Larger Volume and Higher Fat Content of the Pancreatic Head Are Predictive Factors for Postendoscopic Retrograde Cholangiopancreatography Pancreatitis

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Objectives: Acute pancreatitis is the most critical complication of endoscopic retrograde cholangiopancreatography (ERCP). In this study, we investigated the association between the volume/fat content of the pancreatic head and the incidence of post-ERCP pancreatitis (PEP).

Methods: We retrospectively enrolled 157 patients who underwent ERCP. The volume and fat content of the pancreas were calculated by multislice computed tomographic imaging by using a volume analyzer. Multivariate analysis was performed to identify risk factors for PEP.

Results: The mean volumes of the whole pancreas and pancreatic head were significantly larger, and the fat content of the pancreatic head was significantly higher in the PEP group ($P < 0.01$). There were no significant differences in the mean volume and fat content of the pancreatic body and tail in the PEP group. Multivariate analysis revealed that the pancreatic guidewire placement (odds ratio [OR], 12.4; $P < 0.01$), pancreatic head volume (OR, 5.3; $P < 0.01$), and the pancreatic head fat content (OR, 4.8; $P < 0.01$) were independent risk factors for PEP.

Conclusions: The pancreatic head volume and fat content were independent predicting factors of PEP. Quantitative assessment of the pancreas may contribute to the prediction of PEP onset.

Key Words: ERCP, post-ERCP pancreatitis, acute pancreatitis, pancreatic volumetry, pancreatic histogram

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Acute pancreatitis is the most common and serious complication of endoscopic retrograde cholangiopancreatography (ERCP). The incidence rate of post-ERCP pancreatitis (PEP) reportedly ranges from 2.6% to 15.1%.[1–3] Risk factors for PEP are classified as patient-related and endoscopist- or technique-related factors. Patient-related factors include female sex, young age, history of pancreatitis, and sphincter of Oddi dysfunction. Endoscopist- or technique-related factors include difficult cannulation, sphincterotomy, and contrast media injection into the pancreatic duct.[1,2,4–7]

Evaluation of pancreatic volume is of great importance in clinical practice.[8] For example, alterations in pancreatic volume have been reported to be associated with pathological conditions of pancreatic endocrine or exocrine function.[9] Pancreatic volume can be used as a predictor of long-term outcomes or the prevalence of organ-specific diseases after resection of the pancreas.[10,11] Recently, Maruyama et al[12] reported a correlation between whole pancreatic volume and risk of PEP. They identified a large pancreatic volume as a risk factor for PEP.

The pancreatic fat content can be evaluated by analyzing pancreatic attenuation on unenhanced computed tomography (CT).[13] A more sophisticated evaluation involves histogram analysis to quantify the percentage of fat.[13] Hong et al[14] demonstrated that measurement of pancreatic fat content was a useful marker for predicting the formation of pancreatic fistula. Fujisawa et al[15] reported that obesity could be a risk factor for PEP and noted in their obesity group that an excess of subcutaneous adipose tissue might be an especially important factor related to PEP incidence. However, the relationship between pancreatic fat content and the incidence of PEP remains unclear.

Woods et al[16] previously reported that 42% of PEP was located in the pancreatic head rather than in diffuse pancreatic parts. The technique-related reasons for this specificity may be the transpapillary procedures and cannulation trauma of the papilla. However, patient-related factors focused on the pancreatic head have not been investigated previously. In this study, we used 3-dimensional (3D) volumetry, and histogram investigated the potential association of pancreatic head volume and fat content with the incidence of PEP.

MATERIALS AND METHODS

Patients

We retrospectively analyzed 840 patients who underwent ERCP at Shiga University of Medical Science Hospital from January 2016 to February 2020. The reasons for performing ERCP were extraction of choledocholithiasis, biliary drainage, and diagnosis of biliary stricture. The exclusion criteria were as follows: lack of an abdominal CT scan within 3 months before the ERCP procedure, patients with manipulated duodenal papilla, procedures with sphincterotomy, history of sphincterotomy, procedures with balloon endoscopy–assisted ERCP (Billroth II gastrectomy, Roux-en-Y reconstruction), diseases with main pancreatic duct dilatation or a difficult to calculate pancreatic volume (pancreatic cancer, intraductal papillary mucinous neoplasm, biliary pancreatitis, chronic pancreatitis), post- ERCP hyperamylasemia, age younger than 20 years, or pregnancy. Sixty patients were excluded because of a lack of contrast-enhanced CT data. Finally, we evaluated 157 patients (Fig. 1). All patients provided written informed consent before undergoing ERCP. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Shiga University of Medical Science (number R2020-145).

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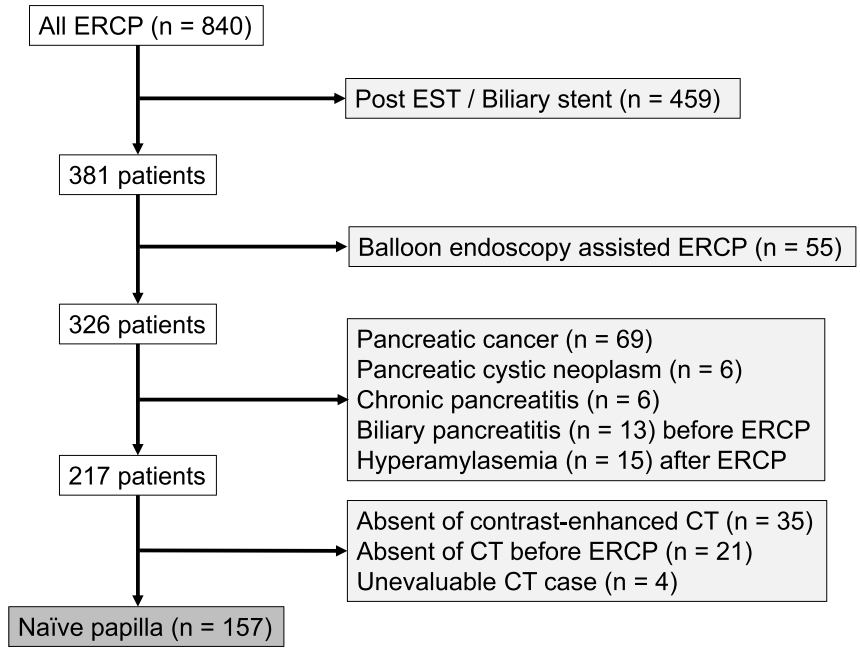


FIGURE 1. Flow diagram. There were 840 patients who received ERCP. We excluded 683 patients with histories of sphincterotomy in 459 patients, procedure with balloon endoscopy assisted ERCP in 55 patients, diseases with main pancreatic duct dilatation or difficult to calculate pancreatic volume (pancreatic cancer, and intraductal papillary mucinous neoplasm, biliary pancreatitis, chronic pancreatitis) in 94 patients, post-ERCP hyperamylasemia in 15 patients, and lack of evaluable CT data in 60 patients. Finally, we evaluated 157 patients.

ERCP Procedures

A combination of midazolam, pentazocine, and dexmedetomidine was used for conscious sedation in all patients. Endoscopic retrograde cholangiopancreatography was performed by using a side-viewing duodenoscope JF260V (Olympus Optical Co, Tokyo, Japan) and an ERCP guide wire Visiglide2 (Olympus Optical Co). A pancreatic duct stent (Geenen 5Fr; Cook Medical, Tokyo, Japan) was placed if the operator required it. An emergency procedure was defined as ERCP performed within 24 hours of admission. Gabexate mesylate (100 mg) was administrated before ERCP in all patients. The infusion volumes ranged from 1500 to 2000 mL in all patients. The use of nonsteroidal anti-inflammatory drugs was determined at the discretion of the physician.

Definition of PEP and Hyperamylasemia

Post-ERCP pancreatitis was diagnosed according to the criteria of Cotton et al,[4] which consist of a rise in serum amylase ≥3-fold above the upper limit of normal along with abdominal pain 24 hours after ERCP that requires >1 additional night of hospital stay. Patients with serum amylase elevation but no abdominal symptoms were diagnosed with hyperamylasemia. We modified the criteria used for the severity of pancreatitis from the extension of hospital stay to the number of days required to start fasting after PEP onset, referring to the classification of Cotton et al[4] and the report of Maruyama et al.[12]

CT Procedures and Pancreatic Volumetry/Histogram

Pancreatic volume was measured by using contrast-enhanced images obtained by continuous 5.0-mm, 320-, 64-row detector CT (Aquilion ONE; Canon Medical Systems, Tochigi, Japan) before ERCP. Computed tomography scan images of precontrast and venous phase were used for evaluation. Computed tomography images were downloaded as digital images to a computer workstation (SYNAPSE; Fujifilm Medical Systems, Tokyo, Japan). Pancreatic volume was determined by using 3D analysis software (Aquarius iNtuition v4.4.12; TeraRecon, Foster, Calif). Pancreatic volume was calculated by selecting the region of interest in the pancreatic parenchyma after manually removing peripancreatic adipose tissue and blood vessels. The pancreas was divided into the head and body/tail using the left edge of the superior mesenteric-portal vein confluence as an index,[17] and the volume of each part was calculated separately (Fig. 2).

Hounsfield unit histogram analysis (HUHA) was performed by using precontrast images and determined by using 3D analysis software. Hounsfield unit histogram analysis has been reported as a qualitative assessment of pancreatic components.[14,18] The percentage of HUHA ≤0 Hounsfield unit (HU) in pancreatic parenchyma represented the fat content. Histograms were automatically constructed by using precontrast CT images. The region of interest was set as a 1-cm-diameter circle at 2 sites in the pancreas: the right edge of the superior mesenteric-portal vein confluence (pancreatic head) and the center of the pancreatic body and tail (pancreatic body/tail)[14] (Fig. 3).

One expert gastroenterologist who was blinded to the clinical information independently assessed all CT images.

Statistical Analysis

Continuous variables related to the baseline characteristics of the 2 groups were compared by using Student *t* test or the Wilcoxon rank sum test. Categorical variables were compared by using the χ^2 or Fisher exact test. Receiver operating characteristic analysis was performed to calculate cutoff values for pancreatic volume and HUHA (<0) ratio. Logistic regression analysis was performed to estimate the risk of PEP. After univariate analysis, all variables with *P* values of <0.10 were included in the multivariate analysis. $P < 0.05$ was considered to be indicative of

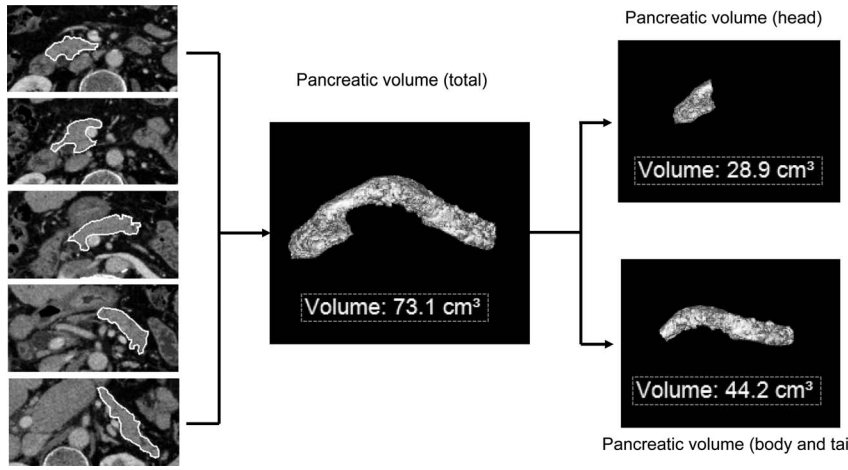


FIGURE 2. Measurement of pancreatic volume. Axial images of contrast-enhanced CT of 5-mm slices were analyzed. The pancreatic parenchyma was manually set to a free region of interest in each slice, and the volume was automatically measured by software. The volume was then calculated by dividing the whole pancreas into the head and the body to tail at the left edge of the portal vein.

statistical significance. All statistical analyses were performed by using EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and Prism version 6.05 (GraphPad, San Diego, Calif).

RESULTS

Of the 157 cases analyzed, PEP occurred in 35 cases. There were no significant differences in patient characteristics between the PEP and non-PEP groups (Table 1). The average length of hospital stay was significantly longer in the PEP group than in the non-PEP group (14.2 [standard deviation {SD}, 10.7] vs 9.2 [SD, 5.9]) ($P = 0.008$). The success rate of biliary cannulation was significantly higher in the non-PEP group (119 of 122 [97.5%] vs 31 of 35 [88.6%]) ($P = 0.04$). The use of biliary cannulation with pancreatic guide wire methods was significantly higher in the PEP group (17 of 35 [48.6%] vs 28 of 122 [23.0%]) ($P < 0.01$). There were no differences in other ERCP procedures or purposes between the 2 groups (Table 2). Severity of PEP was mild in 32 patients (91.4%) and moderate in 3 patients (8.6%), and there was no patient with severe pancreatitis.

The whole pancreatic volume was significantly larger in the PEP group than in the non-PEP group (57.3 [16.3] cm^3 vs 45.2 [16.5] cm^3) ($P < 0.001$) (Table 3). The volume of the pancreatic head was significantly larger in the PEP group than in the non-PEP group (29.9 [10.8] cm^3 vs 20.1 [9.6] cm^3) ($P < 0.0001$). However, there was no significant difference in the pancreatic body and tail volume between the 2 groups.

The percentage of HUHA <0 HU of the pancreatic head was significantly higher in the PEP group than in the non-PEP group (5.8% [5.7%] and 3.1% [3.4%]) ($P < 0.01$). On the other hand, there was no significant difference in the percentage of HUHA <0 HU of the pancreatic body/tail between the PEP and non-PEP groups (Table 3). There was no correlation between the severity of pancreatitis and pancreatic volume (head, body, and tail) or percentage of HUHA <0 of the pancreatic head ($P = 0.24$, 0.10, and 0.98, respectively). The changes in amylase levels before and after ERCP were significantly associated with pancreatic head volume ($P = 0.001$), but not with pancreatic body tail volume ($P = 0.97$) or the fat content ($P = 0.92$).

The cutoff value for predicting PEP of the pancreatic head volume was 27.1 cm^3 (sensitivity, 62.3%; specificity, 78.7%; area under the curve, 0.783). The cutoff value of HUHA <0 HU for predicting PEP was 4.95% (sensitivity, 51.4%; specificity, 74.6%; area under the curve, 0.639) (Fig. 4).

Table 4 shows the results of univariate and multivariate analysis of risk factors for PEP. The multivariate analysis indicated that

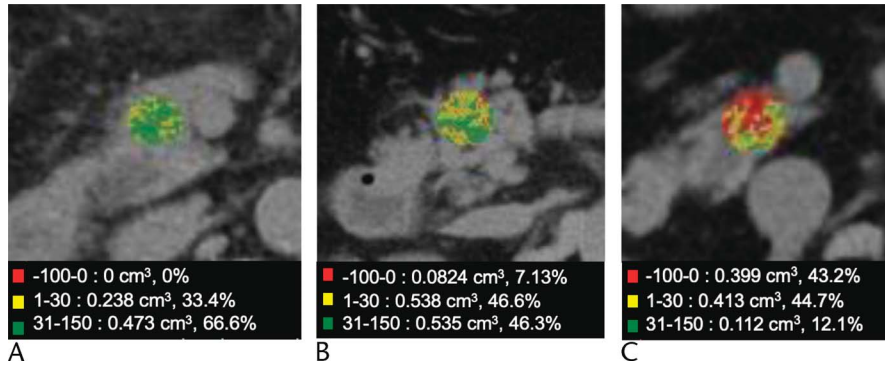


FIGURE 3. Hounsfield unit histogram analysis of pancreatic parenchyma. The HUHA of the pancreas was evaluated on precontrast CT images prior to ERCP. The HUHA was measured automatically by software. The region of interest was set as a 1-cm diameter circle at two sites in the pancreas, the right edge of the superior mesenteric-portal vein confluence (pancreatic head) and at the center of the pancreatic body and tail. Histogram analysis of a 65-year-old man (A) and a 67-year-old man (B), who did not have PEP showed that the contents of HUHA ≤0 HU were 0% and 7.1%, respectively. C, An 85-year-old man who developed PEP, had 43.2% HUHA ≤0 HU.

TABLE 1. Patient Characteristics

	PEP Group (n = 35)	Non-PEP Group (n = 122)	*P*
Age, median (range), y	72.0 (22–88)	74.0 (34–97)	0.61
Sex, male, n (%)	17 (48.6)	74 (60.7)	0.25
BMI, mean (SD), kg/m^2	23.0 (3.5)	22.9 (3.2)	0.49
ASA 1/2/3, n	6/29/0	21/98/3	1
Primary disease, n (%)			
Choledocholithiasis	20 (57.1)	80 (65.6)	0.43
Cholangiocarcinoma	7 (20.0)	19 (15.6)	0.61
Benign biliary stricture	3 (8.6)	6 (4.9)	0.42
Other	5 (14.3)	17 (13.9)	1
Hypertension, n (%)	21 (60.0)	73 (59.8)	1
Diabetes mellitus, n (%)	7 (20.0)	26 (21.3)	1
Dyslipidemia, n (%)	16 (45.7)	37 (30.3)	0.11
Drinking history, n (%)	12 (34.3)	55 (45.1)	0.33
Anticoagulant, n (%)	10 (28.6)	37 (30.3)	1
Acute cholangitis, n (%)	13 (37.1)	50 (45.1)	0.85
Obstructive jaundice, n (%)	17 (48.6)	66 (54.1)	0.57
Laboratory data, median (range)			
Hemoglobin, g/dL	12.7 (7.8–15.9)	12.2 (5.9–18.3)	0.69
WBCs count, 10^3/mm^3	6.0 (2.9–17.2)	5.8 (0.7–35.1)	0.54
Platelet count, 10^3/mm^3	232 (51–397)	207 (4.9–638)	0.84
Albumin, g/dL	3.6 (2.3–4.9)	3.6 (0.99–4.5)	0.27
AST, IU/L	64 (11–1892)	62 (12–2006)	0.23
ALT, IU/L	65 (7–514)	78.5 (6–1905)	0.42
LDH, IU/L	208 (134–1191)	200 (113–1111)	0.41
Total serum bilirubin, mg/dL	1.3 (0.5–22)	1.3 (0.34–30.8)	0.61
BUN, mg/dL	14.4 (5.1–40)	15.4 (3.3–45.1)	0.46
Creatinine, mg/dL	0.7 (0.4–6.3)	0.8 (0.4–19.5)	0.31
CRP, mg/dL	0.9 (0.02–29)	0.6 (0.02–24.1)	0.85
Total serum amylase, U/L	67.0 (28–225)	78.0 (23–338)	0.23
Hospital stays, mean (SD), d	14.2 (10.7)	9.2 (5.9)	<0.01

BMI indicates body mass index; ASA, American Society of Anesthesia classification[19]; WBCs, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; CRP, C-reactive protein.

use of the pancreatic guide wire method (odds ratio [OR], 4.8; 95% confidence interval [CI], 1.8–12.8; $P < 0.01$), pancreatic head volume (≥27.1 cm^3) (OR, 12.4; 95% CI, 4.6–32.9; $P < 0.01$), HUHA <0 of pancreatic head (≥4.95%) (OR, 5.3; 95% CI, 2.0–14.2; $P < 0.01$) were independent risk factors for PEP.

DISCUSSION

The present study demonstrated that larger volume and higher fat content of the pancreatic head were strongly correlated with PEP onset. Multivariate analysis showed that these characteristics were independent risk factors predicting PEP.

The pathophysiology of PEP has not been clearly identified, but PEP is considered to be a multifactorial condition that involves a combination of chemical, mechanical, enzymatic, allergic, and microbial factors.[5] Cannulation trauma and hydrostatic injury caused by overfilling of the pancreatic duct with high osmolarity contrast material induce intracellular activation of proteolytic enzymes, autodigestion, and the release of inflammatory cytokines.[5] Among the pathogenic factors of PEP, cannulation trauma of the papilla is the most common cause of sphincter of Oddi spasm and edema of the papilla, leading to a disturbance of pancreatic juice flow and subsequent acute pancreatic inflammation.[20] Woods et al[16] reported that 42% of PEP occurred in the pancreatic head, which may reflect traumatic and hydrostatic injury around the papilla caused by ERCP procedure.

Recently, the association between pancreatic volume and pancreatic disease has been reported.[21–23] Concerning PEP, Maruyama et al[12] recently showed that a larger total pancreatic volume increased the incidence of PEP. We also observed that the total pancreatic volume was significantly larger in the PEP group than in the non-PEP group and the cutoff value predicting PEP was 45.7 mm^3. A further important finding to emphasize here is that a significant difference was detected only in the pancreatic head volume and not in the body and tail volume. This finding indicates that pancreatic head volume was a better predictive factor for PEP than the total pancreatic volume. The cutoff value predicting PEP was 27.1 mm^3 of the pancreatic head. The reason why a larger pancreatic or head volume is associated with higher incidence of PEP remains unclear. It has been previously reported that chronic pancreatitis protects patients from PEP,[24,25] which may be due to a smaller volume of functional pancreatic parenchyma. This is supported by the findings of Acharya et al[26] showing that increased fibrosis and decreased parenchyma were associated with the severity of acute or chronic pancreatitis. A larger pancreatic volume will have a greater number of functional

TABLE 2. Comparison of ERCP Procedure Between PEP and Non-PEP Group

	PEP Group (n = 35)	Non-PEP Group (n = 122)	*P*
Indication of ERCP, n (%)			
Stone extraction	15 (42.9)	56 (45.9)	0.85
Biliary drainage	14 (40.0)	45 (36.9)	0.84
Diagnosis	6 (17.1)	21 (17.2)	1
Emergency case, n (%)	17 (48.6)	58 (47.5)	1
Trainee for starter, n (%)	20 (57.1)	61 (50.0)	0.57
NSAIDs use	3 (8.6)	7 (5.7)	0.83
Success rate of biliary cannulation, n (%)	31 (88.6)	119 (97.5)	0.04
Procedure time, mean (SD), min	43.4 (21.7)	43.6 (19.1)	1
Biliary cannulation with PGW method, n (%)	17 (48.6)	28 (23.0)	<0.01
ERCP procedure, n (%)			
EST	19 (54.3)	77 (63.1)	0.45
EPBD	4 (11.4)	14 (11.4)	1
EPLBD	2 (5.7)	2 (1.6)	0.22
IDUS	14 (40.0)	35 (28.7)	0.29
Biliary biopsy	1 (2.9)	3 (2.5)	1
Cytology with brush	0	4 (3.3)	0.58
Pancreatic duct stenting	6 (17.1)	7 (5.7)	0.07

NSAIDs indicates nonsteroidal anti-inflammatory drugs; PGW, pancreatic duct guide wire; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation; EPLBD, endoscopic papillary large balloon dilation; IDUS, intraductal ultrasound sonography.

parenchymal or acinar cells. A greater number of cells forming a larger volume might be injured and activated by the ERCP procedure, leading to a high incidence of PEP.

A previous study demonstrated that an excess subcutaneous fat accumulation is a risk factor for PEP,[15] but the relationship between pancreatic fat content and the incidence of PEP remains unclear. In this study, we found that a higher pancreatic head fat content was closely associated with the occurrence of PEP. Adipose tissue secretes various proinflammatory cytokines, such as tumor necrosis factor α and interleukin 6, and plays a role in the pathogenesis of tissue inflammation and metabolic disorders such as obesity and diabetes mellitus.[27,28] Mathur et al[29] reported that a fatty pancreas may be more prone to pancreatitis and that this process is mediated by the first attack of fat accumulation and the second hit of oxidative stress.[29] In this study, differences in fat content were observed between pancreatic head and tail. Matsumoto et al[30] reported uneven fatty replacement of the pancreas, which is associated with obesity and dyslipidemia, and fatty changes were observed only in the pancreatic head. In patients with high fat content of the pancreatic head, ERCP might easily trigger local inflammation and lead to PEP.

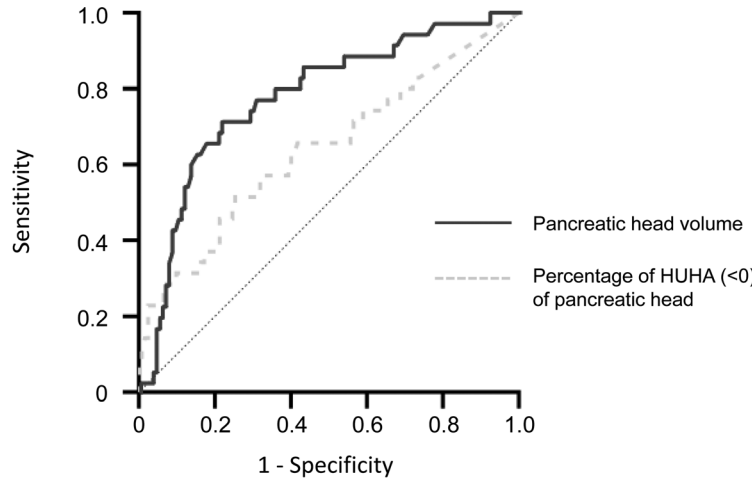
To our knowledge, the current study is the first report to state that a large volume and high fat content of the pancreatic head increase the risk of PEP. Multivariate analysis revealed a larger volume and higher fat content of the pancreatic head to be independent risk factors for PEP. Identification of patient-related predisposing factors of PEP is therefore important to facilitate preprocedural preventive stratification and interventions, which may reduce the incidence of PEP. Our observations might be helpful for developing strategies for PEP prophylaxis such as pancreatic duct stenting, use of rectal nonsteroidal anti-inflammatory drugs, and use of aggressive hydration during and after ERCP.[31]

Despite the clinical implications, there were some limitations that should be considered. First, this was a retrospective analysis of a relatively small number of samples in a single center. Second, the enrolled patients were treated with different therapeutic procedures of ERCP. Although there were no significant differences in the patients' demographic data between the PEP and non-PEP groups, the possibility that different purposes and/or treatment affected the results cannot be discounted. The frequency of PEP was higher than previously reported because the analysis excluded some groups, such as patients who underwent previous endoscopic sphincterotomy or biliary stenting. Third, we did not evaluate pancreatic exocrine function, which might have helped to estimate functional pancreatic parenchyma. We did not evaluate the number of times the guide wire passed through the pancreatic duct, which might have influenced the incidence of PEP. In the future, our findings should be replicated and confirmed in prospective, multicenter, randomized trials with larger numbers of

TABLE 3. Correlation of CT Parameters Between the PEP and Non-PEP Groups

	PEP Group (n = 35)	Non-PEP Group (n = 122)	*P*
Pancreatic parenchymal diameter, mean (SD), mm			
Head	24.1 (4.8)	23.0 (4.0)	0.15
Body and tail	14.8 (3.1)	14.2 (3.1)	0.35
Pancreatic volume, mean (SD), cm^3			
Total	57.3 (16.3)	45.2 (16.5)	<0.001
Head	29.9 (10.8)	20.1 (9.6)	<0.0001
Body and tail	27.4 (7.7)	25.1 (8.7)	0.17
Percentage of HUHA <0 HU, mean (SD), %			
Head	5.8 (5.7)	3.1 (3.4)	<0.01
Body and tail	3.0 (5.4)	3.2 (9.1)	0.93
VAT, mean (SD), cm^2	109.5 (45.6)	114.9 (67.1)	0.66
SAT, mean (SD), cm^2	146.3 (76.3)	127.3 (65.7)	0.15
Abdominal circumference, mean (SD), cm	81.2 (8.7)	79.9 (11.7)	0.53

VAT indicates visceral adipose tissue; SAT, subcutaneous adipose tissue.



Parameters	AUC	Cutoff	Sensitivity	Specificity
Pancreatic head volume	0.783	27.1 cm^3	62.3%	78.7%
Percentage of HUHA <0 of pancreatic head	0.639	4.95%	51.4%	74.6%

FIGURE 4. Receiver operating characteristic curves of prediction parameters for PEP onset. Pancreatic head volume (black line) and HUHA <0 (gray dashed line).

TABLE 4. Risk Factors for PEP Identified by Univariate and Multivariate Analysis

	Univariate Analysis		Multivariate Analysis	
Parameters	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age	1.0 (0.96–1.0)	0.61		
Sex, female	1.6 (0.7–3.7)	0.25		
Use of PGW method	3.1 (1.3–7.5)	<0.01	4.8 (1.8–12.8)	<0.01
Pancreatic volume, head	9.1 (3.7–24.0)	<0.0001	12.4 (4.6–32.9)	<0.01
Pancreatic volume, body and tail	2.5 (0.93–8.0)	0.06		
Percentage of HUHA <0, pancreatic head	3.1 (1.3–7.3)	<0.01	5.3 (2.0–14.2)	<0.01
Percentage of HUHA <0, pancreatic body and tail	1.8 (0.7–4.6)	0.23		

PGW indicates pancreatic duct guide wire.

patients. In addition, it would be desirable to define the interaction between pancreatic volume/fat content and specific PEP prophylactic treatments.[31]

In conclusion, we demonstrated that a larger volume and a higher fat content of the pancreatic head were independent factors predictive of PEP. These novel patient-related risk factors for PEP may be helpful for adapting prophylactic measures to specific patient comorbidities.

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