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PREVALENCE OF PRIMARY PAINLESS CHRONIC PANCREATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background/Objectives: While pain is the predominant symptom of chronic pancreatitis (CP), a subset of patients may experience a painless course. This systematic review aimed to determine the prevalence of primary painless CP.

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Author Contributions:

VKS supervised the study. FAB coordinated the study, extracted the data, performed the statistical analysis, and drafted the manuscript. MF coordinated the study, extracted the data and drafted the manuscript. VSA performed the statistical analysis and drafted the manuscript. AIA extracted the data. KL devised the study design. All authors critically assessed the study design, edited the manuscript, and read and approved the final manuscript. FAB and MF directly accessed and verified the underlying data. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Conflict of Interest: V.K.S. is a consultant for AbbVie and Nestlé Health Science; medical advisory board participant for Envara, and receives grant support from Orgenesis, Theraly, and AbbVie. The remaining authors disclose no conflicts.

Methods: MEDLINE (PubMed), EMBASE and Web of Science Core Collection databases were searched for published studies through September 15, 2020 that included at least 10 consecutive patients with CP and which reported the number with painless CP. The presence of a history of recurrent acute pancreatitis (RAP), exocrine pancreatic insufficiency (EPI), diabetes mellitus (DM) and pancreatic adenocarcinoma (PA) in the painless CP patients was also recorded. A random effects model was used to determine pooled prevalence estimates with 95% confidence intervals (95% CI).

Results: Among the 5,057 studies identified and screened, 42 full-text articles were included in the final analysis. There were a total of 14,277 patients with CP among whom 1,569 had painless CP. The pooled prevalence of painless CP was 12% (95% CI 10–15%). Among a subset of studies that reported on calcifications (n=11), DM (n=12), EPI (n=8) and history of RAP (n=14), the pooled prevalence estimates were 96% (95% CI 73–100%), 51% (95% CI 32–70%), and 47% (95% CI 15–81%), respectively. Alcohol, idiopathic/genetic and other etiologies were attributed to be the cause of painless CP in 32.4%, 56.9% and 8.9% patients, respectively.

Conclusion: Approximately one in ten patients with CP have primary painless disease with the majority being attributable to an idiopathic/genetic etiology. Further research is needed to determine the optimal management of these patients.

Keywords

Abdominal Pain; Chronic Pancreatitis; Diabetes; Exocrine Insufficiency; Pancreatic Calcifications

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory and fibrotic disease of the exocrine pancreas that can lead to abdominal pain as well as symptoms and signs of diabetes mellitus (DM) and exocrine pancreatic insufficiency (EPI). Although abdominal pain is the most prevalent symptom in patients with CP, reported in 60–94%[1], there are patients who have painless CP.

To the best of our knowledge, the first published reports of painless CP were in 1948[2,3] and reported 10–15% of their small CP patient cohorts had painless disease. Painless CP patients are most commonly identified “incidentally” when they undergo abdominal imaging for other reasons and are found to have advanced morphologic findings of CP such as calcifications and/or moderate to marked ductal changes. Others present with signs and symptoms of DM and/or EPI, which prompts abdominal imaging that reveals advanced morphologic findings of CP. This was evident in a recent study which evaluated the signs and symptoms that led to a diagnosis of painless CP in 74 patients[4]. While new-onset DM, steatorrhea and weight loss were reported in 20%, 19% and 16%, respectively, 51% of patients reported no symptoms or signs and were incidentally diagnosed with painless CP.

There are many reasons why establishing the prevalence of painless CP is important. When a patient with painless CP is incidentally identified, clinicians may not periodically assess these patients for the development of complications such as DM and EPI. While the risk of pancreatic adenocarcinoma (PA) among patients with painless CP has not been quantified, it

is likely higher than the general population and these patients should be followed for signs and symptoms concerning for malignancy. Finally, studying and comparing patients with painless and painful CP may help improve our understanding of nociceptive pathways in CP and allow for the development of more targeted therapies[5,6].

Our primary aim was to conduct a systematic review to determine the prevalence of painless CP. Our secondary aims were to determine the prevalence of calcifications, DM, EPI, and PA as well as the distribution of etiologies in patients with painless CP.

MATERIALS AND METHODS

Study Design and Data Collection

We implemented a systematic approach in finding and screening relevant literature by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7]. We queried three databases [MEDLINE (PubMed), Embase and the Web of Science] from their respective dates of inception through September 15, 2020 using a combination of controlled vocabulary and free-text terms for pertinent articles [Supplemental (Appendix)].

Articles were uploaded into a systematic review software (Covidence, Veritas Health Innovation, Melbourne, Australia) and subsequently screened. The references of all relevant articles that were not indexed in the above electronic databases were hand searched (citation chaining) to identify additional articles. Forward and backward chaining were implemented to search for articles. Articles were deemed unavailable if a comprehensive search through interlibrary loan requests and manual searching of medical library holdings by the authors was unsuccessful.

The strategy involved a two-tier process: screening the titles and abstracts followed by full-text articles. Two authors (F.A.B. and A.A.) independently screened and reviewed abstracts and full-text articles. Disagreements were resolved by a third reviewer (M.F.) or consensus-based discussion.

Data Extraction

Data regarding the characteristics and complications of CP were extracted independently by two authors (F.A.B. and M.F.). Disagreements were resolved by a third reviewer or consensus between both reviewers.

Primary Painless CP Definition

We defined primary painless CP as those patients who never reported abdominal pain or experienced an episode of acute pancreatitis. This was previously described by Ammann et al.[8] as a “particular clinical category that manifests by steatorrhea, diabetes, jaundice, or calcification.” We expanded this definition to include painless patients who were “incidentally” diagnosed through cross-sectional imaging obtained for evaluation of other complaints. We excluded studies that classified painless CP as those patients who transitioned from a state of pain to complete pain cessation, often referred to as “burn

out"[9,10]. This includes patients with recurrent AP flares but who remain pain free in between episodes. CP was defined according to the authors of each respective study.

Inclusion Criteria

All studies that reported the prevalence of pain in CP were initially screened. Articles were included for full-text review if they reported on at least 10 consecutive adult (>18 years of age) patients with both painful and painless CP.

Exclusion Criteria

The exclusion criteria included the following: (1) Randomized controlled trials since they have primarily enrolled patients with painful CP; (2) Systematic reviews, review articles, case reports, letters of correspondence and editorials; (3) Data repeated from previously published articles; (4) Studies reporting either the prevalence of painless or painful CP but not both; and (5) Studies reporting on a non-consecutive or selected cohort of patients (e.g., the inclusion of only alcoholic CP).

Risk of Bias Assessment

We used a tool developed by Hoy et al. that was adapted to specifically assess risk of bias in prevalence studies (F.A.B. and M.F.)[11]. This tool consists of nine items that evaluates external and internal validity that can be tabulated into a single numerical score (0–9). A score between 0–3, 4–6 and 7–9 indicates a low, moderate and high risk of bias, respectively.

Statistical Analysis

Heterogeneity between studies was assessed using the I^2 statistic. The I^2 statistic is categorized as low (<25%), moderate (25–50%), and high (>75%). We utilized the random effects model to account for variation in prevalence across studies and obtained pooled estimates with 95% confidence intervals (CI). Further subgroup and meta-regression analyses were planned and performed where possible. Publication bias was assessed using a funnel plot and Egger's test[12]. All analyses were conducted using R (3.6.2, R Foundation, Vienna, Austria) and figures were produced using the metaprop package (Viechtbauer 2010). Results were considered statistically significant if the P value was less than 0.05.

RESULTS

Our search strategy identified 5,057 studies between January 1, 1900 and September 15, 2020. There were 3,386 studies that did not meet the inclusion criteria resulting in 237 studies for full-text review. A total of 42 studies were included in the final analysis [Figure 1].

The details of the 42 studies are shown in Table 1. These studies were published between 1948–2020 and conducted in 15 countries including the United States (n=9), India (n=7), Japan (n=6), Italy (n=5), China (n=4), Germany (n=3), United Kingdom (n=2), France (n=2), Mexico (n=2), South Africa (n=1), Uganda (n=1), Denmark (n=1), Singapore (n=1), Hungary (n=1) and Ukraine (n=1). The risk of bias was classified as low in 38 studies and moderate in 4 studies (Supplemental Table 1).

There were a total of 14,277 patients with CP among whom 1,569 were reported to have painless disease. The pooled prevalence was 12% (95% CI, 10–15%) with an I^2 value of 94% (p<0.01) [Figure 2]. There were 11 studies that reported on the presence of calcification(s) in painless CP patients[2–4,14–20,24]. Among 164 painless CP patients, there were 147 with calcifications resulting in a pooled prevalence of 96% (95% CI, 73–100%) with an I^2 of 84% (p=0.07) [Figure 3]. Additional characteristics of painless CP patients including mean age at diagnosis, gender, race and smoking status were not reported in the majority of studies.

There were 12 studies that assessed patients for DM, using the oral glucose tolerance test (n=7), the American Diabetes Association criteria (n=1) and 4 studies that did not report their diagnostic criteria[2–4,15,17–20,24,26,28,44]. There were 101 patients with DM out of a total of 199 painless CP patients, resulting in a prevalence of 51% (95% CI, 32–70%) with an I^2 of 81% (p=0.23) [Figure 4A]. Data on EPI was available in 8 studies, which included 158 painless CP patients[2–4,18,20,24,26,44]. The prevalence of EPI in painless CP patients was 47% (95% CI, 15–81%) with an I^2 of 91% (p=0.02) [Figure 4B]. In 6 studies, EPI was defined by the presence of steatorrhea and/or direct or indirect tests of pancreatic function including the pancreozymin secretin test, fecal fat measurement, fecal elastase-1 and Lundh's test[3,4,18,24,26,44]. Two studies did not report their diagnostic criteria for EPI[2,20].

There were 9 studies (n=225) that reported the etiology of painless CP[4,14,18,24,26,28,31,37,51]. Alcohol, idiopathic/genetic and other etiologies were attributed to be the cause of painless CP in 73 (32.4%), 128 (56.9%) and 20 (8.9%) of patients, respectively.

There were 2 studies with a total of 188 painless patients that reported 4 (2.1%) patients with PA[4,45]. Hao et al.[45] reported 4 cases of PA after a median follow-up of 8 years, while Amodio et al.[4] reported no cases of PA over a mean follow-up of 2.9 years.

Subgroup Analysis

We conducted planned subgroup and meta-regression analyses on the independent variables to address the possible source(s) for heterogeneity (I^2=94%). The geographical location based on continents, publication year and study bias were analyzed. Studies conducted in Africa had a higher prevalence estimate of painless CP when compared to other continents (Supplemental Table 2). However, meta-regression analysis showed that neither geographical location (p=0.07), publication year (p=0.55) nor study bias (p=0.26) had a significant association with the prevalence estimate of painless CP. Eggers' test did not show publication bias (p=0.90).

DISCUSSION

To the best of our knowledge, this is the first systematic review to specifically assess the prevalence of primary painless CP. We found that approximately one in ten patients with CP have painless disease. We also found that, among painless CP patients, 96% had calcifications, 51% had DM, 47% had EPI, and 57% had an idiopathic or genetic etiology.

The high prevalence of calcifications is likely explained by the fact that the presence of calcification(s) on abdominal radiographs and/or surgery/autopsy, particularly prior to the widespread availability of computed tomography, was required to establish the diagnosis of CP. We found that approximately one in two painless patients will have either DM or EPI. In the majority of studies, data regarding the onset of and follow-up periods for assessing the development of functional deficiencies such as DM and EPI were either not reported or limited. It is possible that the majority of these patients would have developed functional deficiencies if they were followed for longer periods[24,52]. CP may not be apparent when either new-onset DM or EPI is diagnosed. Amodio et al. reported that 72% of painless patients in their cohort were diagnosed with DM either before or at the time of CP diagnosis[4]. Consideration should be given to obtaining abdominal imaging in patients with new onset DM who have also experienced weight loss, have underlying EPI, and/or have obvious risk factor(s) for pancreatitis.

Genetic testing across the studies identified in this systematic review was sparse[4], as most were conducted prior to the discovery of a genetic basis for pancreatitis in 1996. The etiology of CP was attributed to either an idiopathic or genetic cause in 56.9% of patients with painless disease. Further studies will need to be conducted to determine if mutation(s) in certain pancreatitis susceptibility genes are more likely to result in painless CP. There may be other risk factors for CP in painless patients including systemic lupus erythematosus[53] and vascular disease[54,55]. If a correlation with vascular disease was present, we would expect painless patients to be older than those who experience painful CP. A clear deficit of the studies included in our systematic review was limited data on the age of patients at the time of a painless CP diagnosis. Amodio et al.[4] reported a mean age of 61 years, whereas Kamisawa et al.[34] reported a higher prevalence of painless CP in those > 60 compared to those < 60 years of age (73% vs. 39%). Hirth et al. reiterated this, to a lesser extent, by reporting a prevalence of painless CP in elderly vs. non-elderly patients of 21% and 12%, respectively, but did not specify the age cut-offs for the two categories of patients[48].

It is not known why CP can be a “painless” condition as involvement of the intrapancreatic nerves is a hallmark feature of the disease[56]. Differences in pain sensitivity have been reported in adults at the population level[57]. Variants in genes that encode for voltage-gated sodium channels, which are involved in nociceptive signaling, could result in the variable perception of pain[58,59]. The voltage-gated sodium channel alpha subunits 9 (SCN9A) and 10 (SCN10A) genes are known to encode for sodium channel types 1.7 and 1.8, respectively, and mutations in these genes result in an insensitivity to pain[59,60]. SCN10A has been shown to be present in, among many others, the alimentary tract, gallbladder and exocrine pancreas[61]. A study evaluating “hypoalgesic” inflammatory bowel disease (IBD) demonstrated a significantly higher prevalence of a single nucleotide polymorphism of the SCN10A gene (rs6795970) when compared to “non-hypoalgesic” IBD patients[62]. Further research is needed to understand the role of these and other variants in genes that influence nociception among painless patients.

CP, especially hereditary/genetic CP, is an established risk factor for PA. Prior studies evaluating patients with hereditary CP have reported a PA incidence of 19–54% by the 7th decade of life[63–66]. This is a particular concern in painless CP patients, as they are

typically diagnosed later in life, may have had underlying CP for decades and have other risk factors for not only CP but also malignancy such as smoking. It is difficult to derive any conclusions on the association of PA and painless CP as there is very limited published data. Despite the current shortcomings of PA screening in patients with CP, future studies will need to determine whether the frequency of screening should differ among different patients with CP based on etiology, duration of disease, presence of functional deficiencies, and symptoms such as pain.

The benefits or lack thereof of pursuing invasive therapies such as endoscopy and/or surgery in these patients is important to highlight. Guidelines have argued against endoscopy as the risks outweigh the benefits in painless patients[67]. What is not known is whether invasive therapies can prevent the development or progression of DM and/or EPI in these patients. A trial comparing surgery and endoscopy found that those randomized to surgery experienced a delay in the progression of EPI over a mean follow-up of 6.6 years[68]. However, the sample size of this trial was small and did not adjust for the many variables that impact the development of EPI. The more recent ESCAPE trial by the Dutch Pancreatitis Group[69] and Maartense et al.[70] found no impact of surgical intervention on EPI. There are fewer studies which have evaluated the impact of endoscopic intervention on the progression of DM. A recent study showed that early endoscopic intervention delayed the onset of DM in patients with idiopathic CP over 6–7 years follow-up. They found no benefit to endoscopic intervention in those with pre-existing DM, which is common in patients with CP. However, the follow-up period is not long enough for development of DM, especially among idiopathic CP patients[71]. Invasive therapy may be required in painless CP patients who develop structural complications such as distal biliary strictures[72] or pancreaticopleural fistulae[73–75].

The strengths of our study include the inclusion of a systematic review expert (K.L.) who assisted with the identification and assessment of studies, as well as the long period of the review to ensure that we captured all of the initial reports of painless CP and excluded those studies with repeat patients. Another strength of our study was restricting the inclusion of studies to those that reported on a consecutive cohort of patients as this would more likely identify those with painless CP and have broader generalizability to clinical practice.

The lack of uniform diagnostic criteria for CP in the studies included in this systematic review is a common limitation. However, most of these studies used the presence of calcification(s) which continues to be the most universally accepted morphologic finding for diagnosing CP. This has been evident in the various diagnostic criteria for CP introduced over the years, including the American Pancreatic Association guidelines[76], Marseille symposium criteria[77], Cambridge classification[78], and others from groups in Japan[79], Switzerland[80], and Germany[81]. Another limitation is that it is inevitable that there are many patients at an earlier stage of CP who do not have pain and do not have complications of CP such as DM or EPI. This may result underestimate the prevalence estimate. While 93% of the studies included in this systematic review had a low risk of bias, there was high statistical heterogeneity between studies (I^2= 94%). To address this limitation, we utilized the random effects model, conducted planned subgroup and meta-regression analysis, and assessed publication bias. Despite a thorough evaluation, there was no single factor found

that disproportionately contributed to the observed heterogeneity. A combination of factors (e.g., patient characteristics) likely explain the observed heterogeneity[82]. However, we were not able to evaluate patient-specific characteristics such as age, gender, smoking status and etiology of CP due to limited data availability. Another limitation is that point prevalence (reported by cross-sectional studies) are often lower than the cumulative/lifetime prevalence estimates (reported by cohort studies) for clinical variables including pain, AP, DM, EPI and PA. In our study, this distinction is most important for PA as there were only two studies reporting the point/period prevalence of PA in painless CP, which may lead to an underestimation of the true cumulative prevalence. While it is also possible that pain and/or AP could develop after a diagnosis of painless CP, this has been reported to occur in only 0–3.6% of patients over a mean follow-up of 16–60 months[4,26,49]. There is also a potential for a recall bias in those with chronic pain. However, this possibility is likely to be low given that pain, and especially, chronic pain is not easily disassociated from the pain experience of a given patient. Previous studies have showed that current pain, including maximal pain intensity, can be influenced by the recall of painful episodes in pain-free individuals[83] and in those with chronic pain[84]. We attempted to ensure the studies selected reported on a defined painless CP cohort, i.e., patients who had no prior AP or pancreatic-type abdominal pain. There is a possibility that some patients in these studies may have pain "burn-out"[10] which may have been misclassified as painless CP.

In conclusion, approximately 1 in 10 patients experience painless CP with the majority attributable to an idiopathic/genetic etiology. Further research in this patient population is needed to understand the development and management of CP complications as well as the pathophysiology of nociception.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CI	Confidence Interval
CP	Chronic Pancreatitis
DM	Diabetes Mellitus
EPI	Exocrine Pancreatic Insufficiency
PA	Pancreatic Adenocarcinoma

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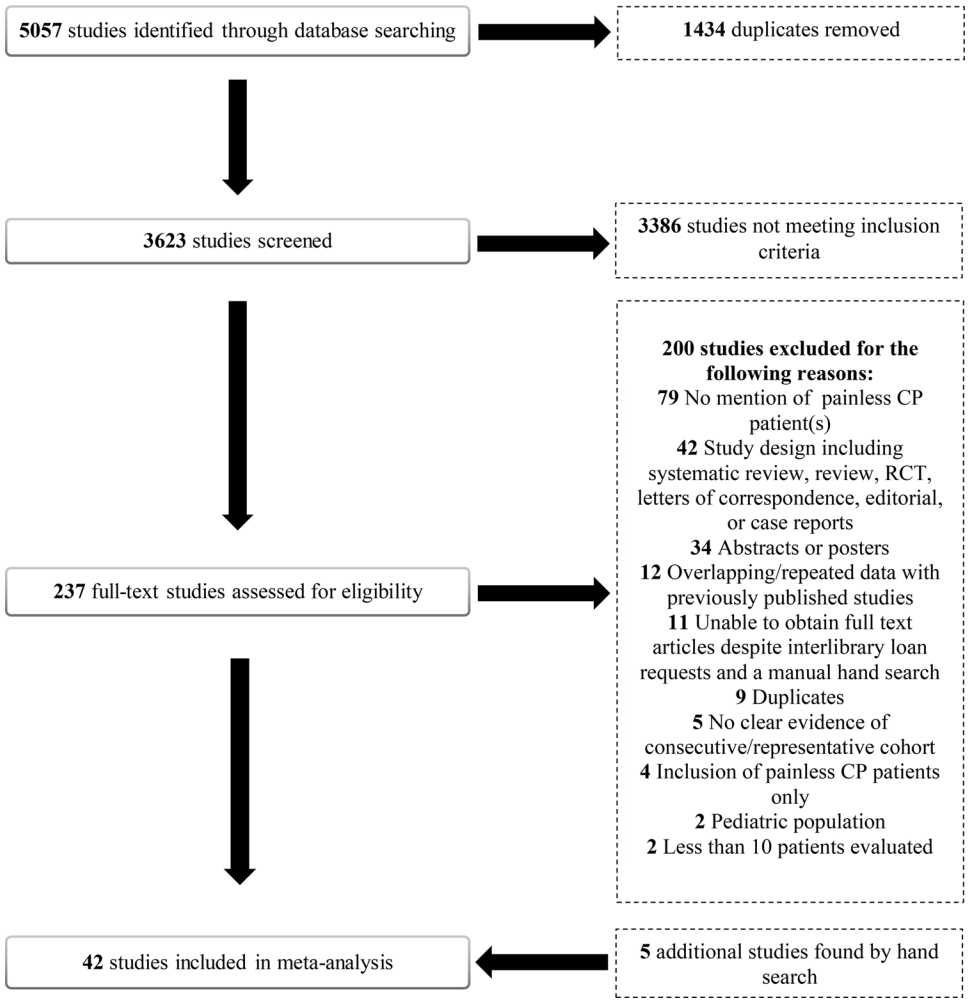

Figure 1:
PRISMA search strategy

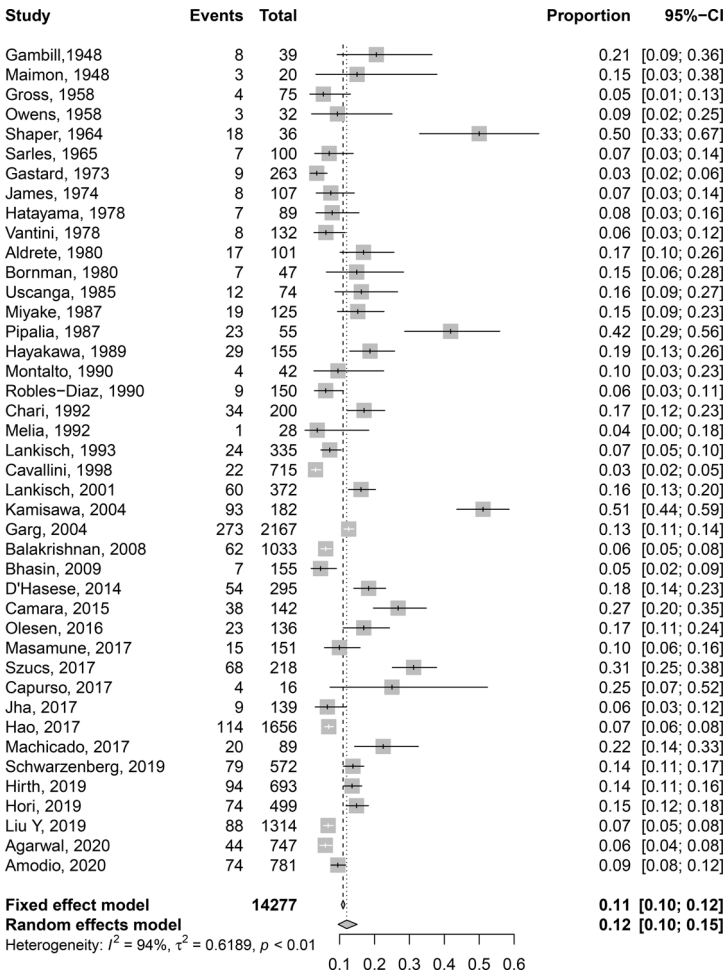

Figure 2:
Forest Plot of the Prevalence of Painless CP

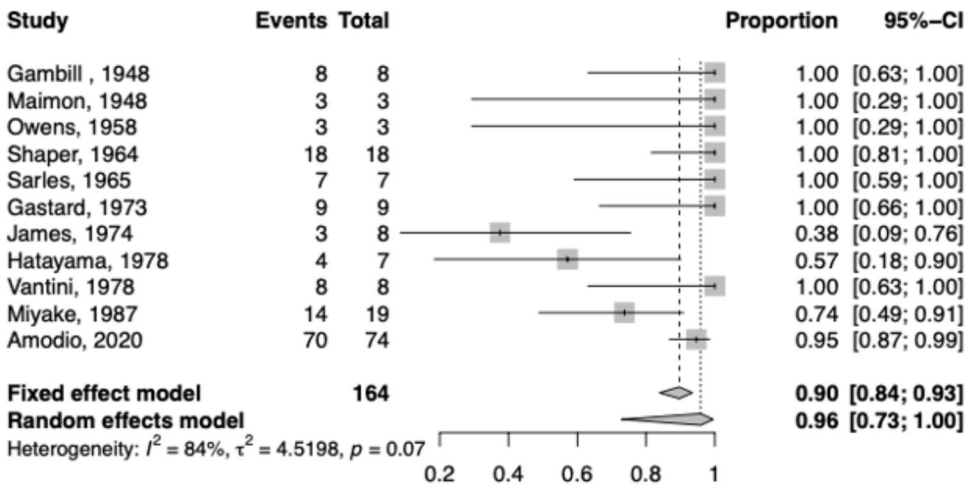

Figure 3:
Forest Plot of Studies Reporting the Prevalence of Calcification(s) in the Painless CP

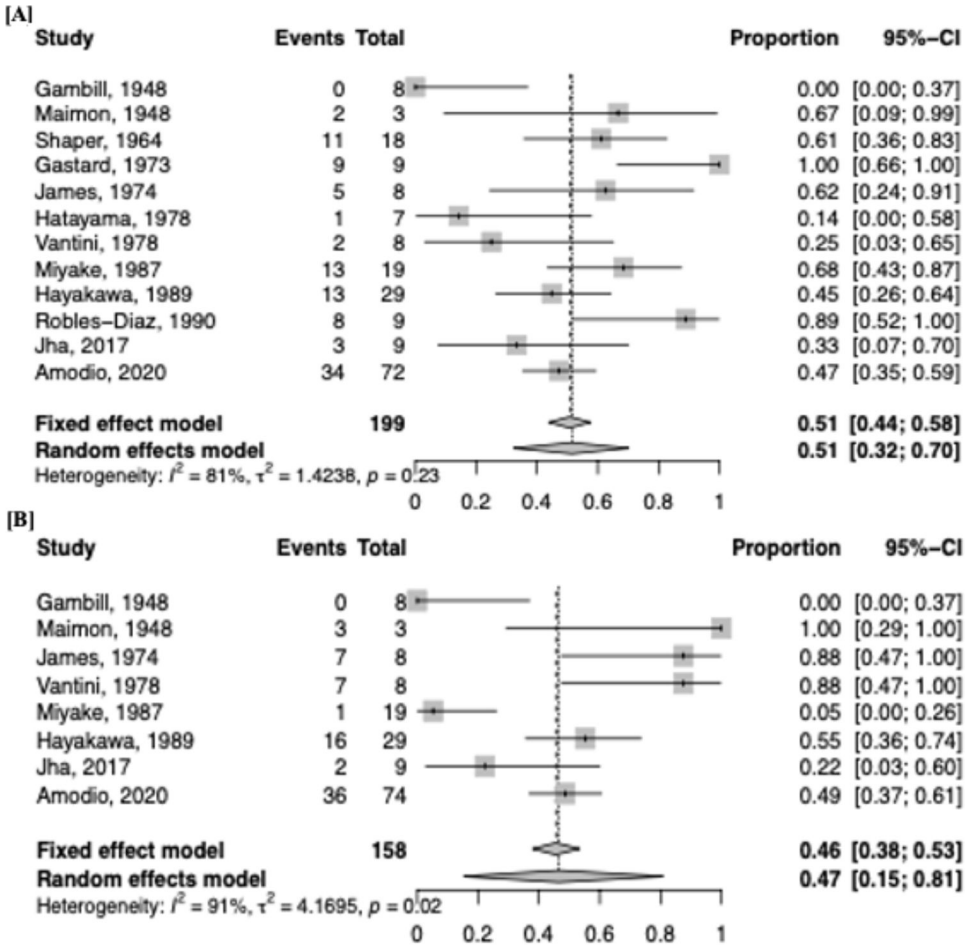

Figure 4:

Forest Plot of Studies Reporting the Prevalence of (A) Diabetes Mellitus (12 Studies) and (B) Exocrine Pancreatic Insufficiency (8 Studies) in the Painless CP

Table 1:

Study Characteristics and Risk of Bias Assessment

Author	Year	Country	Study period	Diagnostic Criteria	Number of patients	Male N (%)	Painless CP N (%)	Risk of Bias Level †
Gambill et al.[2]	1948	USA	1939–1943	NR	39	28 (71.8)	8 (20.5)	Low
Maimon et al.[3]	1948	USA	NR	Imaging evidence of calcification in painless patients; clinical diagnosis in remaining	20	12 (60)	3 (15)	Low
Gross et al.[13]	1958	USA	1956	Pancreatic calcification, diabetes and steatorrhea seen in combination	75	63 (84)	4 (5.33)	Low
Owens et al.[14]	1958	USA	1940–1957	Identification of those with pancreatic calcifications with review of medical records	32	20 (62.5)	3 (9.38)	Moderate
Shaper et al.[15]	1964	Uganda	1958–1962	Retrospective identification of those with pancreatic calcifications with review of medical records	36	28 (77.8)	18 (50)	Low
Sarles et al.[16]	1965	France	NR	Marseilles symposium criteria	100	93 (93)	7 (7)	Low
Gastard et al.[17]	1973	France	NR	Surgical; abdominal radiograph (calcifications) or a combination of several abnormal conditions (diabetes, steatorrhea, radiological evidence)	263	263 (100)	9 (3.42)	Moderate
James et al.[18]	1974	United Kingdom	1968–1973	Marseilles symposium criteria (Groups 3 & 4)	107	71 (66.4)	8 (7.48)	Low
Hatayama et al.[19]	1978	Japan	1960–1977	Oda's modification of the proposed criteria by the Japanese Pancreatic Disease Association	89	62 (70)	7 (7.87)	Low
Vantini et al.[20]	1978	Italy	1970–1977	Radiographic evidence of pancreatic calcifications and/or surgical and histological data.	132	117 (88.6)	8 (6.07)	Low
Aldrete et al.[21]	1979	USA	1968–1977	Surgical or autopsy or radiographic evidence of pancreatic calcification.	101	NR	17 (16.8)	Low
Bornman et al.[22]	1980	South Africa	NR	Clinical history and ERCP	47	NR	7 (14.9)	Low
Uscanga et al.[23]	1985	Mexico	1960–1981	≥ 1 of the following: radiographic evidence of pancreatic calcification(s) (n=58), pancreatic duct abnormalities on ERCP (n=34), and operative biopsy or autopsy (n=46 and n=17, respectively)	74	51 (68.9)	12 (16.2)	Low
Miyake et al.[24]	1987	Japan	1965–1984	Histological findings, pancreatic calcifications on imaging, ERCP findings (Cambridge criteria) and/or a moderate to severe exocrine pancreatic dysfunction.	125	94 (75.2)	19 (15.2)	Low
Pipalia et al.[25]	1987	India	1973–1986	Radiographic evidence of pancreatic calcifications (n=54) and on ERCP (n=1).	55	43 (78.2)	23 (41.8)	Low
Hayakawa et al.[26]	1989	Japan	1978–1981	Radiographic evidence of pancreatic calcifications, histological confirmation,	155	127 (81.9)	29 (18.7)	Low

Author	Year	Country	Study period	Diagnostic Criteria	Number of patients	Male N (%)	Painless CP N (%)	Risk of Bias Level †
				or presence of exocrine insufficiency.				
Montalto et al.[27]	1990	Italy	1979–1984	Radiographic evidence of pancreatic calcifications (n=15); typical disturbances by wirsungraphy (n=17); exocrine pancreatic insufficiency (n=7); surgical/histological (n=3). CT and US were also used in the investigation for the diagnosis and detection of complications	42	30 (71.4)	4 (9.52)	Low
Robles-Diaz et al.[28]	1990	Mexico	1975–1987 (except 1981)	≥ 1 of the following: Radiographic evidence of pancreatic calcifications, pancreatic duct abnormalities on ERCP and histological findings. In the first study period (1975–1980), diagnosis mainly by evidence of pancreatic calcifications on abdominal plain films. In the second study period: plain abdominal films (n=56), ERCP (n=17), CT (n=12) and histologically (n=6)	150	124 (82.7)	9 (6)	Low
Chari et al.[29]	1992	India	1987–1989	≥ 1 of the following: radiographic evidence of pancreatic calcifications confirmed by US, features on ERCP (Cambridge criteria), clinical with US features with pancreatic exocrine insufficiency	200	157 (78.5)	34 (17)	Low
Melia et al.[30]	1992	United Kingdom	1978–1989	Retrospective search of ICD 9 diagnostic codes with subsequent review of medical records	28	28 (100)	1 (3.57)	Moderate
Lankisch et al.[31]	1993	Germany	NR	Clinical history and at least one abnormal secretinpancreozymin test performed more than 3 months after the last pain attack. Faecal fat analyses (n=335) performed at the same time as the SPT and plain abdominal radiograph (n=286). US (n=270), CT (n=43)	335	260 (77.6)	24 (7.16)	Low
Cavallini et al.[32]	1998	Italy	1971–1995	Clinical symptoms associated with an increase in pancreatic enzymes, and on instrumental findings typical of the disease (a Cambridge ERCP score of ≥3; pancreatic calcifications at US/CT; dilated and/or irregular main pancreatic duct at US/CT; and increased echogenicity with parenchymal heterogeneity at US) pancreatic enzymes, and on instrumental findings typical	715	630 (88.1)	22 (3.08)	Low
Lankisch et al.[33]	2001	USA	1976–1982	pancreatic calcification; 4 - typical histological changes; 3, characteristic findings on ERCP; 2 - pancreatic exocrine insufficiency; 2 - attacks of pancreatitis and/or chronic upper abdominal pain; 1 - diabetes mellitus	372	243 (65.3)	60 (16.1)	Low

Author	Year	Country	Study period	Diagnostic Criteria	Number of patients	Male N (%)	Painless CP N (%)	Risk of Bias Level †
Kamisawa et al.[34]	2004	Japan	1976–2003	≥ 1 of the following: pancreatic calcification on CT or US (n=82), histological changes (n=47); surgical (n=37); autopsy (n=10); irregular dilation or narrowing of the pancreatic duct on ERCP (n=160), and an abnormally low bicarbonate concentration combined with either decreased enzyme output or secretory volume based on secretin test results (n=38)	182	162 (89)	93 (51.1)	Low
Garg et al.[35]	2004	China, India, Japan, Singapore	NR	≥1 of following ductal changes on ERCP; positive secretin test; pancreatic calcification(s); and EUS abnormalities	2167	1485 (68.5)	273 (12.6)	Low
Balakrishnan et al.[36]	2008	India	2005–2007	Clinical, structural or functional abnormality of the pancreas. The presence of pancreatic calcifications or ductal irregularity/parenchymal atrophy using US, CT, MRI, MRCP, ERCP or EUS	1033	733 (71.0)	62 (6)	Low
Bhasin et al.[37]	2009	India	1999–2004	Clinical, biochemical, and radiologic investigations. Evidence of pancreatic calcification on abdominal radiograph and/or US and/or abdominal CT, and/or there were characteristic ductal changes on MRCP and/or ERCP	155	101 (65.2)	7 (4.52)	Low
D'Hasese et al.[38]	2014	Germany	NR	Pancreatic tissue samples with review of medical records	295	NR	54 (18.3)	Moderate
Camara et al.[39]	2015	China	2008–2011	Clinical and laboratory tests (pancreatic exocrine function). US, CT, MRI, MRCP, EUS, and ERCP. Angiography and magnetic resonance angiogram were both carried out preoperatively and postoperatively.	142	92 (64.8)	38 (26.8)	Low
Olesen et al.[40]	2016	Denmark	2010–2015	Lüneburg criteria	136	118 (69.4)	23 (17)	Low
Masamune et al.[41]	2017	Japan	2011	Diagnostic Criteria for Early CP (DCECP): 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 EUS or ERCP	151	86 (57)	15 (10)	Low
Szucs et al.[42]	2017	Hungary	2012–2014	M-ANNHEIM classification	218	NR	68 (31.2)	Low
Capurso et al.[43]	2017	Italy	2015	M-ANNHEIM & TIGAR-O classification	16	8 (50)	4 (25)	Low
Jha et al.[44]	2017	India	2010–2013	Clinical, structural, or functional abnormality of the pancreas. Large duct disease: duct dilatation and irregularity and/or	139	116 (83.5)	9 (6.47)	Low

Author	Year	Country	Study period	Diagnostic Criteria	Number of patients	Male N (%)	Painless CP N (%)	Risk of Bias Level †
				pancreatic calcification on imaging and presence clinical symptoms. Small duct disease: parenchymal and ductal changes on EUS (Rosemont criteria)				
Hao et al.[45]	2017	China	2000–2013	≥ 1 of the following: histology; pancreatic calcification confirmed by plain radiography, abdominal US, CT, or echoendoscopy; and, moderate-to-marked pancreatic ductal lesions on pancreatography obtained by ERCP or MRCP (Cambridge classification)	1656	1152 (69.6)	114 (7)	Low
Machicado et al.[46]	2017	USA	1977–2006	Mayo Diagnostic Index	89	50 (56)	20 (22.5)	Low
Schwarzenberg et al.[47]	2019	USA	2000–2014	Either ERCP (Cambridge classification) or MRCP, CT, or EUS (≥ 5 criteria or calcifications), or histologic evidence of CP	572	584 (55) [all patients in study]	79 (13.8)	Low
Hirth et al.[48]	2019	Germany/ Ukraine	1998–2007	M-ANNHEIM classification	693	NR	94 (13.6)	Low
Hori et al.[49]	2019	USA	2013–2015	Accepted criteria for findings on CT, MRI or MRCP, ERCP (Cambridge classification), EUS (presence of 5 findings or Rosemont criteria), pathology, or a combination thereof	499	303 (60.7)	74 (14.8)	Low
Liu et al.[50]	2019	China	2010–2013	Asia-Pacific Consensus	1314	831 (63.2)	88 (6.7)	Low
Agarwal et al.[51]	2020	India	1998–2019	Mayo Clinic diagnostic criteria	747	672 (90)	44 (5.9)	Low
Amodio et al.[4]	2020	Italy	2010–2016	2017 UEG Evidence-Based Guidelines	781	50 (67.6) [Painless group]	74 (9.5)	Low

†Adapted from Hoy et al. NR: Not Reported; CBD: Common Bile Duct; ERCP: Endoscopic Retrograde Cholangiopancreatography; CT: Computed Tomography; US: Ultrasound; SPT: Secretin-Pancreozymin Test; EUS: Endoscopic Ultrasound; MRCP: Magnetic Resonance Cholangiopancreatography