

Novel diagnostics for aggravating pancreatic fistulas at the acute phase after pancreatectomy

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Abstract

AIM: To identify sensitive predictors of clinically relevant postoperative pancreatic fistula (POPF) at the acute phase after pancreatectomy.

METHODS: This study included 153 patients diagnosed as having POPFs at postoperative day (POD) 3 after either open pancreatoduodenectomy or distal pancreatectomy between January 2008 and March 2013. The POPFs were categorized into three grades based on the International Study Group on Pancreatic Fistula Definition, and POPFs of grades B or C were considered to be clinically relevant. The predictive performance for the clinically relevant POPF formation of values at PODs 1, 3 and 5 as well as time-dependent changes in levels of inflammatory markers, including white blood cell count, neutrophil count, total lymphocyte count, C-reactive protein (CRP), procalcitonin level, platelet-

to-lymphocyte ratio and neutrophil-to-lymphocyte ratio, and amylase content in the drain fluid were compared using the receiver operating characteristic (ROC) curve and multivariable analyses. A scoring system for the prediction of clinically relevant POPFs was created using five risk factors identified in this study, and its diagnostic performance was also evaluated.

RESULTS: Over time, 77 (50%) of 153 enrolled patients followed a protracted course and were categorized as having clinically relevant POPFs. ROC curve analyses revealed that changes in CRP levels from POD 1 to POD 3 had the greatest area under the curve value (0.767) and that an elevated CRP level of 28.4 mg/L yielded the most optimal predictive value for clinically relevant POPFs. Multivariable analyses for the risk factors of clinically relevant POPFs identified invasive carcinomas of the pancreas and elevation of the CRP level (≥ 28.4 mg/L, from POD 1 to POD 3) as independent diagnostic factors for clinically relevant POPFs (OR 2.94, 95%CI: 1.08-8.55, $P = 0.035$ and OR 4.82, 95%CI: 1.25-20.2, $P = 0.022$, respectively). A gradual increase in the prevalence of clinically relevant POPFs in proportion to the risk classification score was confirmed. A highly elevated CRP level and a risk score ≥ 8 were significantly associated with a prolonged duration of drain placement and postoperative hospitalization.

CONCLUSION: A steep rise in the serum CRP level from POD 1 to POD 3 was a highly predictive factor for subsequent clinically relevant POPFs.

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Key words: Pancreatectomy; Pancreatic fistula; Prediction; Inflammatory marker; C-reactive protein

Core tip: The diagnostic performance of inflammatory markers and amylase content in drain fluid were com-

pared to identify sensitive predictors of clinically relevant postoperative pancreatic fistulas (POPFs) at the acute phase after pancreatectomy. Receiver operating characteristic curve analyses revealed that the changes in C-reactive protein (CRP) levels from postoperative day (POD) 1 to POD 3 had the greatest area under the curve value for clinically relevant POPFs. Multivariable analyses identified increased elevation of the CRP level as an independent diagnostic factor for clinically relevant POPFs. A steep rise in the CRP level was a highly diagnostic factor for clinically relevant POPFs and may be helpful in selecting the appropriate management for POPFs.

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INTRODUCTION

In general, pancreatectomy is recognized to be a highly invasive surgery. Despite recent advances in surgical methodologies, devices and perioperative management, pancreatectomy is associated with a mortality of approximately 5% and a morbidity of 35%-60%^[1,2]. The incidence of postoperative pancreatic fistulas (POPFs), a surgical complication of particular concern, has been reported to be 20%-40% after pancreatoduodenectomy and 30%-55% after distal pancreatectomy, thereby having a decisive influence on the clinical course after pancreatectomy^[3-6]. Diverse anastomotic procedures, treatment of the pancreatic stump, and the administration of somatostatin analogs have been evaluated by randomized clinical trials with the aim of reducing the prevalence of POPFs^[7-9], but they have not been associated with appreciable improvement.

The aggravation of POPFs can lead to prolonged hospitalization, burgeoning costs of medical treatment, and development into fatal conditions, such as sepsis through abdominal abscesses and intra-abdominal hemorrhages from ruptured aneurysms^[4,5]. In addition, clinically relevant POPFs have been reported to be risk factors for peritoneal recurrences^[10]. Thus, management of POPFs is a high-priority issue in pancreatic surgery. Sensitive diagnostic factors of clinically relevant POPF are needed to identify high-risk patients and strengthen measures aimed at preventing the aggravation of POPFs. The clinical stratification of POPFs was established by the International Study Group on Pancreatic Fistula Definition (ISGPF) in 2005^[11]. The presence or absence of POPFs can be determined at postoperative day (POD) 3 by the amylase content in the drained fluid. The most important issue is whether the POPF subsides promptly

or deteriorates into severe leakage, thereby influencing the clinical course.

Predicting clinically relevant POPFs is often difficult because the amylase content in the drained fluid does not always represent the actual conditions of leakage^[12,13]. Numerous pre- or intraoperative risk factors for postoperative POPFs have been reported: a soft pancreas, a small main pancreatic duct, a fatty pancreas, malnutrition, and obesity^[14-18]. Nevertheless, physicians frequently vacillate on whether or not a POPF becomes prolonged after pancreatectomy. The prediction of the course of POPFs during the early postoperative phase (*i.e.*, POD 3) would enable the appropriate selection from two contrary treatment strategies: the early removal of drainage tubes or retention of the tubes accompanied by scrutiny of the abdomen by imaging studies or the administration of broad-spectrum antibiotics and the use of somatostatin analogs. The early removal of drainage tubes in patients with clinically irrelevant POPFs and the early recovery of patients from clinically relevant POPFs through optimal management would both lead to shortened hospitalizations.

In terms of monitoring inflammation, measurement of the white blood cell (WBC) count, neutrophil count, total lymphocyte count (TLC), C-reactive protein (CRP) levels, and procalcitonin levels, as well as being alert to the presence of the systemic inflammatory response syndrome (SIRS), have been in widespread use^[19,21]. Once a POPF is aggravated, pancreatic fluid leaks into the abdominal cavity and causes local inflammation, secondary infection and, eventually, expansion to a systemic inflammatory response. Thus, the hypothesis that inflammatory markers represent the "momentum" of subsequent POPFs was raised because POPFs induce local and systemic inflammatory responses. No reports have evaluated the associations between the time-dependent changes of postoperative inflammatory markers and the subsequent course of POPF focusing on patients diagnosed as having POPFs at POD 3. To test the hypothesis and to identify sensitive diagnostic factors of clinically relevant POPFs, the inflammatory markers in patients who underwent pancreatectomy were investigated at the acute phase of the postoperative course over time, and their diagnostic values for POPF aggravation were evaluated.

MATERIALS AND METHODS

Ethics

This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Written informed consent for the surgery and the usage of clinical data, as required by the Review Board of Nagoya University (Nagoya, Japan), was obtained from all patients.

Patient characteristics and surgical procedure

Between January 2008 and March 2013, 337 major pan-

createctomies (*i.e.*, pancreatoduodenectomy, distal pancreatectomy and total pancreatectomy) were performed at the Department of Gastroenterological Surgery of Nagoya University. Of these, 23 patients who underwent total pancreatectomy were excluded. Patients without POPFs were excluded because the principal purpose of the current study was to identify the diagnostic factors of aggravation among patients with POPFs. Additionally, patients with postoperative infectious complications, such as wound infection and pneumonia, which might influence the inflammatory status, were excluded. Ultimately, 153 patients who were diagnosed as having POPFs at 3 d after pancreatoduodenectomy or distal pancreatectomy were enrolled. The preoperative backgrounds of the patients, intraoperative conditions, and postoperative course (POPF severity, duration of placement of drainage tube, and postoperative inflammatory markers) were investigated to identify sensitive diagnostic factors of clinically relevant POPFs.

For pancreatoduodenectomies, pancreatic reconstruction was performed by a direct anastomosis between the pancreatic duct and mucosal layer of the jejunal loop. Except for patients with a remarkably dilated main pancreatic duct, a stent tube was inserted into the pancreatic duct. Adhesion of the jejunal wall and the pancreatic stump by one-layer sutures was added^[22,23]. Silastic flexible drains (Blake® drain, Ethicon, Somerville, NJ, United States) were placed at the anterior and posterior surfaces of the pancreatojejunostomy and choledochojejunostomy. For distal pancreatectomies, closure of the main pancreatic duct was performed using a continuous suture. Silastic flexible drains were placed at the anterior and posterior surface of the pancreatic stump.

Definition of pancreatic fistula

Patients were categorized as having developed a grade A, B or C fistula based on the definitions of the ISGPF^[11]. Briefly, POPFs were categorized into three grades: biochemical leak without peripancreatic fluid collection, defined as output containing pancreatic amylase on or after the third postoperative day from an operatively positioned drain with a pancreatic amylase level more than three times the upper serum reference value (grade A); leaks with changes in management and a delay of discharge from the hospital (grade B); and leaks that required percutaneous drainage of a fluid collection or re-exploration for critically ill patients and were associated with an extended stay in the hospital (grade C). POPFs of grades B or C were considered to be clinically relevant POPFs in this study.

Perioperative management

Cephalosporin was administered immediately before surgery and every 3 h during surgery. In all patients, the administration of antibiotics and H₂ blockers was continued routinely thorough POD 3. Oral intake was started routinely 5 d after surgery unless postoperative complications, such as delayed gastric emptying, occurred. Blood-

sugar level was routinely monitored, and appropriate levels were maintained (70 mg/dL ≤ blood-sugar level < 200 mg/dL). The amylase content in the discharge from the closed-suction drains was examined at PODs 1, 3 and 5. Continuous low pressure suction was applied to the abdominal drains to minimize the fluid cavity through POD 4. Abdominal drains were removed at POD 4 in patients without POPFs or replaced as needed until a cure of the POPFs was confirmed in patients with POPFs. Abdominal ultrasonography was performed as needed postoperatively. Percutaneous drainage or the replacement of tubes was employed when signs of inadequate drainage were found.

Evaluation of inflammatory markers

Blood examinations were conducted routinely before surgery and at PODs 1, 3 and 5. The inflammatory markers included the WBC, neutrophil count, TLC, platelet count, and CRP, procalcitonin and serum amylase levels. The procalcitonin level was tested routinely only at POD 3. In addition to the markers mentioned above, the platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were calculated. Time-dependent changes of these factors were also investigated. As indications of systemic inflammatory status, the duration of a high fever (≥ 38 °C), SIRS, and the use of catecholamines were evaluated. The amylase content and bacterial culture in the drain fluids were also examined at PODs 1, 3 and 5 or until drain removal.

To identify the appropriate cutoff value of each marker and time-dependent changes, analyses of receiver operating characteristic (ROC) curves were conducted. The diagnostic performance of inflammatory markers for clinically relevant POPFs was compared using optimal cutoff values determined by analyses of the ROC curves. Selected markers with known risk factors for POPFs were included in the multivariable analyses. Moreover, the influence of the selected diagnostic factors on the duration of drain placement and hospitalization was evaluated.

Risk classification scale for clinically relevant POPFs

A scoring scale for prediction of clinically relevant POPFs was introduced using the risk factors identified in the present study, and the diagnostic performance was evaluated. Parameters that demonstrated significant associations with clinically relevant POPFs in univariate analyses were included in this scoring scale. Then, individual scores were allocated to each parameter in accordance with their odds ratios.

Further evaluation of potent factors

The sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive result and likelihood ratio of a negative result for clinically relevant POPFs were further evaluated among the potent factors identified in this study to compare diagnostic performance. The CRP level on POD 3, increased eleva-

Table 1 Demographics and clinical characteristics of 153 patients *n* (%)

Characteristic	Value
Age (yr), mean (range)	65.2 (28-89)
Male/female	101/52
Preoperative symptom(s)	37 (24)
Diabetes mellitus (preoperative)	39 (25)
History of pancreatitis	20 (13)
Body mass index, mean \pm SD	22.5 \pm 3.5
Procedure	
Pancreatoduodenectomy	103
Distal pancreatectomy	50
Resection of the portal vein	21 (14)
Pathological diagnosis	
Invasive carcinoma of the pancreas	68
Intraductal papillary mucinous neoplasm	35
Carcinoma of the ampulla	13
Cholangiocarcinoma	10
Pancreatic neuroendocrine tumor	8
Other	19
Grade of postoperative pancreatic fistula ¹	
A	76
B	70
C	7

¹Defined according to the International Study Group on Pancreatic Fistula Definition.

tion of the CRP level from PODs 1 to 3, drain amylase content on POD 3 and the risk score were included in this analysis.

Statistical analysis

The qualitative χ^2 test and quantitative Mann-Whitney's *U* test were used to compare the two groups. ROC curve analyses were conducted to evaluate the discrimination of clinically relevant POPFs by the markers of interest. The goodness of fit for clinically relevant POPFs was assessed by comparing the area under the curve (AUC) value, and optimal cutoff values were also determined using the Youden Index. The risk factors for clinically relevant POPFs were evaluated using binomial logistic analyses, and the variables with $P < 0.1$ were entered into the final model. The statistical analyses were performed using JMP[®] ver10 (SAS Institute, NC, United States). A $P < 0.05$ was considered to be significant.

RESULTS

Patient characteristics

The patients' characteristics are summarized in Table 1. The ages of the 153 subjects ranged from 28 years to 89 years (65.2 \pm 10.3 years; mean \pm SD), and the male-to-female ratio was 101:52. Surgery consisted of pancreatoduodenectomy in 103 patients and distal pancreatectomy in 50 patients. In terms of the pathological diagnoses, 68 (44%) subjects had invasive carcinoma of the pancreas. Thirty-nine (25%) patients had diabetes mellitus preoperatively, and 20 (13%) patients had a history of pancreatitis. None of the enrolled participants had active inflam-

matory disease (*e.g.*, cholangitis or pancreatitis) before surgery, suggesting that the postoperative inflammatory status was assessed accurately. All patients were afebrile, and the CRP levels were < 20 mg/L preoperatively. The postoperative mortality rate was 0%. Eventually, 77 (50%) of the 153 enrolled patients followed a protracted course and were categorized as having clinically relevant POPFs. There was no significant difference in the incidence rate of clinically relevant POPFs between the patients who underwent pancreatoduodenectomy and the patients who underwent distal pancreatectomy (54% *vs* 42%, respectively, $P = 0.151$).

ROC curve analyses of postoperative inflammatory markers

The predictive values of postoperative inflammatory markers at each time point and time-dependent changes were evaluated by ROC curve analyses. The AUC values, P values for differences between grade-A and grade-B/C POPFs, and the most optimal cutoff point to predict clinically relevant POPFs are listed in Table 2. The change in the CRP levels from POD 1 to POD 3 had the highest AUC value (0.767), and a further elevation of the CRP level of 28.4 mg/L yielded the most optimal diagnostic value for clinically relevant POPFs. In general, changes from POD 3 to POD 5 were less diagnostic than those from POD 1 to POD 3. Among the markers determined at POD 3, the platelet count and CRP level showed relatively high AUC values (> 0.6). The amylase content in the drain fluid at POD 3 was significantly associated with clinically relevant POPFs ($P = 0.003$; AUC = 0.640; optimal cutoff value 1918 IU/L). Representative ROC curves are shown in Figure 1.

Comparison of diagnostic performance for clinically relevant POPFs

Next, the diagnostic values for clinically relevant POPFs were compared among the well-known risk factors (*e.g.*, the size and texture of the pancreatic duct), postoperative high fever, SIRS, the use of catecholamines, and the inflammatory markers selected by ROC curve analyses and amylase content in the drain fluid at POD 3. Univariate analyses showed that invasive carcinoma of the pancreas, platelet count ($< 164000/\text{mm}^3$, POD 3), CRP level (≥ 158 mg/L, POD 3), CRP elevation (≥ 28.4 mg/L, from POD 1 to POD 3) and amylase content in the drain fluid (≥ 1918 IU/L, POD 3) were significant adverse factors for POPFs (Table 3). Multivariable analyses identified invasive carcinoma of the pancreas and elevation of the CRP level (≥ 28.4 mg/L, from POD 1 to POD 3) as independent diagnostic factors for clinically relevant POPFs (OR 2.94, 95%CI: 1.08-8.55, $P = 0.035$ and OR 4.82, 95% CI: 1.25-20.2, $P = 0.022$, respectively; Table 3). In patients with invasive carcinoma of the pancreas, the ratio of clinically relevant POPF to mild POPF was higher but the total prevalence of POPFs was lower compared with the whole population (Figure 2).

Table 2 Inflammatory markers for clinically relevant postoperative pancreatic fistulas

Marker	POD 1		POD 3			POD 5		Change from POD 1 to 3			Change from POD 3 to 5	
	AUC	P value	AUC	P value	Cutoff	AUC	P value	AUC	P value	Cutoff	AUC	P value
White blood cell count (/mm ³)	0.545	0.343	0.524	0.615	11400	0.588	0.067	0.504	0.939	600	0.557	0.242
Neutrophil count (/mm ³)	0.560	0.198	0.532	0.495	8200	0.591	0.060	0.506	0.898	-3300	0.560	0.215
Total lymphocyte count (/mm ³)	0.524	0.604	0.577	0.097	600	0.541	0.397	0.550	0.285	0	0.518	0.708
Platelet count (/mm ³)	0.540	0.399	0.615	0.014	164000	0.580	0.098	0.603	0.028	-24000	0.549	0.310
Serum amylase (IU/mL)	0.504	0.935	0.580	0.087	136	0.600	0.039	0.502	0.966	-69	0.522	0.643
C-reactive protein (mg/L)	0.534	0.532	0.688	< 0.001	158	0.684	< 0.001	0.767	< 0.001	28.4	0.565	0.200
Procalcitonin (ng/mL)	-	-	0.584	0.451	0.3	-	-	-	-	-	-	-
Neutrophil-to-lymphocyte ratio	0.532	0.497	0.579	0.092	9.6	0.590	0.061	0.537	0.433	-0.3	0.558	0.420
Platelet to lymphocyte ratio	0.517	0.718	0.529	0.557	231	0.557	0.243	0.508	0.858	67	0.539	0.231

P values were of the comparison between grade A and grade B/C as calculated by the Mann-Whitney *U* test. Cutoff values were determined by receiver operating characteristic curve analyses. POD: Postoperative day; AUC: Area under the curve.

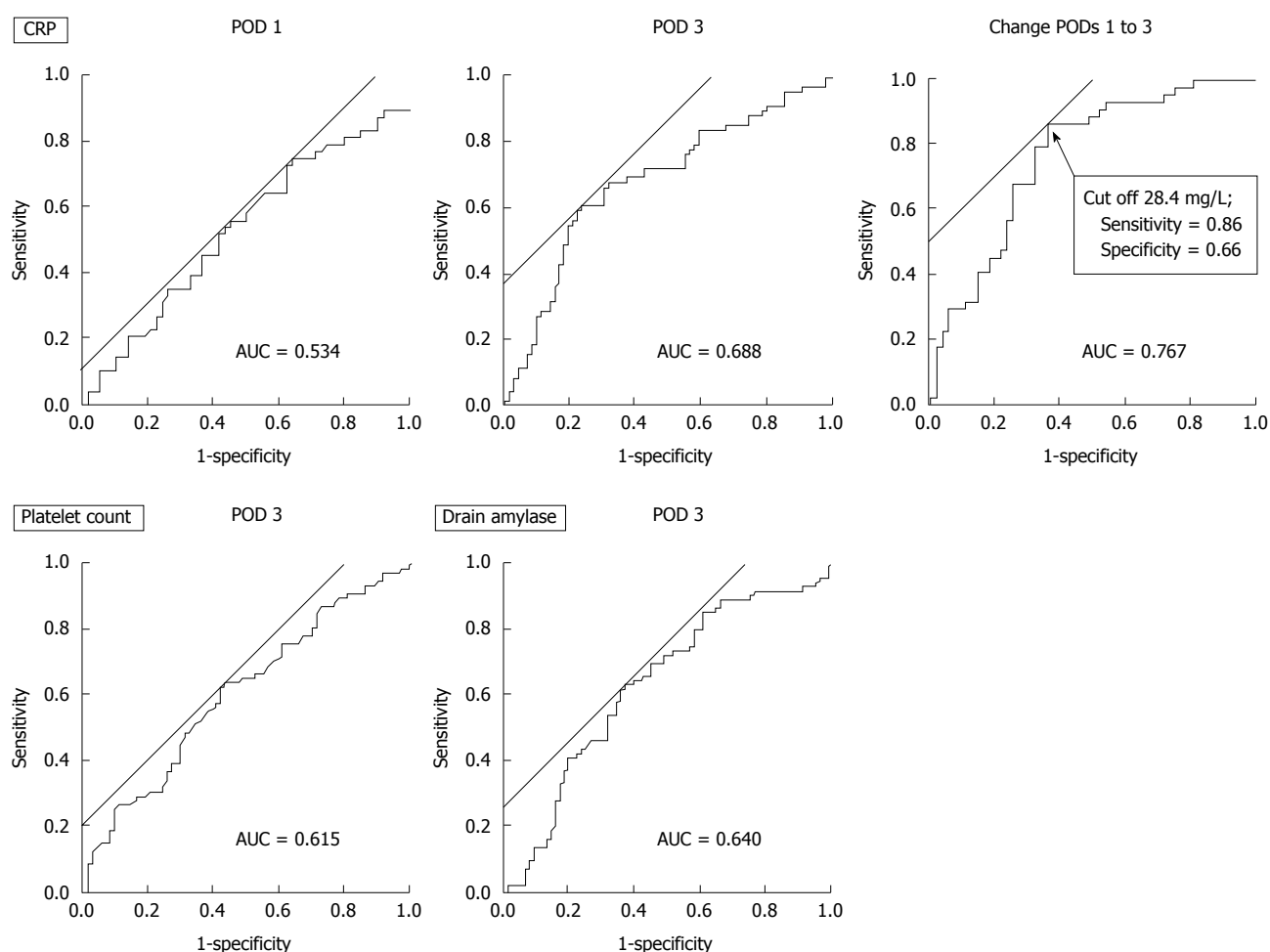


Figure 1 Receiver operating characteristic curves. Receiver operating characteristic curve for the C-reactive protein (CRP) level, platelet count, and amylase content in drain fluid as diagnostic factors for clinically relevant postoperative pancreatic fistulas. The change in the CRP levels from postoperative day (POD) 1 to POD 3 demonstrated the highest area under the curve (AUC) value.

Association of elevation in the CRP level with postoperative course and other markers

Patients with a further elevation in the CRP levels ≥ 28.4 mg/L from POD 1 to POD 3 (high elevation of the CRP level) had a significantly longer duration of drain placement than patients without elevation in the CRP levels (24 and 12 d, respectively; median, $P < 0.001$; Figure 3A).

Consequently, the duration of postoperative hospitalization was significantly greater in patients with high CRP elevations than in patients without high CRP elevations (38.5 and 25.5 d, respectively; median, $P < 0.001$; Figure 3B). High CRP elevation was not significantly associated with the WBC count, neutrophil count, procalcitonin level or bacterial culture in the drain fluid at POD 3.

Table 3 Diagnostic value of clinical factors for clinically relevant postoperative pancreatic fistula

Variable	Univariate			Multivariable		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Age (≥ 65 yr)	1.16	0.61-2.23	0.654			
Gender (male)	1.29	0.66-2.53	0.459			
Diabetes mellitus	1.39	0.67-2.92	0.378			
History of pancreatitis	0.62	0.23-1.59	0.321			
Body mass index (≥ 22)	1.48	0.79-2.82	0.226			
Operative procedure (DP)	1.65	0.83-3.28	0.151			
Invasive carcinoma of the pancreas	2.31	1.21-4.47	0.011	2.94	1.08-8.55	0.035
Operative time (≥ 360 min)	1.33	0.71-2.53	0.376			
Blood loss (≥ 600 mL)	1.83	0.97-3.51	0.063	1.73	0.62-4.86	0.297
Intraoperative transfusion	1.45	0.48-4.59	0.511			
Pancreas texture (soft)	1.46	0.69-3.10	0.322			
Main pancreatic duct (< 4 mm)	1.36	0.70-2.65	0.366			
Persistence of high fever (≥ 38 °C, ≥ 3 d)	1.10	0.57-2.14	0.781			
Persistence of SIRS (≥ 3 d)	1.68	0.88-3.23	0.116			
Usage of catecholamines	1.73	0.68-4.62	0.251			
Total lymphocyte count ($< 600/\text{mm}^3$, POD 3)	1.73	0.74-4.23	0.201			
Platelet count ($< 164000/\text{mm}^3$, POD 3)	2.28	1.20-4.39	0.012	1.28	0.44-3.64	0.646
CRP (≥ 158 mg/L, POD 3)	4.82	2.37-10.2	< 0.001	2.39	0.73-8.03	0.150
Neutrophil-to-lymphocyte ratio (≥ 9.6 , POD 3)	1.84	0.97-3.52	0.061	1.56	0.55-4.40	0.401
CRP elevation (≥ 28.4 mg/L, POD 1 to 3)	11.4	4.35-34.3	< 0.001	4.82	1.25-20.2	0.022
Drain amylase (≥ 1918 IU/mL, POD 3)	3.00	1.57-5.86	0.001	1.50	0.55-4.08	0.423
Drain fluid bacterial culture (positive, POD 3)	1.62	0.68-3.87	0.278			

Analyzed by binomial logistic analyses. DP: Distal pancreatectomy; SIRS: Systemic inflammatory response syndrome; CRP: C-reactive protein; POD: Postoperative day.

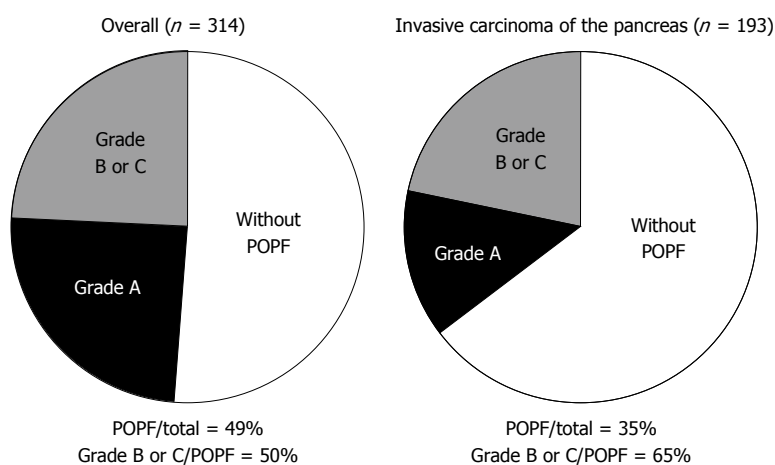


Figure 2 Distribution of postoperative pancreatic fistulas grade in the entire study population as well as patients with invasive carcinoma of the pancreas. POPF: Postoperative pancreatic fistulas.

Risk scoring scale for clinically relevant POPFs

A scoring scale for the prediction of clinically relevant POPFs was developed to enhance the clinical utility of the diagnostic factors detected in this study. Five diagnostic factors (invasive carcinoma of the pancreas, platelet count $< 164000/\text{mm}^3$ at POD 3, CRP ≥ 158 mg/L at POD 3, CRP elevation ≥ 28.4 mg/L from POD 1 to POD 3, and amylase content in the drain fluid ≥ 1918 IU/L at POD 3) were included in the scoring scale because these factors demonstrated a significant association with clinically relevant POPFs. The prevalence of clinically relevant POPFs increased gradually in proportion with the score, from 0% to 100%. The score had a remarkably high goodness of fit for clinically relevant POPFs (AUC = 0.848). A score of 8 yielded the most optimal diagnostic value for clinically relevant POPFs,

thereby supporting the clinical utility of the scoring scale (Figure 4). In addition, patients with a risk score ≥ 8 had a significantly longer duration of drain placement and postoperative hospitalization than patients with a score < 8 (25.5 ± 18.2 and 12 ± 10.6 , 39.5 ± 29.0 and 26.0 ± 10.1 d, respectively; mean \pm SD, $P < 0.001$ for both).

Further evaluation of important factors

Table 4 lists the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive result and likelihood ratio of a negative result of four important factors: the CRP level on POD 3, the increased elevation of the CRP level from POD 1 to 3, the drain amylase content on POD 3 and the risk score. It is worth noting that an increased elevation of the CRP level demonstrated a high negative predictive value (0.857) and

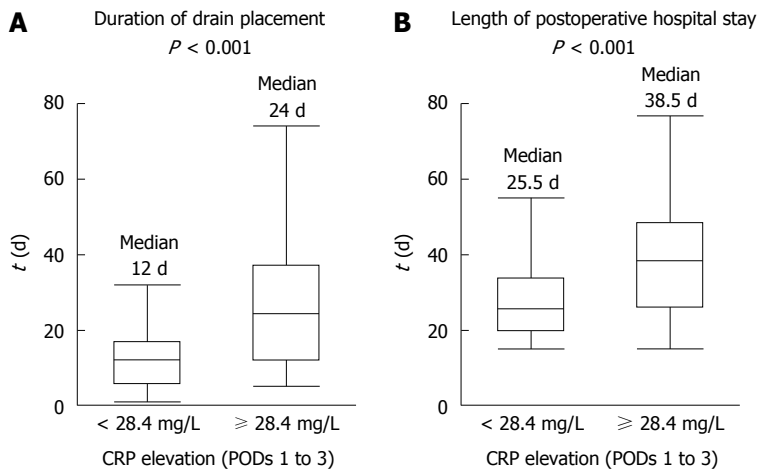


Figure 3 Comparison of duration of drain placement and postoperative hospitalization between two groups categorized by elevation in the C-reactive protein level from postoperative days 1 to 3. A: The duration of drain placement was significantly longer in patients with high elevation of the C-reactive protein (CRP) level than in those without high elevation of the CRP level ($P < 0.001$); B: The duration of postoperative hospitalization was significantly longer in patients with high elevation of the CRP level than in patients without high elevation of the CRP level ($P < 0.001$). POD: Postoperative day.

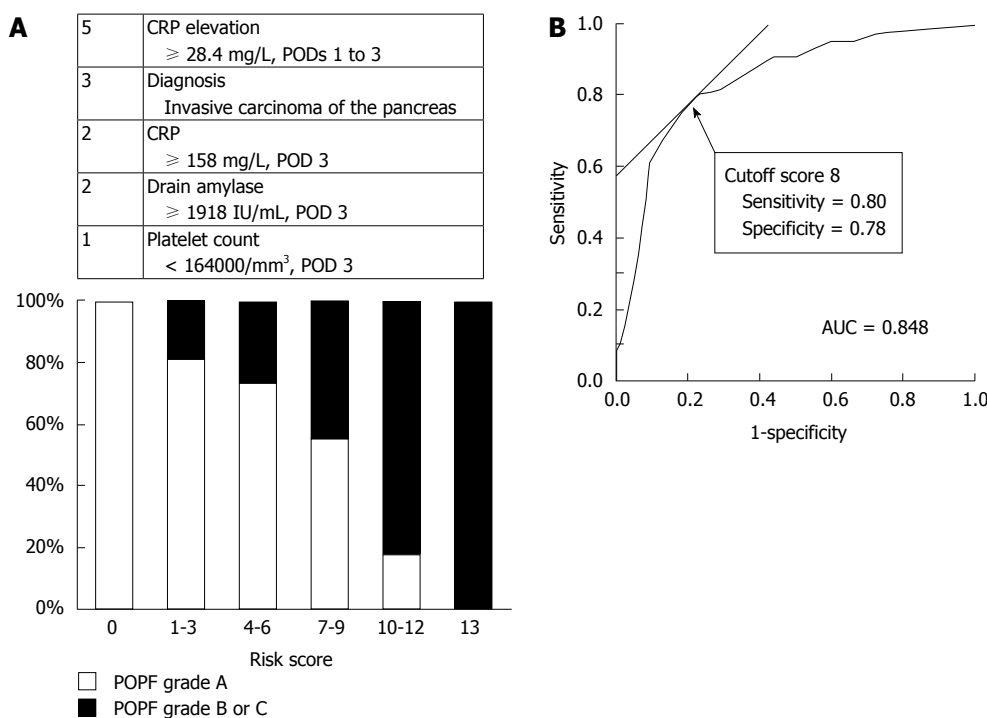


Figure 4 Risk classification scoring scale for clinically relevant postoperative pancreatic fistulas calculated using five parameters. A: Parameters with allocated scores and a bar graph of the prevalence of clinically relevant postoperative pancreatic fistulas (POPFs). Prolonged POPFs increased gradually in proportion to the score from 0% to 100%; B: Receiver operating characteristic curve for the risk score as a diagnostic factor of clinically relevant POPFs. A remarkably high goodness of fit was demonstrated. CRP: C-reactive protein; POD: Postoperative day.

a low likelihood ratio of a negative result (0.212), indicating that it may be useful especially for the prediction of the absence of a clinically relevant POPF. The risk score scale was found to have an additional impact on detecting the presence of clinically relevant POPF.

DISCUSSION

Aggravated POPFs can involve critical complications, such as sepsis and intra-abdominal hemorrhage from ruptured aneurysms, resulting in prolonged hospitalization, increased medical expense, and in the most extreme cases, mortality^[4,5]. In addition, clinically relevant POPFs can lead to an increased risk of recurrences through peritoneal dissemination^[10]. Clinically relevant POPFs are the

most serious problem in the field of pancreatic surgery. The realistic goal is to minimize the extent of POPFs and to limit it to grade A, which has less impact on the postoperative clinical course. To achieve this goal, the early identification of high-risk patients with clinically relevant POPFs is necessary for their subsequent management, including the thorough control of infection, effective drainage, and nutritional care with the aim to localize inflammation and achieve early recovery.

When should surgeons manage POPFs, and what are the definitive criteria in clinical practice? An important “crossroads” may occur at POD 3, when POPFs are usually diagnosed. Management (including drainage and antibiotic administration) after the diagnosis of a POPF at POD 3 depends on whether the POPF is likely to be aggravated.

Table 4 Comparison of diagnostic performance of potent factors for clinically relevant postoperative pancreatic fistula

	Odds ratio	95%CI	P value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio of positive result	Likelihood ratio of negative result
CRP \geq 158 mg/L ¹	4.82	2.37-10.2	< 0.001	0.594	0.767	0.707	0.667	2.552	0.529
CRP elevation \geq 28.4 mg/L ²	11.4	4.35-34.3	< 0.001	0.864	0.643	0.655	0.857	2.418	0.212
Drain amylase \geq 1918 IU/mL ¹	3.00	1.57-5.86	0.001	0.636	0.632	0.636	0.632	1.727	0.576
Risk score \geq 8	12.9	5.13-35.4	< 0.001	0.795	0.768	0.729	0.827	3.427	0.266

¹Values on postoperative day (POD) 3; ²Change from POD 1 to POD 3. P values were analyzed by binomial logistic analyses. CRP: C-reactive protein.

Drainage tubes are removed at the surgeon's request. However, it would be too late to prevent the expansion of a POPF if a course of treatment is determined at POD 5 or later. In the present study, patient inclusion was limited to those diagnosed as having a POPF, and all of the evaluated factors should have been available at POD 3. POPFs are associated with inflammation that is a combination of pancreatic fluid with secondary inflammation by bacterial infection, so inflammatory markers are expected to reflect the momentum of POPFs^[6]. Thus, POD 3 was the ideal time point for the early prediction of clinically relevant POPFs, and the inflammatory markers at POD 3 were evaluated by focusing on universally prevalent markers.

Elevation of the CRP level from POD 1 to POD 3 was found to be an independent risk factor for clinically relevant POPFs with the largest odds ratio, suggesting that it was the most sensitive diagnostic factor of a subsequent clinically relevant POPF. Surprisingly, elevation of the CRP level from POD 1 to POD 3 demonstrated a greater diagnostic performance than well-known major risk factors, such as the size and texture of the pancreatic duct and the amylase content of drain fluid. Within 6 h after stimulation, the CRP level exceeded normal values, and it peaked after 48 h^[24]. CRP has a nearly constant half-life in serum of 19 h^[25]. Therefore, the CRP concentration in serum is determined by its rate of synthesis and reflects the intensity of the stimulus for acute inflammatory responses. The high diagnostic value of elevation of the CRP level from POD 1 to POD 3 could also be explained. First, an inevitable elevation of the CRP level due to surgical stress and local inflammation in resected tissues was confirmed at POD 1 in all patients. The half-life of CRP is 19 h, so the CRP level starts to show a gradual decline at PODs 2-3 in patients without additional inflammatory events, whereas it continues to increase in patients with expanding POPFs. Second, the CRP level can comprehensively reflect the chemical inflammation of the peritoneum due to leakage of the pancreatic fluid as well as coexisting inflammation due to bacterial infection. The well-known inflammatory markers of WBC and neutrophil counts showed less diagnostic value compared with the CRP level, most likely because of their wide normal range, thereby debilitating the decrease by severe infection and influences by factors other than inflammation (*e.g.*, medications)^[26-28]. Procalcitonin is specific only to bacterial infection and does not reflect a

comprehensive inflammatory status (including chemical inflammation caused by pancreatic fluids)^[29]. In addition, elevation in the CRP level from POD 1 to POD 3 is an ideal marker because it is readily measurable in hospitals at low cost and has high diagnostic value for POPFs.

Drain amylase content is superior for determining the presence of POPFs because it directly reflects the leakage of pancreatic fluids. However, the concentration can be strongly influenced by the amount of exudative ascites fluid and the efficacy of drainage, indicating that it does not always increase parallel to the exacerbation of POPFs. Pancreatic texture, which is a well-known risk factor of POPF, is problematic in that it is determined by surgeons subjectively. On the other hand, the CRP level has the advantages that it can be measured objectively and that it enables the evaluation of the degree of comprehensive inflammation easily.

As shown in Figure 2, subjects with invasive carcinoma of the pancreas were less likely to have POPFs, but the POPFs tended to be protracted when they did occur. It has been postulated that the surrounding tissues and the bloodstream around the anastomotic site are diminished by the dissection of lymph nodes, leading to poorer wound healing^[30]. Additionally, the size and texture of the pancreatic duct (which have been recognized as major risk factors for POPFs) were not significantly associated with aggravated POPFs in the present study. Patient assessment revealed that the size and texture of the pancreatic duct increased the formation of POPFs but did not always lead directly to persistent POPFs.

We proposed a novel risk scoring scale for clinically relevant POPFs. The score demonstrated good compatibility with the prevalence of clinically relevant POPFs. The score included five parameters that are available at POD 3 (including changes in the CRP level) that achieved a better goodness of fit for the aggravation of POPFs than changes in the CRP level. The scoring scale can be easily calculated at POD 3, indicating that it would be a convenient and useful method for patient selection. After the diagnosis of POPFs at POD 3, changes in the CRP level and the risk score scale were helpful in determining the subsequent management. In patients with a continuous elevation of the CRP level or a high risk score, frequent physical assessment, a computed tomography, and the culture of drainage fluids may be considered to allow early management of aggravated POPFs. Additionally, the strict control of infection, thorough management

of drains, and administration of somatostatin analogs might be recommended, depending on a patient's condition. Conversely, patients without elevations of the CRP level or a high risk score are not at risk of clinically relevant POPFs, so an early removal of the drains and early discharge from the hospital should be considered. The benefits of early drain removal have been reported by Bassi *et al.*^[31] and Kawai *et al.*^[32], but subsequent abdominal abscesses and in-hospital death have also been observed. Changes in the CRP levels and the risk score scale could help in the selection of patients eligible for the early removal of drains. Welsch *et al.*^[33] reported that a high CRP level (140 mg/L) at POD 4 is a diagnostic factor for overall infectious complications after pancreatectomy. Our results would apply better to clinical practice due to their focus on clinically relevant POPFs at an earlier time point.

The present study had limitations, including a low number of enrolled patients and the retrospective determination of cut-off values in an explorative setting. The inflammatory markers and the amylase content in drain fluid were not examined every day. The measurement of the levels of proinflammatory cytokines such as interleukin-6 would have made this study more complete. Because the results of the current study were exploratory, this analysis may lead to prospective studies evaluating the hypothesis that an elevation of the CRP level from PODs 1 to 3 might have a diagnostic value for the identification of patients with clinically relevant POPFs. Well-designed prospective clinical studies based on changes in the CRP level or the use of a high-performance risk scoring scale at the acute phase after pancreatectomy could help to establish the therapeutic strategies for POPFs.

In conclusion, a steep rise in the serum CRP level from 1 POD to 3 PODs was shown to be a highly diagnostic factor for clinically relevant POPFs and could be helpful in selecting the most appropriate management for POPFs. The scoring scale consisting of five diagnostic factors identified in the current study may provide additional assistance for patient classification.

COMMENTS

Background

Aggravation of postoperative pancreatic fistulas (POPFs) leads to prolonged hospitalization and burgeoning medical costs and can develop into fatal conditions.

Research frontiers

The identification of sensitive diagnostic factors of clinically relevant POPFs are needed to identify high-risk patients and strengthen measures aimed at preventing the aggravation of POPFs.

Innovations and breakthroughs

To date, many pre- and intraoperative risk factors of POPF formation have been reported. However, the selection methods for high-risk patients with aggravated POPFs at the acute phase after pancreatectomy have not been fully discussed. In this study, the elevation of the C-reactive protein (CRP) level was found to be a strong diagnostic factor of a clinically relevant POPF.

Applications

The changes in CRP levels and the risk score can provide a good indication for the management of a POPF, including the early removal of the drainage tubes. The inclusion of proinflammatory cytokines (e.g., interleukin-6) may achieve a further refinement of the risk score.

Terminology

POPF is the most common complication in pancreatic surgeries and can lead to fatal condition. How to control POPFs is one of the most important issues in the field of pancreatic surgery.

Peer review

This retrospective study identifies an increase in CRP as a good marker for predicting aggravation of a POPF. The conclusion of this study can assist surgeons, especially in the appropriate management of POPFs.

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