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ORIGINAL ARTICLE

Clinical Practice Study

Risk factors for pancreatic fistula following pancreaticoduodenectomy: A retrospective study in a Thai tertiary center

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Abstract

AIM

To analyze the risk factors of postoperative pancreatic fistula following pancreaticoduodenectomy in a Thai tertiary care center.

METHODS

We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital from January 2001 to December 2016. Pancreatic fistula were classified into three categories according to a definition made by an International Study Group on Pancreatic Fistula. The risk factors for pancreatic fistula were analyzed by univariate analysis and multivariate logistic regression analysis.

RESULTS
Pancreatic fistula were detected in 88/179 patients (49%) who underwent pancreaticoduodenectomy. Fifty-eight pancreatic fistula (65.9%) were grade A, 22 cases (25.0%) were grade B and eight cases (9.1%) were grade C. Clinically relevant pancreatic fistula were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179 patients). Multivariate logistic regression analysis revealed that soft pancreatic texture (odds ratio = 3.598, 95%CI: 1.77-7.32) was the most significant risk factor for pancreatic fistula. A preoperative serum bilirubin level of > 3 mg/dL was the most significant risk factor for clinically relevant pancreatic fistula according to univariate and multivariate analysis.

CONCLUSION
Soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Key words: Risk factors; Pancreatic fistula; Pancreas; Pancreatectomy; Pancreaticoduodenectomy

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Core tip: Pancreaticoduodenectomy is a high morbidity operation. The most common perioperative complication is postoperative pancreatic fistula. We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital. We found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

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INTRODUCTION

Pancreaticoduodenectomy (PD) is the standard treatment for resectable periampullary and pancreatic tumors. PD is an example of major surgery and is a complicated operation to perform for the general surgeon. Current mortality rates are low; previous reports have suggested a perioperative mortality rate of less than 5%[1-3]. However, high morbidity rates have also been reported, some reaching up to 50%[3-7]. The most common complication following PD is postoperative pancreatic fistula (POPF). POPF is the major cause of complications such as delayed gastric emptying (DGE), postoperative hemorrhage, intra-abdominal infection and increased length of hospital stay (LOH)[8].

Many risk factors have been reported for POPF, including obesity, soft pancreatic texture, small pancreatic duct and low volume center[9-15]. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct[16,17], pancreatogastrostomy[18-20], omental roll-up around pancreaticoenteric (PE) anastomosis[21], application of fibrin sealants around PE anastomosis[22,23] and prophylaxis with somatostatin analogs[24-25]. However, the outcomes of these different methods remain controversial.

Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF[9-13]. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

MATERIALS AND METHODS

Patients

From January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand and were considered for inclusion in the study. Patients who underwent a concomitant hepatic resection were excluded; in the end, a total of 179 patients were included. Patient data were retrospectively reviewed. These included age, gender, weight, BMI, underlying disease, serum albumin, preoperative total bilirubin levels and preoperative biliary drainage (PBD). In addition, we recorded the use of percutaneous transhepatic biliary drainage or placement of an endoscopic internal biliary stent. We also reviewed the type of operation, pancreatic texture, pancreatic duct size, type of PE anastomosis, use of trans-anastomotic pancreatic duct stent, pathological diagnosis, operative time and operative blood loss. Ethical permission for this study was obtained from the hospital's ethics committee.

Preoperative evaluation

The general condition of patients and any co-morbid conditions were preoperatively assessed by a physician, surgeon and internist. The diagnosis and clinical staging of the disease were reviewed preoperatively by a multidisciplinary team including surgeons, radiologists and gastroenterologists.

Operative approach

Routine antibiotic prophylaxis was administered 30 min before the incision. PD is classified into classical PD and pylorus-preserved PD (PPPD) and the type of surgery depended on the surgeon's own preference. Reconstruction after resection was performed using

Child's technique, starting with a pancreaticojejunostomy (PJ). A PJ can be performed using either a invagination or duct to mucosa technique and this was decided based on the surgeon's preference. A trans-anastomotic pancreatic duct stent was placed in selected patients, depending on surgeon's preference. The trans-anastomotic pancreatic duct stent was either internal (in the jejunum) or external (partly outside the body). After PJ, biliary-enteric anastomosis was performed followed by a gastro-jejunostomy or duodeno-jejunostomy. A Braun loop jejunojejunostomy was performed in some patients, according to the surgeon's preference. Pancreatic texture was classified into hard, firm or soft consistency based on palpitation by the surgeon. A closed peri-anastomotic drainage system was placed routinely.

Postoperative complications

After surgery, patients were transferred to a critical care unit or intermediate ward. Routine biochemical analyses of patients' blood were performed. An oral diet was started as soon as the output gastric content was < 400 mL and a positive bowel movement occurred. Parenteral nutrition was initiated if the patients did not have a bowel movement or the gastric content was > 400 mL after postoperative day (POD) 3.

POPF was defined according to International Study Group of Pancreatic Fistula (ISGPF) guidelines by amylase levels that were three times higher in the drainage fluid than the serum. POPFs were classified into three categories: (1) Grade A: Transient pancreatic fistula with no clinical impact; (2) grade B: Required a change in management or adjustment of the clinical course; and (3) grade C: Required a major change in clinical management or deviated from the normal clinical course[26]. Combined grade B + C fistulas were defined as "clinically relevant pancreatic fistula" (CR-POPF). DGE was defined as either nasogastric tube insertion after POD 3 or as the inability to tolerate solid food intake by POD 7. Chyle leakage was defined as a milky drain output or triglyceride levels of > 110 mg/dL in the drain fluid on any POD. Postoperative mortality was recorded as the 30-d mortality and in-hospital mortality.

Statistical analysis

Patient characteristics were compared by *t*-test, Wilcoxon Mann-Whitney test, χ^2 test and Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant. Risk factors were analyzed by univariate and multivariate methods using binary logistic regression analysis. Independent risk factors were expressed as odds ratios (ORs) with 95%CI.

RESULTS

Patient characteristics and perioperative status

A total of 179 consecutive patients (95 males, 84 females) that underwent PD were included. One hundred and twenty-eight (71.5%) patients had classical PD and 51 (28.5%) patients had PPPD. Malignancy was diagnosed in 145 patients (79.9%) as follows: 62 ampullary carcinoma patients (44.8%), 40 pancreatic cancer patients (27.6%), 18 cholangiocarcinoma patients (12.4%) and 11 duodenal cancer patients (7.6%) (Table 1).

Patient characteristics and operative outcomes in patients with and without POPF

POPF were detected in 88 patients (49%). Fifty-eight patients (65.9%) had grade A POPF, 22 patients (25%) had grade B POPFs and eight patients (9.1%) had grade C POPFs. CR-POPF were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179). Table 1 compares the post-PD complications between POPF and no POPF groups. Age, serum albumin levels, operative blood loss, gender, diabetes mellitus and PBD were not statistically different between the two groups. However, statistically significant differences were observed in BMI, preoperative total serum bilirubin, pancreatic duct diameter, operative time, cardiovascular disease, pancreatic texture and trans-anastomotic stent between the two groups. The POPF group had a higher rate of other complications (5.5% *vs* 25%, *P* < 0.001) and a longer LOH (15 d *vs* 25 d, *P* < 0.001).

Risk factors for POPF

Univariate and multivariate analyses were used to identify risk factors for POPF (Table 2). Univariate analyses of the 88 patients with pancreatic fistula revealed the following risk factors for POPF: BMI > 25 (OR 2.38, 95%CI: 1.13-5.03, *P* = 0.005), pancreatic duct diameter (OR 2.765, 95%CI: 1.47-5.18, *P* = 0.002), operative time (OR 2.39, 95%CI: 1.26-4.55, *P* = 0.008), history of cardiovascular disease (OR 3.41, 95%CI: 1.48-7.86, *P* = 0.004), soft pancreatic texture (OR 4.682, 95%CI: 2.47-8.87, *P* < 0.001) and placement of a trans-anastomotic pancreatic duct stent (OR 2.55, 95%CI: 1.31-4.99, *P* = 0.006). Multivariate logistic regression analysis revealed soft pancreatic texture (OR 3.59, 95%CI: 3.01-17.35, *P* < 0.001) as the most significant risk factor for POPF.

Effect of POPF grade on patient characteristics and operative outcomes and predictive factors for CR-POPF

Preoperative total bilirubin and pancreatic reconstruction techniques (duct to mucosa *vs* invagination) were significantly different between grade A POPF and CR-POPF (Table 3). Univariate analysis revealed preoperative total serum bilirubin levels of more than 3 mg/dL as a potential risk factor for grade A POPF (OR 3.749, 95%CI: 1.48-9.51, *P* = 0.005). Multivariate analysis revealed total serum bilirubin levels of more than 3 mg/dL as the most significant predictive factor for CR-POPF (OR 4.50, 95%CI: 1.54-13.15, *P* = 0.006) (Table 4).

DISCUSSION

The most common perioperative complication of PD is

Table 1 Patient characteristics in postoperative pancreatic fistula and no postoperative pancreatic fistula groups

Characteristic data	No POPF (n = 91)	POPF (n = 88)	P-value	95%CI
Age, mean (SD)	60.7 (10.6)	59.1 (11.2)	0.33	58.22-61.44
BMI, median (IQR)	21.4 (20, 23.9)	23.1 (20.8, 25.5)	0.005	22.05-23.22
Albumin, median (IQR)	34.1 (31, 38.3)	34.9 (32, 37.95)	0.667	33.38-35.10
Total bilirubin, median (IQR)	4.1 (1.3, 13.2)	1.3 (0.7, 5.6)	0.002	5.01-7.16
Pancreatic duct diameter (mm), median (IQR)	3 (3, 5)	3 (2, 5)	0.048	3.44-3.99
Operative time, median (IQR)	420 (360, 540)	480 (420, 570)	0.014	448.46-486.23
Blood loss (mL), median (IQR)	1000 (600, 1500)	800 (500, 1500)	0.236	1082-1459.66
LOH day, median (IQR)	15 (12, 20)	25 (17, 39.5)	< 0.001	23.14-32.87
Gender, n (%)				
Male	49 (53.8)	46 (52.3)	0.833	
Female	42 (46.2)	42 (47.7)		
DM, n (%)				
No	64 (70.3)	69 (78.4)	0.216	
Yes	27 (29.7)	19 (21.6)		
Hx of cardiovascular disease, n (%)				
No	82 (90.1)	64 (72.7)	0.003	
Yes	9 (9.9)	24 (27.3)		
PBD, n (%)				
No	36 (39.6)	25 (28.4)	0.116	
Yes	55 (60.4)	63 (71.6)		
Pancreatic texture, n (%)[1]				
Hard/firm	60 (68.2)	27 (31.4)	< 0.001	
Soft	28 (31.8)	59 (68.6)		
Type of resection, n (%)				
PPPD	20 (22.0)	31 (35.2)	0.05	
Classical PD	71 (78.0)	57 (64.8)		
Duct to mucosa *vs* Invagination				
Duct to mucosa	56 (61.5)	63 (71.6)	0.154	
Invagination	35 (38.5)	25 (28.4)		
Stent, n (%)				
No	73 (80.2)	54 (61.4)	0.005	
Yes	18 (19.8)	34 (38.6)		
External *vs* Internal, n (%)				
External	4 (22.2)	12 (36.4)	0.298	
Internal	14 (77.8)	21 (63.6)		
Malignant, n (%)				
No	18 (19.8)	16 (18.2)	0.785	
Yes	73 (80.2)	72 (81.8)		
Final diagnosis, n (%)				
CA ampulla	25 (27.5)	37 (42.1)	0.04	
CA pancreas	28 (27.5)	12 (13.6)		
CA duodenal	8 (8.8)	3 (3.4)		
CA distal CBD	7 (7.7)	11 (12.5)		
Other	26 (28.5)	25 (28.4)		
Grading, n (%)				
No	91 (100)	0	0	
A	0	58 (65.9)		
B	0	22 (25.0)		
C	0	8 (9.1)		
Other complications				
No	86 (94.5)	66 (75.0)	< 0.001	
Yes	5 (5.5)	22 (25.0)		
30-d mortality, n (%)				
No	91 (100)	85 (96.6)	0.117	
Yes	0	3 (3.4)		
Age, n (%)				
< 70	73 (80.2)	73 (82.9)	0.637	
≥ 70	18 (19.8)	15 (17.1)		
BMI, n (%)				
< 25	78 (85.7)	63 (71.6)	0.021	
≥ 25	13 (14.3)	25 (28.4)		
Albumin, n (%)				
≥ 30	75 (82.4)	77 (87.5)	0.342	
< 30	16 (17.6)	11 (12.5)		
Total bilirubin, n (%)				
< 3	41 (45.1)	56 (63.6)	0.013	
≥ 3	50 (54.9)	32 (36.4)		

Pancreatic duct diameter, *n* (%)			
≥ 5	45 (49.4)	23 (26.1)	0.001
< 5	46 (50.6)	65 (73.9)	
Operative time, *n* (%)			
< 420	39 (42.9)	21 (23.9)	0.007
≥ 420	52 (57.1)	67 (76.1)	
Blood loss, *n* (%)			
< 1000	45 (49.5)	54 (61.4)	0.109
≥ 1000	46 (50.5)	34 (38.6)	

[1]*n* = 174 patients. Other complications: DGE, postoperative hemorrhage, chyle leakage. POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

Table 2 Univariate and multivariate logistic regression analysis of postoperative pancreatic fistula risk factors

Variable	Univariate OR (95%CI)	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Age (yr)				
< 70				
≥ 70	0.833 (0.39-1.78)	0.637		
Body mass index (kg/cm^2)				
< 25				
≥ 25	2.381 (1.13-5.03)	0.023	2.081 (0.86-5.03)	0.104
Albumin				
≥ 30				
< 30	0.669 (0.29-1.54)	0.344		
Total bilirubin				
< 3				
≥ 3	0.468 (0.26-0.85)	0.013	1.455 (0.38-5.55)	0.583
Pancreatic duct diameter				
≥ 5 mm				
< 5 mm	2.765 (1.47-5.18)	0.002	3.148 (0.81-12.27)	0.098
Operative time				
< 420 min				
≥ 420 min	2.393 (1.26-4.55)	0.008	1.355 (0.59-3.07)	0.465
Blood loss				
< 1000				
≥ 1000	0.616 (0.34-1.12)	0.11		
Gender				
Male				
Female	1.065 (0.59-1.92)	0.833		
DM				
No				
Yes	0.653 (0.33-1.29)	0.218		
Hx of cardiovascular disease				
No				
Yes	3.417 (1.48-7.86)	0.004	2.612 (0.96-7.08)	0.059
Preop biliary stent (no)				
No				
Yes	1.649 (0.88-3.08)	0.117		
Pancreatic texture				
Hard/firm				
Soft	4.682 (2.47-8.87)	< 0.001	3.598 (1.77-7.32)	< 0.001
Type of resection				
Pylorus-preserved pancreaticoduodenectomy				
Pancreaticoduodenectomy	0.518 (0.27-1.00)	0.051	0.807 (0.37-1.78)	0.597
Duct to mucosa				
Invagination	0.635 (0.34-1.19)	0.156		
Stent (no)				
No				
Yes	2.553 (1.31-4.99)	0.006	1.272 (0.52-3.09)	0.595
External				
Internal	0.500 (0.13-1.87)	0.303		
Malignant (no)				
No				
Yes	1.109 (0.52-2.34)	0.785		
Final diagnosis (CA ampulla)				
CA pancreas	0.324 (0.14-0.76)	0.01	0.439 (0.16-1.19)	0.105
CA duodenal	0.253 (0.06-1.05)	0.058	0.533 (0.11-2.59)	0.435
CA distal CBD	1.062 (0.36-3.11)	0.913	1.188 (0.33-4.29)	0.793
Other	0.650 (0.31-1.37)	0.258	0.543 (0.22-1.35)	0.189

Table 3 Relationships between patient characteristics, operative outcome and postoperative pancreatic fistula grade

Characteristic data	POPF (grading)		*P*-value	95%CI
	A (*n* = 58)	B + C (*n* = 30)		
Age, mean (SD)	59.2 (11.3)	58.8 (11.4)	0.874	56.67-61.46
Body mass index, median (IQR)	23.1 (20.4, 25.1)	23.1 (21.1, 26.5)	0.805	22.62-24.45
Albumin, median (IQR)	34.7 (32, 38)	35.4 (32, 37.9)	0.603	33.38-35.58
Total bilirubin, median (IQR)	0.9 (2, 5)	3.3 (1.2, 12)	0.01	3.44-6.66
Pancreatic duct diameter (mm), median (IQR)	3 (2, 5)	3 (2, 4)	0.175	3.07-3.79
Operative time, median (IQR)	480 (420, 600)	480 (360, 540)	0.49	462.22-511.75
Blood loss (mL), median (IQR)	800 (500, 1500)	900 (600, 1500)	0.071	985.10-1616.95
LOH day, median (IQR)	21 (14, 30)	42.5 (30, 60)	< 0.001	28.14-46.32
Gender, *n* (%)				
Male	34 (58.6)	12 (40.0)	0.097	
Female	24 (41.4)	18 (60.0)		
DM, *n* (%)				
No	45 (77.6)	24 (80.0)	0.794	
Yes	13 (22.4)	6 (20.0)		
Hx of cardiovascular disease, *n* (%)				
No	42 (72.4)	22 (73.3)	0.927	
Yes	16 (27.6)	8 (26.7)		
PBD, *n* (%)				
No	20 (34.5)	5 (16.7)	0.079	
Yes	38 (65.5)	25 (83.3)		
Pancreatic texture, *n* (%)				
Hard/Firm	20 (35.1)	7 (24.1)	0.301	
Soft	37 (64.9)	22 (75.9)		
Type of resection, *n* (%)				
PPPD	24 (41.4)	7 (23.3)	0.093	
PD	34 (58.6)	23 (76.7)		
Duct, *n* (%)				
Duct to mucosa	46 (79.3)	17 (56.7)	0.026	
Invagination	12 (20.7)	13 (43.3)		
Stent, *n* (%)				
No	32 (55.2)	22 (73.3)	0.097	
Yes	26 (44.8)	8 (26.7)		
External *vs* Internal, *n* (%)				
External	8 (32.0)	4 (50.0)	0.42	
Internal	14 (68.0)	4 (50.0)		
Malignant, *n* (%)				
No	12 (20.7)	4 (13.3)	0.396	
Yes	46 (79.3)	26 (86.7)		
Final diagnosis, *n* (%)				
CA ampulla	23 (39.6)	14 (46.7)	0.33	
CA pancreas	8 (13.8)	4 (13.3)		
CA duodenal	3 (5.2)	0		
CA distal CBD	5 (8.6)	6 (20.0)		
Other	19 (32.8)	6 (20.0)		
Age, *n* (%)				
< 70	47 (81.0)	26 (86.7)	0.505	
≥ 70	11 (19.0)	4 (13.3)		
BMI, *n* (%)				
< 25	42 (71.4)	21 (70.0)	0.812	
≥ 25	16 (27.6)	9 (30.0)		
Albumin, *n* (%)				
≥ 30	50 (86.2)	27 (90.0)	0.743	
< 30	8 (13.8)	3 (10.0)		
Total bilirubin, *n* (%)				
< 3	43 (74.1)	13 (43.3)	0.004	
≥ 3	15 (28.9)	17 (56.7)		
Pancreatic duct diameter, *n* (%)				
≥ 5	12 (20.7)	11 (36.7)	0.106	
< 5	46 (79.3)	19 (63.3)		
Operative time, *n* (%)				
< 420	12 (20.7)	9 (30.0)	0.331	
≥ 420	46 (79.3)	21 (70.0)		
Blood loss, *n* (%)				
< 1000	37 (63.8)	17 (56.7)	0.515	
≥ 1000	21 (36.2)	13 (43.3)		

POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

Table 4 Univariate and multivariate logistic regression analysis of risk factors for clinically relevant-postoperative pancreatic fistula

Variable	Univariate OR (95%CI)	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Age (yr)				
< 70				
≥ 70	0.657 (0.19-2.27)	0.507		
BMI (kg/cm^2)				
< 25				
≥ 25	1.125 (0.43-2.96)	0.812		
Albumin				
≥ 30				
< 30	0.694 (0.17-2.84)	0.611		
Total bilirubin				
< 3				
≥ 3	3.749 (1.48-9.51)	0.005	4.506 (1.54-13.15)	0.006
Pancreatic duct diameter (mm)				
≥ 5				
< 5	0.451 (0.17-1.20)	0.11		
Operative time (min)				
< 420				
≥ 420	0.609 (0.22-1.66)	0.334		
Blood loss				
< 1000				
≥ 1000	1.347 (0.55-3.31)	0.516		
Gender				
Male				
Female	2.125 (0.86-5.22)	0.1		
DM				
No				
Yes	0.865 (0.29-2.56)	0.794		
Hx of cardiovascular disease				
No				
Yes	0.954 (0.35-2.58)	0.927		
Preop biliary stent (no)				
No				
Yes	2.631 (0.87-7.92)	0.085	2.24 (0.67-7.49)	0.191
Pancreatic texture				
Hard/firm				
Soft				
Type of resection				
PPPD				
PD	2.319 (0.86-6.27)		1.787 (0.54-5.92)	0.342
Duct to mucosa				
Invagination	2.931 (1.12-7.67)	0.028	2.837 (0.89-9.08)	0.079
Stent (no)				
No				
Yes	0.447 (0.17-1.17)	0.101		
External				
Internal	0.471 (0.09-2.38)	0.362		
Malignant (no)				
No				
Yes	1.695 (0.50-5.80)	0.4		
Final diagnosis (CA ampulla)				
CA pancreas	0.821 (0.21-3.24)	0.779		
CA duodenal	-	-	-	-
CA distal CBD	1.971 (0.51-7.68)	0.328		
Other	0.519 (0.17-1.61)	0.256		

POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality[1-3] and the LOH. Many risk factors for POPF have been reported previously[4-9]. In the present study, the incidence of POPF and the 30-d mortality rate were similar to previous studies. In addition, we identified soft pancreatic texture as a main risk factor for POPF[8-12].

Our multivariate analysis showed that a soft pancreas is the most independent predictive factor for POPF. This is in agreement with previous studies[5,9-12,27]. There are many reasons why soft pancreatic tissue increases the risk of POPF. First, a soft pancreas makes it more difficult to secure PEA because friable pancreatic tissue cannot hold suture tension. As a result, suture materials cut through the pancreatic parenchyma and anastomosis fails. A soft pancreas is also prone to ischemia when manipulated, which disrupts anastomosis. Finally, a soft pancreas has enriched exocrine function and pancreatic enzymes are released when leakage occurs[9,11,27,28].

The assessment of pancreatic texture is controversial and subjective. Pancreatic texture is commonly assessed intraoperatively by palpation. Callery *et al*[11] reported the clinical risk score for POPF based on pancreatic texture, pancreatic duct diameter and intraoperative blood loss. They classified the pancreatic texture as firm or soft[11]. Some studies have classified pancreatic texture as hard, firm or soft, but the distinction between a hard and firm pancreas remains unclear[1,5].

Recently, Ansorge *et al*[29] reported similar risk factors for POPF. They classified the pancreatic texture into four grades, including very hard (severe chronic pancreatitis), hard (fibrotic or atrophic obstructed pancreatic gland), soft (unaffected compact gland), and very soft (unaffected fatty pancreas). They found that 44/100 patients had a hard pancreas. The rate of POPF in the very hard/hard groups was significantly different to that in the soft/very soft groups[29]. There is a newly developed tissue strain imaging technology reflecting tissue fibrosis or stiffness and is integrated into a conventional ultrasound system called acoustic radiation force impulse (ARFI). Lee *et al*[30] and Harada *et al*[30] reported the high accuracy of ARFI for prediction of the stiffness of pancreas preoperatively.

The relationship between soft and fatty pancreatic tissue has been well studied[28-29,32]. A fatty pancreas refers to the increasing infiltration of adipose tissue into the pancreas[28]. Ansorge *et al*[29] found that the softness of pancreatic tissue was strongly associated with fat levels in the tissue. This was supported by previous reports that a fatty pancreas is a risk factor for POPF[13,28,32]. Taken together, these findings suggest that the infiltration of adipose tissue into the pancreas is associated with soft pancreatic texture.

The assessment of pancreatic texture is difficult and subjective. Currently, there are no standard procedures for the intraoperative assessment of pancreatic texture. Pancreatic texture has commonly been assessed intraoperatively by palpation[5,11,29]. In the present study, we also assessed pancreatic texture by palpation. This subjective assessment of pancreatic texture could have differed from surgeon to surgeon.

Unfortunately, it was not possible to assess pancreatic texture during the preoperative evaluation. Tranchart *et al*[33] used computed tomography to predict the occurrence of severe pancreatic fistula following PD. They found that a visceral fat area of more than 84 cm^3 was associated with a fatty pancreas (58.4% *vs* 48.1%, P = 0.005) and was a risk factor for CR-POPF (OR 8.16 95%CI: 2.2-3, P = 0.002). They suggested preoperative assessment of body fat distribution as a means of evaluating fat levels in the pancreas and predicting the occurrence of CR-POPF[33]. In our study, the incidence of CR-POPF is high when compared to previous studies[5,6,11,12]. This could be explained by the lower population of pancreatic cancer in this study that the pancreatic cancer is more likely to obstruct the pancreatic duct and therefore increase fibrosis of the pancreas[11].

Obstructive jaundice was previously regarded as the main factor increasing perioperative morbidity and mortality. The pathophysiology of obstructive jaundice includes increasing endotoxin concentrations in the portal circulation, altered Kupffer cell function affecting the reticuloendothelial system in the liver, over-activation of inflammatory cascades, decreased cellular immunity and renal dysfunction. These manifestations influence the nutritional status of patients. PBD decreased postoperative septic complications in mice by improving liver function, nutritional status, cell-mediated immune function, systemic endotoxemia, cytokine release and the overall immune response[34]. Regarding periampullary obstruction, endoscopic drainage approach today represents the procedure of choice with high succession rate[35,36].

In this study, a preoperative serum bilirubin level of more than 3 mg/dL was a risk factor for CR-POPF. Kimura *et al*[3] reported that serum bilirubin of more than 2.0 mg/dL was a significant preoperative risk factor for higher 30-d and in-hospital mortality rates following PD[3]. Gebauer *et al*[37] found that patients with POPF who underwent repeated surgery had higher in-hospital mortality (0.6 *vs* 0.7, P = 0.002) and total serum bilirubin levels (0.7 *vs* 1.1, P = 0.003) than POPF patients that did not undergo reoperation). In a previous study, multivariate binary logistic regression model analysis revealed that a serum bilirubin level of > 2.0 mg/dL is an independent risk factor for reoperation (OR 25.053, 95%CI: 3.486-180.069)[37]. Some previous studies have identified higher serum bilirubin levels in CR-POPF patients, but these differences were not statistically significant. For example, El Nakeeb *et al*[12] reported a preoperative bilirubin level of 4.6 mg/dL in patients with grade A POPF and 9.7 mg/dL in patients with CR-POPF, but this difference was not significant. This was supported by Braga *et al*[38], who detected higher total serum bilirubin in patients with grade Ⅲ-Ⅳ complications than patients with grade 0-Ⅱ complications (3.5 mg/dL *vs* 1.6 mg/dL). Again, this difference was not statistically significant. Fujii *et al*[39] found that endoscopic internal drainage posed a higher risk for POPF than endoscopic nasobiliary drainage.

In a recent systematic review, Scheufele *et al*[40] reported that POPF rates do not differ between PBD and no drainage groups. However, a higher infectious complications rate was detected in the PBD group. Most of the studies included in this review were retrospective studies, and the most frequent complications were wound-related[40]. A few randomized control trial studies have now been performed by a Dutch group. In these studies, the POPF rate did not differ between PBD and surgery first groups following PD. However, the population in the POPF group was only 16%, which may not have been high enough to obtain sufficient statistical power[31]. Current evidence does not recommend routine PBD because the rate of infectious (usually wound-related) complications is higher. However, a randomized control trial of a large population is needed to clarify this in the case of CR-POPF.

In this study, 66.8% of patients underwent PBD, which is higher than previous reports[39-41]. This could be explained by the fact that Thailand is a low to mid-income country, therefore patients with periampullary tumor and pancreatic cancer usually present with severe obstructive jaundice and have poor nutritional status. Serum bilirubin levels were higher than 15 mg/dL and serum albumin levels were less than 30 mg/dL in most patients. In addition, high-volume centers have patient congestion, limited resources and long waiting lists for operations.

This study was limited by the small study population. A larger population study might have revealed more significant risk factors of POPF.

In conclusion, we have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

ARTICLE HIGHLIGHTS

Research background

Many risk factors have been reported for postoperative pancreatic fistula (POPF), including obesity, soft pancreatic texture, small pancreatic duct and low volume center. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct, pancreatogastrostomy, omental roll-up around pancreaticoenteric (PE) anastomosis, application of fibrin sealants around PE anastomosis and prophylaxis with somatostatin analogs. However, the outcomes of these different methods remain controversial. Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

Research motivation

The most common perioperative complication of pancreaticoduodenectomy is POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality and the LOH. Many risk factors for POPF have been reported previously.

Research objectives

The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

Research methods

The retrospective study design were required by reviewed data from January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand.

Research results

This is the study from tertiary care center from Thailand. To the best of the authors knowledge, this is the largest study from Thailand. The authors found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Research conclusions

The authors have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT is a potential method for predicting a soft pancreas preoperatively. Recently, the newly developed technology of ultrasonography have high accuracy to prediction of the stiffness of pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

Research perspectives

Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. which needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

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