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Risk factors for postoperative pancreatic fistula

Analysis of 170 consecutive cases of pancreaticoduodenectomy based on the updated ISGPS classification and grading system

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Abstract

This study was designed to analyze the risk factors for postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD).

Between September 2015 and August 2017, 170 successive patients underwent a radical PD in the Department of Pancreatic Surgery, Union Hospital, Wuhan. We carried out a retrospective study of these cases and the prospective conditions, which might be related to POPF, were examined with univariate and multivariate analysis. POPF was defined as a drain output of any measurable volume of fluid with an amylase level more than 3 times the upper limit of serum amylase activity on postoperative day 3, accompanied by a clinically relevant condition according to the 2016 update of the International Study Group for Pancreatic Surgery (ISGPS) definition. In our study, the POPF was just referred to as grade B and grade C pancreatic fistula in accordance with the ISGPS consensus, because the former grade A pancreatic fistula is now redefined as a biochemical leak, namely no-POPF, which has no clinical impact and needs no other special therapy.

Pancreatic fistula occurred in 44 (25.9%) patients after PD, with a mean length of hospital stay of 24.98 ± 14.30 days. Thirty-six patients (21.2%) developed grade B pancreatic fistula, and 8 patients (4.7%) had grade C pancreatic fistula. Among patients with grade C pancreatic fistula, 4 patients died, 3 patients were operated on again, and 3 patients developed multiple organ failure.

Univariate analysis showed a significantly important association between POPF and the following factors: pancreas texture (soft vs hard: 39.1% vs 10.3%, $P < .0001$) and fasting blood glucose level (<108.0 mg/dL vs ≥108.0 mg/dL: 32.5% vs 12.5%, $P = .005$). Multivariate logistic regression analysis identified 2 independent factors related to POPF: soft pancreas texture and fasting blood glucose level <108.0 mg/dL.

A soft pancreas and a fasting blood glucose level of <108.0 mg/dL are risk factors for the development of a POPF.

Abbreviations: BL = biochemical leak, DM = diabetes mellitus, ISGPS = International Study Group for Pancreatic Surgery, PD = pancreaticoduodenectomy, PJ = pancreaticojejunostomy, POPF = postoperative pancreatic fistula, SD = standard deviation, TPN = total parenteral nutrition, TEN = total enteral nutrition.

Keywords: complication, pancreas texture, pancreaticoduodenectomy, postoperative pancreatic fistula

1. Introduction

Pancreaticoduodenectomy (PD) is one of the most complex operations undertaken by the Department of General Surgery, and is the main therapy for malignant and some benign diseases in the head of pancreas, the lower common bile duct, and the ampullary region.[1–4] Although surgical techniques and perioperative management are improving constantly,[5–7] the postoperative mortality rate of PD even in high-volume centers is still high, reported to be 1% to 2%.[8–10] Meanwhile, the incidence of postoperative morbidity remains very high, ranging from 10% to 60%,[3,11–19] in which the postoperative pancreatic fistula (POPF) and delayed gastric emptying play a major role.[20–22] POPF remains the primary postoperative complication and mostly accounts for the other intra-abdominal complications, such as postpancreatectomy hemorrhage, intra-abdominal infection, and delayed gastric emptying.[23–27] In some cases, the pancreatic fistula may lead to a catastrophic ending, for example, multiple organ failures, reoperation, and even death, which will prolong the length of hospital stay and add to the medical cost. It is important to identify the risk factors for the development of POPF, and many studies have been published to review the perioperative conditions associated with pancreatic fistula after a PD, including age, sex, body mass index, heart disease, type of pancreaticojejunostomy (PJ) anastomosis, pancreatic texture, diameter of pancreatic duct, blood loss, and preoperative jaundice.[17,26,28–31] Many well-designed trials concerning PJ anastomosis have inspired us to make efforts to reduce the occurrence of POPF.[13,32–34] However, a definitive technique to prevent pancreatic fistula is still debated.[31,35–37]

In this study, we conducted a retrospective study of 170 consecutive patients who had undergone a radical PD in our

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The authors of this work have nothing to disclose.

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Table 1

Indications for pancreaticoduodenectomy.

Variables	N
Site	
Pancreatic head	135 (79.4%)
Lower common bile duct	9 (5.3%)
Duodenum	19 (11.2%)
Ampullary	6 (3.5%)
Retroperitoneal	1 (0.6%)
Postoperative pathology	
Pancreatic adenocarcinoma	81 (47.6%)
Distal cholangiocarcinoma	9 (5.3%)
Ampullary carcinoma	6 (3.5%)
Duodenal carcinoma	2 (1.2%)
Duodenal papillary carcinoma	14 (8.2%)
Duodenal stromal tumor	2 (1.2%)
Duodenal leiomyoma	1 (0.6%)
Pancreatic neuroendocrine tumor	8 (4.7%)
Pancreatic neuroendocrine carcinoma	2 (1.2%)
Serous cystic neoplasm	9 (5.3%)
Solid pseudopapillary neoplasm	7 (4.1%)
Solid pseudopapillary carcinoma	1 (0.6%)
Intraductal papillary mucinous neoplasm	14 (8.2%)
Intraductal papillary mucinous carcinoma	2 (1.2%)
Autoimmune pancreatitis	2 (1.2%)
Chronic pancreatitis	6 (3.5%)
Necrotizing pancreatitis	1 (0.6%)
Pancreatic pseudocysts	1 (0.6%)
Retroperitoneal schwannoma	1 (0.6%)
Pancreatic benign cystic lesion	1 (0.6%)
Total	170

Pancreatic Surgery, Union Hospital, Wuhan, to assess the possible risk factors related to pancreatic fistula after PD.

2. Materials and methods

2.1. Patient selection and data collection

We retrospectively analyzed 170 successive cases who had undergone a radical PD in our Pancreatic Surgery between September 2015 and August 2017. The following clinical data were collected for analysis: sex, age, smoking history, drinking history, hypertension, diabetes, abdominal operation history, biliary drainage, hemoglobin, total bilirubin, serum albumin, fasting blood glucose, pancreatic duct diameter, pancreas texture, surgical procedure, receipt of portal vein resection and reconstruction, receipt of intraoperative blood transfusion, operation time, length of postoperative hospital stay, and postoperative pathology (Table 1). In addition, the postoperative day 3 drainage amylase and other complications were also collected for analysis concerning the occurrence of pancreatic fistula and its classification.

2.2. Surgical procedure

The excision included the pancreatic head, duodenum, antrum of the stomach, proximal jejunum, gallbladder, and common bile duct.[38,39] In addition, regional lymph node resection and a pancreatic tube inserted into the pancreatic duct as a stent were routinely performed. The Child method[34,40] was applied in all patients for reconstruction of the digestive tract. Finally, a rubber drainage tube was placed inferior and superior to the pancreatic-enteric anastomosis and posterior to the hepaticojejunostomy. Prophylactic somatostatin analogues were not routinely used.

2.3. Definition and classification of POPF

In 2016, the International Study Group for Pancreatic Surgery (ISGPS) revised the definition and grading system of POPF (Table 2).[41] According to the updated consensus, the former grade A POPF is redefined as a biochemical leak, and the clinically relevant POPF is redefined as a drain output of any measurable volume of fluid with an amylase level more than 3 times the upper limit of serum amylase activity on postoperative day 3, associated with a clinically relevant condition. Faced with clinically relevant POPF, how do we distinguish the grade B and grade C pancreatic fistula? This issue is easily dealt with using the updated definition and grading system. The POPF that brought about single or multiple organ failure, requiring reoperation or even resulting in death belong to grade C POPF, if not otherwise classified as grade B POPF.

2.4. Statistical analysis

All the statistical analysis was performed using SPSS version 24.0 (IBM, Armonk, NY). Categorical variables were evaluated using the χ^2 test or Fisher exact test. Quantitative data were evaluated with a Student t test, and expressed as means ± standard deviation. All the data were analyzed by univariate analysis. $P < .05$ was regarded as statistically significant. Variables with

Table 2

The revised 2016 International Study Group for Pancreatic Surgery classification and grading of postoperative pancreatic fistula.

Event	BL (NO-POPF)	Grade B POPF	Grade C POPF
Increased amylase activity >3 times upper limit of normal serum value	Yes	Yes	Yes
Persisting peripancreatic drainage >3 wk	No	Yes	Yes
Clinically relevant change in management of POPF*	No	Yes	Yes
POPF percutaneous or endoscopic specific interventions for collections	No	Yes	Yes
Angiographic procedures for POPF related bleeding	No	Yes	Yes
Signs of infection related to POPF	No	Yes	Yes
		without organ failure	with organ failure
Reoperation for POPF	No	No	Yes
POPF-related organ failure†	No	No	Yes
POPF-related death	No	No	Yes

BL = biochemical leak, POPF = postoperative pancreatic fistula.

* Suggests prolongation of hospital or ICU stay, include use of therapeutic agents specifically employed for fistula management or its consequences (of these somatostatin analogs, TPN/TEN, blood product transfusion or other medications).

† Postoperative organ failure is defined as the need for reintubation, hemodialysis, and/or inotropic agents >24 hours for respiratory, renal, or cardiac insufficiency, respectively.

$P < .15$ were entered into the multivariate logistic regression to test the independent risk factors for POPF.

2.5. Ethics statement

Written informed consent was obtained from all patients before participation, and ethical approval was obtained from Human Subjects Protection Committee of the Huazhong University of Science and Technology. In addition, written consent was obtained from the patients, allowing their information to be stored in the hospital's database.

3. Results

3.1. Patients characteristics

This study enrolled 97 male patients and 73 female patients with a mean age of 57.03 ± 11.16 years (group POPF vs group no-POPF: 57.84 ± 11.42 years vs 56.75 ± 11.10 years, $P = .58$). The mean postoperative length of hospital stay was 17.22 ± 9.45 days (group POPF vs group no-POPF: 24.98 ± 14.30 days vs 14.51 ± 4.66 days, $P < .0001$). The mean operation time was 355.46 ± 91.76 minutes (group POPF vs group no-POPF: 360.20 ± 108.73 minutes vs 353.80 ± 85.47 minutes, $P = .69$). In this test, 44 patients (25.9%) were diagnosed with a POPF, among which, 36 patients (21.2%) developed a grade B pancreatic fistula and 8 patients (4.7%) developed a grade C pancreatic fistula. In cases which were classified as grade C pancreatic fistula, 4 patients died, 3 patients were subjected to a reoperation, 3 patients developed multiple organ failure, and the total mortality rate among the whole group of patients in the study was 2.4%(4/170). Among the mortality cases, 3 patients died from multiple organ failure and 1 patient died of a massive abdominal hemorrhage resulting from POPF.

3.2. Univariate analysis for POPF

The risk factors for the development of pancreatic fistula are presented in Table 3. Patients with a soft pancreas texture or a fasting blood glucose level of <108.0 mg/dL were more likely to develop a POPF. The incidence of POPF in patients with soft pancreas texture was 36/92 (39.1%) and that was 8/78 (10.3%) of the patients with hard pancreas texture ($P < .0001$). The incidence of POPF in patients with a fasting blood glucose level of <108.0 mg/dL was 37/114 (32.5%) and that was 7/56 (12.5%) of the patients with a fasting blood glucose level of ≥108.0 mg/dL ($P = .005$). Univariate analysis demonstrated no significant relationship between POPF and the following factors: sex, age, smoking, drinking, hypertension, diabetes, abdominal operation history, biliary drainage, hemoglobin, total bilirubin, serum albumin, pancreatic duct diameter, surgical procedure, portal vein resection reconstruction, or intraoperative blood transfusion. Only a significantly important association was demonstrated between POPF and the following factors: pancreas texture (soft vs hard: 39.1% vs 10.3%, $P < .0001$) and fasting blood glucose level (<108.0 mg/dL vs ≥108.0 mg/dL: 32.5% vs 12.5%, $P = .005$).

Table 3

Univariate analysis of risk factors for postoperative pancreatic fistula.

Variable	POPF Yes, n = 44	POPF No, n = 126	χ^2	P
Sex			0.001	.97
Male	25	72		
Female	19	54		
Age, y			0.071	.79
<65	33	97		
≥65	11	29		
Smoking history			2.804	.09
No	34	80		
Yes	10	46		
Drinking history			2.961	.09
No	36	86		
Yes	8	40		
Hypertension			2.492	.12
No	31	103		
Yes	13	23		
Diabetes			1.000	.32
No	40	107		
Yes	4	19		
Abdominal operation history			0.330	.56
No	37	101		
Yes	7	25		
Biliary drainage			0.256	.56
No	39	115		
Yes	5	11		
Hemoglobin, g/L			0.074	.79
<120	22	60		
≥120	22	66		
Total bilirubin, μmol/L			0.208	.65
<171	33	90		
≥171	11	36		
Serum albumin, g/L			1.194	.28
<35	13	27		
≥35	31	99		
Fasting blood glucose, mg/dL			7.796	.005
<108.0	37	77		
≥108.0	7	49		
Pancreatic duct diameter, mm			3.479	.06
<3	22	43		
≥3	22	83		
Pancreas texture			18.345	<.0001
Soft	36	56		
Hard	8	70		
Surgical procedure			0.157	.69
Laparoscope	7	17		
Laparotomy	37	109		
Portal vein resection and reconstruction			1.243	.27
No	38	116		
Yes	6	10		
Intraoperative blood transfusion			0.063	.80
No	27	80		
Yes	17	46		

POPF = postoperative pancreatic fistula.

3.3. Multivariate logistic regression analysis for POPF

In univariate analysis, smoking, drinking, hypertension, and pancreatic duct diameter were at the limit of a significantly statistical difference (Table 3), with $P < .15$. The conditions mentioned above and the 2 risk factors (pancreas texture, fasting blood glucose) were both analyzed by logistic regression to test the independent risk factors for POPF. Consequently, a soft pancreas texture [odds ratio (OR) = 5.275, $P < .0001$] and a fasting blood glucose level of <108.0 mg/dL (OR = 3.011, $P = .02$) were identified as 2 independent risk factors for POPF (Table 4).

Table 4

Multivariate logistic regression analysis for postoperative pancreatic fistula.

Variables	B	SE	Wals	*P*	OR	95% CI
Pancreas texture	1.663	0.436	14.556	<.0001	5.275	2.245–12.395
Fasting blood glucose	1.102	0.468	5.535	.02	3.011	1.202–7.540

CI = confidence interval, OR = Odds ratio.

4. Discussion

POPF remains the toughest challenge after PD even in specialist units and its occurrence remains the major contributor to morbidity and mortality postoperatively.[25,30] POPF is associated with abdominal abscess, delayed gastric empting, incision infection, abdominal hemorrhage, intestinal fistula, and sepsis after PD.[24,26,42] Recent studies have revealed that many factors, preoperative, intraoperative, and postoperative, influence the development of POPF, which reminds us to do as much as possible to avoid the occurrence of pancreatic fistula.

In 2005, the International Study Group of Pancreatic Fistula developed a definition and grading of POPF that had been a criterion standard in defining POPF,[38] but it still resulted in some confusion in dividing the grade B and grade C pancreatic fistula. In 2016, the ISGPS updated the definition and grading system of POPF,[41] and made clear the difference between grade B and grade C pancreatic fistula. Grade C POPF refers to the pancreatic fistula that needs reoperation or leads to single or multiple organ failure and/or mortality. All of these efforts provided us with a standardized and universally accepted definition and grading system of pancreatic fistula and made it easier to compare different surgical experiences, techniques, and incidence of complications. Our study stuck to the new standard in defining and classifying the POPF.

In many studies, soft pancreatic texture has been widely acknowledged as the most significant risk factor for pancreatic fistula.[43–46] In this study, 92 patients had a soft pancreas (POPF rate: 39.1%), and 78 patients had a hard pancreas (POPF rate: 10.3%). Univariate analysis showed significant statistical differences between the 2 groups (soft pancreas and hard pancreas), suggesting that patients with soft pancreatic parenchyma were more likely to develop a POPF after PD than patients with a hard pancreas. Furthermore, multivariate logistic regression analysis indicated that a soft pancreas was an independent risk factor for the development of POPF. The OR [5.275, 95% confidence interval (CI): 2.245–12.395] demonstrated that the risk of developing a pancreatic fistula in patients with a soft pancreas was 5.257 time greater than that in patients with a hard pancreas. The lower rate of POPF in patients with hard pancreatic parenchyma may be associated with the pancreas exocrine dysfunction resulting from long-term pancreatic fibrosis.

It must be noted that the sources of pancreatic fistula include leaks from PJ anastomosis, leaks from the cut surface of pancreas, leaks associated with the damage to the remnant of the pancreas, and leakage from the needle channel. When referring to pancreatic fistula, we cannot bypass the core step in PD-pancreatic intestinal anastomosis, especially in patients with soft pancreatic parenchyma. To perform a safe and reliable PJ anastomosis, it is essential to comprehend the character of the pancreas as an organ.[47] The parenchymal tissue of the normal pancreas is fragile and contains abundant pancreatic ducts matched with its exocrine function. When performing pancreaticoenteric anastomosis, these features of the pancreas must be taken into consideration, especially in patients with a soft pancreas, because the suture can easily cut the fragile pancreatic tissue and fine pancreatic ducts during suturing and knotting, which leads to pancreatic fistula. It is speculated that too many sutures and tying them too tightly during anastomosis could cause ischemia and necrosis of the pancreatic stump by disturbing the blood flow. When using too many sutures and tying them too tightly pancreatic juice can also leak from the stitch, also resulting in a pancreatic fistula. The all mentioned above to some extent affect the occurrence of postoperative fistula.

Another intriguing finding from our study was that PF rate was higher in patients with a fasting blood glucose level of <108.0 mg/dL. In this study, the fasting blood glucose threshold was 108.0 mg/dL. It was clear that pancreatic endocrine function was closely related to blood glucose. To some degree, patients with a fasting plasma glucose level of ≥108.0 mg/dL probably had either impaired glucose tolerance or evident diabetes mellitus (DM). Hu et al[28] retrospectively analyzed 539 successive cases of PD and summarized that a nondiabetic or blood glucose levels ≤108 mg/dL were risk factors for pancreatic fistula in univariate analysis, although not in multivariate analysis. In this study, 114 patients had a fasting blood glucose level of <108.0 mg/dL (POPF rate: 32.5%) and 56 patients had a fasting blood glucose level of ≥108.0 mg/dL (POPF rate: 12.5%). Univariate analysis indicated significant differences in POPF rates, showing that patients with fasting blood glucose levels of <108.0 mg/dL were more likely to develop pancreatic fistula after PD than patients with fasting blood glucose levels of ≥108.0 mg/dL. Furthermore, multivariate logistic regression analysis indicated that the difference was significant ($P = .02$), meaning that a fasting blood glucose level of <108.0 mg/dL was an independent risk factor for the development of pancreatic fistula after PD. The OR (3.011, 95% CI: 1.202–7.540) demonstrated that the risk of developing pancreatic fistula in patients with a fasting blood glucose level of <108.0 mg/dL was 3.011 time higher than that in patients with a fasting blood glucose level of ≥108.0 mg/dL. A meta-analysis[48] including 16 observational clinical studies revealed that DM was associated with a decreased risk of POPF ($P = .01$). On the contrary, patients without DM were at a higher risk of developing POPF as the pancreas in these patients had more fatty tissue and the pancreas was soft, which could be the same for interpreting why patients with blood glucose levels of <108.0 mg/dL were more likely to develop pancreatic fistula.

Some studies have been designed to investigate the association between the presence of DM and POPF. Lin et al[49] reported that patients without DM were at a higher risk for POPF compared with patients with diabetes (12.0% vs 7.7%). A possible interpretation for this finding was reported by Mathur et al.[22] They concluded that patients with DM may have less fat and more pancreatic fibrosis,[22,50,51] protecting them from developing POPF. Addeo et al[16] reported that the absence of preoperative diabetes was an independent risk factor for pancreatic fistula after PD. Malleo et al[52] concluded that DM was not a risk factor for POPF after PD. The decreased incidence

of POPF in patients with diabetes was likely to be the consequence of a decreased frequency of high risk features of the pancreas that was soft in texture and/or had a small pancreatic duct. These final results in our study supported the hypothesis that patients with diabetes more often had hard pancreatic texture leading to a lower rate of pancreatic fistula after PD.

5. Conclusion

Pancreatic fistula is the most common postoperative complication after PD. In conclusion, a soft pancreas and a fasting blood glucose level of <108 mg/dL are the independent risk factors for POPF after PD. In practice, we should pay more attention to patients with high risk factors to prevent the occurrence of pancreatic fistula.

6. Limitation

On the negative side, however, this is a retrospective, single-center study with a relatively small sample. In the future, we will carry out multicenter prospective study about the analysis of risk factors for POPF based on the newly issued grading system. Especially, it is necessary to perform the association analysis between the pancreatic fibrosis and pancreatic fistula or fasting blood glucose.

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