Original Article

The role of preoperative biliary drainage on postoperative outcome after pancreaticoduodenectomy in patients with obstructive jaundice

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Background: The role of preoperative biliary drainage (PBD) on obstructive jaundice patients is still controversial. The aim of this retrospective study is to clarify the effect of PBD on postoperative outcomes of pancreaticoduodenectomy (PD) and explore a reasonable PBD strategy for periampullary carcinomas (PAC) patients with obstructive jaundice before surgery.

Methods: A total of 148 patients with obstructive jaundice who underwent PD were enrolled in this research and divided into drainage group and no-drainage group according to whether they received PBD. Patients who received PBD were classified into long-term group (>2 weeks) and short-term group (≤2 weeks) according to PBD duration. The clinical data of patients were statistically compared between groups to explore the influence of PBD and its duration. Analysis of pathogens in bile and peritoneal fluid was performed to probe the role of bile pathogens in opportunistic pathogenic bacterial infection after PD.

Results: Of all, 98 patients underwent PBD. The mean duration between drainage and surgery was 13 days. Regarding postoperative outcomes, the incidence of postoperative intra-abdominal infection was significantly higher in the drainage group than the no-drainage group (P=0.026). In patients with total bilirubin (TB) less than 250 µmol/L, postoperative intra-abdominal infection was more frequently observed in the drainage group compared to the no-drainage group (P=0.022). Compared to the short-term drainage group, the proportion of positive ascites culture was significantly higher in the long-term drainage group (P=0.022). There were no statistically significant differences in postoperative complications between short-term group and no-drainage group. The most frequent pathogens detected in bile were *Klebsiella pneumoniae*, hemolytic Streptococcus and Enterococcus faecalis. The most commonly detected pathogens in peritoneal fluid were *Klebsiella pneumoniae*, *Enterococcus faecalis* and Staphylococcus epidermidis which appeared to have a high agreement with pathogens in preoperative bile cultures.

Conclusions: Routine PBD should not be performed in obstructive jaundice PAC patients with TB less than 250 µmol/L. For patients with indications for PBD, the drainage duration should be controlled within 2 weeks. Bile bacteria may represent a major source of opportunistic pathogenic bacteria infection after PD.

Keywords: Pancreaticoduodenectomy (PD); preoperative biliary drainage (PBD); postoperative outcome; obstructive jaundice; pathogenic bacteria

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Introduction

Periampullary carcinomas (PAC) refer to malignant tumors located around the ampulla of Vater, including cancers of pancreatic head or uncinate process, distal common bile duct, Vater ampulla and the second part of the duodenum (1). Radical surgical resection of periampullary cancer is the only potential curative treatment that may offer a long-term survival (2). Pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD) remains the standard surgical method for PAC (3,4). In recent years, the postoperative mortality and morbidity of PD has been reduced, which is largely attributable to the progress of perioperative management, including reasonable preoperative assessment and management, standard intraoperative surgical manipulation, and careful postoperative monitoring and support (5-7).

Obstructive jaundice is one of the most common presenting symptoms of PAC due to the invasion or compression of the common bile duct. About 50% to 80% of PAC patients seek hospital care with a chief complaint of jaundice (8). Unlike non-tumor jaundice, tumor jaundice always persists and could be characterized by a more severe course, higher hyperbilirubinemia and lipid peroxidation (9). Therefore, tumor jaundice tends to significantly affect multiple organ functions and puts patients at higher risk of pathophysiological changes such as liver dysfunction, renal failure, cardiovascular suppression, malnutrition, coagulopathy and immune compromise (10). Moreover, obstructive jaundice could lead to impaired intestinal mucosal barrier and intestinal flora disorders, which further increased the occurrence of perioperative infectious complications. Thus, the adverse events caused by obstructive jaundice should be fully evaluated and reversed prior to operation for a more favorable outcome for PAC patients (11).

Preoperative biliary drainage (PBD) has traditionally been used to ease symptoms of pruritus and cholangitis, as well as improve coagulopathy and renal failure caused by hyperbilirubinemia. Yet, the true clinical impact of PBD remains controversial with mixed results reported in the literature. Earlier investigations have found that restoring enterohepatic circulation before surgery had a considerable effect in terms of reduced morbidity and mortality in patients with jaundice compared to immediate surgery (12,13). There is evidence that PBD could improve immune function and nutritional status, and restore the balance of the intestinal flora (14-16). Contrarily, more recent clinical researchers have found a considerable rise in surgical complications such as wound infections, biliary stricture as well as mortality in patients undergoing routine PBD (17-19). There are also studies showing that in patients with ampullary or pancreatic cancer, PBD has a negative impact on patients' survival time (20,21). However, a recent retrospective study showed PBD should be performed routinely for those patients with serum total bilirubin (TB) level exceeding 250 μmol/L to reduce the overall postoperative complications, post-pancreatectomy hemorrhage (PPH) and postoperative pancreatic fistula (POPF) (22). To date, it remains controversial whether and how PBD should be performed before PD in patients with resectable tumors and obstructive jaundice. Therefore, the purpose of our study is to clarify the effect of PBD on postoperative outcomes of PD and explore a reasonable preoperative drainage strategy through retrospectively analyzing the clinical data of patients with obstructive jaundice undergoing PD in our institution. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-648/rc).

Highlight box

Key findings

- PBD increases the incidence of abdominal infection after PD in obstructive jaundice patients with TB less than 250 μmol/L.
- PBD duration more than 2 weeks increases the rate of positive ascites culture.
- Bile bacteria represent a major source of opportunistic pathogenic bacteria infection after PD.

What is known and what is new?

- PBD and long drainage time would increase the risk of complications after PD.
- TB of 250 μmol/L and duration time of 2 weeks could serve as reference indexes for PBD. Bile culture can guide postoperative antibiotic use.

What is the implication, and what should change now?

- Direct surgery should be considered if preoperative TB was less than 250 μmol/L.
- For patients with indications for PBD, the drainage duration should be controlled within 2 weeks.
- Bile should be routinely collected for culture during drainage or surgery.

Methods

Patients

This retrospective study was conducted in 148 patients with obstructive jaundice undergoing PD in Nanjing Drum Tower Hospital from January 2018 to November 2021. The inclusion criteria were: (I) patients with preoperative obstructive jaundice; (II) patients who underwent PD in our department; (III) patients with no history of chemotherapy or radiotherapy; and (IV) patients with complete clinical and laboratory data were available. In total, there were 368 patients who received PD in our institution between January 2018 and November 2021. Patients were excluded by the following criteria: (I) without preoperative obstructive jaundice; (II) with simultaneous hepatic/colon resection; (III) total pancreatectomy; (IV) incomplete medical records. A total of 220 patients were excluded. Among them, 216 had no preoperative obstructive jaundice, 2 underwent simultaneous hepatic resection, 1 underwent total pancreatectomy, and 1 had incomplete medical records. Finally, 148 patients were included in this retrospective study. Then, the clinical data of these patients were collected and reviewed. The process of our study adhered to the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Nanjing Drum Tower Hospital (No. 2021-271-01). Every patient signed written informed consent for this retrospective study and for the use of their clinical data.

Surgical technique and perioperative management

All patients underwent a multidisciplinary team (MDT) discussion prior to treatment. Some patients received biliary drain inserted pre-admission in digestive medical department for the tumor biopsy. For patients receiving PBD, endoscopic nasobiliary drainage (ENBD) was applied in most patients, while few patients underwent percutaneous transhepatic cholangial drainage (PTCD) when ENBD failed. Endoscopic retrograde biliary drainage (ERBD) was applied to patients before undergoing adjuvant therapy. Patients with high serum TB level who underwent PBD received bile reinfusion combined with enteral nutrition. Classical Whipple procedure or PPPD with Child's reconstruction was performed by the same surgeons with extensive experience in pancreatic surgery according to disease condition. A manual end-to-side pancreaticojejunostomy was performed by Blumgart's methods. Gastrojejunostomy and hepaticojejunostomy were performed on the same jejunal loop. After ensuring that there was no active bleeding and bile leakage, the peritoneal cavity was irrigated with warm saline. At the end of each surgery, two or three intra-abdominal drains were commonly inserted at the anterior and posterior to the hepaticojejunostomy anastomosis. After checking the instruments and gauzes, the surgical incision was sutured.

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 for 7 days after surgery as prophylaxis of POPF. Liquid diet was gradually resumed around POD 2–5 and soft diet after defecation. 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 POD 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.

Data collection and complications

The data we collected to analyze the influence of PBD on postoperative outcomes of PD were described as follows: (I) pre-operative clinical data: age, gender, body mass index (BMI), diabetes mellitus (DM), hypertension, nutritional risk screening index (NRSI) 2002, Patient-Generated Subjective Global Assessment (PG-SGA), cholangitis, tumor nature, PBD, blood indicators; (II) intra-operative clinical data: vessel resection, blood loss volume, operating time; (III) post-operative clinical data: pathology diagnosis, postoperative complications [clinically relevant POPF (CR-POPF), biliary leakage, delayed gastric emptying (DGE), PPH, chylous fistula, surgical site infection (SSI), intra-abdominal infection, bacteremia, pneumonia, and urinary tract infection].

Complications following surgery during the hospital stay or within 90 days after operation were graded according to the Clavien-Dindo classification (23). POPF was defined according to the International Study Group for pancreatic fistula (ISGPF) criteria (24): Grade A (biochemical leak) was a POPF showing no clinical impact; Grade B was a POPF requiring a change in the clinical management of the expected postoperative pathway; Grade C was a grade

B POPF leading to organ failure or to clinical instability for which re-operation would be needed. Grade B/C POPF was defined as CR-POPF. Biliary leakage was defined as bile-like fluid draining from the abdominal tube with a bilirubin concentration more than three times that of serum bilirubin monitored at the same time, which was confirmed by B-ultrasound or CT examination (25). DGE, PPH and their severity were defined according to the ISGPS criteria (26,27). Postoperative infectious complications including SSI, intra-abdominal infection, pneumonia, urinary tract infection and bacteremia were collected in 90 days after the surgery. SSI was defined as superficial incisional SSI, deep incisional or organ/space SSI according to the Centers for Disease Control and Prevention classification (28). Intra-abdominal infection was defined as high grade fever ≥38 ℃ and elevations of white blood cells (WBCs) with positive culture results from surgical site drain fluid within 3 days after surgery. Pneumonia was defined as an infectious complication which requires treatment with antibiotics for a respiratory infection and at least one of the following criteria: new or changed sputum; with a suggestive thoracic image; temperature more than 38 ℃; leucocyte count more than 12,000/μL (29). Urinary tract infection was defined as urinary symptoms with positive urine cultures. 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. P value ≤0.05 was considered statistically significant.

Results

Clinicopathological characteristics of the patients

The clinicopathological characteristics of the 148 patients are shown in *Table 1*. The cohort included 97 men (65.5%) and 51 women (34.5%), with a mean age of 65 years (range, 57–70 years). Among the 148 patients, PBD was performed in 98 patients. Before surgery, 29 (19.6%) patients were complicated with DM, 53 (35.8%) were complicated with hypertension, and 29 (19.6%) had cholangitis. The median values of preoperative serum TB and direct bilirubin (DB) were 154.6 (88.1–241.4) and 112.2 (61.1–168.1) μmol/L, respectively. Among them, 39 (26.4%) patients had TB >250 μmol/L. Postoperative pathological examination showed that 39 (26.4%) patients were diagnosed as pancreatic adenocarcinoma (PDAC), 73 (49.3%) were diagnosed as Vater's ampullary carcinoma (VAC), 25 (16.9%) were diagnosed as distal cholangiocarcinoma (DCC), and 3 (2%) were diagnosed as duodenal carcinoma (DDC). Overall, 80 of 148 (54.1%) patients experienced infectious complications, of which 28 (18.9%) were with serious postoperative complications.

Impact of PBD on patient outcome

Depending on whether PBD was administered, the patients were divided into two groups. According to *Table 1*, 98 patients were enrolled in the drainage group, while 50 patients were enrolled in the no-drainage group. The statistical comparative tests showed statistically significant differences in NRS2002, cholangitis, serum TB, serum DB, WBC, hemoglobin and postoperative intra-abdominal infection (P<0.05 for all, *Table 1*). Compared to the no-drainage group, patients in the drainage group had higher levels of NRS2002 (P=0.005), serum TB (P<0.001), serum DB (P<0.001), WBC (P=0.003) and a lower level of hemoglobin (P=0.003) before surgery. The occurrence of preoperative cholangitis in the drainage group was higher than the no-drainage group (P=0.035). In addition, the incidence of postoperative intra-abdominal infection was significantly higher in the drainage group than the no-drainage group (P=0.026). There was no statistically significant difference between the two groups in regard to other postoperative complications such as CR-POPF, biliary leakage, DGE, PPH, chylous fistula, wound infection, bacteremia, pneumonia and urinary tract infection (P>0.05 for all, *Table 1*).

A subgroup analysis was performed in patients with serum TB ≤250 μmol/L and no cholangitis to evaluate the impact of PBD in patients with a relatively low TB. There were 109 patients with serum TB ≤250 μmol/L. Twenty-four cases were excluded due to cholangitis, and a total of 85 patients were included in the subgroup analysis (*Table 2*). In this subgroup, 46 patients underwent PBD for poor nutritional status or lesion biopsy while 39 did not. In the drainage group, postoperative intra-abdominal infection

Table 1 Clinical characteristic of all patients with obstructive jaundice

Variables	Total (n=148)	Drainage (n=98)	No-drainage (n=50)	P
Age (years), median (IQR)	65.0 (57.0–70.0)	64.0 (57.8–70.0)	68.0 (55.8–73.0)	0.631
Male sex	97 (65.5%)	60 (61.2%)	37 (74.0%)	0.122
BMI (kg/m^2), median (IQR)	22.5 (20.9–24.8)	22.4 (20.5–24.8)	23.0 (21.4–24.9)	0.319
Diabetes mellitus	29 (19.6%)	19 (19.4%)	10 (20.0%)	0.929
Hypertension	53 (35.8%)	36 (36.7%)	17 (34.0%)	0.743
NRS2002, median (IQR)	5.0 (3.0–5.0)	5.0 (4.0–5.0)	4.0 (3.0–5.0)	0.005
PG-SGA, median (IQR)	9.0 (7.0–12.0)	10.0 (7.0–13.0)	8.0 (6.0–10.8)	0.064
Cholangitis	29 (19.6%)	24 (24.5%)	5 (10.0%)	0.035
ALT (U/L), median (IQR)	157.1 (83.3–261.0)	159.5 (84.8–255.8)	153.5 (75.0–266.9)	0.961
AST (U/L), median (IQR)	110.1 (56.6–178.0)	112.4 (64.8–183.4)	103.7 (49.6–158.2)	0.438
AKP (U/L), median (IQR)	430.8 (256.4–638.7)	479.1 (255.4–693.4)	342.7 (258.2–546.5)	0.112
GGT (U/L), median (IQR)	697.6 (322.1–1,042.7)	720.6 (317.8–1,049.2)	671.5 (332.3–1,029.2)	0.830
TB (μmol/L), median (IQR)	154.6 (88.1–241.4)	200.0 (113.3–283.6)	104.6 (45.7–152.1)	<0.001
DB (μmol/L), median (IQR)	112.2 (61.1–168.1)	143.6 (85.2–198.5)	78.6 (32.0–113.1)	<0.001
Albumin (g/L), median (IQR)	33.67 (34.7–38.9)	36.2 (34.0–38.5)	37.4 (35.7–39.2)	0.072
WBC (×10^9/L), median (IQR)	5.6 (4.5–7.3)	6.20 (4.8–7.7)	4.9 (4.4–6.0)	0.003
Hemoglobin (g/L), mean ± SD	119.0±17.1	116.1±18.0	124.8±13.6	0.003
Platelet (×10^9/L), median (IQR)	238.0 (184.8–302.8)	245.5 (198.5–315.5)	224.5 (174.8–267.0)	0.121
Pathology diagnosis				
PDAC	39 (26.4%)	26 (26.5%)	13 (26.0%)	0.945
VAC	73 (49.3%)	51 (52.0%)	22 (44.0%)	0.355
DCC	25 (16.9%)	17 (17.4%)	8 (16.0%)	0.836
DDC	3 (2.0%)	1 (1.0%)	2 (4.0%)	0.549
Others	6 (4.1%)	2 (2.0%)	4 (8.0%)	0.194
Vessel resection	13 (8.8%)	9 (9.2%)	4 (8.0%)	0.947
Operating time (min), mean ± SD	375.0±95.4	366.4±94.7	374.8±97.5	0.615
Blood loss volume (mL), median (IQR)	450 (300–600)	400 (300–700)	500 (300–600)	0.322
Complications				
Major (CD ≥ III)	28 (18.9%)	21 (21.4%)	7 (14.0%)	0.275
CR-POPF	57 (38.5%)	38 (38.8%)	19 (38.0%)	0.927
Biliary leakage	3 (2.0%)	2 (2.0%)	1 (2.0%)	0.987
DGE	45 (30.6%)	26 (26.8%)	19 (38.0%)	0.163
PPH	14 (9.5%)	9 (9.2%)	5 (10.0%)	0.872
Chylous fistula	23 (15.5%)	18 (18.4%)	5 (10.0%)	0.184
Wound infection	5 (3.4%)	4 (4.1%)	1 (2.0%)	0.507
Intra-abdominal infection	60 (40.5%)	46 (46.9%)	14 (28.0%)	0.026
Bacteremia	12 (8.1%)	9 (9.2%)	3 (6.0%)	0.502
Pneumonia	2 (1.4%)	2 (2.0%)	0 (0.0%)	0.309
Urinary tract infection	1 (0.7%)	1 (1.0%)	0 (0.0%)	0.474

IQR, interquartile range; BMI, body mass index; NRS, nutritional risk screening; PG-SGA, Patient-Generated Subjective Global Assessment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphate; GGT, gamma-glutamyl transferase; TB, total bilirubin; DB, direct bilirubin; WBC, white blood cell; SD, standard deviation; PDAC, pancreatic ductal adenocarcinoma; VAC, Vater's ampullary carcinoma; DCC, distal cholangiocarcinoma; DDC, duodenal carcinoma; CD, Clavien-Dindo; CR-POPF, clinically relevant postoperative pancreatic fistula (Grade B/C); DGE, delayed gastric emptying; PPH, post-pancreatectomy hemorrhage.

Table 2 Clinical characteristic of patients with TB ≤250 without cholangitis

Variables	Drainage (n=46)	Non-drainage (n=39)	t/χ^2	P value
Age (years)	62.10±11.71	63.15±10.48	0.440	0.661
Male sex	26 (56.52%)	27 (69.23%)	1.452	0.228
BMI (kg/m^2)	23.43±3.11	23.50±2.85	0.105	0.917
DM	11 (23.91%)	6 (15.38%)	0.959	0.327
Hypertension	17 (36.96%)	13 (33.33%)	0.121	0.728
Smoking	11 (23.91%)	8 (20.51%)	0.141	0.708
Alcohol	8 (17.39%)	4 (10.26%)	0.886	0.347
NRS2002 score	4.31±1.59	3.79±1.56	–1.528	0.130
PG-SGA score	10.36±4.36	8.68±3.84	–1.688	0.096
Pathological diagnosis				
PDAC	19 (41.3%)	10 (25.6%)	2.304	0.129
VAC	20 (43.5%)	19 (48.7%)	0.233	0.629
DCC	5 (10.7%)	7 (17.9%)	0.872	0.350
Others	2 (4.35%)	3 (7.7%)	0.036	0.849
Operative variables				
Time (min)	364.08±100.56	373.88±100.62	0.457	0.649
Blood loss (mL)	400.0 (300.0–700.0)	500.0 (300.0–600.0)	–0.449	0.653
Vessel resection	6 (13.0%)	3 (7.7%)	0.638	0.424
PPPD	19 (41.3%)	11 (28.21%)	1.586	0.208
Complications				
Major (Clavie-Dindo ≥ III)	10 (20.4%)	6 (15%)	0.558	0.455
CR-POPF	16 (34.8%)	16 (41.0%)	0.350	0.554
Biliary leakage	2 (4.4%)	1 (2.6%)	0.197	0.657
DGE	14 (30.4%)	16 (41.0%)	1.037	0.309
PPH	3 (6.5%)	2 (5.1%)	0.074	0.786
Chylous fistula	10 (21.7%)	3 (7.7%)	3.215	0.073
Wound infection	1 (2.0%)	1 (2.6%)	0.014	0.906
Intra-abdominal infection	23 (47.8%)	10 (23.2%)	5.273	0.022
Bacteremia	4 (8.7%)	2 (5.1%)	0.409	0.522
Pneumonia	2 (4.4%)	0 (0.0%)	1.737	0.188
Urinary tract infection	1 (2.2%)	0 (0.0%)	0.858	0.354
Post-operative stays (days)	23.0 (14.0–36.0)	20 (15.0–26.0)	–0.644	0.519
Expense (yuan)	127,445.0 (107,258.3–161,407.8)	118,120.0 (103,778.0–152,668.1)	–0.873	0.382

Data are shown as n (%) or mean ± SD or median (IQR). TB, total bilirubin; BMI, body mass index; DM, diabetes mellitus; NRS, nutritional risk screening; PG-SGA, Patient-Generated Subjective Global Assessment; PDAC, pancreatic ductal adenocarcinoma; VAC, Vater's ampullary carcinoma; DCC, distal cholangiocarcinoma; PPPD, pylorus-preserving pancreaticoduodenectomy; CR-POPF, clinically relevant postoperative pancreatic fistula (Grade B/C); DGE, delayed gastric emptying; PPH, post-pancreatectomy hemorrhage; SD, standard deviation; IQR, interquartile range.

Table 3 Clinical characteristic of patients who underwent PBD

Variables	Drainage (n=98)
TB before ERCP (μmol/L), median (IQR)	200 (113.3–283.6)
DB before ERCP (μmol/L), median (IQR)	143.6 (85.2–198.5)
TB after ERCP (μmol/L), median (IQR)	59.2 (43.5–106.6)
DB after ERCP (μmol/L), median (IQR)	44.2 (32.9–79.9)
TB >250	39
Cholangitis	24
Poor nutrition (NRS ≥3)	84
Duration of drainage (days), median [IQR]	13 [9–19]
Drainage type	
ENBD	76
PTCD	8
ERBD	10
ENBD + PTCD	4
ERCP complications	11
Failure	1
Cholangitis	6
Pancreatitis	1
Hemorrhage	3

PBD, preoperative biliary drainage; TB, total bilirubin; ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range; DB, direct bilirubin; NRS, nutritional risk screening; ENBD, endoscopic nasobiliary drainage; PTCD, percutaneous transhepatic cholangial drainage; ERBD, endoscopic retrograde biliary drainage.

was more frequently observed compared to the no-drainage group (P=0.022, *Table 2*). Besides that, no statistically significant difference was found between the drain group and the no-drain group in regard to demographic characteristics, nutritional status, underlying disease, operation conditions, pathological types and other surgical complications (P>0.05 for all, *Table 2*).

Impact of PBD duration on patient outcome

To assess the impact of PBD duration on patient outcome, a subgroup analysis was performed in patients who underwent PBD. There were 98 patients who underwent PBD prior to PD with a median drainage time of 13 days (*Table 3*). Among them, 24 (24.5%) patients had cholangitis, 39 (39.8%) had a serum TB ≥250 μmol/L, and 84 (85.7%) had a NRS2002 score ≥3. Most patients were treated with ENBD, while a minority were treated with PTCD or ERBD. Post-drainage complications occurred in total of 11 cases (11.2%), including 1 drainage failure (1.0%), 6 cholangitis (6.1%), 1 pancreatitis (1.0%) and 3 (3.0%) hemorrhage. Patients were classified into two groups based on their drainage time. One group comprised 38 patients whose drainage time was more than 2 weeks (long-term group); the other group had 60 patients whose drainage time was less than 2 weeks (short-term group). Compared to the short-term drainage group, the proportion of positive ascites culture was significantly higher in the long-term drainage group (P=0.022, *Table 4*). There were no significant differences between the long-term and short-term drainage groups in terms of demographic characteristics, operation conditions, pathological diagnoses, postoperative complications post-operative stay and treatment expenses (P>0.05 for all, *Table 4*).

To explore whether short-term drainage would lead to increased risk of postoperative infection, a subgroup analysis was conducted between short-term drainage group (n=60, *Table 5*) and no-drainage group (n=50, *Table 5*). Compared to the no-drainage group, patients in short-term group had higher levels of NRS2002 (P=0.028), serum TB (P<0.001), WBC (P=0.030) and a lower level of hemoglobin (P=0.015) before surgery. Besides, the total treatment expense was higher in the short-term group than the no drainage group (P=0.026). There were no statistically significant differences in demographic characteristics, operation conditions, pathological diagnoses, postoperative complications between the two groups (P>0.05 for all, *Table 5*).

Analysis of pathogens in bile and peritoneal fluid

Distribution of pathogens during the perioperative period is shown in *Table 6*. Overall, 98 patients underwent PBD, of which 70 (71.4%) had positive bile culture. The most frequent pathogens detected in bile were Klebsiella pneumoniae, hemolytic Streptococcus and Enterococcus faecalis. Postoperative peritoneal fluid culture was positive in 116 cases. The most commonly detected pathogens in peritoneal fluid were Klebsiella pneumoniae, Enterococcus faecalis and Staphylococcus epidermidis which appeared to have a high agreement with pathogens in preoperative bile cultures.

Discussion

In this retrospective study, we analyzed the impact of PBD

Table 4 Clinical characteristic of patients of long-term and short-term drainage group

Variables	Long-term (n=38)	Short-term (n=60)	P value
Age (years), median (IQR)	67.5 (58.8–72.3)	62.5 (56.3–67.0)	0.114
Male sex	20 (52.6%)	40 (66.7%)	0.165
BMI (kg/m^2), median (IQR)	22.5 (20.2–24.9)	22.3 (20.7–24.8)	0.948
NRS2002 score, median (IQR)	5.0 (4.0–5.3)	5.0 (4.0–5.0)	0.124
PG-SGA score, median (IQR)	10.0 (8.0–12.3)	10.0 (6.0–14.0)	0.564
TB (μmol/L), median (IQR)	219.2 (86.1–290.6)	192.7 (140.3–283.1)	0.519
Positive bile culture	31 (81.6%)	39 (65.0%)	0.097
Pathological			
PDAC	11 (28.9%)	15 (25.0%)	0.666
VAC	18 (47.4%)	33 (55.0%)	0.461
DCC	8 (21.1%)	9 (15.0%)	0.441
Others	1 (2.6%)	3 (5.0%)	0.957
Operating time (min), mean ± SD	381.6±87.2	354.6±98.0	0.209
Blood loss (mL), median (IQR)	550.0 (300.0–825.0)	400.0 (225.0–600.0)	0.188
Vessel resection	5 (13.1%)	4 (6.67%)	0.219
PD/PPPD	17 (44.7%)/19 (50.0%)	22 (36.7%)/40 (66.7%)	0.094
Major complications	9 (23.7%)	12 (20.0%)	0.665
CR-POPF	14 (36.8%)	24 (40.0%)	0.755
Biliary leakage	2 (5.3%)	0 (0.0%)	0.073
DGE	8 (21.1%)	18 (30.0%)	0.305
PPH	2 (5.3%)	7 (11.7%)	0.285
Chylous fistula	6 (15.8%)	12 (20.0%)	0.600
Wound infection	1 (2.6%)	3 (5.0%)	0.564
Intra-abdominal infection	21 (55.3%)	25 (41.7%)	0.189
Bacteremia	2 (5.3%)	7 (11.7%)	0.285
Pneumonia	1 (2.6%)	1 (1.7%)	0.742
Urinary tract infection	0 (0.0%)	1 (1.7%)	0.424
Positive ascites culture	35 (92.1%)	44 (73.3%)	0.022
Post-operative stay (days), median (IQR)	20.0 (14.8–30.8)	22.5 (17.0–33.5)	0.293
Expense (yuan), median (IQR)	120,274.0 (102,611.0–157,394.3)	134,611.0 (115,298.3–162,997.3)	0.115

IQR, interquartile range; BMI, body mass index; NRS, nutritional risk screening; PG-SGA, Patient-Generated Subjective Global Assessment; TB, total bilirubin; PDAC, pancreatic ductal adenocarcinoma; VAC, Vater's ampullary carcinoma; DCC, distal cholangiocarcinoma; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; CR-POPF, clinically relevant postoperative pancreatic fistula (Grade B/C); DGE, delayed gastric emptying; PPH, post-pancreatectomy hemorrhage.

Table 5 Clinical characteristic of patients of no-drainage and short-term drainage group

Variables	No-drainage (n=50)	Short-term (n=60)	P value
Age (years)	68.0 (55.8–73.0)	62.5 (56.3–67.0)	0.252
Male sex	37 (74.0%)	40 (66.7%)	0.403
BMI (kg/m^2)	23.0 (21.4–24.9)	22.3 (20.7–24.8)	0.326
NRS2002 score	4.0 (3.0–5.0)	5.0 (4.0–5.0)	0.028
PG-SGA score	8.0 (6.0–10.8)	10.0 (6.0–14.0)	0.079
TB (μmol/L)	104.6 (45.7–152.1)	192.7 (140.3–283.1)	<0.001
HB (g/L)	124.8±13.6	116.7±19.3	0.015
WBC (×10^9/L)	4.9 (4.4–6.0)	5.9 (4.6–7.4)	0.030
Pathological			
PDAC	13 (26.0%)	15 (25.0%)	0.905
VAC	22 (44.0%)	33 (55.0%)	0.251
DCC	8 (16.0%)	9 (15.0%)	0.885
Others	7 (14.0%)	3 (5.0%)	0.193
Operating time (min)	374.8±97.5	354.6±98.0	0.341
Blood loss (mL)	500 (300–600)	400 (225–600)	0.667
Vessel resection	4 (8.0%)	4 (6.7%)	0.789
Major complications	7 (14.0%)	12 (20.0%)	0.407
CR-POPF	19 (38.0%)	24 (40.0%)	0.831
Biliary leakage	1 (2.0%)	0 (0.0%)	0.271
DGE	19 (38.0%)	18 (30.5%)	0.410
PPH	5 (10.0%)	7 (11.7%)	0.780
Chylous fistula	5 (10.0%)	12 (20.0%)	0.149
Wound infection	1 (2.0%)	3 (5.0%)	0.403
Intra-abdominal infection	14 (28.0%)	25 (41.7%)	0.136
Bacteremia	3 (6.0%)	7 (11.7%)	0.303
Pneumonia	0 (0.0%)	1 (1.7%)	0.359
Urinary tract infection	0 (0.0%)	1 (1.7%)	0.359
Positive ascites culture	38 (76.0%)	44 (73.3%)	0.749
Post-operative stay (days)	20.5 (15.0–26.0)	22.5 (17.0–33.5)	0.326
Expense (yuan)	118,134.0 (102,893.3–155,219.3)	134,611.0 (115,298.3–162,997.3)	0.026

Data are shown as n (%), mean ± SD and median (IQR). BMI, body mass index; NRS, nutritional risk screening; PG-SGA, Patient-Generated Subjective Global Assessment; TB, total bilirubin; HB, hemoglobin; WBC, white blood cell; PDAC, pancreatic ductal adenocarcinoma; VAC, Vater's ampullary carcinoma; DCC, distal cholangiocarcinoma; CR-POPF, clinically relevant postoperative pancreatic fistula (Grade B/C); DGE, delayed gastric emptying; PPH, post-pancreatectomy hemorrhage; SD, standard deviation; IQR, interquartile range.

Table 6 Pathogens distribution of positive bile and ascites culture

Species	Preoperative bile positive patients	Postoperative ascites positive patients
Gram– bacteria		
K. pneumoniae	21	26
E. coli	4	13
E. cloacae	5	12
A. baumannii	3	5
P. aeruginosa	3	8
Gram+ bacteria		
Streptococcus	20	7
E. faecalis	7	25
S. epidermidis	2	18
E. faecium	4	16
S. aureus	2	6
S. haemolyticus	0	12
Fungus	2	10
Others	9	20

K. pneumoniae, Klebsiella pneumoniae; E. coli, Escherichia coli; E. cloacae, Enterobacter Cloacae; A. baumannii, Acinetobacter baumannii; P. aeruginosa, Pseudomonas aeruginosa; E. faecalis, Enterococcus faecalis; S. epidermidis, Staphylococcus epidermidis; E. faecium, Enterococcus faecium; S. aureus, staphylococcus aureus; S. haemolyticus, Staphylococcus haemolyticus.

on PAC patients with obstructive jaundice. We found that PBD did increase the incidence of postoperative intra-abdominal infection in obstructive jaundice patients undergoing PD, but had no significant effect on the incidence of other postoperative complications. In patients with serum TB ≤250 μmol/L and no cholangitis, PBD increased the incidence of postoperative intra-abdominal infection. Furthermore, our data suggested that drainage for more than 2 weeks increased the proportion of positive ascites culture while drainage for less than 2 weeks had no significant influence on postoperative complications. Through culturing patients' bile and ascites, we found the bacterial profiles of bile and ascites were highly consistent.

For patients with PAC, surgical resection is the only treatment of choice for prolonged survival and a chance of cure (30). About 50% to 80% of PAC patients have some degree of obstructive jaundice caused by biliary obstruction at the initial diagnosis. Therefore, PBD has been usually used in obstructive jaundice patients to relieve symptoms of pruritus and cholangitis, and to prevent postoperative complications arising from hyperbilirubinemia (31). Currently recognized PBD criteria for obstructive jaundice include combined acute cholangitis, severe malnutrition, coagulation dysfunction, renal insufficiency, before receiving neoadjuvant therapy, etc. (32,33). Because the severity of obstructive jaundice that mandates PBD has not been defined, the role of PBD on obstructive jaundice patients with resectable tumors is still under debate. Researches have reported that in patients with malignant biliary jaundice requiring surgery, PBD group had significantly less major adverse effects than direct surgery group with no increased mortality observed (34-36). Conversely, there were studies suggesting that PBD lead to an increased overall morbidity and increased the risk of complications including sepsis, wound infections and biliary stricture rate (17,37-39). In a case-matched control study, PBD results in a two-fold increase in post-pancreatectomy infectious complications (40). The systematic review of the value of PBD also could not provide evidence for a clinical benefit of using PBD in jaundiced patients with hilar cholangiocarcinoma planned for surgery (41). Hence, researchers have suggested that PBD should not be routinely performed in obstructive jaundice patients awaiting surgery (42-44). A recent study showed that PBD was not associated with an increase in 30-day mortality or major morbidity but increased superficial SSIs, so PBD should be limited to patients with clear indications (45). In accordance with previous studies, we retrospectively analyzed the effect of PBD on postoperative complications in obstructive jaundice patients undergoing PD in our institution. Overall, the incidence of postoperative abdominal infection in the drainage group was significantly higher than that in the no-drainage group, while other postoperative complications showed no significant differences. On the other hand, patients in the drainage group were combined with poorer nutritional status, higher proportion of cholangitis, higher serum bilirubin level and lower hemoglobin level which may affect postoperative complications. Therefore, a subgroup analysis is necessary for screening patients who really got a negative effect from PBD. The randomized controlled trial by van Der Gaag *et al.* compared PBD with surgery alone for patients with obstructive jaundice and a bilirubin level less than 250 μmol/L. They found that the rates of serious complications were significantly higher in the biliary-drainage group (18). The study also showed that PBD did not necessarily prolong the length of the hospital stay (18). Thus, we screened cases with TB ≤250 μmol/L and no cholangitis as a subgroup analysis based on existing literature. There were no significant differences in preoperative and intraoperative indicators between drainage and no-drainage group, while the incidence of postoperative abdominal infection was still significantly higher in the drainage group. Due to the preventive measure we took, there was no increase in the incidence of serious postoperative complications in this group of patients. In order to reduce the infection, we routinely sutured distal bile duct before dissecting the bile duct and temporarily blocked proximal bile duct with blocking forceps to minimize the bile entering the abdominal cavity. Moreover, we performed bile reinfusion combined with enteral nutrition support for patients with external bile drainage, which could avoid the translocation of intestinal flora caused by bile loss and improve the nutritional status of patients. As a result, increased POPF or hemorrhage reported in other researches was not observed in our study (46). As to patients with high serum bilirubin, the role of PBD remained controversial (47,48). Pamecha *et al.* found that in patients with severe jaundice (TB >256.5 μmol/L), there were no significant differences in operation time, blood transfusion volume, postoperative complications, and hospitalization time between the drainage and no-drainage groups (49). Arkadopoulos suggested that in severe jaundice patients, PBD increased the incidence of postoperative complications, especially infectious complications (19). However, a recent meta-analysis demonstrated that compared to no-PBD, PBD was associated with a greater risk of several kinds of infection and morbidities. However, its ability to reduce postoperative hepatic insufficiency could not be ignored. In patients with a high total serum bilirubin concentration, PBD tends to be a better choice (50). The results of another multicenter study showed that TB exceeding 300 μmol/L was a risk factor for severe complications and short-term survival after PD for pancreatic cancer, so PBD was recommended for better patient outcomes (51). In a retrospective study conducted by Shanghai Ruijin Hospital, the researchers reported that for those patients with serum TB level exceeding 250 μmol/L and undergoing PD, PBD could contribute to lower incidences of overall postoperative complication, grades B and C of PPH, and grades B and C of POPF (22). Due to the small number of severe jaundice cases in our study, further accumulation of such cases is needed to determine the value of PBD in the treatment of patients with severe jaundice. Taken together, our data suggested that in patients with preoperative TB ≤250 μmol/L, PBD increased the risk of postoperative abdominal infection, which was in agreement with previous studies (52-54). Besides, TB more than 250 μmol/L may serve as a reference index for PBD.

In regard to the optimal duration of PBD in patients with obstructive jaundice, the currently available evidence is inconclusive. Animal experiments showed that the function of liver could be restored after 4–6 weeks of drainage. In early studies, adequate drainage was usually recommended (55-57). The multi-center study by five medical centers in Europe presented that delaying surgery up to 1 month after biliary drainage may reduce major morbidity (58). In a randomized controlled trial for cancer of the pancreatic head, the researchers found the delay in surgery since PBD did not impair or benefit survival rate, but a longer time of drainage was significantly associated with lower mortality rate after surgery (59). Yang *et al.* have pointed out that a time interval between PBD and resection greater than 4 weeks did not have a negative impact on short-term surgical outcomes, indicating that postponing surgery may be necessary (57). In recent years, more evidences were inclined to a shortened drainage duration (60,61). The research by Son suggested that the R0 resection rate tended to be lower and the mean length of hospital stay was significantly longer in the long-term drainage group (62). Another study revealed that drainage for more than 2 weeks increased the incidence of postoperative complications, while drainage beyond 6 weeks was associated with poor long-term survival (63). For patients with malignant tumors, prolonged drainage may lead to tumor progression and missed surgical opportunities, affecting the long-term survival of patients. Therefore, PBD duration less than 2 weeks and early surgery may be more appropriate in severely jaundiced patients with periampullary cancer because it could improve both short- and long-term postoperative outcomes. Thus, we also analyzed the impact of PBD time on patient outcomes. In our study, the median duration of PBD was 13 days. The comparative analysis found that the rate of positive ascites culture in short-term group (<2 weeks) was lower than that in long-term group (>2 weeks) with no significant differences in other complications. Besides, no significant differences in postoperative complications were observed between no-drainage group and short-term drainage group, which confirmed the safety of short-term drainage. Thus, we recommended that for obstructive jaundice patients prepared for PD, direct surgery could be considered if preoperative TB was less than 250 μmol/L.

When PBD must be performed, the drainage duration ought to be controlled within 2 weeks if condition permits.

As for the method of PBD, currently there are two main types of biliary drainage: PTCD and EBD, including ENBD and ERBD. Several meta-analyses have reported that in patients with resectable perihilar cholangiocarcinoma, PTCD had a lower rate of procedure-related complications than EBD and was associated with lower rates of pancreatitis and cholangitis (64-66). Compared to PTCD, EBD could be performed through natural orifice and causes less trauma. Meanwhile, tumor brush biopsy could also be conducted which is helpful for preoperative diagnosis. Most importantly, studies have confirmed that PTCD could increase the incidence of tumor metastasis and shorten postoperative overall survival (67,68). Therefore, most patients in this research were treated with EBD according to the present international guidelines (69). Additionally, more attention has been paid to the value of bile bacterial culture in guiding the treatment of postoperative infectious complications (70). In our cohort, microbial growth occurred in almost 70% of bile samples with Gram-negative rods and Enterococcus being the most common pathogens. Bacterial culture in patients with postoperative abdominal infection displayed the roughly same bacteria as previously detected in bile samples, which was consistent with previous studies (69,71). For patients with biliary obstruction, preoperative bile culture would aid in providing appropriate antibiotic coverage so bile should be routinely collected for culture during drainage or surgery.

There are also some limitations of our study. First, it was a retrospective study from a single pancreatic center. Therefore, selection bias was hard to avoid and the quality of our study was not as good as that of a prospective multi-center study. Second, the complications of each PBD method were not analyzed in this study because most patients in our study were treated with EBD, so the results may not be applicable to those patients treated with PTCD. Third, perioperative antibiotic susceptibility was not analyzed in this study, so the guiding role of preoperative bile culture on postoperative antibiotic therapy still needs to be further affirmed. Finally, the sample size was relatively small, so the role of PBD in patients with high serum TB was not clearly investigated in this study. Hence, future prospective studies with larger sample sizes and more complete analysis are warranted to confirm our findings.

Conclusions

In this study, we proposed several improvement strategies for PBD before PD. Routine PBD is not recommended in PAC patients with obstructive jaundice. Direct surgery could be considered if preoperative TB was less than 250 μmol/L. TB more than 250 μmol/L may serve as a reference index for PBD. For patients with indications for PBD, the drainage duration should be controlled within 2 weeks. Bile bacteria may represent a major source of opportunistic pathogenic bacteria infection after PD, which could provide valuable clues for further exploring the pathogenic mechanism of pathogenic bacteria.

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Footnote

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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 process of our study adhered to the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics

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