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Original Article

The Late Phase/Early Phase Ratio of Pancreatic CT Values as a Novel Predictor of Pancreatic Fistula after Distal Pancreatectomy

Masashi Utsumi[a]*, Hideki Aoki[a], Takayuki Yabuki[b], Seiichi Nagahisa[a], Seitaro Nishimura[a], Yuta Une[a], Yuji Kimura[a], Megumi Watanabe[a], Fumitaka Taniguchi[a], Takashi Arata[a], Koh Katsuda[a], Kohji Tanakaya[a], and Yumiko Sato[c]

Departments of [a]Surgery, [b]Radiology, [c]Pathology, National Hospital Organization, Iwakuni Clinical Center, Iwakuni, Yamaguchi 740-8510, Japan

Post-operative pancreatic fistula (POPF) remains the most common complication after distal pancreatectomy (DP). In this retrospective study, we reviewed the data from patients who underwent DP between 2008 and 2019 in our institute to determine whether the late phase/early phase ratio (L/E ratio) by preoperative computed tomography (CT) scan in the pancreas could predict POPF occurrence after DP. We examined the relationship between preoperative or intraoperative factors and the occurrence of POPF after DP using statistical methods in 23 males and 21 females with a mean age of 73. The mean L/E ratio was significantly lower in the POPF group than the non-POPF group ($p = 0.035$). The L/E ratio had moderate diagnostic accuracy, with a calculated optimal cutoff value of 0.77. In univariate analysis, a significant association was noted between POPF and stump thickness ≥ 16.9, body mass index ≥ 27.5, and L/E ratio ≤ 0.77. In the multivariate analysis, the L/E ratio (odds ratio, 5.96; $p = 0.036$) was an independent risk factor for POPF. Our findings suggest that the pancreatic L/E ratio may predict the occurrence of POPF after DP. This measure may be useful in preoperative risk stratification, patient counseling, and perioperative patient management, improving clinical outcomes after DP.

Key words: late phase/early phase ratio, pancreatic fistula, distal pancreatectomy

Distal pancreatectomy (DP) is commonly performed for the treatment of diseases occurring in the body and/or tail of the pancreas. Although perioperative management and operative techniques in pancreatic surgery have improved, post-operative pancreatic fistula (POPF) remains the most common complication after DP [1]. POPF can be triggered by serious incidents such as intra-abdominal abscess and intra-abdominal arterial bleeding, and it can be fatal. As such, identifying patients who are at risk of POPF is critical to decrease morbidity after DP and to improve clinical outcomes.

A soft pancreas is reported to be a risk factor for developing POPF after DP [2-4], and thus pancreatic fibrosis, which leads to decreased softness of the gland, reportedly reduces the risk of POPF. However, few radiological studies have addressed whether the degree of pancreatic fibrosis can be reliably detected and qualified [5,6]. Recently, computed tomography (CT) has emerged as a way to objectively identify the pancreatic texture preoperatively [7-9]. These reports suggest that pancreatic enhancement patterns can be used to assess the level of pancreatic fibrosis, and can thereby serve as a tool to predict the risk of POPF after pancreatoduodenectomy (PD). However, the relevant criteria have

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*Corresponding author. Phone : +81-827-34-1000; Fax : +81-827-35-5600
E-mail : masashi11232001@yahoo.co.jp (M. Utsumi)

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yet to be defined for patients undergoing DP.

In the present study, we evaluated the risk factors for POPF after DP using both clinical features and preoperative CT values and investigated whether preoperative CT values in the pancreas could predict the occurrence of POPF after DP.

Materials and Methods

Patients and data collection. Forty-six patients who underwent DP at the Department of Surgery in the Iwakuni Clinical Center from April 2008 to April 2019 were consecutively recruited in this study. After excluding 2 patients due to a lack of accurate CT data, the remaining 44 patients were included in this study. To evaluate the risk factors for POPF, we investigated preoperative patient data, including sex, age, diabetes, alcohol consumption, smoking status, body mass index (BMI), controlling nutritional status score [10], surgery indications, preoperative serum albumin level, main pancreatic duct diameter, thickness of the stump as determined on the preoperative CT. In addition, we investigated CT attenuation values (late phase/early phase [L/E] ratio) in the pancreatic body as described below. The ethics committee at the Iwakuni Clinical Center approved the study protocol (approval number: 0177). This study is in accordance with the 1975 Declaration of Helsinki.

CT protocol. CT examination was performed using a 320-row multislice CT (Aquilion 320; Cannon Medical Systems Corporation, Tokyo) with the following parameters: reconstructed transverse slice thickness of 5 mm, 0.5 sec/rot, 120 kVp, and pitch factor 0.813. The tube current was set to automated exposure control. Each subject was first examined using unenhanced CT, and was then injected with iodinate contrast medium (Omnipaque 300; GE Healthcare) using a power injector (Nemoto Dual shot GX7). The injection dose was 600 mg iodine per kg of body weight, and the duration was fixed at 30 sec; hence, the injection rate depended on the patient's body weight.

A bolus tracking program was used to optimize the scanning delay for arterial scans. The trigger point was located in the abdominal aorta at the level of the celiac axis, and the trigger threshold was set at 150 Hounsfield units. The scan delays were set at 15 s after the trigger (about 40 sec after injection), and a pancreatic (early) image was obtained. Hepatic (late)- and delayed-phase images were also obtained about 70 and 180 s after injection. The images were saved in DICOM format and transferred to an image workstation using image assessment software (EV Insite version 3.3.0.2; PSP Corporation, Tokyo).

CT evaluation. Two physicians specializing in general surgery (MU. and HA., with 15 and 25 years of experience, respectively) who were blinded to the clinical information independently measured the CT attenuation values on electronically stored CT images. CT images obtained for diagnostic purposes within 30 days before DP were included in this analysis. CT attenuation values were measured on enhanced images obtained in the pancreatic (early) and hepatic (late) phases after contrast administration. CT attenuation values of the pancreatic parenchyma were quantified using Hounsfield unit thresholds by determining the region of interest (ROI) in two points in two segments of the head of the pancreas, which is proximal to the planned resection line (Fig. 1). The mean value for the two segments was computed for each patient. The largest possible spherical ROI was placed so as to avoid the pancreatic duct and extrapancreatic structures. The smallest ROI measured was approximately 3 mm in diameter in a patient with atrophic pancreas. The enhancement ratio expressed as the L/E ratio was calculated as (hepatic phase − unenhanced phase)/(pancreatic phase − unenhanced phase) to indicate delayed-phase enhancement. The L/E ratio at the pancreatic body was used to assess pancreatic firmness.

Operative procedure. All surgeries were performed by a pancreatic surgeon with more than 15 years of experience. The pancreatic thickness of the pancreatic cutting line was measured by intraoperative ultrasonography and preoperative CT. In cases with a pancreatic cutting line of ≤ approximately 15 mm thickness, the pancreas tended to be divided using Endo GIA™ Reload with Tri-Staple™. The Cartridge height of the stapler was selected according to the thickness of the pancreatic cutting line. In cases with a pancreatic cutting line of ≥ approximately 15 mm thickness, the pancreas was cut using a scalpel, and the pancreatic duct was identified and ligated. The cut edge of the pancreas was sutured using 4-0 absorbable monofilament and a fish-mouth closure. The omentum was left between the pancreatic stump and major arteries, including the celiac artery or common hepatic artery, to prevent aneurysms. Two closed suction drains were placed at

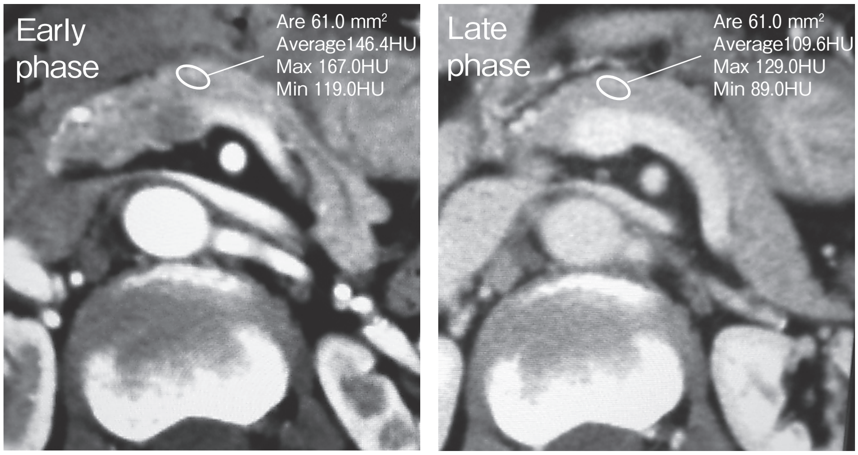

Fig. 1 Measurement of the late phase to early phase ratio. Computed tomography (CT) attenuation values were measured on enhanced images obtained in the pancreatic (early) and hepatic (late) phases after contrast administration. CT attenuation values of the pancreatic parenchyma were quantified using Hounsfield unit thresholds by placing a region of interest in the pancreas body. The enhancement ratio expressed as the late phase/early phase ratio (L/E ratio) was calculated as (hepatic phase − unenhanced phase)/(pancreatic phase − unenhanced phase) to indicate delayed-phase enhancement.
L/E ratio = (late phase-unenhanced phase)/(early phase–unenhanced phase) = 109.6 − 56.5/146.4 − 56.5 = 0.59.

the pancreatic stump and left in the subphrenic space. Prophylactic antibiotics were administered for 3 days after surgery. Somatostatin analogues were not used for the prevention of POPF in any patient.

Classification and detailed definition of POPF. POPF was diagnosed and graded based on the International Study Group on Pancreatic Fistula classification [11]. POPF was diagnosed when the amylase concentration in the drainage fluid on postoperative day 3 was more than three times the upper limit of its normal serum concentration. Grade A POPF is biochemical fistula, and it was defined as measurable fluid output on or after postoperative day 3, with amylase content higher than three times the upper normal serum level. Grade A POPF has no clinical impact on the normal postoperative pathway. Clinically significant POPFs are classified as grades B and C. POPF with an elevated inflammatory response observed in blood examination and following intravenous antibiotic administration was defined as grade B POPF caused by infection. POPF that required drain placement for > 22 days and showed no elevated inflammatory response or did not require antibiotic administration was defined as grade B POPF caused by long-term drain placement. Whenever a major change in clinical management or deviation from the normal clinical pathway was required or organ failure occurred, the fistula was classified as grade C POPF.

Pathologic evaluation. Histologic evaluation of the pancreatic surgical specimens stained by hematoxylin-eosin was performed by an experienced pathologist who was blinded to the radiological findings and clinical data (YS, with 17 years of experience in pathology). Pancreatic fibrosis at the resection margin was graded as: F0, normal parenchyma with no fibrotic change; F1, mild fibrosis with thickening of periductal fibrosis; F2, moderate fibrosis with marked sclerosis of the interlobular septa and no evidence of architectural change; and F3, severe fibrosis with architectural disruption [12]. Two patients were excluded owing to lack of pathological data. Therefore, data from the pathologic evaluation of 42 patients were analyzed.

Statistical analysis. Statistical analyses were performed using the unpaired Student's *t*-test and χ^2 test with Fisher's exact test. All variables were assessed using univariate analyses, and only those showing statistical significance ($p < 0.05$) were evaluated using multivariate logistic analyses to determine the primary independent risk factors for POPF. Values of $p < 0.05$ were considered statistically significant. Diagnostic accuracy was determined by the area under the curve (AUC). The optimal cutoff values were determined by maximizing the Youden index (sensitivity + specificity − 1) [13]. Pearson *r* correlation coefficient was calculated between computed tomography enhancement ratio (late phase/early phase ratio) and pancreatic fibrosis by histology. Statistical analysis was performed using JMP version 9 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. The demographics and clinical characteristics of our cohort are summarized in Table 1. There were 23 males and 21 females, with a mean age of 73 years (range: 44-85 years). The most frequently observed indication for DP was pancreatic ductal carcinoma (17 patients; 38.6%). Of the 44 patients, 15 patients (34.1%) developed Grade B POPF. No patient developed grade C POPF, and the postoperative mortality was 0%. Patients with grade B POPF constituted the POPF group for this study. The non-POPF group consisted of the 29 remaining patients (non-POPF or grade A POPF). Table 2 shows a comparison of the two groups. No differences were observed in sex, age, indication of surgery, drinking history, smoking history, preoperative diabetes, preoperative serum albumin level, and/or anticoagulant therapy.

Table 1 Patient characteristics

Characteristics	n = 44
Preoperative	
Mean age (years)	72.0 ± 8.2
Sex (male/female)	23/21
BMI (kg/m^2)	21.2 ± 4.2
Indication of surgery	
Pancreatic cancer	17
IPMN	13
Metastatic tumor	4
Chronic pancreatitis	2
Others (AIP, NET, trauma, GC)	8
CONUT score	1.9 ± 1.6
Drinking history	21
Smoking history	20
Preoperative serum albumin level (g/dL)	4.01 ± 0.42
Preoperative diabetes	10
Anticoagulant therapy	6
Enhanced CT values	
Late/Early ratio	0.73 ± 0.27
Unenhanced CT value	
MPD (mm)	2.9 ± 2.1
Thickness of the stump (mm)	12.6 ± 4.2
Intraoperative	
Laparoscopic surgery	7
Operative time (min)	358 ± 128
Blood loss (mL)	723 ± 90
Method of closure by Stapler	13
Transfusion	2
Postoperative	
POPF (Grade B/Grade C)	15/0
Duration of in-hospital day	32 ± 20
In-hospital mortality	0
Fibrosis (F0/F1/F2/F3)	11/15/9/7

BMI, body mass index; AIP, autoimmune pancreatitis; NET, neuroendocrine tumor; GC, gastric cancer; CONUT, controlling nutritional status; MPD, main pancreatic duct; POPF, postoperative pancreatic fistula.
Values are presented as mean ± standard deviation with 95% confidence interval or number of patients.

Intra- and perioperative findings. The mean postoperative length of hospital stay (LOS) for the POPF group was 45 ± 6 days, which was significantly longer than that of the non-POPF group with a mean LOS of 22 ± 3 days ($p = 0.005$). No differences were observed in operation time, blood loss, method of closure, diameter of the main pancreatic duct, laparoscopic surgery, transfusion, and/or thickness of the stump.

CT assessment. In the POPF group, the pancreatic parenchyma showed maximum enhancement in the pancreatic phrase and washout in the hepatic phase. In contrast, in the non-POPF group, the pancreas showed decreased enhancement in the pancreatic phase and maintained higher attenuation values in the hepatic phase, consistent with a delayed enhancement pattern. Therefore, the mean value of the L/E ratio was significantly lower in the POPF group than in the non-POPF group (0.61 ± 0.21, 95% confidence interval [CI]: 0.48-0.73 vs. 0.79 ± 0.27, 95% CI: 0.68-0.90; $p = 0.035$). The diagnostic accuracy of the L/E ratio for the occurrence of POPF was evaluated by the AUC, as shown in Fig. 2. The L/E ratio had moderate diagnostic accuracy (AUC: 0.703), with a calculated optimal cutoff value of 0.77. Using this cutoff value, the sensitivity and specificity of the L/E ratio for POPF were 0.857 and 0.593, respectively.

Univariate and multivariate analyses for POPF. The results of the univariate and multivariate analyses for POPF are shown in Table 2 and 3. A significant association was noted between POPF and each of following: stump thickness ≥ 16.9 ($p = 0.039$), BMI ≥ 27.5 ($p = 0.033$), and L/E ratio ≤ 0.77 ($p = 0.018$). The significant preoperative risk factors for POPF that were identified using the univariate analysis were incorporated into a multivariate logistic regression analysis. The

Table 2 Comparison of patient characteristics for the POPF group and non-POPF group

	POPF group (n = 15)	Non-POPF group (n = 29)	*P* value
Mean age (years)	71.3 ± 7.4	71.5 ± 8.8	0.872
Sex (male/female)	10/6	14/14	0.460
BMI (kg/m^2)	21.6 ± 4.8	20.5 ± 3.8	0.408
Indication of surgery			0.339
Pancreatic cancer	6	11	
IPMN	4	9	
Metastatic tumor	1	3	
Chronic pancreatitis	1	1	
Others (AIP, NET, trauma, GC)	3	5	
CONUT score	2.1 ± 1.9	1.8 ± 1.5	0.561
Drinking history	9	10	0.151
Smoking history	7	12	0.889
Preoperative serum albumin level (g/dL)	4.0 ± 0.4	4.0 ± 0.5	0.721
Preoperative diabetes	4	5	0.542
Anticoagulant therapy	2	3	0.721
Enhanced CT values			
Late/Early ratio	0.61 ± 0.21	0.79 ± 0.27	0.035
Unenhanced CT value			
MPD (mm)	2 ± 0.9	3.1 ± 2.5	0.642
Thickness of the stump (mm)	13.9 ± 4.3	11.7 ± 4.0	0.119
Intraoperative			
Laparoscopic surgery	2	5	0.661
Operative time (min)	348 ± 32	363 ± 26	0.732
Blood loss (mL)	724 ± 146	643 ± 91	0.628
Method of closure by Stapler	10	19	0.804
Transfusion	1	1	0.672
Postoperative			
Duration of in-hospital day	45 ± 6	22 ± 3	0.005
Fibrosis (F0/F1/F2/F3)	8/7/1/0	3/8/8/7	0.001

BMI, body mass index; AIP, autoimmune pancreatitis; NET, neuroendocrine tumor; GC, gastric cancer; CONUT, controlling nutritional status; MPD, main pancreatic duct; POPF, postoperative pancreatic fistula.
Values are presented as mean±standard deviation with 95% confidence interval or number of patients.

Table 3 Univariate and multivariate analyses: independent risk factors for POPF

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
BMI ≥ 27.5 kg/m^2	9.00 (0.907–89.26)	0.033	11.89 (0.959–341.1)	0.054
Late/Early ratio ≤ 0.77	5.33 (1.202–23.66)	0.018	5.96 (1.117–49.17)	0.036
Preoperative serum albumin level ≤ 3.8 (g/dL)	3.89 (0.731–20.68)	0.083	1.32 (0.171–12.83)	0.788
Thickness of the stump ≥ 16.9 mm	5.91 (0.991–35.21)	0.039	2.03 (0.213–22.49)	0.528

CI, confidence interval; BMI, body mass index; POPF, postoperative pancreatic fistula.

results showed that the L/E ratio (OR: 5.96; $p = 0.036$) was an independent risk factor for POPF.

Pancreatic fibrosis. The degree of fibrosis was significantly lower in the POPF group than the non-POPF group ($p = 0.001$). Pancreatic fibrosis demonstrated a weak positive correlation with the L/E ratio (Fig. 3) ($r = 0.480$; $p = 0.002$).

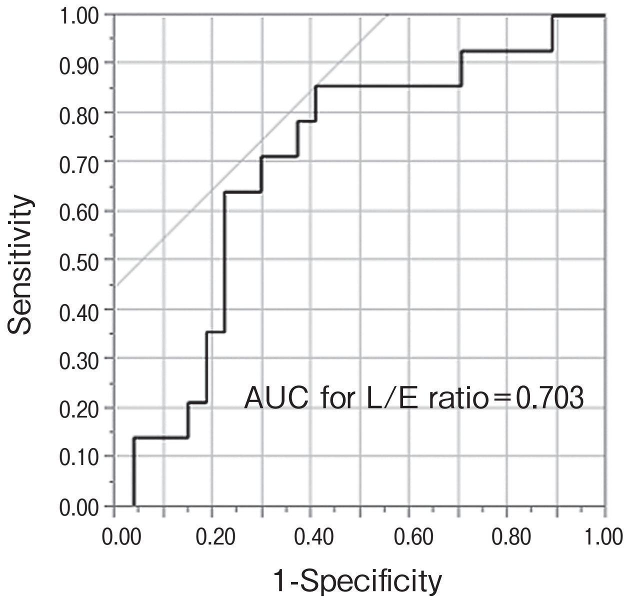

Fig. 2 Evaluation of the diagnostic accuracy of the late phase/early phase ratio (L/E ratio) for the occurrence of post-operative pancreatic fistula (POPF) by area under the curve (AUC) analysis. The L/E ratio had moderate diagnostic accuracy (AUC: 0.703), with a calculated optimal cutoff value of 0.77. Using this cutoff value, the sensitivity and specificity of L/E ratio for POPF were 0.857 and 0.593, respectively.

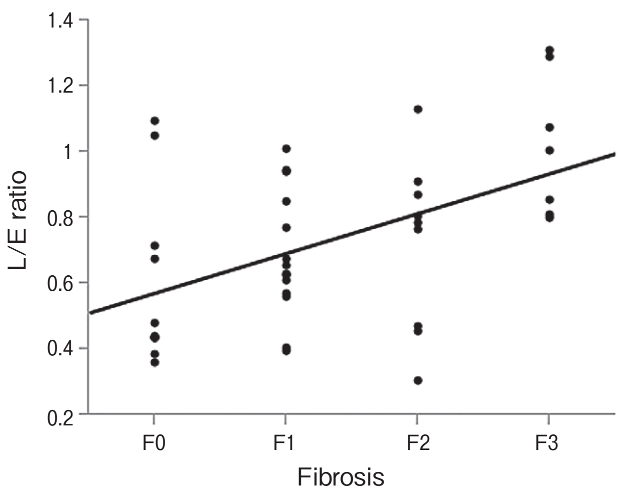

Fig. 3 Correlation between the computed tomography enhancement ratio (late phase/early phase ratio) and pancreatic fibrosis by histology (r = 0.480; P = 0.002).

Discussion

This retrospective analysis revealed that a low L/E ratio by pancreatic CT scan, indicating a soft pancreas, was an independent predictor of POPF after DP. The texture of the pancreatic parenchyma is generally considered one of the most important risk factors for the increased incidence of pancreatic fistula [2-4]. Fibrotic pancreatic tissue is considered less likely to result in pancreatic leakage. Reduced firmness of the pancreas is considered a risk factor for POPF [2-4].

Despite the importance of this parameter, pancreatic firmness assessed solely by the surgeon during surgery may not be accurate. The distinction between the end of the soft area and beginning of the firm area is obscure, and a widely accepted definition of pancreatic texture is lacking. Pancreatic fibrosis increases the firmness of the gland. Hashimoto *et al.* reported that the ratio of the mean pancreatic CT attenuation value (hepatic to pancreatic phase; L/E ratio) upstream from the tumor may assist in the histologic assessment of the degree of pancreatic fibrosis [7]. In accordance with the literature, we observed that patients with a low L/E ratio by pancreatic CT had a higher incidence of pancreatic leakage than those with a high L/E ratio, indicating fibrotic pancreatic parenchyma.

Previous studies described the utility of CT data to determine the risk of POPF after PD [7-9]. There is a difference between POPF after PD and that after DP. While POPF after PD is caused by leakage of pancreatojejunostomy, POPF after DP is caused by leakage of the stump of the remnant pancreas. We considered that the risk factors for POPF would also differ between patients post-PD and post-DP.

In our study, grade B POPF after DP occurred in 15 patients (34.1%); this incidence was higher than that in a recent report [1]. Differences in the patient populations, such as a higher proportion of elderly patients, may partly explain this discrepancy. In addition, we previously tended to place the drainage tube for a long duration regardless of infection or POPF, which may be another reason for the high incidence of POPF in this study.

Various risk factors for POPF after DP have been reported, including male [14, 15], older age [16-18], high BMI [14, 15, 17], diabetes mellitus [17, 19], cartridge size [20], pancreatic thickness [15-17], chronic pancreatitis [21], extended lymphadenectomy [18], and duration of operation [19,22]. In this study, we observed that POPF development was not affected by any patient-specific, surgical, or tumor-related factors, other than pancreatic findings as determined by CT imaging.

As mentioned above, pancreatic texture is an important factor for POPF after DP. However, it is not possible to determine the texture by intraoperative palpation alone. Although elastography using ultrasound is one way to determine preoperative pancreatic stiffness [23], it is not commonly used due to some limitations [23,24]. On the other hand, it has been shown that the L/E ratio determined by dual-phase CT scan is a good indicator of the level of fibrosis in the pancreas [7]. Considering that CT scans are more objective and more readily available, we believe that the enhancement characteristics on preoperative dual-phase pancreatic CT scans are a more reliable index of the firmness of the pancreas, and as such, of the risk of developing POPF after DP. It has been reported that a fibrotic pancreas leads to reduced exocrine activity [25] and less pancreatic juice, which may reduce the risk of POPF. Hence, determining the firmness of the pancreas preoperatively can determine the risk of developing POPF prior to DP. In our study, the histologic degree of pancreatic fibrosis showed correlation with the L/E ratio. Further, pancreatic fibrosis was associated with the occurrence of POPF after DP. Thus, these data suggest that calculating the L/E ratio may be a useful and noninvasive way to assess pancreatic fibrosis preoperatively and stratify the patients who are at a risk of POPF.

Pancreatic fibrosis is one of the characteristics of chronic pancreatitis. The risk factors of chronic pancreatitis are reported as alcohol use, smoking, and autoimmune and genetic factors [26]. We analyzed whether the preoperative clinical factors were associated with the degree of pancreatic fibrosis. However, no significant factor was associated with the L/E ratio (data not shown).

Although to the best of our knowledge, this study is the first to describe the assessment of enhancement characteristics on preoperative dual-phase pancreatic CT as a method to estimate the risk of developing POPF after DP, it has several limitations, including its retrospective design and limited sample size. Further studies are necessary to gain more insight into these associations.

In conclusions, a low L/E ratio by pancreatic CT scan was found to be an independent risk factor for POPF after DP. The results of this study suggest that the risk of clinically relevant POPF can be predicted by measuring pancreatic parenchyma CT values. Therefore, CT enhancement characteristics of the pancreas may be useful in preoperative risk stratification, patient counseling, and perioperative patient management, which will ultimately result in better clinical outcomes after DP.

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