Original Article

Risk factors and microbial spectrum for infectious complications after pancreaticoduodenectomy

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Background: Although the mortality of pancreaticoduodenectomy (PD) has decreased, the morbidity especially infections is still a severe challenge. This study aimed to identify the risk factors and microbial spectrum for infectious complications after PD.

Methods: This retrospective study of 291 consecutive patients who underwent PD between February 2018 and March 2021 was conducted. The clinical data was reviewed and risk factors associated with infectious complications were analyzed. To investigate the microbial spectrum, microorganisms isolated from preoperative bile, drainage fluid and blood were counted.

Results: A total of 110 patients (37.8%) developed postoperative infections. The patients who suffered infections had higher severe complications, prolonged hospitalization and increased expenditures. Three independent risk factors were identified: preoperative biliary drainage (PBD) [odds ratio (OR) 2.082; 95% confidence interval (CI): 1.059–4.091; P=0.033], clinically relevant postoperative pancreatic fistula (CR-POPF) (OR 11.984; 95% CI: 6.556–21.471; P=0.000) and biliary fistula (BF) (OR 3.674; 95% CI: 1.218–11.084; P=0.021). *K. pneumoniae* and *E. faecalis* were the most frequently isolated bacteria in preoperative bile and drainage fluid after PD. *K. pneumoniae* and *S. haemolyticus* were the most common bacteria in bacteremia patients.

Conclusions: PBD, POPF and BF are independent risk factors for infectious complications after PD. To lower the incidence of infection, PBD should be performed only in select cases and efforts should be taken to reduce the POPF and BF. The pathogens of bile and drainage fluid should be monitored throughout the hospital stay.

Keywords: Pancreaticoduodenectomy (PD); infection; risk factors; microbial spectrum

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Introduction

Pancreaticoduodenectomy (PD) is the standard operation for periampullary diseases including malignant and benign. With advancements in surgical methods and perioperative management, the mortality rates have dropped to less than 5% in high-volume centers, while the morbidity remains still high, ranging from 30–60% (1-4). Infection is one of the most prevalent surgical consequences which can not only lead to fatal outcomes such as postoperative pancreatic fistula (POPF), intrabdominal blood, reoperation, etc. but also delay the initiation of adjuvant chemotherapy (5).

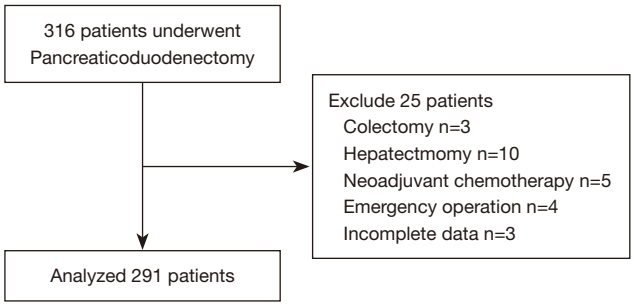

Figure 1 Flow chart of study enrollment.

Besides, infection can prolong hospitalization time and increase hospitalization expenditures (6,7). Thus, it is vital to identify the risk factors and microbial spectrum for infectious complications after PD.

Infectious complications mainly include surgical site infection (SSI), bacteremia, pneumonia and urethra infections. Numerous studies (3,5,8-12) have investigated the risk factors of surgical site infection (SSI) after PD, including age, body mass index (BMI), operation time, significant blood loss, blood transfusion and preoperative biliary drainage, etc. However, few studies focus on all the infectious complications.

The study aimed to investigate the risk factors and microbial spectrum associated with infectious complications after PD which may provide bases for clinical treatment.
We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/gs-21-590).

Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional ethics committee of Nanjing Drum Tower Hospital (No. 2021-271-01) and individual consent for this retrospective analysis was waived.

This retrospective study was conducted in 291 consecutive patients underwent PD in our hospital from February 2018 to March 2021. The clinical data was collected and reviewed. The inclusion criteria included: (I) patients who received PD (II) no history of chemotherapy or radiotherapy. The exclusion criteria included: (I) with simultaneous hepatic/colon resection (II) emergency surgery for trauma (III) total pancreatectomy (IV) incomplete med records (*Figure 1*).

Date collection and perioperative management

Patient demographic characteristics, preoperative laboratory tests, surgical variables and postoperative complications were obtained.

All patients were discussed by the multidisciplinary team (MDT) before received treatments. For patients included in this study, preoperative biliary drainage (PBD) was performed in such situations: serum total bilirubin level was ≥15 mg/dL, preoperative cholangitis occurred, poor nutritional status. Endoscopic nasobiliary drainage (ENBD) was applied in most patients, while few patients through percutaneous transhepatic cholangial drainage (PTCD) and endoscopic retrograde biliary drainage (ERBD). Patients who underwent PBD received bile reinfusion combined with enteral nutrition. Prophylactic antibiotics were intravenously administered for 3 days (on the operation day and postoperative 2 days) in all patients. 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. Somatostatin analogue was given postoperative 7 days as prophylaxis of POPF. Liquid diet was gradually resumed around POD 2–5 and soft diet after defecation. However, supplementary parenteral nutritional or enteral nutrition support was administered to patients with insufficient oral intake after surgery. All drain fluids were analyzed for amylase concentration and bacteria on postoperative days 1, 3, 5, 7. The peripancreatic drain tubes were removed on or after POD 5 when the abdominal CT showed no fluid accumulation and no evidence of POPF or leakage.

Surgical procedures

The operations were performed by the same experienced surgeons. All patients underwent either pylorus-preserving PD or standard PD with Child's reconstruction. A manual end-to-side pancreaticojejunostomy was performed by Blumgart's methods (13). An internal non absorbable pancreatic duct stent was routinely placed during the pancreaticojejunostomy according to the size of the

main pancreatic duct (MPD). Gastrojejunostomy and hepaticojejunostomy were performed on the same jejunal loop. At the end of each surgery, two or three intra-abdominal drains were commonly inserted at the anterior and posterior to the hepaticojejunostomy anastomosis.

Definition of variables

Complications following surgery during the hospital stay or within 90 days after operation was graded according to the Clavien-Dindo classification (14). POPF was defined according to the International Study Group for pancreatic fistula (ISGPF) criteria (15): Grade A (biochemical leak) was no clinical impact; Grade B was requiring a change in the clinical management of the expected postoperative pathway; Grade C was a grade B POPF leads to organ failure or to clinical instability such that reoperation is needed. Grade B/C POPF was defined as clinically relevant POPF (CR-POPF). Postoperative infectious complications classified as surgical site infection (SSI), pneumonia, urinary tract infection and bacteremia, were collected in 90-day after the surgery. SSI was diagnosed according to the guidelines (16) contains superficial incisional SSI, deep incisional and organ/space SSI. Pneumonia was defined as an infectious complication combined with a suggestive thoracic image that improved after antibiotic therapy. Urinary tract infection was defined as clinical conditions related to infection and with positive cultures (17). Bacteremia was defined as two positive blood cultures for a pathogenic bacterium.

Statistical analysis

All data were analyzed using SPSS statistics 23.0 (Armenk, NY: IBM Corp). Categorical variables were presented as n (%) and were compared between the groups using the Chi-squared test or Fisher's exact test, as appropriate. Continuous variables are presented as the mean ± standard deviation (SD) or median with interquartile range (IQR) and were compared by *t*-test or Mann-Whitney *U*-test according to the distribution. Multivariate analysis was performed using a multivariable regression model and included the variables identified by univariate analysis ($P<0.1$). $P\leq0.05$ was considered statistically significant.

Results

Patient characteristics

From February 2018 to March 2021, a total of 316 patients underwent PD and 25 patients were excluded (3 with colectomy, 10 with hepatectomy, 5 with neoadjuvant chemotherapy, 4 with emergency operation and 3 with incomplete data). Finally, 291 patients were included in this study (*Figure 1*). The demographic characteristics, preoperative treatments, laboratory text and operation variables are shown in *Table 1*. The study includes 176 male and 115 female participants, with a median age of 64 years old. Overall, one hundred and ten patients out of 291 (37.8%) patients experienced infections complications. There were no significant differences in gender, BMI, high blood pressure, diabetic mellitus and nutrition score between infection and non-infection groups. The age of patients in the infections group was older than non-infection groups (65 *vs.* 63, P=0.091). The rate of pre-operative cholangitis in the infection group was high than those in non-infection group (40.9% *vs.* 36.5%, P=0.001). The proportion of patients who received PBD was higher in the infection group than the non-infection group, which was of great significance (39.1% *vs.* 24.3%, P=0.008). In addition, the preoperative total bilirubin (TB) was higher in the infection group [16.6 (10.8–63.0) μmol/L *vs.* 14.4 (8.2–57.6) μmol/L; P=0.045]. The malignant comprised a large proportion in the infection group than the non-infection group, without significant difference (74.5% *vs.* 64.6%; P=0.078). There were no significant differences between the two groups regarding the operative variables, such as operative time, blood loss, blood transfusion, etc. (*Table 1*).

Postoperative outcomes

A total of 110 patients (37.8%) developed infectious complications consisting of SSI, bacteremia, pneumonia and urethra infections. SSI was the most common types of infection after operation, accounting for 34.7%. According to the Clavien-Dindo classification, 42 patients (38.2%) in the infection group experienced severe complications (≥ grade III) which were higher than the non-infection group (10.5%) (P<0.05). Patients with infectious complications had a higher incidence of CR-POPF (70.0% *vs.* 17.1%; P<0.001), biliary fistula (10.9% *vs.* 4.4%; P=0.034),

Table 1 Patient characteristics

Variables	Total	Infection (n=110)	No-infection (n=181)	P value
Age, years	64.0 (55.0–70.0)	65.0 (57.0–70.3)	63.0 (52.5–69.0)	0.091
Male sex	176 (60.5)	72 (65.5)	104 (57.5)	0.176
Smoking	70 (24.1)	26 (23.6)	44 (24.3)	0.896
Drinking	49 (16.8)	18 (16.4)	31 (17.1)	0.866
BMI	23.1 (21.4–25.5)	23.85 (21.7–25.7)	22.80 (21.1–25.1)	0.103
Diabetes	54 (18.6)	24 (21.8)	30 (16.6)	0.265
High blood pressure	99 (34.0)	39 (35.5)	60 (33.2)	0.687
Previous laparotomy	88 (30.2)	30 (27.3)	58 (32.0)	0.390
NRS2002 score	4.0 (2.0–5.0)	4.0 (2.0–5.0)	3.0 (2.0–5.0)	0.701
PG-SGA score	8.0 (4.0–10.5)	8.0 (4.0–12.0)	7.0 (4.0–10.0)	0.263
Jaundice	111 (38.1)	45 (40.9)	66 (36.5)	0.449
Cholangitis	29 (10.0)	19 (17.3)	10 (5.5)	0.001
PBD	87 (29.9)	43 (39.1)	44 (24.3)	0.008
ALT (U/L)	44.0 (15.9–101.2)	45.7 (17.9–102.6)	42.0 (14.5–97.2)	0.455
AST (U/L)	29.6 (17.1–62.2)	31.6 (17.3–70.8)	29.1 (16.9–59.3)	0.300
TB (μmol/L)	15.7 (9.1–58.1)	16.6 (10.8–63.0)	14.4(8.2–57.6)	0.045
ALB (g/L)	38.8±3.1	38.6±3.2	38.9±3.0	0.406
CRP	4.5 (2.9–6.5)	4.5 (2.9–7.4)	4.5 (2.9–6.3)	0.627
PAB	206.3±60.2	206.6±60.3	206.1±60.5	0.947
PCT	0.567 (0.12–4.5)	0.073(0.0–0.10)	0.076 (0.0–0.2)	0.912
WBC	5.6 (4.4–6.6)	5.6 (4.4–7.1)	5.6 (4.5–6.5)	0.782
N%	61.8±9.8	62.4±10.0	61.5±9.7	0.430
N count	3.4 (2.6–4.4)	3.4 (2.6–4.5)	3.4 (2.6–4.3)	0.565
L	1.4 (1.1–1.8)	1.4 (1.1–1.8)	1.5 (1.1–1.8)	0.476
Hb (g/L)	124.0 (111.0–136.0)	125.5 (111.0–138.0)	123.0 (111.0–133.5)	0.431
Platelet	216.0 (177.0–259.0)	217.5 (181.8–263.3)	213.0 (176.0–257.5)	0.375
Pathological diagnosis				0.078
Benign/malignant	92/199	28/82	64/117	
Operative variables				
Time	370.0 (310.0–440.0)	385.0 (310.0–448.8)	360.0 (300.0–435.0)	0.124
Pancreatic duct diameter	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.225
Blood loss	400.0 (300.0–600.0)	500.0 (287.5–625.0)	400.0 (300.0–625.0)	0.907
Blood transfusion	0.0 (0.0–700.0)	0.0 (0.0–800.0)	0.0 (0.0–600.0)	0.180
Pancreatic texture (hard)	40 (13.7)	16 (14.6)	24 (13.3)	0.757
Vessel resection	12 (4.1)	5 (4.6)	7 (3.9)	0.778
PD/PPPD	201/90	76/34	125/56	0.996

BMI, body mass index; NRS, nutrition risk screening; PG-SGA, patient-generated subjective global assessment; PBD, preoperative biliary drainage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ALB, albumin; CRP, C-reactive protein; PAB, prealbumin; PCT, procalcitonin; WBC, white blood cell; PD, pancreaticoduodenectomy; PPPD, pylorus preserving pancreaticoduodenectomy; SSI, surgical site infection; CR-POPF, clinically relevant postoperative pancreatic fistula; BF, biliary fistula.

Table 2 Postoperative outcomes

Variables	Infection (n=110)	Non-infection (n=181)	P value
Infectious complication, n (%)			
Incisional SSI	16 (14.6)	–	–
Organ/space SSI	85 (77.3)	–	–
Bacteremia	19 (17.3)	–	–
Pneumonia	7 (7.1)	–	–
Urethra infection	2 (1.8)	–	–
CR-POPF, n (%)	77 (70.0)	31 (17.1)	0.000
Chylous fistula, n (%)	12 (10.9)	25 (13.8)	0.471
BF, n (%)	12 (10.9)	8 (4.4)	0.034
Intrabdominal bleeding, n (%)	17 (15.5)	7 (3.9)	0.000
Clavien-Dindo ≥III, n (%)	42 (38.2)	19 (10.5)	0.000
Postoperative stays (d)	27.0 (20.8–36.0)	16.0 (12.5–21.0)	0.000
Expense (RMB)	136,887.5 (112,117.3–175,765.0)	108,712.0 (89,797.0–130,586.0)	0.000
Mortality, n (%)	1 (0.91)	1 (0.55)	1.000

SSI, surgical site infection; CR-POPF, clinically relevant postoperative pancreatic fistula; BF, biliary fistula.

intrabdominal bleeding (15.5% *vs.* 3.9%; P<0.001) and longer postoperative hospital stays [27 (20.8–36.0) days *vs.* 16 (12.5-21.0) days; P<0.001], higher expense [136,887.5 (112,117.3–175,765.0) yuan *vs.* 108,712.0 (89,797.0–130,586.0) yuan; P<0.001] than those in the non-infection group (*Table 2*).

The outcomes of patients underwent PBD

A total of 87 patients received PBD and most of the patients suffered nutrition risks. About 95.4% patients in the PBD group were malignant which was higher than 56.9% in the non-drainage group (P<0.05). The blood transfusion during the operation was higher in the PBD group though the blood loss was of no significant difference [300 (0–900) mL *vs.* 0 (0–600) mL; P=0.002]. Patients who underwent PBD had a higher incidence of organ/space SSI which resulting in higher expense than the non-PBD group (42.5% *vs.* 23.5%; P=0.001). The major complications (Clavien-Dindo ≥ grade III) and mortality rates had no significant difference in the two groups (26.4% *vs.* 18.6%; P=0.134) (*Table 3*).

Risk factors related to infection complications

The multivariable logistic regression analysis of risk variables for postoperative infection was shown in *Table 4*. Three factors including PBD (OR 2.082; 95% CI: 1.059–4.091; P=0.033), CR-POPF (OR 11.984; 95% CI: 6.556–21.471; P=0.000), BF (OR 3.674; 95% CI: 1.218–11.084; P=0.021) were the independent risk factors for infectious complications.

Preoperative bile postoperative ascites and blood cultures

Table 5 shows the microorganisms in preoperative bile and postoperative drainage. *K. pneumoniae*, *E. faecalis*, and *S. haemolyticus* were the most common bacteria in bile culture. The first three most frequently isolated organisms from drainage fluid were *K. pneumoniae*, *E. faecalis* and *S. epidermidis*. *K. pneumoniae*, *S. aureus* and *S. haemolyticus* were the most common bacteria in bacteremia patients.

Discussion

This study showed that PBD, CR-POPF and BF were substantially associated with postoperative infectious complications after PD. *K. pneumoniae* and *E. faecalis* were the most frequently isolated bacterial pathogens in bile culture and drainage fluid after PD. *K. pneumoniae* and *S. haemolyticus* were the most common bacteria in bacteremia patients.

Table 3 Postoperative outcomes in patients with PBD

Variables	Drainage (n=87)	Non-Drainage (n=204)	P value
Age (years)	64.0 (56.0–69.0)	64.0 (55.0–70.0)	0.785
Male sex	53 (60.9)	123 (60.3)	0.920
Smoking	23 (26.4)	47 (23.0)	0.535
Drinking	18 (20.7)	31 (15.2)	0.252
BMI	22.4 (20.9–24.9)	23.4 (21.5–25.7)	0.086
Diabetes mellitus	19 (21.8)	35 (17.2)	0.347
High blood pressure	33 (37.9)	66 (32.4)	0.358
History of abdominal surgery	26 (29.9)	62 (30.4)	0.931
NRS2002 score	5.0 (3.0–5.0)	3.0 (0.0–5.0)	0.000
PG-SGA score	10.0 (7.0–13.0)	5.0 (3.0–9.0)	0.000
Pathological diagnosis			0.000
Benign	4 (4.6)	88 (43.1)	
Malignant	83 (95.4)	116 (56.9)	
Operative variables			
Time	375.0 (310.0–430.0)	370.0 (301.3–440.0)	0.817
Blood loss	400.0 (300.0–700.0)	400.0 (300.0–600.0)	0.588
Blood transfusion	300.0 (0.0–900.0)	0.0 (0.0–600.0)	0.002
Pancreatic texture(hard)	13 (14.9)	27 (13.2)	0.699
Vessel resection	4 (4.6)	8 (3.9)	0.791
PD/PPPD	54/33	147/57	0.091
Infection	43 (49.4)	67 (32.8)	0.008
Incisional SSI	3 (3.5)	13 (6.4)	0.316
Organ/space SSI	37 (42.5)	48 (23.5)	0.001
Bacteremia	8 (9.2)	11 (5.4)	0.229
Pneumonia	2 (2.44)	5 (2.54)	0.962
Urethra infection	1 (1.0)	2 (1.2)	0.896
CR-POPF	37 (42.5)	71 (34.8)	0.212
Chylous fistula	16 (18.4)	21 (10.3)	0.058
BF	3 (3.2)	17 (8.3)	0.132
Abdominal bleeding	9 (10.3)	15 (7.4)	0.396
Clavien-Dindo ≥III	23 (26.4)	38 (18.6)	0.134
Morality	2 (2.3)	0 (0.0)	0.089
Post-operative stays (d)	21 (8–101)	19 (7–158)	0.142
Expense	134,463 (73,822–287,540)	110,725 (62,202–390,544)	0.000

PBD, preoperative biliary drainage; BMI, body mass index; NRS, nutrition risk screening; PG-SGA, patient-generated subjective global assessment; PD, pancreaticoduodenectomy; PPPD, pylorus preserving pancreaticoduodenectomy; SSI, surgical site infection; CR-POPF, clinically relevant postoperative pancreatic fistula; BF, biliary fistula; TB, total bilirubin.

Table 4 Multivariable analyses of risk factors for infectious complications

Variables	β	OR	95% CI	P
PBD	0.733	2.082	1.059–4.091	0.033
CR-POPF	2.474	11.984	6.556–21.471	0.000
BF	1.301	3.674	1.218–11.084	0.021
Chylous fistula	0.306	1.357	0.561–3.285	0.498
Age	0.018	1.018	0.997–1.039	0.098
TB	–0.001	0.999	1.122–4.144	0.615
Benign or malignant	–0.196	0.822	0.457–1.478	0.512
Cholangitis	0.274	1.315	0.568–3.039	0.522

PBD, preoperative biliary drainage; CR-POPF, clinically relevant postoperative pancreatic fistula; BF, biliary fistula; TB, total bilirubin.

Table 5 Microorganisms cultured positive from bile, ascites and blood

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)
Gram– bacteria				
K. pneumoniae	24	34	23	4
E. coli	6	23	1	2
E. cloacae	6	12	7	1
A. baumannii	15	12	3	–
P. aeruginosa	2	11	2	–
Gram+ bacteria				
E. faecalis	18	30	12	–
S. epidermidis	1	23	7	3
S. haemolyticus	2	23	4	4
E. faecium	4	11	15	–
S. aureus	2	7	4	3
Fungus	0	12	8	2
Others	10	11	4	2

The incidence of postoperative infectious complications was as high as 30–75% and associated with high morbidity, prolonged hospitalization, high rate of readmission and increased expenditures (3,5,18). A multi-institutional study showed that 40.3% of the patients were readmitted for infection complications at 30 days (19). Some studies found that infection resulted in a prolonged hospitalization and 2.5-fold increase in expenditures (11,20). Our study confirmed that infectious complications were the most frequent complication with a rate of 37.8% resulting in an additional 11 days of postoperative hospitalization and ¥28,175 expenditures which are almost in line with the reported literatures.

Periampullary cancer is often complicated with obstructive jaundice, which can induce liver dysfunction, renal failure, cardiovascular suppression, coagulopathy, malnutrition, infection and increase morbidity and mortality (21). PBD including ENBD, ERBD and PTCD was introduced to reduce the above-mentioned serious consequences. However, it remains still controversial

whether routinely PBD before PD can improve surgical outcomes. Several studies indicated that PBD reduced morbidity and mortality after surgery (22,23). However, some other retrospective and meta-analyses of randomized trials showed that routine PBD not only did not reduce morbidity and mortality but also increase the risk of postoperative overall complications, such as infections (24-28). A high-quality multicenter randomized controlled trial (RCT) revealed that routine PBD in patients who received PD increased the rate of complications (29). Recently, a retrospective and propensity score-matched analysis suggested that PBD in patients with serum total bilirubin level exceeding 250 μmol/L had a lower overall postoperative complication, CR-POPF, post-pancreatectomy hemorrhage compared with direct surgery patients after PD. The multicentric study by Sauvanet *et al.* (30) showed serum bilirubin level ≥300 μmol/L increased severe morbidity and decreased long-term survival after PD for pancreatic ductal adenocarcinoma. By analyzing 1,500 consecutive cases, De Pastena *et al.* (31) demonstrated that PBD did not increase major complications and mortality rates after PD, but it increased SSI rates. They advised that PBD should be applied in jaundiced patients with bilirubin value greater than 128 μmol/L. Moghimi *et al.* (32) suggested the cutoff of bilirubin level for PBD should be above 272 μmol/L. Our results showed that PBD did not increase serious complications and mortality after PD which was the same with the reported results (27,31,33). Instead, it was an independent risk factor for the development of postoperative infectious complications, especially organ/space SSI and therefore increase hospitalization and expenditure. Because of the direct link between the duodenum and the biliary tree, PBD allows germs and food debris to migrate into the biliary system, potentially resulting in bile bacterial contamination. The leakage of infected bile juice during surgery increases abdominal contamination and the development of organ/space SSI. Thus, some studies 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 (34-36).

The indications for PBD in our study were acute cholangitis, poor nutrition status and higher bilirubin level. All the patients who underwent PBD were received bile reinfusion combined with enteral nutrition through nasointestinal tube. This may improve the liver function, nutritional status, immune function and reduce systemic endotoxemia. Preoperative cholangitis was reported to be an independent risk factor for postoperative infectious complications (24). However, our study showed preoperative cholangitis was a risk factor but not an independent one. This difference may due to the different treatment strategies.

POPF is a common complication following PD and can be divided into two types: biochemical leak and CR-POPF. CR-POPF is a hazardous type with a high mortality rate of 39% and has been identified as an independent risk factor for SSI with infectious incidence of 61%, which was three times higher than patients without POPF (37). In this study, CR-POPF occurred in 34.7% of the patients and was an independent risk factor for infectious complications resulting in 71.3% of patients suffered infections. The result was similar as reported that POPF was significantly correlated with infections (12,38). The autodigestive effect of leaky pancreatic juice damages surrounding tissue and encourages infections (39). At the same time, infection can affect the healing of pancreaticointestinal anastomosis and further aggravate the severity of POPF (40). Therefore, in clinical practice, it is necessary to closely detect the bacteria in the drainage fluid when CR-POPF occurred. To avoid additional morbidity, effective drainage and thorough antibacterial therapy should be undertaken.

Biliary fistula (BF) is a rare problem that reportedly occurred in 3–8% of patients after PD and scanty attention were paid to it. The bile mixed with intestinal leak from the cholangio-intestinal anastomosis promotes bacterial infection and increases the additional morbidity and mortality (41,42). The present study demonstrated similar results, with BF occurs in 6.9% of patients and a 3.7-fold increased risk of additional infections complications. In addition, BF was associated with an increased risk of late biliary anastomotic stricture which needs minimally invasive interventions (43). As a result, once BF had occurred, effective drainage and antibacterial treatment should be performed to prevent further morbidity.

Earlier researches had shown that 50% to 100% of the infectious sources are identical to intraoperative bile cultures (22,44). As reported (11,44), the most frequently identified organisms in bile were *E. coli*, *K. pneumoniae* and *Enterococci*. *Enterococci* was the most common species followed by *E. coli* and *K. pneumoniae* in postoperative infection sites. In our study, *K. pneumoniae* and *E. faecalis* were the most common organisms both in bile and postoperative ascites which was almost consistent with the

existing reports letting us speculate that intraoperative bile contaminated might promote the abdominal infections after PD. The most frequently isolated microorganism in bile, drainage fluid and blood were *K. pneumoniae* in this study. It is a gram-negative opportunistic pathogen and showed severe multiple drug resistance, including third-generation cephalosporins and aminoglycosides. Short-term probabilistic perioperative antibiotic adapted to the biliary bacterial ecology was shown to be more effective than surgical antibiotic prophylaxis (34).

However, the study was a single-center retrospective study and some selection bias may have been present. Some risk factors such as nutrition risk and long operative time, which reported by previous studies had not significantly associated with infection in this study. This may due to the relatively small sample size. Furthermore, bacterial resistance to antibiotics was not involved in this study which was more valuable for clinical treatment of infection. Further studies are needed to validate our conclusions.

Conclusions

PBD, POPF and BF are substantially related with postoperative infectious complications following PD. To lower the incidence of infection, 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. *K. pneumoniae* was the most frequently isolated microorganism in this study and perioperative antibiotic adapted to the biliary bacterial could be considered especially in the PBD patients.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University College of Medicine (No. 2021-271-01) and individual consent for this retrospective analysis was waived.

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