Original Article

Prevalence and Predictors of Chronic Pancreatitis in Patients with Chronic Abdominal Pain with Negative Endoscopy and Cross-Sectional Imaging

Amporn Atsawarungruangkit MD, BPharm[1], Supot Pongprasobchai MD[2], Nonthalee Pausawasdi MD[2], Varayu Prachayakul MD[2], Somchai Leelakusolvong MD[2]

[1] Department of Medicine, MetroWest Medical Center, Framingham, Massachusetts, USA
[2] Division of Gastroenterology, Department of Medicine, Siriraj Hospital, Bangkok, Thailand

Background: The prevalence of chronic pancreatitis [CP] in chronic abdominal pain [CAP] patients is varied and inconclusive. The clinical predictors of having CP in CAP have not been identified.

Objective: To identify the prevalence of CP by using endoscopic ultrasonography [EUS] in patients with CAP with negative endoscopy and cross-sectional imaging studies.

Materials and Methods: Eligible patients with CAP for more than three months, having negative endoscopic and cross-sectional imaging results, did not meet Rome III criteria of functional gastrointestinal disorders, and underwent EUS were included. CP was diagnosed by EUS using Rosemont criteria. Prevalence of CP was calculated, and logistic regression analysis was performed to identify independent factors associated with the presence of CP.

Results: Of the 92 patients with CAP, 18 had CP and the prevalence was 19.6%. Two factors were found to be independent factors associated with the presence of CP, referred pain to back (OR = 3.23, p = 0.040) and absence of comorbidity (OR = 5.06, p = 0.042).

Conclusion: CP was found in one-fifth of patients with CAP and negative endoscopy and imaging study. Referred pain to back and absence of comorbidity predicted the presence of CP.

Keywords: Abdominal pain, Chronic pancreatitis, Endoscopic ultrasonography, Pain, Pancreatic pain

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Chronic abdominal pain [CAP] is one of the challenging problems in gastroenterology. The incidence of unexplained abdominal pain in primary care setting was 2% to 3%[1-3]. Despite the lack of well-established definition, generally accepted definition of CAP is unexplained abdominal pain persisting for more than three months, either continuously or intermittently. Nearly all patients with CAP have prior medical evaluations but do not yield a diagnosis after history taking, physical examination, basic investigations, upper endoscopy, colonoscopy, and cross-sectional imaging studies.

Among the important etiologies of CAP with negative endoscopy and imaging study, chronic pancreatitis [CP] is an important one to be identified[4]. The prevalence of CP in patients with CAP varies between 3% and 39%[5-9]. The ability to early diagnose CP would have a benefit to patients in both alleviating the pain and slowing the progression of disease using various treatment alternatives e.g., alcohol abstinence[10], smoking cessation[10-12], analgesics, neuropathic drugs[13], pancreatic enzyme[14,15], and antioxidants[16]. However, since the prevalence of CP in CAP seems to vary and could be as low as 3%, searching all CAP patients for early CP using more sophisticated but expensive tools may not be appropriate. Looking for clinical predictors that would increase the pretest probability for CP is another way to help choosing more appropriate patients for further work-up of CP. Unfortunately, such data is lacking.

There are various tools for early diagnoses of CP such as computed tomography [CT], magnetic resonance cholangiopancreatography [MRCP] with or without secretin stimulation [S-MRCP], endoscopic retrograde cholangiopancreatography [ERCP], endo-

Correspondence to:

Pongprasobchai S. Division of Gastroenterology, Department of Medicine, Siriraj Hospital, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-81-2070903, **Fax**: +66-2-4115013
Email: supot.pon@mahidol.ac.th

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scopic ultrasonography [EUS], and direct pancreatic function tests[17]. Recently, EUS has been adopted as an emerging technique to diagnose CP due to its high sensitivity and specificity[18,19], especially in early stage of disease[20,21]. Moreover, EUS is a technique with high safety and a very low complication rate. For these reasons, EUS would be a good diagnostic tool for early CP if it is being used wisely.

The present study aimed to define the prevalence of CP by using EUS in patients with CAP with negative endoscopy and cross-sectional imaging study and identify clinical factors that help predict the diagnosis of CP. Thus, clinician would be able to select patients for EUS more wisely and more appropriately.

Materials and Methods

The present study was a retrospective study performed by reviewing the electronic medical database in Siriraj Hospital, Bangkok, Thailand. The study protocol was approved by the Institutional Review Board of Siriraj Hospital.

Patients

Eligible patients with CAP who underwent EUS between January 2007 and December 2014 were enrolled. The inclusion criteria were 1) 18 years or older, 2) CAP for more than three months, 3) unremarkable findings on upper endoscopy and colonoscopy, 4) no abnormal finding from abdominal imaging studies i.e., ultrasonography [US], CT, magnetic resonance imaging [MRI]/MRCP, and ERCP, 5) no history of recurrent acute pancreatitis, and 6) no symptom that fulfilled Rome III criteria of functional gastrointestinal disorders i.e., functional dyspepsia, and irritable bowel syndrome[22,23].

EUS

All patients underwent EUS using either electronic radial (GF UE160P, Olympus Tokyo, Japan) or curvilinear (GF UC140P, Olympus Tokyo, Japan) echoendoscopes. All endosonographers had experienced of more than 500 pancreatobiliary EUS procedures. All EUS pictures were reviewed by one of the authors (Pongprasobchai S). In case there was discordance between the result of the reviewer and the original report, a third endosonographer (Pausawasdi N or Prachayakul V) was consulted to make a consensus.

Definition of CP

Rosemont classification, EUS-based criteria, was used as criteria for the diagnosis CP in the present study (Table 1)[24,25]. EUS results were classified as consistent to CP, suggestive of CP, indeterminate, and normal. Both consistent to CP and suggestive of CP were considered a positive diagnosis for CP, since recent study showed that the finding of suggestive of CP correlated strongly with the presence of CP by histology[25]. On the other hand, indeterminate and normal were considered as no CP in the present study. The examples of EUS findings that demonstrated CP versus normal pancreas are shown in Figure 1.

Table 1. The Rosemont classification for the endoscopic ultrasonography diagnosis of chronic pancreatitis[24]

Classification	Criteria
I. Consistent with CP	1) 2 major A features 2) 1 major A feature + major B feature 3) 1 major A feature + ≥3 minor features
II. Suggestive of CP	1) 1 major A feature + 0 to 2 minor features 2) Major B feature + ≥3 minor features 3) ≥5 minor features
III. Intermediate for CP	1) Major B feature + 0 to 2 minor features 2) 3 to 4 minor features
IV. Normal	0 to 2 minor features

Major A features: 1) hyperechoic foci with posterior acoustic shadow, 2) lithiasis in main pancreatic duct

Major B feature: honeycomb pattern of lobularity

Minor features: 1) cysts, 2) ductal dilation greater than 3.5 mm, 3) irregular Wirsung duct, 4) dilation of secondary branches greater than 1 mm, 5) hyperchoic walls of Wirsung duct, 6) hyperchoic strands, 7) hyperchoic foci without posterior acoustic shadow, 8) lobularity without honeycomb pattern

Data collection

The patients' baseline characteristics including previous imaging studies and laboratory parameters were obtained from the electronic medical records.

Statistical analysis

All statistical analyses in the present study were conducted with Stata version 13 (StataCorp LP,

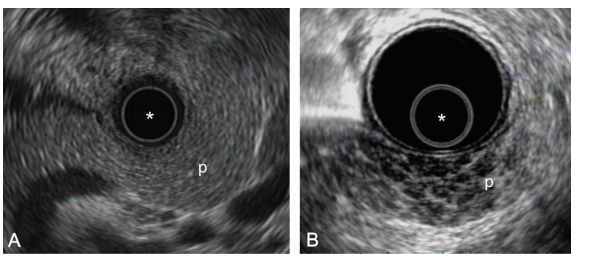

Figure 1. EUS findings of the pancreas (p): (A) normal pancreas (homogenous salt and pepper pattern of the parenchyma), (B) chronic pancreatitis (lobularity with honeycomb pattern). The echoendoscopes are indicated with asterisk (*).

College Station, TX, USA). The continuous data and categorical data were presented in terms of mean, standard deviation [SD], and frequency (percentage), respectively. Student-t test was used to evaluate the difference in the continuous variables between the two groups while Chi-square test or two-sided Fisher's exact test was used to determine the difference in categorical variables between the two dichotomous groups. Variables with a *p*-value of less than 0.10 in the univariate analysis were further analyzed by logistic regression analysis to identify independent predictors of CP. The results were presented as odds ratio [OR] and 95% confidence interval [CI] and *p*-value of less than 0.05 was considered statistical significant.

Table 2. Baseline characteristics of the 92 patients

Factors	Number (%) or mean ± SD
Male gender	38 (41.3)
Age (years)	47.4±14.5
Body mass index (kg/m^2)	22.7±4.3
Comorbidities	
Hypertension	21 (22.8)
Diabetes	17 (18.5)
Dyslipidemia	21 (22.8)
Smoking	
Active smoker	9 (9.8)
Ex-smoker	6 (6.5)
Alcohol drinking	
Active alcohol user	15 (16.3)
Ex-alcohol user	15 (16.3)
History of acute pancreatitis	20 (21.7)
History of amylase/lipase abnormalities	24 (26.1)
History of pancreatobiliary diseases	
Acute pancreatitis	20 (21.7)
Gallstone diseases	8 (8.7)
History of abdominal surgery	17 (18.5)
Recent aspirin/NSAID use within 2 months	9 (9.8)
Recent PPI use within 2 months	17 (18.5)
Weight loss	32 (34.8)
Previous imaging studies	
US	62 (67.4)
CT	62 (67.4)
MRI/MRCP	10 (10.9)
Laboratory parameters	
Amylase (IU/L)	87.3±58.1
Lipase (IU/L)	114.6±193.3
Total protein (g/dL)	7.8±0.7
Albumin (g/dL)	4.4±0.5
AST (IU/L)	38.3±98.3
ALT (IU/L)	35.3±80.1
Alkaline phosphatase (IU/L)	94.0±105.7
Total bilirubin (mg/dL)	0.7±0.4
Direct bilirubin (mg/dL)	0.2±0.3
GGT (IU/L)	140.8±362.6
Fasting blood sugar (mg/dL)	113.9±34.7
Hemoglobin (g/dL)	13.2±3.5
MCV (FL)	84.9±9.4
Platelets (count/mm^3)	282,184±78,654

ALT = alanine transaminase; AST = aspartate transaminase; CT = computed tomography; GGT = gamma glutamyl transpeptidase; MCV = mean corpuscular volume; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; NSAID = non-steroidal anti-inflammatory drugs; PPI = proton pump inhibitors; SD = standard deviation; US = ultrasonography

Results

Patients' demographics

Ninety-two patients with CAP were enrolled to the study, 41.3% were male with the average age 47.4±14.5 years. The baseline characteristics and laboratory parameters are summarized in Table 2.

Characteristics of CAP

Characteristics of CAP are summarized and presented in Table 3, where 89.1% of patients had pain in epigastric area. The average pain duration was 26.6±38.7 months. Referred pain was found in 44.6% and located either in the back (43.5%) or shoulder (1.1%).

Diagnosis of CP

Details of the final diagnoses based on EUS are presented in Table 4. There were 19.6% of patients having CP by EUS (10.9% were consistent with CP and 8.7% were suggestive of CP).

Table 3. Clinical characteristics of chronic abdominal pain

Characteristics	Number (%) or mean ± SD
Pain duration (months)	26.6±38.7
Pain required hospitalization	36 (39.1)
Location	
Epigastric	82 (89.1)
Right upper quadrant	16 (17.4)
Left upper quadrant	10 (10.9)
Periumbilical	4 (4.4)
Referred pain	
Back	40 (43.5)
Shoulder	1 (1.1)

SD = standard deviation

Table 4. Diagnosis of chronic pancreatitis according to the EUS results

Diagnosis	Number (%)
Chronic pancreatitis	
Consistent with chronic pancreatitis	10 (10.9)
Suggestive of chronic pancreatitis	8 (8.7)
No chronic pancreatitis	
Indeterminate	25 (27.2)
Normal	49 (53.3)

Predictors of having CP

Factors associated with the diagnosis of CP were analyzed and presented in Table 5. According to the 14 significant factors by univariate analysis, only two factors were found to be independent factors associated with CP, referred pain (OR 3.23, 95% CI 1.06 to 9.84, $p = 0.040$), and the absence of comorbidity (OR 5.06, 95% CI 1.06 to 24.16, $p = 0.042$). In other words, the odd of having CP significantly increased when patients with CAP had referred pain and the absence of comorbidity.

Discussion

CAP is among one of the frequent problem in clinical practice. Usually, the patients with CAP have undergone multiple investigations including standard lab tests, upper and lower endoscopy, ultrasonography, and cross-sectional imaging studies. Unfortunately, most patients ended up having negative findings[5,26] and might be diagnosed as having functional gastrointestinal disorders. It is possible that proportion of these CAP patients might have CP. The present study illustrated that the prevalence of CP in patients with CAP was 19.6%, as well as identified the referred pain and the absence of comorbidity were predictors of CP in CAP.

The prevalence of CP in patients with CAP varies markedly among studies and methods to diagnose CP. Studies using direct pancreatic function test showed that 22% to 35% of patients with dyspepsia indeed had CP[27-29].

Table 5. Factors associated with the presence of chronic pancreatitis

Factors	Univariate analysis			Multivariate analysis	
	CP (n = 18)	No CP (n = 74)	*p*-value	Odd ratio (95% CI)	*p*-value
Male	11 (61.1)	27 (36.5)	0.057		
Age (years)	41.9±13.5	48.7±14.6	0.075		
Body mass index (kg/m^2)	22.5±3.7	22.8±4.4	0.788		
Absence of comorbidity	16 (88.9)	45 (60.8)	0.024	5.06 (1.06 to 24.16)	0.042
Active/ex-smoker	4 (22.2)	11 (14.9)	0.257		
Active/ex alcohol user	9 (50.0)	21 (28.4)	0.097		
History of acute pancreatitis	7 (38.9)	13 (17.6)	0.061		
History of amylase/lipase elevations	7 (38.9)	17 (23.0)	0.155		
History of pancreatobiliary disease	11 (61.1)	52 (70.3)	0.453		
History of abdominal surgery	0 (0.0)	17 (23.0)	0.037		
Recent aspirin/NSAID use	1 (5.6)	8 (10.8)	0.683		
Recent PPI use	2 (11.1)	15 (20.3)	0.509		
Weight loss	7 (38.9)	25 (33.8)	0.683		
Characteristics of CAP					
Duration	23.1±29.8	27.5±40.7	0.668		
Pain required hospitalization	10 (55.6)	26 (35.1)	0.111		
Refer to back	12 (66.7)	28 (37.8)	0.027	3.23 (1.06 to 9.84)	0.040
Laboratory parameters					
Amylase (IU/L)	108.5±126.9	83.6±41.1	0.439		
Lipase (IU/L)	274.0±433.7	77.1±59.7	0.065		
Total protein (g/dL)	7.9±0.5	7.7±0.7	0.304		
Albumin (g/dL)	4.3±0.5	4.4±0.5	0.496		
AST (IU/L)	86.1±232.0	28.0±15.1	0.053		
ALT (IU/L)	78.9±184.6	25.9±20.0	0.030		
Alkaline phosphatase (IU/L)	174.8±212.9	73.4±32.8	0.001		
Total bilirubin (mg/dL)	0.8±0.7	0.6±0.3	0.094		
Direct bilirubin (mg/dL)	0.3±0.6	0.1±0.1	0.129		
GGT (IU/L)	975.5±1,007.6	52.9±64.2	<0.001		
Fasting blood sugar (mg/dL)	108.4±27.6	115.2±36.4	0.621		
Hemoglobin (g/dL)	13.0±1.7	13.2±3.9	0.900		
MCV (FL)	88.7±8.2	83.8±9.4	0.081		
Platelets (x 10^5 count/mm^3)	329,286±96,354	272,565±71,313	0.047		

ALT = alanine transaminase; AST = aspartate transaminase; CI = confidence interval; CP = chronic pancreatitis; GGT = gamma glutamyl transpeptidase; MCV = mean corpuscular volume; NSAID = non-steroidal anti-inflammatory drugs; PPI = proton pump inhibitors; SD = standard deviation; US = ultrasonography

Values are presented in either number (%) or mean ± SD

Studies using EUS in patients with CAP were less convincing and the reported percentages of CP varied from 3% to 39%[5-9]. Such discordant could arise from differences in the inclusion and exclusion criteria, duration and characteristics of CAP, EUS criteria for CP, sample size, and hospital setting. For example, our reported prevalence (19.6%) is much lower than the 39% reported by Sahai et al[5]. In their study, both dyspeptic patients and patients with high possibility of having pancreatic diseases (based on clinical and imaging results) were included and the study was performed in a highly specific endoscopic center, which could possibly result in a referral bias. In contrast, Siddiqui et al[8] showed much lower prevalence of CP (4%) comparing to our reported because the study aimed to find the sphincter of Oddi dysfunction type III by EUS, thus mainly targeted young female patients with right upper quadrant pain and, hence, might reduce the prevalence of CP. Chang et al[7] prospectively compared upper endoscopy plus either EUS or transabdominal US in patients with chronic upper abdominal pain that had more than six episodes for more than one year and discovered CP in 3%. Recently, Thompson et al[9] reported the prevalence of CP by EUS to be 14%, which is the closest number to the present study. Besides a larger sample size and longer cut-off duration of pain compared to the present study (12 months versus three months), their study and ours shared some common characteristics, such as being retrospective, comparable studying objective, and similar setting.

The present study could identify significant clinical predictors of having CP in patients with CAP, i.e., referred pain to back and the absence of comorbidity. Referred pain is a frequently-cited symptom to suggest pancreatic diseases. Previous study by Sahai el al[5] reported the clinical of suspected pancreatic disease, of which one of the criteria in their study was back pain associated with severe EUS features of CP. The present study supported the relevance of back pain to indicate CP. The presence of comorbidities (e.g., hyperlipidemia, diabetic, and hypertension) inversely associated with the presence of CP in the present study. The reason is unclear, but it is possible that patients with comorbidities could have the chance of diseases other than CP that might cause CAP, e.g., chronic mesenteric ischemia and various functional gastrointestinal disorders, although evidence to support this hypothesis is lacking. Based on the result of the present study, 30% of patients with referred pain would have CP, 26% of patients without comorbidity would do so, and 65% of patients with referred pain but no comorbidity would have CP by EUS. Therefore, by using these two factors as a screening tool, physicians might be able to increase the pre-test probability of CP to make further investigation by EUS more cost-effective.

Although smoking and alcohol drinking are common risk factors for CP, the present study did not find them significantly associated with CP. The reason is difficult to explain, but the authors observed that the frequency of smoking (16%) and alcohol (32%) in the studied population was rather low compared to other studies of CP[30-32], hence, obscuring the differences. This was probably due to the referral bias since patients with CAP and history of significant smoking or alcoholic might already be sought and found to have CP without the need to be referred for EUS.

Amylase and lipase are well-known enzymes associated with pancreatic disease. Mild elevation in patients with CAP might indicate occult CP. In the present study, the authors found higher levels of both enzymes in CP patients compared to the non-CP ones, but the differences did not reach statistical significance. Such results could be explained by the very wide SD of the enzyme level in the CP group, indicating that CP patients could have a wide range of enzyme levels since it depends on the time from onset of the disease. The earlier the course, the higher evidence of detecting elevated enzymes is found[32]. History of acute pancreatitis was also found to have no relationship with CP because the present study already excluded patients with a condition of recurrent AP as such patients are highly expected to have CP, thus, was not a target of the present study.

The present study had numbers of strength. It was conducted in the single center where all patients homogenously presented with severe CAP after negative endoscopy and imaging studies. EUS were performed by three experienced endosonographers in a high-volume center of EUS with more than 500 patients per year, and the EUS findings were described delicately and systematically. Finally, the present study identified significant clinical predictors of having CP in patients with CAP. Such predictors could be considered as a screening tool for considering referring such patients to undergo EUS in a country where EUS is not widely available.

The limitation of the present study is on the nature of retrospective study in a tertiary care setting that usually suffered from confounding and bias including referral bias. Moreover, the present study had a large

female population (58%) with low prevalence of alcohol consumption, which could be considered as a selection bias. Thus, the authors encouraged further investigation in a larger population to validate the results.

Conclusion

CP could be found up to one fifth of patients with CAP with negative endoscopy and imaging studies. Patients with CAP, who had referred pain to the back without any comorbid disease should be aware of having CP.

What is already known on this topic?

CP is one of the important causes of patients with CAP and negative endoscopy and imaging studies. The prevalence varies from 3% to 39%, and that in Thai patients is unknown. It is unclear which clinical predictor could predict the presence of CP in patients with CAP.

What this study adds?

CP diagnosed by EUS was present in one-fifth of CAP patients with negative endoscopy and imaging studies. Factors predictive for the presence of CP were referred pain to back and the absence of comorbid illnesses.

Potential conflicts of interest

The authors declare no conflict of interest.

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