Can We Predict Development of Post-pancreatoduodenectomy Pancreatic Fistula?

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Abstract

Objective: Pancreatic fistula (PF) occurs often after pancreatoduodenectomy (PD) and can lead to further, serious complications. To clarify important predictors of early post-PD PF, we compared clinical variables between patients in whom no or low-grade PF (no fistula or PF-A) developed and patients in whom PF-B or PF-C developed.

Patients and Methods: Included were 54 patients (39 men and 15 women; mean age, 68.7±10.4 years) who underwent PD at our hospital between July 2011 and July 2016. We divided the patients between those in whom no PF or PF-A developed and those in whom PF-B or PF-C developed. We performed between-group comparisons of clinical factors, including especially body mass index; operation time; intraoperative blood loss volume; and C-reactive protein (CRP) concentrations, drain amylase (D-AMY) levels, and procalcitonin (PCT) levels on postoperative days (PODs) 1 and 4. We also compared clinical variables between the 2 groups of patients and performed an ROC analysis of laboratory factors shown to be significant by univariate and multiple regression analyses.

Results: Significant between-group differences were found in overall complications, infectious complications, length of the hospital stay, pancreatic vs. non-pancreatic disorders, relative pancreatic stiffness (hard/soft), size of the pancreatic duct tube, and the CRP concentration on POD 4. Multiple regression analysis showed pancreatic disease (vs. non-pancreatic disease) to be significantly related to occurrence of PF-B. ROC analysis of CRP revealed a POD 4 concentration of 10.9 mg/mL to be predictive of post-PD PF. ROC analysis of the D-AMY levels on PODs 1 and 4, which were also found to be significant, showed levels of 2,257 U/L and 405 U/L, respectively, to be predictors of PF.

Conclusion: PF is the most challenging early post-PD complication. The predictive factor PF-B was the only non–pancreatic disease in multivariate analysis. It appears that post-PD PF can indeed be predicted and that a CRP concentration of 10.9 mg/mL by POD 4 should be considered a signal for drain removal.

Key words
Pancreatoduodenectomy, pancreas fistula, prediction

Introduction
Pancreatic fistula (PF) is a significant postoperative complication of pancreatoduodenectomy (PD); it occurs frequently and often leads to further, serious complications. Persistent PF is associated with such dangerous conditions as intra-abdominal hemorrhage and infection. A number of reported studies have examined risk factors for early post-PD PF and these have fo-
cused particularly on the background clinical factors and management of PF at the time of its occurrence. By fully understanding the risk factors, we will be able to devise means of predicting postoperative PF and reducing its incidence among patients treated by PD. We will also be able to predict the likelihood of transition from low-grade to high-grade PF during the postoperative management period. To further clarify factors those that can be used to predict post-PD PF, we compared clinical variables between patients in whom PF-B or PF-C developed and those in whom no PF or PF-A developed.

**Patients and Methods**

Included in our study were 54 patients (39 men and 15 women, with a mean age of 68.7±10.4 years) who underwent PD at Kawasaki City Municipal Tama Hospital during the 5-year period spanning July 2011 through July 2016. The surgery was performed to treat pancreatic disorders in 36 patients (pancreatic cancer [n=30], intraductal papillary mucinous neoplasm [n=4], endocrine tumor [n=1], and pancreatic abscess [n=1]), biliary disorders in 17 patients (bile duct cancer [n=13] and papillary carcinoma [n=4]), and gastric cancer (n=1).

Standard PD was performed in 4 patients, pylorus-preserving pancreatoduodenectomy (PPPD) in 30 patients, and subtotal stomach-preserving pancreatoduodenectomy (SSPPD) in 20 patients, concomitant portal vein resection was performed in 8 patients. The Child or Traverso method was performed for reconstruction. An end to side pancreaticojejunostomy was performed in two layers using duct-to-mucosal direct anastomosis (PD IIA-1), which includes anastomosis of the pancreatic parenchyma and seromuscular layer of the jejunum performed with penetrating, continuous sutures, incomplete drainage, and placement of an external stent, was applied in all cases.

Steps taken to prevent PF included intraoperative closed-suction drainage; administration of somatostatin analogue octreotide (Sandostatin), intermittent suction achieved with a pancreatic tube (12-cm H₂O; suction ON: 45-seconds, suction OFF: 15 seconds); initiation of water intake on postoperative day (POD) 1, enteral nutrition on POD 2, and solid foods on POD 3; and drain removal on POD 4 or 5.

A second-generation cephalosporin, either cefmetazole or flomoxef, or a cephalosporin conjugate, such as sulbactam/cephoperazone, was used for antimicrobial prophylaxis. These were administered on the day of surgery after anesthesia was induced and then every 3 hours postoperatively.

Postoperative PF was diagnosed on the basis of the International Study Group on Pancreatic Fistula (ISGPF) criteria. For analysis aimed at elucidating factors predictive of post-PD PF, the 54 patients were divided into 2 groups, those in whom grade B PF developed (PF-B group) and those in whom no PF or grade A PF developed (NPF/PF-A group). For analysis aimed at identifying predictors of early PF, the 54 patients were divided between those with grade A/B PF and those without PF.

In addition to occurrence and grade of PF, the following clinical variables were assessed and compared between groups: sex; age; body mass index (BMI); preoperative nutritional status (prealbumin level and prognostic nutritional index); occurrence of one or more postoperative complications; occurrence of delayed gastric emptying (DGE); occurrence of a biliary fistula; occurrence of one or more infectious complications; length of postoperative hospital stay; surgical technique (whether PD, pylorus-preserving PD [PPPD], or subtotal stomach-preserving PD [SSPPD]); whether lymphoadenectomy was performed and whether D1 or D2; whether portal vein resection was performed; whether the patient suffered from a pancreatic or non-pancreatic disorder; whether transfusion was performed and the transfusion volume required; operation time; blood loss volume; relative pancreatic stiffness (hard/soft); size of the pancreatic duct tube (5/6/7.5 Fr); number of sutures; and the white blood cell (WBC) count, C-reactive protein (CRP) concentration, drain amylase (D-AMY) level, and procalcitonin (PCT) level on PODs 1 and 4.

The study was approved by the ethics committee of the St. Marianna University School of Medicine (approval number 3427).

**Statistical analyses**

Values are shown as mean±SD or number and percentage of patients per group. Between-group differences in continuous variables and categorical variables were analyzed by Mann-Whitney U test and chi-squared test, respectively, and variables that were found to be significant were subjected to multiple logistic regression analysis. All statistical analyses were performed with JMP 12 software (SAS Institute Japan, Cary NC, USA), and p<0.05 was considered significant. ROC curves were plotted to test the predictive performance of the CRP concentration on POD 4 and the D-AMY levels on PODs 1 and 4.
Results

Post-PD PF occurred in 14 of the 54 patients: PF-A in 11 patients (20.3%) and PF-B in 3 patients (5.6%). There was no PF-C. Postoperative complications, including PF, occurred in 20 (37.0%) of the 54 patients. Intra-abdominal abscess occurred in all 3 patients in the PF-B group and in 1 patient in the PF-A group. Superficial surgical site infection was observed in 2 patients, and liver abscess with biliary fistula occurred in 1 patient who underwent concomitant hepatic resection. DGE was observed in 4 patients (grade B in 3 patients, grade C in 1 patient), and bile leakage occurred in 2 patients. Lymphatic fistula occurred in 3 patients, postoperative hemorrhage occurred in 1, brainstem infarction in 1, and superior mesenteric vein (SMV) thrombosis in 1 (Table 1).

Patients’ clinical characteristics and operative and postoperative details are shown per PF-B vs. NPF/PF-A group on Table 2, 3 and 4. There was no significant difference in the sex ratio between the PF-B group and the NPF/PF-A group; all 3 patients in the PF-B group were men, and the male:female ratio in the NPF/PF-A group was 15:36. There was also no significant difference in mean age between these 2 groups (74.0±1.7 years and 68.4±10.6 years, respectively).

Table 1. Post-pancreatoduodenectomy complications (n=20 patients)

|                          | Number and percentage of the total 54 study patients |
|--------------------------|------------------------------------------------------|
| PF                       |                                                      |
| Grade A                  | 11 (20.3%)                                           |
| Grade B                  | 3 (5.6%)                                             |
| Grade C                  | 0 (0%)                                               |
| Infection                |                                                      |
| Intra-abdominal abscess  | 4 (14.8%)                                            |
| SSI                      | 2 (3.7%)                                             |
| Liver abscess with biliary fistula | 1 (1.9%)                         |
| DGE                      | 4 (7.4%)                                             |
| Bile leakage             | 2 (3.7%)                                             |
| Lymphatic fistula        | 3 (5.6%)                                             |
| Postoperative hemorrhage | 2 (3.7%)                                             |
| Liver infarction         | 1 (1.9%)                                             |
| Refractory chronic diarrhea| 1 (1.9%)                    |
| Brainstem infarction     | 1 (1.9%)                                             |
| SMV thrombosis           | 1 (1.9%)                                             |

PF pancreatic fistula, SSI surgical site infection.
DGE delayed gastric emptying, SMV superior mesenteric vein

Table 2. Patient characteristics. PF-B group vs. NPF/PF-A group

|                          | PF-B (n=3) | NPF/PF-A (n=51) | P value |
|--------------------------|------------|-----------------|---------|
| Gender (male/female)     | 3/0        | 36/15           | 0.2690  |
| Age                      | 74.0±1.7   | 68.4±10.6       | 0.3737  |
| BMI                      | 22.4±2.2   | 21.5±3.3        | 0.6503  |
| PA                       | 18.2±10.6  | 22.5±7.3        | 0.6720  |
| PNI                      | 48.6±3.7   | 47.5±5.9        | 0.8650  |
| Pancreatic disease (no/yes) | 3/0   | 15/36           | 0.0117  |

PF pancreas fistula, NPF no pancreas fistula, BMI body mass index, PA pre-albumin, PNI prognostic nutrition index.
Table 3. Operative characteristics. PF-B group vs. NPF/PF-A group

|                  | PF-B (n=3) | NPF/PF-A (n=51) | P value |
|------------------|------------|-----------------|---------|
| Surgery performed |            |                 |         |
| (PPPD/SSPPD/PD)  | 3/0        | 27/20/4         | 0.2807  |
| Lymphoadenectomy (D1/D2) | 0/3      | 3/48            | 0.6656  |
| Portal vein resection (no/yes) | 3/0  | 8/43            | 0.4573  |
| Transfusion (no/yes) | 0/3     | 22/28           | 0.1330  |
| Transfusion volume (U) | 6.0±3.5 | 3.3±4.4        | 0.1369  |
| Operation time (minutes) | 424±84  | 495±89        | 0.1800  |
| Intraoperative blood loss (mL) | 1711±960 | 1422±1336 | 0.3079  |
| Pancreatic stiffness (hard/soft) | 0/3     | 30/21          | 0.0463  |
| Pancreatic tube size (5/6/7.5Fr) | 2/1/0   | 5/21/21        | 0.0357  |
| Number of hand movement | 4.7±1.2 | 5.7±1.9       | 0.2801  |

PF cessation, NPF no pancreas fistula, PPPD pylorus-preserving pancreato-duodenectomy, SSPPD subtotal stomach preserving pancreato-duodenectomy, PD pancreato-duodenectomy.

Table 4. Postoperative characteristics. PF-B group vs. NPF/PF-A group

|                  | PF-B (n=3) | NPF/PF-A (n=51) | P value |
|------------------|------------|-----------------|---------|
| Complication (no/yes) | 0/3      | 34/17           | 0.0291  |
| DGE (no/yes) | 3/0        | 47/4            | 0.8807  |
| Bile leakage (no/yes) | 3/0     | 49/2            | 0.7267  |
| Infectious complication (no/yes) | 0/3 | 46/5           | <0.0001 |
| Postoperative stay (days) | 39.7±3.3 | 19.9±7.9       | 0.0052  |

PF cessation, NPF no pancreas fistula, DGE delayed gastric emptying.

As noted above, the PF-B group was made up of 3 patients. The drain was removed on PODs 4, 5, and 8 in patients 1, 2, and 3, respectively, in this group and then reinserted on PODs 9, 11, and 16, respectively, for management of intra-abdominal abscess. The reinserted drains were removed on PODs 17, 28, and 24, respectively, and the patients were discharged.

Factors predictive of PF

Results of the univariate and multiple logistic regression analyses of factors associated with postoperative PF are shown in Tables 2, 3, 4, 5, and 6. Univariate analysis revealed significant differences between the PF-B group and NPF/PF-A group in complications (p=0.0201), infectious complications (p<0.0001), length of the hospital stay (p=0.0052), pancreatic vs. non-pancreatic disorders (p=0.0117), relative pancreatic stiffness (hard/soft) (p=0.0463), size of the pancreatic duct tube (p=0.0357), and the CRP concentration on POD 4 (p=0.0234). Multiple logistic regression analysis revealed a significant difference in the occurrence of PF-B and that of NPF/PF-A in relation to pancreatic vs. non-pancreatic disorders (p=0.02721).

In the analysis designed to identify predictors of PF, we found significant differences between the PF-B group and NPF/PF-A group in the CRP concentration on POD 4 (p=0.0002), in the D-AMY levels on PODs 1 and 4 (p<0.0001), and in the PCT level on POD 4 (p=0.0266) (Table 7), and ROC analysis of the CRP values on POD 4 yielded a cut-off value of 10.9 mg/mL (AUC 0.895, sensitivity 100%, specificity 78%) (Fig. 1) for prediction of postoperative PF. Multivariate analysis showed the D-AMY levels on PODs 1 (p=0.00681) and 4 (p=0.01483) to be predic-
Table 5. WBC, CRP, D-AMY, and PCT on PODs 1 and 4, PF-B group vs. NPF/PF-A group

| POD   | PF-B               | NPF/PF-A          | P value |
|-------|--------------------|-------------------|---------|
|       | WBC (/μL)          | 11133±2021        | 9824±2998 | 0.4500  |
|       | CRP (mg/mL)        | 12.7±6.0          | 8.8±2.7  | 0.1991  |
|       | D-AMY (U/L)        | 6074±4748         | 2685±6267 | 0.0590  |
|       | PCT (ng/mL)        | 3.3±3.9           | 5.2±14.2 | 0.9629  |
| POD 4 | WBC (/μL)          | 8133±2312         | 8394±3079 | 0.9245  |
|       | CRP (mg/mL)        | 15.2±4.2          | 7.6±4.6  | 0.0234  |
|       | D-AMY (U/L)        | 345±306           | 685±1760 | 0.4529  |
|       | PCT (ng/mL)        | 0.9±1.0           | 2.4±5.5  | 0.8260  |

WBC white blood cell count, CRP C-reactive protein, D-AMY drain amylase level, PCT procalcitonin level. POD postoperative days, PF pancreas fistula.

Table 6. Results of multiple logistic regression analysis (NPF/PF-A PF vs. PF-B)

| Odds-ratio     | P-value |
|----------------|---------|
| Pancreatic disease / non-pancreatic disease | 3.86  | 0.02721 |
| Pancreatic tube size                           | 0.06339 |
| Relative pancreatic stiffness (hard / soft)   | 0.99947 |

Table 7. Results of multiple logistic regression analysis of factors predictive of postoperative PF (NPF vs. PF-A/PF-B)

| Univariate analysis | Multiple regression analysis |
|---------------------|-----------------------------|
| Odds ratio          | P-value                     |
| D-AMY POD 4         | <0.0001                     | 6.11  | 0.00681 |
| D-AMY POD 1         | <0.0001                     | 7.01  | 0.01483 |
| PCT POD 4           | 0.0266                      | 0.14764 |
| CRP POD 4           | 0.0002                      | 0.75722 |

PF pancreas fistula, D-AMY drain amylase level, POD postoperative days, PCT procalcitonin. CRP C-reactive protein.

tors of postoperative PF (Table 7). In ROC analysis of the D-AMY levels on PODs 1 and 4 for prediction of PF, we found the cut-off value on POD 1 to be 2,257 U/L (AUC 0.941, sensitivity 86%, specificity 76%) and the cut-off value on POD 4 to be 405 U/L (AUC 0.945, sensitivity 86%, specificity 83%) (Figs. 2, 3).

Discussion

As PD reconstruction techniques have advanced over time, the incidence of PF has decreased. However, when PF does occur, pancreatic digestive enzymes are activated, and this can cause autolysis, which in turn can cause serious postoperative complications, such as hemorrhage. In addition, infection associated with the long-term drain placement used to treat PF can lead to intra-abdominal abscess and subsequent septicemia.

The reported PF-associated complication rate is 16–32%, and although complications have decreased, rates of approximately 20% are still observed, with 10% of these complications occurring in cases of grade B or C PF, i.e., PF that is considered clinically problematic. PF is a major factor responsible for serious, secondary post-PD complications. Thus, it is important for us to be able to predict PF in advance and to initiate early management once PF occurs. We conducted the study described herein to identify fac-
Sensitivity
1-Specificity
False positive

Fig. 1  Receiver operating characteristic (ROC) curve for C-reactive protein (CRP) on postoperative day 4 (POD4)
The area under the curve (AUC) is 0.895, the cutoff value was 10.9, and sensitivity and specificity are 1.00 and 0.78, respectively.

1-Specificity
False positive
Sensitivity

Fig. 2  Receiver operating characteristic (ROC) curve for the drain amylase level (D-AMY) on postoperative day 1 (POD 1) as a predictor of grade A or B pancreatic fistula
The area under the curve (AUC) is 0.941, the cutoff value is 2254, and sensitivity and specificity are 0.86 and 0.76, respectively.

1-Specificity
False positive
Sensitivity

Fig. 3  Receiver operating characteristic (ROC) curve for the drain amylase level (D-AMY) on postoperative day 4 (POD4) as a predictor of grade A or B pancreatic fistula
The area under the curve (AUC) is 0.945, the cutoff value is 405, and sensitivity and specificity are 0.86 and 0.83, respectively.

Reported studies regarding risk factors for PF have shown that PF occurs at a relatively high rate in soft pancreas. Thus, especially in patients with a soft pancreas, it is important to ensure both conscientious, protective intraoperative manipulation and adequate postoperative management.

We found both pancreatic and non-pancreatic disorders, a narrow (5Fr) pancreatic duct tube, and a soft pancreas to be associated with grade B PF. PD performed for pancreatic disease vs. non-pancreatic disease was also shown to be associated with grade B PF. However, many of the patients with a non-pancreatic disorder in whom PF developed were patients with a soft pancreas, a finding consistent with previously reported findings.

Many risk factors other than a soft pancreas have been reported. Aozaza et al. showed disease other than pancreatic cancer, the serum CRP concentration on POD 3, and the D-AMY level on POD 7 to be related to the development of grade B or C PF, with the serum CRP concentration on POD 3 being the most important of these 3 factors. This suggests that it may be possible to predict the occurrence of PF on the basis of the POD 3 serum CRP concentration. We found the POD 4 CRP cut-off value of 10.9 mg/mL to be predictive of PF, and we believe this finding is consistent with that reported by Aosasa et
al. Kawai et al.\textsuperscript{5} reported that an intraoperative blood loss volume $\geq$1,000 mL, a soft pancreas, and a D-AMY level of $\geq$4,000 IU/L on POD 1 are clinically important prognosticators in the management of PF. Kosaka et al.\textsuperscript{6} showed the WBC count, CRP concentration, and D-AMY level on POD 4, depending on their values, to be predictive factors, and they noted that these 3 factors should be used as indicators for drain removal. All of the cases reported by Kosaka et al. in which PF-B developed began as cases of PF-A. According to the ISGPS standards, PF is judged after 3 days. We compared cases of PF-A/B against cases without PF to identify those in which PF-A was likely to develop immediately after surgery, and we found D-AMY on POD 1 to be a useful marker. Our ROC curve showed a POD 1 D-AMY level of 2,257 IU/L to be the cut-off level for development vs. non-development of PF-A or PF-B. The likelihood of long-term PF management increases when this cut-off level is exceeded. Of course, careful surgical manipulation and techniques are important for preventing PF, but preventing progression of PF-A to PF-B or PF-C by appropriate postoperative management is of equal importance.

Retrograde infection via the drain can be an issue. Intraperitoneal infection tends to occur when grade A PF advances to grade B or C. Early drain removal has been practiced to combat retrograde infection, and this practice has contributed to the reduced incidence of PF.\textsuperscript{11} We perform early drain removal in patients with grade A PF when we determine that it is clinically feasible. Currently, however, there are no established criteria regarding the best time to remove the drain in cases of grade A PF. Even in this study, although CRP of POD 4 is univariate analysis, the only significant difference was observed as a variable value. Based on the results, we can derive more than 10.9 mg/ml of CRP which is highly likely to shift from ROC curve to PF-BC, and when it falls below that value it can be one index for early drain extraction. If the reference value for CRP is exceeded on POD 4, then early drain removal should be carefully considered; re-investigation should be performed after a few days to review the decision. Early drain replacement, frequent culturing of the drained fluid, and repeat antibiotic administration and modification are performed in cases requiring long-term drainage. Aiming to prevent secondary infection and transition to grade B or C PF is of utmost importance.

Although our study was conducted at a single-institution and was thus limited by the number of patients, we believe our findings are of clinical importance and that they can be confirmed and even expanded upon in a large-scale study.

**Conclusion**

PF is the most challenging early post-PD complication. The predictive factor for PF - B was the only non-pancreatic disease in multivariate analysis. The CRP value of POD 4 confirmed a significant difference in the variable value in univariate analysis. The cut-off value in the ROC curve of the CRP value of POD 4 is 10.9 mg/ml, and we thought this value can be a possibility of helping to judge the drain removal at the D-AMY high value after POD 4.

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