

A Rapid Predictive System for Pancreatic Fistula after Pancreaticoduodenectomy: A Report from a Low-Volume Center

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Abstract

Background: Postoperative pancreatic fistula (POPF) is a serious complication of pancreaticoduodenectomy (PD).

Methods: We retrospectively reviewed the records of 109 consecutive patients who underwent PD between January 2006 and September 2015 in Saitama City Hospital. Preoperative and intraoperative variables were evaluated by univariate and multivariate logistic regression analyses to establish an immediate prediction model for POPF.

Results: POPF grade A developed in 13 patients [12% (13/109)], grade B in 19 [17% (17/109)], and grade C in 3 [3% (3/109)]. Multivariate analysis demonstrated that the diameter of the main pancreatic duct (dMPD) ≤ 3.2 mm [odds ratio (OR) 4.26, 95% confidence intervals (CIs) 1.45-12.50, $P=0.008$], and operative times ≥ 425 min (OR 10.20, 95% CIs 2.67-39.00, $P<0.001$) were significant independent risk factors for POPF after PD. Using a combination of these two factors, the 109 patients were divided into two groups, and the incidence of POPF in patients with dMPD ≤ 3.2 mm and with operative times ≥ 425 min was significantly higher than in those without them both [62% (26/42) versus 13% (9/67), $P<0.001$]. The predictive accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 77% (84/109), 74% (26/35), 78% (58/74), 62% (26/42), and 87% (58/67), respectively.

Conclusions: Our predictive model of POPF after PD has high accuracy. The immediate ability to predict POPF after PD using our model results in better postoperative management of patients undergoing PD.

Keywords: Postoperative pancreatic fistula; Pancreaticoduodenectomy; Predictive model

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Introduction

Postoperative pancreatic fistula (POPF) is one of the most severe postoperative complications of pancreaticoduodenectomy (PD). This complication, occurring in 2% to 20% of patients after PD, often leads to miserable consequences, such as abscess formation, sepsis, and abdominal hemorrhage. These events result in longer hospital stays, increased hospital costs, and increased post-operative deaths after PD [1,2]. If the development of POPF after PD due to preoperative and intraoperative factors could be predicted immediately, surgeons could better manage

it, resulting in improved morbidity, mortality, and economic losses associated with PD. Perioperative risk or predictive factors, including pancreatic texture, pancreatic duct diameter, anastomosis type, pathology, and blood loss, correlated with POPF and evaluated by multivariate analysis have been described in the literature [2-5]. These factors are very useful for the prediction of POPF. If POPF could be predicted by the time the operation was finished, its postoperative treatment could be initiated as soon as possible. The purpose of this study was to analyze whether it was possible to immediately predict POPF after PD by evaluation of preoperative and intraoperative factors.

Patients and Methods

Study design

The records of 112 consecutive patients who underwent PD between January 2006 and September 2015 for periampullary pathologies, including pancreatic head carcinoma, distal bile duct carcinoma, ampulla of Vater carcinoma, duodenal carcinoma and others, were retrospectively reviewed. Two patients who underwent PD and then died from complications other than POPF within the 8th postoperative day, and one patient who underwent total pancreatectomy, were excluded. The Ethics Review Board of Saitama City Hospital approved this study including the use of the opt-out consent procedure (the approval code; A2714).

Preoperative assessment

The preoperative diagnosis was performed by clinical assessment (age, gender, symptoms, and signs), laboratory investigation (complete blood counts, creatinine, serum total bilirubin level, serum amylase level, and tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9), and multidetector-row computed tomography (MDCT). MDCT was performed immediately upon admission to Saitama City Hospital. The diameter of the main pancreatic duct (dMPD) right above the portal vein was measured in the axial view of the MDCT. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in all patients. The biliary drainage of patients with obstructive jaundice was examined using an endoscopic biliary stent during ERCP.

Surgical procedures

All operations were performed by three experienced surgeons or under their supervision. The total of ten surgeons including those three experienced surgeons operated on the patients and the procedures included conventional PD in 56 patients, pylorus-preserving PD in six patients, and subtotal stomach-preserving PD in 47 patients. Combined portal vein resection was performed in ten patients. The type of digestive tract reconstruction was the Child's modified method in 105 cases and Imanaga's method [6] in four cases. In all cases, pancreaticojejunostomy was performed by end-to-side and duct-to-mucosa anastomosis. No pancreaticogastrostomies were performed. In all patients, the duct-to-mucosa anastomosis was performed with a double layer anastomosis using interrupted 6-0 non-absorbable braided suture (Ethibond Extra, Ethicon, Inc.) or interrupted 5-0 absorbable suture (PDS*II, Ethicon, Inc.). In the double layer suture, the pancreatic parenchyma was sutured to the jejunal wall by 3-0 silk-braided suture (Perma-Hand Silk, Ethicon, Inc.) or 4-0 absorbable-braided suture (Coated VICRYL, Ethicon, Inc.). A 5- or 6-French (Fr) polyvinyl chloride tube (Sumitomo Bakelite, Tokyo, Japan) was inserted into the pancreatic duct as an internal stent in all cases. Omental wrapping of major vessels was performed in 105 cases and fibrin glue (Bolheal, Teijin Pharma Limited, Tokyo, Japan) was employed in four patients. The pancreaticojejunostomies and choledocojejunostomies were drained routinely. In the 11 patients before January 2007, the pancreaticojejunostomy drainage was performed using a 12-

Fr Penrose drain inserting stomach tube (Salem Sump Tube, Nippon Covidien Ltd, Shizuoka, Japan) and the drainage fluid was continuously suctioned. After that date, closed silicone drains (Blake Silicone Drain, Ethicon Inc.) were used for both pancreaticojejunostomies and choledocojejunostomies.

Postoperative management

All patients received prophylactic antibiotics intra-operatively and 3 days to 4 days postoperatively. Prophylactic octreotide was not routinely used. Output volumes from intraoperatively placed drains were recorded daily until the drain was removed. The amylase level of the drainage fluid was measured on postoperative day (POD) 3, whereas in some cases, it was measured on POD 1 or 2 at the discretion of the surgeon because of clinical limitations. In patients without POPF, the drains were removed before the 8th POD. The drains were maintained longer in patients with POPF. The nasogastric tube was typically removed at POD 1, but in six patients who had pylorus-preserving PD, the nasogastric tube was removed between the 6th and 8th POD. The patients resumed meals with a fluid diet followed by a regular diet when they passed flatus.

Definition of POPF

In Saitama City Hospital, POPF was diagnosed using the International Study Group for Pancreatic Fistula (ISGPF) guidelines [1]. According to these guidelines, POPF is defined as any measurable volume of draining fluid on or after POD 3 with amylase content greater than three times the upper normal serum activity from an intraoperatively placed drain. Furthermore, the POPF was graded as A, B, or C by nine clinical criteria of the ISGPF guidelines. POPF Grade A is a so-called "transient fistula" and has no impact on the clinical outcome. POPF Grade B has a clinical impact requiring several treatments such as persistent drainage and radiological intervention. POPF Grade C is the most severe complication and results in sepsis, abdominal hemorrhage, or patient death. In this study, we evaluated drain amylase levels on POD 3; however, in some cases, the evaluation was conducted on POD 1 or 2 at the discretion of the surgeon because of clinical limitations. Patients were considered not to have POPF when the following were noted in the medical records: the drains were removed before POD 8; without measurement of the amylase level of drain fluid; and there was a good postoperative clinical course. Patients were diagnosed as POPF grade B when the fluid appearance of the drain next to the pancreaticojejunostomy was greenish, brown, or infectious without a high amylase content of the drain output.

Data collection

The aim of this study was to determine whether the rapid prediction of POPF by preoperative and intraoperative variables was possible. Therefore, only preoperative and intraoperative data were collected from all patients' baseline history and physical examination records. Preoperative variables included patients' demographics (age and gender), symptoms (diabetes mellitus), characteristics [body mass index (BMI)], laboratory exams [serum albumin, total bilirubin at admission and on the

preoperative day, serum creatinine, and tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)], and preoperative dMPD by MDCT. Intraoperative variables included operative time, amount of blood loss, and need for a blood transfusion.

Statistical analysis

Statistical analyses were performed with R commander (version 2.1.7) based on R (version 3.2.0) and with EZR, which is a modified version of R commander [7]. The R is free to download and install from the Comprehensive R Archive Network (<http://cran.r-project.org/>). The normality of continuous variables examined using the Shapiro-Wilk test. Continuous variables, including albumin and creatinine, which followed normal distributions, were described as mean \pm standard deviation and were examined by the independent two-sample *t*-test. The other continuous variables, which did not follow normal distributions, were expressed as median values with interquartile range and evaluated by the Wilcoxon rank sum test. Categorical variables were analyzed by Pearson's chi-squared test or Fisher's exact test. *P* values < 0.050 were considered to be statistically significant. Variables with *P* < 0.100 by univariate analysis were entered into a logistic regression analysis. Receiver operating characteristics (ROC) analyses were performed to determine the cut-off values using Youden index. Continuous variables were converted into binary variables based on cut-off values. The results of logistic regression analysis were described as odds ratios (OR) with 95% confidence intervals (95% CIs). The estimation of the prediction of POPF was performed by the predictive accuracy, sensitivity, specificity, and positive and negative predictive value (PPV and NPV) calculated on the basis of the incidence of POPF in the two groups into which the patients were divided by using a combination of the significant risk factors.

Results

Histological examination revealed the diagnosis in 94 in the 109 patients; pancreatic head carcinoma (n=41), distal bile duct carcinoma (n=30), ampulla of Vater carcinoma (n=20) and duodenal carcinoma (n=3). The diagnosis in the other 15 patients was duodenal gastrointestinal tumor in 2, cystic duct carcinoma in 1, metastatic pancreatic head carcinoma in 1, colon carcinoma invading to the duodenum in 1, intraductal papillary mucinous neoplasm in 4, mucinous cystic tumor in 1, neuroendocrine tumor in 1 and benign disorders in 4. The administration of prophylactic antimicrobial agents is shown in (Table 1). In a total of 109 patients, the overall incidence of POPF was 35/109 (32%). The patients with grades A, B, and C POPF were 13 [12% (13/109)], 19 [17% (19/109)], and 3 [3% (3/109)], respectively. All grade C patients experienced abdominal hemorrhage from a pseudoaneurysm of the gastroduodenal artery stump or the common hepatic artery and underwent radiological intervention. No patients died from POPF in Saitama City Hospital.

The preoperative and intraoperative variables that were evaluated by univariate analysis are shown in (Table 2). The univariate analysis was performed using nine preoperative variables and three intraoperative variables. There was a significant difference

between the median dMPD of patients with POPF and without POPF (*P*=0.004). The operative times of patients with POPF were significantly longer than those of patients without POPF (*P*=0.044). The univariate analysis demonstrated that serum level of total bilirubin at admission and CA19-9 were not statistically significant but tended to be lower in patients with POPF. A ROC curves demonstrated that the cut-off values of 4 variables with *P* < 0.100, dMPD, operative time, total bilirubin at admission and CA19-9 were 3.2 mm, 425 min, 7.5 mg/dl and 46.4 U/ml, respectively, of which the area under the curve (AUC) were 0.671, 0.620, 0.604 and 0.607, respectively. These results are shown in (Table 3).

These four variables were further evaluated using multivariate analysis. (Table 4) shows the results of the logistic regression analysis. Both dMPD \leq 3.2 mm and operative times \geq 425 min were significant independent risk factors associated with the incidence of POPF (*P*=0.008 and <0.001, respectively) and the OR and 95% CIs of each was 4.26 and 10.20, and 1.45-12.50 and 2.67-39.00, respectively.

The 109 patients in this study were divided into two groups using the combination of dMPD and operative time. Group A comprised patients with dMPD \leq 3.2 mm and operative time's \geq 425 min. Group B comprised those without dMPD \leq 3.2 mm or without operative time's \geq 425 min. The incidence of POPF in groups A and B were 62% (26/42) and 13% (9/67) (*P*<0.001), respectively (Table 5), and the predictive accuracy, sensitivity, specificity, PPV, and NPV were 77% (84/109), 74% (26/35), 78% (58/74), 62% (26/42), and 87% (58/67), respectively (Table 6).

Discussion

POPF after PD is one of the most important complications correlating to patient death with adverse effects on the medical economy. In spite of advancements in surgical techniques and perioperative patient care, POPF develops in 2% to 20% of patients undergoing PD [1]. This suggests that the prevention of POPF is very difficult. Therefore, improved postoperative management of POPF after PD could lead to reduced mortality and financial savings. The immediate prediction of POPF after PD is necessary to rapidly institute the treatment of POPF with better outcomes.

A great number of studies have described the risk factors for POPF after PD. Age, gender, diabetes mellitus, diameter of the main pancreatic duct, pancreatic texture, pathological diagnosis, amount of blood loss, and operative time are independent risk factors in multivariate analyses [3,8-14]. It has been shown

Table 1: The administration of prophylactic antimicrobial agents.

Agent	No. (%)
Sulbactam/Cefoperazone	53 (53)
Cefmetazole	35 (32)
Flomoxef	8 (7)
Cefazolin	3 (3)
Others*	5 (5)

*Ceftadizime (n=1) Cefepime (n=1) Piperacillin (n=1) Amikacin (n=1) Vancomycin (n=1)

Table 2: Univariate analysis of preoperative and intraoperative variables (n%).

Variables	POPF (N=35)	No POPF (N=74)	P value
Preoperative			
Age (year)	70 (62.5–73.5)	69 (61.5–74.8)	0.966
Gender			
Male	22 (63)	45 (61)	1
Female	13 (37)	29 (39)	
Diabetes mellitus			
Yes	10 (29)	23 (31)	0.966
No	25 (71)	51 (69)	
BMI, kg/m ²	22.5 (20.8–24.5)	21.3 (19.2–23.2)	0.106
Serum albumin, mg/dl, bilirubin, mg/dl	3.7 ± 0.5	3.6 ± 0.5	0.182 [†]
At admission	1.5 (0.8–6.6)	3.4 (0.9–11.3)	0.081
On the preoperative day	0.8 (0.6–1.2)	1.0 (0.7–1.6)	0.113
Serum creatinine, mg/dl	0.72 ± 0.17	0.72 ± 0.19	0.955 [†]
Tumor marker			
CEA, ng/ml	2.7 (1.7–3.7)	2.4 (1.7–3.7)	0.733
CA19-9, U/ml	26.1 (11.9–75.8)	54.7 (19.9–233)	0.071
dMPD, mm	2.5 (1.8–3.1)	3.5 (2.2–5.9)	0.004
Intraoperative			
Operative time, min	487 (451–542)	457 (391–520)	0.044
Blood loss, ml	885 (668–1288)	881 (560–1229)	0.448
Transfusion			
Yes	3 (9)	10 (16)	0.543 ^{††}
No	32 (91)	64 (84)	

Values are expressed as median (interquartile range) or mean ± standard deviation.
 BMI body mass index, CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19-9, dMPD the diameter of the main pancreatic duct
[†] independent two-sample t test
^{††} Fisher's exact test

Table 3: A ROC analysis of variables with P < 0.100 by univariate analysis.

Variables	cut-off value	AUC	Sensitivity	Specificity
dMPD, mm	3.2	0.671	0.8	0.554
Operative time, min	425	0.62	0.914	0.419
Total bilirubin at admission, mg/dl	7.5	0.604	0.857	0.365
CA19-9, U/ml	46.4	0.607	0.686	0.554

AUC area under curve, dMPD the diameter of the main pancreatic duct

Table 4: Multivariate logistic regression analysis.

Variables	OR	95% CIs	P value
dMPD, mm			
≤ 3.2 vs. >3.2	4.26	1.45–12.50	0.008
Operative time, min			
≥ 425 vs. <425	10.2	2.67–39.00	<0.001
Total bilirubin at admission, mg/dl			
≤ 7.5 vs. >7.5	2.22	0.59–8.38	0.238
CA19-9, U/ml			
≤ 46.4 vs. >46.4	1.85	0.60–5.74	0.286

dMPD the diameter of the main pancreatic duct, OR odds ratio, CIs confidence intervals.

that the occurrence of POPF seems to be intricately associated with preoperative, intraoperative, and postoperative variables. We assessed the preoperative and intraoperative variables in univariate and multivariate analyses in order to predict POPF immediately after PD.

We revealed that the dMPD and operative time were statistically significant risk factors in a logistic regression analysis. Our study showed that POPF developed more frequently in patients with dMPD ≤ 3.2 mm than in those with dMPD > 3.2 mm. Previous reports, including prospective or retrospective studies, were

Table 5: The incidence of POPF in group A and group B (n%).

Group	POPF (N=35)	no POPF (N=74)	P value
Group A	26 (62)	16 (38)	<0.001
Group B	9 (13)	58 (87)	

Group A; patients with dMPD \leq 3.2 mm and operative times \geq 425 min
Group B; patients without dMPD \leq 3.2 mm or without operative time \geq 425 min

Table 6: The estimation of the prediction for POPF.

Accuracy	77% (84/109)
Sensitivity	74% (26/35)
Specificity	74% (26/35)
PPV	62% (26/42)
NPV	62% (26/42)

PPV positive predictive value, NPV negative predictive value

consistent with our findings and described that dMPD was a significant risk factor for POPF after PD [11,15]. Furthermore, we showed that there was a statistically significant correlation between the operative time and incidence of POPF. The patients with operative time's \geq 425 min developed POPF approximately 10 times as frequently as those with operative times $<$ 425 min. A previous study also described that the operative time was a significant risk factor based on a multivariate analysis [14].

Using the combination of only these two significant variables, dMPD and operative time, we developed a predictive method for POPF. The predictive accuracy of our method was high at 77%. Our model had low sensitivity and high specificity. This means that POPF is very likely to develop in the patients diagnosed with POPF after PD by our model, but our model will not detect all cases of POPF after PD. It is possible for surgeons to better predict and manage POPF immediately after PD using our model. A recent study [16] revealed that intra-operative amylase concentration in peri-pancreatic fluid is an effective variable for a predictive modeling for POPF. This implies the possibility of refining our predictive model by utilizing intra-operative amylase concentration in peri-pancreaticojejunostomy fluid as a relevant predictor.

Our system predicts not only clinically relevant POPF but also POPF grade A. Some studies have reported predictive systems for POPF grades B or C [17-19], and were very useful;

however, we think it is important to estimate all grades of POPF. There was a case where a drain that was inserted following a pancreaticojejunostomy was removed due to the absence of abnormal discharge; however, infectious discharge was later discovered, and the drain was reinserted with fistulography. We thus evaluated this patient as POPF Grade B. While this case is rare, this suggests that patients diagnosed with POPF Grade A or no POPF could actually have POPF Grade B and we should therefore also predict POPF grade A. Several definitions of POPF after PD were proposed using drain output and/or amylase levels of drain fluid [20-23]; the ISGPF guidelines have become the gold standard for POPF diagnosis since 2005. However, as our previously mentioned case showed, it is essential to carefully observe the postoperative clinical course of patients undergoing PD even if they do not fulfill the ISGPF guidelines.

Though we revealed that our method had high accuracy for the prediction of POPF after PD, there are some weak points in our system. Our study is based on a small number of patients. Many reports about POPF after PD comprise a large number of patients and some studies have more than two hundred patients [3,5,13,17-19]. As our institute is not a high-volume center, we had difficulty accumulating patients undergoing PD. The biggest problem with our method is that we were unable to validate it. In a previous report that included a large number of cases undergoing PD, the cases were divided into two groups to develop a predictive system, which was then validated in another group [18]. As we showed in this report, it is essential to validate predictive models; however, it was difficult for us to validate our model because of the small number of cases that underwent PD in Saitama City Hospital. We understand that it is necessary to validate our model in the future with a prospective study based on further accumulation of patients undergoing PD.

Conclusion

In conclusion, we developed an immediate predictive system with high predictive accuracy for POPF of all grades after PD using a combination of two risk factors. Our model may be very useful for surgeons to better predict and subsequently rapidly treat POPF after PD.

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