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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Prospective study of early chronic pancreatitis diagnosed based on the Japanese diagnostic criteria

Atsushi Masamune[1] · Tatsuhide Nabeshima[1] · Kazuhiro Kikuta[1] · Shin Hamada[1] · Eriko Nakano[1] · Kiyoshi Kume[1] · Atsushi Kanno[1] · Ai Sato[2,3] · Yuichi Tachibana[4] · Osamu Inatomi[5] · Satoshi Yamamoto[6] · Tsukasa Ikeura[7] · Seiji Futagami[8] · Masashi Taguchi[9] · Keiji Hanada[10] · Kyoko Shimizu[11] · Masanobu Kageoka[12] · Tomotaka Saito[13] · Takaaki Eguchi[14] · Kensuke Kubota[15] · Mamoru Takenaka[16] · Atsushi Mima[17] · Atsushi Irisawa[2,3] · Tetsuhide Ito[4] · Akira Andoh[5] · Kazuo Inui[6] · Yoshifumi Takeyama[18] · Hiroki Yamaue[19] · Kazuichi Okazaki[7] · Tooru Shimosegawa[1]

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Abstract

Background Chronic pancreatitis (CP) is a fibro-inflammatory disease of the pancreas. Early diagnosis and intervention, before CP becomes established and irreversible, are essential to improve the long-term outcomes. The world's first diagnostic criteria for early CP were proposed in Japan in 2009, but their clinical utility remains elusive. This study aimed to clarify whether patients with early CP progress to definite CP.

Methods This is a multicenter, prospective study. Patients diagnosed as having early CP according to the Japanese diagnostic criteria were prospectively followed for 2 years. Clinical profiles including symptoms, drinking and smok-

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✉ Atsushi Masamune
amasamune@med.tohoku.ac.jp

[1] Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

[2] Department of Gastroenterology, Fukushima Medical University Aizu Medical Center, Aizuwakamatsu, Japan

[3] Department of Gastroenterology, Dokkyo Medical University School of Medicine, Mibu, Japan

[4] Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[5] Department of Medicine, Shiga University of Medical Science, Otsu, Japan

[6] Department of Gastroenterology, Bantane Hospital, Fujita Health University, Nagoya, Japan

[7] Department of Gastroenterology and Hepatology, Kansai Medical University, Osaka, Japan

[8] Department of Internal Medicine, Division of Gastroenterology, Nippon Medical School, Tokyo, Japan

[9] Third Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

[10] Department of Gastroenterology, JA Onomichi General Hospital, Onomichi, Japan

[11] Department of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

[12] Department of Gastroenterology, Fujieda Municipal Hospital, Fujieda, Japan

[13] Department of Gastroenterology, University of Tokyo, Tokyo, Japan

[14] Department of Gastroenterology and Hepatology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

[15] Department of Endoscopy, Yokohama City University Hospital, Yokohama, Japan

[16] Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan

[17] Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

[18] Department of Surgery, Kindai University Faculty of Medicine, Osaka, Japan

[19] Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

ing status, laboratory data, imaging findings and treatments were analyzed.

Results Among the 83 patients who completed the 2-year follow-up period, four (4.8%) patients progressed to definite CP. The diagnosis of 48 (57.8%) patients was unchanged, and that of 31 (37.3%) patients was downgraded. All the four progressive patients were male, alcohol-related, smokers (3 current and 1 ever), and continued drinking. Comparison of the clinical profiles between the progression group ($n = 4$) and non-progression group ($n = 79$) revealed that etiology (alcohol-related), smoking status and presence of acute pancreatitis episodes were associated with the progression to definite CP.

Conclusions The Japanese diagnostic criteria could identify some patients before the progression to definite CP, while the majority of the patients did not progress. Trial registration number: UMIN000015992.

Keywords Alcohol · Diagnosis · Endoscopic ultrasonography · Functional dyspepsia · Smoking

Abbreviations

AP	Acute pancreatitis
BT-PABA	*N*-benzoyl-L-tyros-*p*-amino benzoic acid
CP	Chronic pancreatitis
CT	Computed tomography
DCECP	Diagnostic criteria for early chronic pancreatitis
EUS	Endoscopic ultrasonography
MRCP	Magnetic resonance cholangiopancreatography
SD	Standard deviation

Introduction

The recently proposed mechanistic definition defines chronic pancreatitis (CP) as a pathological fibro-inflammatory syndrome of the pancreas in individuals with risk factors who develop persistent pathological responses to parenchymal injury or stress [1]. When advanced, CP is characterized by irreversible morphological changes, pain, and/or exocrine and endocrine dysfunction of the pancreas [1–3]. In the advanced stage, symptoms including severe chronic pain, maldigestion and diabetes mellitus profoundly hinder the quality of life. Importantly, CP is a risk factor for the development of pancreatic cancer [4]. Since advanced CP is progressive and irreversible [1–3], early diagnosis and medical interventions are essential to improve the long-term outcomes of CP patients. However, the definition and diagnosis of early CP are challenging and controversial as the changes are subtle and overlap those of other disorders [1, 5, 6].

In 2009, the world's first diagnostic criteria for early CP (DCECP) were proposed in Japan [7]. The nationwide epidemiological survey of early CP in Japan revealed that the estimated number of early CP patients in 2011 was 5410, which accounted for about 8% of those who developed advanced CP [8, 9]. Although the concept of early CP has been increasingly recognized, no consensus statement could be achieved for diagnostic criteria as well as a definition of early CP [6]. One reason for the controversy is that there is no clear evidence that the DCECP can identify subjects who will progress to definite CP. To clarify this issue, we here conducted a prospective study of patients with early CP diagnosed according to DCECP.

Methods

Study design

A multicenter, prospective study of adult patients with early CP diagnosed according to DCECP was performed [7]. A total of 16 tertiary-care institutions in Japan participated in this study. The recruitment period began in July 2014. We performed consent interviews individually, and written informed consent was obtained from all participants. This study was approved by Institutional Review Board of all participating institutions, and registered at the University Hospitals Medical Information Network (#UMIN000015992). This study was originally designed with a 5-year follow-up period, but the intermediate analysis was performed with a 2-year follow-up period because DCECP was scheduled to be revised by the Japan Pancreas Society in 2019.

The diagnosis of early CP and CP

Early CP was diagnosed according to DCECP [7]. The DCECP includes four clinical features (recurrent upper abdominal pain, abnormal pancreatic enzyme levels in the serum or urine, abnormal pancreatic exocrine function, and continuous heavy drinking of alcohol equivalent to or more than 80 g/day of pure ethanol) and imaging findings of early CP on endoscopic ultrasonography (EUS) or endoscopic retrograde cholangiopancreatography (Supplementary Table 1). A diagnosis of early CP can be made if a patient does not justify a diagnosis of definite or probable CP, but satisfies at least two of four clinical features and imaging findings of early CP. Definite and probable CP was diagnosed according to the revised Japanese diagnostic criteria 2009 [7], based on imaging criteria for definite CP

findings and probable CP findings, respectively. If the subjects had probable CP findings and two or more of the first three clinical signs, they were diagnosed as having definite CP.

Follow-up

Detailed clinical information including sex, age, drinking and smoking status, clinical symptoms, laboratory data, imaging findings, acute pancreatitis (AP) episodes, and treatments were sent to the data-monitoring center at the Division of Gastroenterology, Tohoku University Graduate School of Medicine, at the time of entry, 1 year and 2 years after the entry.

Statistics

Data are shown as mean ± standard deviation (SD). Continuous variables were compared using paired or unpaired Student's *t* test. Chi square test and Fisher's exact *t* test (when one or more expected cell frequencies were < 5) were used for comparison of proportions. Statistical analyses were performed using the SPSS version 20.0 statistical analysis software (SPSS Inc., Chicago, IL). A two-sided *P* value of < 0.05 was considered statistically significant.

Results

By the end of November, 2016, 88 patients with early CP diagnosed according to the DCECP were enrolled. The characteristics of the enrolled subjects are shown in Supplementary Table 2. Fifty-three (60.2%) patients were male and 48 (54.5%) patients were idiopathic. During the 2-year follow-up period, 5 patients failed to visit the hospitals and the remaining 83 patients were further analyzed.

As shown in Table 1, 49 (59.0%) patients were male and 45 (54.2%) patients were idiopathic. The number of positive clinical features in DCECP was 2 in 51 (61.4%) patients, 3 in 29 (34.9%) patients, and 4 in 3 (3.6%) patients. Among the four clinical features, recurrent upper abdominal pain was most frequently found; it was observed in 69 (83.1%) patients. Seventy-two (86.7%) patients underwent the *N*-benzoyl-L-tyros-*p*-amino benzoic acid (BT-PABA) test to evaluate the pancreatic exocrine function, and half of the patients showed urinary PABA excretion rates were less than 70%. Excessive alcohol consumption of more than 80 g/day was observed in 35/38 (92.1%) patients with alcohol-related early CP. Regarding the imaging findings, all the 78 patients were diagnosed by EUS findings. The number of positive imaging findings for early CP on EUS was 2 in 22 (26.5%) patients, 3 in 37 (44.6%) patients, 4 in 19 (22.9%) patients, and 5 in 5 (6.0%) patients. Seventeen (20.5%) patients were current smokers and 12 (14.5%) were ever smokers. Eighteen (21.7%) patients had previous episodes of AP.

After 2 years, 4/83 (4.8%) patients progressed to definite CP. The characteristics of these 4 patients are shown in Table 2. Figure 1 shows computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) images at entry and 2 years later in a patient (case #1 in Table 2) who progressed to definite CP after 2 years. All these 4 patients were male and alcohol-related (Table 2). All the four patients continued drinking alcohol after entry; three patients continued alcohol drinking as before and one patient continued drinking with decreased amounts of alcohol. Three patients were current smokers and one was ever smoker. Three of these 4 patients had previous episodes of AP, and two of four had AP attacks during the 2-year follow-up period. In the remaining 79 patients who did not progress to definite CP, the diagnosis of 48 (60.8%) patients remained as early CP and that of 31 (39.2%) patients was downgraded because they did not fulfil the DCECP due to the number of positive clinical features < 2 ($n = 25$, 80.6%), the number of EUS findings < 2 ($n = 4$, 12.9%), and both ($n = 2$, 6.5%) (Table 3). No patients with idiopathic early CP as well as those with alcoholic early CP who abstained progressed to definite CP. Patients whose diagnosis was downgraded were less frequently observed in alcohol-related early CP patients than in idiopathic patients ($P = 0.006$). In these 79 patients, the numbers of positive clinical features and EUS findings were significantly decreased after 2 years (Table 4). Of note, the number of positive clinical features was decreased both in patients with alcoholic ($P = 0.001$) and idiopathic ($P < 0.001$) early CP, whereas the number of positive EUS findings was decreased in idiopathic early CP patients ($P = 0.014$), but not in alcohol-related early CP patients ($P = 0.83$). The proportion of patients presenting recurrent upper abdominal pain was decreased after 2 years in both patients with alcohol-related early CP and those with idiopathic early CP. However, the proportion of patients presenting abnormal pancreatic enzyme levels was decreased after 2 years in patients with idiopathic early CP, but not in those with alcoholic early CP (Table 4).

We compared the clinical profiles between the 4 patients who progressed to definitive CP after 2 years ("progression group") and the remaining 79 patients ("non-progression group"). Alcohol-related etiology, the presence of previous AP episodes and AP episodes during the follow-up period, drinking status after entry, and smoking habit were associated with the progression to definite CP (Table 5). The administration of oral protease inhibitor camostat mesylate and pancrelipase was not associated with the progression to definite CP.

Table 1 Characteristics of the 83 early CP patients who completed 2-year follow-up

Sex, male, *n* (%)	49 (59.0)
Age at entry, mean ± SD (range)	59.0 ± 14.4 (22–83)
Etiology, *n* (%)	
Idiopathic	45 (54.2)
Alcoholic	38 (45.8)
Number of positive clinical signs, mean ± SD	2.42 ± 0.57
Recurrent upper abdominal pain, *n* (%)	69 (83.1)
Abnormal pancreatic enzyme level, *n* (%)	61 (73.5)
Abnormal pancreatic exocrine function, *n* (%)[a]	36 (50)
Alcohol consumption > 80 g/day, *n* (%)	35 (42.2)
Number of positive EUS findings, mean ± SD	3.08 ± 0.86
Smoking status	
Current, *n* (%)	17 (20.5)
Ever, *n* (%)	12 (14.5)
Never, *n* (%)	54 (65.0)
Previous AP episode, *n* (%)	17 (20.5)

AP acute pancreatitis, *EUS* endoscopic ultrasonography, *SD* standard deviation

[a]BT-PABA test was not performed in 11 patients

Table 2 Clinical profiles of the four patients who progressed to definite CP

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Male
Age at entry	41	54	70	71
Etiology	Alcoholic	Alcoholic	Alcoholic	Alcoholic
Number of positive clinical signs	3	3	3	2
Recurrent upper abdominal pain	Yes	Yes	Yes	No
Abnormal pancreatic enzyme level	Yes	Yes	No	Yes
Abnormal pancreatic exocrine function	No	No	Yes	Unknown
Alcohol consumption > 80 g/day	Yes	Yes	Yes	Yes
Number of positive EUS findings	3	3	4	3
Previous AP episodes	Yes	Yes	Yes	No
AP episodes during the 2-year follow-up period	Yes	Yes	No	No
Drinking status after entry	Continued	Temperance	Continued	Continued
Smoking status	1 Pack/day	2 Packs/day	1 Pack/day	Ex-smoker
Smoking status after entry	Continued	Continued	Continued	Continued
Camostat mesylate	No	Yes	Yes	Yes
Pancrelipase	No	No	No	No

AP acute pancreatitis, *EUS* endoscopic ultrasonography

Discussion

This is the first prospective study of early CP patients diagnosed according to the Japanese diagnostic criteria. The major findings of this study are as follows. (1) Among the 83 patients who completed the 2-year follow-up period, four (4.8%) alcohol-related patients progressed to definite CP, the diagnosis of 48 (57.8%) patients was unchanged, and that of 31 (37.3%) patients was downgraded; (2) alcohol-related etiology, AP episodes, drinking status after entry, and smoking status were associated with the progression to definite CP; (3) the diagnosis of early CP was downgraded mainly due to the decreased number of positive clinical features, whereas improvement of the EUS findings was uncommon. These results suggest that DCECP could identify some patients, especially those who continued to consume alcohol, before its progression to definite CP, although the progression was rare within the 2-year time frame.

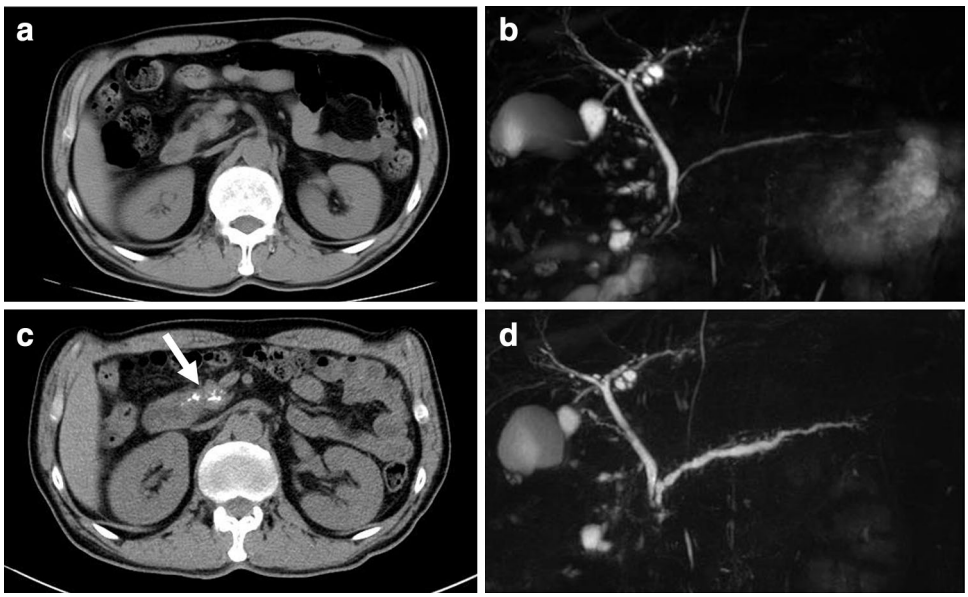

Fig. 1 Imaging findings of the patient with early CP who progressed. CT (**a**, **c**) and MRCP (**b**, **d**) findings at entry (**a**, **b**) and after 2 years (**c**, **d**) are presented. After 2 years, CT revealed pancreatic calcifications (arrow) and MRCP revealed dilatation of main pancreatic duct

Table 3 Diagnosis of the 83 patients after 2 years stratified by etiology and drinking status

Etiology, *n* (%)	Drinking status after entry, *n* (%)	Diagnosis after 2 years, *n* (%)	Reason for downgraded diagnosis, *n* (%)
Idiopathic: 45 (54.2)	–	Remain as early CP: 22 (48.9)	
		Downgraded: 23 (51.1)	No fulfillment of clinical signs: 18 (78.3)
			No fulfillment of EUS findings: 3 (13.0)
			No fulfillment of both: 2 (8.7)
Alcoholic: 38 (45.8)	Abstinence: 13 (34.2)	Remain as early CP: 10 (76.9)	
		Downgraded: 3 (23.1)	No fulfillment of clinical signs: 2 (66.7)
			No fulfillment of EUS findings: 1 (33.3)
	Temperance: 10 (26.3)	Progressed to definite CP: 1 (10)	
		Remain as early CP: 6 (60)	
		Downgraded: 3 (30)	No fulfillment of clinical signs: 3 (100)
	Continued drinking as before: 15 (39.5)	Progressed to definite CP: 3 (20)	
		Remain as early CP: 10 (66.7)	
		Downgraded: 2 (13.3)	No fulfillment of clinical signs: 2 (100)

CP chronic pancreatitis, *EUS* endoscopic ultrasonography, *SD* standard deviation

Comparison of the progression group and non-progression group revealed that life style-related factors such as alcohol drinking and cigarette smoking were associated with the progression to definite CP. All the four patients continued drinking alcohol after the diagnosis of early CP; three patients continued alcohol drinking as before and one patient continued drinking but with decreased amounts of alcohol. In addition, three patients were current smokers and one was an ever smoker. This is not surprising because the majority of the CP patients in Japan have these features [8]. Alcohol use and smoking are well-known risk factors for CP [10, 11] and previous studies have shown that alcohol use and smoking are the largest risk factors for the development of CP in patients with AP. Takeyama et al. [12] reported that the incidence of recurrent pancreatitis, transition to CP, and diabetes mellitus was higher in patients who continued drinking than in those who abstained. In the nationwide survey of alcoholic pancreatitis in Japan, the risk of pancreatitis recurrence within 2.1 years was 2.5-fold greater in patients who continued drinking but with decreased amounts and 7.1-fold in patients who continued drinking as before compared with the patients who completely abstained [13]. In addition, it has been increasingly recognized that smoking is an important risk factor for CP independent of alcohol use [14]. A nationwide survey on alcoholic CP in Japan

Table 4 Changes in numbers of positive clinical signs and EUS findings in patients who did not progress to definite CP

	At entry	After 2 years	*P* value
All (n = 79)			
Number of positive clinical signs, mean ± SD	2.41 ± 0.57	1.75 ± 0.85	< 0.001
Recurrent upper abdominal pain, n (%)	66 (83.5)	39 (49.4)	< 0.001
Abnormal pancreatic enzyme level, n (%)	58 (73.4)	47 (59.5)	0.09
Abnormal pancreatic exocrine function, n (%)[a]	35 (51.5)	22 (32.4)	0.037
Alcohol consumption > 80 g/day, n (%)	31 (39.2)	31 (39.2)	1.00
Number of positive EUS findings, mean ± SD	3.08 ± 0.87	2.77 ± 0.99	0.042
Alcoholic (n = 34)			
Number of positive clinical signs, mean ± SD	2.56 ± 0.66	2.06 ± 0.69	0.001
Recurrent upper abdominal pain, n (%)	24 (70.6)	14 (41.2)	0.027
Abnormal pancreatic enzyme level, n (%)	18 (52.9)	17 (50)	1.00
Abnormal pancreatic exocrine function, n (%)[a]	14 (45.2)	9 (29.0)	0.29
Alcohol consumption > 80 g/day, n (%)	31 (91.2)	31 (91.2)	1.00
Number of positive EUS findings, mean ± SD	3.06 ± 0.78	3.03 ± 0.94	0.83
Idiopathic (n = 45)			
Number of positive clinical signs, mean ± SD	2.29 ± 0.46	1.51 ± 0.89	< 0.001
Recurrent upper abdominal pain, n (%)	42 (93.3)	25/45 (55.6)	0.024
Abnormal pancreatic enzyme level, n (%)	40 (88.9)	30/45 (66.7)	0.013
Abnormal pancreatic exocrine function, n (%)[a]	21 (56.8)	13 (35.1)	0.10
Alcohol consumption > 80 g/day, n (%)	0 (0)	0 (0)	1.00
Number of positive EUS findings, mean ± SD	3.09 ± 0.95	2.58 ± 0.99	0.014

CP chronic pancreatitis, *EUS* endoscopic ultrasonography, *SD* standard deviation

[a]BT-PABA test was not performed in 3 patients with alcoholic early CP and 8 patients with idiopathic early CP

revealed that heavy smoking was an independent risk factor for CP [13]. Smoking cessation during the first years after the CP onset reduced the risk of developing pancreatic calcifications [15]. On the other hand, the administration of camostat mesylate and pancrelipase was not associated with the disease progression in our study. These results indicate that proper intervention in the life style including abstinence from alcohol and smoking cessation is important for preventing the progression to definite CP in early CP patients.

In addition to the drinking and smoking status, AP episodes were associated with the progression to definite CP in early CP patients. In the progression group, three patients had previous episodes of AP, and two of them had AP attacks during the 2-year follow-up period. These findings are in agreement with the sentinel AP event hypothesis, according to which preceding AP attacks are a prerequisite for the development of CP [16]. A meta-analysis of 14 studies dealing with 8492 patients showed that the pooled prevalence of CP was 10% in patients after the first AP occurrence and 36% in patients after recurrent AP [17]. Again, alcohol use and smoking were the largest risk factors for CP in AP patients. In the nationwide survey of early CP in Japan, the clinical profiles of early CP patients with previous AP episodes were similar to those of definite CP patients [9]. The proportions of male and alcoholic cases were compatible with those of definite CP. In addition, the age at disease onset was older in all patients with early CP than that of established CP, but it was younger in early CP patients with previous AP episodes. These results suggest that previous AP episodes would contribute to the specific identification of subjects who might eventually progress to definite CP. Along this line, the mechanistic definition adopts the progressive model of CP consisting of five disease stages "at risk", "AP-recurrent AP", "early CP", "established CP" and "end-stage CP" [6]. Although recurrent AP and early CP might be occasionally overlapping in clinical settings, these two stages are distinct. Early CP should be recognized as CP with the persistent pathological inflammation which do not occur in the normal response to AP or recurrent AP [6]. Transition of recurrent AP to early CP involves detection of biochemical, structural or functional biomarkers of CP [1].

The time-frame of progression between sentinel AP episode, recurrent AP, and CP remains varies among individuals, but usually takes years [1, 18]. AP patients progress to CP at different rates according to etiology, with

Table 5 Comparison of the clinical features between the patients who progressed to definite CP (progression group) and those who did not (non-progression group)

	Progression group (n = 4)	Non-progression group (n = 79)	P value
Sex, male, n (%)	4 (100)	45 (57.0)	0.14
Age at entry, mean ± SD	59.0 ± 14.3	58.7 ± 14.5	0.96
Etiology, n (%)			0.04
Idiopathic	0 (0)	45 (57.0)	
Alcoholic	4 (100)	34 (43.0)	
Number of positive clinical signs at entry, mean ± SD	2.75 ± 0.5	2.41 ± 0.57	0.24
Number of EUS findings at entry, mean ± SD	3.25 ± 0.5	3.08 ± 0.87	0.69
Previous AP episode, n (%)	3 (75)	14 (17.7)	0.026
AP episode during the 2-year follow-up period, n (%)	2 (50)	0 (0)	0.002
Drinking status after entry, n (%)[a]			0.28
Abstinence	0 (0)	13 (38.2)	
Temperance/continued	4 (100)	21 (61.8)	
Smoking status, n (%)			0.013
Current/ever	4 (100)	25 (31.6)	
Never	0 (0)	54 (68.4)	
Camostat mesylate, n (%)	3 (75)	50 (63.3	1.00
Pancrelipase, n (%)	0 (0)	34 (43.0)	0.14

AP acute pancreatitis, *CP* chronic pancreatitis, *SD* standard deviation

[a]Patients with alcohol-related early CP only

alcohol-related having the highest risk, and presence or absence of recurrent AP, as shown in a population-based study in Allegheny County, Pennsylvania [18]. Since DCECP was scheduled to be revised in 2019, the follow-up period in our study was 2 years, which might be short especially in subjects with non-alcoholic etiology and those without recurrent AP. Even with this short follow-up period, 4 patients progressed to definite CP, suggesting the utility of DCECP to identify some patients with high risk of progression. It is of interest to see whether more subjects would progress to definite CP during the longer follow-up period.

Very recently, Sheel et al. [5] from Liverpool reported a retrospective study of patients with the initial findings of minimal change CP based on clinical factors and EUS findings. They showed that 12/40 (30%) patients with minimal change EUS findings developed radiological and/or histological features of definite CP within a median follow-up period of 30 months. In agreement with the results of our study, drinking status (consumption $>$ 62 units per week of alcohol $>$ 1 year) and smoking status (current smoker) were associated with the progression to definite CP. Among the 28 non-progressive patients with minimal change EUS findings, only two fulfilled the DCECP based on consideration of the clinical features. Among the 12 progressive patients, 6 patients had more than 2 clinical features and 2 EUS findings, indicating that 6/12 (50%) patients could be diagnosed as having early CP according to DCECP. These results support the utility of DCECP to identify subjects who later develop definite CP.

Diagnosis of early CP, especially idiopathic early CP, is challenging. The low frequency of progression might result from the low specificity of the DCECP; non-pancreatic diseases such as functional dyspepsia contaminated the idiopathic early CP data [9]. Indeed, none of the patients with idiopathic early CP progressed to definite CP in this study. Low diagnostic specificity might be a reason why the concept of early CP is still controversial and no clear consensus has been reached [6]. The mechanistic definition provides a framework for diagnostic criteria by taking into account risk factors, biomarkers of inflammation, pain, and functional status within the clinical context. Assessment of risk factors such as pancreatitis-associated pathogenic mutations might be helpful to identify early CP patients. Currently, the diagnostic criteria for CP including those for early CP are under revision by the Japan Pancreas Society. More accurate diagnosis of early CP will lead to effective identification of the individuals who are likely to progress to definite CP and improvement of prognosis in these subjects.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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