[Title]

Current Situation and Problems in Diagnosis of Early Chronic Pancreatitis

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[Running title]
Diagnosis of early chronic pancreatitis

[Abstract]
Objectives: The Japan Pancreas Society introduced the concept of early chronic pancreatitis (ECP) in 2009, but its epidemiology remains unclear. This study investigated challenges in ECP diagnosis.
Methods: ECP was diagnosed in four cohorts between April 2019 and November 2021 using the Clinical Diagnostic Criteria for Chronic Pancreatitis 2019. These cohorts included patients with abdominal/back pain, abnormal pancreatic enzyme levels, ECP suspected due to other reasons, and those who underwent endoscopic ultrasonography (EUS) for other diseases.
Results: A total of 2502 cases were analyzed and 150 (40 alcoholic and 110 non-alcoholic) cases with ECP findings on EUS were included. ECP was confirmed in 14 (9%) cases, including 9 (22.5%) alcoholic and 5 (4.5%) non-alcoholic cases. ECP was confirmed in 15%, 0%, 2.2%, and 0.13% cases in the four cohorts, respectively. ECP was confirmed in 10 (48%) of the 21 (14%) cases with pancreatic pain.
Conclusions: ECP diagnostic rate was low, particularly in non-alcoholic cases, but was slightly higher in cases with pancreatic pain. The diagnostic rate was highest in the abdominal/back pain group. Further studies are required to establish appropriate diagnostic criteria for ECP.

[Key words]
early chronic pancreatitis, endoscopic ultrasonography, pancreatic pain

[Introduction]

Chronic pancreatitis (CP) is an irreversible condition caused by persistent pancreatic injury or stress[1)] and has a poor prognosis because of complications, including diabetes and pancreatic cancer. [2)]

To improve prognosis of CP, early diagnosis and intervention are necessary. In 2009, Japan Pancreas Society (JPS) proposed clinical diagnostic criteria for chronic pancreatitis (CDCCP) definition of ECP, it was the first diagnostic criteria for early chronic pancreatitis (ECP) in the world[3)]. In CDCCP2009, ECP was diagnosed when diagnostic items and imaging findings were met (Table1). As EUS can evaluate pancreatic parenchyma and ductal change because of its spatial resolution [4) 5)], it is important in the diagnosis of ECP, which must capture subtle findings that do not lead to CP. Internationally, a consensus proposal named “mechanistic definition” including the concept of ECP was developed in 2016 [1)]. The mechanistic definition defined CP as a fibrotic and inflammatory syndrome of the pancreas that occurs in patients with genetic, environmental, or other risk factors. It also defines ECP as a reversible stage of chronic pancreatitis.

In 2019, CDCCP2019 was published, revising CDCCP2009 to increase diagnostic specificity. [6)] CDCCP2019 included back pain, pancreatitis-related genes, and history of acute pancreatitis in the diagnostic criteria and reduced the criteria for heavy alcohol consumption from 80 g to 60 g of pure ethanol.

The criteria for endoscopic ultrasonography (EUS) findings were simplified and definitions were

added. Patients with imaging findings and ≥ 3 diagnostic items were diagnosed as confirmed ECP, while imaging findings with two diagnostic items were diagnosed as probable ECP **(Table 1)**.

The concept of ECP consists of clinical findings (abdominal pain, genetic factor, history of alcohol, history of acute pancreatitis), abnormality of pancreatic enzyme, and imaging findings[5]. Similarly, ~~Clinically,~~ ECP may be suspected in three groups of patients in clinical practice. The first group includes patients with abdominal pain; differential diagnoses include peptic ulcers, functional dyspepsia (FD), and gastroesophageal reflux disease (GERD), among others. [7] The second group includes patients with an incidental finding of abnormal pancreatic enzyme levels. These patients are usually asymptomatic, which makes the diagnosis difficult. The third group includes cases with ECP findings on EUS performed for other reasons. ECP can be diagnosed by performing EUS on the first two groups and by checking for clinical signs on the last group.

Although > 10 years have passed since the concept of ECP was introduced, the number of patients diagnosed with ECP remains small, particularly among non-alcoholic cases[8]. Therefore, its epidemiology is unclear and there are no appropriate treatment guidelines. The purpose of this study was to determine retrospectively the number of ECP cases using EUS based on CDCCP2019. We focused on the three cohorts previously mentioned and evaluated the clinical problems in ECP diagnosis.

[Materials and methods]

Study design

This was single-center, retrospective analysis performed between April 2019 and November 2021 at Juntendo University Hospital. The study was approved by the ethics committee of Juntendo University and informed consent was obtained through an opt-out on the university website.

Patients

Patients who underwent EUS between April 2019 and November 2021 at Juntendo University Hospital with findings of ECP were included. Patients diagnosed with malignant tumors and definite CP based on CDCCP2019 were excluded.

EUS findings

EUS was performed using EG-580UT, EG-740UT (Fujifilm Holdings Corp., Tokyo, Japan), GF-UCT260, and GF-UE260 (Olympus Corp., Tokyo, Japan) devices. Pancreatologists with an experience of at least 500 EUSs performed or supervised the procedure. And examination before CDCCP2019 was published, two pancreatologists reviewed and assessed the EUS images based on CDCCP 2019. EUS findings in CDCCP 2019 include: (1) hyperechoic foci or strands, (2) lobularity, (3) hyperechoic main pancreatic duct (MPD) margins, and (4) dilated side branches. The presence of two or more of these findings, including at least one of the first two, was required**.**

Reasons for EUS

We established several cohorts based on the reasons for performing EUS.

A total of 2502 EUS examinations were performed during the study period, which were divided into two major cohorts, suspected ECP (n = 260) and other diseases (including pancreatic cysts, pancreatic tumors, biliary disease, high tumor marker levels; n = 2242).

The suspected ECP group was further subdivided into those who underwent EUS for abdominal or back pain (n = 54), abnormal pancreatic enzyme levels (n = 61), and other reasons (other suspected ECP group: including MPD dilatation or stricture and acute pancreatitis, etc.; n = 145). In case symptoms or pancreatic enzyme abnormalities were identified later on chart review, the reason at the time EUS was ordered was recorded as "reason for EUS". Thus, a total of four cohorts were defined.

A total of 157 cases had ECP findings on EUS. Seven cases were excluded (five pancreatic cancers, one esophageal cancer, and one confirmed CP) and 150 cases were included **(Figure 1)**.

ECP diagnosis

The CDCCP 2019 includes the following diagnostic criteria: (1) repeated upper abdominal pain or back pain, (2) abnormal pancreatic enzyme levels in the serum or urine, (3) abnormal pancreatic exocrine function, (4-1) continuous heavy drinking of alcohol equivalent to or more than 60g/day of pure ethanol, (4-2) pancreatitis-related genetic abnormalities, and (5) history of acute pancreatitis. These diagnostic items were analyzed by reviewing charts. Patients who fulfilled ≥ 3 diagnostic items were diagnosed with definite ECP, while those who fulfilled 2 items were diagnosed as probable ECP. In addition, patients with only 1 diagnostic item were labeled as "possible ECP".

Abnormal pancreatic enzyme levels in the serum or urine

Serum and urine pancreatic enzyme levels, including pancreatic amylase, lipase, trypsin, phospholipase A2, elastase 1, and urinary amylase, were analyzed. To increase the specificity, total amylase abnormalities were not considered pancreatic enzyme abnormalities.

Repeated upper abdominal or back pain

Based on the current diagnostic criteria, symptoms of FD and GERD were considered "repeated upper abdominal or back pain". Therefore, we had to differentiate between pancreatic pain (PP) and non-PP. We defined PP when any of the following were met; 1)back pain, 2)pain that is associated with alcohol or fat intake 3)pain that improves with camostat mesylate or pancrelipase.

History of acute pancreatitis

Patients were considered to have a history of idiopathic acute pancreatitis if alcoholic, cholelithic, and hypertriglyceridemic causes could be ruled out.

[Results]

Patient characteristics

During the study period, 2502 patients who underwent EUS at Juntendo University were reviewed and 150 cases were enrolled **(Figure 1)**.

Patient characteristics are shown in **Table 2**. The mean age (range) was 62 (20–85) years and 110 patients (73%) were male. Repeated upper abdominal or back pain, abnormal pancreatic enzyme levels

in the serum or urine, and abnormal pancreatic exocrine function, continuous heavy drinking of alcohol equivalent to or more than 60g/day of pure ethanol, and pancreatitis-related genetic abnormalities were present in 43 (29%), 83 (55%), 0 (not analyzed), 40 (27%), and 0 (not analyzed) patients, respectively.

ECP diagnosis

Among the 150 included cases (40 non-alcoholic and 110 alcoholic cases), 14 (9.3%) were definite ECP, including 5 non-alcoholic (5/110; 4.5%) and 9 alcoholic (9/40; 22.5%) cases.

There were 43 (28.6%) probable ECP cases, including 21 non-alcoholic (21/110; 19%) and 22 alcoholic (22/40; 55%) cases, and 61 (41%) possible ECP cases, including 52 non-alcoholic (52/110; 47.3%) and 9 alcoholic (9/40; 22.5%) cases **(Table 3).**

Among the 2502 patients who underwent EUS, there were 0.6% (14/2502), 1.7% (43/2502), and 2.4% (61/2502) definite, probable, and possible ECP cases, respectively.

ECP diagnosis based on the reason for EUS

ECP diagnosis was analyzed based on the reason for EUS (**Table 4)**. Suspected ECP and other disease groups included 47 (31%) and 103 (69%) patients, respectively. In the suspected ECP group, the number of cases per diagnosis for definite, probable, and possible ECP and those negative for any diagnostic items were 11 (23%), 24 (51%), 12 (26%), and 0, respectively. In the other disease group, the numbers were 3 (2.9%), 19 (18%), 49 (48%), and 32 (31%), respectively.

A comparison of the 2502 cases who underwent EUS and the number of included cases for each of the four groups (abdominal or back pain, abnormal pancreatic enzyme levels, other suspected ECP, and other disease groups) are as follows.

The abdominal or back pain group (n = 54) included 25 (46%) cases that had ECP findings on EUS, including 8 (15%), 15 (28%), 2 (3.7%), 0 (0%) cases of definite, probable, and possible ECP and those negative for diagnostic items, respectively.

In the abnormal pancreatic enzyme levels group (n = 61), 2 cases (3.3%) were included, i.e., 1 (1.6%) case of confirmed and possible ECP each.

In other ~~the~~ suspected ECP group (n = 145), 20 cases (14%) were included: 3 (2.1 ~~.21~~%), 8 (5.5%), 9 (6.2%), and 0 (0%) confirmed, probable, and possible ECP and cases negative for diagnostic items, respectively.

In the other diseases group (n = 61), 2 cases (3.3%) were included, including 0 (0%), 1 (1.6%), 1 (1.6%), and 0 (0%) definite, probable, and possible ECP and cases negative for diagnostic items, respectively **(Figure 2).**

ECP diagnosis based on symptoms

ECP cases sorted by symptoms are shown in **Table 5**. Among the 44 patients who reported repeated upper abdominal or back pain, 21 were included in the PP group. They included 10 (48%), 10 (48%), and 1 (5%) as definite, probable, and possible ECP cases. Among the 15 non-alcoholic cases, 14 were

definite or probable ECP cases. In the non-PP group, 3 (13%), 12 (52%), and 8 (35%) were definite, probable, and possible ECP cases.

Characteristics of definite ECP cases

In the present study, 13 patients were diagnosed with confirmed ECP **(Table 6)**, including 9 (9/13; 69%) males, 4 (4/13; 31%) non-alcoholic ECP, and 9 (9/13; 69%) alcoholic ECP cases. All four non-alcoholic cases had pancreatic pain and idiopathic acute pancreatitis, and fulfilled three diagnostic criteria each. Among the alcoholic patients, four and five patients fulfilled four and three criteria, respectively. Two of the 13 patients underwent EUS, but not for suspected ECP; both these patients had alcoholic ECP.

[Discussion]

In this study, we examined the number of patients in each ECP diagnostic category based on CDCCP 2019. Among the 150 ECP patients with EUS findings of ECP, 13 (9%), 44 (29%), 61 (41%), and 32 (21%) were diagnosed as definite, probable, and possible ECP and negative for any diagnostic items, respectively. Among the definite ECP cases, 69% (9/13) were alcoholic and 31% (4/13) were non-alcoholic cases. Among the probable ECP cases, alcoholic and non-alcoholic were 50% (22/44) each. A Japanese nationwide survey based on CDCCP 2009[8)] reported that most of the ECP cases were idiopathic (47.7%) and female (43%). However, large number of the CP are males and alcoholics. This difference was a drawback of CDCCP2009. Therefore, CDCCP was revised in 2019 to increase its

specificity. The present study shows a higher incidence of definite ECP among alcoholic and male individuals, which was the intended outcome of CDCCP 2019.

Elucidating the pathogenesis of ECP and establishing appropriate treatment is a future challenge, which will require accumulating cases and monitoring their long-term follow-up.

For alcoholic ECP, a correlation between alcohol consumption and progression has been reported. In a prospective study in Japan based on CDCCP2009[9], 4 of 83 ECP cases progressed to CP in the two years follow up, all of them were alcoholic ECP and continued to drink. In contrast, 13 alcoholic ECP cases abstained from alcohol and 3 of them improved from ECP. As the criteria for heavy alcohol consumption was lowered in the CDCCP 2019, more cases will be diagnosed, and as more cases are accumulated, the pathogenesis of the disease will be better understood.

Meanwhile, the pathogenesis of non-alcoholic ECP is poorly understood, which constitutes a challenge for the future. In the two year prospective study[9], 22 of 45 non-alcoholic ECP cases remained ECP, 23 cases improved from ECP, and no cases progressed to CP. Thus, the evidence for non-alcoholic ECP is insufficient, it is necessary to collect and research a sufficient number of cases, since the "mechanistic definition" also includes risk factors for CP other than alcohol[1]. But the number of cases diagnosed as non-alcoholic ECP is small, making it difficult to elucidate the pathogenesis. In fact, in this study, only 4 of the 110 non-alcoholic cases with ECP findings on EUS were diagnosed as definite ECP, while 9 of the 40 alcoholic cases were diagnosed as definite ECP. The reason for this can be

attributed to undeveloped diagnostic criteria.

Some diagnostic items were changed and added to the 2019 revision of CDCCP[6] (Table 1). However, the diagnosis of non-alcoholic cases remains problematic.

“Pancreatitis-related genetic abnormalities” was added for non-alcoholic cases as a parallel to “continuous heavy drinking of alcohol”. An association between PRSS and SPINK1 and hereditary pancreatitis has been reported[10) 11)], and mechanistic definition has also identified genetic factors as a risk for CP. International consensus statements for ECP diagnosis also reports genetic factors as an important consideration[12)]. However, genetic testing for ECP can only be performed at the research level, and there is currently no evidence for an association between ECP and genetic abnormalities.

Already included in CDCCP2009, “abnormal pancreatic exocrine function” has some problems. First, it is difficult to assess because of the complexity of the evaluation method. In Japan, only the N-Benzoyl-L-tyrosine p-aminobenzoic acid (BT-PABA) test is covered by insurance, which requires urine storage for 6 hours and multiple results must show a functional decline to fulfill the criteria. Besides, the test has low accuracy because of the PABA metabolic pathway and drug interactions. In addition, its effectiveness for evaluating exocrine dysfunction in ECP is questionable. Although pancreatic exocrine function was not assessed in this study, there were no cases with fatty stool or diarrhea that may suggest pancreatic exocrine hypofunction. A Japanese nationwide survey reported that 13.9% of the cases had “abnormal pancreatic exocrine function”, [8)] but symptoms related to

exocrine function remain unknown.

"History of acute pancreatitis" was also added to CDCCP 2019, but only a few cases meet this criterion. In the present study, only 17% (25/150) of the cases had a history of acute pancreatitis.

Furthermore, CDCCP 2019 requires three or more diagnostic items to confirm the diagnosis of ECP, while CDCCP 2009 required two or more diagnostic items for the diagnosis. Therefore, it is difficult to confirm the diagnosis of non-alcoholic ECP unless the "repeated upper abdominal or back pain", "abnormal pancreatic enzyme levels in the serum or urine", and "history of acute pancreatitis" are present.

International consensus statements for ECP diagnosis consider CDCCP to be limited by the inclusion of heavy alcohol consumption as a diagnostic item. [12] Therefore, non-alcoholic ECP may be considered a separate entity to that of alcoholic ECP. To improve the diagnostic criteria and to clarify the pathophysiology of ECP, probable non-alcoholic ECP should be treated and followed up like definite ECP.

Besides the low number of diagnoses, the accuracy of diagnosis is also a problem. In CDCCP 2019, symptoms of FD and GERD are considered a single item, which may lead to overdiagnosis. Symptoms of FD, GERD, and other diseases need to be differentiated from pancreatic symptoms. To address this issue, the present study trialed the concept of PP. The large numbers and proportions of definite and probable ECP cases in the PP group suggest that overdiagnosis may be avoided.

Medication efficacy in abdominal pain management was also used to diagnose PP based on previous reports. Yamawaki et al. reported that pancrelipase and camostat mesylate were more effective for epigastric pain in ECP compared to FD. [7] Sai et al. reported that the efficacy of camostat mesylate increased with an increase in the number of EUS findings. [13] Symptoms that were not included in the previous diagnostic criteria may help elucidate ECP pathophysiology.

We also classified the patients on the basis of the reason for EUS into suspected ECP or other diseases group. Suspected ECP cases were further classified into three subgroups: abdominal or back pain, abnormal pancreatic enzyme levels, and other suspected ECP groups. The abdominal or back pain group had the greatest proportion of definite and probable ECP cases (15% and 28%, respectively). Therefore, interventions for symptomatic cases, particularly those with PP, are advisable. The abnormal pancreatic enzyme levels group (without symptoms) had the lowest proportion of EUS findings (3.3%).

The “other diseases” group also had some notable findings. The proportion of cases with ECP findings on EUS (4.6%; 103/2242) in this group was lower compared to the suspected ECP group (21%; 54/260). These included 3 definite and 19 probable ECP cases, who underwent EUS for biliary tract disease, pancreatic cysts, or other reasons. The concept of ECP was proposed in Japan and is not yet widely recognized. Future studies are required to accumulate ECP data and elucidate its pathogenesis. Therefore, interviews and examinations focused on ECP should be performed even in patients

undergoing EUS for reasons unrelated to ECP. Meanwhile, widespread recognition of this disease concept is required. However, it has been suggested that imaging findings of ECP should not be overestimated. [12] Sato et al. reported that EUS findings of ECP may be present even in healthy individuals. [14] Sekine et al. analyzed the EUS findings and surgical ECP specimens, and found that only lobularity reflected the pathological findings. [15] Thus, validation of ECP findings in EUS is also an issue for the future.

CDCCP is a diagnostic criterion adopted only this in Japan, and it is not clear whether ECPs diagnosed with CDCCP truly progress to CP. To elucidate the pathophysiology of ECP, it will be necessary to accumulate ECP cases and develop appropriate diagnostic criteria through long-term follow-up, including factors discussed in this study.

The present study had the following limitations. First, it was a single-center, retrospective study with no follow-up. Second, CDCCP is a diagnostic criterion unique to Japan. Third, since EUS findings of ECP were analyzed by reviewing previous images, the incidence may have been underestimated.

[Conclusions]

This study highlights difficulties in the diagnosis of non-alcoholic ECP. The CDCCP 2019 requirements for diagnosis are very different for non-alcoholic and alcoholic cases. However, cases with PP had a relatively high incidence of ECP. Standards for evaluation of exocrine function and genetic abnormalities should be established. Further studies are required to accumulate ECP data and

establish diagnostic criteria based on symptoms and imaging findings characteristic of ECP.

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Figure 1: Flow diagram of the study

ECP: early chronic pancreatitis; EUS: endoscopic ultrasonography; CP: chronic pancreatitis

*1 Regardless of pancreatic enzyme abnormalities

*2 Without abdominal or back pain

*3 Suspicion based on other imaging, history of acute pancreatitis, etc.

*4 Other pancreatic diseases, biliary disease, etc.

Figure 2: Diagnosis based on EUS

ECP: early chronic pancreatitis; EUS: endoschopic ultrasonography; CP: chronic pancreatitis

*1 Regardless of pancreatic enzyme abnormalities

*2 Without abdominal or back pain

*3 Suspicion based on other imaging, history of acute pancreatitis, etc.

*4 Other pancreatic diseases, biliary disease, etc.

*5 Cases diagnosed with malignant tumors and definite CP were excluded

*6 Definite, probable, and possible ECP and those negative for all diagnostic items

Table 1. Diagnostic items and imaging findings for ECP in CDCCP 2009 and 2019

CDCCP2009	**CDCCP2019**
ECP: two or more diagnostic items and <A> or <B> in imaging findings	Definite ECP: three or more diagnostic items and <A> or <B> in imaging findings Probable ECP: two diagnostic items and <A> or <B> in imaging findings
【Diagnostic items】	【Diagnostic items】
(1) Repeated upper abdominal pain	(1) Repeated upper abdominal pain or back pain
(2) Abnormal pancreatic enzyme levels in the serum or urine	(2) Abnormal pancreatic enzyme levels in the serum or urine
(3) Abnormal pancreatic exocrine function	(3) Abnormal pancreatic exocrine function
(4) Continuous heavy drinking of alcohol equivalent to or more than 80g/day of pure ethanol	(4) Continuous heavy drinking of alcohol equivalent to or more than 60g/day of pure ethanol or pancreatitis-related susceptibility genes
	(5) History of acute pancreatitis
【Imaging findings】	【Imaging findings】
<A> EUS findings: two or more findings including at least one of (1)-(4)	<A> EUS findings: two or more findings including (1) or (2) or both
(1) Lobularity, honeycombing type	(1) Hyperechoic foci of Strands
(2) Nonhoneycombing lobularity	(2) Lobularity
(3) Hyperechoic foci	(3) Hyperechoic MPD margin
(4) Stranding	(4) Dilated side branches
(5) Cysts	
(6) Dilated side branches	
(7) Hyperechoic MPD margin	
<B> Irregular dilatation of three or more branch pancreatic ducts on ERCP	<B>Irregular dilatation of three or more branch pancreatic ducts on ERCP or MRCP

ECP: early chronic pancreatitis; CDCCP: clinical diagnostic criteria for chronic pancreatitis; EUS: endoscopic ultrasonography; MPD: main pancreatic duct; ERCP: endoscopic retrograde cholangiopancreatography ; MRCP: magnetic resonance cholangiopancreatography

Table2. Patient characteristics

Cases		150*1
Age	Mean (range)	62 (20-85)
Sex	Male	110 (73%)
Smoking (brinkman index)	0	75 (50%)
	1-399	36 (24%)
	≧ 400	39 (26%)
Steatorrhea	0	0 (0%)
Diagnostic items of CDCCP 2019		
Repeated upper abdominal pain or back pain		43 (29%)
	Upper abdominal pain	39 (26%)
	Back pain	12 (8%)
Abnormal pancreatic enzyme levels in the serum or urine		83 (55%)
	Pancreatic amylase	22 (15%)
	Lipase	57 (38%)
	Trypsin	53 (35%)
	Phospholipase A2	29 (19%)
	Elastase 1	9 (6%)
	Urinary amylase	1 (0.7%)
Continuous heavy drinking of alcohol equivalent to or more than 60g/day of pure ethanol		40 (27%)
History of acute pancreatitis		25 (17%)
	Alcoholic	6 (4%)
	Gall stone	1 (0.7%)
	Idiopathic	18 (12%)
Reason for EUS		
	Suspect of ECP*3	47 (32%)
	Other disease	103 (69%)

CDCCP: clinical diagnostic criteria for chronic pancreatitis; ECP: early chronic pancreatitis

*1 All 150 cases fulfilled the imaging findings of ECP based on CDCCP 2019

*2 Abnormal pancreatic exocrine function and pancreatitis-related susceptibility gene were not evaluated in this study

*3 Abdominal or back pain, abnormal pancreatic enzyme levels, history of acute pancreatitis, suspected at another hospital, etc.

Table3. Number of positive CDCCP 2019 diagnostic items

	≧3 items (Definite ECP)	2 items (Probable ECP)	1item (Possible ECP)	Negative for any items	Total
Cases	14 (9%)	43 (29%)	61 (41%)	32 (21%)	150*
Non-alcoholic cases	5	21	52	32	110
Alcoholic cases	9	22	9	0	40

CDCCP: clinical diagnostic criteria for chronic pancreatitis; ECP: early chronic pancreatitis

*1 All 150 cases fulfilled the imaging findings of ECP based on CDCCP 2019

Table 4: Number of positive CDCCP 2019 diagnostic items based on the reason for EUS

	≧3 items (Definite ECP)	2 items (Probable ECP)	1item (Possible ECP)	Negative for any items	Total
Cases	14 (9.3%)	43 (29%)	61 (41%)	32 (21%)	150*1
Suspect of ECP*2	11 (23%)	24 (51%)	12 (26%)	0	47
Non-alcoholic cases	4	16	11	0	31
Alcoholic cases	7	8	1	0	16
Other disease	3 (2.9%)	19 (18%)	49 (48%)	32 (31%)	103
Non-alcoholic cases	1	5	41	32	79
Alcoholic cases	2	14	8	0	24

CDCCP: clinical diagnostic criteria for chronic pancreatitis; EUS: endoscopic ultrasonography; ECP: early chronic pancreatitis

*1 All 150 cases fulfilled the imaging findings of ECP based on CDCCP 2019

*2 Abdominal or back pain, abnormal pancreatic enzyme levels, history of acute pancreatitis, suspected at another hospital, etc.

Table 5: Number of positive CDCCP 2019 diagnostic items based on the symptoms

	≧3 items (Definite ECP)	2 items (Probable ECP)	1item (Possible ECP)	Negative for any items	Total
Cases	14 (9.3%)	43 (29%)	61 (41%)	32 (21%)	150*1
Pancreatic pain*2	10 (48%)	10 (48%)	1 (5%)	-	21
Non-alcoholic cases	5	9	1	-	15
Alcoholic cases	5	1	0	-	6
Non pancreatic pain	3 (13%)	12 (52%)	8 (35%)	-	23
Non-alcoholic cases	0	7	8	-	15
Alcoholic cases	3	5	0	-	8
No symptom	1 (1%)	21 (20%)	52(49%)	32 (30%)	106
Non-alcoholic cases	0	5	43	32	80
Alcoholic cases	1	16	9	-	26

CDCCP: clinical diagnostic criteria for chronic pancreatitis; ECP: early chronic pancreatitis

*1 All 150 cases fulfilled the imaging findings of ECP based on CDCCP 2019

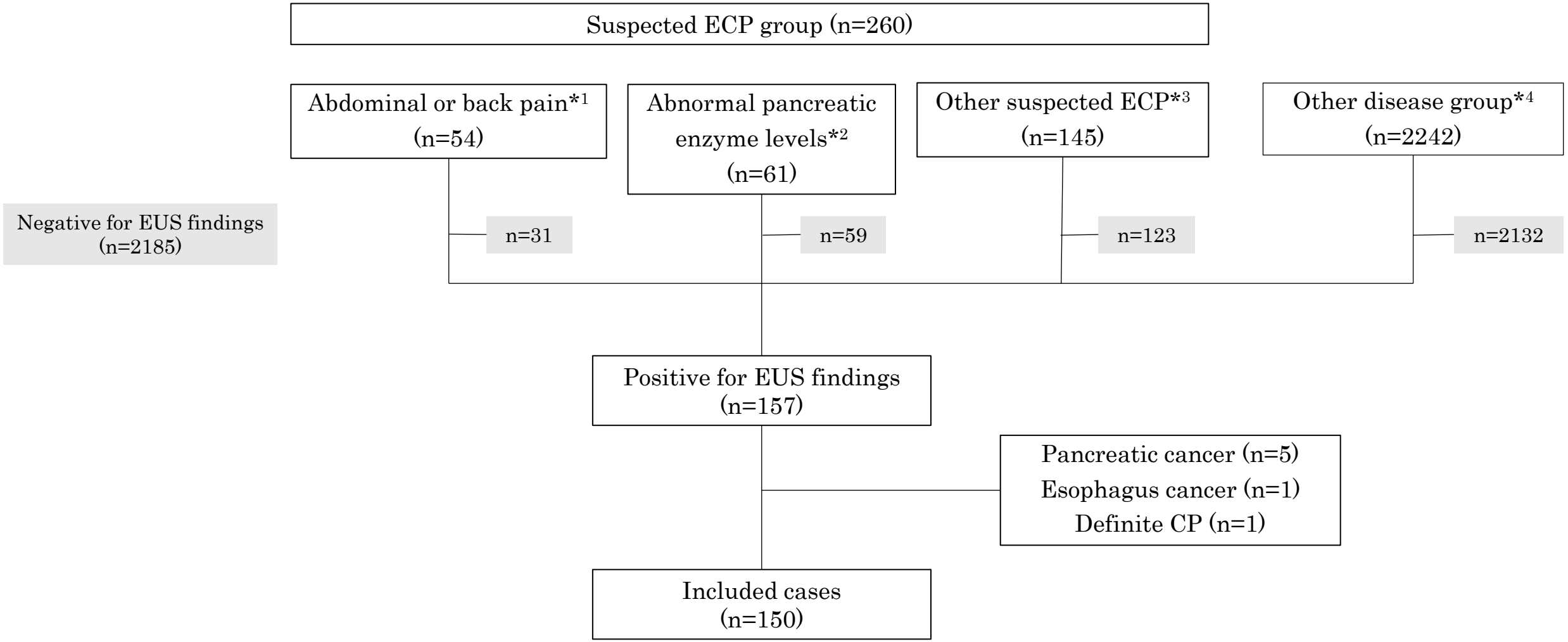
*2 Back pain/symptoms associated with alcohol or fat intake/medicine (pancrelipase, camostat mesyl) effectiveness

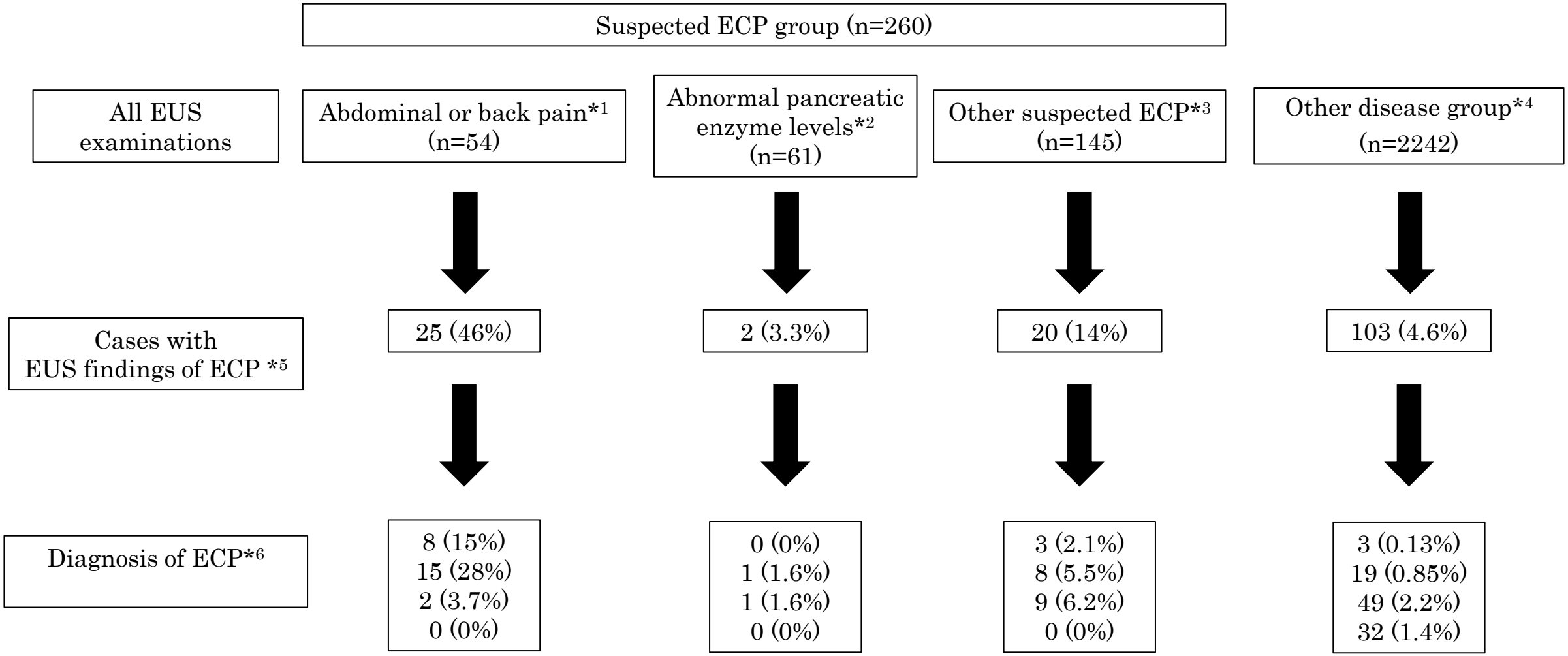
Table 6: Characteristics of definite ECP cases

Case	Age (years)	Sex	Alcohol intake (g/day)*	Etiology of ECP	Abdominal pain	Back pain	PP/Non-PP	Abnormal pancreatic enzyme levels	History of AP (±: etiology)	Reason for EUS	Number of positive diagnostic items in CDCCP 2019
1	66	M	20	Non-alcoholic	+	-	PP	+	+: Idiopathic	Suspect of ECP	3
2	66	F	0	Non-alcoholic	+	-	PP	+	+: Idiopathic	Suspect of ECP	3
3	66	F	0	Non-alcoholic	+	+	PP	+	+: Idiopathic	Suspect of ECP	3
4	45	F	10	Non-alcoholic	+	-	PP	+	+: Idiopathic	Pancreatic cyst	3
5	36	F	20	Non-alcoholic	+	+	PP	+	+: Idiopathic	Suspct of ECP	3
6	61	F	120	Alcoholic	+	-	PP	+	-	Suspect of ECP	3
7	59	M	100	Alcoholic	+	-	Non-PP	+	+: Alcoholic	Suspect of ECP	4
8	59	M	60	Alcoholic	+	+	PP	+	+: Idiopathic	Suspect of ECP	4
9	56	M	200	Alcoholic	-	-	-	+	+: Alcoholic	Suspect of pancreatic neoplasm	3
10	54	M	80	Alcoholic	+	-	Non-PP	+	-	Suspect of ECP	3
11	49	M	80	Alcoholic	+	-	PP	+	+: Alcoholic	Suspect of ECP	4
12	46	M	80	Alcoholic	+	-	Non-PP	+	-	Suspect of ECP	3
13	43	M	80	Alcoholic	-	+	PP	+	-	Suspect of ECP	3
14	33	M	120	Alcoholic	+	-	PP	+	+: Alcoholic	Pancreatic duct stenosis	4

ECP: early chronic pancreatitis; PP: pancreatic pain; AP: acute pancreatitis; EUS: endoschopic ultrasonography; CDCCP: clinical diagnostic criteria for chronic pancreatitis

* Pure ethanol equivalent


Suspected ECP group (n=260)
Abdominal or back pain*1 (n=54)
Abnormal pancreatic enzyme levels*2 (n=61)
Other suspected ECP*3 (n=145)
Other disease group*4 (n=2242)
Negative for EUS findings (n=2185)
n=31
n=59
n=123
n=2132
Positive for EUS findings (n=157)
Pancreatic cancer (n=5)
Esophagus cancer (n=1)
Definite CP (n=1)
Included cases (n=150)


Suspected ECP group (n=260)
All EUS examinations
Abdominal or back pain*1 (n=54)
Abnormal pancreatic enzyme levels*2 (n=61)
Other suspected ECP*3 (n=145)
Other disease group*4 (n=2242)
Cases with EUS findings of ECP *5
25 (46%)
2 (3.3%)
20 (14%)
103 (4.6%)
Diagnosis of ECP*6
8 (15%)
15 (28%)
2 (3.7%)
0 (0%)
0 (0%)
1 (1.6%)
1 (1.6%)
0 (0%)
3 (2.1%)
8 (5.5%)
9 (6.2%)
0 (0%)
3 (0.13%)
19 (0.85%)
49 (2.2%)
32 (1.4%)