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Analysis of Risk Factors for Post-Pancreaticoduodenectomy Pancreatic Fistula

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Abstract

Purpose The aim of the present study is the analysis of risk factors of postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD).

Methods Clinical data of 277 patients undergoing a PD at Shengjing Hospital between January 2014 and October 2015, were collected. Peri-operative risk factors associated with POPF were analyzed.

Results Overall incidence of POPF was 49.1%. In univariate analysis, diabetes mellitus, intraoperative blood loses, serum bilirubin concentration, intra-abdominal thickness, pancreatic duct diameter, and specimen pathology correlated with fistula rates. Independent risk factors for POPF by multivariate analysis were pancreatic duct diameter and pathology.

Conclusion Pancreatic duct diameter of 3mm or less, and pathology of ampullary carcinoma, duodenal carcinoma, distal cholangiocarcinoma are independent risk factors for POPF after pancreaticoduodenectomy.

Key Words pancreaticoduodenectomy · pancreatic fistula · pancreatic duct diameter · pathology.

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Authors' Contributions

· Study conception and design: Xianmin Bu; Acquisition of data: Feng Wang, Weiguang Zhou,

Weichao Yang; Analysis and interpretation of data: Feng Wang; Drafting of manuscript: Feng Wang; Critical revision of manuscript: Changjun jia, Xianmin Bu.

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Ethics approval and consent to participate This study was a retrospective analysis of medical records, and investigated in accordance with the relevant regulations, including the Declaration of Helsinki. The Ethical Committee of Shengjing Hospital had confirmed that no ethical approval was required. Due to the retrospective design and the use of fully anonymized clinical data, the need for informed consent was officially waived by the Ethical Committee of Shengjing Hospital.

Consent for Publication Not applicable.

Data availability statements The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions regarding patient clinical records.

1. Introduction

Pancreaticoduodenectomy is the classic surgical procedure for treating benign and malignant diseases of the periampullary region of the bile duct and pancreas. In 1898, Italian surgeon Codivilla reported the first single-stage pancreaticoduodenectomy. The patient died 18 days after surgery, likely due to pancreatic fistula or severe steatorrhea [1]. In 1909, German surgeon Kausch performed the first successful pancreaticoduodenectomy [2]. In 1935, Dr. Whipple and colleagues published a landmark article in which the operation was divided into two stages: the first stage involved biliary decompression and gastrointestinal anastomosis to improve the patient's jaundice and nutritional status, followed 3-4 weeks later by a second-stage resection of the tumor along with the pancreatic head and duodenum [3]. Because it was believed at the time that the digestive function of pancreatic juice would threaten anastomotic healing, and that the pancreas was not essential to survival, the pancreatic stump was simply oversewn and closed. The discovery of vitamin K changed the bleeding tendency of jaundiced patients, allowing Whipple and colleagues to design and successfully perform the procedure as a single-stage operation, which was continually refined thereafter and came to be commonly known as the "Whipple procedure." In 1944, Child modified the reconstruction sequence: first performing a pancreaticojejunal anastomosis at the end of the jejunum, followed by a hepaticojejunostomy, and finally a gastrojejunostomy (end-to-side), restoring gastrointestinal continuity in the order of pancreas, bile duct and stomach. This differed from Whipple's method and sequence of anastomosis and became known as the "Child method" of digestive tract reconstruction, which gradually developed into the widely used clinical technique.

However, these numerous technical breakthroughs did not substantially improve surgical outcomes. Literature published in the 1960s reported that surgical complication rates for pancreatic cancer reached as high as 60%, with mortality rates approaching 25%. It was not until the late 1980s, as a large number of pancreatic surgery centers emerged worldwide, that improvements in surgical technique and accumulated experience, better patient selection criteria, standardized perioperative management and the widespread adoption of nutritional support, along with advances in anesthesia and intensive care, brought post-PD mortality down to below 5%. Nevertheless, the overall complication rate has remained high as 30% 50%, with pancreatic fistula considered the most significant, occurring in approximately 20%-25% of cases-a rate that seems difficult to accept compared with other types of GI reconstruction. Furthermore, given the potential dangers associated with pancreatic fistula, which can lead to secondary complications such as intra-abdominal infection, delayed gastric emptying (DGE), sepsis, hemorrhage, and multiple organ failure, it has become the weakest link in the entire treatment process.

This study retrospectively analyzed the clinical data of 277 patients who underwent PD at the Department of General Surgery, Shengjing Hospital of China Medical University, between January 2014 and October 2015, to analyze and identifying the risk factors influencing the occurrence of postoperative pancreatic fistula.

2. Material and Methods

2.1 Definition and Grading of Postoperative Pancreatic Fistula

In 2005, the International Study Group on Pancreatic Fistula (ISGPF) proposed a standardized definition of pancreatic fistula, defined as a measured amylase concentration in the abdominal drainage fluid on or after postoperative day 3 that is more than three times the upper limit of normal serum amylase. Based on the patient's clinical presentation and its impact on the course of diagnosis and treatment, pancreatic fistula was classified into three grades: A, B, and C [4]. Grade A is the most common and represents a transient pancreatic fistula. Patients are typically asymptomatic, and it has no significant effect on the clinical pathway and does not prolong hospital stay. Grade B requires corresponding adjustments to the current treatment plan. Patients are usually kept nil by mouth and rely on enteral and/or parenteral nutritional support. If symptoms such as abdominal pain, fever, or elevated white blood cell count occur, targeted antibiotic therapy should be selected, and adequate drainage must be ensured; the use of somatostatin and its analogues may also be considered. In Grade C pancreatic fistula, patients may present with unstable vital signs, sepsis and organ dysfunction, and often require intensive care or reoperation (Table 1).

2.2 General Data

Clinical data were collected and compiled from 277 patients who underwent PD at the Department of General Surgery, Shengjing Hospital, between January 2014 and October 2015. Among all patients, there were 168 males and 109 females, giving a male-to-female ratio of 1.5:1, with a mean age ranging from 19 to 81 years (58±10 years). Pathological diagnoses were broadly classified as follows: pancreatic cancer (32.5%), duodenal cancer (22.4%), cholangiocarcinoma (19.5%), ampullary adenocarcinoma (10.1%), chronic pancreatitis (7.2%), and other pathological types (8.3%).

2.3 Statistical Methods

All data were recorded and analyzed using SPSS 19.0 software. Univariate analysis was performed on 19 factors potentially associated with the occurrence of postoperative pancreatic fistula, using the Chi-square test and Fisher's exact test, with $P < 0.05$ considered statistically significant. Variables found to be statistically significant were then entered into a binary logistic regression model for multivariate analysis, with a significance threshold of $P < 0.05$, in order to determine the independent risk factors for pancreatic fistula following pancreaticoduodenectomy.

3. Results

3.1 Postoperative Pancreatic Fistula and Other Complications

Among all 277 patients who underwent PD in this cohort, POPF occurred in 136 cases (49.1%), including 63 cases (22.7%) of Grade A, 59 cases (21.3%) of Grade B, and 14 cases (5.1%) of Grade C. Overall, 13 deaths (4.7%) occurred during the perioperative period (within 90 days postoperative), of which 9 (6.6%) were pancreatic fistula fistula-related deaths. The overall complication rate was 71.8%, and the mean postoperative hospital stay was 24.13±14.17 days.

3.2 Univariate and Multivariate Analysis of POPF

Risk factors for pancreatic fistula after PD can be divided into three categories: patient-related factors, disease-related factors, and surgical factors. Patients related factors include sex, ASA grade, jaundice and the presence of comorbidities such as diabetes mellitus and coronary artery disease. Disease-related factors generally include the type of primary disease, pancreatic duct diameter, whether the pancreatic duct is located close to the dorsal aspect, degree of tumor progression, and whether major vessels such as the portal vein are invaded. Surgical factors mainly refer to operative time, intraoperative blood loss, the method of pancreaticoenteric anastomosis, and placement of pancreatic/biliary stent tubes.

Univariate analysis showed that six factors-prior history of diabetes, perioperative serum total bilirubin level, intra-abdominal thickness, main pancreatic duct diameter, intraoperative blood loss, and postoperative pathological type-were significantly associated with the incidence of pancreatic fistula after PD ($P < 0.05$) (see Table 2). These six associated factors were then entered as independent variables, with the occurrence of POPF as the dependent variable, into a logistic regression analysis. The results indicated that a pancreatic duct diameter ≤3 mm and pathological diagnoses other than pancreatic cancer or pancreatitis were independent risk factors for the occurrence of pancreatic fistula after PD (Table 3).

4. Discussion

Pancreatic fistula remains the most common complication after PD, with an incidence of approximately 49% in this cohort. When patients develop postoperative pancreatic fistula, particularly Grade B or C fistula, targeted treatment strategies tailored to the patient's specific condition are often required, such as drainage tube irrigation and screening for delayed intra-abdominal bleeding. If not managed promptly or appropriately, Grade III or higher Clavien-Dindo complications such as intra-abdominal infection and hemorrhage may occur, increasing the reoperation rate, prolonging hospital stay, and adding to patients' financial and psychological burden.

This analysis indicates that patients with a prior history of diabetes have a lower risk of POPF than those without diabetes-that is, comorbid diabetes appears to have a certain protective effect against pancreatic fistula after PD. A possible explanation is that diabetes leads to reduced body fat content, particularly reduced pancreatic fat content, along with greater fibrosis of the pancreatic parenchyma, making the pancreaticojejunal anastomosis more secure and less prone to leakage [5].

Jaundice is the presenting complaint for many patients; in this study, approximately 54% patients presented with varying degrees of preoperative jaundice, and when a patient's serum total bilirubin exceeded 171umol/L, the risk of POPF was significantly increased. It is worth noting that preoperative biliary drainage to reduce bilirubin did not effectively lower this risk. Severe jaundice impairs the liver's synthetic function and detoxification capacity. Biliary obstruction prevents bile from flowing smoothly into the intestine, weakening the inhibitory effect of bile salts on gram-negative bacteria in the gut. In addition, jaundice can affect the body's coagulation mechanisms and may even accompanied by dysfunction of multiple organs, including the kidneys [6]. For obstructive jaundice, clinical interventions such as ENBD, PTCD, and other forms of external biliary drainage, or internal drainage via biliary stents, can be used to control preoperative bilirubin levels. This remains of a subject of international debate: whether preoperative biliary drainage can improve the incidence and mortality of complications such as pancreatic fistula after PD, and which patients would benefit from it, requires further high-quality research to clarify and identify in the future.

Because PD is a complex procedure involving multiple important organs and major blood vessels in and out of the abdominal cavity, with long operative times and substantial surgical trauma, an increase in intraoperative blood loss is often unavoidable. This study found that when overt intraoperative blood loss exceeded 800ml, the body compensates with redistribution of blood flow, leading to hypoperfusion of intra-abdominal tissues, which is unfavorable for anastomosis between the duct and mucosa, also between pancreatic capsule and jejunal serosa. Under such circumstances, if hemodynamic disturbance occurs, subsequent rapid fluid resuscitation by the anesthesiologist may further aggravate tissue edema, threatening the healing of the anastomosis and surgical wound.

Intra-abdominal thickness, as a parameter, has been used by the hepatobiliary-pancreatic surgery department at Japan's National Cancer Center Hospital to preoperatively predict the incidence of pancreatic fistula after PD [7]. In the prediction scoring system proposed by Yamamoto et al., this value is obtained by measuring, at the level of the umbilicus on preoperative CT images, the distance between the inner border of the rectus abdominis muscle (i.e., the inner surface of the linea alba) and the posterior wall of the abdominal aorta. A high BMI is widely recognized as a risk factor for POPF; earlier studies have noted that a pancreas containing more adipose tissue-positively correlated with BMI and referred to as a "fatty pancreas"-is more prone to fistula formation after PD [8], which also reflects higher visceral fat content in the abdominal organs of patients with higher body fat. Because BMI is commonly used in medicine to describe the degree of obesity, and intra-abdominal thickness is closely associated with BMI, this parameter can also more directly reflect the depth of surgical

manipulation and the difficulty of surgical field exposure and tissue mobilization.

A small pancreatic duct diameter is currently a widely accepted independent risk factor for POPF internationally [5-9]. When the main pancreatic duct diameter is ≤3 mm, pancreatic juice secretion is significantly higher than in pancreases with a larger duct diameter [10]. As an important factor that surgeons can, to some extent, manage through anastomotic technique and method, a small main pancreatic duct diameter directly increases the technical difficulty of duct-to-mucosa anastomosis, particularly for less experienced young surgeons. Pancreatic duct diameter can be measured via preoperative CT scan, selecting the pancreatic cross-section at the point where the SMV joins the portal vein trunk [11]. Intra-abdominal thickness can be measured at the same time, which may be of some help in preoperatively estimating a patient's likelihood of developing POPF.

This study also found that when the pathological diagnosis of the primary disease was ampullary carcinoma, duodenal malignancy, distal cholangiocarcinoma, or similar types-that is, pathological types other than pancreatic cancer (PDAC) or chronic pancreatitis-this was an independent risk factor for pancreatic fistula after PD. Ampullary carcinoma, duodenal tumors, cystic pancreatic tumors, islet cell tumors, and distal cholangiocarcinoma are often accompanied by a soft pancreas and a non-dilated pancreatic duct[12,13,14]. In contrast, when the pathological diagnosis is pancreatic adenocarcinoma or chronic pancreatitis, the pancreas typically shows varying degrees of fibrosis and pancreatic duct dilation, resulting in a comparatively lower risk of POPF than other pancreatic pathology [15,16].

5.Conclusion

Overall, pancreatic fistula after PD remains a major challenge for pancreatic surgeons. Through thorough preoperative, intraoperative and postoperative assessment of the risk of pancreatic fistula, and my implementing individualized treatment based on each patient's specific circumstances, it is possible to reduce the incidence of high grades of Clavien-Dindo complications such as clinical-relevant POPF, thereby providing the best treatment approach and outcomes.

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Tables

Table 1. ISGPF Classification of POPF

Grade	*A*	*B*	*C*
Clinical conditions	Well	Often well	Ill appearing/ bad
Specific teatment*	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/ positive	Positive
Persistent drainage (after 3 weeks)†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

US, Ultrasonography; *CT,* computed tomographic scan; *POPF,* postoperative pancreatic fistula.
*Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
†With or without a drain in situ.

Table 2. Univariate Analysis of POPF after PD

Factors	POPF	Non-POPF	Chi-sq	P value
Sex				
Male	84	84	0.139	0.401
Female	52	57		
Age				
≥60	65	78	1.570	0.12
< 60	71	63		
Hypertension				
Yes	34	35	0.001	0.542
No	102	106		
CAD				
Yes	7	9	0.194	0.428
No	129	132		
T2DM				
Yes	22	37	4.309	0.026*
No	114	104		
Tobacco				
Yes	48	57	0.344	0.323
No	80	82		

Prior operation (abdominal)				
Yes	32	27	0.792	0.229
No	104	114		
Pancreatitis				
Yes	5	10	1.577	0.161
No	131	131		
Cholangititis				
Yes	3	2	0.242	0.483
No	133	139		
Preoperative biliary drainage				
Yes	18	15	0.445	0.315
No	118	126		
Preoperative TBil (umol/L)				
≥171	46	32	4.238	0.027*
<171	90	109		
Preoperative Alb (g/L)				
≥40	58	60	0.000	0.542
<40	78	81		
Intra-abdominal thickness (mm)				
>70	49	44		
≤70	46	69	3.336	0.046*
Pancreatic duct diameter (mm)				
>3	37	75		
≤3	80	52	18.453	0.000*
Operation time (min)				
≥400	65	65		
<400	71	76	0.080	0.436
Blood loss (ml)				
≥800	10	23	5.295	0.016*
<800	126	118		
PJ anastomosis				
Duct-to-mucosa	69	65	0.596	0.257
Dunking or Others	67	76		

Pancreatic duct stent				
Yes	120	115	2.398	0.083
No	16	26		
Pathology				
Pancreatic. cancer or pancreatitis	33	68	17.158	0.000*
others	103	73		

Table 3. Independent Risk Factors for POPF by Multivariate Analysis

Associated factors	OR value（95%CI）	P value
T2DM	1.809（1.279 – 3.254）	0.122
Preoperative Tbil	2.723（2.715 – 2.732）	1.002
Intraoperative blood loss	2.718（2.715 – 2.718）	0.392
Intra-abdominal thickness	2.743（2.702 – 2.784）	0.263
Pancreatic duct diameter	2.134（1.911 – 2.438）	0.001*
Postoperative pathology	1.458（1.208 – 2.130）	0.006*