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ORIGINAL ARTICLE–LIVER, PANCREAS, AND BILIARY TRACT

Nationwide epidemiological survey of chronic pancreatitis in Japan: introduction and validation of the new Japanese diagnostic criteria 2019

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Abstract

Objectives To provide updated clinico-epidemiological information on chronic pancreatitis (CP) in Japan.

Methods We conducted a two-stage nationwide epidemiological survey; the number of CP patients was estimated in the first-stage survey, and their clinical features were examined in the second-stage survey. We surveyed patients with CP who had visited hospitals in 2016 and were diagnosed according to the Japanese diagnostic criteria 2009 (DC2009). Furthermore, we validated the new Japanese diagnostic criteria (DC2019) in patients with early CP diagnosed according to DC2009.

Results The number of patients with definite/probable CP in 2016 was 56,520 (prevalence, 44.5 per 100,000 persons), and that of early CP was 4470 (prevalence, 3.5 per 100,000 persons). We obtained detailed clinical information of 2150 patients with definite/probable CP and 249 patients with early CP. Compared with the early CP cases, the definite/probable CP cases had higher proportions of male (4.8 vs. 1.3), alcohol-related etiology (72.0% vs. 45.8%), smoking history (69.6% vs. 41.0%), diabetes mellitus (42.3% vs. 19.3%), and past history of acute pancreatitis (AP) (50.4% vs. 22.1%). Among the patients with early CP diagnosed according to DC2009, 93 (37.3%) were diagnosed with early CP according to DC2019, but the diagnosis of the remaining 156 (62.7%) patients was downgraded. Alcohol-related etiology, smoking history, early disease onset, and past history of AP were associated with the maintenance of early CP diagnosis in DC2019.

Conclusion We clarified the current status of CP in Japan. Further validation studies are warranted to clarify the diagnostic utility of DC2019.

Keywords Alcohol · Early chronic pancreatitis · Endoscopic ultrasonography · MRCP · Smoking

Abbreviations

AP	Acute pancreatitis
BT-PABA	N-benzoyl-l-tyrosyl-p-aminobenzoic acid
CI	Confidence interval
CP	Chronic pancreatitis
DC	Japanese clinical diagnostic criteria for chronic pancreatitis
DM	Diabetes mellitus
EUS	Endoscopic ultrasonography
HP	Hereditary pancreatitis: MRCP, magnetic resonance cholangiopancreatography
SD	Standard deviation

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Introduction

Chronic pancreatitis (CP) is defined in the recently proposed mechanistic definition [1] as a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress. When advanced, symptoms including severe chronic pain, maldigestion, and diabetes mellitus (DM) profoundly hindered the quality of life of the patients [1–3]. CP is a well-known risk factor for pancreatic cancer [1–3]. To clarify the clinico-epidemiological status of CP, nationwide epidemiological surveys have been conducted in Japan mainly by the Research Committee of Intractable Pancreatic Diseases, under the support of the Ministry of Health, Labor and Welfare of Japan, every 4–5 years [4–7]. The number of CP patients was estimated to be 32,000 in 1994 [4], 42,000 in 1999 [5], 45,200 in 2002 [6], 47,100 in 2007 [7], and 66,980 in 2011 [8]. In addition to the trend of the number of patients with CP, these surveys revealed the clinical practice of CP including etiology, diagnosis, and management in Japan [9]. Up-to-date information in real-world clinical practice is essential for better understanding and management of CP as well as the validation and revision of the diagnostic criteria and guidelines.

In 2009, the Japanese clinical diagnostic criteria for CP were proposed (DC2009) [10]. DC2009 was unique in that the world's first diagnostic criteria for early CP were proposed, aiming to improve the long-term prognosis of patients with CP by early diagnosis and therapeutic intervention [10]. Thereafter, a nationwide epidemiological survey of early CP and prospective study of patients with early CP were conducted to validate DC2009 [11, 12]. The nationwide survey revealed that the clinical profiles differed between patients with early CP and those with definite CP [11]. In a prospective study, DC2009 could identify some patients before the progression to definite CP, but the majority of the patients did not progress [12]. These studies suggested the need to revise DC2009 to select patients who eventually progress to definite CP more specifically. In 2019, the Japan Pancreas Society proposed the revised DC2009, namely, "Clinical diagnostic criteria for CP 2019 (DC2019)" [13]. DC2019 has several characteristic features, including (i) incorporation of mechanistic definition of CP, (ii) revision of diagnostic items for early CP, and (iii) upgrading magnetic resonance cholangiopancreatography (MRCP) as an imaging modality (Table 1, Supplementary Table 1, Supplementary Table 2).

To provide updates on clinic-epidemiological information of CP and early CP in Japan, we conducted a nationwide epidemiological survey of CP and early CP according to DC2009. In addition, we validated DC2019 in patients with early CP diagnosed according to DC2009.

Materials and methods

We conducted a two-stage survey. The first-stage survey aimed to estimate the number of patients with CP and early CP, and the second-stage survey aimed to elucidate the clinical features of CP and early CP. This study was performed in accordance with the principles of the Declaration of Helsinki, and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (article#: 2015-1-519, 2017-1-163, 2018-1-409).

Diagnosis of CP and early CP according to DC2009

Definite and probable CP was diagnosed according to DC2009 [10] based on the imaging criteria for definite 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. In DC2009, early CP was diagnosed using a combination of four clinical signs (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 3). Early CP can be diagnosed if a patient does not justify a diagnosis of definite or probable CP, but satisfies at least two of four clinical signs and imaging findings of early CP.

Diagnosis of early CP according to DC2019

In DC2019 [13], early CP was diagnosed using a combination of five clinical signs (recurrent upper abdominal or back pain, abnormal pancreatic enzyme levels in the serum or urine, abnormal pancreatic exocrine function, continuous heavy drinking of alcohol equivalent to or more than 60 g/day of pure ethanol or mutation in the pancreatitis-associated gene such as *PRSS1* and *SPINK1*, and past history of acute pancreatitis [AP]) and imaging findings on EUS, MRCP, or endoscopic retrograde cholangiopancreatography (Table 1). Imaging findings on EUS were consolidated from 7 items in DC2009 to 4 items; lobularities with and without honeycombing were consolidated to lobularity; hyperechoic foci without shadowing and stranding were consolidated to hyperechoic foci (non-shadowing) or strands; and cysts were removed from the diagnostic items. Early CP can be diagnosed if a patient

Table 1 Japanese clinical diagnostic criteria for CP 2019 [13]

Diagnostic items for CP
① Characteristic imaging findings
② Characteristic histological findings
③ Repeated upper abdominal or back pain
④ Abnormal pancreatic enzyme levels in the serum or urine
⑤ Abnormal pancreatic exocrine function
⑥ Continuous heavy drinking of alcohol equivalent to ≧60 g/day of pure ethanol or mutation in the pancreatitis-associated gene
⑦ Past history of acute pancreatitis
Imaging findings of early CP
Either a or b
a. More than two features among the following four EUS findings including 1) or 2)
1) Hyperechoic foci (non-shadowing) or strands
2) Lobularity
3) Hyperechoic MPD margin
4) Dilated side branches
b. Irregular dilatation of more than three side branches on MRCP or ERCP
Definite CP: either a or b
a. Definite findings of ① or ②
b. Probable findings of ① or ②, plus more than two items among ③, ④, and ⑤
Probable CP
Probable findings of ① or ②
Early CP
More than three items among ③ ∼ ⑦ plus imaging findings of early CP

Note 1: Differential diagnosis from other pancreatic diseases especially pancreatic cancer and intraductal papillary mucinous neoplasm is important

Note 2: If imaging findings of early CP was absent, a diagnosis of possible CP could be made in the patients without ① and ②, but with more than three items among ③ ∼ ⑦ after ruling out other diseases. Imaging examinations including EUS are recommended for the patients with possible CP

Note 3: Patients with only two items among ③ ∼ ⑦ and imaging findings of early CP are regarded as possible early CP after ruling out other diseases, and require careful follow-up. Footnote: Long-term prognosis should be clarified in patients with early CP

CP chronic pancreatitis; *ERCP* endoscopic retrograde cholangiopancreatography; *EUS* endoscopic ultrasonography; *MPD* main pancreatic duct; *MRCP* magnetic resonance cholangiopancreatography

does not justify a diagnosis of definite or probable CP, but satisfies at least three of five clinical signs and imaging findings of early CP (Supplementary Fig. 1).

First-stage survey

Our target subjects were patients with CP who visited the selected hospitals in 2016. The list of hospitals for the survey was based on the hospital yearbook 2016 (R&D Co., Ltd., Nagoya, Japan). We obtained a list of critical care and emergency centers from the website of the Japanese Association for Acute Medicine (https://www.jaam.jp/html/shisetsu/qq-center.htm). The departments of internal medicine, gastroenterology, surgery, and digestive surgery were listed and subjected to stratified random sampling. The sampling rates were approximately 5, 10, 20, 40, 80, 100, and 100% for the stratum of hospitals with less than 100, 100–199, 200–299, 300–399, 400–499, and 500 beds or more, and affiliated university hospitals, respectively. Because this survey also dealt with AP [14], critical care and emergency centers were classified as a special stratum and all of them were selected for the survey.

In June 2017, a questionnaire asking the number of CP patients who visited their hospitals in 2016 was directly mailed to 2502 departments randomly chosen as described earlier [15]. After the collection of the first questionnaire online, the number of patients with CP, along with the 95% confidence interval (CI), was estimated based on the assumption that the response from departments was independent of the frequency of patients using the formulae as

Table 2 Etiology of definite/probable CP

Etiology	Total, *n* (%)	Male, *n* (%)	Female, *n* (%)
Idiopathic	498 (23.7)	299 (17.2)	199 (55.0)
Alcoholic	1513 (72.0)	1377 (79.1)	136 (37.6)
Hereditary/Familial	34 (1.6)	22 (1.3)	12 (3.3)
Biliary	18 (0.9)	14 (0.8)	4 (1.1)
Hyperlipidemia	11 (0.5)	8 (0.5)	3 (0.8)
Pancreas divisum	9 (0.4)	7 (0.4)	2 (0.6)
Autoimmune pancreatitis	9 (0.4)	6 (0.3)	3 (0.8)
Surgery	4 (0.2)	3 (0.2)	1 (0.3)
IPMN	3 (0.1)	1 (0.1)	2 (0.6)
Drug	2 (0.1)	2 (0.1)	0 (0)
Chronic renal failure	1 (0.0)	1 (0.1)	0 (0)
Total	2102 (100)	1740 (100)	362 (100)

CP chronic pancreatitis; *IPMN* intraductal papillary mucinous neoplasm

previously described [16, 17]. We used the population of Japan in 2016 (n = 126,933,000) to calculate the incidence rate.

Second-stage survey

In June 2018, we sent the second questionnaire to the departments reporting that they had patients with CP or early CP in the first questionnaire. The second questionnaire was collected online by the end of March 2019. Because some items of the questionnaire were unanswered, the number of patients subjected to analyses varied among the items.

Statistical analysis

Unknown or undescribed cases were excluded from the statistical analysis. Continuous variables are shown as mean ± standard deviation (SD) and were compared using Student's t-test. For the comparison of proportions, we used the chi-square test and Fisher's exact test (when there is at least one cell in the contingency table of the expected frequencies below five). Statistical analyses were performed using the SPSS version 20.0 statistical analysis software (SPSS Inc., Chicago, IL) or JMP Pro version 14 (SAS Institute, Cary, NC). P value < 0.05 was considered significant.

Results

First-stage survey

A total of 854 out of 2502 departments responded to the first questionnaire (response rate, 34.1%) and 10,339 patients with CP and 1028 patients with early CP were reported (Supplementary Table 4). We estimated the number of patients with CP as 56,520 (95% CI 50,760–62,270), with a prevalence rate of 44.5 per 100,000 persons, and that of patients with newly-diagnosed CP as 14,740 (95% CI 13,150–16,330), with an incidence of 11.6 per 100,000 persons. In the case of early CP, the estimated number of patients with early CP was 4470 (95% CI 3640–5290), with a prevalence rate of 3.5 per 100,000 persons, and that of patients with newly-diagnosed early CP was 1680 (95% CI 1430–1930), with an incidence of 1.3 per 100,000 persons. Compared with the 2011 surveys [8, 11], the estimated numbers of patients with CP and early CP were decreased by 15.6 and 17.2%, respectively (Supplementary Fig. 2).

Second-stage survey

In the second survey, we obtained detailed clinical information in 2,150 (1914 definite and 236 probable) patients with CP and 249 patients with early CP.

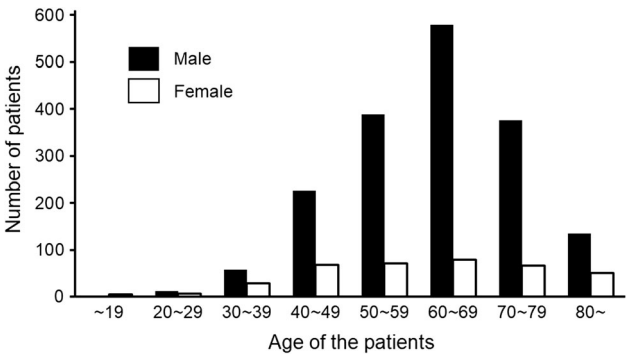

Fig. 1 Age distribution of patients with definite/probable CP according to sex

Table 3 Comparison of complications between alcoholic CP and idiopathic CP

Complications	Total (%)	Alcoholic CP (%)	Idiopathic CP (%)	*P* value[#]
Diabetes mellitus	893/2112 (42.3)	637/1479 (43.1)	201/499 (40.3)	0.28
Pancreatic exocrine dysfunction	524/1596 (32.8)	372/1108 (33.6)	122/400 (30.5)	0.26
Calcifications	1435/2130 (67.4)	1045/1487 (70.3)	299/501 (59.7)	< 0.001
Pseudocyst	532/2120 (25.1)	439/1483 (29.6)	56/501 (11.2)	< 0.001
Bile duct stenosis	304/2116 (14.4)	249/1483 (16.8)	35/499 (7.0)	< 0.001
Pseudoaneurysm	76/2122 (3.6)	68/1487 (4.6)	6/499 (1.2)	0.001
Ascites	42/2120 (2.0)	39/1484 (2.6)	2/501 (0.4)	0.001
Pleural effusion	40/2120 (1.9)	37/1487 (2.5)	1/499 (0.2)	< 0.001
Duodenal stenosis	28/2111 (1.3)	24/1475 (1.6)	2/501 (0.4)	0.04

CP chronic pancreatitis [#]: alcoholic CP vs. idiopathic CP

Clinical profiles of definite/probable CP cases

The male-to-female sex ratio was 4.8:1 (1777 men and 373 women). The mean age (SD) was 61.9 (13.3) years: 62.2 (12.6) years in men and 60.2 (16.4) years in women (Fig. 1). The most affected ages were 60–69 years in both male and female patients. The mean age at disease onset was 54.5 (15.2) years: 54.9 (14.3) in males and 52.5 (18.6) years in females (Supplementary Fig. 3).

Alcoholic and idiopathic CP accounted for 72.0 and 23.7% of cases, respectively. Alcohol was the most common cause (79.1%) in male patients, while idiopathic was the most common cause in female patients (55.0%). Smoking history was reported in 1970 cases, and 1372 (69.6%) were smokers (750 current and 622 ex-smokers). A total of 992 (561 current and 431 past) out of 1243 (79.8%) patients with alcoholic CP and 193/465 (41.5%) patients with idiopathic CP had a smoking history. If stratified by sex, 1247/1623 (76.8%) male and 125/347 (36.0%) female patients with CP had a smoking history. These figures were higher than those in the Japanese general population between 50 and 59 years (54.3% in men and 16.3% in women) in 2016. Previous AP episodes were reported in 1024/2032 (50.4%) cases.

The complications are shown in Table 3. DM was reported in 893/2112 (42.3%) patients, and pancreatic exocrine dysfunction was reported in 524/1596 (32.8%) patients. For the assessment of pancreatic exocrine dysfunction, the N-benzoyl-l-tyrosyl-p-aminobenzoic acid (BT-PABA) test was performed in 268/2136 (12.5%) cases, and the results were reported in 255 cases. Urinary PABA excretion was decreased ($\leq$ 70%) in 172 (67.5%) cases. Pancreatic calcifications and pseudocysts were reported in 1435/2130 (67.4%) and 532/2120 (25.1%) cases, respectively. We compared the frequency of complications between patients with alcoholic CP and idiopathic CP. Compared with idiopathic CP, alcoholic CP had a higher frequency of calcifications, pseudocysts, bile duct stenosis, pseudoaneurysm, ascites, pleural effusion, and duodenal stenosis.

Table 4 shows the treatment. Camostat mesilate, a protease inhibitor, was used in 1205/1977 (61.0%) cases. Digestive enzymes were used in 756/2057 (36.8%) cases. Among the 172 patients with pancreatic exocrine dysfunction on the BT-PABA test, 97 (56.4%) received enzyme therapy. The name of the digestive enzymes was reported in 728 cases; pancrelipase was most commonly used in 522 (71.7%) cases, followed by berizym combination granules in 118 (16.2%) and excelase combination granules in 51 (7.0%) cases. Endoscopic therapy was performed in 707/2121 (33.3%) cases, extracorporeal shock wave lithotripsy in 328/2107 (15.6%), and surgery in 345/2091 (16.5%). Compared with idiopathic CP, alcoholic CP had a higher frequency of patients receiving camostat mesilate, digestive enzymes, endoscopic therapy, and surgery.

Table 4 Comparison of treatment between alcoholic CP and idiopathic CP

Treatment	Total (%)	Alcoholic CP (%)	Idiopathic CP (%)	*P* value[#]
Camostat mesilate	1205/1977 (61.0)	829/1358 (61.0)	267/479 (55.7)	0.042
Digestive enzymes	756/2057 (36.8)	568/1450 (39.2)	150/486 (30.9)	0.001
Endoscopic therapy	707/2121 (33.3)	522/1497 (34.9)	138/499 (27.7)	0.003
ESWL	328/2107 (15.6)	234/1485 (15.8)	73/497 (14.7)	0.62
Surgery	345/2091 (16.5)	264/1479 (17.8)	60/497 (12.1)	0.004

CP chronic pancreatitis; *ESWL* extracorporeal shock wave lithotripsy. [#]: alcoholic CP vs. idiopathic CP

Clinical profiles of early CP cases

We collected detailed clinical information on 249 patients (141 men and 108 women; male-to-female ratio, 1.3:1) fulfilling the diagnostic criteria for early CP according to the DC2009. The distributions of age stratified by sex are shown in Supplementary Fig. 4. The mean age (SD) was 59.7 (12.8) years: 61.6 (12.8) in men and 57.1 (13.7) in women. The mean age at disease onset was 54.5 (14.1) years: 56.2 (14.2) in men and 52.4 (13.7) in women. Idiopathic and alcohol were the two most common etiologies, accounting for 51.0 and 45.8% of cases, respectively. In male patients, the most common cause was alcoholic (65.2%), followed by idiopathic (30.5%). In female patients, idiopathic pancreatitis accounted for the majority of the cases (77.8%).

Of the 249 patients with early CP, 177 (71.1%) fulfilled 2 clinical signs in the diagnostic criteria, 63 (25.3%) patients fulfilled 3, and 9 (3.6%) fulfilled 4. A total of 221 (88.8%) patients had recurrent upper abdominal pain, and 195 (78.3%) had abnormal pancreatic enzyme levels in the serum or urine. Sixty-seven (26.5%) patients had pancreatic exocrine dysfunction. Ninety-six (38.6%) patients, all alcoholic early CP, had a history of continuous heavy alcohol consumption equivalent to or more than 80 g/day of pure ethanol. Of note, 19/114 (16.7%) patients were diagnosed with alcoholic early CP although the amount of alcohol consumption was less than 80 g/day. Fifty-five (22.1%) patients had a past history of AP. Patients with a past history of AP had earlier disease onset than those without (49.5 ± 15.8 years vs. 55.9 ± 13.3 years; $P = 0.023$).

Comparison of clinical profiles between the definite/probable CP and early CP cases

We then compared the clinical profiles of 249 patients with early CP with those of 2150 patients with definite/probable CP (Table 5). The proportions of female cases and idiopathic cases were higher in patients with early CP compared with those in patients with definite/probable CP. The mean age at disease onset was 54.5 years in both groups. The proportions of patients with smoking history, DM, and past history of AP were lower in patients with early CP than in those with definite/probable CP. Of note, age at disease onset in patients with early CP with a past history of AP was 49.5 ± 15.8 years, which was younger than that in patients with definite/probable CP ($P = 0.004$).

Validation of DC2019 in patients with early CP diagnosed according to DC2009

The Japan Pancreas Society proposed the revised clinical diagnostic criteria for CP in 2019 (DC2019) [13]. Although the definition of continuous alcohol drinking was decreased to 60 g/day of pure ethanol, and pancreatitis-associated gene mutation and past history of AP were newly incorporated, three, but not two, diagnostic items are required

Table 5 Comparison of clinical profiles between definite/probable CP and early CP

	Definite/probable CP (*n*=2150)	Early CP (*n*=249)	*P* value
Sex			< 0.001
Male, *n* (%)	1777 (82.7)	141 (56.6)	
Female, *n* (%)	373 (17.3)	108 (43.4)	
Age[#]	61.9 ± 13.3	59.7 ± 13.4	0.014
Age at onset[#]	54.5 ± 15.2	54.5 ± 14.1	0.97
Etiology			< 0.001
Alcoholic, *n* (%)	1513 (72.0)	114 (45.8)	
Idiopathic, *n* (%)	498 (23.7)	127 (51.0)	
Others, *n* (%)	91 (4.3)	8 (3.2)	
Smoking history			< 0.001
Yes (current and past), *n* (%)	1372 (69.6)	102 (41.0)	
No, *n* (%)	598 (30.4)	147 (39.0)	
Diabetes mellitus			< 0.001
Yes, *n* (%)	893 (42.3)	48 (19.3)	
No, *n* (%)	1219 (57.7)	201 (80.7)	
Past history of AP			< 0.001
Yes, *n* (%)	1024 (50.4)	55 (22.1)	
No, *n* (%)	1008 (49.6)	194 (77.9)	

[#]: Data are shown as mean ± standard deviation. *AP* acute pancreatitis; *CP* chronic pancreatitis

Table 6 Comparison of the clinical features between the patients whose diagnosis remained as early CP and those whose diagnosis was downgraded according to DC2019

	Early CP group (n = 93)	Downgraded group (n = 156)	P value
Sex			0.09
Male, n (%)	59 (63.4)	82 (52.6)	
Female, n (%)	34 (36.6)	74 (47.4)	
Age[#]	58.3 ± 14.7	60.5 ± 12.5	0.21
Age at onset[#]	51.9 ± 15.3	56.0 ± 13.2	0.034
Etiology			< 0.001
Idiopathic, n (%)	31 (33.3)	96 (61.5)	
Alcoholic, n (%)	59 (63.4)	55 (35.3)	
Others, n (%)	3 (3.2)	5 (3.2)	
Smoking status			0.036
Current/ever, n (%)	45 (51.7)	57 (37.7)	
Never, n (%)	42 (48.3)	94 (62.3)	
Number of positive clinical signs in DC2009[#]	2.66 ± 0.58	2.13 ± 0.41	< 0.001
Number of positive EUS findings in DC2009[#]	3.15 ± 0.80	2.78 ± 0.90	0.001
EUS findings in DC2019			
Hyperechoic foci (non-shadowing) or strands, n (%)	90 (96.8)	152 (97.4)	0.72
Lobularity, n (%)	37 (39.8)	39 (25.0)	0.016
Hyperechoic MPD margin, n (%)	63 (67.7)	86 (55.1)	0.06
Dilated side branches, n (%)	14 (15.1)	29 (18.6)	0.60
Past history of AP			< 0.001
Yes, n (%)	45 (48.4)	10 (6.4)	
No, n (%)	48 (51.6)	146 (93.6)	
Diabetes mellitus			0.51
Yes, n (%)	16 (17.2)	32 (20.6)	
No, n (%)	77 (82.8)	123 (79.4)	

[#]: Data are shown as mean ± standard deviation. *AP* acute pancreatitis; *CP* chronic pancreatitis; *DC2019* Japanese clinical diagnostic criteria for CP 2019; *EUS* endoscopic ultrasonography; *MPD* main pancreatic duct

for the diagnosis of early CP in DC2019. Similar EUS findings were consolidated; lobularities with and without honeycombing were consolidated to lobularity, and hyperechoic foci without shadowing and stranding were consolidated to hyperechoic foci (non-shadowing) or strands. We therefore validated DC2019 in patients with early CP diagnosed according to DC2009. Among the 249 patients with early CP diagnosed according to DC2009, the diagnosis of 93 (37.3%) patients remained as early CP, and that of 156 (62.7%) patients was downgraded because they did not fulfill the DC2019 due to the number of positive clinical features < 3 (n = 112, 71.8%), the number of EUS findings < 2 (n = 23, 14.7%), and both (n = 21, 13.5%). Therefore, revision of the clinical features affected the diagnosis more than that of EUS findings. Among the 177 patients whose positive diagnostic items were two in DC2009, 37 patients fulfilled DC2019 because they had past history of AP (n = 27), drinking history of ≥ 60 g in ethanol (n = 6), both past history of AP and drinking history of ≥ 60 g in ethanol (n = 3), and a *SPINK1* mutation (n = 1). The diagnosis of the 156 downgraded cases according to DC2019 was as follows: possible early CP in 112 cases, possible CP in 23 cases, and other diseases (if any) in 21 cases.

We compared the clinical profiles between the 93 patients whose diagnosis remained as early CP ("early CP group") and those whose diagnosis was downgraded according to DC2019 ("downgraded group"). The numbers of positive clinical signs and EUS findings were higher in the early CP group than in the downgraded group. Alcohol-related etiology, smoking history, early disease onset, and past history of AP were associated with the maintenance of early CP diagnosis according to DC2019 (Table 6). Regarding the EUS findings in DC2019, lobularity was more frequently detected in the early CP group than in the downgraded group (P = 0.016).

Discussion

Here, we conducted a nationwide epidemiological survey to clarify the current status of CP in Japan. The estimated number of patients with definite/probable CP in 2016 was 56,520, with a prevalence rate of 44.5 per 100,000 persons, and that of patients with newly diagnosed CP was 14,740, with an incidence of 11.6 per 100,000 persons. These figures are roughly similar to those in Western countries. A meta-analysis of three studies showed that the annual incidence of CP was 9.6 per 100,000 persons [18]. The prevalence of CP in Europe ranges from 44.0 to 143 per 100,000 persons [19, 20] and from 41.8 to 91.9 per 100,000 persons in the United States [21, 22]. Compared with those in the 2011 survey [8], the prevalence and incidence of CP in Japan decreased in 2016 by 15.6 and 17.2%, respectively. As in the case of other Western countries, the consumption of alcohol and tobacco, the two major risk factors for CP [1–3], has been decreasing in the last two decades in Japan (https://www.nta.go.jp/english/publication/agency_report/index.htm) (https://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html). Importantly, alcohol consumption and smoking ratio in women, especially young women, are steady. In females, the proportion of alcoholic CP increased from 29.5% in 2011 to 37.6% in 2016. The smoking ratio in these patients in women was 70.4%, which is much higher than that in the general female population (8.2%). Female patients develop alcoholic CP at younger ages, with shorter duration and smaller cumulative amounts of alcohol consumption than male patients [23]. Proper lifestyle management of female patients with pancreatitis requires more attention.

Compared with patients with idiopathic CP, those with alcoholic CP developed complications and required treatments including endoscopic therapy and surgery more frequently. This is consistent with previous studies showing that patients with alcoholic CP have a more severe course of CP than those with idiopathic CP [24, 25]. Very recently, Olesen et al. [26] reported distinct complication clusters associated with etiological risk factors. They showed that alcoholic etiology was associated with inflammatory complications such as pseudocysts, ascites, and pleural effusion, whereas smoking was associated with fibrosis-related complications such as pancreatic duct lesions, common bile duct stenosis, and duodenal stenosis [26]. On the other hand, although enzyme therapy was more frequently performed in patients with alcoholic CP, we were unable to demonstrate an association between alcoholic etiology and pancreatic exocrine dysfunction. One explanation may be the difficulty in diagnosing pancreatic exocrine dysfunction in Japan due to the limited availability and accuracy of the pancreatic exocrine function test. Currently, the BT-PABA test is the only test covered by medical insurance. The fecal elastase-1 test, which is commonly performed in Europe [27], cannot be used in daily practice in Japan. The BT-PABA test indirectly measures the pancreatic exocrine function, but it is not feasible, less sensitive, and less specific [28]. In this survey, the BT-PABA test was performed in only 12.5% of cases. Importantly, even in patients showing pancreatic exocrine dysfunction on the BT-PABA test, nearly half of the patients did not receive pancreatic enzyme therapy. Proper diagnosis and management of pancreatic exocrine dysfunction are essential to improve the quality of life in patients with CP.

A previous nationwide survey in 2011 and prospective study of early CP showed that the clinical profiles differed between the patients with definite CP and early CP [11, 12]. This 2016 survey confirmed this finding: a higher proportion of female and idiopathic cases but lower proportions of cases with smoking history, DM, and past history of AP in early CP. These results further support the need to revise DC2009 to select patients who are likely to progress more efficiently. In DC2019 [13], we focused on the assessment of risk factors for CP; we adopted past history of AP and genetic factors as new diagnostic items. AP and recurrent AP are important processes leading to early CP in the mechanistic definition [1]. Although the age at disease onset was similar between the patients with definite/probable CP and early CP, it was earlier in patients with early CP with a history of AP than in those with definite/probable CP. Regarding genetic factors, we identified p.R122H and p.N29I mutations in the *PRSS1* gene and p.N34S and c.194 + 2 T > C mutations in the *SPINK1* gene as typical pancreatitis-associated mutations in DC2019. In the Japanese diagnostic criteria for hereditary pancreatitis (HP) [29], the diagnosis of HP can be made in the presence of these *PRSS1* mutations, even if a family history of pancreatitis was absent. A meta-analysis of 24 studies showed that the overall risk of CP due to the *SPINK1* p.N34S mutation was 11.0-fold, of which 15.0-fold for idiopathic CP [30]. A meta-analysis of 13 studies showed that the *SPINK1* c.194 + 2 T > C mutation is a very strong risk factor in East Asia, where this mutation increases the CP risk by 73.2-fold [31] In addition, in a nationwide survey of HP in Japan, *PRSS1* and *SPINK1* mutations were found in 41 and 36% of the families, respectively [32]. Currently, genetic testing of pancreatitis-associated genes is not covered by medical insurance and conducted on a research basis in Japan. The inclusion of other pancreatitis-associated mutations, such as the recently identified *TRPV6* [33] in the diagnostic criteria, requires further discussion.

Among the 249 patients with early CP diagnosed according to DC2009, the diagnosis of 37% of cases

remained as early CP, but that of the remaining 63% was downgraded mainly due to insufficient fulfillment of the diagnostic items. This finding was expected because DC2019 intended to increase the specificity of its diagnostic ability [13]. The maintenance of early CP diagnosis was associated with alcohol-related etiology, smoking history, early disease onset, and the presence of a past history of AP. These profiles are similar to those in patients with definite/probable CP, suggesting the ability of DC2019 to identify patients who are at a high risk for progression more efficiently. Incorporation of MRCP findings would contribute to the diagnosis of early CP in daily practice because EUS is not widely performed and endoscopic retrograde cholangiopancreatography is rarely performed for the diagnosis of CP in Japan. Further prospective studies are warranted to validate DC2019.

This study has several limitations. This is a retrospective study, and cases reported in the second survey did not fully resemble the 56,520 estimated CP cases because cases reported from small hospitals were limited due to the low sampling and response rates. The overall response rate in the first survey (34.1%) was lower than that in the 2011 survey (45.8%). Nevertheless, this study has several strengths. We could assess the trend of the estimated numbers of patients with CP over decades because we used the same framework of the previous nationwide epidemiological surveys. Detailed clinical information, including diagnosis, lifestyle, imaging findings, and management, was available in more than 2000 patients treated across Japan in a single year. This is the first study to validate DC2019 in patients with early CP diagnosed according to DC2009. We expect that the up-to-date information obtained in this study would contribute to the improved prognosis of patients with this intractable disease.

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Compliance with ethical standards

Conflict of interest Masamune A received a lecture fee from Mylan EPD.

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