Original Article

Clinical, Radiological, and Endosonographic Features to Predict Severe Pancreatic Exocrine Insufficiency in Patients with Chronic Pancreatitis: A Cross-Sectional Study

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Background: Severe pancreatic exocrine insufficiency [PEI] is an important consequence of chronic pancreatitis [CP], causing maldigestion and malnutrition. However, the necessary diagnostic tools are usually unavailable or impractical.

Objective: To identify and evaluate the diagnostic performance of clinical, radiological, and endosonographic [EUS] features to diagnose severe PEI in patients with CP.

Materials and Methods: All patients with CP were tested with fecal elastase-1 [FE-1] and then divided into severe PEI (FE-1 <15 µg/g) and non-severe PEI (FE-1 ≥15 µg/g). Clinical, radiological, and endoscopic data were collected and compared. Features associated with severe PEI were identified by univariate and multivariate analyses and their diagnostic accuracy was calculated.

Results: The present study enrolled 49 CP patients, 27 (55%) with severe PEI. The patients' clinical characteristics were similar except history of visible steatorrhea was more common in severe PEI than in non-severe PEI (37% versus 9.1%, $p = 0.024$). Computed tomographic findings of pancreatic atrophy were more common in severe PEI (78.2% versus 50%, $p = 0.050$). The total number of EUS features were significantly higher in severe PEI (5.3±1.6 versus 3.8±1.4, $p = 0.025$). All patients with 7 EUS or more features had severe PEI, and none of those with less than three EUS features had severe PEI.

Conclusion: Steatorrhea, pancreatic atrophy on computed tomography [CT] and the number of EUS features of CP were associated and predictive of severe PEI. Seven or more EUS features indicated severe PEI, while less than three EUS features ruled out severe PEI.

Keywords: Chronic pancreatitis, Endoscopic ultrasonography, Fecal elastase, Pancreatic exocrine insufficiency, Predictor

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Pancreatic exocrine insufficiency [PEI] is a long-term consequence of chronic pancreatitis [CP] and can be found during initial presentation in 75% of patients[1]. The severity of PEI can be classified as mild to moderate PEI, and severe PEI. In mild to moderate PEI, the pancreatic enzyme output is lower than normal (range 10% to 99% of normal), but sufficient function remains to maintain normal digestion[2]. This degree of severity is not clinically important. In contrast, severe PEI, in which pancreatic enzyme output is less than 10% of normal, can cause fat maldigestion, steatorrhea, and malnutrition[2-4]. However, some patients with severe PEI are subclinical and have only vitamin and micronutrient deficiency[2].

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The consequences of symptomatic severe PEI are obvious, while those of subclinical severe PEI (enzyme output less than 10% but no obvious symptom) are less clear. However, it has been shown recently that CP patients with subclinical severe PEI had deficiencies in micronutrients, trace elements, and fat-soluble vitamins and might have increased risk of premature atherosclerosis and cardiovascular diseases[5]. Therefore, early detection and treatment of severe PEI, either symptomatic or subclinical, is critical[2].

Currently, diagnosing severe PEI is usually impractical. Quantitative 72-hour fecal fat measurement by van de Kamer's method[6] is the gold standard for diagnosing steatorrhea, which indicates the presence of severe PEI. However, the method is awkward and impractical. Direct (tube) pancreatic function tests [PFT] (secretin or cholecystokinin stimulation tests) are labor-intensive and invasive. All indirect PFTs are usually insensitive. However, two indirect PFTs have

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gained acceptance for diagnosing severe PEI and they are the ^{13}C-mixed triglyceride [MTG] breath test[7] and the fecal elastase-1 [FE-1] assay[8,9]. The ^{13}C-MTG breath test is accurate and practical but still unavailable in many countries. FE-1 is a good diagnostic tool for severe PEI[8-12]; using a cut-off of less than 15 µg/g of stool. FE-1 has a 93% sensitivity and 82% specificity for severe PEI[9].

In many developing countries, quantitative fecal fat measurement, ^{13}C-MTG breath test, and the FE-1 test are unavailable outside the medical schools. Therefore, the only available method to diagnose severe PEI is a history of steatorrhea. Qualitative stool Sudan III staining is used frequently in clinical practice despite the low sensitivity. Another approach is to use pancreatic morphological findings to predict severe PEI and a small number of studies have shown that computed tomography [CT][13], endoscopic retrograde cholangiopancreatography [ERCP][13], and endoscopic ultrasonography [EUS][14] may be useful in this regard. The combination of detailed clinical, radiological, and EUS findings may be an option to predict severe PEI in CP patients.

The aim of the present study is to determine the clinical, radiological, and EUS findings that help predict the presence of severe PEI in patients with CP.

Materials and Methods

Study population and design

Between May 2013 and May 2014, all patients with CP attended and followed-up at the Division of Gastroenterology, Siriraj Hospital, Bangkok, Thailand were prospectively enrolled. Eligible patients had CP and were 18-years-old or older. All participants provided written informed consent before enrollment and the study was approved by the Siriraj Institutional Review Board.

Diagnosis of CP

The diagnosis of CP was based on patients' clinical presentations and imaging studies according to the Cambridge Classification for CT scans and ERCP[15,16], Rosemont Classification for EUS[17], and plain abdominal radiographs showing pancreatic calcifications, a protocol that has been recently endorsed by the American Pancreatic Association Practice Guidelines[18].

Diagnosis of severe PEI

The FE-1 was used as the gold standard for the diagnosis of severe PEI in the present study. FE-1 levels were measured by ELISA (Schebo® pancreatic elastase 1, Schebo Biotech AG, Giessen, Germany). The lower limit of detection was 15 µg/g of stool and the upper limit of detection was 500 µg/g of stool. PEI was classified to severe PEI (FE-1 as 15 µg/g or less of stool) and non-severe PEI (FE-1 more than 15 µg/g of stool) according to a previous study in non-operated CP patients[9].

CT, ERCP, and EUS findings

All CT findings were reviewed by one of the investigators (Pongprasobchai S) who is a pancreatologist and who was blinded to the FE-1 results. In cases of a conflicting opinion between the investigator's reading and the original radiological report, a third person, a specialized gastrointestinal radiologist, was consulted for the final opinion and to reach consensus. ERCP and EUS findings were also reviewed by the same investigator. In cases of conflicting results between the investigator and the original endoscopic reports, additional endosonographer (Prachayakul V or Pausawasdi N) was consulted to reach consensus.

Data collection and outcome measurement

The authors collected patients' demographic data and imaging and endoscopic findings. The primary outcomes for the study were the prevalence of severe PEI in CP patients, and the clinical, radiological, and EUS features associated with the presence of severe PEI.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (IBM SPSS Statistics, version 20.0, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, or median for non-normal distributions. To compare between groups, Student's t-test, or the Mann-Whitney U-test were used for continuous data and the Chi-square or Fisher's exact test were used for categorical data. A *p*-value of 0.05 or less was considered statistically significant. Sensitivity, specificity, positive likelihood ratios [LR+], negative likelihood ratio [LR-], positive predictive value [PPV], and negative predictive value [NPV] of the significant predictors to diagnose severe PEI were calculated and expressed in percent and 95% confidence interval [CI].

Results

Patient characteristics

Of the 51 potential participants, 49 were eligible

Table 1. Participants' clinical characteristics according to the severity of pancreatic exocrine insufficiency

Characteristics	All patients (n = 49)	Severe PEI		*p*-value
		No (n = 22)	Yes (n = 27)	
Age (years), mean ± SD	51.8±13.9	50.6±15.0	52.9±13.1	0.577
Male, n (%)	39 (79.6)	19 (86.4)	20 (74.1)	0.478
BMI (kg/m^2), mean ± SD	20.5±4.0	21.7±4.2	19.5±3.6	0.057
Smoking, n (%)				
No	19 (39.6)	10 (45.5)	9 (34.6)	0.444
Yes	20 (41.7)	7 (31.8)	13 (50.0)	0.203
Ex-smoker	9 (18.8)	5 (22.7)	4 (15.4)	0.713
Etiology of CP, n (%)				
Alcoholic	34 (69.4)	15 (68.2)	19 (70.4)	0.869
Early-onset idiopathic	8 (16.3)	5 (22.7)	3 (11.1)	0.440
Late-onset idiopathic	5 (10.2)	2 (9.1)	3 (11.1)	1.000
Tropical pancreatitis	1 (2.0)	0 (0.0)	1 (3.7)	1.000
Hypercalcemia	1 (2.0)	0 (0.0)	1 (3.7)	1.000
Symptoms and complications, n (%)				
Duration (months), median (range)	71 (1 to 456)	38.5 (1 to 360)	72 (4 to 456)	0.026
Recurrent acute pancreatitis	20 (40.8)	10 (45.5)	10 (37.0)	0.551
Chronic abdominal pain	26 (53.1)	12 (54.5)	14 (51.9)	0.851
Chronic diarrhea/malabsorption	10 (20.4)	3 (13.6)	7 (25.9)	0.478
Weight loss	12 (24.5)	3 (13.6)	9 (33.3)	0.111
Visible steatorrhea	12 (24.5)	2 (9.1)	10 (37.0)	0.024
Pancreatic pseudocyst	10 (20.4)	3 (13.6)	7 (25.9)	0.478
Inflammatory head mass	6 (12.2)	3 (13.6)	3 (11.1)	1.000
CBD stenosis	5 (10.2)	1 (4.5)	4 (14.8)	0.362
Pseudoaneurysm	2 (4.1)	1 (4.5)	1 (3.7)	1.000
Asymptomatic	2 (4.1)	1 (4.5)	1 (3.7)	1.000
Underlying disease, n (%)				
Cirrhosis	7 (14.3)	2 (9.1)	5 (18.5)	0.436
Diabetes	27 (55.1)	10 (45.5)	17 (63.0)	0.220
Insulin-dependent diabetes	15 (30.6)	5 (22.7)	10 (37.0)	0.280
Hypertension	11 (22.4)	6 (27.3)	5 (18.5)	0.510
Hyperlipidemia	11 (22.4)	5 (22.7)	6 (22.2)	1.000
Coronary artery disease	2 (4.1)	1 (4.5)	1 (3.7)	1.000
Chronic kidney disease	2 (4.1)	1 (4.5)	1 (3.7)	1.000

BMI = body mass index; CBD = common bile duct; CP = chronic pancreatitis; PEI = pancreatic exocrine insufficiency; SD = standard deviation

and enrolled in the study. Two patients were excluded because of incomplete information. Patients' baseline characteristics are shown in Table 1. The mean age was 51.8 years and 39 (79.6%) were male. The common etiologies were alcoholic CP (69.4%), followed by idiopathic CP (26.5%). Common clinical manifestations were chronic abdominal pain (53.1%), recurrent acute pancreatitis (40.8%), and weight loss or steatorrhea (24%). More than half of the patients (55.1%) had diabetes.

FE-1 and the prevalence of severe PEI

The FE-1 levels were consistent with severe PEI in 27 patients (55.1%) and non-severe PEI in 22 patients (44.9%). The distribution of the FE-1 levels in all patients is shown in Figure 1.

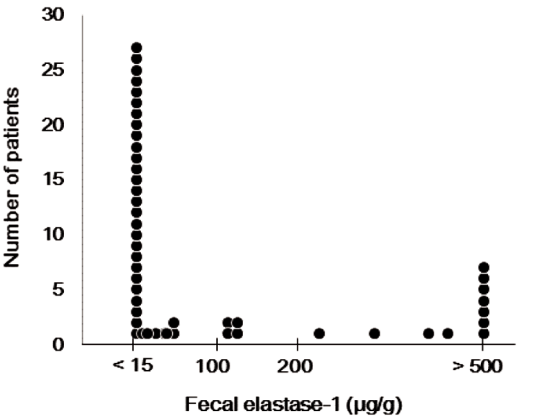

Figure 1. Fecal elastase-1 [FE-1] levels in the 49 participants. Twenty-seven patients had FE-1 levels <15 µg/g and were classified as having severe pancreatic exocrine insufficiency.

Clinical predictors of severe PEI

Patients with and without severe PEI had almost

similar demographics, etiologies, symptoms, and comorbid illnesses (Table 1). Steatorrhea was the only feature associated with severe PEI (37% versus 9.1%, $p = 0.024$). Two patients without severe PEI also had steatorrhea (FE-1 17.9 and 87.9 µg/g). The former case almost reached the cut-off level for severe PEI and the latter case had previous double bypass surgery (choledochojejunostomy and gastrojejunostomy).

The presence of diabetes and insulin-dependent diabetes were not associated with the presence of severe PEI.

Imaging predictors of severe PEI

The image study findings are shown in Table 2. Plain abdominal radiography was performed in 28 patients (57%) and CT scan in 44 patients (90%). Pancreatic calcifications on plain abdominal radiographs did not differ between patients with or without severe PEI (73.3% versus 88.9%, $p = 0.630$). From CT scan, 80% of the patients had severe CP according to the Cambridge Classification. However, only pancreatic atrophy on CT scan was associated with severe PEI (78.2% versus 50%, $p = 0.050$). The presence of main pancreatic duct [MPD] dilatation or an MPD stone were not different between the two groups.

EUS predictors of severe PEI

EUS was performed in 19 patients (39%) and the types of EUS findings were similar among the two groups. The Rosemont Classification (consistent or suggestive of CP) was not associated with the presence of severe PEI. However, the number of EUS features of CP was significantly higher in the severe PEI group versus the non-severe group (5.3±1.6 versus 3.8±1.4 features, respectively, $p = 0.040$) (Table 3). All patients with total EUS score of 7 or more had severe PEI and none of the patients with EUS score of less than three had severe PEI.

ERCP and magnetic resonance cholangiopancreatography findings

ERCP with pancreatography was performed in three patients and all showed abnormal MPD, more than three abnormal side branches, and MPD obstruction. These patients also had severe PEI. Magnetic resonance cholangiopancreatography was performed in two cases with one patient showing MPD dilatation, calcifications, and pancreatic atrophy and the other showing MPD dilatation, an MPD stone, and pancreatic atrophy. One of the two patients had severe PEI.

Table 2. Image study findings according to the severity of pancreatic exocrine insufficiency

Imaging studies	Severe PEI		*p*-value
	No	Yes	
Plain abdominal radiography, n (%)	(n = 9)	(n = 19)	
Pancreatic calcifications	8 (88.9)	14 (73.3)	0.630
CT, n (%)	(n = 20)	(n = 24)	
Pancreatic duct dilatation	15 (75.0)	20 (83.3)	0.710
Pancreatic duct stone	12 (60.0)	18 (75.0)	0.287
Calcifications	16 (80.0)	19 (79.2)	1.000
Pancreatic atrophy	10 (50.0)	18 (78.2)	0.050

CT = computed tomography; PEI = pancreatic exocrine insufficiency

Table 3. Endosonographic findings according to Rosemont classification and association with the severity of pancreatic exocrine insufficiency

EUS features	Severe PEI		*p*-value
	No (n = 9)	Yes (n = 10)	
Major A			
Hyperechoic foci with shadow	8 (88.9)	8 (80.0)	1.000
MPD stone	3 (33.3)	2 (20.0)	0.628
Major B			
Lobularity with honeycombing	2 (22.2)	3 (30.0)	1.000
Minor			
Lobularity without honeycombing	2 (22.2)	1 (10.0)	0.582
Hyperechoic foci	6 (66.7)	8 (80.0)	0.628
Hyperechoic stranding	6 (66.7)	8 (80.0)	0.628
Cysts	0 (0.0)	3 (30.0)	0.211
Irregular MPD	1 (11.1)	3 (30.0)	0.582
Dilated side branches	1 (11.1)	2 (20.0)	1.000
Dilated MPD	6 (66.7)	7 (70.0)	1.000
Hyperechoic MPD margin	3 (33.3)	4 (40.0)	1.000
EUS consistent with CP	5 (55.6)	8 (80.0)	0.350
EUS suggestive of CP	4 (44.4)	2 (20.0)	0.350
Total EUS features, mean ± SD (range)	3.8±1.4 (2 to 6)	5.3±1.6 (3 to 8)	0.040

CP = chronic pancreatitis; EUS = endoscopic ultrasonography; MPD = main pancreatic duct; PEI = pancreatic exocrine insufficiency

Diagnostic performances of the identified features of severe PEI

The sensitivity, specificity, likelihood ratios, PPV and NPV of the presence of steatorrhea, pancreatic atrophy, and total number of EUS features are shown in Table 4. For the EUS features, a receiver operating characteristics curve, Figure 2 showed that five or more EUS features had the best overall performance to indicate severe PEI (sensitivity 70% [95% CI 35 to 92], specificity 67% [95% CI 31 to 91]). However, seven or more EUS features had 100% specificity and PPV to indicate severe PEI, while less than three EUS features ruled out severe PEI.

Discussion

The diagnosis of severe PEI in patients with CP

Table 4. Diagnostic performances of the identified features of severe pancreatic exocrine insufficiency

Findings	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-	PPV (95% CI)	NPV (95% CI)
Visible steatorrhea	37 (20 to 58)	91 (69 to 98)	4.1	0.7	83 (51 to 97)	54 (37 to 70)
Pancreatic atrophy on CT	75 (53 to 89)	50 (28 to 72)	1.5	0.5	64 (44 to 81)	63 (36 to 84)
≥3 EUS features of CP	100 (66 to 100)	22 (4 to 60)	1.3	0.0	59 (33 to 81)	100 (20 to 100)
≥4 EUS features of CP	90 (54 to 99)	44 (15 to 77)	1.6	0.2	64 (36 to 86)	80 (30 to 99)
≥5 EUS features of CP	70 (35 to 92)	67 (31 to 91)	2.1	0.5	70 (35 to 92)	67 (31 to 91)
≥6 EUS features of CP	30 (8 to 65)	89 (51 to 99)	2.7	0.8	75 (22 to 99)	53 (27 to 78)
≥7 EUS features of CP	30 (8 to 65)	100 (63 to 100)	-	0.7	100 (31 to 100)	56 (31 to 79)

CP = chronic pancreatitis; CT = computed tomography; EUS = endoscopic ultrasound; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value

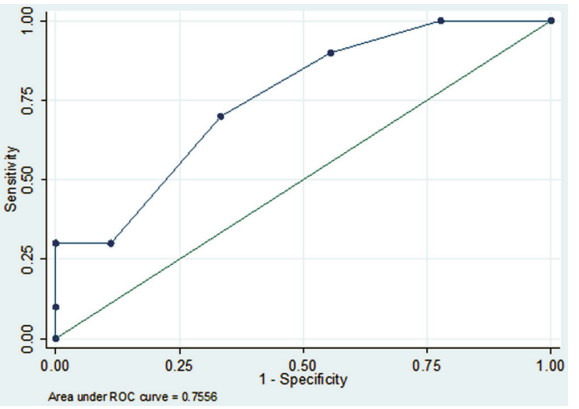

Figure 2. Receiver operating characteristics curve demonstrating the different characteristics of the number of EUS features of chronic pancreatitis and the diagnosis of severe pancreatic exocrine insufficiency.

is essential because it impacts patients' morbidity, whether the severe PEI is symptomatic or subclinical[2]. However, the recommended diagnostic methods for severe PEI other than the presence of visible steatorrhea are usually impractical or unavailable in most parts of the world. In the present study, the authors demonstrated that the clinical characteristics are mostly unreliable to predict the presence of severe PEI except the presence of visible steatorrhea itself. However, radiological finding (pancreatic atrophy by CT), and EUS finding (seven or more EUS features) could help predict severe PEI, which would be useful in patients without visible steatorrhea. The authors also found that less than three EUS features could rule-out severe PEI.

The baseline characteristics of CP in the present study were comparable to those in the literature[19-21]. Most of our patients (69%) were alcoholic CP and the remainder were primarily idiopathic CP. The common clinical manifestations were chronic abdominal pain, recurrent acute pancreatitis, weight loss and steatorrhea. Forty-two percent of our patients smoked, which was also common in CP[19-21].

The prevalence of severe PEI identified by low FE-1 in the present study (55%) was higher than in other studies[12,22]. This might have resulted from differences in the methods used to diagnose severe PEI and a possible selection bias because in our country, CP is not as well-recognized among physicians as acute pancreatitis. Therefore, early CP is probably undiagnosed, and established CP patients usually have severe full-blown disease, causing the high prevalence of severe PEI in the present study.

Regarding the clinical characteristics to predict severe PEI, the authors found that a history of visible steatorrhea was the only characteristic that suggested severe PEI. This seems straightforward and confirms our knowledge that steatorrhea is specific, but insensitive, to indicate severe PEI, since only 37% of severe PEI patients in the present study had steatorrhea. The authors found two patients with non-severe PEI with steatorrhea. One of these patients had false negative FE-1 by the FE-1 level of 17.9 µg/g, which almost reached the cut-off level for severe PEI in our study, and the other had a history of previous double bypass surgery, which might have predisposed him to small intestinal bacterial overgrowth syndrome and cause steatorrhea. In the present study, the authors did not include nutrition parameters, which are important and likely predictive for severe PEI. This was because many patients in the present study already received pancreatic enzyme replacement empirically before enrolling to the study, which might already correct the abnormal nutritional parameters, if they were presented before.

Although smoking increases the risk of PEI[23], this was not demonstrated in the present study. Diabetes, particularly insulin-dependent diabetes, logically favors pancreatic endocrine insufficiency and, generally, endocrine insufficiency occurs later than PEI[19-21]. Therefore, the presence of diabetes,

particularly insulin-dependant diabetes, should be associated with severe PEI and a recent study confirmed diabetes and severe PEI diagnosed by ^{13}C-MTG breath test[24]. However, the authors could not demonstrate diabetes as a predictor for severe PEI. The exact reason is unknown but may be a result of the small number of patients with diabetes in our study.

A small number of previous studies have suggested that the severity of pancreatic morphology is associated with pancreatic exocrine function[13,25,26]. However, only one study demonstrated that certain findings were associated with severe PEI as diagnosed by direct PFT: MPD dilatation, MPD stone, and pancreatic atrophy[13]. Another recent study also discussed an association between pancreatic calcifications and PEI diagnosed by ^{13}C-MTG breath test[24]. In the present study, the authors demonstrated that pancreatic atrophy was the only associated feature. Pancreatic calcifications, MPD stone, and MPD dilatation can occur early in the course of CP[19,21]; therefore, these are less likely to indicate severe PEI, which is a very late consequence of CP. However, pancreatic atrophy is more directly related to pancreatic parenchymal volume and possible a better predictor of severe PEI than the ductal features, as shown in our study.

The present study also confirmed the results of Domínguez-Muñoz et al[14] that EUS is helpful in predicting severe PEI. In their study, the presence of eight or more EUS criteria of CP predicted severe PEI diagnosed by ^{13}C-MTG breath test. In the present study, EUS was performed in 40% of the patients. This was because EUS is not a routine investigation for CP. It is usually performed when other imaging studies for the diagnosis of CP are negative, equivocal, or endoscopic therapy (for abdominal pain) is planned. Nevertheless, our results were quite similar to the previous study that the presence of seven or more EUS features was very predictive of severe PEI. Also, the presence of less than three EUS features could rule-out severe PEI, with confidence. The authors believe that the proposal of two cut-off points (one for ruling-in and one for ruling-out severe PEI) would be more useful in clinical practice than trying to find a single best cut-off point, which is rarely perfect. In patients with three to six EUS criteria, quantitative fecal fat measurement, FE-1, ^{13}C-MTG breath test or any pancreatic function testing would be necessary. The authors propose the clinical use of these predictors for severe PEI, as shown in Figure 3.

The strength of the present study is the inclusion of all clinical, radiological, and EUS features to help diagnose severe PEI. However, there are also

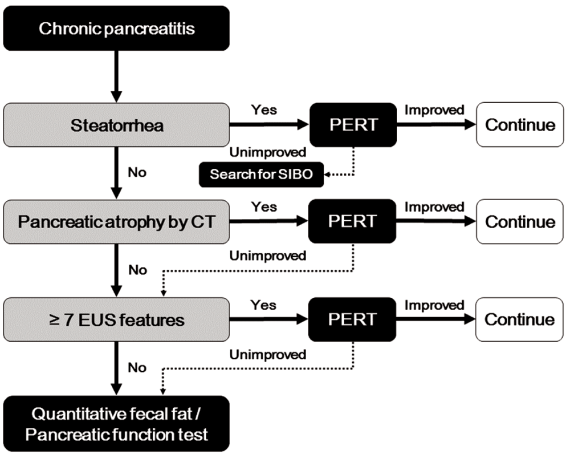

Figure 3. Algorithm for the clinical use of the predictors of severe pancreatic exocrine insufficiency (CT, computed tomography; EUS, endoscopic ultrasonography; PERT, pancreatic enzyme replacement therapy; SIBO, small intestinal bacterial overgrowth).

limitations. First, the number of patients was small. However, this is difficult to resolve because CP is not a common or well-recognized disease among physicians in our country, even though our institute is highly interested in pancreatic diseases. Second, the diagnostic standard for severe PEI in the present study was FE-1, not the well-accepted quantitative fecal fat measurement or direct PFT. However, both quantitative fecal fat measurement and direct PFT are unavailable in Thailand and in most developing countries. The authors believe that the quantitative fecal fat measurement or direct PFT will eventually be replaced by more convenient methods such as ^{13}C-MTG breath test[7] or FE-1[9], as were used in the present study.

Conclusion

A history of visible steatorrhea, pancreatic atrophy by CT, and the number of EUS features were significant predictors for severe PEI. Seven EUS features or more indicated severe PEI, and less than three excluded severe PEI.

What is already known on this topic?

Severe PEI in CP is important and can be diagnosed by direct PFT, indirect PFT and quantitative fecal fat measurement.

What this study adds?

A history of visible steatorrhea, pancreatic atrophy by CT, and the number of EUS features were significant predictors for severe PEI. Seven EUS features or more

indicated severe PEI and less than three excluded severe PEI.

Authors' contributions

Pongprasobchai S and Thanathanee P developed the concept and collected the data, Pausawasdi N and Prachayakul V provided and reviewed the EUS images, Pongprasobchai S and Thanathanee P analyzed and interpreted the data and prepared the manuscript, Leelakusolvong S and Tanwandee T revised the manuscript for important intellectual content, all authors read and approved the final manuscript.

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Potential conflicts of interest

The authors declare no conflict of interest.

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