



ORIGINAL ARTICLE

Natural history, clinical characteristics, outcomes, and long-term follow-up of pain-free chronic pancreatitis

Awais Ahmed¹, Ishani Shah¹, Rachel Bocchino², Steven D. Freedman¹, Darshan J. Kothari³ and Sunil G. Sheth^{1,*}

¹Department of Medicine, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; ²Department of Medicine, Division of Internal Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; ³Department of Medicine, Division of Gastroenterology, Duke University, Durham, NC, USA

*Corresponding author. Department of Medicine, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Rabb 423, Boston, MA 02215, USA. Email: ssheth@bidmc.harvard.edu

Abstract

Background: Chronic pancreatitis (CP) is characterized by chronic abdominal pain and functional insufficiency. However, a small subset of patients with prior acute pancreatitis (AP) and/or underlying risk factors for developing CP may be pain-free at diagnosis and may have a different clinical course. We aimed to compare the clinical characteristics, outcomes, and healthcare utilization between CP patients with and without pain.

Methods: Reviewed patients with established CP were followed in our Pancreas Center between January 2016 and April 2021. Patients without risk factors for developing CP and/or without AP prior to their diagnosis and only with incidental radiologic features of CP were excluded, so as to minimize confounding factors of pancreatopathy unrelated to CP. Patients were divided into painful and pain-free groups to analyze differences in demographics, outcomes, and healthcare utilization.

Results: Of 368 CP patients, 49 (13.3%) were pain-free at diagnosis and had remained so for >9 years. There were no significant differences in body mass index, race, sex, or co-morbidities between the two groups. Pain-free patients were older at diagnosis (53.9 vs 45.7, $P=0.004$) and had less recurrent AP (RAP) (43.8% vs 72.5%, $P<0.001$) and less exocrine pancreatic insufficiency (EPI) (34.7% vs 65.7%, $P<0.001$). Pain-free patients had less disability (2.2% vs 22.0%, $P=0.003$), mental illness (20.4% vs 61.0%, $P<0.001$), surgery (0.0% vs 15.0%, $P=0.059$), and therapeutic interventions (0.0% vs 16.4%, $P=0.005$) for pain.

Conclusions: We described a unique subset of patients with underlying risk factors for CP and/or prior AP who were pain-free at diagnosis. They were older at diagnosis, had less EPI and RAP, and overall favorable outcomes with minimal resource utilization.

Key words: chronic pancreatitis; pain-free; pancreatic insufficiency; diabetes

Introduction

Chronic pancreatitis (CP) is a complex syndrome characterized by a progressive fibro-inflammatory process resulting in

pancreatic atrophy, calcifications, dilated and irregular ducts, and functional deficiencies in patients with underlying metabolic, environmental, genetic, and other risk factors [1, 2].

Submitted: 9 November 2022; **Revised:** 15 December 2022; **Accepted:** 28 December 2022

© The Author(s) 2023. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-sen University

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

For commercial re-use, please contact journals.permissions@oup.com

Abdominal pain is often the most debilitating symptom in CP and a predictor of poor quality of life, disability, and opioid use [3, 4].

While the majority of patients with CP exhibit chronic pain, there is a subset of patients who do not have pain [5, 6]. A recent meta-analysis identified patients with painless CP with a pooled prevalence of 12%, who were mainly diagnosed based on imaging studies. Among CP patients, a pooled prevalence of 96% had calcifications, which included incidental findings of calcification, and approximately half were asymptomatic and without functional pancreatic insufficiencies [5]. Moreover, there was limited information on the risk factors for CP and preceding episodes of acute pancreatitis (AP). Amodio et al. [6] similarly identified 74 older patients without pain who had morphological changes of CP, but 72% had no identifiable risk factors for developing CP and half had no pancreatic exocrine insufficiency or diabetes. In these studies, data on demographics, clinical characteristics, and outcomes were not reported.

A leading hypothesis for the development of CP is the sentinel acute pancreatitis event theory, in which the initial episode of AP in patients with underlying genetic, environmental, or metabolic factors primes the pancreas for progression to CP, especially if there are repeated inflammatory events [7]. However, some studies show that some patients with CP may not have had a preceding episode of documented AP [7, 8]. Hence, it is unclear whether morphological changes and symptoms alone constitute definitive CP based on the recently accepted mechanistic definition in the absence of fibro-inflammatory triggers (predisposing risk factors/preceding AP) [1].

Notably, patients who have classical symptoms of CP, including long-standing pain, can become pain-free over several years [9–11]. Historically, this has been attributed to “burnout” of the gland, especially in alcohol-related CP [9]. Thus the mechanism for the evolution of painless CP remains unclear and maybe in part due to modulation in the perception of central pain over time [12].

Patients with definitive CP who are pain-free at initial diagnosis are an intriguing subset of CP patients, as they lack the most debilitating symptom of CP, which drives poor outcomes in this population [3, 4]. Recognizing and studying these patients can potentially provide the substrate for improving our understanding of disease progression and pain pathways, and improve strategies of pain management of classic painful CP.

In this study, we sought to examine the prevalence, clinical characteristics, outcomes, and resource utilization of patients with CP who had no pain at diagnosis but had underlying risk factors and/or preceding AP and were followed longitudinally for nearly a decade in our Pancreas Center. We also sought to compare their characteristics with patients with classical painful CP.

Methods

Patient selection and study design

We performed a retrospective study on all adult patients with a diagnosis of CP followed at our outpatient Pancreas Center in a tertiary care hospital, identified between January 1, 2016 and April 30, 2021 (Ethics committee approval number: 2018P000613).

Diagnosis of CP

The diagnosis of CP was confirmed based on the presence of clinical symptoms and definitive radiologic features (pancreatic calcifications, ductal abnormalities, pancreatic atrophy [based on subjective assessment of the radiologist], reduced T1 signal) on cross-sectional imaging (computed tomography [CT] or magnetic resonance cholangiopancreatography [MRCP]) and/or endosonographic features [13]. Asymptomatic changes related to pancreatopathy caused by aging, diabetes, exposure to tobacco, and alcohol use, such as calcifications and ductal irregularities, may make the diagnosis of CP challenging [14]. Therefore, patients diagnosed with CP via endoscopic ultrasound (EUS) were included only if they met the Rosemont criteria “consistent with CP” (Supplementary Table 1) [15]. In addition, given the inter-observer agreement and accuracy of EUS-guided CP diagnosis, we combined underlying metabolic, genetic, environmental, or other risk factors as well as preceding episodes of AP, and pancreatic exocrine and endocrine insufficiency to support the diagnosis of CP [16–18].

Definitions and study groups

We use the term “pain-free CP” to define patients who had documented evidence of underlying risk factors for CP, including AP, recurrent AP (RAP), and/or abdominal pain prior to their diagnosis of CP, but did not report any pain at the time of initial CP diagnosis (first CT/MRCP/EUS that showed CP) and remained pain-free in longitudinal follow-up. In the pain-free CP group, imaging or EUS that led to the initial CP diagnosis was most commonly done for other reasons, such as evaluation of exocrine insufficiency or follow-up of an AP episode in the Pancreas Center. We differentiated this group from “primary painless CP” as these patients were initially in a state of pain (preceding AP attacks) and evolved into a state that was completely free of pain at the time of initial diagnosis. Patients who had no risk factors for CP, had never reported pain, or did not have AP prior to their diagnosis of CP (primary painless CP) were excluded from our study. Therefore, patients with incidental radiologic or morphologic changes characteristic of CP were excluded.

The etiology of CP was definitively established for each patient as best we could. Patients were diagnosed with “idiopathic CP” only after a thorough evaluation for all risk factors was performed, including genetic testing when indicated. Genetic testing whenever possible was performed in all young adults with CP (<35 years of age) without a clear risk factor for pancreatitis.

Exocrine pancreatic insufficiency (EPI) was diagnosed by means of fecal elastase testing (<100 µg/g) and/or characteristic symptoms of malabsorption such as steatorrhea and weight loss. Diabetes was diagnosed on the basis of a hemoglobin A1c level of >6.5%, as defined by the American Diabetic Association [19].

We then divided our patients into two groups: (i) patients who did not report any abdominal pain since diagnosis of CP were included in the “pain-free CP” group and (ii) those who reported CP-related abdominal pain at the time of diagnosis of CP or thereafter, including intermittent or daily pain, were included in the “painful CP” group.

Data collection and outcomes of interest

We collected clinical data of all patients, including demographic characteristics such as age, gender, body mass index (BMI), risk

factors, etiology, as well as active gastrointestinal symptoms including abdominal pain pattern. We also collected data on complications of CP such as EPI, diabetes (pre-existing, early-onset, and late-onset), pancreatic cancer, as well as anatomical complications. We defined “pre-existing diabetes” if it was reported >2 years prior to CP diagnosis, “early-onset” if onset of diabetes occurred within 2 years of CP diagnosis, and “late-onset” if onset of diabetes was after 2 years of CP diagnosis [20]. We obtained data on the average number of CP flares requiring hospitalization in the preceding 24 months, endoscopic procedures for pain control, surgeries for CP-related pain, and the average number of imaging studies, such as CT and MRCP.

Statistical analysis

We performed univariate analyses to compare patients between the “pain-free” and “painful” CP groups. All outcomes were evaluated for normality. Categorical variables are presented as proportions and continuous variables as means with standard deviations (SDs). All analyses were performed using the R software (version 3.6.1, R Core Team 2018a, Vienna, Austria) within RStudio (version 1.1463, RStudio, Inc., Vienna, Austria) using the Tidverse (Wickham, 2017) package.

Results

A total of 368 patients fulfilled diagnostic criteria for CP, of whom 49 (13.3%) were pain-free at diagnosis and 319 (86.7%) had painful CP (127 had daily pain and 192 had intermittent pain). None of the patients with painful CP was ever pain-free after their CP diagnosis.

Pain-free CP

In the pain-free group, predisposing risk factors (etiological and/or prior AP) were identified in all 49 patients (Table 1). Twenty-two patients had one risk factor and 27 had two or more. Among the 49 pain-free patients, 44 (89.8%) had an identifiable etiology for CP and 5 were idiopathic; 34 (69.4%) had prior AP. All five patients with idiopathic CP had prior episodes of AP. Approximately 50% of the patients (25/49) had either EPI or diabetes: 5 only with EPI, 8 only with diabetes, and 12 with both.

Comparison between pain-free CP and painful CP

The patients of the pain-free group were significantly older (68.1 vs 57.3 years, $P < 0.001$) with a diagnosis at a more advanced age (53.9 vs 45.7 years, $P = 0.004$) than patients with painful CP (Table 2). There were no differences noted in the BMI ($P = 0.076$), race ($P = 0.749$), sex ($P = 0.286$), or Charlson Co-morbidity Index ($P = 0.671$) between the two groups. A higher proportion of

patients with disability were reported in the painful group than in the pain-free group (22.0% vs 2.2%, $P = 0.003$). There was no difference in time to follow-up between the study groups, averaging between 8 and 10 years ($P = 0.118$). Although both groups had similar mean numbers of RAP episodes prior to developing CP (3.58 vs 4.76, $P = 0.090$), the proportion of patients with RAP was significantly lower in patients with pain-free CP (43.8% vs 72.5%, $P < 0.001$).

There was similar prevalence of alcohol-related CP (32.7% vs 37.5%), but higher prevalence of genetic-related CP (12.2% vs 1.6%) and lower prevalence of idiopathic CP (10.2% vs 19.1%) in the pain-free group ($P = 0.004$).

There were significantly lower rates of EPI in the pain-free CP vs painful CP group (34.7% vs 65.7%, $P < 0.001$). Prevalence of diabetes including pre-existing diabetes was similar in both groups (40.8% vs 44.5%, $P = 0.206$). A higher proportion of late-onset diabetes was seen in the pain-free CP group (25.0% vs 13.3%), whereas a higher proportion of early-onset diabetes was seen in the painful CP group (10.0% vs 29.5%).

A significantly lower prevalence of mental health illness (anxiety and depression) was seen in the pain-free CP group (20.4% vs 61.0%, $P < 0.001$). Recreational tetrahydrocannabinol use was significantly lower in the pain-free group than in the painful group (4.1% vs 23.4%, $P = 0.004$). Opioid use was only seen in the painful CP group. There were no flares of CP reported in the pain-free group, with mean flares of 2.70 (SD 3.40) in painful CP. Although not statistically significant, pancreatic malignancy was not seen in pain-free CP and 15 patients (4.7%) went on to develop pancreatic malignancy in painful CP.

The modality of diagnosis was similar across all three cohorts, using a combination of MRCP, CT, and EUS ($P = 0.378$). After establishing CP diagnosis, the mean number of CTs since diagnosis was lower in the pain-free group (1.76 vs 3.55, $P < 0.001$). Therapeutic interventions such as celiac blocks were only seen in the painful group and not in the pain-free group (0.0% vs 16.4%, $P = 0.005$).

Discussion

Our study described clinical characteristics and outcomes in patients with pain-free CP over a mean follow-up of 9 years since initial diagnosis, comparing them with painful CP patients followed during the same period in our Pancreas Center. A diagnosis of CP in the pain-free group with abnormal imaging, symptoms of EPI or diabetes, or follow-up for prior AP or RAP was made in the setting of established radiologic or EUS criteria when patients were referred to our Pancreas Center. Although promising, newer diagnostic modalities such as EUS elastography or EUS with secretin stimulation [21] were not used to diagnose CP in the present study. The prevalence of pain-free CP

Table 1. Risk factors, etiology, and functional deficiencies in pain-free chronic pancreatitis

Etiology (n = 49)	Risk factors for CP				Pancreatic insufficiency		
	Prior AP (n = 34)	Alcohol (n = 16)	Smoking (n = 26)	Genetic (n = 6)	Exocrine insufficiency (n = 17)	Diabetes (n = 20)	Both (n = 12)
Alcohol (n = 16)	16 (100.0%)	16 (100.0%)	9 (56.2%)	0 (0.0%)	7 (43.8%)	10 (62.5%)	7 (43.8%)
Genetic (n = 6)	4 (66.7%)	0 (0.0%)	1 (16.7%)	6 (100.0%)	2 (33.3%)	2 (33.3%)	1 (16.7%)
Tobacco use (n = 19)	6 (31.5%)	0 (0.0%)	16 (84.2%)	0 (0.0%)	7 (36.8%)	5 (26.3%)	3 (15.8%)
Idiopathic (n = 5)	5 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)
Other (n = 3)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)

Number of patients with one risk factor: 22; number of patients with more than one risk factor: 27. Other: biliary, hypertriglyceridemia, drugs.

Table 2. Demographics, clinical features, and outcomes in chronic pancreatitis

Characteristic	Pain-free CP group (n = 49)	Painful CP group (n = 319)	P-value
Mean age, years (SD)	68.1 (15.1)	57.3 (14.1)	<0.001
Mean BMI, kg/m ² (SD)	27.1 (5.07)	25.5 (5.35)	0.076
Mean age at diagnosis of CP, years (SD)	53.9 (14.8)	45.7 (15.4)	0.004
Mean time since diagnosis, years (SD)	9.81 (6.05)	8.12 (5.77)	0.118
Female sex	19 (38.8%)	154 (48.1%)	0.286
Race			0.749
White	35 (72.9%)	238 (74.6%)	
Black	6 (12.5%)	33 (10.3%)	
Hispanic	1 (2.1%)	16 (5.0%)	
Other	6 (12.5%)	32 (10.0%)	
Disabled	1 (2.2%)	65 (22.0%)	0.003
Mean CCI (SD)	0.86 (1.10)	1.06 (1.10)	0.671
Clinical features			
Risk factor			0.004
Alcohol	16 (32.7%)	120 (37.5%)	
Genetic	6 (12.2%)	5 (1.6%)	
Idiopathic	5 (10.2%)	61 (19.1%)	
Smoking	19 (38.8%)	103 (32.2%)	
Other ^a	3 (4.8%)	30 (9.4%)	
History of recurrent AP	21 (43.8%)	232 (72.5%)	<0.001
Mean number of AP attacks prior to developing CP (SD)	3.58 (1.56)	4.76 (5.02)	0.090
Exocrine insufficiency	17 (34.7%)	209 (65.7%)	<0.001
Diabetes mellitus ^b	20 (40.8%)	142 (44.5%)	0.206
Pre-existing	13 (65.0%)	81 (57.0%)	
Early-onset	2 (10.0%)	42 (29.5%)	
Late-onset	5 (25.0%)	19 (13.3%)	
Pancreatic malignancy	0 (0.0%)	15 (4.7%)	0.237
Recreational THC use	2 (4.1%)	75 (23.4%)	0.004
Opioid use	0 (0.0%)	189 (58.4%)	<0.001
Modality of diagnosis			0.378
MRI	29 (59.1%)	157 (49.1%)	
EUS#	10 (20.4%)	91 (28.4%)	
CT	10 (20.4%)	72 (22.5%)	
Mental health illness	10 (20.4%)	195 (61.0%)	<0.001
Anxiety	5 (10.2%)	71 (22.2%)	
Depression	5 (10.2%)	124 (38.8%)	
Health care utilization			
Mean number of flares requiring hospitalizations in the last 2 years (SD)	0.00 (0.00)	2.70 (3.40)	<0.001
Mean number of CTs since diagnosis (SD)	1.76 (1.28)	3.55 (3.05)	<0.001
Mean number MRIs since diagnosis (SD)	2.00 (2.00)	2.29 (1.91)	0.357
Mean number of ERCs since diagnosis (SD)	0.00 (0.00)	1.44 (2.01)	<0.001
Mean number of EUS since diagnosis (SD)	1.02 (1.31)	1.00 (1.19)	0.930
Celiac blocks	0 (0.0%)	52 (16.4%)	0.005
Surgery for CP	0 (0.0%)	49 (15.5%)	0.059

CCI, Charlson Co-morbidity Index; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed topography; AP, acute pancreatitis; CP, chronic pancreatitis; THC, tetrahydrocannabinol.

^aBiliary, hypertriglyceridemia, drugs.

^bEarly-onset: within 2 years of diagnosis. Late-onset: after 2 years of diagnosis. #Definitive criteria based on Rosemont classification.

was 13.3%. These patients were characterized by an older age at diagnosis and lower prevalence of RAP, with approximately half experiencing EPI or diabetes. These patients had more favorable outcomes with respect to disability, mental illness, and health-care utilization.

Pain-free vs primary painless CP

Our pain-free group of patients is distinct from the recently described entity of primary painless CP who usually have no history of prior AP and also do not consistently have underlying

etiological risk factors to develop CP [5, 6]. The current mechanistic definition for CP encourages a decreased reliance on morphological changes in the pancreas, as fibrosis and ductal changes correlate poorly with the clinical syndrome of CP, including symptoms of pain and EPI [1]. Furthermore, it allows stratifying patients based on risk factors combined with imaging findings to assess for early or probable CP, which serves as a potential opportunity to prevent progression to end-stage disease. However, it remains to be seen how morphological changes play a role in the syndrome of CP in the absence of risk factors and clinical symptoms. Given the uncertainty of the

clinical relevance of incidental morphologic changes and the challenge of applying the current definitions of CP to these patients, we chose to exclude them in our assessment of pain-free CP. We included patients who definitively met currently accepted diagnostic criteria with supporting clinical features and predisposing risk factors for CP to ensure a uniform application of the CP definition and eliminate potentially erroneous diagnoses. As seen in studies on primary painless CP, $\leq 72\%$ of patients had no risk factors and $>90\%$ of patients had only imaging findings without supporting clinical features to suggest CP, with less than half of the patients exhibiting functional deficiencies [5, 6]. In contrast, in our pain-free group, all patients had contributing risk factors (etiological and/or prior AP) and half had evidence of pancreatic insufficiency. Our cohort is also different from the previously described entity of “late-onset idiopathic CP” [21] as more than one-third of our patients had alcoholic CP.

Age and pain-free CP

The advanced age of our patients with pain-free CP is not readily explained by current literature [11]. Ageing can affect sensory patterns of pain perception and modulation resulting in higher pain thresholds that may alter pain inhibition and may be a contributing factor [22, 23]. Older age may be a marker of a more insidious process, manifesting less severe symptoms, leading to a delayed presentation. These patients may be different from the entity of idiopathic senile CP in which pancreatic calcifications were noted, presumably related to decreased perfusion from arteriopathy, in $\leq 25\%$ of older males with mild pain [23]. Age-related morphological and functional changes have also been reported in asymptomatic patients [22].

Recurrent AP

Recurrent AP increases the risk of progression to CP [24, 25]. The hypothesis pointing to pancreatic burnout with repeated episodes of pancreatitis and long-standing CP has been suggested as one of the mechanisms for absence of pain and functional insufficiency, both temporally related to prolonged disease duration [7–9]. There is a paucity of data to support or explain the mechanism by which this phenotype develops. This may represent an end stage of CP or pancreatic burnout that can be seen in $\leq 38\%$ of patients with CP, especially with alcohol use and prolonged duration [9]. However, in our study, we reported a lower proportion of RAP in pain-free CP and the majority had non-alcoholic CP. It is possible that previous episodes of AP/RAP in these patients elicited milder inflammatory responses with mild symptoms, therefore delaying medical attention, leading to a delayed diagnosis. Importantly these patients were already pain-free at the time of CP diagnosis and did not have “burned-out” disease such as long-standing pain of CP with eventual resolution of pain. Our findings suggest there may be alternate mechanisms contributing to the development of a pain-free phenotype in addition to RAP and it warrants investigation in future studies.

Pancreatic insufficiency

EPI is commonly associated with CP and reported in $\leq 60\%$ – 90% of patients and a large population-based study has shown a higher prevalence of EPI among patients with RAP and alcohol-related CP [24, 25]. In our study, EPI was reported in 65.7% patients with painful CP, but only 34.7% of patients in pain-free CP. The reason for this wide discrepancy between the groups remains unclear, but the increased prevalence of RAP, resulting

in progressive parenchymal injury, seen in our group of painful CP, is a possible explanation. Furthermore, the presence of EPI can lead to abdominal symptoms of bloating and distention from malabsorption, and can also contribute to pain in these patients, which may explain the higher prevalence of EPI in the painful CP group [23, 24]. Additional disease-specific characteristics, previously reported, such as severity of prior AP, degree of parenchymal necrosis, and ductal abnormalities, may have contributed, but these were not examined in our study [26]. We reported that half of all our CP patients had diabetes, which is similar to the prevalence reported previously [22, 27]. A higher proportion of patients in the pain-free group had late onset of diabetes, but early-onset diabetes was seen more frequently in patients with painful CP. A possible explanation for this finding may be due to more rapid progression of disease in painful CP among other factors, but it certainly warrants further investigation.

Pancreatic cancer

CP is associated with an ≤ 8 -fold increase in the risk of pancreatic cancer [28]. Although not statistically significant, 15 patients in the painful CP group developed pancreatic adenocarcinoma whereas none in the pain-free CP group did, despite older age at diagnosis and otherwise similar BMI, tobacco use, rates of diabetes, and disease duration across both groups. An obvious reason is not evident in our study, but we hypothesize that milder and limited inflammation in pain-free CP may be associated with reduced risk of malignancy. However, this warrants further investigation in future studies.

Disability and healthcare utilization

Pain-related disability and unemployment are significant factors in impairing quality of life in CP [4]. In our study, we reported higher disability prevalence in patients with painful CP (22.0%) and only one patient reporting disability in the pain-free group. The lower prevalence of mental health illness in the pain-free group is a notable finding. Pain is a subjective response and its association with depression and anxiety has been widely reported [29–31]. Chronic pain may be a manifestation of depression and depression may be the result of chronic pain. Similarly, anxiety disorders are common in patients with chronic pain, second only to depression, and they often co-exist [29]. Thus it is not surprising that the painful CP group has a higher prevalence of mental health illness.

From a healthcare utilization aspect, as expected, pain-free CP patients did not require any opioids. Similarly, use of recreational tetrahydrocannabinol was higher in the painful CP group because tetrahydrocannabinol has an anti-nausea effect and it is a beneficial adjunct for pain management and an appetite stimulant [32]. Therapeutic interventions, specifically endoscopic retrograde cholangiopancreatography, celiac blocks, and surgery, were not performed in the pain-free group. Furthermore, none of the pain-free CP patients developed AP or flares requiring hospitalization over a mean follow-up period of 9 years. This is an important outcome, as one may hypothesize that these patients are in clinical remission, in the absence of pain and without flares over long-term follow-up. We also noted that patients with painful CP did not become pain-free during the same follow-up period. This is in contrast to the large Dutch study by Kempeneers et al. [33], which reported that patients alternated between different patterns of continuous and intermittent pain. It again emphasizes the limitation of

capturing the subjective variations of pain perception in a retrospective manner. Differences in patient population in terms of healthcare access, socioeconomic status, and risk factors may also be contributory.

To our knowledge, this study is the first to report long-term outcomes in patients who are pain-free at the time of diagnosis of CP, with established underlying etiological risk factors and/or preceding AP/RAP. The strengths of the study include a well-defined population of CP patients who fully meet current diagnostic criteria for CP, excluding patients with incidentally noted primary painless CP. We examined the natural history of pain-free CP with long-term follow-up of nearly a decade since CP was diagnosed. We were able to report patient demographics and disease-specific characteristics such as pancreatic insufficiency, analgesic use, healthcare utilization, and disability in these patients, which have previously not been studied. An inherent limitation of a retrospective review is missing data, such as subjective pain not reported during follow-up or unreported outside hospitalizations or emergency department visits. As the patients in the study had consistent follow-up in our Pancreas Center, these missing data are expected to be small in number. Another limitation of the study is that we did not have information on the severity of AP episodes in several CP patients or data on the time from initial AP event to the development of CP.

Conclusions

In our validated groups of CP patients, we identified 13.3% of patients who were clinically pain-free at initial diagnosis and with a significantly less morbid disease course over long-term follow-up. These patients were characterized by an older age and with lower prevalence of RAP, EPI, disability, mental health illness, and healthcare utilization. This phenotype constitutes a unique subset of CP patients and may provide a substrate for future investigation to better understand the pathophysiology of pain in CP.

Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

A.A.: study design, planning and supervision, acquisition of data, statistical analysis, drafting manuscript, and final approval of manuscript. I.S.: study design, planning, acquisition of data, final approval of manuscript. R.B.: acquisition of data, study design, final approval of manuscript. S.D.F.: study planning, design, and final approval of manuscript. D.K.: study design, planning, and final approval of manuscript. S.G.S.: study design, planning and supervision, drafting manuscript, and final approval of manuscript.

Funding

There is no funding to disclose pertaining to this study.

Acknowledgements

No acknowledgements.

Conflict of Interests

None declared.

References

- Whitcomb DC, Frulloni L, Garg P et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016;16:218–24.
- Löhr JM, Dominguez-Munoz E, Rosendahl J et al.; HaPanEU/UEG Working Group. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J* 2017;5:153–99.
- Pezzilli R, Morselli Labate AM, Ceciliato R et al. Quality of life in patients with chronic pancreatitis. *Dig Liver Dis* 2005;37:181–9.
- Machicado JD, Amann ST, Anderson MA et al. Quality of life in chronic pancreatitis is determined by constant pain, disability/unemployment, current smoking, and associated comorbidities. *Am J Gastroenterol* 2017;112:633–42.
- Bhullar FA, Faghih M, Akshintala VS et al.; P-QST Consortium. Prevalence of primary painless chronic pancreatitis: a systematic review and meta-analysis. *Pancreatology* 2022;22:20–9.
- Amodio A, De Marchi G, de Pretis N et al. Painless chronic pancreatitis. *Dig Liver Dis* 2020;52:1333–7.
- Olesen SS, Drewes AM, Novovic S et al. The sentinel acute pancreatitis event hypothesis revisited. *Pancreatology* 2019;19:614–5.
- Hori Y, Vege SS, Chari ST et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. *Pancreatology* 2019;19:224–9.
- Hirth M, Weiss C, Hardt P et al. Analysis of the course of chronic pancreatitis: pancreatic burnout rates are only increased in a subgroup of patients with alcoholic chronic pancreatitis. *Pancreas* 2019;48:726–33.
- Faghih M, Phillips AE, Kuhlmann L et al.; Pancreatic Quantitative Sensory Testing (P-QST) Consortium. Pancreatic QST differentiates chronic pancreatitis patients into distinct pain phenotypes independent of psychiatric comorbidities. *Clin Gastroenterol Hepatol* 2022;20:153–61.e2.
- Lankisch PG, Lohr-Happe A, Otto J et al. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. *Digestion* 1993;54:148–55.
- Lautenbacher S, Peters JH, Heesen M et al. Age changes in pain perception: a systematic-review and meta-analysis of age effects on pain and tolerance thresholds. *Neurosci Biobehav Rev* 2017;75:104–13.
- Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: a review. *Jama* 2019;322:2422–34.
- Lee LS, Andersen DK, Ashida R et al. EUS and related technologies for the diagnosis and treatment of pancreatic disease: research gaps and opportunities-summary of a National Institute of Diabetes and Digestive and Kidney Diseases workshop. *Gastrointest Endosc* 2017;Nov 86:768–78.
- Catalano MF, Sahai A, Levy M et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009;69:1251–61.
- Trikudanathan G, Munigala S, Barlass U et al. Evaluation of Rosemont criteria for non-calcific chronic pancreatitis (NCCP) based on histopathology: a retrospective study. *Pancreatology* 2017;17:63–9.

17. Yamabe A, Irisawa A, Bhutani MS et al. Validity of endoscopic ultrasound findings of chronic pancreatitis: evaluation from the viewpoint of disease risk factors. *Digestion* 2021;**102**:289–97.
18. Nakaoka K, Hashimoto S, Miyahara R et al. Current status of the diagnosis of chronic pancreatitis by ultrasonographic elastography. *Korean J Intern Med* 2022;**37**:27–36.
19. American Diabetes A2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S13–27.
20. Bellin MD, Whitcomb DC, Abberbock J et al. Patient and disease characteristics associated with the presence of diabetes mellitus in adults with chronic pancreatitis in the United States. *Am J Gastroenterol* 2017;**112**:1457–65.
21. DeWitt JM, Al-Haddad MA, Easler JJ et al. EUS pancreatic function testing and dynamic pancreatic duct evaluation for the diagnosis of exocrine pancreatic insufficiency and chronic pancreatitis. *Gastrointest Endosc* 2021;**93**:444–53.
22. Löhr J-M, Panic N, Vujasinovic M et al. The ageing pancreas: a systematic review of the evidence and analysis of the consequences (Review). *J Intern Med* 2018;**283**:446–60.
23. Ammann R, Sulser H. "Senile" chronic pancreatitis; a new nosologic entity? Studies in 38 cases. Indications of a vascular origin and relationship to the primarily painless chronic pancreatitis. *Schweiz Med Wochenschr* 1976;**106**:429–37.
24. Ahmed Ali U, Issa Y, Hagensaar JC et al.; Dutch Pancreatitis Study Group. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol* 2016;**14**:738–46.
25. Machicado JD, Chari ST, Timmons L et al. A population-based evaluation of the natural history of chronic pancreatitis. *Pancreatology* 2018;**18**:39–45.
26. Ammann RW, Heitz PU, Klöppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. *Gastroenterology* 1996;**111**:224–31.
27. Beyer G, Habtezion A, Werner J et al. Chronic pancreatitis. *Lancet* 2020;**396**:499–512.
28. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. *Am J Gastroenterol* 2017;**112**:1366–72.
29. Woo AK. Depression and anxiety in pain. *Rev Pain* 2010;**4**:8–12.
30. Phillips AE, Faghieh M, Drewes AM et al.; Pancreatic Quantitative Sensory Testing (P-QST) Consortium. Psychiatric comorbidity in patients with chronic pancreatitis associates with pain and reduced quality of life. *Am J Gastroenterol* 2020;**115**:2077–85.
31. Dunbar EK, Saloman JL, Phillips AE et al. Severe pain in chronic pancreatitis patients: considering mental health and associated genetic factors. *J Pain Res* 2021;**14**:773–84.
32. Barlowe TS, Koliiani-Pace JL, Smith KD et al. Effects of medical cannabis on use of opioids and hospital visits by patients with painful chronic pancreatitis. *Clin Gastroenterol Hepatol* 2019;**17**:2608–9.e1.
33. Kempeneers MA, Issa Y, Verdonk RC et al.; Dutch Pancreatitis Study Group. Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. *Gut* 2021;**70**:1724–33.