

# World Journal of *Gastroenterology*

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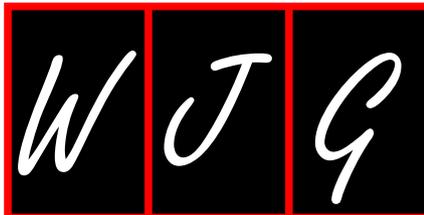
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Randomized Clinical Trial

## Drainage fluid and serum amylase levels accurately predict development of postoperative pancreatic fistula

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### Abstract

#### AIM

To investigate potential biomarkers for predicting postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD).

#### METHODS

We prospectively recruited 83 patients to this study. All patients underwent PD (Child's procedure) at the Division of Hepatobiliary and Pancreas Surgery at the First Bethune Hospital of Jilin University between June 2011 and April 2015. Data pertaining to demographic variables, clinical characteristics, texture of pancreas, surgical approach, histopathological results, white blood cell count, amylase and choline levels in the serum, pancreatic/gastric drainage fluid, and choline and amylase levels in abdominal drainage fluid were included in the analysis. Potential correlations between these parameters and postoperative complications such as, POPF, acute pancreatitis, hemorrhage, delayed gastric emptying, and biliary fistula, were assessed.

#### RESULTS

Twenty-eight out of the 83 (33.7%) patients developed POPF. The severity of POPF was classified as Grade A in 8 (28%) patients, grade B in 16 (58%), and grade C in

4 (14%), according to the pancreatic fistula criteria. On univariate and multivariate logistic regression analyses, higher amylase level in the abdominal drainage fluid on postoperative day (POD)1 and higher serum amylase levels on POD4 showed a significant correlation with POPF ( $P < 0.05$ ). On receiver operating characteristic curve analysis, amylase cut-off level of 2365.5 U/L in the abdominal drainage fluid was associated with a 78.6% sensitivity and 80% specificity [area under the curve (AUC): 0.844;  $P = 0.009$ ]. A cut-off serum amylase level of 44.2 U/L was associated with a 78.6% sensitivity and 70.9% specificity (AUC: 0.784;  $P = 0.05$ ).

### CONCLUSION

Amylase level in the abdominal drainage fluid on POD1 and serum amylase level on POD4 represent novel biomarkers associated with POPF development.

**Key words:** Pancreaticoduodenectomy; Complication; Amylase; Pancreatic fistula

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**Core tip:** In this study, we sought to identify biomarkers that could help predict the risk of postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy. Diagnosis of POPF was based on the International Study Group of Pancreatic Fistula criteria. Association between POPF and various clinical and biochemical parameters was assessed. Amylase level in the abdominal drainage fluid on postoperative day 1 and serum amylase level on postoperative day 4 showed a significant association with POPF and represent novel biomarkers associated with POPF development.

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## INTRODUCTION

Pancreaticoduodenectomy (PD) is a common operative approach for treatment of various malignant diseases of the distal biliary duct, the head of pancreas, and the peri-ampullar region. It is also widely acknowledged as one of the most challenging surgical procedures. PD is associated with substantial perioperative mortality (2%-5% even in high-volume centers) and morbidity (30%-50%)<sup>[1,2]</sup>. Postoperative pancreatic fistula (POPF) is one of the most important complications of PD; reported incidence rates range from 2% to 25%<sup>[3]</sup>. POPF often leads to further complications, such as hemorrhage and abdominal abscess, and is associated

with increased length of hospital stay<sup>[3,4]</sup>. POPF and other PD-associated complications have necessitated the development of new surgical modalities, like a combination of pancreaticojejunostomy with duct-mucosa pancreaticojejunostomy; however, the incidence of POPF following PD continues to be a concern<sup>[5]</sup>.

Various pre-operative and intra-operative factors, such as preoperative jaundice and diameter of the pancreatic duct, are associated with POPF; however, these factors are not reliable predictors of POPF<sup>[6,7]</sup>. Biochemical markers in serum and drainage fluid may reflect the disease progression, and it is of translational significance to investigate their correlation with clinical characteristics and their potential value as predictors of POPF. In this study, we sought to identify potential predictors of POPF development, which may help optimize the treatment of these patients in clinical practice.

## MATERIALS AND METHODS

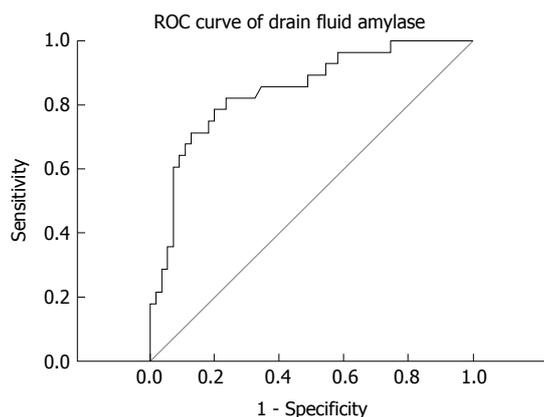
### Study design

We prospectively recruited 83 patients to this study. All patients underwent PD at the Department of Hepatobiliary and Pancreatic Surgery at the First Bethune Hospital of Jilin University between June 2011 and April 2015. Preoperative, intraoperative and postoperative data were collected for each patient. Preoperative variables of interest included age, sex, history of diabetes, jaundice, plasma protein levels and pre-operative intervention for jaundice (if any). Intraoperative variables included pancreatic consistency, diameter of pancreatic duct, and the technique used for pancreatic anastomosis. Postoperative data included the results of pathological examination, pancreatic and gastric drainage volume, and complications after operation, such as POPF, hemorrhage, acute pancreatitis, delayed gastric emptying (DGE), and biliary fistula (Table 1).

Severity of POPF was classified as grade A, B or C, as defined by the International Study Group of Pancreatic Fistula<sup>[8]</sup>. Association between surgical outcomes and results of routine serological and biochemical investigations was assessed. The study protocol complied with the principles of the Declaration of Helsinki, and was approved by the Institutional Ethics Committee at the First Hospital of Jilin University. All patients had provided informed consent prior to their enrolment.

### Details of clinical management

Forty-three patients received PD with a pancreatic drainage tube (size: 6, 7 or 8) anastomosed to the pancreatic parenchyma during the *pancreatico-jejuno-stomy*; the tube was then drawn out through the distal bowel. In the remaining 40 patients, the standard Child's procedure was performed with placement of external pancreatic drainage tube (size: 6, 7 or 8), which was fixed to the pancreatic parenchyma



**Figure 1 Receiver operating characteristic curve analysis of amylase activity in drainage fluid.** A cut-off value of 2365.5 U/L was associated with 78.6% sensitivity, 80% specificity, 66.7% PPV and 88% NPV for POPF (AUC: 0.844,  $P = 0.009$ ). ROC: Receiver operating characteristic; POPF: Postoperative pancreatic fistula; NPV: Negative predictive value; PPV: Positive predictive value; AUC: Area under the curve.

**Table 1 Definitions of postoperative complications after pancreaticoduodenectomy**

Complication	Definition
POPF	Drainage fluid amylase activity on or after postoperative day 3 is at least three times the upper limit in normal serum
Ascites	Ultrasound evidence of ascites depth > 5 cm
Hemorrhage	Requires postoperative transfusion of $\geq 2$ U isogenic red blood cells
Biliary fistula	Abdominal drainage produces bilious fluid at 50 mL/d after surgery
DGE	Indwelling stomach tube for > 10 d

POPF: Postoperative pancreatic fistula; DGE: Delayed gastric emptying.

and left in the bowel. All patients were treated with cefoperazone and sulbactam (3.0 g/Q12 h) for the first 4 postoperative days (PODs) to prevent infection. Postoperatively, prophylactic intravenous octreotide was administered at a dose of 0.6 mg/24 h for 3 d to reduce the amount of pancreatic secretion.

**Statistical analysis**

Statistical analyses were conducted using SPSS software (version 19.0; SPSS Inc., IBM, Armonk, NY, United States). Univariate and multivariate analyses were performed to identify factors significantly related to POPF. Receiver operating characteristic (ROC) curve analysis was performed to assess the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the identified variables. A  $P$  value of less than 0.05 was considered indicative of statistical significance.

**RESULTS**

**Incidence of POPF**

Out of 83 patients, 28 (33.7%) eventually developed

**Table 2 Summary of postoperative complications**

Complication	Cases, $n = 30$	Incidence, %
POPF	28	33.7
Type A	8	28
Type B	16	58
Type C	4	14
Ascites	4	10
Hemorrhage	7	17.5
Biliary leakage	1	2.5
DGE	1	2.5
Postoperative acute pancreatitis	1	2.5

POPF: Postoperative pancreatic fistula; DGE: Delayed gastric emptying.

POPF. The severity of POPF was classified as grade A in 8 (28%) patients, grade B in 16 (58%) and grade C in 4 (14%) (Table 2).

**High amylase level predicts POPF development**

We first categorized the patients as POPF and non-POPF groups, and then compared the levels of different parameters between the two groups (Table 3). On univariate analysis, amylase level in the abdominal drainage fluid on POD1 and serum amylase level on PODs 1 and 4 were correlated with POPF development ( $P < 0.05$ ) (Table 4).

Multivariate logistic regression analysis confirmed that amylase level in abdominal drainage fluid on POD1 and serum amylase level on POD4 were independent predictors of POPF (Table 5). On ROC curve analysis, a cut-off amylase level of 2365.5 U/L in the abdominal drainage fluid on POD1 as predictor of POPF was associated with 78.6% sensitivity, 80% specificity, 66.7% PPV and 88% NPV [area under the curve (AUC): 0.844;  $P = 0.009$ ] (Figure 1). Similarly, a cut-off serum amylase level of 44.2 U/L on POD4 was associated with a 78.6% sensitivity and 70.9% specificity (AUC: 0.784;  $P = 0.05$ ; Figure 2). The specificity of these associations was further highlighted by the observation that neither white blood cell (WBC) counts nor choline and albumin levels correlated with POPF development.

**DISCUSSION**

The Whipple procedure for PD for the treatment of benign and malignant tumors in the head of pancreas and the peri-ampullar region is one of the most technically challenging surgical procedures, with long duration of surgery and a high rate of associated complications<sup>[9,10]</sup>. The reported rates of postoperative complications following PD range from 30%-70%, and postoperative mortality rates have remained approximately 5% even in high-volume centers<sup>[11]</sup>. POPF accounts for 2%-25% of all complications of PD<sup>[12]</sup>. The advent of novel surgical modalities for pancreaticojejunostomy, such as the duct-mucosa pancreaticojejunostomy or pancreatic duct stent

**Table 3** General risk factors for pancreatic leakage

Variable	POPF (n = 14)	Non-POPF (n = 26)	t/z/χ <sup>2</sup>	P value
Age in yr	54.18 ± 6.945	54.04 ± 10.447	0.065	0.948
Sex				
Male	20 (71.4)	32 (58.2)	1.391	0.337 <sup>1</sup>
Female	8 (28.6)	23 (41.8)		
Blood loss in mL	300 (200, 575)	200 (200, 600)	-1.266	0.205
Pancreatic duct diameter in mm				
> 3	11 (39.3)	33 (60.0)	3.196	0.104 <sup>1</sup>
< 3	17 (60.7)	22 (40.0)		
Preoperative low plasma protein				
Yes	7 (25.0)	12 (21.8)	0.106	0.786 <sup>1</sup>
No	21 (75.0)	43 (78.2)		
Preoperative relief of jaundice				
Yes	4 (14.3)	4 (7.3)	1.048	0.433 <sup>1</sup>
No	24 (85.7)	51 (92.7)		
Preoperative jaundice				
Yes	18 (64.3)	34 (61.8)	0.048	1.000
No	10 (35.7)	21 (38.2)		
Surgical type				
External drainage of PD	12 (42.9)	27 (49.1)	0.289	0.647 <sup>1</sup>
Internal drainage of PD	16 (57.1)	28 (50.9)		
Diabetes				
Yes	2 (7.1)	0 (0.0)	4.026	0.111 <sup>1</sup>
No	26 (92.9)	55 (100.0)		
Duration of surgery in min	267.5 (240.0, 327.5)	280.0 (235.0, 335.0)	-0.082	0.935
Hospitalization period in days	15.00 (13.00, 18.00)	21.50 (18.00, 27.75)	-4.385	< 0.001
Drainage fluid amylase level on POD1 in U/L	6017.5 (2494.5, 11752.5)	890.0 (350.0, 1500.0)	-5.110	< 0.001
Serum amylase level in U/L				
POD1	379.5 (157.5, 627.5)	124.0 (80.0, 165.0)	-4.091	< 0.001
POD4	30.0 (30.0, 50.0)	61.5 (45.5, 150.0)	-4.435	< 0.001
Serum albumin				
POD1	29.5 (25.3, 34.3)	30.7 (26.6, 33.0)	-0.125	0.900
POD3	30.1 (25.7, 34.6)	30.4 (27.1, 33.2)	-0.111	0.912
POD5	30.8 (27.8, 34.4)	31.4 (28.4, 36.9)	-0.718	0.473
Choline				
POD1	4957 (4022, 4957)	5242 (4048, 6715)	-0.876	0.381
POD3	3481 (2626, 4518)	4056 (3345, 5020)	-1.425	0.154
POD5	3268 (2696, 4537)	4024 (3248, 5069)	-1.580	0.114
WBC count				
POD1	14.73 (10.84, 18.75)	15.49 (12.42, 18.41)	-0.751	0.452
POD3	14.90 (11.74, 18.64)	13.54 (10.34, 16.58)	-1.112	0.266
POD5	11.99 (9.65, 15.56)	11.24 (9.17, 14.79)	-0.510	0.610
Pathology examination result			2.445	0.485
Cholangiocarcinoma	12 (42.9)	29 (52.7)		
Pancreatic carcinoma	3 (10.7)	8 (14.5)		
Ampullary carcinoma	3 (10.7)	7 (12.7)		
Other	10 (35.7)	11 (20.0)		

Data are presented as n (%). <sup>1</sup>Fisher's exact test. POPF: Postoperative pancreatic fistula; PD: Pancreaticoduodenectomy; WBC: White blood cell; POD: Postoperative day.

implantation, has not resulted in major improvement. Therefore, early detection of POPF development and adequate timely intervention is important to improve surgical outcomes in these patients<sup>[13-17]</sup>. There is a paucity of tools to identify patients who are at risk of development of POPF. Here, we report our prospective study to identify potential predictors of POPF. The results suggest that monitoring of amylase levels in drainage fluid and serum as biomarkers is quite promising.

Various factors have been linked to POPF in previous studies. These include pancreatic consistency, pancreatic duct diameter, and the results of assessment

by the pathologist<sup>[18-22]</sup>; however, their predictive value has been shown to be relatively poor and not intuitive. In the present study, we observed an obvious correlation between amylase levels in the ascitic fluid on POD1 and the serum amylase level on POD4 with the occurrence of POPF. Cloyd *et al*<sup>[20]</sup> reported that serum amylase level on POD1 (> 140 U/L) predicts POPF with 81.5% sensitivity, 55.5% specificity, 29.3% PPV, and 93% NPV<sup>[23]</sup>. Likewise, some researchers demonstrated that drainage fluid amylase level on POD1 (> 350 U/L) can predict POPF with a 79% specificity, 100% sensitivity, 41% PPV, and 100% NPV. Furthermore, Popiela *et al*<sup>[24]</sup> showed that the drainage

**Table 4 Results of univariate analysis showing risk factors for postoperative pancreatic fistula**

Factor	$\beta$	SE	Wald $\chi^2$	OR (95%CI)	P value
Age in yr	0.023	0.037	0.397	1.024 (0.952-1.101)	0.529
Sex, female/male	-0.586	0.500	1.375	0.557 (0.209-1.482)	0.241
Blood loss in mL	0.000	0.001	0.257	1.000 (0.999-1.001)	0.612
Pancreatic duct diameter, > 3 mm/< 3 mm	-0.841	0.475	3.135	0.431 (0.170-1.094)	0.077
Preoperative low plasma protein, yes/no	0.178	0.545	0.106	1.194 (0.410-3.476)	0.744
Preoperative relief of jaundice, yes/no	0.754	0.749	1.012	2.125 (0.489-9.227)	0.314
Preoperative jaundice, yes/no	0.106	0.482	0.048	1.112 (0.432-2.861)	0.826
Internal or External drainage of PD	0.251	0.468	0.289	1.286 (0.514-3.214)	0.591
Diabetes, yes/no	21.952	28420.722	0.000	3.417E9 (0.000)	0.999
Pathology examination result, ampullary carcinoma/ pancreatic carcinoma/cholangiocarcinoma	0.241	0.182	1.757	1.273 (0.891-1.819)	0.185
Duration of surgery in min	0.000	0.003	0.008	1.000 (0.995-1.005)	0.928
Drainage fluid amylase level, POD1 > 5000 U/L	0.000	0.000	10.293	1.000 (1.000--1.000)	0.001
Serum amylase level					
POD1 > 140 U/L	0.004	0.001	9.982	1.004 (1.001-1.006)	0.002
POD4 > 140 U/L	0.013	0.005	7.752	1.013 (1.004-1.022)	0.005
Serum albumin					
POD1	0.000	0.045	0.000	1.000 (0.916, 1.092)	0.994
POD3	-0.006	0.044	0.020	0.994 (0.911, 1.084)	0.887
POD5	-0.023	0.044	0.277	0.977 (0.897, 1.064)	0.599
Choline					
POD1	-0.016	0.041	0.149	0.984 (0.908, 1.067)	0.700
POD3	0.033	0.046	0.521	1.034 (0.945, 1.131)	0.470
POD5	0.007	0.053	0.016	1.007 (0.908, 1.117)	0.898
WBC count					
POD1	0.000	0.000	1.153	1.000 (1.000, 1.000)	0.283
POD3	0.000	0.000	1.298	1.000 (0.999, 1.000)	0.255
POD5	0.000	0.000	2.026	1.000 (0.999, 1.000)	0.155

POPF: Postoperative pancreatic fistula; PD: Pancreaticoduodenectomy; WBC: White blood cell; POD: Postoperative day.

**Table 5 Results of multivariate logistic regression analysis showing risk factors for postoperative pancreatic fistula**

Predictor	$\beta$	SE	Wald $\chi^2$	OR (95%CI)	P value
Amylase level, POD1 > 5000 U/L	0.000	0.000	6.728	1.000 (1.000--1.000)	0.009
Serum amylase, level POD1 > 140 U/L	0.001	0.002	0.243	1.001 (0.998-1.004)	0.622
Serum amylase level, POD4 > 140 U/L	0.009	0.004	3.826	1.009 (1.000-1.017)	0.050

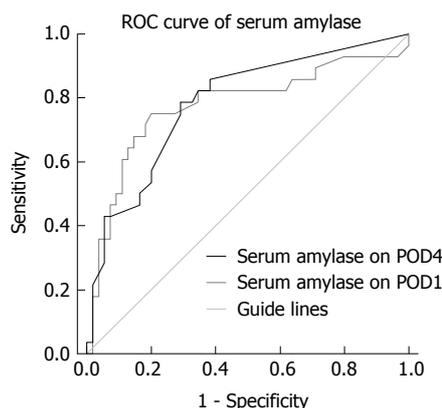
POPF: Postoperative pancreatic fistula; POD: Postoperative day.

fluid amylase level (> 5000 U/L) on POD1 is a reliable predictor of POPF. Kawai *et al*<sup>[25]</sup> also found that the ratio of total amylase in drainage fluid could predict POPF. Our results are consistent with these previous publications, which indicate that amylase level in ascitic fluid on POD1 and blood amylase on POD4 could be used to identify patients who are most likely to suffer from this complication after PD.

Of note, we did not observe a significant association of albumin and WBC counts with POPF. Kawai *et al*<sup>[25]</sup> reported that serum albumin levels (< 3.0 g/d) and serum WBC count (> 9800 mm<sup>3</sup>) on POD4 predicted grades B and C POPF with a 69% sensitivity, a 96% specificity, an 88% PPV, and an 85% NPV. Relles *et al*<sup>[26]</sup> found that serum albumin (< 2.5 mg/L) and blood urea nitrogen (> 10 mg/dL) on POD1 were important predictors of perioperative morbidity following PD<sup>[27]</sup>. However, in our study, the level of serum albumin through POD1, POD3 and POD5 did not correlate

with the development of POPF. Considering that acute stress can affect serum albumin level and WBC counts<sup>[28]</sup>, these may not be appropriate measures to gauge the risk of POPF. A prospective trial showed that postoperative albumin levels were not associated with risk during abdominal operation<sup>[29]</sup>. Welsch *et al*<sup>[29]</sup> also reported poor specificity of serum WBC as a predictor of POPF. Our results are consistent with these reports. In addition, no significant association of POPF with cholinesterase level was observed on POD1, POD3 and POD5, which suggests that POPF may not have an obvious relationship with the postoperative change in hepatic reserve.

In our study, a cut-off amylase level of 2365.5 U/L in ascitic fluid on POD1 predicted POPF with 78.6% sensitivity, 80% specificity, 66.7% PPV, and 88% NPV. We hypothesize that in patients with POPF, the higher level of amylase in drainage fluid on POD1 derives from the failed pancreaticojejunal anastomosis, which



**Figure 2 ROC curve analysis of serum amylase activity.** A cut-off value of 44.2 U/L on POD4 was associated with a 78.6% sensitivity and 70.9% specificity for POPF (AUC: 0.784,  $P = 0.05$ ). ROC: Receiver operating characteristic; POPF: Postoperative pancreatic fistula; AUC: Area under the curve.

leads to POPF.

Serum amylase has been used for diagnosis of acute pancreatitis for > 70 years; however, increased serum amylase levels are also observed in other diseases of salivary glands, oviduct epithelium and proximal duodenum, which limits its specificity for the diagnosis of pancreatitis. Intuitively, this should be less of a concern with respect to drainage fluid or generally following PD<sup>[30]</sup>. Indeed, in our study, serum amylase on POD4 showed a significant correlation with POPF, although serum amylase on POD1 did not effectively predict POPF. We found that serum amylase on POD4 of 44.2 U/L was an effective maker; however, this value is within the normal range of serum amylase, and thus serum amylase level on POD4 higher than 100 U/L is probably more appropriate. Serum amylase on POD4 with a discriminatory threshold of 100 U/L can predict POPF with 42.9% sensitivity, 55% specificity, 75% PPV, and 76.1% NPV. In the early postoperative stage, ischemic injury to pancreatic tissues caused by surgical damage to blood vessels, intraoperative and postoperative hypovolemia, and surgical stress leads to elevation of serum amylase<sup>[31]</sup>. However, no statistically significant correlation was observed between serum amylase level on POD1 and pancreatic leakage, and no correlation was found between serum amylase and POPF in theory, whereas absorption of exudates from pancreatic anastomosis cannot explain such a phenomenon. On the other hand, we believe that elevation in serum amylase level on POD4 reflects the preliminary establishment of a collateral pancreatic anastomosis, and that correction of hypovolemia may reflect the condition of pancreatic juice derived from accessory pancreatic duct or residual pancreatic section instead of the obstructed main pancreatic duct. Moreover, the erosion effect of amylopsin and trypsin on blood vessel can also increase the absorption speed and the amount of amylopsin into the blood, which reflects the increased

serum amylase. Thus, blood amylase level on POD4 is of certain predictive value for the occurrence of POPF.

In our study, we found that amylase activity in drainage fluid on POD1 and serum amylase activity on POD4 could accurately predict POPF, whereas serum albumin and prealbumin did not show a significant predictive value. Measurement of amylase level in drainage fluid on POD1 and the serum amylase level on POD4 is a relatively easy and economical method. Our results support the use of amylase to predict POPF.

This may allow for timely interventions, such as increased duration of antibiotic and octreotide therapies, that may help prevent POPF and allow for timely risk-communication to the patient. It is also another procedure in the processing carried out in our medical center.

## COMMENTS

### Background

Identification of patients who are at high risk of postoperative pancreatic fistula (POPF) in the immediate postoperative period after is a key imperative to improve surgical outcomes of pancreaticoduodenectomy (PD). Biochemical markers in serum and drainage fluid may reflect disease progression, and it is of translational significance to investigate their correlation with clinical characteristics and their potential use to predict the risk of POPF. In this study, we sought to identify potential predictors of POPF development, which may help optimize the treatment of such patients in clinical practice.

### Research frontiers

Although anastomosis techniques used for PD significantly improves, the incidence of PD-associated POPF remains relatively high. POPF is a major threat to patients who undergo PD. Thus, early and accurate prediction of POPF is essential to achieve optimal surgical outcomes.

### Innovations and breakthroughs

Previous studies have found several biochemical factors, such as serum amylase level on postoperative day (POD)1, drainage fluid amylase level on POD1, and a combination of serum albumin and leukocyte count as predictors of POPF. However, some of these markers have low positive predictive value. We demonstrate that amylase level in drainage fluid on POD1 and serum amylase level on POD4 are better predictors of POPF than those proposed earlier.

### Applications

Measurement of amylase level in serum and drainage fluid is relatively straightforward and inexpensive. These two investigations can help identify patients who are at an increased risk of POPF. This may allow for timely interventions, such as increased duration of antibiotic and octreotide therapies, that may help prevent POPF. It is also another procedure in the processing carried out in our medical center.

### Terminology

Although several biochemical factors have been shown to predict POPF in previous studies, we found that just amylase levels in drainage fluid on POD1 and serum amylase level on POD4 could accurately predict POPF, whereas serum albumin and prealbumin were found to have negligible predictive value.

### Peer-review

In this manuscript, the authors correlate the postoperative clinical factors with POPF rate, including prospectively 83 patients with PD, and analyzed the potential correlation between biomarkers and postoperative complications such as a pancreatic fistula.

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