Significance of Preoperative Pancreatic MRI Findings in Predicting Factors for Postoperative Pancreatic Fistula after Distal Pancreatectomy for Pancreatic Cancer: A Retrospective Study

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Research

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Abstract

Background: Postoperative pancreatic fistula (POPF) is the most serious complication of distal pancreatectomy (DP). For patients with pancreatic cancer (PC), POPF can have a negative effect on both short- and long-term prognoses. This study aimed to identify clinical outcomes of POPF after DP for PC and predictive factors for POPF.

Methods: This retrospective, single-institution study comprised 48 patients with PC who underwent open DP (excluding simultaneous resection of other organs and other pancreatic diseases) between January 2010 and December 2020 at the Gifu University Hospital. We statistically analyzed patient-, pancreas-, cancer-, and surgery-related factors for predicting outcomes and risk factors for POPF.

Results: According to the International Study Group of Pancreatic Fistula (ISGPF) definition and grading, 11 (22.9%) of 48 patients had POPF grades B and C. Among 22 related factors, POPF was significantly associated with pancreatic width ($p = 0.04$) and the pancreas-to-muscle signal intensity ratio (SIR) on T1-weighted magnetic resonance imaging (MRI, $p = 0.02$) in univariate analysis. In multivariate analysis, both pancreatic width (≥23 mm, odds ratio [OR] 9.37; 95% confidence interval [CI] 1.22–202.40; $p = 0.03$) and SIR on T1-weighted MRI (≥1.37, OR 17.10; 95% CI 2.38–359.04; $p = 0.003$) were identified as independent predictive factors for POPF.

Conclusion: Pancreatic width and pancreas-to-muscle SIR on T1-weighted MRI significantly correlated with POPF after DP for PC. These parameters may be potential imaging biomarkers for predicting POPF in pancreatic surgery.

Background

Distal pancreatectomy (DP) is an established procedure for pancreatic cancer (PC) located in the body and/or tail of the pancreas. Although surgical techniques and perioperative management for DP have significantly improved over recent decades, the complication rate following DP remains high [1–6]. In particular, the incidence of postoperative pancreatic fistula (POPF) is high (10–60%), with mortality rates of < 2%. Secondary complications of POPF have been reported to be postoperative bleeding, intra-abdominal abscess, delayed gastric emptying, and sepsis [7–9]. Consequently, when POPF-related complications occur, further surgery and treatment for POPF are frequently required. Moreover, postoperative hospital stays have been reported to be longer and perioperative mortality has been reported to increase. Additionally, the introduction of postoperative adjuvant chemotherapy may be delayed, which may then lead to an increased recurrence rate and a poor prognosis. Therefore, accurate detection of perioperative factors that can predict POPF after DP is needed urgently.

Previous studies have reported various risk factors for POPF after DP [10–27]; however, a clear consensus has not yet been established, with some reported risk factors for POPF being subjective and poorly reproducible. Previously, we studied the potential value of magnetic resonance imaging (MRI) in evaluating pancreatic properties [28, 29] and reported that the pancreas-to-muscle signal intensity ratio

(SIR) on T1-weighted MRI significantly correlated with pancreatic fibrosis, and that it may be a potential biomarker for predicting POPF.

The objectives on this study were to identify the clinical outcomes of POPF after DP for PC and to identify predictive factors through evaluating related factors. We aimed to improve patient outcomes through identifying predictive factors to prevent the development of severe POPF-related complications.

Methods

Study population

In this single-center retrospective study, we enrolled 88 consecutive patients who underwent elective open DP at Gifu University Hospital between January 2010 and December 2020. All procedures were conducted by expert surgeons who had qualified through the board certification system of the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS).

We conducted our study in accordance with the World Medical Association Declaration of Helsinki and the study was approved by the Ethics Committee of Gifu University (approval number: 2021-026). We excluded 40 patients in total (tumor histopathology other than adenocarcinoma, n = 38; simultaneous resection of other organs, n = 2), and a total of 48 patients with primary PCs were included in this study (Fig. 1).

Definition of POPF

In this study, we only included clinically symptomatic POPF. Therefore, only grades B and C pancreatic fistulas were defined as POPF (Grade B, symptomatic fistula requiring therapeutic intervention such as antibiotics and percutaneous drainage; Grade C, symptomatic fistula associated with a severe general condition of patients, sepsis, and multiorgan failure requiring aggressive treatment in the intensive care unit and surgical intervention), based on International Study Group of Pancreatic Fistula (ISGPF) definitions [30].

Patient-, pancreas-, cancer-, and surgery-related factors for POPF

Patient-, pancreas-, cancer-, and surgery-related factors were included in the analysis (Fig. 2).

The patient-related factors were age, sex, body mass index (BMI), diabetes mellitus, modified Glasgow prognostic score (mGPS) (score, 0 or 1/2), prognostic nutritional index (PNI), preoperative tumor marker level (carcinoembryonic antigen [CEA], normal upper limit at 5 ng/ml; and carbohydrate antigen 19 – 9 [CA19-9], normal upper limit at 37 ng/ml), and preoperative chemotherapy.

The pancreas-related factors were pancreatic thickness and width, which we measured above the superior mesenteric vein (SMV) using preoperative computed tomography (CT) scans; intraoperative

findings of pancreatic texture (soft or hard); and pancreas-to-muscle SIR on preoperative T1-weighted MRI. The signal intensity of the pancreatic parenchyma above the SMV and the paraspinal muscle was measured using fat-suppressed axial T1-weighted fast field echo imaging (Fig. 3). The pancreas-to-muscle SIR was calculated using the following equation: [SI of the pancreatic parenchyma] / [SI of the paraspinal muscle].

The cancer-related factors were tumor location, maximum tumor diameter, and the pathological Union for International Cancer Control (8th edition) TNM classification [31].

Surgery-related factors included operation time, blood loss, blood transfusion, and techniques for pancreatic transections (hand-sewn or stapler).

The clinical outcomes of POPF after DP for PC

The clinical outcomes of POPF after DP for PC were the amylase level ratio of drainage fluid and serum (D-AMY/S-AMY), the white blood cell (WBC) count and C-reactive protein (CRP) levels on postoperative day 1 (POD1) and day 3 (POD3), POPF diagnosis day, POPF grade, postoperative death within 30 days, hospital stay, and the overall survival (OS) days after DP.

Statistical analysis

Continuous variables are expressed as median values, and categorical and ordinal variables are expressed as frequencies (percentages). OS was calculated in months from the date of DP to the date of the last follow-up, and a log-rank test was used to evaluate differences between the groups in the univariate analysis.

For comparisons of variables between the POPF and non-POPF groups, a Fisher's exact test was used for categorical variables, and a Mann-Whitney U test was used for continuous and ordinal variables. To test the independence of predictive factors for POPF, significant variables in the univariate analyses were included in the final logistic regression model.

Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) value to assess the validity of discriminating recurrence in enrolled patients. Youden's index was used to determine the optimal cut-off point to calculate both specificities and sensitivities in the ROC curve analysis.

The limit of statistical significance for all analyses was defined as a 2-sided p-value of 0.05. All statistical analyses were performed using JMP software (SAS Institute Inc., Cary, NC, USA).

Results

Patient clinical outcomes after DP for PC

In total, 48 patients had undergone DP for PC; the median age was 72.5 years (range, 42–84 years), 28 (41.7%) patients were male, and 20 (58.3%) patients were female. Symptomatic POPF occurred in 11 (22.9%) patients.

Patient clinical outcomes after DP for PC are summarized in Table 1. The median time at which POPF was confirmed was POD 9 (range, 7–25 days), the median time until hospital discharge was 43 days postoperatively (range, 12–81 days), and 2 patients had died within 30 postoperative days.

Table 1
Comparison of clinical outcomes between patient with and without POPF after distal pancreatectomy

	Overall patients (n = 48)	**Patients with POPF (n = 11)**	**Patients without POPF (n = 37)**	**p-value**
	Value (%)	**Value (%)**	**Value (%)**	
D-AMY/S-AMY				
POD1	8.05 (0.25-315.11)	28.74 (0.54-315.11)	6.39 (0.25–55.84)	0.059
POD3	4.63 (0.93-402.81)	32.27 (0.98-402.81)	3.97 (0.93-117.11)	< 0.01¶
WBC (×10^3/μl)				
POD1	12.07 (5.34–26.49)	13.68 (10.35–26.49)	11.63 (5.34–17.80)	0.07
POD3	12.43 (6.4–23.9)	14.10 (7.5-21.71)	11.63 (6.4–23.9)	0.14
CRP (mg/dl)				
POD1	9.31 (0.18–15.14)	9.98 (4.02–14.3)	8.91 (0.18–15.14)	0.24
POD3	14.50 (2.13–26.52)	20.1 (10.7-25.92)	14.00 (2.13–26.52)	0.11
Diagnosis days of POPF (day)	-	9 (7–25)	-	-

Data are expressed as median (range) or number of patients

D-AMY/S-AMY: Drain amylase / Serum amylase

POD: postoperative day

WBC: white blood cell count

CRP: c-reactive protein

POPF: postoperative pancreatic fistula

¶: International Study Group (ISGPS) definition and grading of POPF

§:Overall survival was calculated in months from the date of the surgery to the date of the last follow-up. In the univariate analysis, the log-rank test was used to evaluate differences between groups.

	Overall patients (n = 48)		Patients with POPF (n = 11)		Patients without POPF (n = 37)		p-value
	Value	(%)	Value	(%)	Value	(%)	
Grade of POPF¶							
Grade B	-		9	(81.8)	-		-
Grade C	-		2	(18.2)	-		
Postoperative death within 30 days	2	(4.2)	2	(18.2)	0	(0.0)	0.048
Hospital days (days)	14 (10–81)		43 (12–81)		13 (10–20)		< 0.01
Overall survival days§ (days)	854 (12-3961)		328 (12-2375)		881 (45-3961)		0.01
Data are expressed as median (range) or number of patients							
D-AMY/S-AMY: Drain amylase / Serum amylase							
POD: postoperative day							
WBC: white blood cell count							
CRP: c-reactive protein							
POPF: postoperative pancreatic fistula							
¶: International Study Group (ISGPS) definition and grading of POPF							
§:Overall survival was calculated in months from the date of the surgery to the date of the last follow-up. In the univariate analysis, the log-rank test was used to evaluate differences between groups.							

A comparison between patients with and without POPF indicated that there were significant differences in D-AMY/S-AMY at POD3 ($p < 0.01$), postoperative death within 30 days ($p = 0.048$), hospital days ($p < 0.01$), and OS days after surgery ($p = 0.01$).

Predictive factors of POPF after DP for PC

Table 2 shows a summary of 22 patient -, pancreas-, cancer-, and surgery-related factors. No significant between-group differences were found in terms of patient-, cancer-, and surgery-related factors. Among pancreas-related factors, POPF was significantly associated with pancreatic width ($p = 0.04$) and pancreas-to-muscle SIR on T1-weighted MRI ($p = 0.02$). ROC curve analyses showed that both pancreatic width and pancreas-to-muscle SIR on T1-weighted MRI could predict POPF in enrolled patients with an AUC of 0.7113 and 0.7611, respectively (Fig. 4a, 4b). At a pancreatic width cut-off value of 23 mm, sensitivity and specificity were found to be 81.8% and 64.9%, respectively. At a cut-off value of + 1.37 for

pancreas-to-muscle SIR on T1-weighted MRI, sensitivity and specificity were found to be 88.9% and 63.3%, respectively. Combination ROC analyses showed an increased AUC value of 0.8370 (sensitivity, 77.8%; specificity, 86.7%; Fig. 4c).

Table 2
Univariate analysis for predictive factors of POPF after distal pancreatectomy for pancreatic cancer

		Overall patients (n = 48)		Patients with POPF (n = 11)		Patients without POPF (n = 37)		p-value
		Value	(%)	Value	(%)	Value	(%)	
Patient related-	Age (years)	72.5 (42–84)		70 (63–82)		73 (42–84)		0.67
	Sex	28	(41.7)	6	(54.5)	22	(59.5)	0.77
	Male	20	(58.3)	5	(45.5)	15	(40.1)	
	Female							
	BMI (kg/m^2)	22.4 (16.2–31.9)		23.0 (20.1–26.3)		21.8 (16.2–31.9)		0.38
	Diabetes mellitus	18	(37.5)	3	(27.2)	15	(40.1)	0.50
	mGPS							0.81
	0	37	(77.0)	9	(81.8)	28	(75.7)	
	1or2	11	(23.0)	2	(18.2)	9	(24.3)	
	PNI	42.2 (36.3–57.5)		49.0 (41.1–53.6)		49.4 (36.4–57.5)		0.23
	Preoperative	8	(16.7)	3	(27.3)	5	(13.5)	0.30
	CEA elevation							
	Preoperative	32	(66.7)	8	(72.7)	24	(64.9)	0.75
	CA19-9 elevation							
	Preoperative chemotherapy	15	(31.3)	3	(27.3)	12	(32.4)	0.75
Pancreas related-	Thickness (mm)	11 (3–24)		11 (9–14)		11 (3–24)		0.90
	Width (mm)	22 (13–35)		24 (18–35)		21 (13–35)		0.04*
	Intraoperative							
	pancreas texture	31	(64.6)	7	(63.6)	24	(64.9)	1.00
	Soft	17	(35.4)	4	(36.4)	13	(35.1)	
	Hard							
	SIR on T1-weighted MRI	1.32 (0.82–1.86)		1.61 (1.25–1.86)		1.23 (0.82–1.75)		0.02*
Cancer	Location							

related-	Pb	31	(64.6)	5	(45.5)	26	(70.3)	0.16
	Pt	17	(35.4)	6	(54.5)	11	(29.7)	
	Tumor size (mm)	22 (4–70)		21 (14–40)		25 (4–70)		0.40
	T status¶							0.74
	T1	12	(25.0)	3	(27.3)	9	(24.3)	
	T2	27	(56.3)	7	(63.6)	20	(54.0)	
	T3	8	(16.7)	1	(9.0)	7	(18.9)	
	T4	1	(2.1)	0	(0.0)	1	(2.7)	
	N status¶	25	(52.1)	4	(36.4)	21	(56.8)	0.49
	N0	23	(47.9)	7	(63.6)	16	(43.2)	
	N1							
	Stage¶							0.64
		23	(47.9)	5	(45.5)	18	(48.6)	
		14	(29.2)	3	(27.3)	11	(29.7)	
		8	(16.7)	2	(18.2)	6	(16.2)	
		3	(6.3)	1	(9.1)	2	(5.4)	
Surgery related-	Time (min)	277 (143–564)		270 (195–473)		283 (143–564)		0.58
	Blood loss (ml)	330 (20-1840)		180 (50-1840)		410 (20-1840)		0.09
	Transfusion	8	(16.7)	1	(9.1)	7	(18.9)	0.66
	Resection procedure							
	Hand-sewn	23	(47.9)	4	(36.4)	19	(51.4)	0.50
	Stapler	25	(52.1)	7	(63.6)	18	(48.7)	

Data are expressed as median (range) or number of patients

POPF: postoperative pancreatic fistula

BMI: body mass index

mGPS: modified Glasgow Prognostic Score

PNI: Prognostic Nutritional Index

CEA: Carcinoembryonic antigen level, normal upper limit at 5ng/ml

CA19-9: Carbohydrate antigen 19 – 9 level, normal upper limit at 37ng/ml
SIR on T1-weighted MRI: The pancreas-to-muscle signal intensity ratio on unenhanced T1-weigthed magnetic resonance imaging
¶: UICC TNM classification(the 8th edition)
▯: $p < 0.05$

In multivariate analysis, both pancreatic width (≥ 23 mm, odds ratio [OR] 9.37; 95% confidence interval [CI] 1.22–202.40; p = 0.03) and pancreas-to-muscle SIR on T1-weighted MRI (≥ + 1.37, OR 17.10; 95% CI 2.38–359.04; p = 0.003) significantly correlated with POPF (Table 3).

Table 3
Multivariate analysis for predictive factors of POPF after distal pancreatectomy for pancreatic cancer

Predictive factors	p- value	Odds ratio	95% Confidence Interval
Pancreatic width (≧ 23mm)	0.03▯	9.37	1.22–202.40
SIR on T1-weighted MRI (≧ 1.37)	0.003▯	17.10	2.38-359.04
SIR on T1-weighted MRI: The pancreas-to-muscle signal intensity ratio on unenhanced T1-weigthed magnetic resonance imaging			
Youden's index was used to determine the optimal cut-off point to calculate the specificities and sensitivities in the ROC analysis.			
▯: $p < 0.05$			

Discussion

POPF is the most serious complication of pancreatic surgery and leads to other secondary complications, such as postoperative bleeding, intra-abdominal abscess, delayed gastric emptying, and sepsis [7–9]. In this study, patients with POPF showed a significant increase in both hospital days and postoperative mortality. Furthermore, short-term outcomes and postoperative OS were both significantly shorter. POPF may affect the long-term prognosis of patients with PC, as there was no significant between-group difference in terms of patient- and cancer- backgrounds. Moreover, the median time to POPF diagnosis in this study was 9 days (range, 7–25), making early diagnosis difficult with routine postoperative examination. Therefore, early intervention based on the prediction of POPF may contribute to an improvement in long- and short-term outcomes.

In previous studies, various factors such as age, sex, BMI, intraoperative blood loss, operating time, transfusion, technique for pancreatic resection, pancreatic texture, and pancreatic thickness have been reported to be risk factors for POPF after DP [10–27]. However, some risk factors, especially surgery-related factors, may include confounding biases. In addition, an intraoperative finding of pancreatic

texture, the so-called 'soft pancreas,' is considered a characteristic risk factor, but such a finding is subjective without clear criteria. In this study, the pancreas width and pancreas-to-muscle SIR on T1-weighted MRI significantly correlated with POPF. Both factors are quantitative and objective, based on preoperative images; therefore, they can be used as predictive biomarkers for POPF.

Previously, we investigated the correlation between preoperative pancreatic MRI features and the histopathological features of pancreatic surgical specimens [28]. We found that the pancreas-to-muscle SIR on fat-suppressed T1-weighted MRI was significantly associated with pancreatic fibrosis. This is because normal pancreatic parenchyma exhibits relative hyperintensity on T1-weighted MRI, as pancreatic juice is rich in glycoproteins, and the endoplasmic reticulum within the pancreatic cells contributes to the T1 shortening effect; however, the signal intensity gradually decreases with progression of pancreatic atrophy, fibrosis, interstitial edema, or fat deposition [32, 33]. Moreover, in another study [29], we reported that the frequency of POPF after pancreaticoduodenectomy was significantly higher in patients without PC than in those with PC and was inversely related to pancreatic fibrosis. Based on these findings, we proposed that the pancreas-to-muscle SIR on fat-suppressed T1-weighted MRI might be a potential imaging biomarker for predicting POPF reflecting pancreatic fibrosis. Interestingly, a similar result was obtained in this study, which focused on DP for PC. Furthermore, the cut-off value for the POPF prediction calculated using ROC analysis in this study (1.37) was close to those reported in our previous studies (1.11 and 1.41).

Previous research suggests that the pancreatic shape of the resection site may be related to the development of POPF, with several previous studies having reported that the shape of the pancreas, especially in terms of thickness, has a significant correlation with POPF [13, 17, 18, 34]. In this study, no significant difference was found in terms of pancreatic thickness; however, pancreatic width correlated significantly with POPF. Therefore, we hypothesized that an increase in the dissected area of the pancreas may cause: (i) an increase in pancreatic juice leakage from the cross section, and (ii) a decrease in the compression effect with the stapler. There are two possible reasons why pancreatic thickness did not show a significant difference in this study. First, the median pancreatic thickness in this study (11 mm) was slightly lower than that reported in previous studies (12–14 mm) [13, 17, 18, 34]. This may partly be because our study was limited to patients with PC. Second, 50% of the patients in this study had undergone pancreatic resection without using staplers. Kawai et al. reported an association between pancreatic thickness and resection procedure methods in patients with POPF after DP [34]. Their results showed that pancreatic thickness was significantly associated with the incidence of POPF in the stapler resection group only.

This study had some limitations. This retrospectively designed study was undertaken at a single institution, and involved a small number of study patients. The relatively small sample size may have caused a selection bias. This limitation should be considered when evaluating our study results. A prospective, multi-centered study is needed involving a larger number of patients in future.

Conclusions

Our results suggest that pancreatic width, measured on preoperative CT and pancreas-to-muscle SIR on T1-weighted MRI, significantly correlated with POPF after DP for PC. This finding is consistent with that of our previous studies. These simple parameters may be potential imaging biomarkers for predicting POPF in pancreatic surgery. POPF may cause a worsening in short-term outcomes and long-term patient prognoses; therefore, we consider that early intervention involving an early diagnosis is of major importance when treating PC.

List Of Abbreviations

AUC, area under the curve; BMI, body mass index; CA19-9, carbohydrate antigen 19 – 9; CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; D-AMY, amylase level of drain fluid; DP, distal pancreatectomy; ISGPF, International Group of Pancreatic Fistula; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; mGPS, modified Glasgow prognostic score; MRI, magnetic resonance imaging; OR, odds ratio; OS, overall survival; PC, pancreatic cancer; PNI, prognostic nutritional index; POD, postoperative day; POPF, postoperative pancreatic fistula; ROC, receiver operating characteristic; S-AMY, amylase level of serum; SIR, signal intensity ratio; SMV, superior mesenteric vein; WBC, white blood cells

Declarations

Ethics approval and consent to participate: The present study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Gifu University (approval number ‘2021-26’). As this study was a retrospective study and did not include any potentially identifiable patient data, informed consent was not obtained from the enrolled patients. This retrospective study was approved by our Institutional Review Board.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used during this study are available from the corresponding author upon reasonable request.

Competing interests: K. Yoshida has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Novartis Pharma K.K., and Sanofi K.K., and research funding from Ajinomoto Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ono Pharmaceutical Co., and Yakult Honsha Co., Ltd., outside the submitted work.

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Authors' contributions: MF conceived the study concept and planned the design as the principal investigator. MF interpreted the results and wrote the manuscript draft.

KM, TH, and KY revised the manuscript draft through adding intellectual content and providing critical advice. MF, KM, TH, RY, HT, YT, NO, NM, TT, and KY obtained the data and provided critical comments to improve the manuscript and gave final approval for submission.

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Figures

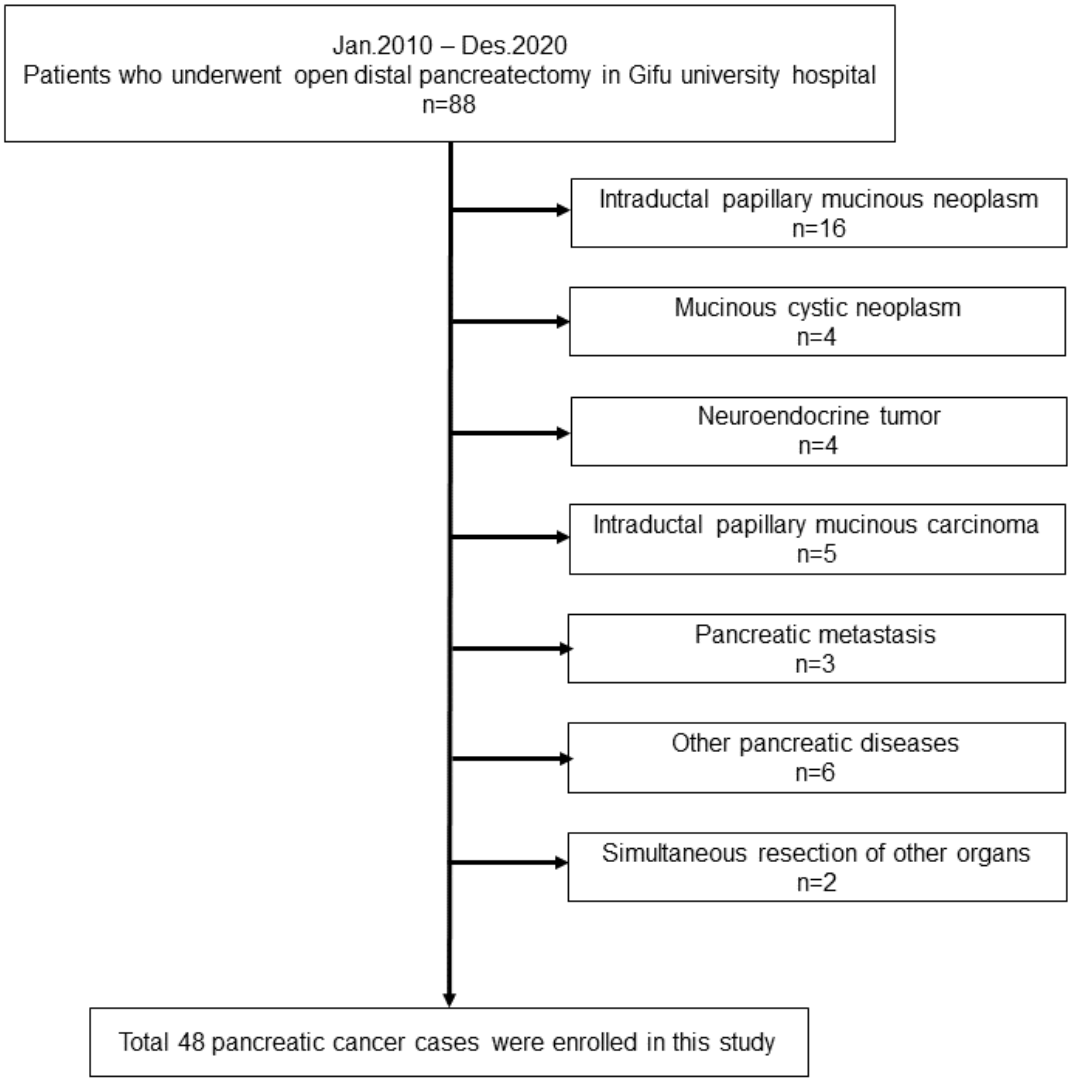

Figure 1

Exclusion criteria

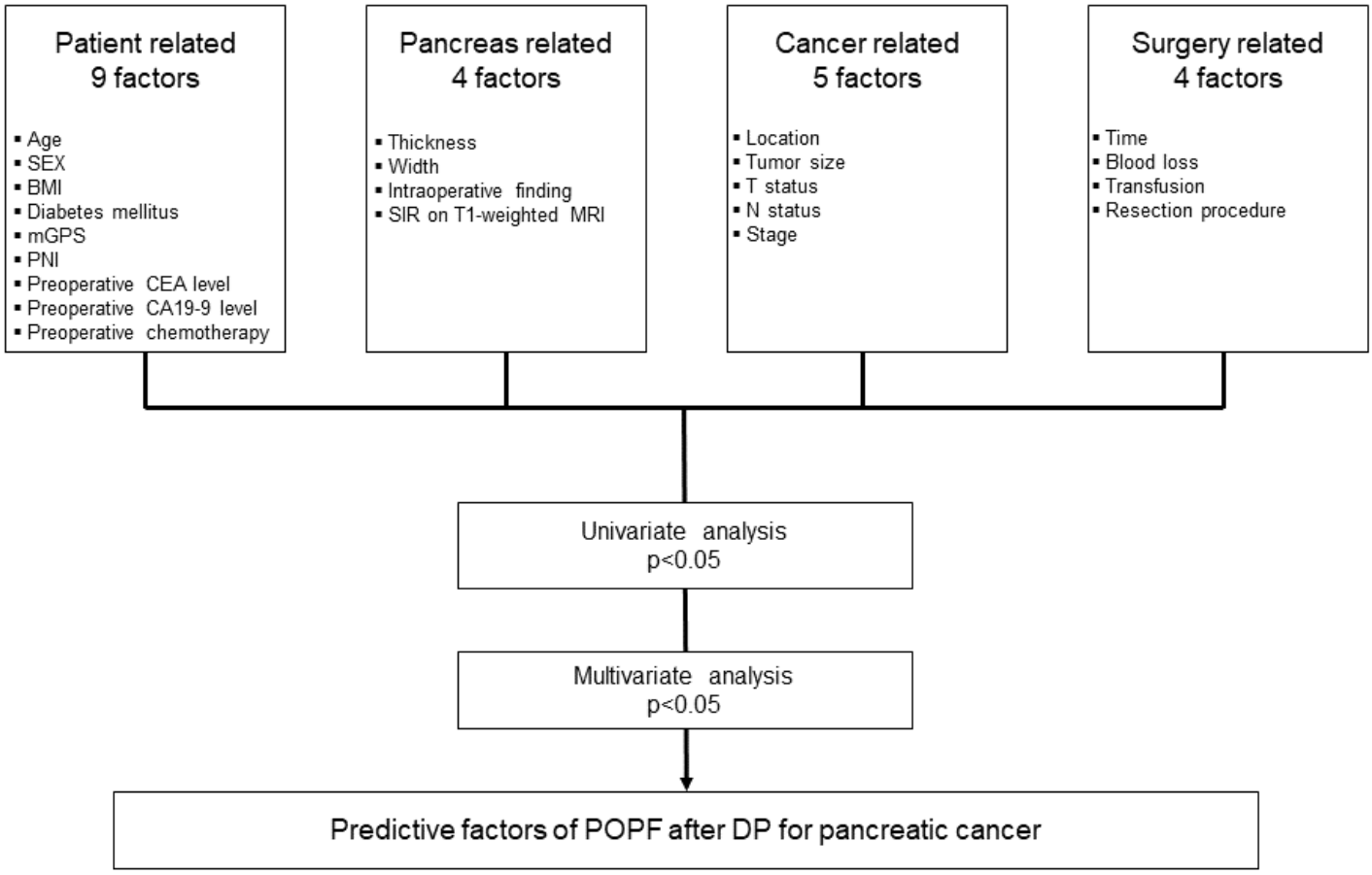

Figure 2

Analysis flow chart for identifying predictive factors for POPF after DP for pancreatic cancer

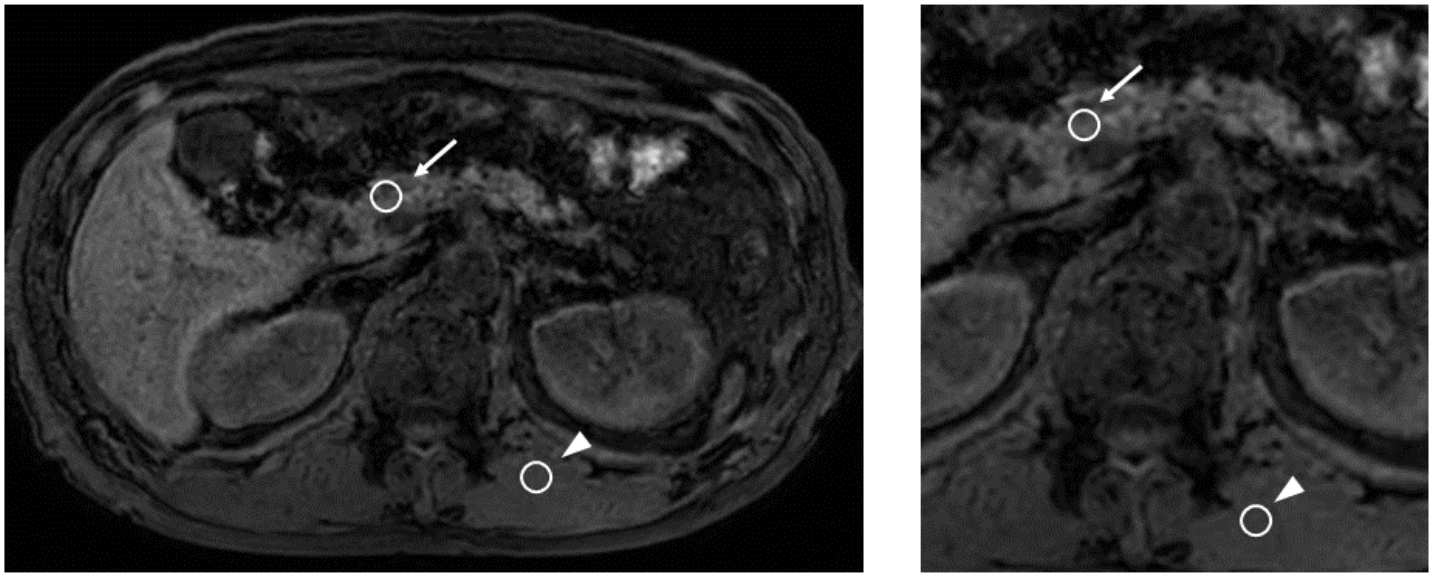

Fig.3

Figure 3

The pancreas-to-muscle SIR on fat-suppressed axial T1-weighted MRI was calculated by [SI of the pancreatic parenchyma] (arrow) / [SI of the paraspinal muscle] (arrowhead).

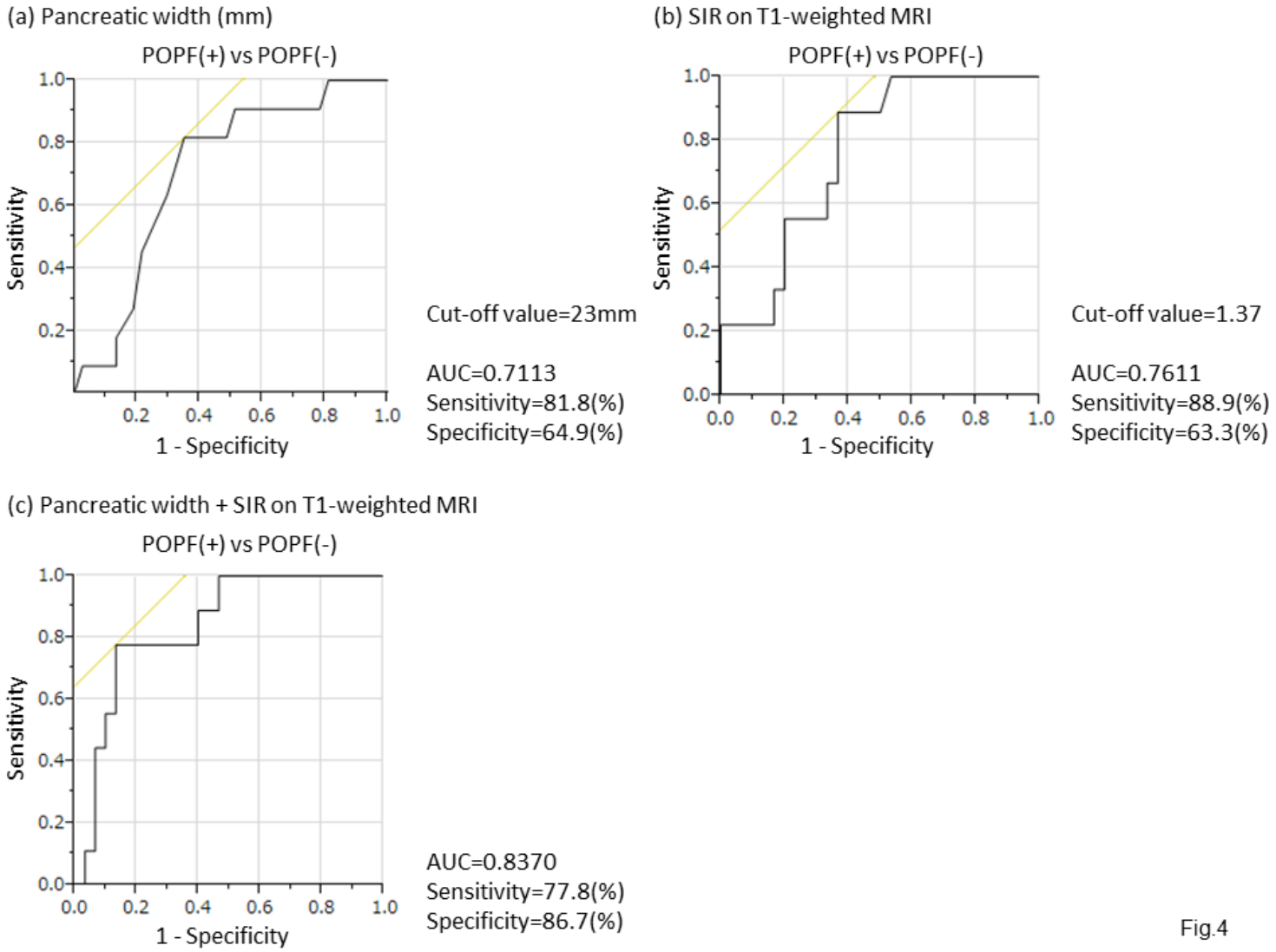

Figure 4

Receiver operating characteristics (ROC) curve analysis of pancreatic width measured on preoperative CT and SIR on T1-weighted MRI for discriminating to POPF. Pancreatic width yielded an area under curve (AUC) of 0.7113 with 81.8 % sensitivity and 64.9 % specificity (a), and SIR on T1-weighted MRI yielded an AUC of 0.7611 with 88.9 % sensitivity and 63.3 % specificity (b). Combined ROC analysis revealed that the combination of these parameters yielded an AUC of 0.8370 with 77.8 % sensitivity and 86.7 % specificity (c).