

Prodromal Signs and Symptoms of Chronic Pancreatitis A Systematic Review

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Goal: We aimed to extract the percent of signs and symptoms at the time of diagnosis from published studies and to pool these using meta-analytic techniques.

Background: Delayed or misdiagnosis of chronic pancreatitis may occur because the signs and symptoms are nonspecific and varied.

Study: We performed a systematic review of studies reporting the signs and symptoms of chronic pancreatitis at diagnosis. The percentage of patients with each sign and symptom was extracted and random-effects meta-analyses used to calculate pooled percentages.

Results: In total, 22 observational studies were included. Across 14 studies, 55% of chronic pancreatitis patients were classified as having alcoholic etiology. Abdominal pain was the most common symptom (76%), and weight loss was reported in 22% of patients. Jaundice occurred in 11% of patients and steatorrhea in 3%. Half of the patients had a history of acute pancreatitis, and 28% had diabetes mellitus at diagnosis. Heterogeneity between the studies was high for all signs and symptoms.

Conclusions: This research has identified some common features of patients with chronic pancreatitis, but the high heterogeneity makes it difficult to draw solid conclusions. Carefully designed studies to examine the signs and symptoms leading up to a diagnosis of chronic pancreatitis, and common combinations, are required. These would enable the development of a tool to aid in the early

identification of chronic pancreatitis in the primary care setting, with potential for improved short-term and long-term outcomes for patients.

Key Words: diagnosis, pancreatic diseases, primary care
(*J Clin Gastroenterol* 2022;56:e1–e10)

Chronic pancreatitis occurs relatively uncommonly. The limited data available suggests that crude incidence ranges from ~4 to 8/100,000 population per year.^{1–4} It is thought, however, that these rates have been underestimated due to lack of diagnostic tools that are sufficiently sensitive to diagnose patients with early chronic pancreatitis⁵ and incomplete identification of cases based on clinical presentation.⁶

People living with chronic pancreatitis experience reduced quality of life, largely attributable to pain^{7–10} and weight loss,^{8,9} and the negative impact of the disease on employment patterns^{7,8,11} and social life. Early diagnosis is important for the management of symptoms and for reducing deterioration of pancreatic function. Dietary counseling and pancreatic enzyme replacement therapy can be implemented early to minimize malabsorption and

Received for publication December 15, 2020; accepted March 8, 2021.

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Supported by Mylan. Mylan played no role in the conduct of the study or the revision of the manuscript.

B.S.T.: helped in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis. S.P.: helped in study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding. B.D.: helped in study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. A.J.M.: helped in study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. D.C.: helped in study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. A.G. and Z.H.: helped in acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. J.A.W.: helped in study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. R.E.N.: helped in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding.

B.D. received a consultancy fee from Mylan for involvement on the expert panel: diabetes of the Exocrine Pancreas, as well as an educational grant (Handbook of Clinical Pancreatology) and a travel grant from Mylan. S.P. received a consultancy fee from Mylan for involvement on the expert panel: diabetes of the Exocrine Pancreas. A.J.M. received a consultancy fee from Mylan for involvement on the expert panel: diabetes of the Exocrine Pancreas. The remaining authors declare that they have nothing to disclose.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jcge.com.

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DOI: 10.1097/MCG.0000000000001544

TABLE 1. Description of Study Methods

References	Study Design and Setting	Main Research Question	Basis of Diagnosis	Reviewers
Agarwal et al ¹⁹	Retrospective cross-sectional; hospital pancreas clinic	Compare the natural course of alcoholic, idiopathic juvenile and idiopathic senile chronic pancreatitis	Mayo Clinic Diagnostic Criteria*	B.S.T. and Z.H.
Malka et al ²⁰	Prospective cohort; single hospital	The progression of diabetes mellitus in patients with chronic pancreatitis	At least one of: (i) ductal changes on (Cambridge grading score ≥ 3), (ii) typical histology, (iii) pancreatic calcifications on plain radiography, CT, US, EUS	B.S.T. and R.E.N.
Schwarzenberg et al ²¹	Cross-sectional; retrospective review of a prospective database; multicenter	Compare the natural course of adult and pediatric chronic pancreatitis	Definitive evidence of CP on endoscopic retrograde cholangiopancreatography using the Cambridge classification or MRCP, CT scan, or EUS (≥ 5 criteria or calcifications), or histologic evidence of CP	B.S.T. and Z.H.
Hirth et al ²²	Retrospective cross-sectional; multicentre hospital	Evaluate risk factors for pancreatic burnout in chronic pancreatitis	M-ANNHEIM†—definite and probable CP	B.S.T. and Z.H.
Machicado et al ²³	Retrospective cross-sectional; population-based	Examine the natural course of chronic pancreatitis	Mayo Clinic Diagnostic Criteria*	B.S.T. and Z.H.
Hao et al ²⁴	Cross-sectional; retrospective review prospective database; hospital	Compare the natural course of alcoholic and idiopathic chronic pancreatitis	Asia-Pacific consensus: pancreatic calcification, pancreatic ductal changes, abnormal pancreatic function, endoscopic ultrasound abnormalities, or histology	B.S.T. and Z.H.
Issa et al ²⁵	Retrospective cross-sectional; multicentre	Comparison and evaluation of diagnostic tools for chronic pancreatitis	Compares diagnostic tools (M-ANNHEIM, Lünburg, and Bülcher). Data from the Specialist diagnosis extracted	B.S.T. and Z.H.
Sheel et al ²⁶	Retrospective population-based; single hospital	Evaluation of diagnostic criteria of patients previously diagnosed with acute pancreatitis, chronic abdominal pain syndrome or minimal change endoscopic ultrasound of the pancreas	Japanese diagnostic criteria‡	B.S.T. and Z.H.
Hirota et al ²⁷ (data from Masamune et al ²⁸)	Retrospective survey; cross-sectional; multicentre hospital survey	Describe the prevalence, incidence and characteristics of chronic pancreatitis	Japanese diagnostic criteria‡ Includes cases of early CP (n = 6/1728)	B.S.T. and Z.H.
Hirota et al ²⁹	Retrospective survey; cross-sectional; multicentre hospital survey	Describe the prevalence, incidence and characteristics of chronic pancreatitis	Japanese diagnostic criteria‡ Definite and probable CP included	B.S.T. and Z.H.
Wang et al ³⁰	Prospective survey; cohort study; multicentre hospital	Describe the prevalence and characteristics of chronic pancreatitis	At least one of: (i) ductal changes on ERCP and/or MRCP (Cambridge grading score ≥ 3), (ii) a positive pancreatic exocrine function test, (iii) pancreatic calcifications, and (iv) EUS abnormalities suggestive of CP§	
Chen et al ³¹	Retrospective cross-sectional; hospital	Describe the clinical features of chronic pancreatitis	Japanese diagnostic criteria‡	B.S.T. and A.G.
Ryu et al ³²	Retrospective cross-sectional; multicentre hospital	Describe the clinical features of chronic pancreatitis and the associated risk of pancreatic cancer	Typical history and CT evidence of pancreatic calcification, or ERCP evidence of pancreatic ductal changes	B.S.T. and A.G.
Kimura et al ³³	Retrospective cross-sectional; single hospital	Describe the clinical features of patients with chronic pancreatitis complicated by bile duct stricture	Japanese diagnostic criteria‡	

Cavallini et al ³⁴	Prospective cohort; single hospital	Examine the natural course of chronic pancreatitis	Abdominal pain associated with an increase in pancreatic enzymes; and ≥ 1 of: ductal change evident on ERCP (Cambridge grading score ≥ 3), pancreatic calcifications and/or irregular main pancreatic duct at ultrasound and CT; and increased echogenicity with parenchymal heterogeneity at US	B.S.T. and A.G.
Balaji et al ³⁵	Prospective cohort; single hospital	Prevalence and clinical features of tropical chronic pancreatitis	≥ 1 of abdominal pain, diabetes mellitus, malabsorption/malnutrition, and, pancreatic calculi on x-ray, or abnormal US and abnormal bentiromide test	B.S.T. and A.G.
Chari et al ³⁶	Retrospective cross-sectional; multicentre hospital	Clinical features of alcoholic chronic pancreatitis and tropical chronic pancreatitis	≥ 1 of pancreatic calculi on x-ray (all patients) and US; ERCP evidence CP (Cambridge criteria); Abdominal pain with US evidence of CP and PEI (fecal chymotrypsin < 5.8 U/g)	B.S.T. and A.G.
Thomas et al ³⁷	Retrospective cross-sectional; single hospital	Surgical patients: Clinical features of tropical chronic pancreatitis	Pancreatic calculi, irregular pancreatic duct, cyst or bile duct stricture on x-ray or US, and/or pancreatic/biliary suctal abnormalities on ERCP, operative pancreatography or percutaneous transhepatic cholangiography	B.S.T. and A.G.
Hayakawa et al ³⁸	Retrospective cross-sectional; single hospital	Compare the natural course of alcoholic and idiopathic chronic pancreatitis	Radiologic evidence of pancreatic calcification, histology or presence of exocrine insufficiency	B.S.T. and A.G.
Masamune et al ²⁸	Retrospective survey; cross-sectional; multicentre hospital survey	Describe the clinicoepidemiological features of early chronic pancreatitis	Japanese diagnostic criteria for early chronic pancreatitis	B.S.T. and Z.H.
Masamune et al ³⁹	Prospective cohort study; multicentre hospital	Identify patients which patients with early chronic pancreatitis progress to definite chronic pancreatitis	Japanese diagnostic criteria for early chronic pancreatitis	B.S.T. and Z.H.
Wakabayashi et al ⁴⁰	Prospective cross-sectional; single hospital	Identify clinical signs and symptoms to distinguish early chronic pancreatitis among antiacid therapy-resistant functional dyspepsia patients	Japanese diagnostic criteria for early chronic pancreatitis	B.S.T. and Z.H.

*According to the Mayo Clinic Diagnostic Criteria for CP, a diagnosis of definite CP is established is a score of ≥ 4 is established based on the following: typical histology for CP (4); pancreatic calcifications (imaging method not specified) (4); characteristic findings on endoscopic retrograde cholangiopancreatography (3); pancreatic exocrine insufficiency [steatorrhea defined by abnormal qualitative or quantitative fecal fat excretion > 7 g/d, or abnormal cholecystokinin test result (normal range trypsin output $(25.3-54.2 \times 10^3$ U/h), lipase output $(77.2-322 \times 10^3$ U/h)] (2); attacks of pancreatitis or chronic upper abdominal pain (2); diabetes mellitus (disturbed glucose tolerance requiring continuous control by diet alone or with addition of oral agents or insulin) (1).⁴

†According to the M-ANNHEIM criteria, the following features are required for a diagnosis of CP: Probable CP required mild ductal alterations, or pseudocysts, or a pathologic test of pancreatic exocrine or endocrine function. Definite CP required the detection of calcifications, moderate or marked ductal lesions, or persistent exocrine insufficiency requiring enzyme supplementation, or a typical histology of pancreatic tissue. Borderline CP required a typical clinical history of the disease but without any of the aforementioned criteria of definite or probable disease.²²

‡According to the Japanese Diagnostic criteria 1 and/or 2 are required for a diagnosis of definite CP¹: characteristic imaging findings (calcifications, calculus, ductal morphologic changes),² characteristic histologic findings of loss of exocrine parenchyma with irregular predominantly interlobular fibrosis. Probable CP diagnosed if probable finding of CP plus ≥ 3 of: upper abdominal pain, abnormal pancreatic enzyme levels in serum or urine, abnormal pancreatic exocrine function, or continuous heavy drinking ≥ 80 g/d.²⁷

§EUS criteria include > 2 of: hyperechoic foci, hyperechoic strands, parenchymal lobularity, irregular pancreatic duct margins, hyperechoic pancreatic duct margins, visible pancreatic side branches, pancreatic duct dilation, shadowing calcifications, and cysts.

||According to the Japanese Diagnostic criteria for early chronic pancreatitis, at least 2 of the following are required; upper abdominal pain, abnormal pancreatic enzyme levels in serum or urine, abnormal pancreatic exocrine function, or continuous heavy drinking ≥ 80 g/d, plus imaging findings of early CP on endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography (features ≥ 2).¹⁸

CP indicates chronic pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangio-pancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; PEI, pancreatic exocrine insufficiency; US, ultrasound.

thereby help prevent weight loss and complications of nutritional deficiencies.¹² Patients should undergo regular assessments for osteoporosis and risk of fractures resulting from fat-soluble vitamin malabsorption, as well as routine fasting glucose and glycated hemoglobin for assessment of diabetes.¹² Patients with chronic pancreatitis are at significantly increased risk of developing pancreatic cancer; close follow-up is recommended for 5 years following diagnosis to avoid overlooking an associated malignancy.¹³

Patients with chronic pancreatitis present with a range of signs and symptoms, but none is sufficiently specific to make a diagnosis with certainty. Many people with chronic pancreatitis do not exhibit a typical presentation; about half have no alcohol history^{4,14} and many do not have severe pain.¹⁵ This presents a challenge for primary care physicians, potentially leading to misdiagnosis, delayed diagnosis, or even death⁴ without detection of the disease. Providing information about the prevalence of different signs and symptoms in patients with chronic pancreatitis may help clinicians to select patients for targeted diagnostic investigations. Pooled estimates of the prevalence of symptoms of chronic pancreatitis at presentation, based on a systematic review of the literature, have not previously been calculated. We thus undertook to extract the percent of signs and symptoms from published studies, to pool these using meta-analytic techniques, and to understand sources of heterogeneity between studies.

MATERIALS AND METHODS

Study Selection

This study was conducted in accordance with the PRISMA statement for the reporting of systematic reviews and meta-analyses.¹⁶ We searched the PubMed and EMBASE databases for manuscripts published prior to the 9th April 2020. The search included terms for the disease (“pancreatitis, chronic”), and for the signs and symptoms for diagnosis (e.g. “prodromal symptoms”, “signs and symptoms”, “diagnosis”). The search was restricted to humans, adults, full-text and text available in English. A full overview of the search methods and final list of search terms is included in Supplementary Material 1 (Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>).

Eligibility Criteria

Studies were eligible if they reported the number of patients with radiologically confirmed chronic pancreatitis, and the number of patients presenting with specific signs and symptoms at the time of diagnosis, or within 12 months of diagnosis. We excluded case studies as these generally describe very uncommon presentation of disease. We excluded 1 study focused on autoimmune pancreatitis. Cases of autoimmune pancreatitis reported in the included studies were unable to be excluded, but the numbers were likely to be very small.¹⁷ Results from studies that described characteristics of possible early chronic pancreatitis according to the Japanese diagnostic criteria¹⁸ (see footnote of Table 1 for details) have been reported separately to those that reported probable or definite chronic pancreatitis.

Screening and Data Extraction

Two authors (B.S.T. and R.E.N.) independently screened the titles and abstracts; B.S.T. and 1 of 2 authors (A.G. or Z.H.) reviewed the full text to determine eligibility. Differences in assessments (and data extraction and quality

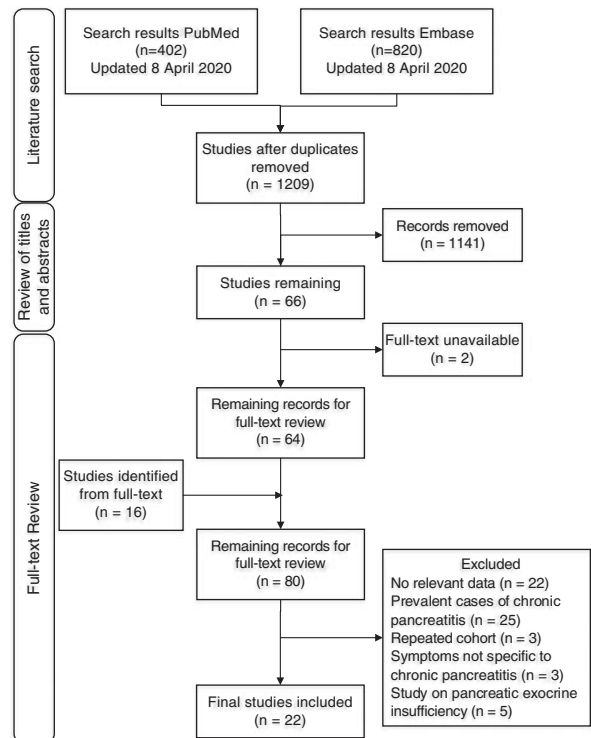


FIGURE 1. Flow diagram of literature search results. CP indicates chronic pancreatitis; PEI, pancreatic exocrine insufficiency.

assessment discussed later) were resolved through consultation between the assessing authors, with further consultation with the senior author (R.E.N.) where necessary.

Data were extracted independently by 2 authors (B.S.T., and A.G. or Z.H.) and included the following: first author, title, year of publication, date of review, study type, country of originating data, start and end dates of the study, the study size, the social context (eg, hospital, general practice), age, and sex. For each symptom and sign described, the number of people for whom the factor was examined (denominator), and the number of people with the factor (numerator), or the total percentage of people with the factor were extracted. These were collected separately for patients with alcoholic chronic pancreatitis and those with chronic pancreatitis of idiopathic/other aetiologies if they were reported separately. As tropical pancreatitis has no clear diagnostic criteria,⁵ this was grouped with idiopathic chronic pancreatitis. We did not include risk factors for chronic pancreatitis in the systematic review as these have been previously studied.^{41–45}

Quality Assessment

The main quality considerations were the representativeness of the sample, and the validity of the diagnosis and symptoms ascertainment. We modified 3 questions from the Newcastle-Ottawa quality assessment scale for cohort studies⁴⁶ to assess the quality of studies in this review (Supplementary Material 2, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>).

Statistical Analysis

The percentage of patients presenting with each sign and symptom was extracted from all studies. We pooled these percentages using a random-effects model,

implemented using the Metaprop command in Stata 15.1. Outcomes are presented as pooled percentages of chronic pancreatitis cases presenting with each sign or symptom. We performed the meta-analyses separately for alcoholic and idiopathic/other etiology where data was available from at least 2 studies. We presented the prevalence of abdominal pain and diabetes mellitus separately according to whether the study was conducted in a western or non-western country, and abdominal pain and acute pancreatitis within strata defined by quality assessment score. Abdominal pain was stratified by whether the criteria for diagnosis included abdominal pain, as this may selectively include patients with this symptom. Too few studies prevented further stratified analyses. We calculated the I^2 index as an indicator of heterogeneity. All results have been presented, regardless of evidence of statistical heterogeneity between the studies.

RESULTS

Search Results

We identified 1209 individual studies through our searches of PubMed and Embase (Fig. 1). After review of title and abstracts, 66 studies remained. The full text of the manuscripts was not available for 2 studies. A further 16 studies were identified from the reference lists of the remaining 64. Of the 80 studies, 22 did not provide details about signs and symptoms of chronic pancreatitis, 25 reported symptoms of prevalent cases (ie, > 1 y following diagnosis) or the time of the symptoms relative to diagnosis was unclear, and 8 studies reported signs and symptoms relating to a diagnosis of pancreatic enzyme insufficiency, epigastric pain syndrome, or pancreatic cancer. Three studies were excluded because the cases likely cross over with another study included in the review; in 2 of these^{14,47} the data were included in another manuscript,²¹ and 1 study was excluded¹⁵ because the cases were from the same region and diagnosed within the time period of another study.²³ We included 22 studies, 3 of which reported signs and symptoms of cases with early chronic pancreatitis.^{26,28,39,40}

Study Characteristics

Sixteen were retrospective cross-sectional and 6 were prospective cohort studies (Table 1). The included studies were published between 1989 and 2020 and were conducted in 11 different countries; India and Japan were the most common originating countries (Table 2).

Quality Assessment

Details about the quality assessment are included in Supplementary Material 2 and Supplementary Table 1 (Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). Nine studies were good quality, 11 were fair quality and 2 were poor quality. Ten studies maintained a prospective database, or administered a study-specific questionnaire to patients or their treating clinicians; the remaining 12 studies reviewed clinical records for information about signs and symptoms at diagnosis.

Signs and Symptoms

The number of participants from the 19 studies evaluating chronic pancreatitis (excluding those focused on early pancreatitis) was 11,635 patients. From 14 studies, 5728/10,362 (55%) of cases were diagnosed with alcoholic chronic pancreatitis and 45% were diagnosed with chronic pancreatitis of idiopathic or other etiology (Table 2). Data on

signs and symptoms of chronic pancreatitis could be extracted separately for alcoholic and idiopathic/other etiology from 11 studies.^{19,22–24,26,27,29,35–38}

Abdominal pain was the most common presenting symptom, with a pooled estimate of 76%; this decreased to ~65% for chronic pancreatitis that was idiopathic/other (Table 3). Heterogeneity was high, with estimates for individual studies ranging from 31% to 100% (Supplementary Fig. 1a, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). Two studies in particular had unusual characteristics. The study with the lowest percentage of patients with pain was a field study in which residents of households were interviewed to identify those with possible signs of pancreatic disease in a region of high incidence of diabetes mellitus, and imaging was subsequently used to diagnose chronic pancreatitis.³⁵ The study with the highest percentage identified the cohort on the basis of abdominal pain.³⁴ When these 2 studies were excluded, the pooled estimate remained at 75%; estimates for individual studies ranged from 48% to 100%, and the heterogeneity remained high. Pain occurred more frequently in western than in non-western populations (90% vs. 70%) but within these groups heterogeneity remained high (Supplementary Fig. 1c, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). When the pooled analysis was stratified by quality assessment score, the percentage of patients with abdominal pain from studies with a quality score of “poor” was much smaller, but this finding was due to a single study (Supplementary Fig. 1d, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). The inclusion of abdominal pain as one of the diagnostic criteria did not alter the findings (Supplementary Fig. 1e, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>).

Weight loss was the next most common symptom, with approximately a fifth of cases (22%) reporting weight loss around the time of diagnosis. However only 4 studies provided weight loss data and there was high heterogeneity, with the prevalence of weight loss ranging from 8% to 43% (Supplementary Fig. 2a, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). Steatorrhea was reported in 3% of patients in 1 study³⁴ and 20% of patients in another²⁵ (Supplementary Fig. 4, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). Jaundice was a sign of chronic pancreatitis in ~11% of cases, while upper gastrointestinal bleeding only occurred in 1% of cases (Table 3).

Medical History

Half of chronic pancreatitis cases had a history of acute pancreatitis; this was more common among those with alcoholic etiology than in those with idiopathic/other chronic pancreatitis (53% vs. 37%). Diabetes mellitus was reported in approximately a third of cases (Table 3). The percentage of patients with diabetes mellitus at diagnosis was almost 3-fold higher in non-western countries than in western countries (38% vs. 14%) (Supplementary Fig. 7c, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>).

Table 3 lists other signs and symptoms that were reported by fewer than 3 studies. One study reported dyspepsia in 45% of cases and anemia in 29%.³¹ Another study reported that 28% of cases were overweight and 16% were obese.²¹

Forest plots for all pooled analyses are included in Supplementary Figures 1 to 7 (Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>).

TABLE 2. Description of the Study Populations

References	Country	Time Period	Total Sample	Included Sample	Years of Age, Mean (SD)	Sex, n (%)	Etiology, n (%)
Agarwal et al ¹⁹	India	1998-2019	1415	747*	ACP: 40 (±10) ISCP: 48 (±9)	Male (ACP): 532 (98.5) Male (ISCP): 140 (67.6)	ACP: 540 (72.3) ISCP: 207 (27.7)
Malka et al ²⁰	France	1973-1996	453	453	NA	Male: 387 (85.4) Female: 66 (14.6)	ACP: 385 (85.0) ICP/other: 68 (15)
Schwarzenberg et al ²¹	USA	2000–2014	1287	1063†	49.1 (±13.4)	Male: 584 (54.9) Female: 479 (45.1)	NA
Hirth et al ²²	Germany and Ukraine	1998-2007	741	274‡	ACP: 48 (40-57)§ ICP: 50 (36-65)§	NA	ACP: 391 (52.7) ICP/other: 350 (47.2)
Machicado et al ²³	USA	1977–2006	89	89	49.1 (±13.4)	Male: 50 (56.2) Female: 39 (43.8)	ACP: 46 (51.7) ICP/other: 43 (48.3)
Hao et al ²⁴	Spain	January 2000-December 2013	2037	2037	43.5 (±15.4)	Male: 1428 (70.1) Female: 609 (29.9)	ACP: 404 (19.8) ICP/other: 1633 (80.2)
Sheel et al ²⁶	United Kingdom	November 2015-November 2016	12	12	39.7 (32.5-46)§	Male: 9 (75) Female: 3 (25)	ACP: 8 (66.6) ICP/other: 4 (33.4)
Issa et al ²⁵	The Netherlands	December 2003-March 2007	50	50	NA	NA	NA
Hirota et al ²⁷ (data from Masamune et al ²⁸)	Japan	January 1, 2011-December 31, 2011	1728	1518	52.9 (±15.4)	Male: 1233 (81) Female: 243 (16) Unknown: 47 (3)	ACP: 1171 (77.1) ICP/other: 347 (22.9)
Hirota et al ²⁹	Japan	January 1, 2007-December 31, 2007	1236	1236	59.4 (±13.9)	Male: 1010 (81.7) Female: 226 (18.3)	ACP: 862 (69.7) ICP/other: 374 (30.3)
Wang et al ³⁰	China	May 1, 1994-April 30, 2004	2008	2008	48.9 (±15.0)	Male: 1305 (65.0) Female: 703 (35.0)	ACP: 705 (35.1) ICP/other: 1303 (67.9)
Chen et al ³¹	China	January 1997-December 2004	104	104	54.6 (±14.9)	Male: 63 (60.6) Female: 41 (39.4)	ACP: 29 (27.9) ICP/other: 75 (72.1)
Ryu et al ³²	South Korea	2001-2004	814	814	50.6 (±13.9)	Male: 699 (85.9) Female: 115 (14.1)	ACP: 523 (64.3) ICP/other: 291 (35.7)
Kimura et al ³³	Japan	April 1984-March 2001	8	8	53.4	Male: 7 (87.5) Female: 1 (12.5)	NA
Cavallini et al ³⁴	Italy	1971-1995	715	715	40.8 (±11.4)	Male: 630 (88.1) Female: 85 (11.9)	ACP: 526 (73.6) ICP/other: 189 (26.4)
Balaji et al ³⁵	India	April 1983-March 1984	36	36	ICP: 32.8 (±12.6)	Male: 13 (36.1) Female: 23 (63.9)	ICP/other: 36 (100)
Chari et al ³⁶	India	January 1987-December 1989	200	200	ACP: 44.1 (±7.9) ICP: 32.6 (±11.9)	Male: 157 (78.5) Female: 43 (21.5)	ACP: 50 (25) ICP/other: 150 (75)
Thomas et al ³⁷	India	September 1983-March 1988	116	116	31	Male: 85 (73.3) Female: 31 (26.7)	ICP/other: 116 (100)
Hayakawa et al ³⁸	Japan	1978–1981	155	155	ACP: 45.2 (±1.0) ICP: 42.6 (±1.9)	Male (ACP): 86 (97.7) Male (ICP): 41 (61.2)	ACP: 88 (56.8) ICP/other: 67 (43.2)
Masamune et al ²⁸	Japan	January 2011-December 2011	151	151	60.4 (13.8)	Male: 86 (57) Female: 65 (43)	Early chronic pancreatitis ACP: 72 (47.7) ICP/other: 79 (52.3)

Masamune et al ³⁹	Japan	July 2014–November 2016	88	88	59 (± 14.9)	Male: 53 (60) Female: 35 (40)	Early chronic pancreatitis ACP: 37 (42) ICP/other: 51 (58)
Wakabayashi et al ⁴⁰	Japan	April 2013–April 2016	25	25	59.5 (± 3.1)	Male: 9 (36) Female: 16 (64)	Early chronic pancreatitis

* Juvenile chronic pancreatitis excluded.
 † Pediatric cases excluded.
 ‡ Limited to disease duration < 1 y.
 § Median (IQR).
 || Data limited to alcoholic and idiopathic etiology.
 ACP indicates alcoholic chronic pancreatitis; ICP, idiopathic chronic pancreatitis; ISCP, idiopathic senile chronic pancreatitis; NA, not available.

Early Chronic Pancreatitis

Alcoholic chronic pancreatitis was reported in 46% of patients with early chronic pancreatitis, based on 2 studies (Table 2). Abdominal pain was the most common symptom (pooled prevalence 72%), but 1 study reported only 32% with abdominal pain (Supplementary Fig. 8, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). A quarter of cases had a history of acute pancreatitis (Supplementary Fig. 9, Supplemental Digital Content 1, <http://links.lww.com/JCG/A726>). In 1 study postprandial pain and early satiety were reported in 56% and 28% of cases, respectively (Table 4).⁴⁰

DISCUSSION

The diagnostic complexity of chronic pancreatitis is well known.⁴⁸ A number of tools provide criteria to guide the pathway to making a definitive diagnosis,^{49,50} but for primary care physicians the challenge is in identifying which patients should begin down this pathway. We performed a systematic review and meta-analysis to identify all published studies that reported the presenting symptoms and/or signs for people with chronic pancreatitis, and to pool estimates across these studies. While abdominal pain was the most common symptom, and half of patients had a history of acute pancreatitis, the heterogeneity between studies was very high for every sign and symptom.

We stratified the presentation of results according to whether or not patients were considered to have chronic pancreatitis of alcoholic etiology. However, the definition for making this classification differed between studies. The consumption of > 80 g of alcohol per day was considered heavy alcohol consumption by many, but not all, studies. Some studies included a different cutoff for women, and the duration of heavy alcohol consumption required to make a diagnosis of alcoholic chronic pancreatitis ranged between 2 and 10 years. Other studies did not provide specific details about how this was determined. The study that reported the highest percentage of alcoholic chronic pancreatitis cases used the lowest cutoff of 60 g of alcohol per day for 2 years.²⁰ There is a need to standardize the definition of alcoholic pancreatitis to enable comparisons of prevalence, symptoms, and outcomes across studies.

Our findings accord with previous work suggesting that abdominal pain is the most common presenting symptom of chronic pancreatitis in western populations.⁴⁸ Although the percentage of patients presenting with abdominal pain was lower in non-western populations, it was still the most common symptom. However, abdominal pain is nonspecific, and differentiating possible chronic pancreatitis from other causes of abdominal pain is complicated because the characteristics of abdominal pain caused by chronic pancreatitis vary both within and between individuals.⁴⁸ Moreover, abdominal pain can diminish with disease progression,⁴⁸ so the timing of diagnosis may account for some of the variability between studies. Two studies of patients with early chronic pancreatitis reported that the vast majority of patients experienced abdominal pain around the time of diagnosis,^{28,39} while 2 studies of definite chronic pancreatitis reported small numbers of patients with abdominal pain but relatively large numbers of patients with diabetes mellitus³⁵ and malabsorption,³⁸ suggesting later diagnosis. Later diagnosis may also explain the lower percentage of patients with abdominal pain and higher percent with diabetes mellitus and malabsorption in non-western compared with western populations.

TABLE 3. Pooled Estimates of Percentage of Chronic Pancreatitis Patients With Each Sign/Symptom, Stratified by Alcoholic and Idiopathic/Other Etiology Where Possible

Sign or Symptom	No. Studies/Chronic Pancreatitis Cases	Pooled Estimate % (95% Confidence Interval)	Heterogeneity Between Studies I^2 (%)
Abdominal pain	N = 9652		
All cases	15 studies/7317 cases	76 (68, 82)	98.04
Alcoholic*	7 studies/2173 cases	78 (69, 86)	95.86
Idiopathic/other*	9 studies/2177 cases	65 (52, 76)	96.78
Weight loss	N = 2240		
All cases	4 studies/288 cases	22 (6, 43)	96.30
Jaundice	N = 2867		
All cases	4 studies/290 cases	11 (1, 28)	98.38
Steatorrhea	N = 761		
All cases	2 studies/28 cases	3 (2, 4)	—
Upper gastrointestinal bleed	N = 3470		
All cases	3 studies/38 cases	1 (0, 3)	90.33
Acute pancreatitis	N = 3226		
All cases	7 studies/1606 cases	51 (28, 74)	99.36
Alcoholic*	2 studies/103 cases	53 (46, 60)	—
Idiopathic/other*	2 studies/63 cases	37 (30, 44)	—
Diabetes mellitus	N = 9667		
All cases	17 studies/2250 cases	28 (19, 38)	98.85
Alcoholic* [†]	9 studies/1011 cases	34 (20, 50)	97.28
Idiopathic/other* [†]	11 studies/708 cases	32 (19, 46)	98.03

*The numbers of events stratified by alcoholic and idiopathic/other etiology do not total all cases because these numbers were only available for some studies.

[†]Higher pooled estimates are due to the restricted studies for which stratification was possible.

Sociocultural factors, including beliefs, social systems, and health care systems, may influence the stage of disease when patients present with symptoms; although the data are inadequate, it has been suggested that such factors may contribute to the heterogeneity of chronic pain across different countries and cultures.⁵¹

Removing the 3 studies that focused on tropical pancreatitis^{35–37} from the analyses of chronic pancreatitis of nonalcoholic etiology did not alter the pooled means for abdominal pain, diabetes mellitus or malabsorption. Aside from tropical pancreatitis, we were unable to separate other etiologies included with idiopathic chronic pancreatitis, but the numbers of these (including autoimmune, obstruction, familial, genetic, and others) combined made up ~10% of cases and it is unlikely that symptoms at presentation differ sufficiently to modify the pooled results.^{27,28,32}

A history of episodes of acute pancreatitis is common among patients with chronic pancreatitis, and it has been

estimated that a quarter of patients with a first attack of acute pancreatitis will progress to chronic pancreatitis within ~3.5 years.⁵² However we found large heterogeneity between studies, and our pooled estimate suggests that up to half of patients present with chronic pancreatitis with no prior history of acute episodes. Thus while a history of acute pancreatitis would increase the index of suspicion for chronic pancreatitis, its absence should not rule out investigations of the pancreas in patients with symptoms such as abdominal pain.

We did not specifically include studies that reported on risk factors for chronic pancreatitis, but among the papers included here, we estimated that 54% of patients had a history of excessive alcohol consumption and 70% were current or past smokers. These findings highlight the importance of assessing these risk factors when considering a possible diagnosis of chronic pancreatitis.

It is possible that the identification of individual symptoms and signs was not complete for all studies, particularly those that used retrospective reviews of the clinical records to ascertain symptoms. Lack of evidence of a symptom in the clinical notes may not mean that the patient did not experience that symptom, but rather it was not specifically assessed or recorded. Studies that maintained a prospective database, or administered a patient symptom questionnaire are more likely to provide complete and reliable data. We attempted to account for potentially incomplete assessment of symptom presence or absence of symptoms in the quality assessment, but heterogeneity remained high when studies were stratified by the quality assessment score.

A limitation of this analysis is that patients who never receive a diagnosis because their signs and symptoms at presentation are not typically associated with pancreatic disease are not represented in these studies. Sensitivity of imaging for pancreatic calcifications in the diagnosis of chronic pancreatitis is between 75% and 82%, depending on the modality, with the exception of abdominal ultrasound

TABLE 4. Other Signs and Symptoms That Were Not Included in the Pooled Calculations

Sign or Symptom	Events/Cases (%)
Anemia ³¹	30/104 (28.8)
Ascites ³¹	10/104 (9.6)
	35/2008 (1.7)
Dyspepsia ³¹	45/104 (45.3)
Family history of acute pancreatitis ²¹	71/1063 (6.7)
Family history of chronic pancreatitis ²¹	81/1063 (7.6)
Anorexia ²⁶	4/12 (33.3)
Obese ²¹	163/1050 (15.5)
Overweight ²¹	289/1050 (27.5)
Underweight ²¹	102/1050 (9.7)
Early chronic pancreatitis	
Postprandial abdominal pain ⁴⁰	14/25 (56.0)
Diabetes mellitus ²⁸	14/149 (9.0)
Early satiety ⁴⁰	7/25 (28.0)

which is less sensitive.⁵³ Some signs and symptoms experienced by people that are incorrectly diagnosed as not having chronic pancreatitis may be under-represented in these studies. Specificity for all imaging modalities is extremely high, so it is unlikely that the signs and symptoms described in the studies are for conditions other than chronic pancreatitis. In addition most studies do not describe the combinations of symptoms and signs that occur in patients with chronic pancreatitis and understanding these may assist to identify patients with atypical symptoms due to chronic pancreatitis.

For the primary care physician, identifying patients for whom testing of the pancreas should be performed is complex because the symptoms are not specific and do not present consistently across patients. Our research has identified some common features of patients with chronic pancreatitis, but the high heterogeneity, some of which is likely related to study design, makes it difficult to draw solid conclusions. To develop a tool that can be used in primary care to help identify patients that should undergo investigations of the pancreas, research studies are needed that: (i) specifically query patients newly diagnosed with chronic pancreatitis about their symptoms and risk factors leading up to diagnosis, using standardised tools; and (ii) analyze combinations of signs, symptoms, and risk factors to identify combinations that are most reliable indicators of chronic pancreatitis. If such a tool can be derived it may lead to earlier diagnosis, enabling appropriate therapy to commence and improving the quality of life for patients through better management of pain and other symptoms. Early diagnosis of chronic pancreatitis will also facilitate monitoring for diabetes mellitus, complications of malabsorption and pancreatic cancer, improving long-term outcomes for these patients.

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