Risk Factors and Management of Postoperative Pancreatic Fistula Following Pancreaticoduodenectomy: Single-center Experience

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Summary: Pancreatic fistula (PF) remains the most frequent complication after pancreaticoduodenectomy (PD). This study was undertaken to explore the risk factors of postoperative PF following PD and discuss the management of PF in our center. A single-center respective study, involving 241 patients who underwent PD between September 2015 and June 2018, was conducted. Differences in the demographic data, preoperative, intraoperative and postoperative variables between the group with PF [International Study Group on Pancreatic Surgery (ISGPS) grade B/C] and the group without PF (no PF and ISGPS grade BL) were evaluated. The diagnosis and grading of PF were in strict accordance with ISGPS. Risk factors were analyzed by univariate analysis and multivariate logistic regression analysis. The results showed that postoperative PF occurred in 50 (20.7%) of the patients; 25 (10.4%) patients had a PF type BL, 46 (19.1%) patients developed a PF type B and 4 (1.6%) had a PF type C. Univariate analysis showed that fasting blood glucose (P=0.02), pancreatic texture (P< 0.001) and pancreatic duct diameter (P=0.01) were correlated with PF. Multivariate logistic regression analysis identified one independent risk factor for postoperative PF: soft pancreatic texture (OR=3.251, P=0.002). Among the cases, there were three postoperative deaths, giving a 60-day hospital mortality rate of 1.2% (3/241), and the mortality related to PF was 4.0% (2/50). One of the patients died from multiple organ failure caused by postoperative abdominal hemorrhage. In conclusion, soft pancreatic texture is an independent risk factor for PF. Surgeons should be well aware of this risk factor when performing a PD.
Key words: pancreaticoduodenectomy; pancreatic fistulae; risk factors; complication; pancreatic texture

Pancreaticoduodenectomy (PD) was first introduced by Codivilla *et al* in 1943[1]. It has been the preferred therapeutic method for treating various types of benign and malignant diseases in the pancreatic-ampullary region and the head of the pancreas. Although, with advances in surgical techniques and perioperative management, the performance of PD has been greatly improved, this procedure remains one of the most complicated operations in abdominal surgery and results in high postoperative morbidity and mortality rates, 30% to 40% or more and less than 4%[2, 3], respectively.

Pancreatic fistula (PF), the most common complication after PD, can lead to other abdominal complications, such as abdominal abscess formation, delayed gastric emptying, postoperative delayed hemorrhage, and pseudoaneurysms. All of these complications mainly result from the PF-related abdominal infection and inflammation[4–6]. Despite marked progress in the treatment of PF, PF still gives rise to a prolonged hospital stay, increased medical costs and readmissions. It can even lead to a fatal ending, such as multiple organ dysfunction syndrome and death.

Pancreatic surgeons worldwide have been paying peculiar attention to the prevention and management of PF. A number of clinical trials examined the reconstruction techniques for PF[7–9], modified drainage regimens[10–12], or administration of so-matostatin[13, 14]. In clinical setting, efforts are made to develop different pancreatic anastomoses to prevent the occurrence of postoperative PF, among which, end-

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to-side pancreaticojejunal anastomosis by Kakita *et al*[15] and binding pancreaticojejunostomy by Peng *et al*[16] were widely adopted for their low PF rate. Some studies suggested that the use of somatostatin and its analogues could dramatically reduce the occurrence of PF[14, 17, 18]. Additionally, the risk factors for PF have been extensively studied, and many strictly designed studies investigated the correlation between PF and perioperative variables[19–21]. The soft pancreatic parenchyma was revealed to be well-accepted risk factor for PF[3, 22–24] and is used intraoperatively to choose the proper pancreatic anastomosis.

As there is no optimal indicator to forecast PF and the most suitable method to prevent its occurrence, in this study, we analyzed the risk factors of PF in an attempt to lower the rate of postoperative PF.

1 MATERIALS AND METHODS

1.1 Study Design

Clinical data of consecutive patients who underwent PD at the Department of Pancreatic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology between September 2015 and June 2018 were retrospectively reviewed. The perioperative data, including patient-related variables, preoperative laboratory test-related variables, treatment-related variables and specimen-related variables, were collected. Additionally, all postoperative complications were recorded for analysis, with a special focus on the occurrence of PF, mortality, and duration of drainage. Written informed consent was obtained from all patients before participation, and ethics approval was obtained from the Human Subjects Protection Committee of Huazhong University of Science and Technology.

1.2 Preoperative Preparation

After the patients were admitted to the hospital, they were subjected to routine preoperative assessments, including demographic data (age, sex), personal history (smoking, drinking), past medical history (hypertension, diabetes mellitus, abdominal operation history and so on), laboratory tests [complete blood count, liver function, renal function, and tumor markers, such as carcinoenbryonic antigen (CEA), cancer antigen-199 (CA199), cancer antigen-125 (CA-125)] and radiological assessments (abdominal ultrasound, magnetic resonance imaging, and abdominal enhanced computed tomography). Patients with severe jaundice selectively underwent preoperative biliary drainage by percutaneous transhepaticcholangial drainage (PTCD) or endoscopic retrograde cholangiopancreatography (ERCP). Whether to perform biliary drainage was based on the comprehensive evaluation of the patients' mental state, nutritional status and liver function. Patients with poor nutrition and anemia were given nutritional support therapy (enteral nutrition or parenteral nutrition) and a blood transfusion or supplementation of albumin if necessary.

1.3 Surgical Procedures

All the procedures were performed by five surgeons. Most of the patients were treated with standard PD combined with standard lymphadenectomy, and some patients underwent extended pancreatectomy as a result of the intraoperative findings. In this study, 215 patients (89.2%) underwent standard PD and 26 patients (10.8%) extended PD, of whom 21 patients (8.7%) had portal vein excision and reconstruction and 5 patients (2.1%) had colectomy. In the standard pancreatectomy, the head of the pancreas was excised, as well as the uncinate process of the pancreas, antrum of the stomach, the duodenum, the proximal jejunum, the common bile duct, and the gall bladder. Additionally, improved Child's technique, referring to end-to-side duct-to-mucosa pancreatic-enteric anastomosis (retrocolic), end-to-side hepaticojeju-nostomy (retrocolic) and gastrojejunal anastomosis, was used for gastrointestinal reconstruction in a sequential order. A support tube was placed in the pancreatic duct of all patients. In the end, rubber drainage tubes were placed anterior or posterior to the pancreaticojejunostomy and choledochojejunostomy anastomosis. The patients who were older or had a poor nutritional status or had high risk for postoperative complications were placed with jejunostomy tubes for enteral nutrition until the patients' intestinal function was restored.

1.4 Postoperative Management

All patients were taken care of in the pancreatic intensive care unit for at least three days before being transferred to the ward. All patients received prophylactic antibiotics intraoperatively and postoperatively. Prophylactic somatostatin and its analogues were given to patients with high risk for PF.

Outputs from intraoperatively placed drains were calculated daily, and the amylase content of the drainage fluid was detected on and after postoperative day 3. When the patients' clinical condition changed dramatically, bacterial cultures and fungicultures were conducted as well. The drains were removed when there were no PF, bile leakage, hemorrhage or abdominal collection. The nasogastric tube was removed from most patients 3 to 5 days after operation, and was re-dwelled if patients presented with marked abdominal distension or vomiting. The patients were allowed to have an oral feeding on a fluid diet once the bowel movement restarted. Semi-liquid diet and regular diet were given when patients could tolerate the oral diet.

An abdominal computed tomography was performed routinely for all patients, and was repeated if intra-abdominal collection was suspected. Computed tomography-guided percutaneous catheter drainage

(PCD) or ultrasonic gastroscope-guided drainage was carried out if there was abdominal collection or even abdominal abscess.

1.5 Definitions

PF is an abnormal communication between the pancreatic ductal epithelium and another epithelium surface containing pancreas-derived, enzyme-rich fluid[25]. PF was diagnosed in strict accordance with the International Study Group on Pancreatic Surgery (ISGPS), which refers to PF as a drain output of any measurable volume of fluid with an amylase level that is more than three times the upper limit of normal serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative PF, occurring on or after postoperative day 3[26]. The grade of severity may be defined only after the course of "fistula" event has evolved completely, and its ultimate effect on the outcome can be assessed. The former grade A PF is redefined as "BL", which is no longer considered a true PF or an actual complication and does not affect the normal postoperative recovery. The grade B and C PFs refer to the defined leakage involving increased amylase activity in the drainage fluid with a clinically relevant condition and require a change in the management of the expected postoperative process. Whenever a grade B PF leads to organ failure, reoperation or even death, the PF becomes a grade C fistula.

The pancreas texture was divided into two groups based on the extent of the pancreatic fibrosis of postoperative specimen. The "soft" group was characterized by no significant fibrosis, and the "firm" group by periductal or intralobular fibrosis. The main pancreatic duct size was recorded in the operation reports and patients were divided into two groups according to the main pancreatic duct diameter, as follows: (1) a dilated main pancreatic duct, defined as a main duct greater than 3 mm; (2) a non-dilated pancreatic main duct, defined as a main duct less than 3 mm.

1.6 Statistical Analysis

Statistical analysis of the data in this study was performed using SPSS 24.0 (IBM, USA). For quantitative data, analysis was performed by independent sample Student's *t*-test or Mann-Whitney *U* test, as appropriate. For qualitative data, Chi-square test or Fisher's exact test was used as appropriate. Data were presented, when appropriate, as means±standard deviation (SD). Statistical tests were two-tailed and a $P<0.05$ was considered to be statistically significant. All data were analyzed by univariate analysis and only variables reaching a $P<0.05$ were entered into multivariable logistic regression analysis to determine the independent risk factors for postoperative PF. Results were presented as odd ratios (OR) and their 95% confidence intervals (CI).

2 RESULTS

2.1 Patients Characteristics

This study consisted of 144 male patients and 97 female patients, with a mean age of 56.87±11.47 years old. The mean length of hospital stay was 17.38±9.22 days (PF *vs.* non-PF: 27.22±13.25 days *vs.*14.81±5.47 days, $P<0.001$). The mean operation time was 359.54±89.30 min (PF *vs.* non-PF: 369.48±95.71 min *vs.* 356.94±87.63 min, $P=0.59$). The indications for PD included pancreas mass in 186 patients (77.2%), duodenal tumor in 26 patients (10.8%), lower common bile duct (CBD) tumor in 14 patients (5.8%), ampullary tumor in 12 patients (5.0%), gastric tumor in 2 patients (0.8%) and retroperitoneal tumor in 1 patient (0.4%). In addition, the postoperative pathological types are shown in table 1.

2.2 Morbidity and Mortality

Among the 241 patients, 50 patients (20.7%) were diagnosed with postoperative PF, of whom 46 patients (19.1%) were classified as grade B and 4 (1.6%) as grade C. In patients diagnosed with grade C PF, two patients died of sepsis resulting from abdominal infection, one patient underwent reoperation for abdominal bleeding and one patient underwent reoperation for a small bowel perforation.

Other complications were identified as follows: 45 (18.7%) cases of abdominal infection, 8 (3.3%) cases of abdominal bleeding, 4 (1.7%) cases of gastrointestinal hemorrhage, 8 (3.3%) cases of biliary fistula, 14 (5.8%) cases of delayed gastric emptying, 4 (1.7%) cases of chylous ascites, 8 (3.3%) cases of wound infection/fat liquefaction, 1 (0.4%) case of ventral hernia, 4 (1.7%) cases of intestinal obstruction, 10 (4.1%) cases of lung infection/pleural effusion, 8 (3.3%) cases of central venous catheter infection, 4 (1.7%) cases of deep vein thrombosis, 2 (0.8%) cases of pulmonary embolism, 1 (0.4%) case of small bowel perforation and 6 (2.5%) cases of urinary tract infection.

The in-hospital and 60-day mortality was 3 patients in all cases (1.2%); 2 (2/50) patients died due to sepsis associated with PF and 1 patient died due to multiple organ failure resulting from abdominal bleeding on postoperative day 1. Additionally, 7 patients (2.9%) underwent a second operation, 4 (4/50) patients underwent CT-guided PCD, and 2 (2/50) patients were given ultrasonic gastroscope-guided drainage.

2.3 Risk Factors for PF

Potential risk factors for the development of PF were divided into four categories: patient-related factors (table 2), preoperative laboratory test-related factors (table 3), procedure-related factors (table 4) and specimen-related factors (table 5). All of the variables were assessed by univariate analysis to determine their relationship with PF. Most of the risk factors showed no statistical significance. However, a statistically

Table 1 Indications for pancreaticoduodenectomy

	Number of patients	Leakage (%)	*P*
Site			0.31
Pancreas	186	36 (19.4)	
Duodenum	26	7 (28.0)	
Lower CBD	14	5 (35.7)	
Ampulla of Vater	12	1 (8.3)	
Stomach	2	1 (50)	
Retroperitoneal space	1	0 (0)	
Pathology			0.18
Pancreatic adenocarcinoma	116	20 (17.2)	
Lower CBD cancer	14	5 (35.7)	
Duodenal papillary adenocarcinoma	20	4 (20.0)	
Ampullary adenocarcinoma	11	0 (0)	
Gastrointestinal stromal tumor	3	1 (33.3)	
Duodenal carcinoma	3	1 (33.3)	
Chronic pancreatitis	15	2 (13.3)	
Autoimmune pancreatitis	2	0 (0)	
Intraductal papillary mucinous neoplasm	19	4 (21.1)	
Solid pseudopapillary neoplasm	11	3 (27.3)	
Pancreatic neuroendocrine neoplasm	11	4 (36.4)	
Serous cystic neoplasm	9	2 (22.2)	
Others	7	4 (57.1)	

Fisher's exact test. CBD: common bile duct

Table 2 Patient-related risk factors for PF

Variables	All patients (*n*=241)	PF (*n*=50)	Non-PF (*n*=191)	*P* value
Age (year)	56.82±11.47	56.88±10.67	56.81±11.70	0.88‡
<65	177	36	141	0.80†
≥65	64	14	50	
Gender				0.78†
Male	144	29	115	
Female	97	21	76	
Drinking				0.19†
Yes	66	10	56	
No	175	40	135	
Smoking				0.14†
Yes	84	13	71	
No	157	37	120	
Hypertension				0.76†
Yes	54	12	42	
No	187	38	149	
Diabetes mellitus				0.10†
Yes	31	3	28	
No	210	47	163	
Coronary artery disease				0.37†
Yes	7	0	7	
No	234	50	184	
Abdominal surgery				0.84†
Yes	41	9	32	
No	200	41	159	
Biliary drainage				0.69†
Yes	23	6	17	
No	218	44	174	

All results were presented as *n* or mean±SD as appropriate. ‡Mann-Whitney U test; †Chi-squared test

significant association was observed between PF and the following risk factors: fasting blood glucose (<108.0 mg/dL *vs.* ≥108.0 mg/dL: 25.3% *vs.* 12.0%, *P*=0.02), pancreatic texture (soft *vs.* firm: 29.8% *vs.* 10.0%, *P*<0.001) and pancreatic duct diameter (<3 mm *vs.* ≥3 mm: 29.7% *vs.* 15.3%, *P*=0.01).

When the three risk factors (fasting blood glucose, pancreatic texture, and pancreatic duct diameter)

Table 3 Preoperative laboratory test-related risk factors for PF

Variables	All patients (*n*=241)	PF (*n*=50)	Non-PF (*n*=191)	*P* value
White blood cell (G/L)	6.07±3.63	5.67±1.70	6.18±3.98	0.66‡
Hemoglobin (g/L)				0.78†
<120	111	24	87	
≥120	130	24	104	
Total bilirubin (μmol/L)				0.62†
<171	180	36	144	
≥171	61	14	47	
Albumin (g/L)				0.94†
<35	52	11	41	
≥35	189	39	150	
Creatinine (μmol/L)	67.23±18.30	66.62±11.19	67.39±19.76	0.67‡
Fasting blood glucose (mg/dL)				0.02†
<108.0	158	40	118	
≥108.0	83	10	73	
CA-199	301.46±437.39	211.69±390.82	324.96±446.75	0.08‡
CA-125	24.09±30.39	23.65±39.84	24.20±27.52	0.24‡
CEA	5.20±18.75	9.15±39.89	4.16±5.22	0.18‡

All results were presented as *n* or mean±SD as appropriate. ‡Mann-Whitney *U* test; †Chi-squared test

Table 4 Treatment-related risk factors for PF

Variables	All patients (*n*=241)	PF (*n*=50)	Non-PF (*n*=191)	*P* value
Somatostatin				0.45†
Yes	183	40	143	
No	58	10	48	
Laparotomy/laparoscopy				0.67†
Laparotomy	216	44	172	
Laparoscopy	25	6	19	
Vascular resection				0.99†
Yes	21	4	17	
No	220	46	174	
Standard/extended resection				0.48†
Standard	215	46	169	
Extended	26	4	22	
Blood transfusion				0.53†
Yes	92	21	71	
No	149	29	120	
Operation time (min)	359.54±89.30	369.48±95.71	356.94±87.63	0.59‡

All results were presented as *n* or mean±SD as appropriate. ‡Mann-Whitney *U* test; †Chi-squared test

Table 5 Specimen-related risk factors for PF

Variables	All patients (*n*=241)	PF (*n*=50)	Non-PF (*n*=191)	*P* value
Pancreatic parenchyma				<0.001†
Soft	131	39	92	
Firm	110	11	99	
Pancreatic duct (mm)				0.01†
<3	91	27	64	
≥3	150	23	127	
Surgical indication				0.55†
Malignant	172	34	138	
Benign	69	16	53	

†Chi-squared test

identified in the univariate analysis were entered into the mul-tivariate logistic regression analysis, it was shown that pancreatic texture was the independent risk factor for the development of PF (table 6). Patients with soft pancreatic texture were more likely to progress to have PF than those with a firm pancreas (OR=3.252; *P*=0.002). Pancreatic duct diameter (*P*=0.080) and fasting blood glucose (*P*= 0.057) were within the limits of statistical difference.

2.4 Management of PF

Whenever there is a deviation in the normal clinical progress of a patient, it is rational to suspect

Table 6 Multivariate logistic regression analysis for PF

Variables	B	S.E.	Wald	Sig.	Exp(B)	95% CI	
						Lower	Upper
Pancreatic texture	1.179	0.379	9.677	0.002	3.251	1.547	6.834
Pancreatic duct diameter	0.589	0.336	3.062	0.080	1.802	0.932	3.484
Fasting blood glucose	-0.753	0.396	3.615	0.057	0.471	0.217	1.023

B: regression coefficient; Wald: χ^2 value; Sig: *P* value; Exp(B): OR

the occurrence of PF. The possibly associated signs are as follows: unexpected upper abdominal discomfort (abdominal pain and abdominal distention), fever, leukocytosis, increasing tachycardia or just feeling unwell without apparent etiology. Furthermore, surgeons should be alert to high drain of amylase, a persistent high drain output, altered drain color and quality, and other complications such as severe wound infection and hemorrhage[27]. According to the newly ISGPS definition of PF, we routinely tested the amylase content of a drain on postoperative day 3. In our daily practice, even though the initial drain amylase was normal on postoperative day 3, repeat detection of the amylase was still necessary to uncover previously undiagnosed leakage or newly developed leakage[28], especially before the abdominal drainage tube was removed. Besides, once the PF was confirmed, appropriate conservative and even aggressive treatments are the key to good prognosis.

The conservative treatment is the cornerstone of postoperative PF management. Patients were primarily subjected to the conservative management without interventional treatment. These measures included administration of antibiotics, somatostatin or octreotide, enteral or total parenteral nutritional support. More than 90% patients could be cured by conservative therapy[29]. The role of octreotide and somatostatin in reducing the development of PF remains controversial[30, 31]. We used octreotide and somatostatin in PF cases and in patients considered to have high risk pancreas because octreotide or somatostatin prophylaxis was found to be an effective approach to mitigate the negative impact of PF in our clinical practice. In patients with PF, most of whom were not allowed to accept oral feeding, the nutritional support treatment, including enteral nutrition (through an operatively placed nasojejunal tube or a feeding jejunostomy) and parenteral nutrition, was as vital as effective drainage and must be maintained throughout the entire treatment course. If there were clinical signs of abdominal infection, such as progressive abdominal pain, peritoneal tenderness, fever above 38.5°C or leukocytosis, it was imperative to use sensitive antibiotics intravenously and adjust the type of antibiotics in accordance with the culture of the drainage fluid.

In about half of the patients, PF is associated with a peripancreatic collection[32], which may remain asymptomatic, but due to its risk of abdominal abscess formation or development toward vascular erosion, early intervention of a peripancreatic collection was required. The principle was to ensure proper drainage of PF effectively, which could be maintained with abdominal drains placed intraoperatively or with new drains placed percutaneously using ultrasound or computed tomography, for the majority of PF to be cured conservatively. Close attention must be paid to keep drainage open. Otherwise, it might result in abdominal pain, abdominal distention and even retroperitoneal infection, which could lead to a rapid deterioration of the patients' condition.

In clinical practice, for patients with severe or persistent PF, sometimes invasive treatment is inevitable. The CT-guided PCD was the primary therapy for peripancreatic abscess/fluid (fig. 1). With the development of the endoscopic techniques, some cases unsuitable for PCD could undergo ultrasonic gastroscope-guided drainage. For some patients whose abdominal infection is difficult to control, operative

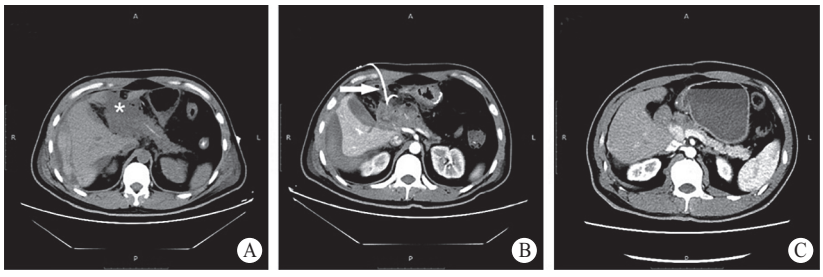

Fig. 1 Computed tomography guided PCD for peripancreatic fluid collection after PD
A: peripancreatic fluid collection (as indicated by an asterisk) around the pancreatic anastomosis; B: The CT-guided PCD was performed, leaving a drainage tube (as indicated by solid arrow) to keep the drainage open. C: An abdominal enhanced CT showed that the peripancreatic fluid collection disappeared before hospital discharge.

intervention such as relaparotomy with surgical drainage of the anastomotic area was considered before overwhelming retroperitoneal sepsis and multisystem organ failure occurred. In some severely septic patients after multiple interventions, the most radical choice must be made, such as resection of the pancreatic remnant or a complete pancreatectomy, which is clearly a definitive solution to PFs. Actually, very few patients need such extreme treatment as total pancreatectomy because of its high mortality. The poor quality of life and the definitive occurrence of postoperative exocrine and endocrine insufficiency for patients limit its application, but sometimes it may be the desperate "last resort" to salvage the patients. Indeed, sometimes a more aggressive, earlier re-exploration might have avoided the need of complete pancreatectomy in some patients and thereby decreased the accompanying morbidity and mortality[33].

In all, when a more serious presentation of retroperitoneal sepsis with abscess formation could not be controlled, surgical intervention must be performed promptly and decisively to prevent the destruction of the peripancreatic tissues and blood vessels with the potential for severe abdominal hemorrhage. Patients with PF tended to develop delayed hemorrhage, which is preferably treated by angiography and embolization of the bleeding vessels. This management is effective in stopping the bleeding in about 80% patients[34]. It is necessary to repeat surgery if angiographic embolization, drug therapy and blood transfusion fail to control hemorrhage.

3 DISCUSSION

Postoperative PF is a common and serious complication following PD and is partially responsible for subsequent complications[25, 35, 36]. Although the conservative treatment of PF is usually effective[29], it will lead to prolonged hospital stay, increased medical cost and readmission; it can also result in a lethal massive abdominal hemorrhage and septicemia[37–39]. Therefore, it is imperative to prevent PF and diagnose it at early time. In this study, we identified the risk factors of PF in order to take effective measures to decrease the incidence of PF.

In previous studies, PF was found to be correlated with comorbidities, with coronary artery disease reported as a risk factor, arterial hypertension as a protective factor[19], the absence of diabetes related to the occurrence of pancreatic leakage[24, 40]. In this study, however, no statistical significance was noted in the incidence of pancreatic leakage between patients with or without comorbidities. It was shown that the leakage rate was lower in patients with a fasting blood glucose ≥108.0 mg/dL (12.0%) than that in those with a fasting blood glucose level <108.0 mg/dL (25.3%), but the statistical difference was not significant (P=0.057).

Various strategies have been proposed and tested to prevent the development of PF after PD, including prophylactical use of medications and refinements of anastomotic techniques, but no single method has proved suitable for all patients. In terms of pancreatic anastomosis, pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) are the two most commonly used techniques, the optimality of which has been controversial[41–44]. In this study, we employed PJ when performing PD as the surgeons were most familiar with this pancreaticoenteric anastomosis and this method was independent of the diameter of the pancreas. Somatostatin and its analogues are proved to reduce pancreatic juice. In this study, 186 patients were administered with somatostatin or octreotide postoperatively. Univariate analysis showed that there was no statistically significant difference in PF rates (P=0.45) between patients given somatostatin or octreotide or not, which was consistent with some studies[45, 46]. A meta-analysis[47], involving a total of 1918 patients, summarized that somatostatin and its analogues did not reduce the mortality rate after PD (P= 0.545) but did reduce the total morbidity (P=0.003) and pancreas-specific complications (P<0.001). Several clinical trials suggested a favorable effect of the drugs in reducing the occurrence of PF[17, 18]. Larger multi-center randomized, prospective controlled studies are still needed to evaluate the effect of somatostatin and its analogues on prevention of PF after PD.

With the advances of minimally invasive surgery, laparoscopic pancreaticoduodenectomy (LPD) firstly introduced in 1994[48] is gaining popularity in recent years. Although it is the most challenging abdominal operation, this procedure has been shown safe and feasible when performed by experienced surgeons in high-volume centers[49]. LPD has its advantages over open PD in terms of earlier oral intake, decreased intraoperative blood loss, shorter hospital stay, less pain and faster recovery[50–53]. However, some studies revealed that LPD might be associated with higher rates of PF[54, 55]. In this study, there was no significant difference in the PF rate between patients undergoing open PD and LPD. In our study, the LPD was almost performed by one surgeon who has specialized experience and expertise in open PD, laparoscopic cholecystectomy and laparoscopic distal pancreatectomy. Besides, this surgeon has modified the method of pancreatic anastomosis, which can be simply done in open or minimally invasive pancreatic surgery with low rate of PF. Additionally, patients who underwent minimally invasive PD were highly selected. For example, patients with appropriate body mass index or resectable tumor based on the results of preoperative radiology were amenable to LPD. But we have to admit that the number of patients who

underwent LPD is small, and the selection bias could not be totally avoided.

Characteristics of the pancreatic parenchyma were recognized as a determining factor for the development of PF after PD[24, 56, 57]. A great number of studies revealed soft pancreatic texture as the most significant risk factor for PF[3, 23, 58]. In this study, 131 patients had a soft pancreas and 110 patients had a hard pancreas, with the PF rate being 29.8% and 10.0%, respectively. Univariate analysis suggested that patients with a soft pancreas were at a higher risk to develop PF than those with a firm pancreas (P<0.001). Additionally, multivariate logistic regression analysis indicated that a soft pancreatic parenchyma was an independent risk factor for PF after PD (OR=3.251; 95% CI: 1.547–6.834; P=0.002). Patients with a soft gland were 3.251-fold more likely to develop a PF than those with a firm gland.

It is widely recognized that a fibrotic pancreas facilitates the pancreatic anastomosis, whereas the soft pancreas makes it difficult to perform an anastomosis. There is a higher risk of damage to the pancreatic parenchyma and fine pancreatic duct during suturing and knotting of a soft pancreas, which leads to an insecure pancreatic anastomosis and results in pancreatic leakage[21]. It has been reported that the quality of the pancreas is related to the diameter of the pancreatic duct and pancreatic juice secretion[4]. A soft pancreas is usually accompanied by s small pancreatic duct[23, 59] and abundant pancreatic juice secretion[60, 61]. The pancreatic duct diameter was found to be correlated with PF[62]. When the incidence of PF was compared based on the main pancreatic duct size, pancreatic leakage occurred in 27 of 91 patients (29.7%) with pancreatic duct <3 mm, in 23 of 150 patients (15.3%) with pancreatic duct ≥3 mm, but there was no significant difference in the PF rate between those with pancreatic duct <3 mm and ≥3 mm. When performing PD, the surgeons should take this risk factor into consideration and achieve a satisfactory pancreatic anastomosis to reduce the occurrence of PF.

There are several limitations in our study. This study was of the retrospective nature. The sample size enrolled in this study was small and the statistical bias could not be avoided completely. Further clarification of the risk factors is still required through large, multi-center, high-quality, randomized trails.

In conclusion, our study demonstrated that soft pancreas was a strong predictor for postoperative PF after PD. Attention should be paid to patients with soft pancreas, and an appropriate pancreatic anastomosis should be selected based on the texture of the pancreas. The postoperative patients should be closely monitored, and patients with a PF should be treated promptly to avoid fatal complications.

Conflict of Interest Statement

The authors declare no conflict of interests.

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