



Has the pancreatic fistula already occurred in the operation? An intraoperative predictive factor of clinical relevant-postoperative pancreatic fistula after the distal pancreatectomy^{☆,☆☆}



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ABSTRACT

Purpose: The aim of this study was to assess the predictive effect of intraoperative amylase value from pancreatic remnant on the development of clinical relevant-postoperative pancreatic fistula after distal pancreatectomy.

Methods: Patients undergoing distal pancreatectomy between June 2017 and October 2018 were studied retrospectively. The intraoperative amylase value was measured followed by drain fluid for amylase on postoperative day 3. The analysis of clinical relevant-postoperative pancreatic fistula predictors was carried out using the logistic regression. The receiver operating characteristic analysis was performed to evaluate the discriminative capacity of intraoperative amylase value as a predictive risk factor.

Results: The study population consisted of 40 patients. The clinical relevant-postoperative pancreatic fistula occurred in 13 patients, no grade C pancreatic fistula (PF). The intraoperative amylase value correlated significantly with clinical relevant-postoperative pancreatic fistula. An intraoperative amylase value > 3089 U/L was proposed as the cut-off level to predict clinical relevant-postoperative pancreatic fistula by the receiver operating characteristic curve. The sensitivity, specificity and accuracy of this level were respectively 84.6%, 88.9% and 88.5%. The multivariate logistic regression analysis revealed that intraoperative amylase value and suture closure for the pancreatic stump were the significant predictive risk factors for the clinical relevant-postoperative pancreatic fistula.

Conclusion: The intraoperative amylase value can be early and easily measured as a predictive risk factor, which seems useful for postoperative management of clinical relevant-postoperative pancreatic fistula after distal pancreatectomy. While, the stapler closure might be a feasible way for the pancreatic transection during the operation.

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INTRODUCTION

Distal pancreatectomy (DP) is considered a safe curative surgical treatment for tumors confined to the pancreatic body and tail. The incidence of clinical relevant postoperative pancreatic fistula (CR-POPF) after DP has been reported between 10% and 30% [1–4], which was the major cause of morbidity and mortality after pancreatic resection. According to the International Study Group for Pancreatic Fistula (ISGPF) [5], the definition for a CR-POPF is a threefold increase in the level of abdominal drain fluid amylase concentration compared with the serum amylase level on the postoperative day 3 with clinically relevant change in management. In order to reduce the incidence of CR-POPF, drain amylase value on

the first postoperative day was measured to predict the occurrence of CR-POPF [6–8]. Further researches [4,9,10] were carried out to prove the relevance between CR-POPF and the intraoperative amylase value (IAV) in peri-pancreatic fluid during the pancreatic operation. These findings implied the development of pancreatic fistula was early occurred during the operation and should be early prevented. Christopher, et al. [10] demonstrated the IAV was significantly associated with the development of POPF after DP. However, due to the few cases in their study, the CR-POPF which would cause severe consequences was not discussed. Furthermore, rare report mentioned the exact level of intraoperative amylase value combined with other predictive risk factors for of CR-POPF after distal pancreatectomy. Thus, in the present study, we aimed to demonstrate the exact level of IAV and other independent risk factors for the formation of CR-POPF and evaluate the discriminative capacity of IAV after DP.

From June 2017 to October 2018, 40 patients who underwent DP in the pancreatic disease center at Ruijin Hospital for pathologies of all kinds with data available on IAV were included in this study. Perioperative data were collected and recorded for analysis.

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Surgical Technique and Intraoperative Amylase Collection. All operations were performed by one surgery team. Either suture ($n = 5$, using Ethicon Suture Prolene 5–0) and stapler ($n = 35$, using Covidien Endo GIA Ultra Universal Stapler 60 mm 2.5/3.5 mm) closure for the pancreatic remnant were carried out during the distal pancreatectomy. A drain was routinely placed near the pancreatic transection site and along the left hemidiaphragm. Drain fluids were collected on the third postoperative day for the measurement of amylase.

Fluid for IAV was collected at the final period of the operation. After closure for the pancreatic remnant, 500 mL saline was used to irrigate the abdomen especially the pancreatic remnant and suctioned clearly. A dry gauze was placed at the pancreatic transection site for 5mins. The wet gauze was wrung out and the fluid was collected and sent for the amylase analysis at once. (Fig 1).

Definition and Grading of POPF. According to international study group of pancreatic fistula (ISGPF), the postoperative pancreatic fistula (POPF) was defined as a threefold increase in the level of abdominal drain fluid amylase concentration compared with the serum amylase level on the post-operative day 3. POPF was graded A,B and C, of which grade A was regarded as biochemical leak and grade B/C were regarded as clinical relevant-postoperative pancreatic fistula (CR-POPF) [5].

Statistical Analysis. Statistical analysis of this study was performed by using SPSS software (IBM SPSS Statistics 22.0). Continuous variables were presented as means with standard deviation, while categorical variables were expressed as frequencies with percentage. The Mann–Whitney U test or the student's t test was used for continuous variables. The chi-square test was used for categorical variable. All tests were 2-tailed. Correlations between categorical and continuous variables were evaluated with logistic regression. A receiver operating

characteristic (ROC) curve was displayed to evaluate the discriminative capacity of IAV after DP. While, a cut-off of ROC curve with maximum sensitivity and specificity was used to predict the occurrence of CR-POPF. P values <0.05 were considered significant.

RESULTS

Patient Characteristics. A total of 40 patients underwent DP in the pancreatic disease center at Ruijin Hospital from June 2017 to October 2018 were included in this study, of which 24 were male. The mean age of all patients was 47.05 years. The average length of hospital stay was 23 days. 18 patients had pancreatic ductal adenocarcinoma (PDAC), 1 patient had acinar cell carcinoma, 11 patients had intra-ductal papillary mucinous neoplasm, 1 patient had pancreatic neuroendocrine tumor (PNET), 2 patients had chronic pancreatitis, 1 patient had solid pseudopapillary tumor (SPT), 4 patients had serous cystadenoma (SCN) and 2 patients had mucinous cystic neoplasm (MCN). (shown in Table 1).

Comparison of Patient Characteristics, Operative Variables, and Postoperative Outcomes with the CR-POPF. Based on the definition of POPF from ISGPF, 12 patients did not develop a pancreatic fistula, 15 patients had biochemical leak (grade A), 13 patients had CR-POPF (grade B), no grade C pancreatic fistula occurred. Among patients with grade B pancreatic fistula, 12 patients left the hospital with drain in abdomen, of which 11 patients were placed the drain over 3 weeks. The other 2 patients were repositioned the placed drain by percutaneous drainage. All CR-POPFs were resolved without any other further complications. Besides pancreatic fistula, no other complications was developed in this study, including postoperative hemorrhage, delayed gastric emptying, bile leak, etc.

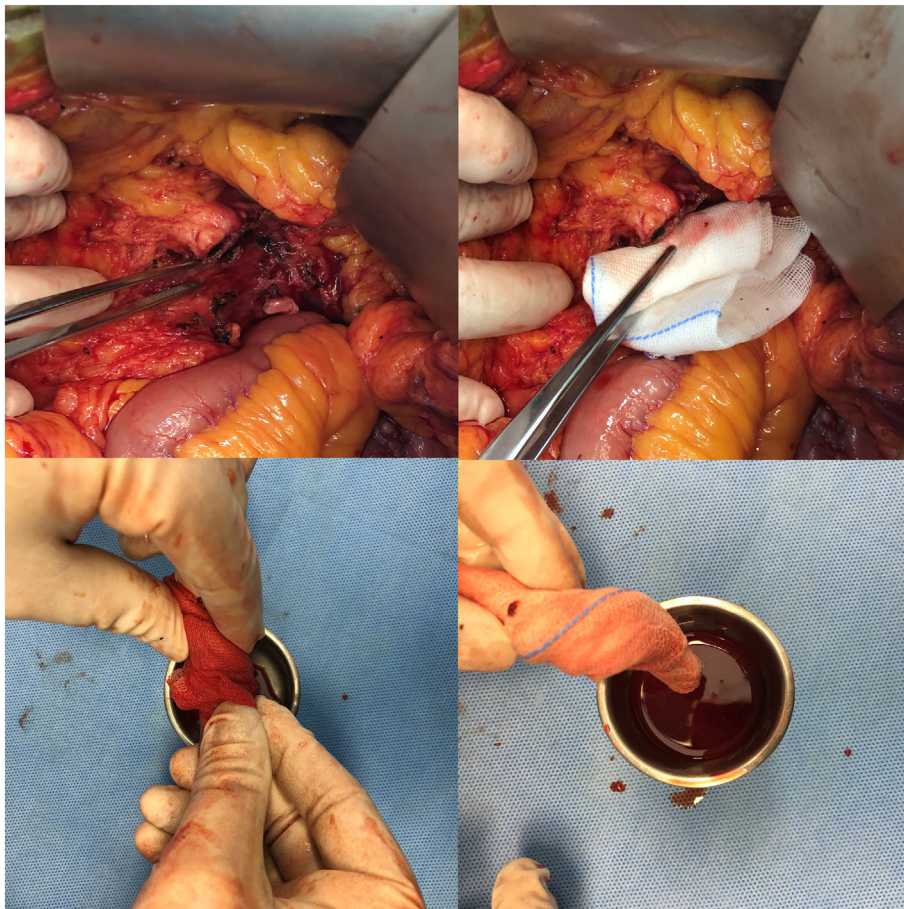


Fig 1. Procedures for intraoperative amylase collection.

Table 1
Clinical characteristics of 40 patients undergoing DP

Parameter	n	Percentage (%)
Male	24	60
Female	16	40
Age (mean)	47.05	
Hospital stay (mean, days)	23	
Histology		
PDAC	18	45
acinar cell carcinoma	1	2.5
IPMN	11	27.5
PNET	1	2.5
Chronic pancreatitis	2	5
SPT	1	2.5
SCN	4	10
MCN	2	5

The association between patient characteristics, intraoperative variables, and postoperative outcomes and the development of CR-POPF is shown in Table 2. The IAV was found significantly higher in those patients with a CR-POPF than in those with no PF and a grade A fistula (6786.00 ± 4228.97 vs 1561.56 ± 1187.26 U/L, $p < 0.01$). There were no significant differences between these two groups of patients in

Table 2
Univariate analysis of the predictive factors for CR-POPF

Parameters	PF (n = 40)		P value
	CR-POPF (n = 13)	Negative/grade A (n = 27)	
Age (years)	57.46 ± 14.90	64.15 ± 12.40	.143
Gender			
Male	7	17	.581
Female	6	10	
Body mass index (kg/cm ²)	23.94 ± 3.65	22.24 ± 3.37	.155
Cardiovascular diseases			
Yes	2	4	1.000
No	11	23	
Smoking			
Yes	1	7	.353
No	12	20	
Alcoholism			
Yes	1	4	.898
No	12	23	
Diabetes			
Yes	2	7	.731
No	11	20	
Hypertension			
Yes	5	12	.720
No	8	15	
CA19–9(U/L)	113.64 ± 226.39	819.05 ± 2843.51	.381
Preoperative albumin (g/L)	41.38 ± 5.58	39.92 ± 3.57	.322
Preoperative total protein (g/L)	70.92 ± 8.40	67.26 ± 5.61	.109
Preoperative hemoglobin (g/L)	137.92 ± 12.11	129.74 ± 16.41	.119
Operation time (mins)	248.46 ± 108.44	213.5 ± 66.06	.301
Blood loss (mL)	373.08 ± 328.26	429.63 ± 533.90	.728
Tumor mass (cm)	3.25 ± 1.68	4.08 ± 1.91	.195
Pancreatic remnant texture			
Soft	9	18	1.000
Hard	4	9	
Pancreatic remnant closure			
Suture	4	1	.056
Stapler	9	26	
Main pancreatic duct size			
> = 3 mm	8	12	.311
<3 mm	5	15	
Histopathology			
Benign	9	12	.141
Malignant	4	15	
IAV (U/L)	6786.00 ± 4228.97	1561.56 ± 1187.26	.001
Postoperative hemoglobin (g/L)	122.46 ± 11.03	121.67 ± 16.05	.873
Postoperative albumin (g/L)	30.54 ± 2.73	30.22 ± 3.25	.764
Postoperative total protein (g/L)	55.23 ± 4.15	55.52 ± 4.43	.843

Table 3
Comparison of IAV from two methods of pancreatic remnant closure

	Suture closure (n = 5)	Stapler closure (n = 35)	P value
IAV (U/L)	3365.00 ± 4263.77	3244.43 ± 3506.25	.944
Operation time (mins)	339.00 ± 76.95	208.41 ± 70.24	.000
Blood loss (mL)	1060.00 ± 971.08	318.57 ± 274.15	.001

term of age, gender, BMI, cardiovascular disease, smoking, alcoholism, diabetes, hypertension, CA19–9, preoperative albumin/total protein/hemoglobin, operation time, blood loss, tumor mass, pancreatic texture, main pancreatic duct size, histopathology and postoperative albumin/total protein/hemoglobin on postoperative day 3. Among 40 patients, 5 patients were performed the pancreatic remnant closure by suture, and the others were used the stapler. Comparing to the stapler closure, the suture closure might have a higher incidence of CR-POPF after distal pancreatectomy (25.71% vs 80%, $P < 0.1$). However, the IAV from the pancreatic remnant closed by these two methods (suture 3365.00 ± 4263.77 U/L vs. stapler 3244.43 ± 3506.25 U/L, $p = 0.944$) had no significant difference. Moreover, those 5 patients with suture closure seemed to be suffered from the operation, in which patients had more operation time and blood loss than the others (339.00 ± 76.95 vs 208.41 ± 70.24 mins, $p < 0.001$; 1060.00 ± 971.08 vs 318.57 ± 274.15 mL, $p = 0.001$). (shown in Table 3).

Among all the grades of pancreatic fistula, the mean of IAV was 3259.50 U/L with standard deviation 3502.7 U/L. The IAV of patients with no pancreatic fistula was the lowest (1055.83 ± 722.62 U/L), comparing that of patients with grade A (2006.13 ± 1301.43 U/L) and grade B (6786.00 ± 4228.97 U/L). the IAV was significantly different from each other, which was shown in Table 4.

ROC curve for IAV. The ROC curve for IAV is presented in the Fig 2. The area under the curve (AUC) was 0.885 (95%CI 0.756–1.000, $p < 0.001$). An IAV of 3089 U/L was found as the best cut-off value to predict the CR-POPF which had the highest sensitivity (84.6%) and specificity (88.9%).

Predictive Risk Factors for CR-POPF in DP Patients. In this study, a multivariate logistic regression analysis was used to find out those predictive risk factors for CR-POPF. Table 5 reveals that the IAV (OR = 2.0, 95%CI 1.000–3.003) and the suture closure (OR = 1.1, 95%CI 1.029–1.349) for pancreatic remnant were the significant predictive risk factors for the development of CR-POPF ($p < 0.05$). None of the other variables were significantly associated with the CR-POPF, including age, gender, BMI, smoking, diabetes, hypertension, Cardiovascular diseases, CA19–9, preoperative albumin/total protein/hemoglobin, operation time, blood loss, tumor mass, pancreatic texture, main pancreatic duct size, histopathology and postoperative albumin/total protein/hemoglobin on postoperative day 3.

DISCUSSION

The pancreatic fistula (PF) was regarded as one of the most common complication after pancreatic resection. The predictive scoring systems to classify the risk of development of PF after pancreaticoduodenectomy (PD) were established and widely used [11–13]. However, until now an appropriate predictive system for PF after distal pancreatectomy (DP) had not be established yet. In present study, the result of univariate and multivariate analysis revealed that the IAV and the suture closure were the significant predictive risk factors for the CR-POPF after DP.

Table 4
Comparison of IAV among all grades of pancreatic fistulas (PF)

	No PF (n = 12)	Grade A (n = 15)	Grade B (n = 13)	P value
IAV (U/L)	1055.83 ± 722.62	2006.13 ± 1301.43	6786.00 ± 4228.97	.000

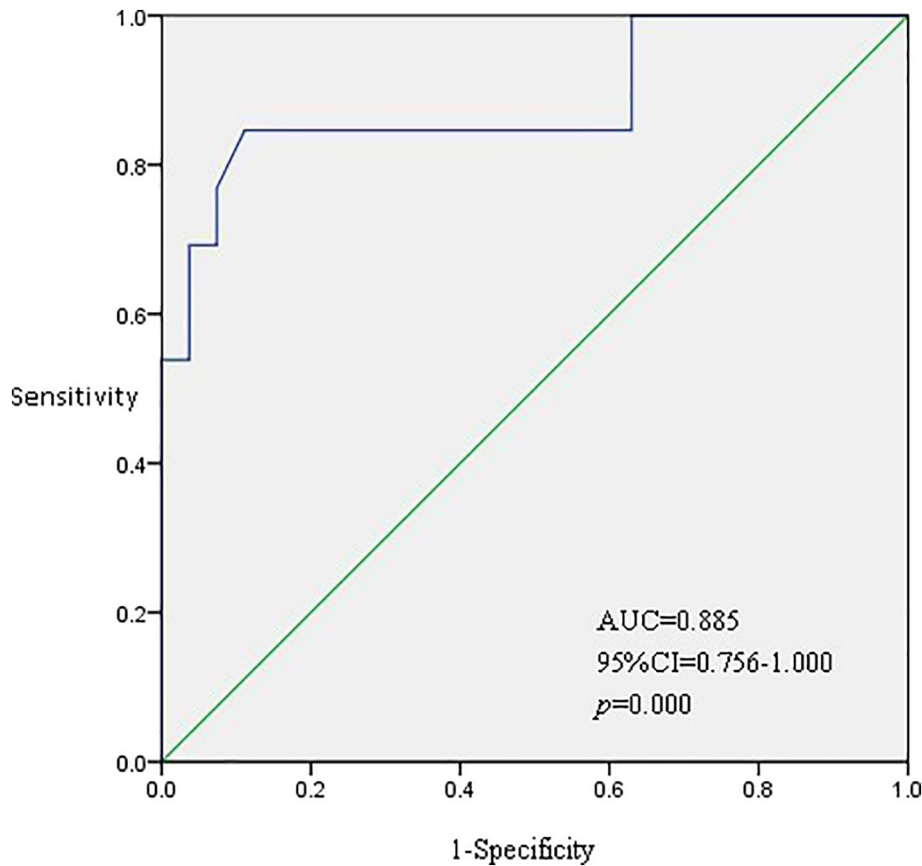


Fig 2. ROC curve for the IAV.

Enrico Molinari, et al. [6] proved that the amylase value in drains (AVD) on postoperative day 1 was a significant predictive factor of PF development, which was supported by the other study [8]. Due to this consequence, the author suggested that the drains management should be based on the evidence of the further prospective randomized clinical trial (RCT) on AVD which was already carried out. In the present study, the IAV was the significant predictive risk factor for the CR-POPF after DP. The cut-off value with high sensitivity and specificity was 3089 U/L. Obviously, the IAV could be obtained earlier than the AVD, which meant more predictive. The patients with IAV over 3089 U/L had 2 times risk of development of CR-POPF than the others. The high IAV suggested the pancreatic fistula had already occurred in the operation. The previous study [10] had reached the same consequences. The leakage of the branch pancreatic duct might be the main cause of the instant high IAV which we attempt to approve in our further research. However, it should be noticed that the drains were placed more than 3 weeks in some patients which was diagnosed the grade B POPF according to the ISGPF. It might be ameliorated by following the recommendation of the enhanced recovery after surgery (ERAS) or the early drain removal management [14–16]. Moreover, in our study the IAV was examined in the lab and the result was always obtained after the operation. If the high IAV was occurred, we couldn't make any

amelioration such as reinforcement of the pancreatic transection site during the operation. Therefore, in the further research we would pay attention to the real-time intraoperative amylase analysis and attempt to reduce the incidence of CR-POPF by reinforcing the potential fistula site just in the operation. The use of a chymotrypsin probe to visualize the pancreatic juice leaking was realized in a swine model [17], but Yamashita, et al. [18], have found it was technically difficult to collect enough amounts of pancreatic juice for the chymotrypsin probe in humans in the operation, the pancreatic leaking visualization by chymotrypsin probe was not instant. A proper real-time visible solvent for pancreatic juice was still hard to be found. The subgroup analysis showed that the high IAV not only predicted the occurrence of CR-POPF, but also implied the high grade of this complication. No grade C POPF, defined as whenever a grade B POPF leads to organ failure or to reoperation or even to death, was found in the study. Thus, the correlation between IAV and grade C POPF remained unknown.

To avoid the development of CR-POPF, the closure of pancreatic remnant was always the hotspot of the researches. Some studies [4,19,20] indicated that the different methods of pancreas stump closure correlated with the POPF. A large multicenter retrospective study [3] on risk factors for POPF after DP was done in the year of 2017, about 2026 cases were included. The results from this study found that different method of pancreatic stump closure did not affect the development of POPF. Our study indicated that the suture closure could lead to CR-POPF, which was supported by the recent systematic review [19]. Longer operation time and more blood loss suggested the operation procedure was difficult. Thus, contrary to the stapler closure as usual, the suture closure was enforced to be performed. It should be reminded that our study was non-randomized. The method of closure was left to the discretion of the surgeon, the suture closure was usually performed in the complex operation in which the pancreatic transection site was hard to be dissociated or the pancreas was too thick to be closed by

Table 5
Multivariate analysis of the predictive factors for CR-POPF

	P value	Odds ratio	95% confidence interval
IAV (U/L)	.012	2.0	1.000–3.003
Pancreatic remnant closure (suture/stapler)	.047	1.1	1.029–1.349

the stapler. A prospective RCT from multi-institutions on the closure of pancreatic remnant after DP was required to carry out.

From the results of our study, the IAV seemed to be an excellent predictive risk factor for the CR-POPF after DP. But it was still far from the establishment of predictive scoring system. The characteristics including age, obesity, preoperative hypoproteinemia, small main pancreatic duct size, soft pancreatic texture, etc. were proved to be the predictive risk factors by the other studies [3,21,22]. Due to the lack of patients, these risk factors mentioned above were not found significant in our study. The predictive scoring system for PD was established, but the predictive system for the DP or middle-pancreatectomy was still a blank.

In conclusion, the current study indicated that the intraoperative amylase value and the suture closure for the pancreatic stump were significant predictive risk factors for the CR-POPF after DP. The prevention or the management of PF should be carried out during the operation rather than later. Further studies were required to validate these findings of this study.

AUTHOR CONTRIBUTION

Study conception and design: Weishen WANG, Jiancheng WANG.
Acquisition of data: Hao QIAN.
Analysis and interpretation of data: Weishen WANG, Jiewei LIN.
Drafting of manuscript: Weishen WANG, Yuanchi WENG.
Critical revision: Jun ZHANG, Jiancheng WANG.

DECLARATION OF COMPETING INTEREST

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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