World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i46.17491

World J Gastroenterol 2014 December 14; 20(46): 17491-17497
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

RETROSPECTIVE STUDY

Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy

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Received: March 17, 2014 Revised: April 25, 2014
Accepted: August 13, 2014
Published online: December 14, 2014

Abstract

AIM: To explore the morbidity and risk factors of postoperative pancreatic fistula (POPF) following pancreaticoduodenectomy.

METHODS: The data from 196 consecutive patients who underwent pancreaticoduodenectomy, performed by different surgeons, in the General Hospital of the People's Liberation Army between January 1st, 2013 and December 31st, 2013 were retrospectively collected for analysis. The diagnoses of POPF and clinically relevant (CR)-POPF following pancreaticoduodenectomy were judged strictly by the International Study Group on Pancreatic Fistula Definition. Univariate analysis was performed to analyze the following factors: patient age, sex, body mass index (BMI), hypertension, diabetes mellitus, serum CA19-9 level, history of jaundice, serum albumin level, blood loss volume, pancreatic duct diameter, pylorus preserving pancreaticoduodenectomy, pancreatic drainage and pancreaticojejunostomy. Multivariate logistic regression analysis was used to determine the main independent risk factors for POPF.

RESULTS: POPF occurred in 126 (64.3%) of the patients, and the incidence of CR-POPF was 32.7% (64/196). Patient characteristics of age, sex, BMI, hypertension, diabetes mellitus, serum CA19-9 level, history of jaundice, serum albumin level, blood loss volume, pylorus preserving pancreaticoduodenectomy and pancreaticojejunostomy showed no statistical difference related to the morbidity of POPF or CR-POPF. Pancreatic duct diameter was found to be significantly correlated with POPF rates by univariate analysis and multivariate regression analysis, with a pancreatic duct diameter $\leqslant$ 3 mm being an independent risk factor for POPF (OR = 0.291; P = 0.000) and CR-POPF (OR = 0.399; P = 0.004). The CR-POPF rate was higher in patients without external pancreatic stenting, which was found to be an independent risk factor for CR-POPF (OR = 0.394; P = 0.012). Among the entire patient series, there were three postoperative deaths, giving a total mortality rate of 1.5% (3/196), and the mortality associated with pancreatic fistula was 2.4% (3/126).

CONCLUSION: A pancreatic duct diameter $\leqslant$ 3 mm is an independent risk factor for POPF. External stent drainage of pancreatic secretion may reduce CR-POPF mortality and POPF severity.

Key words: Pancreaticoduodenectomy; Pancreatic fistula; Complication; Pancreatic duct

Core tip: While pancreaticoduodenectomy (PD) remains the only curative option for some benign and malignant diseases of the pancreas peri-ampullary region and head, it is inherently difficult and associated with high morbidity and mortality rates. The most important factor of morbidity and mortality following PD is the appearance of postoperative pancreatic fistula (POPF). The Chinese PLA General Hospital performs 200 to 400 PD procedures per year. Analysis of our case series showed that a pancreatic duct diameter $\leqslant$ 3 mm is an

independent POPF risk factor. External stent drainage of pancreatic secretion may reduce mortality of clinically relevant-POPF and alleviate POPF severity.

Liu QY, Zhang WZ, Xia HT, Leng JJ, Wan T, Liang B, Yang T, Dong JH. Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy. *World J Gastroenterol* 2014; 20(46): 17491-17497 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i46/17491.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i46.17491

INTRODUCTION

Advances in surgical techniques and the correlated materials for pancreaticoduodenectomy (PD) have lead to an increase in the volume of PD procedures performed each year[1-7]. PD has emerged as a preferred therapeutic method for treating various types of benign and malignant diseases of the pancreatic peri-ampullary region and head. Nevertheless, this procedure remains technically difficult and is associated with high morbidity and mortality rates[8-10]. Currently, the most important factor of morbidity and mortality following PD is the development of postoperative pancreatic fistula (POPF). The rate of POPF has remained unacceptably high, according to the latest studies, which have reported anastomotic breakdown in 11.4% to 44.7% of patients worldwide[11-13]; these morbidity rates of POPF are particularly troubling when compared with leakage rates of most other gastrointestinal anastomoses, which are notably lower. The occurrence of clinically relevant (CR)-POPF is associated with prolonged length of hospitalization and increased costs of care, as it necessitates additional testing and procedures, which culminate in increased risk of further morbidities and possibly mortality. Unfortunately, no standardized definition of POPF has yet been agreed upon by the global healthcare community that would permit standard reporting and appropriate comparison of results between different studies. The purpose of this study was to determine possible risk factors that may be associated with the onset of POPF after PD.

MATERIALS AND METHODS

Subject enrollment and data collection

A retrospective review was conducted of the 196 patients who underwent PD between January 1st, 2013 and December 31st, 2013 in the Department of Hepatobiliary Surgery of the Chinese People's Liberation Army General Hospital (Beijing, China). The following demographic and clinical data were collected for analysis: patient sex, age, body mass index (BMI), indications for surgery, presence of hypertension, presence of diabetes mellitus, serum CA19-9 level, presence of jaundice, serum albumin level, operative blood loss volume, pancreatic duct diameter, receipt of pylorus-preserving PD, receipt of pancreatic duct drainage, and receipt of pancreaticojejunostomy. In addition, data on postoperative complications were collected for analysis, with a specific focus on occurrence of pancreatic fistula, mortality, and duration of postoperative hospital stay. No patient was excluded from the case series.

Operative procedure

Patients underwent either pylorus preserving or classic (hemigastrectomy) PD. Pancreatic and biliary system reconstruction was performed in a retrocolic fashion, and anticolic reconstruction was implemented for the gastro/duodenojejunostomy. If possible, a pancreatic tube with several perforations was inserted into the pancreatic duct and fixed at the edge of the transected pancreatic duct, to serve as a stent from the jejunum. In some cases, an external stent was placed across the pancreaticojejunal anastomosis and through the abdominal wall to facilitate external drainage of the pancreatic duct. The choice of pancreaticojejunostomy duct-to-mucosa anastomosis or invaginated anastomosis technique was made according to the surgeon's preference. No pancreaticogastrostomy was performed in the case series. Drain placement was anterior or posterior to the pancreaticojejunostomy and choledochojejunostomy anastomosis. Prophylactic octreotide was not routinely used.

Classification and detailed definition of POPF

To date, no definitive profile of POPF has been agreed upon the global medical community. As such, the standard definition of POPF proposed by the International Study Group on Pancreatic Fistula (ISGPF) was chosen for use in the current study (Table 1)[14], in which pancreatic leakage is evaluated according to the presence of drainage fluid, in any measurable volume, with an amylase content that is more than three times the upper normal limit of that in serum, occurring on or after postoperative day 3. ISGPF-based diagnosis of POPF is further classified into grades A, B, and C according to the clinical influence on the patient's hospitalization process and ultimate outcome. The focal point was further concentrated by characterizing cases according to the concept of "clinically relevant" POPF, which describes a stage of the condition often used to discriminate patients with asymptomatic biochemical POPF from those with the clinical disorder who require therapeutic intervention or are at risk of death. For CR-POPF, when POPF cases showed concomitant symptoms of pyrexia, abdominal pain, and/or leukocytosis, anti-infective therapy was considered necessary; these cases represented POPF progression to grade B. Cases requiring an invasive therapeutic manipulation represented POPF progression to grade C (Table 1).

Statistical analysis

Quantitative data are expressed as mean ± SD and the significance of inter-group differences was evaluated using an independent sample Student's *t* test. Categorical variables were evaluated by the Fisher's exact test and

Table 1 Main parameters for postoperative pancreatic fistula grading

Grade	A	B	C
Clinical conditions	Well	Often well	Ⅲ appearing/bad
Specific treatment[1]	No	Yes/no	Yes
US/CT, if obtained	Negative	Negative/ positive	Positive
Persistent drainage, after 3 wk[2]	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

[1]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue, and/or minimally invasive drainage; [2]With or without a drain in situ. CT: Computed tomography scan; POPF: Postoperative pancreatic fistula; US: Ultrasonography.

χ^2 test. All of the variables were assessed by univariate analyses, and only those variables showing statistical significance ($P < 0.05$) were evaluated by multivariate logistic analyses to determine the main independent risk factors for POPF. The statistical software package SPSS 19.0 (IBM Corp., Armonk, NY, United States) was used for all analyses. A *P*-value less than 0.05 was interpreted as statistically significant for all tests.

RESULTS

The study population consisted of 122 males and 74 females, with a mean age of 57 ± 11.5 years old. The indications for PD included ampullary carcinoma in 60 (30.6%) patients, pancreatic head tumor in 58 (29.6%) patients, distal cholangiocarcinoma in 48 (24.5%) patients, duodenal carcinoma in 13 (6.6%) patients, chronic pancreatitis in 11 (5.6%) patients, and uncinate process tumors in six (3.1%) patients. The mean postoperative length of hospital stay was 19.7 ± 11.2 d.

A total of 126 (64.3%) patients were diagnosed with POPF, with 62 (49.2%) classified as grade A, 53 (42.1%) classified as grade B, and 11 (8.7%) classified as grade C. The total incidence of CR-POPF was 32.7%.

The total mortality rate among the study population was 1.5% (3/196). All three of the postoperative deaths were due to massive abdominal hemorrhage resulting from POPF.

When the demographic and clinical variables were assessed by univariate analysis to determine the relationship with POPF, there was no statistical significance detected for patient age, sex, BMI, presence of hypertension, presence of diabetes mellitus, serum CA19-9 level, history of jaundice, serum albumin level, operative blood loss volume, pylorus preserving PD or pancreaticojejunostomy (Table 2). Thus, none of these variables showed predictive value for POPF. However, two of the perioperative risk factors - pancreatic duct diameter and pancreatic duct drainage - showed statistically significant association with POPF. Patients with a pancreatic duct diameter ≤ 3 mm had a significantly higher rate of POPF than those with a pancreatic duct diameter > 3 mm (78.1% *vs* 51.0%; $P = 0.000$), and patients who received external drainage of the pancreatic juice had a significantly lower rate of CR-POPF than those who received enteral drainage (21.3% *vs* 37.8%; $P = 0.023$).

When these two risk factors associated with POPF were analyzed by multivariate logistic regression, both showed significant correlation with POPF and/or CR-POPF (Table 3). Specifically, the pancreatic duct diameter ≤ 3 mm was identified as an independent risk factor for POPF (OR = 0.291; $P = 0.000$) and CR-POPF (OR = 0.399; $P = 0.004$), while the use of external pancreatic stenting (external drainage) was identified as an independent risk factor for CR-POPF (OR = 0.394; $P = 0.012$).

DISCUSSION

CR-POPF (grade B and grade C POPF) is the most common and challenging PD complication, having the potential to trigger a lethal delayed massive hemorrhage and septicemia[15-17]. CR-POPF was overwhelmingly the most frequent reason of fatal complications in our case series, with the totality of deaths directly resulting from POPF complicated with delayed massive hemorrhage. Recently, the ISGPF recommended a standard definition of POPF, and it has met with a great deal of acceptance among the global medical community. Having a standardized definition of POPF, and its various gradations, will benefit clinicians and researchers alike since it will allow for equitable comparisons of cases from different centers.

Despite the long-standing lack of a unified definition of this condition, some variables are recognized as risk factors, including male sex, old age, obesity, pre-operative jaundice, creatinine clearance disorder, operative blood loss volume and coronary artery disease[18-24]. However, only the variable of advanced age (> 70 years old) has been shown by multiple studies, including prospective studies, to be a predictive factor related to failure of anastomosis leading to POPF[25]. Surgery-related factors, including high-volume operative blood loss, less experienced (low-volume practice) surgeon, longer duration of the operative procedure and type of pancreaticojejunostomy anastomosis, may also be risk factors. A multi-institutional study confirmed the Fistula Risk Score as a valid tool for predicting development of CR-POPF after PD. In particular, Callery *et al*[26] reported that a simple 10-point Fistula Risk Score (based on small pancreatic duct, soft texture pancreas, high-risk pathology and high operative blood loss volume) is capable of precisely forecasting CR-POPF following PD. This prediction strategy is easy and convenient and amenable to widespread adoption so that surgeons may predict, diagnose, and deal with this severe complication in a timely manner.

Pylorus-preserving PD has the advantage of helping the patient to achieve a good nutritional status postoperatively but is, unfortunately, associated with a significantly

Table 2 Univariate analysis of predictors for pancreatic fistula following pancreaticoduodenectomy

Characteristic	POPF occurrence				CR-POPF occurrence			
	Yes	No	*P* value	χ^2	Yes	No	*P* value	χ^2
Sex			0.429	0.625			0.715	0.134
Male	81	41			41	81		
Female	45	29			23	51		
Age in years			0.492	0.471			0.119	2.433
⩾ 60	53	33			23	63		
< 60	73	37			41	69		
BMI in kg/m^2			0.696	0.153			0.052	3.791
⩾ 25	38	23			14	47		
< 25	88	47			50	85		
Hypertension			0.728	0.121			0.930	0.008
Yes	39	20			19	40		
No	87	50			45	92		
Diabetes mellitus			0.431	0.621			0.959	0.003
Yes	18	13			10	21		
No	108	57			54	111		
Serum CA19-9 in mg/L			0.257	1.285			0.774	0.082
> 37	65	42			34	73		
⩽ 37	61	28			30	59		
Pre-operative jaundice			0.638	0.222			0.147	2.102
Yes	71	37			40	68		
No	55	33			24	64		
Serum albumin in g/L			0.572	0.319			0.498	0.460
< 35	18	8			10	16		
⩾ 35	108	62			54	116		
Blood loss in mL			0.109	2.576			0.639	0.220
⩾ 600	16	15			9	22		
< 600	110	55			55	110		
Pancreatic duct diameter in mm			0.000	15.696			0.008	6.952
⩽ 3	75	21			40	56		
> 3	51	49			24	76		
Pylorus-preserving			0.798	0.066			0.159	1.987
Yes	57	33			34	56		
No	69	37			30	76		
Pancreatic drainage			0.800	0.064			0.023	5.180
External	40	21			13	48		
Enteral	86	49			51	84		
Pancreatico-jejunostomy			0.307	1.043			0.766	0.089
Duct-to-mucosa	117	62			59	120		
Invagination	9	8			5	12		

CR-POPF: Clinically relevant postoperative pancreatic fistula; POPF: Postoperative pancreatic fistula.

Table 3 Logistic regression for predictors of pancreatic fistula following pancreaticoduodenectomy

Variable	B	SE	Wals	*P* value	OR	95%CI
Total PF						
Pancreatic duct diameter	-1.233	0.318	15.056	0.000	0.291	0.156-0.543
Clinically relevant PF						
Pancreatic duct diameter	-0.919	0.321	8.171	0.004	0.399	0.213-0.749
Pancreatic drainage	-0.932	0.370	6.339	0.012	0.394	0.191-0.813

B: Regression coefficient; PF: Pancreatic fistula; Wals: χ^2 value.

higher incidence of delayed gastric emptying[27-29]. Studies have also shown that the pylorus-preserving technique does not provide any advantage related to pancreatic fistula formation. Many techniques have been proposed for the pancreaticojejunostomy anastomosis reconstruction to prevent the development of a POPF, but there remains controversy as to which of these is the best approach[30-33]. A review of the literature on the various types of pancreaticojejunal anastomosis reported suggests that duct-to-mucosa anastomosis has been more widely practiced than the invagination anastomosis technique[34,35]. However, in our case series no differences were found between the groups receiving either of these two techniques for the rates of mortality, POPF, and CR-POPF.

In the current study, pancreatic duct diameter cor-

related with POPF rates significantly in univariate analysis and multivariate regression, and the pancreatic duct diameter was identified as an independent risk factor for POPF. The pancreatic duct diameter has been proposed to be associated with the texture of the pancreatic parenchyma, a feature that is helpful for performing a duct-to-mucosa reconstruction of pancreaticojejunostomy anastomosis. POPF has also been shown to be associated with pancreatic duct diameter, and this was demonstrated with our case series as well. In our study, none of the 11 patients with chronic pancreatitis developed POPF, which agrees with previous studies showing that POPF incidence is much lower than that for other pancreatic diseases[36]. Moreover, the pancreatic duct diameter independently correlated with an increased rate of POPF. The collective data in the literature indicates that POPF mainly contributes to early postoperative morbidity and hospitalization time. Consequently, drainage data may be helpful for confirming the development of chemical POPF, but the lesion severity can only be judged by clinical results. Patients that are considered more susceptible to development of a POPF, such as those with a small pancreatic duct diameter ($\leqslant$ 3 mm), may require more careful clinical observation[37].

Another intriguing finding from our study was that the CR-POPF rate was higher in patients without an external pancreatic stent; this finding agrees with previous studies which have suggested that drainage of the exocrine pancreatic secretions may alleviate the severity of POPF[38]. Our study also identified the use of enteral drainage as an independent risk factor for CR-POPF. To date, however, there has been no agreement as to whether a pancreatic duct stent for internal or external drainage can decrease the incidence of POPF following PD. Based on the findings from the current study, the external pancreatic tube drainage of the pancreatic secretion from the anastomosis was beneficial, and permitted more precise placement of sutures as well; these features may have served to protect the pancreatic duct from suture injury, thereby decreasing the incidence of POPF.

In conclusion, a pancreatic duct diameter $\leqslant$ 3 mm is independently correlated with increased rate of POPF, which itself is a primary contributor to early postoperative morbidity and prolonged hospitalization time. External drainage of pancreatic secretions, using an external stent across the pancreaticojejunal anastomosis, may significantly reduce the mortality of CR-POPF and alleviate the severity of POPF.

COMMENTS

Background

Pancreaticoduodenectomy (PD) has emerged as a standard treatment for various benign and malignant diseases of the pancreatic peri-ampullary region and head. Nevertheless, this procedure is inherently difficult and associated with high morbidity and mortality rates. The most important factor of morbidity and mortality following PD is the development of postoperative pancreatic fistula (POPF), which principally contributes to early postoperative morbidity, prolonged hospitalization time, and PD-related mortality.

Research frontiers

Advances in surgical techniques and the correlated materials for PD have led to an increase in the volume of PD procedures performed each year. In contrast, the rate of POPF has not improved in tandem with the increased practice of PD, according to recent large series studies performed worldwide. The morbidity rate of POPF is unacceptable when compared to the leak rates related to most other gastrointestinal anastomoses.

Innovations and breakthroughs

Pancreatic duct diameter was found to be independently correlated with an increased rate of POPF. POPF contributes to early postoperative morbidity, prolonged hospitalization time, and mortality among the PD-treated patient population. External drainage of bile and pancreatic secretions could reduce the mortality among patients with clinically relevant postoperative pancreatic fistula (CR-POPF; grade B and C POPF) and alleviate the severity of POPF.

Applications

Diagnosis of POPF and CR-POPF following PD should be made with strict adherence to the International Study Group on Pancreatic Fistula definition; when put into routine practice by clinicians across the globe, this unified definition will likely allow for more equitable comparison of these cases among institutions. Patients at higher risk for developing a POPF, such as those with a small pancreatic duct diameter ($\leqslant$ 3 mm), may require more careful clinical observation. Drainage of pancreatic secretions, through an external pancreatic stent, may reduce the mortality of CR-POPF and alleviate the severity of POPF.

Terminology

Pancreaticoduodenectomy is the preferred therapeutic treatment for several forms of benign and malignant diseases involving the pancreatic peri-ampullary region and head. Postoperative pancreatic fistula is the most common adverse event following a pancreaticoduodenectomy.

Peer review

This case series retrospective study was conducted at a very high level of scientific accuracy and its presentation is high quality. The findings from this study are helpful, as they confirm a few of the new ideas in the management of post-Whipple pancreatic fistulas. Readers with interest in POPF will find this paper beneficial and informative.

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P- Reviewer: Iacono C, Osian G, Tang Y **S- Editor**: Qi Y
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ISSN 1007-9327