

# Prediction of Clinically Relevant Pancreatic Fistula in the Early Phase after Distal Pancreatectomy

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## ABSTRACT

**Background** Postoperative pancreatic fistula remains a major complication after distal pancreatectomy. We investigated the predictors of clinically relevant PF in the early phase after distal pancreatectomy. **Methods** Between July 2009 and March 2017, 101 consecutive patients underwent distal pancreatectomy at Hyogo College of Medicine. The postoperative data were collected, and the predictors for cPF after distal pancreatectomy were identified. **Results** cPF was identified in 34 (34%) patients. In the multivariate analysis, 2 factors (serum C-reactive protein (CRP)  $\geq 10$  mg/dL and amylase value in drain (d-AMY)  $\geq 1200$  U/L) were found to be independently the predictive factors of cPF on postoperative day 4 (odds ratio, 6.4; 95% confidence interval, 2.4-16.8,  $p < 0.001$  and odds ratio, 3.4; 95% confidence interval, 1.3-8.9,  $p = 0.011$ , respectively). A scoring scale for the prediction of cPF was developed. Serum CRP  $\geq 10$  mg/dL (Score: 2) and d-AMY  $\geq 1200$  U/L (Score: 1) were included in the scoring scale, and a score of 2 yielded the optimal diagnosis value for cPF (AUC=0.780). Therefore, only 1 factor—CRP  $\geq 10$  mg/dL—was found to be independently predictive of cPF on POD 4. **Conclusion** Serum CRP  $\geq 10$  mg/dL was found to be a predictive factor for cPF on POD 4 after distal pancreatectomy.

## INTRODUCTION

The mortality rate of Distal Pancreatectomy (DP) has fallen to  $< 5\%$ ; however, the procedure still has a high morbidity rate (16%-50%) despite recent progress in surgical techniques and perioperative management [1, 2, 3, 4, 5, 6]. Pancreatic Fistula (PF) is one of the main complications after DP and can be associated with additional complications, such as Intra-Abdominal Hemorrhaging (IAH) and abscess [7, 8, 9]. Therefore, determining the factors predicting PF after DP would be valuable.

We previously reported that the White Blood Cell count (WBC), C-Reactive Protein (CRP), and Amylase value in drain (d-AMY) on Postoperative Day (POD) 4 were predictive factors for clinically relevant PF (cPF) after pancreaticoduodenectomy [10].

In this study, we focused on postoperative clinical findings on POD 4 to detect the early symptoms of cPF and investigated statistically proven predictors of cPF in order to determine the optimum strategy for safe drain management after DP.

## PATIENTS AND METHODS

### Patients

A total 101 consecutive patients who underwent DP at Hyogo College of Medicine between July 2009 and March 2017 were retrospectively investigated. The postoperative clinical findings on POD 4 were assessed as follows: serum albumin, WBC count, CRP, and serum amylase were obtained from blood tests; and drainage fluid was collected from an abdominal drain placed beside the pancreatic stump and assessed for quantity, color, and d-AMY. The color of the drainage fluid was assessed by the definition of International Study Group on Pancreatic Fistula (ISGPF) as previously described: dark-brown, greenish, milky water and clear spring water were considered sinister appearances [11]. The color of drainage fluid was considered "unusual" if it was sinister according to the definition. The highest body temperature was chosen as the body temperature for the day. The grading of PF was made according to the ISGPF definition [11]. Grade B/C PF was considered to be cPF. Delayed Gastric Emptying (DGE) and postpancreatectomy hemorrhaging were also defined according to the definitions proposed by the International Study Group of Pancreatic Surgery (ISGPS) [12, 13]. The thickness of the pancreatic parenchyma at the resection line was measured on Computed Tomography (CT) before surgery. Mortality was defined as death in the hospital or within 30 days after surgery.

The study was approved by the ethics committee of Hyogo College of Medicine (No. 2673).

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**Keywords** C-Reactive Protein; Pancreatectomy; Pancreatic fistula

**Abbreviations** BMI body mass index; PF pancreatic fistula; DP distal pancreatectomy

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## Surgical Procedure

All of the surgical procedures were performed by a gastroenterologist surgeon who was board-certified in Japan. There were no strict criteria for selecting the method of pancreatic stump closure, and the method of pancreatic stump closure and the transection line of the pancreas were left to the surgeon's discretion. The patients mainly underwent one of three types of pancreatic stump closure: the clamp-crushing of the pancreatic parenchyma by means of the Child-Kelly procedure with Main Pancreatic Duct ligation (MPD), resection of pancreatic parenchyma by ultrasonic scissors with MPD ligation, or stapler closure. For malignant tumor, radical resection of the distal pancreas with regional lymph-node dissection and splenectomy was performed. For benign or low-grade malignant tumor, laparoscopic Spleen-Preserving Distal Pancreatectomy (SPDP) was indicated. After DP, a closed drain (20 Fr) was placed near the stump of the remnant pancreas. No patient was administered octreotide after surgery.

## Statistical Analyses

The data were expressed as median values. The chi-squared test, Fisher's exact test, and Mann-Whitney *U* test were used for the comparison of categorical variables, as appropriate. A Receiver Operating Characteristics (ROC) curve was constructed in order to determine the optimal cut-off values for the serum albumin, WBC, CRP, serum amylase, d-AMY, quantity of drain fluid, and body temperature as predictive factors of cPF. *P* values of <0.05 were considered to indicate statistical significance. Statistical analyses were performed using the SPSS software program, version 21.0 (SPSS Company, Chicago, IL, USA).

## RESULTS

### The Patient Characteristics and Intraoperative Outcomes

The patient characteristics and intraoperative outcomes are listed in **Table 1**. A total of 101 patients enrolled in this study, comprising 52 men and 49 women with a median age of 71 years old (range, 11-90 years old). The most common disease was pancreatic cancer (47%), followed by intraductal papillary mucinous neoplasm (14%). Patients underwent open surgery (n=77) and laparoscopic surgery (n=24). DP was performed in 85 (84%) patients, and SPDP was performed in 16 (16%) patients. The median operative time was 379 minutes (range, 138-769 minutes). The median blood loss was 435 mL (range, 10-3300 mL). Soft pancreatic texture, portal vein resection, celiac artery resection, and contiguous organ resection were noted in 79, 3, 4, and 12 patients, respectively. The median pancreatic thickness was 10.1 mm (range, 3.9-18.6 mm).

### The Postoperative Complications and Outcomes

The postoperative complications and outcomes are shown in **Table 2**. cPF was identified in 34 (34%) patients.

DGE, IAH, intra-abdominal abscess, and wound infection were 9 (9%), 4 (4%), 3 (3%), and 6 (6%) patients, respectively. No patients underwent re-operation. One death occurred due to cerebral infarction.

### Univariate and Multivariate Analyses of Postoperative Findings on POD 4

Univariate and multivariate analyses were performed in order to identify the predictive factors of cPF on POD 4. The ROC curve revealed a cut-off value of 3.0 g/dL for the serum albumin (area under the curve [AUC]=0.491), 10,000  $\mu$ /L for the WBC count (AUC=0.621), 10 mg/dL for the CRP (AUC=0.774), 52 U/L for the serum amylase (AUC=0.393), 1200 U/L for the d-AMY (AUC=0.691), 12 mL for the quantity of drain fluid (AUC=0.434), and 37.3°C for the body temperature (AUC=0.572). In the univariate analysis, 5 parameters with *p*<0.1 were chosen for the multivariate analysis: WBC, CRP, drainage fluid (color

**Table 1.** The patient characteristics and intraoperative outcomes.

Age, year	71 (range: 11-90)
Gender, male/female	52 (51%)/49 (49%)
Body mass index	21.4 (range: 13.8-32.6)
Diabetes mellitus, yes/no	32 (32%)/69 (68%)
Serum amylase, U/L	77 (range: 26-921)
<b>Disease</b>	
Pancreatic cancer	48 (47%)
Intraductal papillary mucinous neoplasm	14 (14%)
Mucinous cystic neoplasm	10 (10%)
Neuroendocrine tumor	7 (7%)
Solid pseudopapillary neoplasm	5 (5%)
Other	17 (17%)
<b>Surgical procedure</b>	
Distal pancreatectomy	85 (84%)
Spleen preserving distal pancreatectomy	16 (16%)
Operative time, min	379 (range: 138-769)
Intraoperative blood loss, mL	435 (range: 10-3300)
Pancreatic texture, soft/hard	79 (78%)/22 (22%)
Portal vein resection, yes/no	3 (3%)/98 (97%)
Celiac artery resection, yes/no	4 (4%)/97 (96%)
Contiguous organ resection, yes/no	12 (12%)/89 (88%)
Pancreatic thickness, mm	10.1 (range: 3.9-18.6)

**Table 2.** The postoperative complications and outcomes.

<b>Pancreatic fistula</b>	
Grade A	43 (43%)
Grade B	34 (34%)
Grade C	0 (0%)
<b>Delayed gastric emptying</b>	
Grade A	5 (5%)
Grade B	3 (3%)
Grade C	1 (1%)
<b>Intra-abdominal hemorrhage</b>	
Grade A	0 (0%)
Grade B	1 (1%)
Grade C	3 (3%)
Intra-abdominal abscess	3 (3%)
Wound infection	6 (6%)
Re-operation	0 (0%)
Mortality	1 (1%)

and d-AMY), and body temperature. In the multivariate analysis, 2 factors (CRP and d-AMY) were found to be independently the predictive of cPF on POD 4 (odds ratio, 6.4; 95% confidence interval, 2.4-16.8,  $p < 0.001$  and odds ratio, 3.4; 95% confidence interval, 1.3-8.9,  $p = 0.011$ , respectively) (Table 3).

**Risk Scoring Scale Analysis for cPF**

A scoring scale for the prediction of cPF was developed. Two independently predictive factors (CRP  $\geq 10$  mg/dL at POD 4 (Score: 2) and d-AMY  $\geq 1200$  U/L at POD 4 (Score: 1)) were included in the scoring scale (Figure 1a).

The prevalence of cPF increased gradually in proportion with the score, from 6% to 68% (Figure 1b). The score had a goodness of fit for cPF. A score of 2 yielded the optimal diagnosis value for cPF (AUC=0.780) (Figure 1c). Therefore, only one factor CRP  $\geq 10$  mg/dL—was found to be independently predictive of cPF on POD 4.

**Screening Accuracy and Predictive Power**

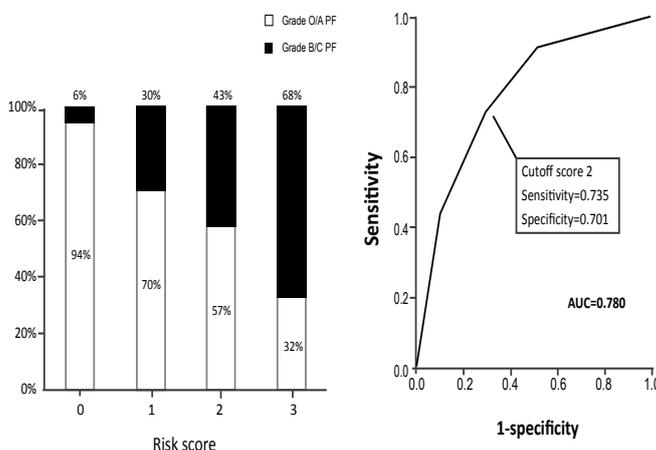
The classification table based on the outcomes of the predictive probability demonstrated sensitivity, specificity, positive predictive value, and negative predictive value were 73.5%, 70.1%, 55.6%, and 83.9% respectively (Table 4).

**Table 3.** Univariate and multivariate analysis of postoperative findings on POD 4.

		Univariate analysis			Multivariate analysis		
		Grade 0/A (n=67)	Grade B/C (n=34)	p value	Odds ratio	95% CI	p value
<b>Blood examination</b>							
Albumin (g/dL)	<3.0	31	14	0.627			
	$\geq 3.0$	36	20				
WBC ( $10^2/\mu\text{L}$ )	<100	50	19	0.056	2.1	0.8-5.8	0.143
	$\geq 100$	17	15				
CRP (mg/dL)	<10	47	9	<0.001	6.4	2.4-16.8	<0.001
	$\geq 10$	20	25				
Amylase (U/L)	<52	26	18	0.176			
	$\geq 52$	41	16				
<b>Drainage fluid</b>							
d-AMY (U/L)	<1200	46	13	0.003	3.4	1.3-8.9	0.011
	$\geq 1200$	21	21				
Unusual color	yes	15	15	0.024	1.4	0.5-4.4	0.536
	no	52	19				
Quantity (mL)	<12	22	11	0.961			
	$\geq 12$	45	23				
Body temperature ( $^{\circ}\text{C}$ )	<37.3	23	16	0.072	1.4	0.5-3.8	0.553
	$\geq 37.3$	44	18				

CRP C-Reactive Protein; d-AMY Amylase value in drain; POD Postoperative Day; WBC White Blood Cell count

Risk factor	Parameter	Risk score
Serum CRP	$\geq 10$ mg/gL, POD 4	2
d-AMY	$\geq 1200$ U/L, POD 4	1



**Figure 1.** (a) Parameters with allocated scores. (b) Bar graph of the prevalence of clinically relevant pancreatic fistula. (c) Receiver operating characteristic curve for the risk score as a diagnostic factor of clinically relevant pancreatic fistula.

AUC area under the curve; CRP C-Reactive Protein; d-AMY: Amylase value in drain; PF Pancreatic Fistula; POD Postoperative Day.

**Table 4.** Screening accuracy and predictive power.

Observed	Predicted	
	Grade 0/A	Grade B/C
Grade 0/A	47	20
Grade B/C	9	25
	Sensitivity	73.5%
	Specificity	70.1%
	PPV	55.6%
	NPV	83.9%

NPV Negative Predictive Value; PPV Positive Predictive Value

## DISCUSSION

Recently, Kawai *et al.* [14] reported that the early removal of drains on POD 4 can reduce intra-abdominal infections in patients without symptoms of PF. However, early drain removal may increase the risk of worsening of intra-abdominal abscesses developed due to latent PF. It is difficult to detect the incidence of latent PF because of its few symptoms without d-AMY elevation [15]. To manage drain safety in the early phase after DP, it is necessary to predict the prospective incidence of cPF, including latent PF.

Several studies reported risk factors of cPF after DP using patient characteristics, intraoperative factors, such as the Body Mass Index (BMI) [16, 17], intraoperative blood loss [18], and thickness of pancreatic parenchyma [19, 20]. The postoperative clinical and laboratory data might include the integration of most risk factors of cPF and they were the final outcomes of the surgical treatment. In this study, we hypothesized that postoperative clinical and laboratory data could predict the incidence of cPF after DP. To verify this hypothesis, we analyzed only the postoperative clinical and laboratory data in order to try to predict cPF by univariate and multivariate analyses. Serum CRP  $\geq 10$  mg/dL and d-AMY  $\geq 1200$  U/L on POD 4 were found to be independently predictive factors of cPF in the multivariate analysis. Maggino *et al.* [21] reported that the drain amylase value on POD 1 of 2000 U/L optimized cPF prediction after DP. We also analyzed the predictive factors for cPF on POD 1 and 7; however, there were no independent predictive factors for cPF.

We proposed a risk scoring scale analysis for cPF. The score included serum CRP (score: 2) and d-AMY (score: 1), which were available on POD 4 and achieved a goodness of fit for cPF. A score of 2 yielded the optimal diagnosis value for cPF, so serum CRP  $\geq 10$  mg/dL or serum CRP  $\geq 10$  mg/dL and d-AMY  $\geq 1200$  U/L were considered risk factors for cPF. Therefore, serum CRP  $\geq 10$  mg/dL was considered an independent risk factor for cPF. Early drain removal on POD 4 can thus be recommended in patients with serum CRP  $< 10$  mg/dL. In high-risk cPF patients with serum CRP  $\geq 10$  mg/dL on POD 4, a series of examination to detect infection, such as bacterial culture of drain fluid and abdominal CT examinations, are recommended instead of drain removal.

In the present study, serum CRP  $\geq 10$  mg/dL was found to be an independent risk factor for cPF with the highest odds ratio, suggesting that it was the most sensitive

predictive factor of cPF. CRP is an acute-phase protein and a valuable marker for detecting an inflammatory response and postoperative recovery, and it has a nearly constant half-life in serum of 19 h [22]. Welsch *et al.* [23] reported that serum CRP  $> 140$  mg/L at POD 4 was a diagnostic factor for overall infectious complications after pancreatectomy. Kanda *et al.* [24] reported that elevation of the serum CRP level ( $\geq 28.4$  mg/L, from POD 1 to POD 3) was a high predictive factor for cPF after pancreatectomy. It was thought that these data supported our result in this study.

The present study is associated with some limitations, including the relatively small number of patients and the retrospective nature of the study. In the future, prospective studies should be performed based on the data of this study.

## CONCLUSION

Serum CRP  $\geq 10$  mg/dL was a predictive factor for cPF on POD 4 after DP. Our simplified criteria may contribute to safe drain management in the early phase after DP.

## Conflicts of interest

The authors declare no conflicts of interest in association with the present study.

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