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RESEARCH

Clinical characteristics and predictive factors of postoperative intra-abdominal abscess after distal pancreatectomy

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Abstract

Purpose The postoperative mortality rate of distal pancreatectomy is lower than that of pancreaticoduodenectomy, although persistent complications may occur after distal pancreatectomy. Fluid collection (FC) is frequently observed after distal pancreatectomy; however, FC may occasionally progress to postoperative intra-abdominal abscess (PIAA), which requires conservative or progressive interventional treatment. This study aimed to compare the status between patients with or without PIAA, identify predictive factors for PIAA and clinically relevant postoperative pancreatic fistula, and investigate the clinical characteristics of patients with PIAA with interventional drainage.

Methods We retrospectively reviewed data of patients who underwent distal pancreatectomy between January 2012 and December 2019 at two high-volume centers, where hepatobiliary-pancreatic surgeries were performed by expert specialist surgeons. Logistic regression analysis was performed to determine the predictive factors for PIAA.

Results Overall, 242 patients were analyzed, among whom 49 (20.2%) had PIAA. The median postoperative period of PIAA formation was 9 (range: 3–49) days. Among the 49 patients with PIAA, 25 (51.0%) underwent percutaneous ultrasound, computed tomography, or endoscopic ultrasound-guided interventions for PIAA. In the univariate analysis, preoperative indices representing abdominal fat mass (i.e., body mass index, subcutaneous fat area, and visceral fat area) were identified as predictive factors for PIAA; in the multivariate analysis, C-reactive protein (CRP) level (continuous variable) on postoperative day (POD) 3 (odds ratio: 1.189, 95.0% confidence interval: 1.111 – 1.274; $P < 0.001$) was the only independent and significant predictive factor for PIAA.

Conclusions CRP level on POD 3 was an independent and significant predictive factor for PIAA after distal pancreatectomy.

Keywords Abdominal fat · Abscess · Drainage · Fistula · Pancreatectomy

Introduction

Pancreatic surgery is associated with a high rate of complications, occasionally resulting in postoperative mortality [1, 2]. The mortality rate of distal pancreatectomy (DP) is lower than that of pancreaticoduodenectomy [2, 3], although persistent complications may occur after distal pancreatectomy. The representative complication after pancreatectomy is clinically relevant postoperative pancreatic fistula (CR-POPF); however, we often encounter postoperative intra-abdominal abscess (PIAA) after pancreatic surgery. Many studies [4–6] have analyzed risk factors for CR-POPF, surgical techniques, and postoperative management to prevent CR-POPF after distal pancreatectomy. However, PIAA after

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distal pancreatectomy is seldom discussed and has not been widely reported.

Fluid collection (FC) is frequently observed after distal pancreatectomy [7, 8]. Yoshino et al. [8] have reported that FC occurs in most patients (94.5%) after distal pancreatectomy. FC is generally insignificant, although it may occasionally progress to PIAA, which requires conservative or progressive interventional treatments. If the amylase level of the PIAA collected by specific intervention is thrice the upper limit of institutional normal serum values, PIAA is regarded as CR-POPF [9]. In contrast, patients without intra-abdominal abscess who undergo peripancreatic drainage for over 3 weeks may also develop CR-POPF and not PIAA; thus, PIAA and CR-POPF overlap each other. Most studies have focused on CR-POPF [6], and no report has revealed clinical data and predictive factors for PIAA. Hence, in this study, we focused on PIAA and speculated that it might have distinct mechanisms and preventive measures separate from CR-POPF.

Therefore, the primary aim of our study was to evaluate the status between patients with or without PIAA and identify predictive factors for PIAA and CR-POPF. Our secondary aim was to investigate the clinical characteristics of patients with PIAA with interventional drainage.

Methods

Patients

Data of patients who underwent open or laparoscopic distal pancreatectomy (ODP and LDP, respectively), laparoscopic spleen preserving distal pancreatectomy (LSPDP), and distal pancreatectomy with celiac axis resection (DPCAR) at the Department of Surgery of Keio University School of Medicine and the Department of Surgery of Saiseikai Yokohamashi Tobu Hospital, where hepatobiliary-pancreatic surgeries were performed by expert specialist surgeons, between January 2012 and December 2019 were retrospectively reviewed. We excluded patients who underwent emergency surgeries, such as traumatic surgery. We divided patients into two groups according to the presence or absence of PIAA. This retrospective observational study used the "opt-out" method of the two hospitals. This study was approved by the Ethics Committee of Keio University School of Medicine (ethical approval number: 20140389). The research was conducted according to the Declaration of Helsinki 1975.

Definition of PIAA and CR-POPF

Distinguished from simple FC, which is often defined as a cyst-like lesion around the pancreatic resection [7, 10] (Fig. 1a), PIAA is defined as FC with definitive encapsulation, enhanced thick wall, or air bubbles [11] (Fig. 1b). PIAA was assessed using enhanced abdominal multidetector-row computed tomography (CT). All imaging files were reviewed by radiologists specializing in abdominal imaging, who were naive to the clinical data, such as fever, white blood cell counts (WBC), or C-reactive protein (CRP). PIAA was diagnosed only by radiological findings. Although bacterial infection caused by an abscess was confirmed by a drain culture or punctured fluid collected from some interventions (i.e., percutaneous ultrasound, CT, or endoscopic ultrasound-guided interventions), all patients were not provided interventions for PIAA, and we could not evaluate each patients' culture. Thus, we focused on radiological findings that can be easily assessed and frequently obtained postoperatively in clinical settings.

POPF was determined according to the criteria established in 2016 by the International Study Group of Pancreatic Fistula Classification [9] and we classified POPF of grade B or C as CR-POPF. In this report [9], patients requiring interventional drainage for POPF-related collections were categorized differently into grades B and C, and we distinguished PIAA from other types of CR-POPF because no report has revealed clinical data and predictive factors for PIAA.

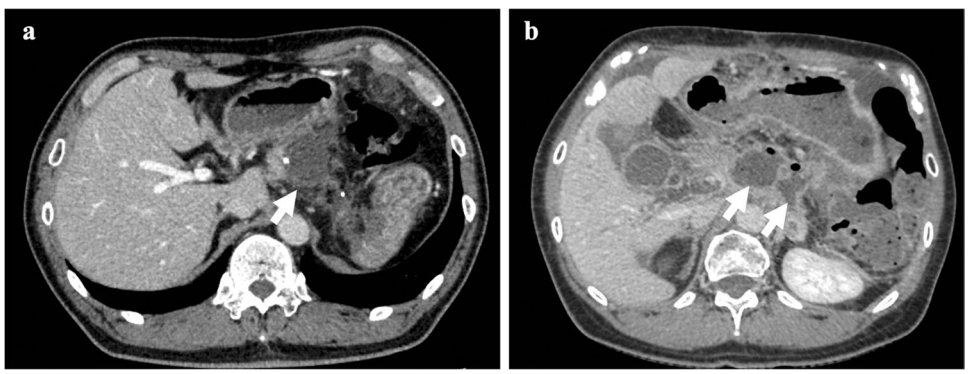

Fig. 1 Imaging of fluid collection and postoperative intra-abdominal abscess after distal pancreatectomy. **a** Fluid collection. **b** Postoperative intra-abdominal abscess

Surgical procedure

The surgeries performed included ODP, LDP, LSPDP, and DPCAR for malignant tumors, benign tumors, and others. The typical procedure for ODP was as follows: mobilization was commenced after opening the gastrocolic ligament, and the short gastric vessels are divided. Subsequently, the splenic artery was detected using an anterior approach, and then the inferior edge of the pancreas was mobilized to define the splenic vein. After the dissection of major vessels, the pancreas was then dissected using a linear stapler, occasionally after 20–30 min of pre-compression using 1 or 2 intestinal forceps, or suturing closure using the fish-mouth technique with the ligation of the main pancreatic duct. The standard approach for LDP typically involved placing 4 or 5 ports with initial access in the umbilicus. The stomach was flipped up using a 2–0 nylon and a flat-type Penrose drain or the Nathanson Hook Liver Retractors. The choice of closure techniques for the pancreas was mainly according to each surgeon's decision or the hardness of the pancreas. The pancreatic resection line was classified into portal vein level and non-portal vein level. One or two Blake drains (19-Fr; Ethicon, USA) were positioned, near the pancreatic resection line to the left sub-phrenic fossa. Operative drains were managed at the discretion of the treating surgeon, which was generally based on drain amylase measurement described later. The prescribed antibiotics were normally first- or second-generation cephalosporins taken preoperatively and postoperatively within 24 h. If patients developed infections, an appropriate sensitive antibiotic was administered. Postoperative CT scan was employed routinely on postoperative day 7, whilst for patients with high fever with data suggestive of high inflammation (i.e., high WBC, CRP), CT scan was performed within 1 week after surgery.

Drain removal and PIAA treatment

Drains positioned near the pancreatic resection line to the left sub-phrenic fossa were generally removed within 1 week by referring to the drain amylase level and drain properties, blood tests, fever, and physical findings. We avoided long-term drain retention that could have resulted in retrograde infection, and believed that early removal was necessary; we did not perform routine exchange of drains. Treatment of PIAA was not determined in detail. Although we considered administering antibacterial drugs for all cases of PIAA, whether we should have chosen a specific intervention or conservative treatment for PIAA was uncertain. The selection between conservative treatment or interventional treatment as the first-line treatment for PIAA mainly depended on each surgeon's discretion.

Clinical and radiological data collection

Preoperative demographic and clinical variables included age, sex, body mass index (BMI), diabetes mellitus, antithrombotic drugs, surgical procedures, and laboratory data (especially focused on WBC and albumin, CRP, and serum and drain amylase levels). Radiological parameters, including skeletal muscle, subcutaneous fat area (SFA), visceral fat area (VFA), and pancreatic parenchyma diameter at the resection line, were determined using preoperative plain or contrast-enhanced CT [12]. The skeletal muscle, SFA, and VFA were semiautomatically measured by manually outlining them on CT images of the third lumbar vertebra and setting the density at a threshold of − 190 to − 30 HU using OSIRIX®. After surgery, blood tests were routinely conducted until postoperative day (POD) 7, and the drain amylase levels were examined on POD 1, 3, or 5 if necessary. Operative time, blood loss, intraoperative transfusion, CR-POPF, PIAA, postpancreatectomy hemorrhage, drain culture, postoperative hospital stays, and readmission were also evaluated.

Statistical analyses

The patients were divided into two groups based on PIAA status, and the clinical characteristics of both groups were evaluated. Categorical variables were compared using the chi-squared or Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U*-test. Significant variables in the univariate analysis ($P < 0.05$) were included in the multivariate analysis to identify independent predictive factors for PIAA and CR-POPF using a logistic regression analysis to adjust for other competing factors. The optimal cut-off points for PIAA were estimated using a receiver operating characteristic (ROC) curve analysis. Moreover, we evaluated the clinical characteristics of PIAA with drainage and without drainage. All statistical analyses were conducted using the Statistical Package for the Social Sciences for Macintosh, software version 26.0 (IBM Corp., Armonk, NY, USA). P values < 0.05 were considered significant.

Results

Patient characteristics in the PIAA group

Overall, 245 patients underwent distal pancreatectomy between January 2012 and December 2019 at two high-volume centers. Among those patients, three were excluded for having undergone ODP for traumatic surgery. Therefore, 242 patients were finally enrolled for the analysis. Among the 242 patients, 49 (20.2%) had PIAA, and 41 (16.9%) had

Table 1 Demographic and clinical characteristics between PIAA (+) and PIAA (−)

	Total ($N=242$)	PIAA (+) ($N=49$, 20.2%)	PIAA (−) ($N=193$, 79.8%)	P value
Age (yrs)	69 (18–94)	66 (39–86)	70 (18–94)	0.138
Sex (male/female)	130/112	35/14	95/98	0.071
Body mass index (kg/m^2)	22.4 (14.4–36.2)	23.9 (16.3–32.5)	22.1 (14.4–36.2)	0.001
Subcutaneous fat area (cm^2)	100.0 (3.0–307.2)	122.7 (38.4–307.1)	94.3 (3.0–307.2)	0.014
Visceral fat area (cm^2)	97.2 (1.1–400.4)	152.4 (9.1–366.3)	90.6 (1.1–404.4)	0.001
Diabetes mellitus	66 (27.3%)	14 (28.6%)	51 (26.4%)	0.851
Antithrombotic drugs	42 (17.4%)	13 (26.5%)	31 (16.1%)	0.072
Skeletal muscle area (cm^2)	110.4 (51.5–195.6)	122.1 (72.4–195.6)	106.1 (51.5–187.4)	0.069
Drain culture	4.2 (2.5–5.6)	4.3 (3.2–5.2)	4.2 (2.5–5.6)	0.196
Disease				0.139
Pancreatic cancer	123 (50.8%)	20 (40.8%)	103 (53.4%)	
Intraductal papillary mucinous neoplasm	40 (16.5%)	10 (20.4%)	30 (15.5%)	
Pancreatic neuroendocrine tumor	23 (9.5%)	6 (12.4%)	17 (8.8%)	
Mucinous or serous cystic neoplasm	24 (9.9%)	4 (8.2%)	20 (10.4%)	
Solid pseudopapillary neoplasm	12 (4.7%)	1 (2.0%)	11 (5.7%)	
Metastatic tumor	8 (3.3%)	3 (6.1%)	5 (2.6%)	
Others	12 (5.0%)	5 (10.2%)	7 (3.6%)	
Surgical procedure				0.417
Distal pancreatectomy	126 (52.1%)	22 (44.9%)	104 (53.9%)	
Laparoscopic distal pancreatectomy	95 (39.3%)	22 (44.9%)	73 (37.8%)	
Laparoscopic spleen preserving distal pancreatectomy	12 (5.0%)	4 (8.2%)	8 (4.1%)	
Distal pancreatectomy with celiac axis resection	9 (3.7%)	1 (2.0%)	8 (4.1%)	
Closure technique of the pancreas				0.383
Stapler	155 (64.0%)	34 (69.4%)	121 (62.7%)	
Hand-sewn	87 (36.0%)	15 (30.6%)	72 (37.3%)	
With gastrointestinal resection	20 (8.3%)	7 (14.3%)	13 (6.7%)	0.082
Fibrin sealant	103 (42.6%)	19 (38.8%)	84 (43.5%)	0.530
Pancreatic resection line				0.503
Portal vein level	153 (63.2%)	33 (67.3%)	120 (62.2%)	
Pancreatic body or tail	89 (36.8%)	16 (32.7%)	73 (37.8%)	
Pancreatic parenchyma diameter at resection line (mm)	12.4 (2.1–24.7)	12.3 (5.1–23.7)	12.4 (2.1–24.7)	0.871
Operative time (min)	284 (73–705)	322 (160–705)	284 (73–643)	0.071
Blood loss (g)	150 (5–4990)	166 (5–4990)	150 (5–4650)	0.164
Intraoperative transfusion	11 (4.5%)	4 (8.2%)	7 (3.6%)	0.173
Clinically relevant postoperative pancreatic fistula	41 (16.9%)	25 (51.0%)	16 (8.3%)	< 0.001
Postpancreatectomy hemorrhage	7 (2.9%)	2 (4.1%)	5 (2.6%)	0.431
Laboratory data on postoperative day 1				
White blood cell (× 103/μl)	11,340 (4600–28,700)	11,100 (7270–19,500)	11,340 (4600–28,700)	0.628
Albumin (g/l)	3.0 (2.0–4.5)	3.1 (2.0–4.5)	3.0 (2.0–4.1)	0.283
Serum amylase (U/l)	204 (20–4189)	217 (94–2680)	200 (20–4189)	0.306
Drain amylase (U/l)	2464 (14–357,460)	3452 (166–357,460)	2251 (14–67,100)	0.026
C-reactive protein (mg/dl)	5.64 (0.02–16.89)	5.68 (0.77–16.89)	5.56 (0.02–16.84)	0.079
Laboratory data on postoperative day 3				
White blood cell (× 103/μl)	11,900 (5000–25,100)	13,600 (6570–21,400)	11,500 (5000–25,100)	0.013
Albumin (g/l)	2.9 (1.9–4.2)	2.9 (1.9–3.6)	2.9 (2.2–4.2)	0.111
Serum amylase (U/l)	53 (14–3772)	44 (14–413)	53 (17–3772)	0.443
Drain amylase (U/l)	449 (5–339,400)	1015 (43–55,390)	389 (5–339,400)	< 0.001

Table 1 (continued)

	Total ($N=242$)	PIAA (+) ($N=49$, 20.2%)	PIAA (−) ($N=193$, 79.8%)	P value
C-reactive protein (mg/dl)	13.93 (0.01–39.49)	20.18 (5.48–39.49)	12.29 (0.01–33.90)	< 0.001
Drain culture				
Positive in postoperative day 1	3 (1.2%)	0 (0.0%)	3 (1.6%)	0.506
Positive in postoperative day 3	7 (2.9%)	3 (6.1%)	4 (2.1%)	0.149
Postoperative hospital stay (day)	15 (6–127)	23 (9–127)	14 (6–58)	< 0.001
Readmission	13 (5.4%)	5 (10.2%)	9 (4.7%)	0.138

Values in median

Abbreviations: *PIAA*, postoperative intra-abdominal abscess

CR-POPF. The rate of FC or FC without PIAA was 85.5%. The demographic and clinical characteristics of the PIAA and non-PIAA groups are shown in Table 1. The preoperative indices representing abdominal fat mass (i.e., BMI, SFA, and VFA) were higher in the PIAA group than in the non-PIAA group. The drain amylase level, white blood cell count, and CRP level on POD 3 were also higher in the PIAA group than in the non-PIAA group.

Predictive factors for PIAA/CR-POPF and comparison between PIAA patients with and without drainage

The predictive factors associated with PIAA and CR-POPF are shown in Table 2. In the univariate analysis, preoperative indices representing abdominal fat mass (i.e., BMI, SFA, and VFA) were identified as predictive factors for PIAA but not for CR-POPF. In the multivariate analysis, the CRP level (continuous variable) on POD 3 (PIAA, odds ratio: 1.189, 95.0% confidence interval: 1.111 − 1.274, $P < 0.001$; CR-POPF, odds ratio: 1.139, 95.0% confidence interval: 1.066 − 1.217, $P < 0.001$) was the only independent and significant predictive factor for both PIAA and CR-POPF. The ROC curve analysis revealed that the optimal cut-off values of CRP levels on POD 3, BMI, SFA, and VFA for PIAA were 15.8 mg/dl, 23.6 kg/m^2, 92.9 cm^2, and 94.3 cm^2, respectively (Fig. 2). The demographic and clinical characteristics of PIAA patients ($N=49$ [20.2%]) with/without drainage and the details of PIAA patients with drainage are shown in Tables 3 and 4, respectively. The median postoperative period of PIAA formation was 9 (range, 3–49) days. Among the 49 patients with PIAA, 25 (51.0%) underwent percutaneous ultrasound, CT, or endoscopic ultrasound-guided interventions for PIAA. Among the 25 patients who had PIAA with drainage, 23 patients (92.0%) already had their intra-abdominal drainage tubes removed, which were inserted intraoperatively; most patients had PIAA after the removal of the intraoperative drainage tubes. All patients with drainage were diagnosed as having CR-POPF because amylase levels in puncture abscess were thrice the upper limit of the institutional normal serum values. Among 25 patients with some drainage for PIAA, 7 patients were not evaluated for PIAA culture. Among those 18 patients, 9 (50.0%) patients had some bacterial infection, such as *Staphylococcus*, *Enterococcus*, *Corynebacterium*, and *Pseudomonas aeruginosa*.

Discussion

This study's main finding was that the CRP level on POD 3 was an independent and significant predictive factor for PIAA and CR-POPF after distal pancreatectomy. In the univariate analysis, preoperative indices representing abdominal fat mass (i.e., BMI, SFA, and VFA) were identified as predictive factors for PIAA but not for CR-POPF. The median postoperative period of PIAA formation was 9 days; PIAA patients with drainage had a higher preoperative HbA1c level, and open surgery for distal pancreatectomy was performed more frequently for PIAA patients with drainage than for those without drainage.

Intra-abdominal abscess is a surgical site infection that often occurs after gastrointestinal surgery and is occasionally the cause of postoperative mortality [13, 14]. PIAA is diagnosed when symptoms (e.g., abdominal pain and fever) and increased inflammation level according to laboratory data are noted, and CT findings, such as FC with definitive encapsulation, enhanced thick wall, or air bubbles, are observed postoperatively [14]. In this study, the definition of PIAA was mainly dependent on CT findings checked by two of three radiologists regardless of the culture of the abscess, because we did not perform percutaneous ultrasound, CT, or endoscopic ultrasound-guided interventions for all PIAA patients, and could not collect culture of PIAA. Although most procedures were not contaminated operations, and there were PIAA patients with lower drain amylase levels on PODs 1 and 3, some patients developed PIAA after removal of the prophylactic intra-abdominal drains that were inserted intraoperatively.

After distal pancreatectomy, FC is frequently observed [7], and Yoshino et al. [8] reported that FC occurred in most patients (94.5%) postoperatively and that it disappeared

Table 2 Predictive perioperative factors for PIAA and CR-POPF

Factor	PIAA						CR-POPF					
	Univariate			Multivariate			Univariate			Multivariate		
	P value	Odd ratio	95%Cl for Exp(B)	*P* value	Odd ratio	95%Cl for Exp(B)	*P* value	Odd ratio	95%Cl for Exp(B)	*P* value	Odd ratio	95%Cl for Exp(B)
Age (yrs)	0.716	0.996	0.974–1.018				0.377	1.012	0.986–1.038			
Sex (male)	0.027	0.469	0.240–0917	0.699	0.870	0.428–1.767	0.066	0.513	0.252–1.045			
Body mass index (kg/m^2)	0.002	1.153	1.054–1.262	0.863	0.982	0.794–1.214	0.542	1.030	0.937–1.132			
Subcutaneous fat area (cm^2)	0.031	1.006	1.001–1.012	0.456	1.004	0.993–1.015	0.679	1.001	0.995–1.008			
Visceral fat area (cm^2)	0.001	1.006	1.003–1.010	0.723	0.999	0.992–1.005	0.100	1.003	0.999–1.007			
Diabetes mellitus	0.851	1.069	0.533–2.146				0.297	1.466	0.714–3.008			
Antithrombotic drugs	0.076	1.972	0.932–4.176				0.009	2.810	1.296–6.095	0.147	1.894	0.798–4.491
Preoperative albumin level (g/l)	0.204	1.655	0.761–3.599				0.831	0.916	0.408–2.056			
Skeletal muscle area (cm^2)	0.008	1.015	1.004–1.026	0.890	1.001	0.983–1.020	0.086	1.010	0.999–1.023			
Surgical procedure (open vs laparoscopic)	0.164	0.640	0.341–1.201				0.080	1.892	0.927–3.863			
Closure technique of the pancreas (stapler vs hand-sewn)	0.384	0.741	0.378–1.455				0.926	1.034	0.514–2.077			
With gastrointestinal resection	0.094	2.308	0.868–6.138				0.007	3.818	1.450–10.052	0.255	2.070	0.592–7.237
Fibrin sealant	0.530	0.814	0.429–1.547				0.059	0.496	0.239–1.026			
Pancreatic resection line (portal vein vs pancreatic tail)	0.503	1.255	0.646–2.438				0.015	2.784	1.224–6.336	0.075	2.439	0.915–6.501
Pancreatic parenchyma diameter at resection line (mm)	0.552	1.022	0.952–1.097				0.622	0.980	0.905–1.061			
Operative time (min)	0.008	1.004	1.001–1.007	0.736	1.001	0.996–1.005	< 0.001	1.006	1.003–1.009	0.906	1.000	0.995–1.004
Blood loss (g)	0.040	1.000	1.000–1.001	0.454	1.000	1.000–1.000	0.007	1.001	1.000–1.001	0.344	1.000	1.000–1.000
Laboratory data on POD 3												
White blood cell (×103/µl)	0.169	1.000	1.000–1.000				0.113	1.000	1.000–1.000			
Albumin (g/l)	0.060	0.453	0.199–1.033				0.493	0.735	0.304–1.774			
Serum amylase (U/l)	0.272	0.998	0.996–1.001				0.369	0.999	0.996–1.001			
Drain amylase (U/l)	0.980	1.000	1.000–1.000				0.373	1.000	1.000–1.000			
C-reactive protein (mg/dl)	< 0.001	1.190	1.123–1.262	< 0.001	1.189	1.111–1.274	< 0.001	1.129	1.071–1.190	< 0.001	1.139	1.066–1.217

Abbreviations: *CR-POPF*, clinically relevant postoperative pancreatic fistula; *PIAA*, postoperative intra-abdominal abscess; *POD*, postoperative day

within 1 year in the majority of these patients (77.5%). Generally, FC is insignificant; however, FC occasionally progresses to PIAA, thereby requiring conservative or progressive treatment. Most studies have focused on CR-POPF; to our knowledge, this study is the first to reveal clinical data and predictive factors for PIAA after distal pancreatectomy. We speculated that there might be another mechanism and other preventive measures against PIAA after surgery compared to POPF.

The mechanism for PIAA formation was unclear, although the occurrence of PIAA may be deeply involved with subclinical and potential leakage of pancreatic juice and the amount of intra-abdominal fat. Although the drain amylase levels on POD 1 or POD 3 were not a predictive factor for PIAA or CR-POPF in this study, subclinical and potential leakage of pancreatic juice may be accelerated by functional distal obstruction of the sphincter of the Oddi complex at the ampulla or an increase in food intake [15, 16], and this leakage later becomes evident after several PODs. Meanwhile, many surgeons believe that the amount of intra-abdominal fat tissue is an important risk factor for postoperative complications [17]. Sledzianowski et al. [2] have revealed that obesity is a risk factor for intra-abdominal morbidity after distal pancreatectomy. In this study, preoperative indices representing abdominal fat mass (i.e., BMI, SFA, and VFA) were identified as predictive factors for PIAA but not for CR-POPF. Hence, patients with CR-POPF without forming intra-abdominal abscess who had peripancreatic drainage for over 3 weeks might not have obesity or have less amount of intra-abdominal fat. Therefore, PIAA may not occur postoperatively if there is less visceral adipose tissue around the surgical site, which may be dissolved by pancreatic juice and may be the origin of surgical site infection, even if subclinical and potential leakage of pancreatic juice may continue to occur postoperatively.

Several studies have revealed that an elevated postoperative CRP level is an early indication of CR-POPF after pancreaticoduodenectomy, although there are few reports

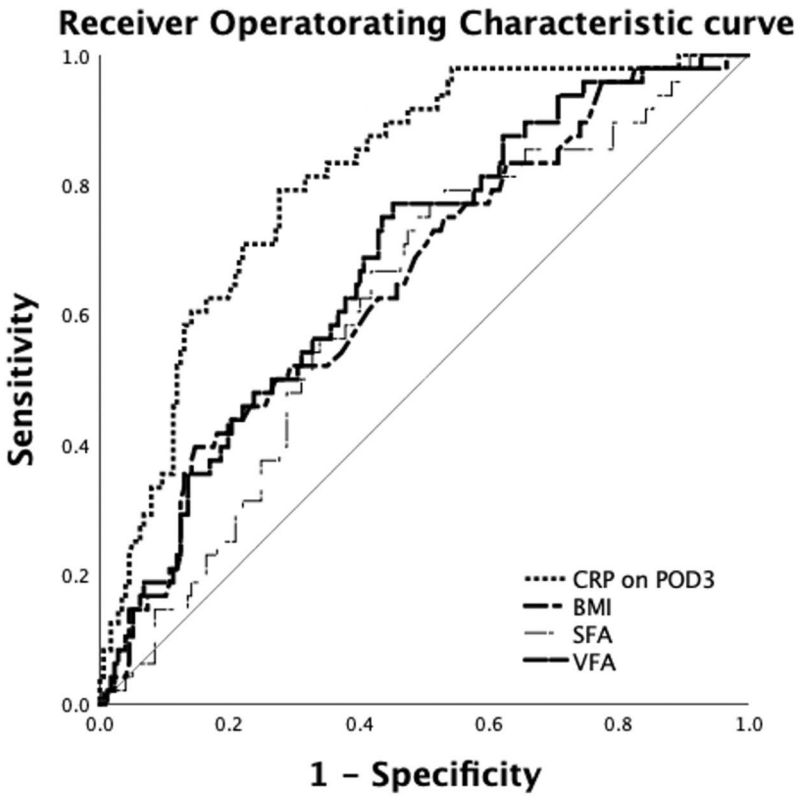

Fig. 2 Receiver operating characteristic curve of CRP levels on POD 3, as well as BMI, SFA, and VFA. BMI, body mass index; CRP, C-reactive protein; POD, postoperative day; SFA, subcutaneous fat area; VFA, visceral fat area

Factor	Cut off point	AUC	Sensitivity	Specificity	P value
CRP on POD 3 (mg/dl)	15.8	0.810	0.796	0.721	<0.001
BMI (kg/m^2)	23.6	0.653	0.531	0.705	0.001
SFA (cm^2)	92.9	0.622	0.771	0.547	0.010
VFA (cm^2)	94.3	0.678	0.750	0.508	<0.001

Abbreviations: AUC, area under the curve; BMI, body mass index; CRP, C-reactive protein; POD, postoperative day; SFA, subcutaneous fat area; VFA, visceral fat area

on distal pancreatectomy [6]. Our study revealed that the CRP level on POD 3 was an independent and significant predictive factor for PIAA after distal pancreatectomy. The CRP level on POD 3 is clinically important information, and monitoring the CRP level may help prevent PIAA formation. First, if the CRP level on POD 3 is normal or mildly elevated, early removal may be considered to prevent retrograde infection due to prolonged drain placement [9]. Furthermore, it may be effective to extend the duration of prophylactic intra-abdominal drainage for a few more days to permit examination of the contents of the drain fluid (i.e., amylase, microbiology). It may also serve as a therapeutic drainage, if the CRP level on POD 3 is increased. In this case, the drain should be exchanged weekly to avoid biofilm formations, a culprit of delayed healing. In this study, the postoperative drain was removed on day five in patients with no POPF, and previous evidence indicates that the rate of POPF for DP is higher than that of pancreaticoduodenectomy [18]. Although it is assumed that early removal is important to avoid retrograde infection, clinicians may consciously delay drain removal after DP. Second, the elevation of CRP levels occurs due to subclinical and potential POPF; thus, delaying the resumption of food intake may be practical [16]. Finally, a high CRP level suggests unspecific inflammations such as a chemical inflammation owing to POPF, a bacterial inflammation, or both. Therefore, administration of antibacterial drugs should be considered, although the cause of FC infection after distal pancreatectomy is unknown [19, 20].

The choice between a specific intervention or conservative treatment for PIAA is uncertain and mainly depends on each surgeon's discretion. Thus, the first-line treatment for PIAA remains unclear. Here, the postoperative stay of PIAA patients with interventional drainage was longer than that of those without these treatments (28 days vs 17.5 days, $P < 0.001$) because most PIAA patients with interventional drainage had conservative treatments initially. Our data also showed that more patients in the drainage group had diabetes mellitus, high HbA1c levels, and open surgery. Diabetes mellitus is a known risk factor for postoperative complications after various surgeries [21, 22], and a meta-analysis [23] has revealed that laparoscopic surgery in patients with obesity reduces surgical site infection in open surgery across general abdominal surgical procedures; thus, we may consider interventional treatments for PIAA initially for these patients. Among PIAA patients with interventional drainage, amylase levels in all punctured abscesses were thrice the upper limit of institutional normal serum values. This high amylase level in the punctured abscess may have occurred

Table 3 Demographic and clinical characteristics between PIAA patients with/without drainage

	Drainage (+) ($N=25$, 51.0%)	Drainage (−) ($N=24$, 49.0%)	P value
Age (yrs)	67 (43–86)	66 (39–81)	0.661
Sex (male/female)	20/5	15/9	0.091
Body mass index (kg/m^2)	24.4 (19.6–31.4)	22.9 (16.3–32.5)	0.473
Subcutaneous fat area (cm^2)	128.4 (53.0–225.4)	116.5 (38.4–307.1)	0.473
Visceral fat area (cm^2)	161.9 (54.2–324.5)	111.9 (9.1–366.3)	0.473
Skeletal muscle area (cm^2)	134.3 (81.1–195.6)	109.7 (72.4–163.3)	0.063
Diabetes mellitus	10 (40.0%)	4 (16.7%)	0.067
Surgical procedure			0.015
Open	16 (64.0%)	7 (29.2%)	
Laparoscopic	9 (36.0%)	17 (70.8%)	
Preoperative HbA1c (%)	6.2 (5.7–10)	5.9 (5.0–13.0)	0.039
Preoperative albumin (g/l)	4.2 (3.5–5.2)	4.2 (3.2–4.7)	0.909
Operative time (min)	372 (173–598)	277 (160–705)	0.149
Blood loss (g)	400 (5–4990)	100 (5–1941)	0.043
C-reactive protein (mg/dl) at POD 1	7.34 (3.57–14.18)	5.06 (0.77–16.89)	0.354
C-reactive protein (mg/dl) at POD 3	20.59 (12.11–39.49)	19.70 (5.48–31.43)	0.473
Drain amylase (U/l) at POD 1	3250 (192–16,017)	3452 (166–357,460)	0.889
Drain amylase (U/l) at POD 3	1255 (100–20,300)	1002 (43–55,390)	1.000
Drain culture positive within POD 5	3 (12.0%)	2 (8.3%)	0.966
Postoperative period of forming PIAA	9 (6–20)	9 (3–49)	0.682
Postoperative hospital stay (day)	28 (11–127)	17.5 (9–65)	0.003
Readmission	3 (12.0%)	2 (8.3%)	0.696

Values in median

Abbreviations: *PIAA*, postoperative intra-abdominal abscess; *POD*, postoperative day

Table 4 Demographic and clinical characteristics of PIAA with drainage

No	Age	Sex	DM	Procedure	Postoperative period of forming PIAA	Drain amylase on POD1 (U/l)	Drain amylase on POD3 (U/l)	Punctured abscess amylase (U/l)	Drainage methods	Culture of PIAA
1	78	M	−	DP	8	6973	20,300	3801	Percutaneous US	*Staphylococcus schleiferi*
2	50	M	−	DP	12	13,840	2570	Not evaluated	Percutaneous US	*Corynebacterium*
3	67	M	−	DP	7	1895	3236	Not evaluated	Percutaneous US	Methicillin-resistant *Staphylococcus aureus*
4	43	F	+	DP	9	2981	1456	Not evaluated	Percutaneous US	*Pseudomonas aeruginosa*
5	65	M	−	DP	16	1023	354	120,760	EUS	*Klebsiella oxytoca, Staphylococcus epidermidis*
6	63	M	+	DP	7	1089	1255	Not evaluated	Percutaneous US	Not evaluated
7	86	F	+	DP	10	1256	479	2000	Percutaneous US	*Enterococcus faecium, Pseudomonas aeruginosa*
8	73	M	+	DP	8	13,958	12,475	Not evaluated	Percutaneous US	Not evaluated
9	48	M	−	DP	7	2917	100	42,750	Percutaneous US	Negative
10	69	M	+	LDP	9	4946	736	441	Percutaneous US	*Pseudomonas aeruginosa*
11	66	M	+	LDP	17	1769	471	Not evaluated	EUS	Not evaluated
12	61	M	+	DP	7	6100	4297	15,000	Percutaneous US	Not evaluated
13	83	F	−	DP	10	2663	4335	130,146	Percutaneous US	Negative
14	54	M	−	DP	6	2609	655	29,117	CT	*Staphylococcus epidermidis, Staphylococcus lugdunensis*
15	57	M	−	LDP	9	16,017	5309	4626	Percutaneous US	Not evaluated
16	72	M	−	DP	11	10,134	6793	785	Percutaneous US	Negative
17	65	M	−	DP	7	4033	257	500	Percutaneous US	Not evaluated
18	69	M	−	DP	8	192	1866	22,547	Percutaneous US	Not evaluated
19	69	F	−	LDP	6	2201	449	29,336	Percutaneous US	Negative
20	71	M	−	DP	13	3836	2413	31,286	CT	Negative
21	67	M	−	LDP	9	3519	151	4250	CT	Negative
22	73	F	+	LDP	13	3626	273	1863	CT	Negative
23	71	M	+	LDP	7	3469	879	68,500	Percutaneous US	Negative
24	58	M	−	LSPDP	20	10,992	3696	52,600	EUS	*Corynebacterium jeikeium*
25	64	M	+	LDP	7	2705	121	6165	CT	Negative

Abbreviations: *CT*, computed tomography; *DP*, distal pancreatectomy; *EUS*, endoscopic ultrasoundgraphy; *F*, female; *LDP*, laparoscopic distal pancreatectomy; *LSPDP*, laparoscopic spleen preserving laparoscopic pancreatectomy; *M*, male; *PIAA*, postoperative intra-abdominal abscess; *POD*, postoperative day; *US*, ultrasoundgraphy

secondarily owing to the inflammatory extension of the pancreatic stump from PIAA. Although interventional treatments may occasionally result in secondary events, the use of various interventions has been recently increasing and becoming gradually safe, especially in special hospitals [24, 25]. In the future, studies should further investigate predictive factors for PIAA in patients with CR-POPF.

This study had several limitations. First, due to the retrospective nature of the study, selection bias and unmeasured confounding may have also affected the results regarding surgical procedures, antibiotic use, timing of postoperative CT scan, and drain management, although surgeries were performed by expert specialist surgeons and therefore selection bias was likely minimized. Recently, laparoscopic distal pancreatectomy for pancreatic cancer has been included in insurance coverage in Japan; thus, the number of laparoscopic distal pancreatectomies for pancreatic cancer has been increasing. Second, since this study was conducted in two high-volume hepatobiliary-pancreatic centers in Japan, external validation is required for generalizability. Third, the timing of intervention for PIAA was also based on the subjective judgment of each surgeon. Collectively, future prospective research studies are needed to confirm and evaluate these preliminary findings. Finally, the definition of PIAA may appear vague, but the average sensitivity for detecting infection, based on multidetector-row computed tomography (MDCT) alone, is more than 80% [26]. In this report, fluid collections containing gas or high attenuation fluid were significant predictors of infection. Although the ability to predict infection in a fluid collection based on imaging findings alone is limited, we selected MDCT as the gold standard for the detection of infection because MDCT has acceptable accuracy for infection and is the best diagnostic imaging method for abdominal abscess. Moreover, although we could not confirm definitive bacterial infection for all PIAA patients with some drainage, this may be because of a low quantity of collected samples, some bacterial species with high nutritional requirements, and long duration or early administration of antibiotics [27]. According to a nationwide survey that revealed that approximately 49% of severe sepsis hospitalizations have been described as culture-negative [28], our results for the detection rate of the culture may be appropriate, although our data were not intended for analysis of sepsis.

In conclusion, in the univariate analysis, preoperative indices representing abdominal fat mass (i.e., BMI, SFA, and VFA) were identified as predictive factors for PIAA, and the CRP level on POD 3 was an independent and significant predictive factor for PIAA and CR-POPF after distal pancreatectomy. PIAA may not occur postoperatively if there are less visceral adipose tissues around the surgical site, which may be dissolved by pancreatic juice, even if subclinical and potential leakage of pancreatic juice may continue to occur postoperatively.

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Declarations

Disclosure of ethical statements The protocol for this research project has been approved by a suitably constituted Ethics Committee of Keio University School of Medicine, and it conforms to the provisions of the Declaration of Helsinki, Committee of Keio University School of Medicine, Approval No. 20140389.

Conflict of interest Dr. Kitagawa reports grants and personal fees from ASAHI KASEI PHARMA CORPORATION; grants and personal fees from TAIHO PHARMACEUTICAL CO., Ltd.; grants and personal fees from CHUGAI PHARMACEUTICAL CO., Ltd.; grants and personal fees from EA Pharma Co., Ltd.; grants and personal fees from Yakult Honsha Co. Ltd.; grants and personal fees from Otsuka Pharmaceutical Co., Ltd.; grants from Takeda Pharmaceutical Co., Ltd.; grants and personal fees from Otsuka Pharmaceutical Factory Inc.; grants from KAKEN PHARMACEUTICAL CO., Ltd.; grants and personal fees from Astellas Pharma Inc.; grants from MEDICON INC.; grants and personal fees from DAINIPPON SUMITOMO PHARMA Co., Ltd.; grants and personal fees from Toyama Chemical Co., Ltd.; grants from Kyouwa Hakkou Kirin Co., Ltd.; grants and personal fees from ONO PHARMACEUTICAL CO., Ltd.; grants and personal fees from NIHON PHARMACEUTICAL CO., Ltd.; grants from TSUMURA & CO.; grants from FUJIFILM Toyama Chemical Co., Ltd.; grants from Nippon Covidien Inc.; grants from Eisai Co., Ltd.; grants from TEIJIN PHARMA LIMITED; and personal fees from SHIONOGI & CO., Ltd.

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