Operative risk factors for clinically relevant-postoperative pancreatic fistula after pancreaticoduodenectomy: a prospective multicenter cohort study

Mohammed A. Omar[a], Alaa A. Redwan[b], Marwa N. Alansary[c], Ayman Kamal[d]

[a]General Surgery Department, South Valley University, Qena, Egypt, [b]General Surgery Department, Sohag University, Sohag, Egypt, [c]Anesthesia and Intensive Care Department, South Valley University, Qena, Egypt, [d]General Surgery Department, Helwan University, Helwan, Egypt

Correspondence to Mohammed Ahmed Omar, Hepatobiliary and Pancreatic Surgery Unit, General Surgery Department, Qena Faculty of Medicine, South Valley University, 83523, Qena, Egypt. Tel: (+002)0963228628; Mobile: (+002)01064184848; fax: +0963219887; e-mail: mohamed_ali@med.svu.edu.eg

Received: 25 July 2023
Revised: 12 August 2023
Accepted: 8 August 2023
Published: 7 December 2023

The Egyptian Journal of Surgery 2023, 42:848–858

Background
Pancreatic fistula remains the most dangerous complication after pancreatoduodenectomy (PD). This study aimed to identify the operative risk factors for clinically relevant-postoperative pancreatic fistula (CR-POPF) after PD.
Methods
This prospective multicenter cohort study investigated the association between CR-POPF and operative risk factors in 107 patients who underwent PD at three tertiary centers from August 2017 to July 2022.
Results
The incidence of CR-POPF was 26.2%. With univariate analysis, soft pancreatic texture, pancreatic duct diameter (≤3 mm), right-sided pancreatic transection, absorbable suture, pancreatico-enteric anastomosis invagination technique, non-stented pancreatic drainage, internal pancreatic drainage, long anastomotic time (>40 min), and R1 resection margin were risk factors for CR-POPF. Multivariate analysis identified four independents risk factors for CR-POPF: (1) soft pancreatic texture (OR 0.219; 95% CI 0.061–0.792; $P<0.021$), (2) small main pancreatic duct diameter (OR 0.280; 95% CI 0.086–0.910; $P<0.034$), (3) right-sided pancreatic transection (OR 0.168; 95% CI 0.032–0.881; $P<0.035$), and (4) non-stented pancreatic drainage (OR 3.771; 95% CI 1.147–12.401; $P<0.029$).
Conclusion
The incidence of CR-POPF after PD is reduced significantly by left-sided pancreatic transection and pancreatic drainage. Soft pancreatic texture and small main pancreatic duct diameter are independent risk factors for CR-POPF, and clinically postoperative prophylactic measures should be implemented as soon as possible.

Keywords:
clinically relevant pancreatic fistula, pancreaticoduodenectomy, risk factors

Egyptian J Surgery 42:848–858

1110-1121

Background

Pancreaticoduodenectomy (PD) is a common treatment for benign and malignant periampullary and pancreatic disorders [1,2]. PD is technically difficult and has up to 50% morbidity and 5% mortality [2,3]. Postoperative pancreatic fistula (POPF) is the most serious and life-threatening complication of PD, with total POPF ranging from 7–60% and clinically significant (CR) POPF from 7–42% [4,5]. CR-POPF causes abdominal abscesses, delayed stomach emptying, pseudoaneurysms, and bleeding, with a 40% mortality rate [2]. Also, it increases hospitalization, healthcare expenses, and reinterventions, lowering patient quality of life [5].

Despite improvements in surgical procedures and postoperative care, CR-POPF remains the most difficult and severe complication of PD [4], and it represents the main issue prohibiting surgeons from performing PD [2]. CR-POPF risk factors include patient-related factors (age, sex, obesity, preoperative bilirubin level, pancreatic texture, main pancreatic duct diameter (MPDD), and pathological type) and surgical procedure-related factors (type of PD, types of anastomoses, methods of pancreatic reconstruction, blood loss and transfusion, operative time, and surgeon's experiences) [2,6]. However, no single factor has been identified, but several factors have been identified across several studies. As the CR-POPF rate decreases, morbidity and mortality rates will decrease [5]. The best surgical procedure to reduce CR-POPF rates is still debated, but pancreaticojejunostomy (PJ) versus pancreaticogastrostomy (PG), end-to-side vs. end-to-end PJ, duct-to-mucosa vs. dunking anastomosis, and internal versus external stents are all options. This study identified operative risk factors for CR-POPF

post-PD to decrease fistula and ensure diligent follow-up for high-risk patients.

Methods

This study is a prospective multicenter cohort study. Ethical committee approval for the study was obtained. The study was registered in the ClinicalTrials.gov database. This work has been reported per the STROCSS guidelines [7]. Written informed consent was obtained from all participants.

Trial design and participants

This prospective multicenter cohort study included all consecutive patients (107 patients) treated with PD from August 2016 to July 2022 in three tertiary centers. The inclusion criteria were patients with resectable distal CBD carcinoma, periampullary carcinoma, duodenal carcinoma, and carcinoma of the head of the pancreas, American Society of Anesthesiologists (ASA) scores I & II, patients aged ≤70 years, and agreement to complete the study. Patients with benign disease, trauma, who receive neoadjuvant therapy, and double primary cancers were excluded.

Data collection included patient demographics, clinical presentations, and operative details.

Preoperative assessment

All patients were evaluated clinically, laboratory, and radiologically. A detailed medical history and complete examination of all cases were done. Laboratory tests included complete blood picture, random blood sugar, coagulation profile, renal function tests, liver function tests, serum amylase and lipase, serology markers, and tumor markers (CEA, CA 19-9). Radiological evaluations included abdominal ultrasound (US), computed tomography (CT), and/or magnetic resonance cholangiopancreatography (MRCP) scan for confirmation of the diagnosis, staging, assessment of the operability, and the underlying status of the pancreas. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) and stenting or percutaneous transhepatic drainage (PTD) were done according to the patient's condition.

Operative procedure

All operations were done by experienced skilled hepatobiliary surgeons (HBS) in the form of standard PD or pylorus-preserving PD (PPPD) with standard steps. The pancreatic parenchyma texture was assessed subjectively by the surgeon as either soft or firm. The pancreatic neck's parenchyma was transected by a sharp scalpel, electrocautery device, or ultrasonically activated device (Harmonic). The level of pancreatic neck transection may be right (at the right of the left side of the portal vein) or left-sided pancreatic transection (at the left of the left side of the portal vein) was done. The MPDD was measured with a small ruler. Segmental resection of the portal vein (PV) and/or superior mesenteric vein (SMV) was done when indicated. D2 lymphadenectomy was routinely carried out. The pancreatico-enteric anastomosis was done either in the form of PG or PJ with duct-to-mucosa or invagination anastomosis technique. The pancreatico-enteric anastomosis was done either with absorbable (polydioxanone – PDS II or Polyglactin 910 – Vicryl) or nonabsorbable suture (polypropylene – Prolene or Polyester – Dacron) in the form of continuous, interrupted, or combined techniques. The anastomosis was not covered with any grafts or sealants. Pancreatic drainage was done either internally with a 5-Fr, 6 cm long pancreatic stent (Wilson-Cook Medical Inc., Winston-Salem, NC) or externally with a Nelaton tube that was placed across the anastomosis and came out through the anterior abdominal wall. Different pancreatic transection and reconstruction techniques were chosen according to the surgeon's discretion for each case. Three drains were inserted intraabdominal (peripancreatic, subhepatic, and pelvic) away from vascular structures. The drains may be active (suction drain) or passive (Nelaton catheter or nasogastric tube). A magnifying surgical loupe (6.0×) was used in some cases.

Study design

Patients were divided into two groups according to the occurrence or absence of CR-POPF, and 20 potential intraoperative risk factors for CR-POPF were evaluated.

Postoperative assessment

The patients were followed up to detect CR-POPF. Oral fluid was started on the 3rd postoperative day (POD). All patients received 3rd generation cephalosporin, somatostatin, or octreotide for 7–10 days postoperatively. Amylase level was measured on the 3rd, 5th, and 7th POD from the peripancreatic drain fluid. All drains were removed when there was no discharge.

Outcomes

The primary outcome was CR-POPF. CR-POPF was defined according to the 2016 update of the International Study Group of Pancreatic Fistula (ISGPS) definition and grading [8]. In our hospitals, the threshold for POPF was an amylase level >300 IU/l. The resection margin was evaluated

postoperatively. The anesthetist reported estimated blood loss (EBL) and blood transfusion volume.

The following variables were evaluated as potential operative-related risk factors for the CR-POPF: type of PD (standard PD or PPPD), pancreatic parenchyma texture (firm or soft), method of pancreatic transection (scalpel, electrosurgical device or harmonic), level of pancreatic neck transection (right or left), MPDD, vessels resection, mass size, type of pancreatico-enteric anastomosis (PG or PJ), anastomotic techniques (duct-to-mucosa or invagination), suture material (absorbable or nonabsorbable), suture technique (continuous, interrupted or combined), pancreatic drainage, type of pancreatic drainage (external or internal), EBL, blood transfusion, type of intraabdominal drain (closed active or closed passive), anastomotic and operative time, use of surgical loupe, and resection margin (R0 or R1).

Statistical analysis

We used IBM SPSS statistics for Windows v. 26 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as counts and proportions, and quantitative variables were presented as either mean and standard deviation (SD) for normally distributed variables and median and inter-quartile range (IQR, Q1–Q3) for non-normally distributed variables. We used the χ^2 test, Student's t-test, and Mann-Whitney U test, where appropriate. We analyzed the significant operative risk factors in the univariate analysis by a multivariate logistic regression analysis to determine the independent risk factors correlated with CR-POPF reporting as odds ratios (OR) with their 95% confidence interval (CI). A P value ≤ 0.05 was considered statistically significant for all tests.

Results

Overall series

From 107 patients evaluated, 28 (26.2%) developed CR-POPF compared to 79 (73.8%) without CR-POPF.

Preoperative data

The patient's demographic data are shown in Table 1. There were no statistically significant differences between the two groups in age, Sex, body mass index, American Society of Anesthesiologists scores, tumor site, preoperative intervention, and laboratory investigations (Table 1).

Operative data

Operative parameters were compared for patients with and without CR-POPF (Table 2). The parameters analyzed, pancreatic textures, levels of neck transection, MPDD, anastomotic techniques, pancreatic drainage, types of pancreatic drainage, anastomotic time, use of surgical loupe, and resection margins, showed statistically significant differences between the two groups. In contrast, the types of PD, methods of pancreatic transection, vessels

Table 1 Patients demographic data

Variables	CR-POPF (*n*=28)	No CR-POPF (*n*=79)	*P value*
Age (years), mean±SD	55.7±4.6	54.5±3.5	0.15
Sex (Male), *n* (%)	16 (57.1)	46 (58.2)	0.92
BMI, mean±SD	26.4±2.7	26.9±2,8	0.44
ASA score, *n* (%)			0.99
ASA 1	5 (17.9)	14 (17.7)	
ASA II	23 (82.1)	65 (82.3)	
Tumor site, *n* (%)			0.72
Pancreatic tumors	16 (57.1)	38 (48.1)	
Bile duct tumors	8 (28.6)	24 (30.4)	
Ampullary tumors	4 (14.3)	15 (19)	
Duodenal tumors	0 (0)	2 (2.5)	
Preoperative intervention, *n* (%)			0.83
ERCP and stent	11 (39.3)	26 (32.9)	
PTD	3 (10.7)	9 (11.4)	
Laboratory investigations,			
TBIL, mg/dl (mean±SD)	16.2±5.6	16.2±5.3	0.99
Albumin, g/dl (mean±SD)	3.2±0.3	3.2±0.2	0.64
CA 19-9, U/ml (median, IQR)	502.5 (293.2–3251.7)	546 (345–4316)	0.77

ASA, American Society of Anesthesiologists; BMI, body mass index; CA 19 –9, carbohydrate antigen 19-9; CR-POPF, clinically relevant – postoperative pancreatic fistula; ERCP, endoscopic retrograde cholangiopancreatography; PTD, percutaneous transhepatic drainage; TBIL, total bilirubin.

resection, mass size, types of pancreatico-enteric anastomosis, suture materials, suture techniques, estimated blood loss and transfusion, types of abdominal drain, and operative time showed no statistically significant differences between the two groups (Table 2).

Univariate and multivariate analyses of risk factors for CR-POPF

Operative variables associated with CR-POPF at the $P \leq 0.05$ univariate level of statistical significance were included in a multivariate logistic regression analysis. With univariate analysis, soft pancreatic texture, right-sided pancreatic transection, small pancreatic duct

Table 2 Operative characteristics

Variables	CR-POPF (*n*=28)	No CR-POPF (*n*=79)	*P value*
Types of PD, *n* (%)			0.74
Standard PD	20 (71.4)	59 (74.7)	
PPPD	8 (28.6)	20 (25.3)	
Pancreatic textures, *n* (%)			0.0001
Firm	7 (25)	56 (70.9)	
Soft	21 (75)	23 (29.1)	
Methods of pancreatic transection, *n* (%)			0.7
Scalpel	11 (39.3)	29 (36.7)	
Electrocautery	9 (32.1)	32 (40.5)	
Harmonic	8 (28.6)	18 (22.8)	
Level of pancreatic transection, *n* (%)			0.001
Right-sided	19 (67.9)	25 (31.6)	
Left-sided	9 (32.1)	54 (68.4)	
MPDD (cm), mean (SD)	2.7±0.44	3.4±0.75	0.001
PV / SMV segmental resection, *n* (%)	1 (3.6)	3 (3.8)	0.96
Mass size (cm), mean (SD)	3.1±0.6	3.1±0.6	0.99
Types of pancreatico-enteric anastomosis, *n* (%)			0.16
PG	12 (42.9)	46 (58.2)	
PJ	16 (57.1)	33 (41.8)	
Anastomotic techniques, *n* (%)			0.007
Duct-to-mucosa	7 (25)	43 (54.4)	
Invagination	21 (75)	36 (45.6)	
Suture materials, *n* (%)			0.1
Nonabsorbable suture	17 (60.7)	34 (43)	
Absorbable suture	11 (39.3)	45 (57)	
Suture techniques, *n* (%)			0.81
Continuous	10 (35.8)	33 (41.8)	
Interrupted	9 (32.1)	25 (31.6)	
Combined	9 (32.1)	21 (26.6)	
Pancreatic drainage, *n* (%)			0.001
Yes	11 (39.3)	58 (73.4)	
No	17 (60.7)	21 (26.6)	
Types of pancreatic drainage, *n* (%)			0.041
External	4 (36.4)	31 (53.4)	
Internal	7 (63.6)	27 (46.6)	
Estimated blood loss (ml), mean (SD)	657.14±147.64	627.22±144.29	0.351
Blood transfusion (ml), mean (SD)	892.86±208.9	860.8±225.55	0.511
Types of abdominal drain, n (%)			0.74
Passive	18 (64.3)	48 (60.8)	
Active	10 (35.7)	31 (39.2)	
Anastomotic time (min), mean (SD)	45.64±8.64	38.48±7	0.001
Operative time (min), mean (SD)	503.57±31.76	500.89±28.47	0.678
Surgical loupes use, n (%)	9 (32.1)	45 (57)	0.02
Resection margin, n (%)			0.019
R0	16 (57.1)	63 (79.7)	
R1	12 (42.9)	16 (20.3)	

CR-POPF, clinically relevant – postoperative pancreatic fistula; MPDD, main pancreatic duct diameter; PD, pancreaticoduodenectomy; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; PPPD, pylorus-preserving pancreaticoduodenectomy; PV, portal vein; SMV, superior mesenteric vein. Bold numerals indicate a statistically significant difference.

diameter (≤3 mm), absorbable suture, pancreatico-enteric anastomosis invagination technique, non-pancreatic drainage, internal pancreatic drainage, long anastomotic time (>40 min), and R1 resection margin were risk factors for CR-POPF. With multivariate analysis, soft pancreatic texture, right-sided pancreatic transection, small pancreatic duct diameter (≤3 mm), and non-pancreatic drainage were the independent operative risk factors for the CR-POPF (Table 3).

Discussion

A CR-POPF is one of the commonest and most challenging complications post-PD that was subsequently associated with serious complications which increase hospital stay, morbidity, and mortality [2,3]. Recent studies showed a variable incidence of CR-POPF ranging from 5–40% [4,5]. This wide variation may be attributed to a different definition of CR-POPF [4,5]. In this study, we adopted the recommended standard definition of CR-POPF established by the ISGPF [8]. The incidence of POPF was 51.4%, and CR-POPF was 26.2%, consistent with results from high-volume centers [4,5,9].

Several risk factors associated with CR-POPF after PD have been reported and discussed in the literature [4,5]. These risk factors include patient-related risk factors such as male Sex, old age, obesity, preoperative jaundice, preoperative morbidity, neoadjuvant therapy, histopathological diagnosis, pancreatic texture, and MPDD [2,3,6], or procedure-related risk factors such as resection type, pancreatic stump reconstruction type, suture material, operative blood loss and transfusion volume, operative time, and surgeon and center experience [1,3,6,9]. This study focused on the operative-related risk factors associated with CR-POPF after PD.

Huang attributed the pancreatic leak post-PD to the lose pancreatico-enteric anastomosis and the delayed recovery of gastrointestinal function, causing retention of mixed digestive fluids, which can have a strong corrosive and increased tension effect on the pancreatico-enteric anastomosis [10]. Proper surgical technique, perioperative management, and awareness of risk factors are essential to decrease the incidence of CR-POPF [11]. Efforts to decrease the CR-POPF included modifications of pancreatico-enteric anastomosis (PG vs. PJ and duct-to-mucosa vs. invagination technique), anastomotic stenting, and

Table 3 Univariate and multivariate analysis for operative risk factors for clinically relevant – postoperative pancreatic fistula

	Univariable analysis		Multivariable analysis	
Independent variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Type of PD, standard PD vs. PPPD	0.847 (0.323–2.222)	0.736		
Pancreatic textures, firm vs. soft	7.304 (2.732–19.531)	0.0001	0.219 (0.061–0.792)	0.021
Methods of pancreatic resection				
Scalpel vs. Electrocautery	1.349 (0.489–3.718)	0.563		
Scalpel vs. Harmonic	0.853 (0.289–2.523)	0.774		
Levels of pancreatic transection, left vs. right-sided	4.560 (1.810–11.488)	0.001	0.168 (0.032–0.881)	0.035
MPDD,>3 mm vs.≤3 mm	4.645 (1.766–12.221)	0.001	0.280 (0.086–0.910)	0.034
PV/SMV segmental resection, yes vs. no	1.066 (0.106–10.688)	0.957		
Mass size, >2 cm vs.≤2 cm	1.245 (0.525–2.954)	0.619		
Type of anastomosis, PG vs. PJ	0.795 (0.335–1.877)	0.603		
Anastomotic technique, duct-to-mucosa vs. invagination	0.352 (0.139–0.894)	0.025	1.576 (0.401–6.188)	0.514
Suture material, nonabsorbable vs. absorbable	2.509 (1.027–6.128)	0.040	0.416 (0.124–1.396)	0.156
Suture technique				
Continuous vs. interrupted	0.842 (0.298–2.381)	0.745		
Continuous vs. combined	0.707 (0.247–2.028)	0.518		
Pancreatic drainage, yes vs. no	0.234 (0.094–0.581)	0.001	3.771 (1.147–12.401)	0.029
Type of pancreatic drainage, external vs. internal	8.333 (2.025–34.286)	0.001	0.1 (0.11–0.912)	0.061
Estimated Blood loss,≤500 ml vs.>500 ml	0.707 (0.253–1.975)	0.507		
Blood transfusion,≤500 ml vs.>500 ml	0.707 (0.253–1.975)	0.507		
Type of drain, active vs. passive	1.162 (0.475–2.846)	0.742		
Anastomotic time,≤40 vs.>40 min	0.336 (0.138–0.818)	0.014	3.063 (0.895–10.480)	0.075
Operative time,≤480 vs.>480 min	0.921 (0.342–2.479)	0.870		
Surgical loupes, yes vs. no	2.263 (0.928–5.518)	0.069		
Resection margin, R0 vs. R1	0.339 (0.134–0.857)	0.019	1.080 (0.206–5.678)	0.927

MPDD, main pancreatic duct diameter; PD, Pancreaticoduodenectomy; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; PPPD, pylorus-preserving pancreaticoduodenectomy; PV, portal vein; SMV, superior mesenteric vein. Bold numerals indicate a statistically significant difference.

drainage (internal vs. external), anastomotic site support by topical agents (Fibrin glue) or autologous graft (omentum or falciform ligament), and postoperative pharmacological therapy (somatostatin or its analog) to decrease the postoperative pancreatic secretions [4,5]. Patient stratification based on precise risk factors may result in the careful postoperative management of high-risk patients [1,6,11].

The standard PD is still performed today, although many surgeons recently recommend PPPD, which offers the benefit of achieving an excellent postoperative nutritional status [12]. Conversely, PPPD is associated with increased delayed gastric emptying and questionable cancer resection radicality [12]. There is still a debate regarding which procedure is the best. This study revealed no statistically significant difference between the standard PD and PPPD on CR-POPF rate (P=0.736), and this was comparable with many published studies [1,2,13].

The soft pancreas is the commonest recognized independent risk factor for CR- POPF [4,6,14–16]. This study confirmed this observation and proved the soft pancreatic parenchyma was an independent risk factor of CR-POPF (OR 0.219, 95% CI 0.061–0.792; P<0.021). On the contrary, in the univariate analysis, Ryu *et al.* [17] and Sugimoto *et al.* [11] revealed a soft pancreas as a risk factor for CR-POPF. At the same time, they failed to be approved as an independent risk factor in the multivariate analysis. Moreover, a meta-analysis by Vallance *et al.* [18] and a recent study by Qureshi *et al.* [19] revealed a soft pancreas was not a risk factor for a CR-POPF. There are several explanations for this association. First, the soft pancreas is more liable to intraoperative injury and ischemia. It is more likely that the sutures will break the pancreatico-enteric anastomosis, creating a pancreatic fistula contrary to the firm pancreatic parenchyma that firmly grips sutures [13,20]. Second, a soft pancreas is rarely associated with dilated main pancreatic ducts [20]. Third, it's believed that a soft pancreas has better exocrine activity, and the secreted pancreatic juice rich in proteolytic enzymes will cause POPF [13,20].

The method of pancreatic transection plays a significant role in the occurrence of CR-POPF [21]. Different methods for pancreatic transection were studied in the literature as conventional surgical division by sharp scalpel, diathermy, or energy-based sealing devices. Energy-based sealing devices such as harmonic scalpel and LigaSure have been used widely in the last 10 years [21]. It has the advantage of good hemostasis and sealing the small pancreatic duct branches at the pancreatic transection surface, decreasing the incidence of minor POPF. On the other hand, the main pancreatic duct orifice will be sealed and difficult to be identified. Also, coagulation necrosis may jeopardize the healing of pancreatico-enteric anastomosis, which could increase the incidence of CR-POPF [21]. The thermal injury of transection by electrocautery may result in acute pancreatitis, which could increase the incidence of CR-POPF [21]. Although surgical scalpel transection causes less tissue damage, it results in excessive bleeding [22]. There is currently no accepted method for proper pancreatic transections. Takao et al. [23] revealed no POPF after harmonic scalpel in pancreatic transection.

On the contrary, Takahashi *et al.* [24] showed a significantly increased risk of POPF with a harmonic scalpel, and they reported that ultrasonic pancreas transections were less effective than scalpel transections at lowering the incidence of CR-POPF. Moreover, it results in major morbidities and very high costs. This study revealed no statistically significant differences regarding the pancreatic parenchyma resection using a sharp scalpel, ultrasonically activated scalpel, and electrosurgical device (P=0.564, P=0.774), and this result was comparable with Okabayashi [13].

The cornerstone for proper anastomosis is good vascularization. Based on the anatomical concept of vascular watershed, the pancreatic neck is an intermediate zone between the head and body of the pancreas with poor vascularization based on the vascularity of the head and body of the pancreas [25]. Resection of the head of the pancreas may jeopardize the neck vascularity, affecting the healing of the pancreatico-enteric anastomosis, which in turn encourages the occurrence of CR-POPF. Few studies reported the correlation between pancreatic stump vascularization and the incidence of CR-POPF [14]. Strasberg *et al.* [26] reported a significant correlation between improper pancreatic stump vascularization and the occurrence of CR-POPF. Bardol *et al.* [14] and Jwa *et al.* [27] reported that standard pancreatic neck transection is an independent risk factor for CR-POPF, and extended pancreatic transection could prevent the occurrence of CR-POPF. Bardol *et al.* [14] advised shifting the level of transection >7 mm to the left side of the portal vein, especially in high-risk patients aiming to decrease the occurrence of CR-POPF. They explained their result based on the

concentric position of the MPD in the body and the eccentric position neck level [14,27]. This study revealed that right-sided pancreatic neck transection was an independent risk factor for CR-POPF (OR 0.168; 95% CI 0.032–0.881; $P<0.035$).

Main pancreatic duct diameter has been reported as an independent risk factor for CR-POPF. The most widely used cutoff value for the MPDD associated with CR-POPF was 3 mm [1,6]. Although, Sugimoto *et al.* [11] reported a cutoff value of 2 mm for MPDD was more accurate than that of 3 mm. MPDD may be measured preoperatively by CT scan or intraoperatively by ultrasound or a small ruler [11]. In our study, small MPDD (≤3 mm) was an independent risk factor of CR-POPF (OR 0.280, 95% CI 0.086–0.910; $P<0.034$). This finding was consistent with many previous studies [1,2,4,14–16]. On the contrary, a few studies [9,13,19] failed to show that a small MPDD is a risk factor for CR-POPF. There are several explanations for this association. First, small MPDD can hold fewer sutures making the anastomosis more challenging and narrower and increasing the likelihood of obstruction or disruption [4]. Second, dilated MPD is usually associated with the fibrotic texture of pancreatic diseases, which may explain the decreased incidence of CR-POPF post-PD [28].

Vascular resection may be indicated in some cases with vascular infiltration. Many recent studies and meta-analyses [11,15,16] reported that venous resection (PV/SMV segmental resection) and large tumor size (2 cm) were significant protective factors for CR-POPF. They explained this result based on vascular resection usually associated with a large tumor which usually necessitates a preoperative neoadjuvant therapy that results in blockage of the MPD and increased pancreatic stiffness. Also, vascular resection encourages the R0 radicality of the resection [15]. On the contrary, Shyr *et al.* [29] and Bardol *et al.* [14] reported that vascular resection and tumor size did not decrease the incidence of CR-POPF, and our results agreed with this results ($P=0.957$ and $P=0.619$, respectively).

Dealing with the pancreatic stump is the most important factor in reducing CR-POPF [2]. Several procedures have been used to decrease POPF, such as PJ (duct to mucosa, invagination technique, binding technique, isolated Roux loop) [30–33], PG [34], and pancreatic duct occlusion (ligation, use of biologic glues or sealants) [2,35]. PG or PJ are the two commonest techniques for pancreatic remnant reconstruction after PD. However, published studies reported conflicting results regarding which reconstructive organ is the best for anastomosis and associated with decreased POPF rate [36]. PG has the following potential benefits: (1) it is simple, easy, and has a low incidence of tension and ischemia due to the closed proximity of the pancreatic stump to the stomach, (2) good anastomotic healing due to rich gastric wall vascularity, (3) the gastric acidity protects the anastomosis by inhibiting the activation of pancreatic enzymes, (4) continuous pancreatic secretion aspiration via nasogastric tube also reduces pancreatic secretion load and shortens the time for autodigestion, and (5) easy management of leakage or hemorrhage by gastroscopy instead of reoperation [37,38]. However, it has some drawbacks: (1) it is associated with more postoperative bleeding due to the rich gastric blood supply [39], (2) it is associated with early pancreatic insufficiency as a result of inactivation of the pancreatic enzyme by the gastric acidity [39] or pancreatic duct obstruction by overgrowth of the gastric mucosa [40], (3) increased postoperative delayed gastric emptying [38]. Many studies revealed a lower incidence of CR-POPF for PG when compared with PJ [36,37,41,42]. Based on his explanation for the mechanism of pancreatic leak after PD, Huang *et al.* [10] proved no impact of pancreatico-enteric anastomosis techniques on the CR-POPF rates. Many RCTs and meta-analyses [43–47] supported this, which revealed no statistically significant difference in the CR-POPF rate between PG and PJ. In this study, pancreatic-enteric anastomosis was not a risk factor for CR-POPF ($P=0.603$).

Several pancreatico-enteric anastomotic techniques were assessed to prevent CR-POPF with variable results. A review of published literature reported that duct-to-mucosa anastomosis has been more widely performed than the invagination anastomosis technique [43,44] and is associated with long-term anastomotic patency [45]. Since it is technically challenging, duct-to-mucosa anastomosis was previously done for patients with firm pancreas and dilated MPD. In contrast, it has been recommended recently regardless of the pancreatic texture or the MPDD. Several studies have compared duct-to-mucosa and invagination techniques' correlation with CR-POPF with conflicting results [46]. Three RCTs [47–49] reported a statistically significant lower rate of CR-POPF with invagination PJ compared to duct-to-mucosa PJ. On the contrary, three RCTs [46,50,51] and 4 meta-analyses [52–55] reported no statistically significant difference in CR-POPF rate between both techniques. In this study, we reported a statistically significant lower rate of CR-POPF with invagination

techniques (OR 0.352 95% CI 0.139–0.894, $P<0.025$) but failed to confirm it as an independent risk factor in the multivariate analysis (OR 1.576 95% CI 0.401–6.188, $P=0.514$).

The patient, the tissue, and the suture characteristics usually determine the choice of suture material. Various types of suture material have various mechanical characteristics and tissue reactions. The ideal suture should have good knot security, high tensile strength, ease of handling, minimal tissue reaction, and resist infection. Monofilament sutures cause less tissue trauma and resist infection more than braided sutures. Multifilament sutures are characterized by easy handling and frequently offer tighter, more secure knots [56]. Sutures used for pancreatico-enteric anastomosis are often in direct contact with bile and pancreatic juice enzymes. Few studies extensively discussed the effect of these highly digestive fluids on surgical sutures materials [57]. Theoretically, Suture material can affect the frequency and the severity of POPF [9]. CR-POPF necessitates several weeks for optimal healing after numerous surgical interventions [58].

In comparison to nonabsorbable sutures, all absorbable sutures retain only 25% of their tensile strength after 6 weeks [56], so we can assume that nonabsorbable suture-made pancreatico-enteric anastomosis can resist dehiscence and reduce the frequency and severity of CR-POPF after PD [9]. Andrianello *et al.* [9] revealed no significant difference in CR-POPF rate between PJ performed with nonabsorbable and absorbable suture, but only grade A and B and no grade C POPF occurred in the nonabsorbable suture PJ group. Our study revealed that absorbable sutures were a risk factor for CR-POPF (OR 2.509, 95% CI 1.027–6.128, $P=0.04$), but we failed to confirm this result in the multivariate analysis (OR 0.416, 95% CI 00.124–1.396, $P=0.156$).

Chen *et al.* [59] and Han *et al.* [60] reported that continuous anastomosis has a lower incidence of pancreatic injury, anastomotic stenosis, and CR-POPF. On the contrary, Burch *et al.* [61] showed no significant difference in CR-POPF rate between single-layer continuous and two-layer interrupted anastomosis. We found no statistically significant difference in CR-POPF rates between continuous, interrupted, and combined suture anastomosis ($P=0.745$ and $P=0.518$, respectively).

The corroding effect of pancreatic juice on the anastomotic site is one of the most important risk factors for CR-POPF [62]. Huang [10] reported that proper dealing with pancreatic juice can significantly prevent CR-POPF. He advised pancreatic duct stenting after PD as the stent will precisely identify the MPD to avoid improper suturing. Additionally, it supports anastomosis by lowering the pressure in the MPD and enhancing pancreatic stump drainage [1,10]. However, there is controversy regarding the correlation between pancreatic duct drainage and its methods and the occurrence of CR-POPF after PD [1]. Many previous studies and meta-analyses [63–65] revealed a statistically significant reduction in CR-POPF rate after pancreatic stenting. On the contrary, many recent studies and meta-analyses [19,66–68] revealed no statistically significant difference in CR-POPF rate between the stent and non-stent groups. In this study, non-stenting pancreatic-enteric anastomosis was an independent risk factor for CR-POPF (OR 3.771 95% CI 1.147–12.401, $P<0.029$).

Theoretically, external pancreatic drainage has the following potential benefits over internal drainage: (1) prevents reverse flow back of pancreatic juice to the anastomosis, which might be occurred by internal duct drainage, (2) significantly reduces the high anastomotic tension, enhances blood flow, and guards against anastomotic necrosis, (3) preventing pancreatic juice activation by enterokinase in the intestine, which lowers the risk of disrupting the anastomosis, (4) optimal evaluation of the daily variations in pancreatic juice quantities and characteristics as an early predictor for POPF, and (5) avoid the risk of spontaneous stent migration and retention in the intestine or the pancreas with subsequent complications and the required interventions for its removal [10]. On the contrary, external pancreatic drainage has some drawbacks: (1) a security issue or the risk of its associated discomfort and long-term effects with the placement of a stent (duct dilatation and endocrine dysfunction), (2) pancreatitis or obstruction of the pancreatic duct may develop as a result of mechanical injury to the anastomotic site during the removal of the pancreatic drainage stent, and (3) water-electrolyte imbalance, malnutrition, and internal environment instability as a result of excessive pancreatic juice loss [69]. The optimal technique to reduce CR-POPF between the external and internal pancreatic drainage remains controversial [62,69]. Many studies [1,66,70] revealed that the external stent could statistically significantly reduce the CR-POPF rate compared with the internal stent. On the contrary, many studies [69,71,72] showed no statistically significant difference between the two

techniques in reducing the incidence of CR-POPF. Our study reported internal drainage as a risk factor for CR-POPF (OR 8.333, 95% CI 2.025–34.286, $P<0.001$), but we failed to obtain this result in the multivariate analysis (OR 0.1, 95% CI 0.11–0.912, $P<0.061$).

Pancreaticoduodenectomy may be associated with massive bleeding during the pancreas's dissection, mobilization, or transection [73]. The EBL is often imprecise and unreliable during surgery [74]. Niu *et al.* [4] attributed the inaccurate EBL data to variable incorrect measurement methods, and they reported that the EBL must be measured after deducting the weight of the saline solution used for lavage from the weight of the sponges. Few papers reported intraoperative blood loss as a risk factor for CR-POPF. Pratt *et al.* [75]. and Cheng *et al.* [76] reported that intraoperative blood loss (>1000 ml) was an independent risk factor for CR-POPF. Lin *et al.* [77] and Yeo *et al.* [78] reported that blood transfusion was a risk factor for POPF. In this study, EBL and blood transfusion were not statistically significant risk factors associated with CR-POPF. This finding was consistent with many previously published studies [1,2,4,14,16].

The effect of intraabdominal drains and their different types on the incidence of CR-POPF after PD remains controversial [79]. In our study, we placed surgical intraabdominal drains for all patients. Most centers insert a prophylactic intraabdominal drain after PD [6]. The effect of the type of intraabdominal drain was discussed briefly in the literature [6]. Closed drainage is the commonest, either in active or passive form. Unfortunately, Active drainage may be associated with negative pressure on the fresh anastomosis, and passive drainage may be associated with improper drainage [80]. Kone *et al.* [80] reported no statistically significant difference between active and passive closed drainage in the incidence of CR-POPF. Our study demonstrated no statistically significant difference in rates of CR-POPF between the active and passive closed intraabdominal drain ($P=0.742$).

Among the risk factors, a long operative time was demonstrated as a statistically significant risk factor for CR-POPF [63,77] and an independent risk factor for CR-POPF by De Castro *et al.* [81]. However, three other studies failed to report it as a risk factor [2,13,15]. In our study, operative time was not a statistically significant risk factor for CR-POPF ($P=0.870$). Our study revealed a long anastomotic time (>40 min) as a risk factor for CR-POPF (OR 0.336 95% CI 0.138–0.818, $P<0.014$). However, it failed to nominate it as an independent risk factor in the multivariate analysis (OR 3.063 95% CI 0.895–10.480, $P<0.075$**)**.

Theoretically, better vision will enable more accurate surgical techniques, reducing the incidence of CR-POPF [82]. Wada *et al.* reported a significant reduction of CR-POPF after a surgical microscope. In our study, there was no difference in the incidence of CR-POPF between surgical loupe magnification and ordinary vision ($P=0.069$). Bardol *et al.* [14] reported that the resection margin does not affect the incidence of CR-POPF. In our study, R1 resection was a risk factor for CR-POPF (OR 0.339 95% CI 0.134–0.857, $P<0.019$). However, it failed to nominate it as an independent risk factor in the multivariate analysis (OR 1.080 95% CI 0.206–5.678, $P<0.927$).

Strengths and limitations of the study

This study has many strengths. First, the data collected was prospective. Second, it was a multicenter study. Third, it included a relatively large sample size. On the other side, there are some limitations of this study. First, the pancreatic texture was assessed subjectively at the discretion of the operating surgeon. Second, some decisions, such as the type of resection, the type of anastomosis, ...etc. was done based on surgeon preference.

Conclusion

In conclusion, Multivariate analysis comparing patients with and without CR-POPF identified four independent risk factors for the development of CR-POPF: (1) soft pancreatic texture, (2) small MPDD (≤3 mm), (3) right-sided pancreatic transection, and (4) non-stented pancreatic anastomosis. These findings could assist in the early prediction of CR-POPF after PD and help in optimal management. Also, it supports the use of pancreatic drainage and left-sided pancreatic transection as a factor in reducing fistula formation rates.

Acknowledgements

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Liu QY, Zhang WZ, Xia HT, Leng JJ, Wan T, Liang B, *et al.* Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy. World J Gastroenterol 2014; 20:17491–17497.

2 Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005; 11:2456–2461.

3 Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg 2015; 220:530–536.

4 Niu C, Chen Q, Liu S, Zhang W, Jiang P, Liu Y. Clinical validation of the risk scoring systems of postoperative pancreatic fistula after laparoscopic pancreatoduodenectomy in Chinese cohorts: A single-center retrospective study. Surgery 2022; 171:1051–1057.

5 Hedges EA, Khan TM, Babic B, Nilubol N. Predictors of postoperative pancreatic fistula formation in pancreatic neuroendocrine tumors: A national surgical quality improvement program analysis. Am J Surg 2022; 224:1256–1261.

6 ElNakeeb A, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, *et al.* Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience) World J Surg 2013; 37:1405–1418.

7 Mathew G, Agha R, Group S. STROCSS 2021: Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021; 96:106165.

8 Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, *et al.* The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017; 161:584–591.

9 Andrianello S, Pea A, Pulvirenti A, Allegrini V, Marchegiani G, Malleo G, *et al.* Pancreaticojejunostomy after pancreaticoduodenectomy: Suture material and incidence of postoperative pancreatic fistula. Pancreatology 2016; 16:138–141.

10 Huang JJIJoS. A commentary on' Does pancreatic duct stent placement lead to decreased postoperative pancreatic fistula rates after pancreaticoduodenectomy? A meta-analysis'. Int J Surg 2022; 103:106707. 2022: 106930-

11 Sugimoto M, Takahashi S, Gotohda N, Kato Y, Kinoshita T, Shibasaki H, *et al.* Schematic pancreatic configuration: a risk assessment for postoperative pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg 2013; 17:1744–1751.

12 Hackert T, Hinz U, Pausch T, Fesenbeck I, Strobel O, Schneider L, *et al.* Postoperative pancreatic fistula: We need to redefine grades B and C. Surgery 2016; 159:872–877.

13 Okabayashi T, Kobayashi M, Nishimori I, Sugimoto T, Onishi S, Hanazaki K. Risk factors, predictors and prevention of pancreatic fistula formation after pancreatoduodenectomy. Journal of hepato-biliary-pancreatic surgery 2007; 14:557–563.

14 Bardol T, Delicque J, Hermida M, Herrero A, Guiu B, Fabre JM, *et al.* Neck transection level and postoperative pancreatic fistula after pancreaticoduodenectomy: A retrospective cohort study of 195 patients. Int J Surg 2020; 82:43–50.

15 Kielbowski K, Bakinowska E, Ucinski R. Preoperative and intraoperative risk factors of postoperative pancreatic fistula after pancreaticoduodenectomy – systematic review and meta-analysis. Pol Przegl Chir 2021; 93:1–10.

16 Zhang B, Yuan Q, Li S, Xu Z, Chen X, Li L, *et al.* Risk factors of clinically relevant postoperative pancreatic fistula after pancreaticoduodenectomy: A systematic review and meta-analysis. Medicine 2022; 101:e29757.

17 Ryu Y, Shin SH, Park DJ, Kim N, Heo JS, Choi DW, *et al.* Validation of original and alternative fistula risk scores in postoperative pancreatic fistula. J Hepatobiliary Pancreat Sci 2019; 26:354–359.

18 Vallance AE, Young AL, Macutkiewicz C, Roberts KJ, Smith AM. Calculating the risk of a pancreatic fistula after a pancreaticoduodenectomy: a systematic review. HPB 2015; 17:1040–1048.

19 Qureshi S, Ghazanfar S, Quraishy MS, Rana R. Stented Pancreatico-duodenectomy: Does it lead to decreased pancreatic fistula rates? A prospective randomized study. J Pak Med Assoc 2018; 68:348–352.

20 Lee SE, Jang JY, Lim CS, Kang MJ, Kim SH, Kim MA, *et al.* Measurement of pancreatic fat by magnetic resonance imaging: predicting the occurrence of pancreatic fistula after pancreatoduodenectomy. Ann Surg 2010; 251:932–936.

21 Wu CH, Chen CH, Ho TW, Shih MC, Wu JM, Kuo TC, *et al.* Pancreatic neck transection using a harmonic scalpel increases risk of biochemical leak but not postoperative pancreatic fistula after pancreaticoduodenectomy. HPB (Oxford) 2021; 23:301–308.

22 Lamsa T, Jin HT, Nordback PH, Sand J, Luukkaala T, Nordback I . Pancreatic injury response is different depending on the method of resecting the parenchyma. J Surg Res 2009; 154:203–211.

23 Takao S, Shinchi H, Maemura K, Aikou T. Ultrasonically activated scalpel is an effective tool for cutting the pancreas in biliary-pancreatic surgery: experimental and clinical studies. J Hepatobiliary Pancreat Surg 2000; 7:58–62.

24 Takahashi S, Gotohda N, Kato Y, Konishi M. Measure of pancreas transection and postoperative pancreatic fistula. J Surg Res 2016; 202:276–283.

25 Skandalakis LJ, Rowe JS Jr, Gray SW, Skandalakis JE. Surgical embryology and anatomy of the pancreas. Surg Clin North Am 1993; 73:661–697.

26 Strasberg SM, Drebin JA, Mokadam NA, Green DW, Jones KL, Ehlers JP, *et al.* Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002; 194:746–758. discussion 59-60

27 Jwa EK, Hwang S. Extended pancreatic transection for secure pancreatic reconstruction during pancreaticoduodenectomy. Ann Hepatobiliary Pancreat Surg 2017; 21:138–145.

28 Yoon JH, Lee JM, Lee KB, Kim SW, Kang MJ, Jang JY, *et al.* Pancreatic steatosis and fibrosis: quantitative assessment with preoperative multiparametric MR imaging. Radiology 2016; 279:140–150.

29 Shyr BU, Chen SC, Shyr YM, Wang SE. Surgical, survival, and oncological outcomes after vascular resection in robotic and open pancreaticoduodenectomy. Surg Endosc 2020; 34:377–383.

30 Chen XP, Huang ZY, Lau JW, Zhang BX, Zhang ZW, Chen YF, *et al.* Chen's U-suture technique for end-to-end invaginated pancreaticojejunostomy following pancreaticoduodenectomy. Ann Surg Oncol 2014; 21:4336–4341.

31 Peng SY, Wang JW, Hong DF, Liu YB, Wang YF. Binding pancreaticoenteric anastomosis: from binding pancreaticojejunostomy to binding pancreaticogastrostomy. Updates Surg 2011; 63:69–74.

32 Fujii T, Sugimoto H, Yamada S, Kanda M, Suenaga M, Takami H, *et al.* Modified Blumgart anastomosis for pancreaticojejunostomy: technical improvement in matched historical control study. J Gastrointest Surg 2014; 18:1108–1115.

33 Malleo G, Bassi C. Pancreas: Reconstruction methods after pancreaticoduodenectomy. Nat Rev Gastroenterol Hepatol. 2013; 10:445–446.

34 Zhang X, Ma L, Gao X, Bao H, Liu P, Aziz A, *et al.* Pancreaticogastrostomy versus pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. Surg Today 2015; 45:585–594.

35 Martin I, Au K. Does fibrin glue sealant decrease the rate of anastomotic leak after a pancreaticoduodenectomy? Results of a prospective randomized trial. HPB 2013; 15:561–566.

36 Ibrahim R, Abounozha S, Nawara H, Alawad A, In Whipple's procedure, which anastomotic technique has lower leak rate; Pancreaticogastostomy or Pancreatojejunostomy? Ann Med Surg 2021; 61:158–160.

37 Topal B, Fieuws S, Aerts R, Weerts J, Feryn T, Roeyen G, *et al.* Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. Lancet Oncol 2013; 14:655–662.

38 Lei P, Fang J, Huang Y, Zheng Z, Wei B, Wei H. Pancreaticogastrostomy or pancreaticojejunostomy? Methods of digestive continuity reconstruction after pancreaticodudenectomy: a meta-analysis of randomized controlled trials. Int J Surg 2014; 12:1444–1449.

39 Hallet J, Zih FS, Deobald RG, Scheer AS, Law CH, Coburn NG, *et al.* The impact of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction on pancreatic fistula after pancreaticoduodenectomy: meta-analysis of randomized controlled trials. HPB 2015; 17:113–122.

40 Fang WL, Su CH, Shyr YM, Chen TH, Lee RC, Tai LC, *et al.* Functional and morphological changes in pancreatic remnant after pancreaticoduodenectomy. Pancreas 2007; 35:361–365.

41 Qin H, Luo L, Zhu Z, Huang J. Pancreaticogastrostomy has advantages over pancreaticojejunostomy on pancreatic fistula after pancreaticoduodenectomy. A meta-analysis of randomized controlled trials Int J Surg 2016; 36:18–24.

42 Guerrini GP, Soliani P, D'Amico G, Di Benedetto F, Negri M, Piccoli M *et al.* Pancreaticojejunostomy Versus Pancreaticogastrostomy After Pancreaticoduodenectomy: An Up-to-date Meta-Analysis. J Invest Surg 2016; 29:175–184.

43 Haane C, Mardin WA, Schmitz B, Dhayat S, Hummel R, Senninger N, *et al.* Pancreatoduodenectomy-current status of surgical and perioperative techniques in Germany. Langenbecks Arch Surg 2013; 398:1097–1105.

44 Zenoni SA, Arnoletti JP, de la Fuente SG. Recent developments in surgery: minimally invasive approaches for patients requiring pancreaticoduodenectomy. JAMA Surg 2013; 148:1154–1157.

45 Popiela T, Kedra B, Sierzega M, Gurda A. Risk factors of pancreatic fistula following pancreaticoduodenectomy for periampullary cancer. Hepatogastroenterology 2004; 51:1484–1488.

46 Berger AC, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, *et al.* Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg 2009; 208:738–747. discussion 47-9

47 Senda Y, Shimizu Y, Natsume S, Ito S, Komori K, Abe T, *et al.* Randomized clinical trial of duct-to-mucosa versus invagination pancreaticojejunostomy after pancreatoduodenectomy. Br J Surg 2018; 105:48–57.

48 Bai X, Zhang Q, Gao S, Lou J, Li G, Zhang Y, *et al.* Duct-to-Mucosa vs Invagination for Pancreaticojejunostomy after Pancreaticoduodenectomy: A Prospective, Randomized Controlled Trial from a Single Surgeon. J Am Coll Surg 2016; 222:10–18.

49 Xu J, Zhang B, Shi S, Qin Y, Ji S, Xu W, *et al.* Papillary-like main pancreatic duct invaginated pancreaticojejunostomy versus duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy: A prospective randomized trial. Surgery 2015; 158:1211–1218.

50 Singh AN, Pal S, Mangla V, Kilambi R, George J, Dash NR, *et al.* Pancreaticojejunostomy: Does the technique matter? A randomized trial. J Surg Oncol 2018; 117:389–396.

51 El Nakeeb A, El Hemaly M, Askr W, Abd Ellatif M, Hamed H, Elghawalby A, *et al.* Comparative study between duct to mucosa and invagination pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized study. Int J Surg 2015; 16(Pt A):1–6.

52 Lyu Y, Li T, Wang B, Cheng Y, Zhao S. Selection of pancreaticojejunostomy technique after pancreaticoduodenectomy: duct-to-mucosa anastomosis is not better than invagination anastomosis: A meta-analysis. Medicine 2018; 97:e12621.

53 Kilambi R, Singh AN. Duct-to-mucosa versus dunking techniques of pancreaticojejunostomy after pancreaticoduodenectomy: Do we need more trials? A systematic review and meta-analysis with trial sequential analysis. J Surg Oncol 2018; 117:928–939.

54 Zhang S, Lan Z, Zhang J, Chen Y, Xu Q, Jiang Q, *et al.* Duct-to-mucosa versus invagination pancreaticojejunostomy after pancreaticoduodenectomy: a meta-analysis. Oncotarget 2017; 8:46449–46460.

55 Sun X, Zhang Q, Zhang J, Lou Y, Fu Q, Zhang X, *et al.* Meta-analysis of invagination and duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy: An update. Int J Surg 2016; 36(Pt A): 240–247.

56 Greenwald D, Shumway S, Albear P, Gottlieb L. Mechanical comparison of 10 suture materials before and after in vivo incubation. J Surg Res 1994; 56:372–377.

57 Muftuoglu MA, Ozkan E, Saglam A. Effect of human pancreatic juice and bile on the tensile strength of suture materials. Am J Surg 2004; 188:200–203.

58 Malleo G, Pulvirenti A, Marchegiani G, Butturini G, Salvia R, Bassi C. Diagnosis and management of postoperative pancreatic fistula. Langenbecks Arch Surg 2014; 399:801–810.

59 Chen Y, Ke N, Tan C, Zhang H, Wang X, Mai G, *et al.* Continuous versus interrupted suture techniques of pancreaticojejunostomy after pancreaticoduodenectomy. J Surg Res 2015; 193:590–597.

60 Han HJ, Choi SB, Lee JS, Kim WB, Song TJ, Suh SO, *et al.* Reliability of continuous suture of pancreaticojejunostomy after pancreaticoduodenectomy. Hepatogastroenterology 2011; 58:2132–2139.

61 Burch JM, Franciose RJ, Moore EE, Biffl WL, Offner PJ. Single-layer continuous versus two-layer interrupted intestinal anastomosis: a prospective randomized trial. Ann Surg 2000; 231:832–837.

62 Xiang Y, Wu J, Lin C, Yang Y, Zhang D, Xie Y, *et al.* Pancreatic reconstruction techniques after pancreaticoduodenectomy: a review of the literature. Expert Rev Gastroenterol Hepatol 2019; 13:797–806.

63 Duffas JP, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, *et al.* A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. Am J Surg 2005; 189:720–729.

64 Dong Z, Xu J, Wang Z, Petrov MS. Stents for the prevention of pancreatic fistula following pancreaticoduodenectomy. Cochrane Database Syst Rev 2016; 2016:CD008914.

65 Xiong JJ, Altaf K, Mukherjee R, Huang W, Hu WM, Li A, *et al.* Systematic review and meta-analysis of outcomes after intraoperative pancreatic duct stent placement during pancreaticoduodenectomy. Br J Surg 2012; 99:1050–1061.

66 Guo C, Xie B, Guo DJIJoS. Does pancreatic duct stent placement lead to decreased postoperative pancreatic fistula rates after pancreaticoduodenectomy? A meta-analysis. 2022: 106707.

67 Singh K, Kaman L, Tandup C, Raypattanaik N, Dahiya D, Behera A. Internal stenting across the pancreaticojejunostomy anastomosis and main pancreatic duct after pancreaticoduodenectomy. Pol Przegl Chir 2021; 93:1–5.

68 Cai H, Lu F, Zhang M, Cai Y, Wang X, Li Y, *et al.* Pancreaticojejunostomy without pancreatic duct stent after laparoscopic pancreatoduodenectomy: preliminary outcomes from a prospective randomized controlled trial. Surg Endosc 2022; 36:3629–3636.

69 Zhang GQ, Li XH, Ye XJ, Chen HB, Fu NT, Wu AT, *et al.* Internal Versus External Drainage With a Pancreatic Duct Stent For Pancreaticojejunostomy During Pancreaticoduodenectomy for Patients at High Risk for Pancreatic Fistula: A Comparative Study. J Surg Res 2018; 232:247–256.

70 Wang S, Wang X, Li L, Dai H, Han J. Association of preoperative obstructive jaundice with postoperative infectious complications following pancreaticoduodenectomy. Hepatogastroenterology 2013; 60:1274–1279.

71 Zhao Y, Zhang J, Lan Z, Jiang Q, Zhang S, Chu Y, *et al.* Are internal or external pancreatic duct stents the preferred choice for patients undergoing Pancreaticoduodenectomy? A meta-analysis. Biomed Res Int 2017; 2017:1367238.

72 Chen Y, Zhu X, Huang J, Zhu Y. End-to-side penetrating-suture Pancreaticojejunostomy: A Novel Anastomosis Technique. J Am Coll Surg 2015; 221: e81–e 86.

73 Rosso E, Bachellier P, Oussoultzoglou E, Scurtu R, Meyer N, Nakano H, *et al.* Toward zero pancreatic fistula after pancreaticoduodenectomy with pancreaticogastrostomy. Am J Surg 2006; 191:726–732. discussion 33-4

74 Rothermel LD, Lipman JM. Estimation of blood loss is inaccurate and unreliable. Surgery 2016; 160:946–953.

75 Pratt WB, Callery MP, Vollmer CM Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. World J Surg 2008; 32:419–428.

76 Cheng Q, Zhang B, Zhang Y, Jiang X, Zhang B, Yi B, *et al.* Predictive factors for complications after pancreaticoduodenectomy. J Surg Res 2007; 139:22–29.

77 Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 2004; 8:951–959.

78 Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, *et al.* A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995; 222:580–588. discussion 8-92

79 Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, *et al.* Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 2010; 252:207–214.

80 Kone LB, Maker VK, Banulescu M, Maker AV. Should Drains Suck? A Propensity Score Analysis of Closed-Suction Versus Closed-Gravity Drainage After Pancreatectomy. J Gastrointest Surg 2021; 25:1224–1232.

81 de Castro SM, Kuhlmann KF, Busch OR, van Delden OM, Lameris JS, van Gulik TM, *et al.* Incidence and management of biliary leakage after hepaticojejunostomy. J Gastrointest Surg 2005; 9:1163–1171. discussion 71-3

82 Wada K, Traverso LW. Pancreatic anastomotic leak after the Whipple procedure is reduced using the surgical microscope. Surgery 2006; 139:735–742.