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ORIGINAL ARTICLE

The attenuation value of preoperative computed tomography as a novel predictor for pancreatic fistula after pancreaticoduodenectomy

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Abstract

Purpose Pancreatic fistula (PF) is the most serious complication following pancreaticoduodenectomy (PD). This study was performed to identify new clinical factors that may predict the development of PF after PD to improve perioperative management.

Methods Seventy-five consecutive patients who underwent PD from 2012 to 2015 were evaluated. The patients' perioperative data including the computed tomography (CT) parameters were collected. The minimum, maximum, and mean CT attenuation values (HU_{min}, HU_{max}, and HU_{mean}, respectively) were extracted from the pancreatic parenchyma (≥ 100 pixels), and the standard deviation of these values (HU_{SD}) was determined from the slice in which the superior mesenteric and splenic veins were merged. PF was defined as grade B or C according to the International Study Group for Pancreatic Fistula criteria.

Results The PF occurrence rate (grade B or C) was 25.3% in 75 patients. A multivariate analysis identified a larger HU_{SD} (odds ratio 3.092; 95% CI 1.018–9.394) and higher amylase concentration in drainage fluid on postoperative day 1 (odds ratio 1.0001; 95% CI 1.00001–1.00022) as significant risk factors for PF.

Conclusions The HU_{SD} of preoperative CT attenuation values in the pancreatic parenchyma was found to be an independent predictor for PF after PD and it might therefore positively contribute to the perioperative management of PD.

Keywords Pancreatic fistula · Computed tomography · Attenuation value · Pancreaticoduodenectomy

Introduction

Pancreatic fistula (PF) is generally recognized as the most serious complication following pancreaticoduodenectomy (PD) [1, 2]. Extensive efforts have been made to reduce the development of PF after PD. However, PF remains problematic; the recently reported incidence rates classified by the International Study Group for Pancreatic Fistula (ISGPF) criteria [3] ranged from 5 to 28% [4, 5]. Postoperative PF is caused by the leakage of pancreatic juice after surgical intervention involving pancreatic ductal damage. Subsequent bacterial infection in the pancreatic juice results in clinically concerning PF, which can lead to abscess formation and pseudo-aneurysms with potential rupture [3]. An appropriately placed drainage tube can help to localize the pancreatic juice and PF; however, a retrograde infection may be introduced along the tube [6]. Although early removal of the drainage tube is known to reduce the occurrence of infectious PF [1, 2], removing the drain too early or placing no drain in patients with occult infectious PF may result in serious and life-threatening complications. As a result, the placement of drainage tubes for longer or shorter than appropriate durations may lead to a vicious cycle of infectious PF. The early removal of the drainage tube has therefore been recommended [1, 2]. Knowledge of the major preoperative risk factors for PF is vital for clinicians and may improve the PD outcomes because such knowledge can influence postoperative management, especially that of drainage tubes. Preoperative assessment of patient-related

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factors is also very important to predict and manage postoperative complications, including PF. The predictive factors associated with postoperative PF include higher age, male sex, advanced disease stage, jaundice, biliary infection, high body mass index (BMI), obesity, narrow main pancreatic duct (MPD), long operative time, high intraoperative blood loss volume, and soft pancreatic texture [3, 7]. Among these, soft pancreatic parenchyma is one of the most well-known and important risk factors for postoperative PF [8–11] and is intraoperatively and qualitatively assessed. In contrast, computed tomography (CT) is the most common imaging modality used for preoperative assessment worldwide and its parameters are objective and quantitative [12].

A "hard" pancreas is caused by chronic inflammation, such as chronic pancreatitis [13], and it reduces the risk of developing PF after pancreatic surgery [8, 13–15]. Accordingly, we considered that the preoperative CT parameters may reflect histostructural changes in the pancreas. In the present study, we assessed the ability of CT attenuation values and their variability to predict postoperative PF in patients undergoing PD.

Patients and methods

Patients

We retrospectively reviewed the records of 75 consecutive patients who underwent elective PD from January 1, 2012, to December 31, 2015, at Tottori University Hospital. All patients underwent preoperative blood testing within 2 weeks and a CT scan within 1 month prior to the operation. Preoperative data were collected regarding age, sex, BMI, serum albumin (Alb) concentration, total bilirubin (T bil) concentration, Eastern Cooperative Oncology Group performance status (ECOG-PS), American Society of Anesthesiologists (ASA) physical status, various CT parameters (described below), preoperative tumor markers [carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen], and the presence or absence of preoperative biliary infection within 2 weeks, preoperative biliary drainage, medical history of diabetes mellitus or hypertension, steroid administration, or neoadjuvant chemotherapy. The following intraoperative and postoperative data were evaluated: pancreatic texture (soft or hard), degree of lymph node dissection, operative time, intraoperative blood loss, amylase level in the drainage fluid and serum on postoperative days (PODs) 1 and 3, tumor histology, pathological stage according to the Union for International Cancer Control classification of cancer, PF classification according to the ISGPF, and admission period. The Fistula Risk Score of each individual was calculated and categorized into two groups (0–6 points, negligible, low or intermediate risk; 7–10 points, high risk) [16]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this study, the approval of the Ethics Committee of Tottori University Faculty of Medicine was obtained (approved no. 1604A007). This article does not contain any studies with animals performed by any of the authors. For this type of study (retrospective), formal consent is not required.

CT scan analysis

All patients underwent a preoperative multidetector (64 sections) CT scan with the Aquilion CX 64-slice model (Toshiba Corporation, Tokyo, Japan). Unenhanced scans were followed by dynamic contrast-enhanced scans. Contrast-enhanced scans were used only to distinguish the boundary between pancreatic parenchyma and vessels/tumors. The images were saved in DICOM format and transferred to an image workstation with dedicated image assessment software (Centricity Enterprise Web; GE Medical Systems, Fairfield, CT, USA).

As previously reported, CT parameters were obtained with some modification [17, 18]. The unenhanced scan was used to generate a CT reconstruction of the upper abdomen with 5-mm thickness. The CT density (attenuation) values in the pancreas and spleen were evaluated by manually drawing an oval region of interest (ROI) > 100 pixels on the parenchyma of each organ (Fig. 1a–c, f), carefully avoiding other structures such as vessels, the MPD, tumor site, and artifact zones. The ROIs were drawn 5 times in the same CT slice, and the mean value of the respective data was regarded as each patient's representative value. The obtained crude attenuation values [minimum (HU_{min}), maximum (HU_{max}), mean (HU_{mean}) and standard deviation of these values (HU_{SD}) as well as variance of those CT attenuation values of all pixels in each ROI] were expressed in Hounsfield units (HU). The CT slice in which the superior mesenteric and splenic veins merged were chosen for measurement of the pancreatic parenchyma (Fig. 1a, b, f); five patients were excluded because the pancreatic parenchyma was indistinct and thus, immeasurable despite careful observation (Fig. 1d). Next, the ratio of the crude densities (HU_{min}, HU_{max}, and HU_{mean}) of the pancreas over the HU_{mean} in the spleen was calculated: (HU_{min}, HU_{max}, or HU_{mean} of ROIs in pancreas)/(HU_{mean} of ROIs in spleen). The data obtained in this manner were regarded as each patient's representative data. As described previously [19], the spleen was chosen as a reference as it does not contain any fat tissue.

The maximal diameter of the MPD and thickness of the pancreas in front of the superior mesenteric vein were also

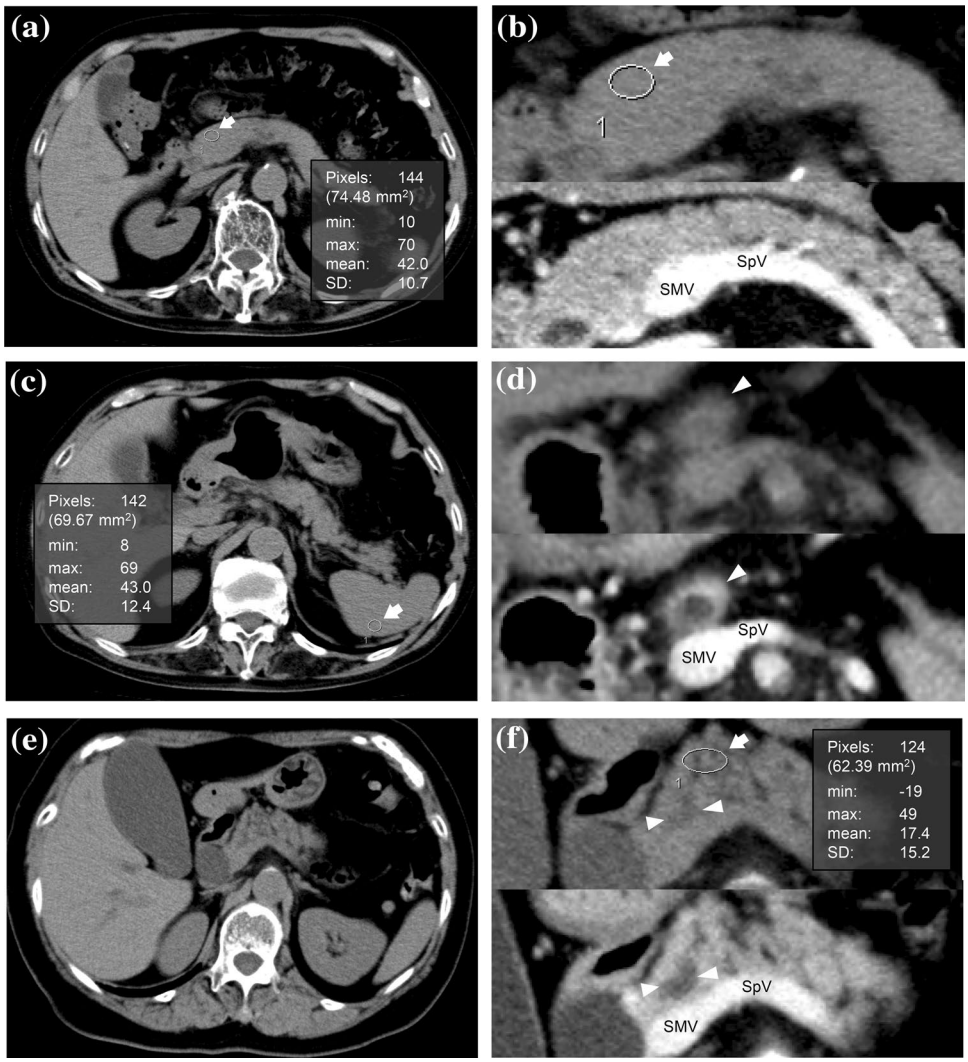

Fig. 1 **a, b** Measurement of the CT attenuation values (HU_{min}, HU_{max}, HU_{mean}) and standard deviations of these values (HU_{SD}) in the region of interest (ROI) of the pancreatic parenchyma in front of the superior mesenteric vein (SMV) in the CT slice in which the SMV and splenic vein (SpV) merge. Arrows indicate the ROIs. In **b** upper, plain CT; lower, contrast-enhanced CT. **c** CT attenuation value measurements in the ROI of the spleen. **d** Case 41. The pancreas was so atrophic that the CT values of the parenchyma could not be measured. Arrowheads show the dilated main pancreatic duct and atrophied pancreatic parenchyma. Four other patients were excluded for this reason. Upper, plain CT; lower, contrast-enhanced CT. **e, f** Case 74. In this case, HU_{SD} was as high as 15.2 (HU), and fat infiltration was observed not only in the ROI, but also in whole pancreatic parenchyma. In **f** Upper, plain CT; lower, contrast-enhanced CT. Arrowheads indicate the dilated main pancreatic duct

measured using the late arterial or portal venous phase for better identification of each structure.

Surgical technique

All patients underwent classic PD, pylorus-preserving PD (PPPD), or subtotal stomach-preserving PD (SSPPD) by three surgeons specializing in pancreatic surgery. All operations were performed via an open approach, and the degree of locoregional lymphadenectomy was determined according to the preoperative diagnosis. Child reconstruction with pancreaticojejunostomy was performed for all patients, and the type of pancreaticojejunal anastomosis was decided by the surgeons during the procedure. In all cases of pancreaticojejunostomy, either the Kakita reconstruction method (three or four interrupted penetrating sutures) or a slightly modified version of the Blumgart reconstruction method (one to three transpancreatic/jejunal seromuscular sutures to completely cover the pancreatic stump with the jejunal serosa) was employed. Additionally, plastic stents for internal drainage were inserted into the MPD in all patients prior to pancreaticojejunostomy. Three abdominal drains were routinely placed during the procedure: including 2 next to the pancreaticojejunal anastomosis and 1 next to the biliojejunal anastomosis.

PF classification

PF was defined as abdominal drain output containing an amylase concentration of ≥ 3 times the serum value measured on POD 3. PF was stratified by severity into biochemical leakage (BL), B, or C according to the ISGPF classification [3]. Patients with grade B and C postoperative PF were analyzed together owing to the relevant effects on the clinical course. Five patients were excluded from CT attenuation value measurement because of the atrophic change in the pancreatic parenchyma (Fig. 1d). In addition, they did not develop postoperative PF.

Statistical analysis

IBM SPSS Statistics for Macintosh, version 23.0 (IBM Corp., Armonk, NY, USA) was used for all graph drawing and statistical analyses, and a 2-sided p value of < 0.05 was considered to be statistically significant. Continuous data are presented as the mean ± standard deviation or median with range, as indicated. The Mann–Whitney U test and Chi-squared test were used to evaluate the differences in continuous and categorical variables, respectively. Univariate and multivariate logistic regression analyses were used to identify preoperative clinical risk factors for grade B/C PF. In addition, to evaluating the factors associated with larger HU_{SD}, a stepwise multiple linear regression analysis was performed; for this analysis, the following factors were employed (BMI, the presence of DM, CA19-9, MPD, the thickness of pancreatic parenchyma, the presence of soft pancreas and the amylase level of serum/drain on postoperative day 1). Diagnostic accuracy was determined by the area under the receiver operating characteristic curve (AUC). The AUC was computed using the nonparametric trapezoidal method [20], and 95% confidence intervals (CIs) were obtained using the approach described by DeLong et al. [21]. The optimal cutoff values were determined by maximizing the Youden index (sensitivity + specificity − 1) [22].

Results

Patient characteristics

From January 2012 to December 2015, 75 PD procedures were performed in our surgical department. The patient characteristics are summarized in Table 1.

The study population included 45 males and 30 females with a mean age of 70.1 ± 10.6 years. The preoperative mean BMI and Alb concentration and median T bil concentration of all patients were 22.37 ± 2.63 kg/m^2, 3.93 ± 0.54 g/dL, and 0.6 (range 0.2–5.6) mg/dL, respectively. In total, 72 patients (96.0%) had an ECOG-PS of 0 or 1, and 70 patients (93.3%) had an ASA physical status of 1 or 2. Neoadjuvant chemotherapy was administrated to 7 patients (9.3%), and 34.6 and 53.3% of patients had a history of diabetes mellitus and hypertension, respectively. Most patients underwent SSPPD, and 7 patients underwent PD or PPPD. Sixteen patients (21.3%) underwent anastomosis using the Kakita method and 59 patients (78.7%) underwent anastomosis using the Blumgart method. Sixty-eight patients (90.7%) underwent D2 lymphadenectomy. The median operation time was 517 min (range 309–786), and the median blood loss volume was 440 mL (range 100–2140). During the operation, the surgeons judged 38 patients' pancreatic texture to be "soft" and 37 to be "hard" based on palpation. According to the ISGPF criteria, 56 had BL (74.7%), 18 had

Table 1 Patient characteristics

Characteristics	$n = 75$
Preoperative	
Age (years)	70.1 ± 10.6
Sex (male/female)	45/30
BMI (kg/m^2)	22.37 ± 2.63
ECOG-PS (0/1/2/3)	57/15/3/0
ASA physical status (1/2/3)	12/58/5
Medical history	
DM	26
HT	40
Biliary infection*	16
Biliary drainage†	38
Steroid use‡	2
Neoadjuvant chemotherapy	7
Chemical examination of blood	
Albumin (g/dL)	3.93 ± 0.54
Total bilirubin (mg/dL)	0.6 (0.2–5.6)
CEA (ng/mL)	2.9 (0.0–310.3)
CA19-9 (U/mL)	28.1 (0.0–6820.1)
CT values	
Min (HU)§¶	0.086 ± 0.36
Max (HU)§¶	1.27 ± 0.31
Mean (HU)§¶	0.71 ± 0.29
SD (HU)§	10.6 ± 2.3
MPD (mm)	4.8 ± 2.5
Thickness (mm)	12.5 ± 2.9
Intraoperative	
Operative procedure	
Classic PD	2
PPPD	15
SSPPD	58
Degree of lymph node dissection (D 0/1/2)	3/4/68
Portal vein resection (yes/no)	14/61
Reconstruction method(Kakita/Blumgart)	16/59
Operation time (min)	517 (309–786)
Blood loss (mL)	440 (100–2140)
Pancreatic texture (soft/hard)	38/37
Postoperative	
PF	
Biochemical leakage	56
Grade B	18
Grade C	1
Amylase level on postoperative day 1	
Serum (IU/L)	1179 (12–3953)
Drain (IU/L)	210 (12–275,321)
In-hospital mortality	1
Histological diagnosis	
Pancreatic cancer or tumor	51
Bile duct cancer or tumor	14
Papillary cancer of the duodenum	7
Other malignancies	2

Table 1 (continued)

Characteristics	$n=75$
Benign pancreatic lesion	1
Pathological stage (0**/I/II/III/IV)††	12/9/9/21/24
Postoperative hospital stay (days)	23 (10–216)
Fistula risk score (0–6points/7–10points)	57/18

BMI, body mass index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists, *DM* diabetes mellitus, *HT* hypertension, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CT* computed tomography, *HU* Hounsfield unit, *SD* standard deviation of CT values in region of interest, *MPD* main pancreatic duct, *PD* pancreaticoduodenectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *SSPPD* subtotal stomach-preserving pancreaticoduodenectomy

*During 1 week before the operation, the presence of biliary infection was determined by the attending surgeons

**Including benign and precancerous lesions

†Any preoperative biliary drainage procedure (percutaneous–transhepatic, endoscopic nasobiliary/retrograde)

‡Any route of administration within 1 week before the operation (enteral, inhalational, intravenous) except transdermal

§Five patients were excluded because of atrophic and unmeasurable changes in the pancreatic parenchyma

¶Standardized by splenic mean CT attenuations

††According to UICC classification of cancer

grade B (24.0%), and 1 had grade C (1.3%). Postoperative grade B or C PFs were observed in 19 patients (25.3%; 95% CI 15.5–35.2%), with 1 case of in-hospital mortality (1.3%; 95% CI 0.0–3.9%). The median length of postoperative hospitalization was 23 days (range 10–216). Postoperative histological examinations revealed that 51 patients (68.0%) had pancreatic cancer or pancreatic tumors with malignant potential (i.e., intrapapillary mucinous neoplasm, solid pseudopapillary neoplasm, or pancreatic neuroendocrine tumor), but the remaining 24 patients had cancer arising from the biliary tract ($n=14$) or duodenal papilla ($n=7$), other malignancies (duodenal gastrointestinal tumor, $n=1$; invasion of transverse colon cancer to the pancreatic head, $n=1$), and benign pancreatic lesions (autoimmune pancreatitis, $n=1$). The Fistula Risk Score was calculated for each patient, and clinical outcomes were evaluated across two discrete risk zones, as described in the original work (0–6 points: negligible, low, and intermediate risk group or 7–10 points: high risk group) [16]. In grade B/C PF group, the proportion of patients classified as high risk was significantly higher than that of patients with lower-risk scores ($p<0.001$, Table 2).

Predictive factors prior to POD 3 for postoperative grade B/C PF

Table 2 demonstrates the associations between the pre- and post-surgical parameters and grades of PF after surgery. A univariate logistic analysis determined that patients with elevated levels of CA 19-9, dilated MPD, a high HU_{min}, a low HU_{SD}, a thin pancreatic parenchyma, a hard pancreatic texture, and a low amylase concentration in serum and drain fluid on POD 1 had significant associations with BL. A further multivariate logistic regression analysis confirmed that a both high HU_{SD} (odds ratio 3.092; 95% CI 1.018–9.394) and an elevated drain amylase concentration (odds ratio 1.0001; 95% CI 1.00001–1.00022) were statistically significant independent predictive factors for grade B/C PF after PD (Table 3). The comparison of drain amylase levels on POD 1 between patients with a hard and soft pancreatic texture indicated that the levels on POD 1 were significantly higher in the group of patients with a soft pancreatic texture (318 versus 7443 IU/L, $p<0.001$, Table 4). In a similar comparison, HU_{SD} was larger, MPD was thinner, and the serum amylase levels were significantly higher in the group with a soft pancreatic texture ($p=0.015$, <0.001, and $=0.002$, respectively, Table 4). However, the parameter "pancreatic texture" was eliminated based on the findings of a logistic regression analysis.

HU_{SD} as a postoperative PF predictor

Comparison of the HU_{SD} values between patients with BL and patients with grade B/C PF is shown in Fig. 2a. The HU_{SD} was significantly larger in patients with grade B/C PF ($p<0.001$). The diagnostic accuracy of HU_{SD} regarding the occurrence of postoperative PF (grade B/C) was evaluated by the AUC, as shown in Fig. 2b. The HU_{SD} had high diagnostic accuracy (AUC 0.899; 95% CI 0.797–1.000), with a calculated optimal cutoff value of 11.6 HU. Using this cutoff value, the sensitivity and specificity of HU_{SD} for postoperative PF (grade B/C) were 0.842 (95% CI 0.680–0.933) and 0.922 (95% CI 0.861–0.955), respectively. In addition, the estimated optimal cutoff value of 11.6 HU for HU_{SD} yielded a positive predictive value of 0.800 (95% CI 0.646–0.886) and a negative predictive value of 0.940 (95% CI 0.878–0.974). Furthermore, in order to examine the clinical factors related to HU_{SD}, we performed a linear regression analysis. The factors that showed a statistically significant tendency or difference (factors with p value <0.1, Table 2) were chosen for the regression analysis. The analysis revealed the BMI, pancreatic parenchyma, and soft pancreatic texture to be independently and significantly associated with HU_{SD} values (Table 5). In addition, a comparison of HU_{SD} values in the high risk group according to the Fistula Risk Score (7–10 points) and the lower-risk group (0–6 points) indicated that the former had significantly larger HU_{SD} values ($p=0.011$, Fig. 3).

Table 2 Comparison of patient characteristics prior to postoperative day 3

Characteristics	Biochemical leak	Grade B or C PF	*p* value
Age*	64.9 ± 6.7	71.9 ± 5.7	0.563
Sex†			
Male	32 (57.1%)	13 (68.4%)	0.430
Female	24 (42.9%)	6 (31.6%)	
BMI (kg/m^2)*	22.0 ± 2.5	23.4 ± 2.4	0.054
ECOG-PS†			
0	40 (71.4%)	17 (89.4%)	0.251
1	13 (23.2%)	2 (10.5%)	
2	3 (5.4%)	0 (0.0%)	
ASA physical status†			
1	6 (10.7%)	6 (31.6%)	0.100
2	46 (82.1%)	12 (63.2%)	
3	4 (7.1%)	1 (5.2%)	
Medical history†			
DM	23 (41.1%)	3 (15.8%)	0.054
HT	29 (51.8%)	11 (57.9%)	0.791
Biliary infection‡	13 (23.2%)	3 (15.8%)	0.747
Biliary drainage§	27 (48.2%)	11 (57.9%)	0.597
Steroid use¶	2 (3.6%)	0 (0.0%)	
Neoadjuvant chemotherapy†	5 (8.9%)	2 (10.5%)	
Chemical examination of blood*			
Albumin (g/dL)	3.94 ± 0.58	3.89 ± 0.42	0.678
Total bilirubin (mg/dL)	0.6 (0.2–5.6)	0.7 (0.4–4.9)	0.458
CEA (ng/mL)	3.4 (0.0–310.3)	2 (1.2–51.1)	0.105
CA19-9 (U/mL)	38.5 (0.8–6820.1)	12.3 (0.0–288.8)	0.017
CT values*			
HU_{min} (HU)**††	0.156 ± 0.308	−0.101 ± 0.427	0.024
HU_{max} (HU)**††	1.24 ± 0.314	1.366 ± 0.300	0.130
HU_{mean} (HU)**††	0.718 ± 0.287	0.706 ± 0.303	0.942
HU_{SD} (HU)**	9.78 ± 1.71	12.9 ± 1.99	< 0.001
MPD (mm)	5.22 ± 2.55	3.59 ± 2.11	0.010
Thickness (mm)	12.0 ± 2.95	14.0 ± 2.29	0.011
Operative procedure†			
Classic PD	1 (1.8%)	1 (5.3%)	0.445
PPPD/SSPPD	55 (98.2%)	18 (94.2%)	
Degree of lymph node dissection†			
D0	3 (5.3%)	2 (10.5%)	0.381
D1	4 (7.1%)	0 (0.0%)	
D2	49 (87.5%)	17 (89.5%)	
Portal vein resection†	14 (25.0%)	0 (0.0%)	0.150
Reconstruction method†			
Kakita	9 (16.1%)	7 (36.8%)	0.056
Blumbart	47 (83.9%)	12 (63.2%)	
Operation time (minute)*	521 (309–775)	496 (403–786)	0.836
Blood loss (mL)*	435 (100–1,830)	440 (215–2,140)	0.688
Pancreatic texture†			
Soft	21 (37.5%)	17 (89.5%)	< 0.001
Hard	35 (62.5%)	2 (10.5%)	
Amylase level on postoperative day 1*			
Serum (IU/L)	219 (12–2,342)	507 (75–3,953)	0.002
Drain (IU/L)	656.5 (12–42,531)	11,906 (704–27,5321)	< 0.001

Table 2 (continued)

Characteristics	Biochemical leak	Grade B or C PF	*p* value
Fistula Risk Score[†]			
0–6 points (negligible–intermediate risk)	49 (87.5%)	8 (42.1%)	< 0.001
7–10 points (high risk)	7 (12.5%)	11 (57.9%)	

PF pancreatic fistula, *CI* confidence interval, *BMI* body mass index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists, *DM* diabetes mellitus, *HT* hypertension, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *CT* computed tomography, *HU* Hounsfield unit, *SD* standard deviation of CT values in region of interest, *MPD* main pancreatic duct, *PD* pancreaticoduodenectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *SSPPD* subtotal stomach-preserving pancreaticoduodenectomy

*Mann–Whitney *U* test

**Five patients were excluded because of atrophic and unmeasurable changes in the pancreatic parenchyma

[†]Chi-square test

[‡]Any preoperative biliary drainage procedure (percutaneous–transhepatic, endoscopic nasobiliary/retrograde)

[§]During 1 week before the operation, the presence of biliary infection was determined by the attending surgeons

[¶]Any route of administration within 1 week before the operation (enteral, inhalational, or intravenous) except transdermal

[††]Standardized by splenic mean CT attenuations

Table 3 Univariate and multivariate analysis: independent risk factors for PF

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Chemical examination of blood				
CA19-9 (U/mL)	0.996 (0.991–1.001)	0.159		
CT values				
HU_{min} (HU)*[†]	0.122 (0.023–0.642)	0.013	2.490 (0.024–260.8)	0.701
HU_{SD} (HU)[†]	2.488 (1.603–3.862)	< 0.001	3.092 (1.018–9.394)	0.046
MPD (mm)	0.728 (0.557–0.950)	0.019	0.872 (0.485–1.567)	0.646
Thickness (mm)	1.303 (1.054–1.612)	0.014	1.353 (0.797–2.297)	0.263
Amylase level on postoperative day 1				
Serum (IU/L)	1.001 (1.0002–1.002)	0.013	1.001 (0.9997–1.0027)	0.106
Drain (IU/L)	1.0001 (1.00004–1.0002)	0.001	1.0001 (1.00001–1.00022)	0.037

PF pancreatic fistula, *CI* confidence interval, *CA19-9* carbohydrate antigen 19-9, *CT* computed tomography, *HU* Hounsfield unit, *SD* standard deviation of CT values in region of interest, *MPD* main pancreatic duct

*Standardized by splenic mean CT attenuations

[†]Five patients were excluded because of atrophic and unmeasurable changes in the pancreatic parenchyma

Discussion

PD is routinely performed for the resection of neoplasms in the periampullary region of the pancreas and is the only curative treatment for malignancies that originate from this region [23]. PD is a complex surgical procedure, and its associated mortality and morbidity rates were recently reported to be < 5% and 40–50%, respectively, even in a high-volume center [24–26]. Major complications include PF, delayed gastric emptying, and surgical site infections. Among them, PF is one of the most worrisome complications after PD and may result in a longer hospital stay, increased health care costs, need for re-interventions, and other life-threatening complications [26, 27]. As for other cancers, major complications after surgery have a negative influence on patient survival [28–30]. Several risk factors for PF after PD have been identified, and various methods to reduce the rate of PF have been reported so far [31–33]; however, no definitive methods to prevent PF have yet been established. Consequently, the timely ability

Table 4 Comparison of clinical factors by texture of the pancreas

Variables	Soft	Hard	*p* value
Chemical examination of blood*			
CA19-9 (U/mL)	25.6 (0.0–4242.6)	29 (0.8–6820.1)	0.255
CT values*			
HU_{min} (HU)†‡	0.115 ± 0.44	0.054 ± 0.24	0.228
HU_{SD} (HU)‡	11.25 ± 2.44	9.93 ± 1.84	0.015
MPD (mm)	3.57 ± 1.98	6.08 ± 2.42	< 0.001
Thickness (mm)	12.4 ± 3.09	12.6 ± 2.77	0.966
Amylase level on postoperative day 1*			
Serum (IU/L)	430.5 (54–2,070)	118 (12–3,953)	0.002
Drain (IU/L)	7443 (116–275,321)	318 (12–30,460)	< 0.001

CA19-9 carbohydrate antigen 19-9, *CT* computed tomography, *HU* Hounsfield unit, *SD* standard deviation of CT values in region of interest, *MPD* main pancreatic duct

*Mann–Whitney *U* test

†Standardized by splenic mean CT attenuations

‡Five patients were excluded because of atrophic and unmeasurable changes in the pancreatic parenchyma

to predict and identify PF in patients undergoing PD is vitally important for the effective management of PF.

In the current study, grade B/C PF after PD occurred in 19 patients (25.3%; 95% CI 15.4–35.2%); this incidence is higher than that in recent reports [4, 5]. Differences in the patient population, such as a higher population of elderly individuals, may be one explanation for this result. In addition, all patients in our department undergo a drain surveillance culture on PODs 1 and 3, and those with positive cultures are more readily classified as grade B PF than those with negative cultures due to longer duration of drainage tube placement. This may be another reason for our higher incidence of grade B/C PF. As mentioned in the introduction, a soft pancreatic texture is commonly regarded as a strong risk factor for PF [8–10]; however, there is no way to determine the texture by intraoperative palpation alone. Elastography, an ultrasound stiffness measurement modality, is one way to determine preoperative pancreatic stiffness, and the use of elastography in patients with pancreatic tumors has previously been described [34, 35]. However, this technique is not commonly used due to limitations in accessing the device and inaccurate results caused by technical limitations, the skill of the examiner, and the anatomical characteristics of the pancreas [35, 36]. CT is the most widely used method for assessing hepatobiliary and pancreatic disease and is useful for determining the optimal treatment strategy [12]. The biggest difference between elastography and CT is the objectivity of each technique. In addition, preoperatively obtained CT data can be measured whenever needed, even postoperatively if the data are stored. Consequently, we focused on the assessment of the parameters obtained from CT, and a high HU_{SD} was identified as an independent risk factor for the development of clinically relevant PF. In this study, HU_{SD} was identified as a predictive risk factor for PF, and we speculated that fat infiltration in the pancreas may be closely associated with the CT attenuation values (HU_{min} and HU_{SD}). Additional analysis also supports

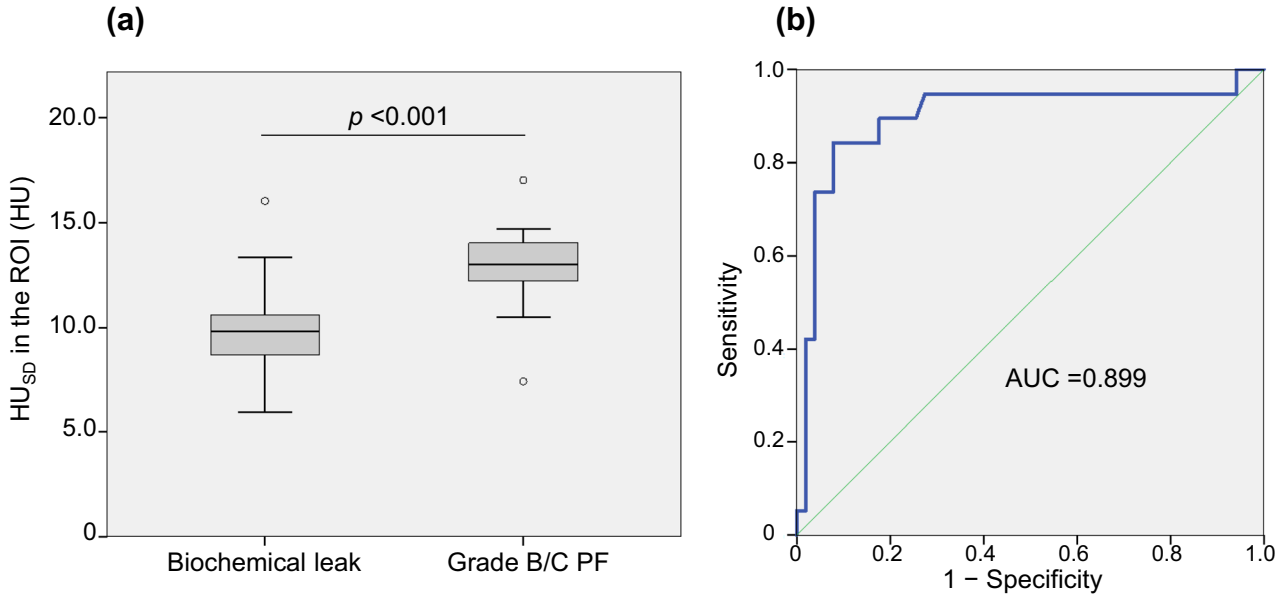

Fig. 2 **a** Comparison of HU_{SD} between two groups: patients with and without grade ≥ B pancreatic fistula (PF) (Mann–Whitney *U* test). **b** Receiver operating characteristic curves for the diagnostic accuracy of HU_{SD} in predicting postoperative grade B/C PF. *AUC* area under the receiver operating characteristic curve, *ROI* region of interest

Table 5 A multivariate stepwise regression analysis of factors associated with a larger HU_{SD}

Factors	Univariate			Multivariate		
	B (95% CI)	β	*p* value	B (95% CI)	β	*p* value
BMI (kg/m^2)	0.451 (0.269–0.634)	0.513	< 0.001	0.405 (0.232–0.578)	0.460	< 0.001
DM	− 0.455 (− 1.595–0.685)	− 0.096	0.428			
CA19-9 (U/mL)	− 0.0004 (− 0.001–0.0001)	− 1.586	0.117			
MPD (mm)	− 0.09	− 0.105	0.386			
Thickness (mm)	0.264 (0.083–0.446)	0.332	0.005	0.184 (0.027–0.340)	0.231	0.022
Pancreatic texture (Soft pancreas)	1.320 (0.279–2.361)	0.293	0.014	1.462 (0.609–2.315)	0.325	0.01
Amylase level on postoperative day 1						
Serum (IU/mL)	− 0.00008 (− 0.001–0.001)	− 0.024	0.843			
Drain (IU/mL)	0.00001 (0–0.00003)	0.206	0.087			

B unstandardized regression coefficient, *CI* confidence interval, *β* standardized regression coefficient, *BMI* body mass index, *DM* diabetes mellitus, *CA19-9* carbohydrate antigen 19-9, *MPD* main pancreatic duct

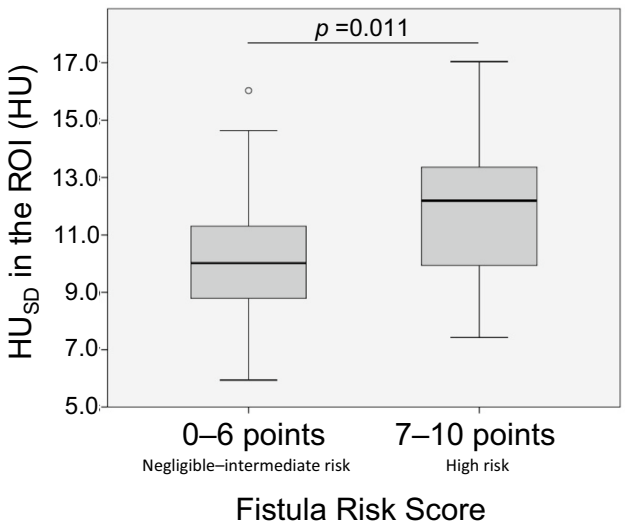

Fig. 3 Comparison of HU_{SD} between the groups: patients with Fistula Risk Score of ≥ 7 or ≤ 6 points (Mann–Whitney *U* test)

this assumption: a higher BMI was related to larger HU_{SD} (Table 5). The degree of fat infiltration has been reported to be significantly correlated with the CT attenuation value of the pancreas [18]. Obesity is one of the PF risk factors after PD, suggesting that the HU_{SD} value may increase due to obesity and accompanying pancreatic fat infiltration (Fig. 1e, f). Although HU_{SD} includes some errors to a greater or lesser degree, the data should also reflect histopathological changes (Fig. 4). These errors may change after adjusting the equipment or choosing the CT image-acquiring protocols. Future studies may reveal differences in the HU_{SD} among facilities. As shown in Fig. 2b, HU_{SD} had strong diagnostic accuracy for predicting postoperative grade B/C PF, with a calculated optimal cutoff value of 11.6 HU. With a high accuracy, HU_{SD} was identified to be a significant independent predictor of clinically concerning PF as shown in Fig. 2, and an HU_{SD} of ≥ 11.6 HU should raise a high degree of suspicion for grade B/C PF after PD. Pharmacological or surgical intervention may be recommended in these higher-risk PF groups, whereas the absence of a drainage tube may help reduce the probability of PF in lower-risk groups.

In this study, we found a correlation between grade B/C PF and HU_{SD}, Fistula Risk Score, and also clarified the relationship between HU_{SD} and Fistula Risk Score. To the best of our knowledge, the present study is the first to show the predictability of PF based on the HU_{SD} of the pancreatic parenchyma in patients undergoing PD. Patients with a high HU_{SD} of the pancreas should therefore be screened for the potential development of clinically concerning PF, and active intervention in these patients may help reduce the occurrence of PF.

This study is associated with several limitations, including its retrospective design, limited sample size, and obscure relationship between CT values and histological changes. Further studies are necessary to gain more insight into these relationships. Preoperative knowledge in predicting a high risk of grade B/C PF in patients undergoing PD will positively contribute to the prevention of future outbreaks and better management of PF.

In conclusion, a larger HU_{SD} and higher amylase concentration in the drainage fluid on POD 1 were found to be independent risk factors for PF. The results of this study suggest that the risk of clinically relevant PF (grade B/C) can be predicted by measuring the pancreatic parenchyma CT values. Preoperative CT assessments may be useful for identifying the optimal postoperative pharmacological interventions and drain management after PD.

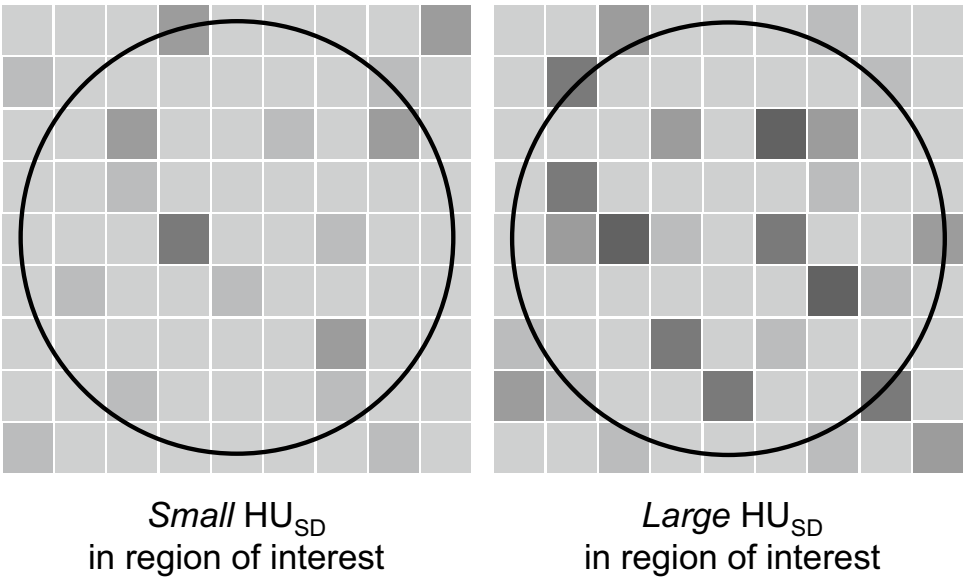

Fig. 4 A schematic description of hypothesis to explain changes in HU_{SD}. In solid organs, histological changes such as fat infiltration might reflect changes in HU_{SD}. In the right panel, HU_{min} is smaller and HU_{SD} is larger than that in the left panel. Circles represent the regions of interest. Each square represents a CT pixel, and the color brightness represents the CT attenuation value in each pixel

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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