3	-
<i>P. aeruginosa</i>	2	11	2	-
<b>Gram+</b>				
<b>bacteria</b>				
<i>E. faecalis</i>	18	30	12	-
<i>S. epidermidis</i>	1	23	7	3
<i>S. haemolyticus</i>	2	23	4	4
<i>E. faecium</i>	4	11	15	-
<i>S. aureus</i>	2	7	4	3
<b>Fungus</b>	0	12	8	2
<b>Others</b>	10	11	4	2

**Comment 14: Discussion:**

-In the line 229, it is possible to know the kind of antibiotics recommended?

**Reply 14:** Thank you for your valuable comments. Some studies including RCT study showed that prophylactic antibiotics target only 30% of the bacteria in patients with PBD and therapeutic antibiotics based on the results of preoperative bile cultures such

as piperacillin and tazobactam can reduce surgical infections [7-9]. This was revised in page 11 and line 240 to 241.

**Comment 15:** Other suggestions:

-It is important to know the local microbiome of every institution in order to choose the antibiomatic prophylaxis.

**Reply 15:** Thank you for your good and useful advice. We will investigate and count the common microbiome in our hospital.

**Comment 16:** Other suggestions:

-According to the results of your study, do you consider any change in your clinical practice for the future?

**Reply 16:** Thanks for your helpful guidance. The results of this study are the first time that we explored the situation of infection and the risk factors of infection in our team, which is of certain value for us to prevent infection. We will be more cautious in choosing preoperative biliary drainage and take measures to minimize the BF and POPF. Further, more clinical research will be taken to explore the use of antibiotics in the perioperative period especially in PBD patients.

**Comment 17:** Other suggestions:

-What kind of antibiotic do you usually use? Do you think that it is necessary to change them? Do you think that it is necessary to use anti-enterococcus antibiotic?

**Reply 17:** Thank you for your comments. The most commonly used prophylactic antibiotic before surgery is Ceftriaxone and therapeutic antibiotic is Cefoperazone Sodium and Sulbactam Sodium. According to the results, the most common bacteria in bile and ascites were *K. pneumoniae*. The therapeutic antibiotic in our team is effective. However, the drug resistance results of bacteria were not yet recorded which is helpful to the selection of antibiotics and further study is needed. In patients with absence of culture results and suspected infection, we usually use Cefoperazone Sodium and Sulbactam Sodium to treat. When there is positive or suspected enterococcus infection, we will use Vancomycin to fight the infection.

## Reference

1. Akashi M, Nagakawa Y, Hosokawa Y, T, et al. Preoperative cholangitis is associated with increased surgical site infection following pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci.* 2020 Sep;27(9):640-647.
2. Weimann A, Braga M, Carli F, et al. ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr.* 2017 Jun;36(3):623-650.
3. Afaneh C, Gerszberg D, Slattery E, et al. Pancreatic cancer surgery and nutrition management: a review of the current literature. *Hepatobiliary Surg Nutr.* 2015 Feb;4(1):59-71.
4. Sandini M, Honselmann K C, Birnbaum D J, et al. Preoperative Biliary Stenting and Major Morbidity After Pancreatoduodenectomy: Does Elapsed Time Matter?: The FRAGERITA Study Group [J]. *Ann Surg*, 2018, 268(5): 808-14.

5. Son J H, Kim J, Lee S H, et al. The optimal duration of preoperative biliary drainage for periampullary tumors that cause severe obstructive jaundice [J]. *American Journal of Surgery*, 2013, 206(1): 40-6.
6. Eshuis W J, van der Gaag N A, Rauws E A, et al. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage [J]. *Ann Surg*, 2010, 252(5): 840-9.
7. Degrandi O, Buscail E, Martellotto S, et al. Perioperative antibiotherapy should replace prophylactic antibiotics in patients undergoing pancreaticoduodenectomy preceded by preoperative biliary drainage. *J Surg Oncol*. 2019 Sep;120(4):639-645.
8. Sudo T, Murakami Y, Uemura K, et al. Specific antibiotic prophylaxis based on bile cultures is required to prevent postoperative infectious complications in pancreatoduodenectomy patients who have undergone preoperative biliary drainage. *World J Surg*. 2007 Nov;31(11):2230-5.
9. Okamura K, Tanaka K, Miura T, et al. Randomized controlled trial of perioperative antimicrobial therapy based on the results of preoperative bile cultures in patients undergoing biliary reconstruction. *J Hepatobiliary Pancreat Sci*. 2017 Jul;24(7):382-393.