Clinical course and prognosis of medically managed patients with small vs. large duct chronic pancreatitis

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Clinical course and prognosis of medically managed patients with small vs. large duct chronic pancreatitis

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Abstract

Background and Aim: The clinical course and prognosis of medically managed patients with small duct and large duct chronic pancreatitis (CP) has been scarcely investigated. We investigated all-cause mortality and progression of endocrine and exocrine function in a medically managed cohort of patients with small duct CP and compared them to patients with large duct CP.

Methods: This was a retrospective cohort study of 198 consecutive patients with definitive CP according to M-ANNHEIM criteria. Patients were classified as large or small duct cases based on pancreatic duct morphology on cross sectional imaging. We compared all-cause mortality and rates of diabetes and exocrine insufficiency (EPI) between patient subgroups using Kaplan-Meier and multivariate-adjusted Cox Proportional Hazard Models. In a subgroup of patients with follow-up imaging studies, changes in anteroposterior (AP) diameter of the pancreatic head (n=120) and body (n=122) as well as changes in pancreatic duct morphology (n=121) was studied.

Results: The mean age of subjects were 58 ± 12 years and 70% were male. Large duct CP was seen in 75 patients (38%) and small duct CP by 123 patients (62%). The five-year mortality rate was compared between patient subgroups (HR: 1.07; 95% CI 0.56–2.07) as was the rate of new onset diabetes (HR: 1.55; 95% CI 0.77–3.13). In contrast, new onset of EPI was more prevalent in patients with large duct CP (HR: 1.77; 95% CI 1.10–2.86; P=0.019). Large duct CP was also associated with greater loss of pancreatic parenchyma in the head (coefficient -2.9 mm; 95% CI -4.0–-1.6; P<0.001). Seventeen (14%) with follow-up imaging changed their pancreatic duct morphology at follow-up, with the majority of patients developing large duct disease (82%).

Conclusion: Medically managed patients with large duct CP have an excess risk of EPI and pancreatic atrophy compared to their counterparts with small duct CP.

Introduction

Chronic Pancreatitis (CP) is an irreversible fibro-inflammatory disease, characterized by parenchymal and ductal change, with progressive development of exocrine pancreatic insufficiency (EPI), diabetes mellitus and chronic pain syndromes.1-3 It arises secondary to toxic metabolic exposure (alcohol), autoimmunity, recurrent episodes of acute pancreatitis or pancreatic duct obstruction.4

The natural course of CP remains uncharted regardless of the considerable amount of published research on CP in recent years.5 Akin to 1986, uncertainty concerning diagnosis, classification and therapeutic options still exist to this day, and may in part originate from inadequate exploration of disease course.5-8 In 1994, Layer et al. proposed CP to be classified based on etiology; alcoholic, idiopathic or early idio-pathic CP.9 The spectrum of aetioligias has subsequently expanded to include hereditary CP and autoimmune CP.10 Today, however, CP may be classified as large duct or small duct,
i.e. with or without dilatation/obstruction of the main pancreatic duct, as interventional treatment options are partly dependent on ductal morphology.\textsuperscript{7,8,11–13} The majority of investigations on endoscopic therapy have been concerned with pain relief, whereas the effect of endoscopic therapy on pancreatic function has been scarcely explored.\textsuperscript{13–17} In addition, the existing literature has investigated the natural course of CP in the scope of etiology.\textsuperscript{5,6,9,18}

With this in mind, we aim to explore and compare the disease course of medically managed patients with small and large duct CP in relation to mortality, EPI, and diabetes in the scope of morphology. As large duct CP exhibits more morphological features associated with more severe disease states on the Cambridge classification system, we hypothesized patients with large duct CP to have worse prognosis compared to patients with small duct CP.\textsuperscript{19}

**Methods**

**Study Design**

This was a retrospective monocenter cohort study conducted at Departments of Gastroenterology and Radiology, Aalborg University Hospital, Denmark. The study cohort comprised of consecutive adult patients with CP (≥18 years) who visited the outpatient clinic between June 2011 and March 2020 with no prior history of endoscopic treatments. Patients had a definitive diagnosis of CP according to M-ANNHEIM diagnostic criteria. Patient’s Medical records were reviewed between 01.01.1994 and 10.31.2020 to evaluate mortality, EPI, and diabetes. In a subgroup cohort with available follow-up imaging, pancreatic morphology was assessed on images derived from computed tomography and magnetic resonance imaging at baseline and follow-up. The study was approved by the North Denmark Region Committee on Health Research Ethics (2020-038989).

**Subject characteristics**

Information on subject demographics and etiology were derived from patients’ medical records. Classification of etiology was based on the TIGAR-O system; idiopathic, alcoholic, or other.\textsuperscript{20} Smoking habits were defined as current smoking status and categorized as never, past, or current smoker. Alcohol consumption was reported as current weekly consumption of alcohol units, classified as abstainers, light-to-moderate use, heavy use, or very heavy use.\textsuperscript{21} Clinical pain scores were defined as no pain, intermittent pain, or constant pain.\textsuperscript{22}

**Evaluation of exocrine and endocrine pancreatic function**

Status of exocrine and endocrine function at follow-up were derived from patients’ medical records. EPI was evaluated by initial prescription date of pancreatic enzyme replacement therapy. Diabetes was assessed by initial prescription date of antidiabetics or earliest available HbA1c (IFCC) > 48 mmol/l.

**Evaluation of pancreatic morphology**

Radiologic assessments of computed tomography and magnetic resonance images were performed by one reader (MBM) with guidance of a radiologist in training (ES). Pancreatic morphology was evaluated on T2-weighted or FIESTA images for magnetic resonance imaging and axial computed tomography images using Picture Archiving and Communication System. The same modality, within a patient, was used for baseline and follow-up. For assessment of parenchymal thickness, the anteroposterior (AP) diameter was measured in standardized position in the head and body of pancreas.\textsuperscript{23} Points of measurement on images at baseline were placed side-by-side to images at follow-up to ensure further homogeneity in points of measurement. Two-point measurements were positioned on the image with the widest diameter while avoiding cystic lesions. The presence of ductal obstruction (yes/no), was defined as a focal abrupt caliber change with upstream dilatation on magnetic resonance imaging and magnetic resonance cholangiopancreatography. On computed tomography, the presence of ductal obstruction was dependent on visible intraductal calculi.\textsuperscript{24}

**Statistical analysis**

Data are expressed as mean ± SD for continuous variables and numbers (percentages) for categorical variables unless otherwise indicated. Baseline characteristics between patients with large vs small duct CP were compared by Fisher’s exact test or Student’s t-test. Follow-up time was reported as median (interquartile range). Survival curves were constructed using the Kaplan-Meier method and Cox Proportional Hazard Regression Models were used to analyze the association between pancreatic duct morphology (small vs. large duct CP) and survival, EPI, and diabetes. Models were adjusted for age and sex. Effect sizes were expressed as hazard ratios (HRs) with p values and 95% confidence intervals (CIs). Change in AP diameter of the pancreatic head and body between baseline and follow-up was analyzed using univariate and multivariate linear regression analysis adjusted for age, sex, and...
time between imaging studies. Effect-sizes were expressed as coefficients with \( p \) values and 95% CIs. Statistical significance was defined as a two-tailed \( p \) value <0.05. The software package STATA/MP 17.0 (SataCorp LP, College Station, Texas, USA) was used.

**Results**

**Demographic and clinical characteristics**

A total of 255 consecutive patients were initially screened, of which 57 patients were excluded, see Figure 1. The overall characteristics of the 198 patients included in the final study cohort are presented in Table 1. 123 patients were classified as small duct CP and 75 as large duct CP. Mean age was 58 ± 12 years at baseline, and 70% were male. Male predominance was observed in large duct CP (80%) vs small duct CP (63%) (\( P=0.01 \)). At baseline, patients with large duct CP had a higher diabetes prevalence (43%) vs small duct CP (24%) (\( P=0.004 \)). Similarly, pancreatic enzyme replacement therapy was more frequent in large duct CP (47%) vs small duct CP (28%) (\( P=0.007 \)). Distributions of etiology, smoking status, alcohol consumption and pain patterns were proportionate between groups.

### Table 1. Demographic and characteristics of the study cohort at baseline.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All</th>
<th>Small duct</th>
<th>Large duct</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td>0.061</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>58.2</td>
<td>57</td>
<td>60.3</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>138 (70%)</td>
<td>78 (63%)</td>
<td>60 (80%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td>0.468</td>
</tr>
<tr>
<td>Alcohol</td>
<td>119 (60%)</td>
<td>71 (58%)</td>
<td>48 (64%)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>55 (28%)</td>
<td>38 (31%)</td>
<td>17 (22%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>24 (12%)</td>
<td>14 (11%)</td>
<td>10 (13%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>0.874</td>
</tr>
<tr>
<td>Never smoker</td>
<td>26 (13%)</td>
<td>16 (13%)</td>
<td>10 (13%)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>45 (23%)</td>
<td>26 (21%)</td>
<td>19 (25%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>115 (58%)</td>
<td>74 (60%)</td>
<td>41 (55%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>12 (6%)</td>
<td>7 (6%)</td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td>0.111</td>
</tr>
<tr>
<td>Abstainer</td>
<td>115 (58%)</td>
<td>77 (63%)</td>
<td>38 (51%)</td>
<td></td>
</tr>
<tr>
<td>Light to moderate use</td>
<td>38 (19%)</td>
<td>20 (16%)</td>
<td>18 (24%)</td>
<td></td>
</tr>
<tr>
<td>Heavy use</td>
<td>12 (60%)</td>
<td>9 (7%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Very heavy use</td>
<td>15 (8%)</td>
<td>10 (8%)</td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>18 (9%)</td>
<td>7 (6%)</td>
<td>11 (15%)</td>
<td></td>
</tr>
<tr>
<td>Pain pattern</td>
<td></td>
<td></td>
<td></td>
<td>0.137</td>
</tr>
<tr>
<td>No pain</td>
<td>69 (35%)</td>
<td>39 (32%)</td>
<td>30 (40%)</td>
<td></td>
</tr>
<tr>
<td>Intermittent pain</td>
<td>71 (36%)</td>
<td>48 (39%)</td>
<td>23 (31%)</td>
<td></td>
</tr>
<tr>
<td>Constant pain</td>
<td>47 (24%)</td>
<td>32 (26%)</td>
<td>15 (20%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>11 (6%)</td>
<td>4 (3%)</td>
<td>7 (9%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>61 (31%)</td>
<td>29 (24%)</td>
<td>32 (43%)</td>
<td>0.004</td>
</tr>
<tr>
<td>PERT</td>
<td>70 (35%)</td>
<td>35 (28%)</td>
<td>35 (47%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

PERT: pancreatic exocrine replacement therapy

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**Figure 1.** Enrolment of patients in the primary analysis including mortality, new-onset diabetes, and EPI. The imaging-subanalysis below was limited to patients with available follow-up imaging. EPI: exocrine pancreatic insufficiency.
Mortality
Mortality was assessed in 198 patients, see Figure 2a. Median survival time was 5.18 years (IQR: 3.15–7.22). After 5 years, 21% of patients with large duct CP died compared to 19% with small duct CP (HR 1.07; 95% CI, 0.56–2.07), see Table 2.

New-onset diabetes
New-onset of diabetes was evaluated in 137 patients, see Figure 2b. Median time of developing diabetes was 5.01 years (IQR: 3.00–7.18). After five years, 40% of patients with large duct CP had diabetes compared to 26% with small duct CP (HR 1.55; 95% CI, 0.77–3.13), see Table 2.

New-onset exocrine pancreatic insufficiency (EPI)
New-onset of EPI examined in 128 patients, see Figure 3. The median time of developing EPI was 2.23 years (IQR: 0.26–5.95). After five years, 75% of patients with large duct CP had EPI compared to 52% with small duct CP (HR 1.77; 95% CI, 1.10–2.86; P=0.019), see Table 2.

Table 2. All-cause mortality and clinical outcomes in patients with small vs. large duct chronic pancreatitis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Small Duct</th>
<th>Large Duct</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>23 patients at risk</td>
<td>16 patients at risk</td>
<td>1.18 (0.62–2.24)</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>24 patients at risk</td>
<td>17 patients at risk</td>
<td>1.42 (0.72–2.82)</td>
</tr>
<tr>
<td>New onset EPI</td>
<td>46 patients at risk</td>
<td>30 patients at risk</td>
<td>2.00 (1.26–3.18)</td>
</tr>
</tbody>
</table>

EPI: exocrine pancreatic insufficiency HR; hazard ratio
#Age and sex adjusted

Figure 2. Kaplan-Meier plots illustrating proportion of patients alive (a) and proportion of patients without diabetes (b) in patients with large duct CP — (black) and small duct CP — (gray) within 5 years. No statistical difference was found in either analysis between large duct CP and small duct CP. CP: chronic pancreatitis.

Changes in pancreatic morphology
Change in AP diameter of the pancreatic head and body was assessed in 120 and 122 patients, respectively. See Figure 4. Median follow-up time for imaging was 2.65 years (IQR: 1.56–4.54). The mean change of AP diameter of the pancreatic head was -2.7 ± 3.7 mm in the large duct group vs. -0.1 ± 2.6 mm in the small duct group (coefficient -2.9 mm, 95% CI, -4.0–-1.6; P<0.001). In contrast, the mean change of AP diameter of the pancreatic body was -1.9 ± 2.5 in the large duct group vs -1.1 ± 3.1 in the small duct group (coefficient -0.8 mm, 95% CI, -2.0–0.4), see Table 3.

Change in pancreatic duct morphology from baseline to follow-up was evaluated in 83 patients with small duct CP and 38 patients with large duct CP, see Figure 5. Seventeen patients (14%) changed their pancreatic duct morphology at follow-up, of which 82% developed large duct disease.
Discussion

To our knowledge, this is the first study exploring the natural course of disease in medically managed patients with CP, in which patients are classified according to pancreatic duct morphology, i.e. small and large duct CP. After five years, we found no statistically significant difference in mortality or new-onset of diabetes between large duct CP compared to small duct CP, although new-onset of diabetes seemed more prevalent in patients with large duct CP (40% vs 26%). In contrast, we found EPI to be significantly more predominant in large duct CP compared to small duct CP (P=0.019). Furthermore, we found patients with large duct CP to atrophy significantly more in the pancreatic head compared to patients with small duct CP (P<0.001), while no difference between large duct CP and small duct CP was found in the pancreatic body.

Mortality in small vs large duct CP

All-cause mortality in Danish patients with definitive CP is 4-fold higher compared to the general population, encouraging further investigation and advances. We found no difference in all-cause mortality between medically-managed patients with large duct disease compared to those with small duct disease. This may imply an even distribution of factors promoting mortality across groups. Smoking, heavy consumption of alcohol and pain intensity are risk factors of mortality but were evenly distributed between groups within this study. Moreover, literature has found individuals with CP to have higher risk of death from cancer, and to have higher incidences of associated comorbidities, including cancer, cerebrovascular disease, chronic pulmonary disease, diabetes and chronic renal disease. In support of this notion, multiple studies have suggested CP to rarely be the direct cause of mortality in contrast to the multivisceral complications secondary to smoking and alcoholism. This may reaffirm current interventional treatment strategies, which emphasize pain reduction and quality of life. Interestingly, Levy et al. found patients with CP who had attacks of acute pancreatitis to have 42% lower rate of mortality compared to CP patients without. This effect was suggested to be a derivative of lower alcohol consumption secondary to pain, and a similar effect was observed in patients who underwent surgery. However, alleviation of pain in patients with CP has been shown to improve quality of life and mortality, and a reduction in pain has generally been found to allow for better lifestyles and to prevent comorbidities.

Diabetes in small vs large duct CP

A larger proportion of medically managed patients had diabetes at follow-up in the large duct group (43%) compared to the small duct group (26%), but not with statistical significance. Interestingly, Aslam et al. found strictures and calcifications of the pancreatic duct in patients with CP to impose significant risk in developing diabetes, while dilatation of the pancreatic duct did not. Taken together with our findings, this may suggest that morphological features are associated with unique risk profiles and subsequent complications. Furthermore, this may imply that distinct morphological features may not be strictly limited to small duct or large duct CP, as strictures, for instance, may be seen in both large duct and small duct CP. Moreover, it is unknown whether these morphological features differ in risk profiles depending on whether the feature is present in large or small duct CP. For instance, intraductal calcification or strictures may be seen in both small and large duct CP, and may present different risk profiles dependent on the underlying pathophysiological disease mechanism. Pancreatic parenchymal calcifications, albeit not a defining feature of either small or large duct CP, has been identified as an independent risk factor of diabetes in patients with CP, and is thought to be a marker of disease progression. One cohort study examining 1,695 patients with CP found male sex, alcohol abuse, steatorrhea, biliary strictures and distal pancreatectomy to be independent risk factors of diabetes.
This wide array of different risk factors attests to the multifaceted pathogenesis of diabetes in CP. It is theorized, in part, to evolve with loss of beta cells mediated by inflammatory cell infiltration with t-cell mediated inflammation of islets with subsequent fibrosis. It is associated with hypoglycemia and angiopathy, in addition to before-mentioned comorbidities. Moreover, literature has established diabetes as an independent risk factor of mortality in patients with CP. Thus, if incidence of diabetes truly were higher in patients with large duct CP, this would potentially manifest as increased mortality in the same group. This effect was perhaps not evident due to a follow-up time limited to five years.

Lastly, one study found no difference in incidence of diabetes when comparing conservatively managed CP patients and CP patients treated with endoscopy. However, this study effectively compared endoscopic treatment in eligible large duct patients (which we excluded) to non-eligible large and small duct patients. Interestingly, they found endoscopic intervention to delay onset of diabetes in up to 4 years in patients with idiopathic large duct disease. However, the prevalence of diabetes at follow-up remained unchanged. This finding may be viewed together with Aslam et al., which found pancreatic ductal calcifications to predict the early development of diabetes. Thus, these findings may suggest ductal calcifications to augment development of diabetes, and endoscopy to provide a transient anti-inflammatory or protective effect against diabetes with large duct CP.

**EPI in small vs large duct CP**

Previous literature has established 63 – 87% of patients with CP to develop EPI within five years of diagnosis. We found a significant predominance of EPI in medically managed patients with large duct CP (75%) compared to patients with small duct CP (52%) after five years. This may be related to a higher degree of acinar cell death, hyperplasia and hypertrophy of ductal cells and duct periductal fibrosis secondary to obstruction of the pancreatic duct in patients with large duct CP. A prospective study cohort of 324 patients investigating the effect of pancreatectoduodenectomy on EPI found obstructive pathologies to be an independent risk factor in developing EPI. However, that study defined obstructive pathologies to not only include CP, but also pancreatic malignancies, which were excluded from our study. The obstructive mechanism partly driving EPI may be somewhat identical to our study. In addition, it is widely accepted that exocrine dysfunction and ductal morphological changes develop in parallel. Intraductal calcifications and dilatation of the main pancreatic duct, i.e. defining features of large duct CP, have independently been associated with higher risk of EPI. The effect of endoscopic therapy on ductal changes remains uncertain. Endoscopic therapy has not demonstrated any benefit in preserving exocrine function in patients with CP.
Notably, exocrine function has been found to deteriorate more significantly in large duct CP with unsuccessful endoscopic therapy, i.e. remaining filling defects of the main pancreatic duct on magnetic resonance cholangiopancreatography, compared to large duct CP treated with successful endoscopic therapy. A hard pancreas, indicative of fibrosis and later disease stage, has furthermore been found to be an independent risk factor of EPI. Taken together, these findings may suggest interventional therapy to benefit prognosis of EPI in large duct CP if performed earlier.

Pancreatic morphology in small vs large duct CP

Total pancreatic volume is a determinant of endocrine cell mass and a decrease in volume is associated with multiple disorders. Loss of pancreatic parenchyma is a normal characteristic of aging, and is expected in CP. We found the AP diameter of the pancreatic head in medically managed large duct patients to diminish more significantly after five years compared to small duct patients. Insufficient literature exists on this matter, even so, one study found endoscopic therapy to be beneficial in reducing volume loss in patients with large duct CP compared to large duct patients who did not. It may therefore be hypothesized that the extent of obstruction is correlated with loss of pancreatic volume. However, we observed no difference in AP diameter of the pancreatic body when comparing large duct and small duct CP. This may indicate that the pancreatic body is more resistant to atrophy from obstruction of the pancreatic duct in contrast to the pancreatic head. Previous studies have demonstrated pancreatic function to be dependent on parenchymal volume. With our findings of EPI in mind, it may be suggested that loss of parenchymal volume in the pancreatic head demonstrates a larger association with the development of EPI compared to loss of volume in the pancreatic body. This has not been investigated directly, albeit studies have found pancreatic resection to lead to the development of EPI. In accordance with our findings, pancreaticoduodenectomies impose the greatest risk of EPI compared to other pancreatic resections, except for total pancreatectomy.

Furthermore, we visualized the possibility of medically managed patients to change group between baseline and follow-up based on pancreatic duct morphology. To our knowledge, this change has been scarcely explored in past literature. We found 14% of patients to change morphology from baseline to follow-up, with 82% developing large duct disease. This may be a reflection of ongoing disease progression, as the morphological features present in large duct CP correspond to more severe disease stages in the Cambridge Classification System for CT/MRI. In contrast, 8% developed small duct CP, demonstrating that in a few cases, the defining morphological features of large duct CP spontaneously resolve. This change was described in a case study; a patient with intraductal calcifications and dilatation of the main pancreatic duct spontaneously resolved both, perhaps due to auto-ductal drainage via fistulas or auto chemical dissolution.

Clinical implications

It is unclear whether the classification of CP as large duct and small duct disease is to be viewed as distinct stages in the progression of disease, or as dynamic stages in which patients can alternate between over the course of disease. Nonetheless, it may be beneficial for patients to have small duct CP instead of large duct CP.
The effect of endoscopic treatment on disease course remains uncertain, albeit improvements in pancreatic duct morphology and pancreatic parenchyma have been identified. These findings may warrant discussion and investigation of whether the indication for endoscopic therapy should be expanded to include large duct CP patients without pain. Second, patients with large duct CP may need more frequent monitoring for the development of EPI. Third, our findings suggest it may beneficial to monitor for a potentially disadvantageous transformation to large duct CP, especially if it possible to reverse the transformation by endoscopic therapy.

Limitations
This is a retrospective observational study with multiple limitations. The study was susceptible to selection bias, information bias and confounding. The heterogenous manifestation, diagnostic uncertainty and incomplete understanding of disease stages challenge the notion of equal disease stage and time of diagnosis at baseline, and may be viewed as a source of selection bias. Moreover, new-onset of diabetes and EPI were dependent on information retrieval through medical records, which is non-systematic and limited. Monitoring for new-onset diabetes and EPI was insufficiently standardized, thus susceptible to surveillance bias, as symptomatic patients may have been more frequently monitored. The same effect may have occurred in the imaging subanalysis as reflected by the participation rate. The psychosocial difficulties and low compliance of patients with CP may introduce additional bias. Smoking habits and consumption of alcohol are relevant in disease progression, and were not accounted for besides at baseline, potentially introducing confounding. Moreover, these habits are prone to underreporting. Potential confounders, including pancreatic parenchymal calcifications, biliary strictures, and pancreatic fibrosis were not measured in this study. The restriction to only include medically managed patients with CP should be considered limiting in terms of generalizability of the study. Differences in the defining features of large duct CP between imaging modalities may have been a source of misclassification bias. On computed tomography, a visible obstructive element was necessary for the classification of large duct CP, while this was not the case on magnetic resonance imaging. Assessment of imaging parameters was conducted by one reader, reported without double entry of values, and was not reviewed. Image dates were not blinded, thus making the imaging analysis susceptible to confirmation bias. Measurement of pancreas size may further have been influenced due to imaging derived from different scanners with different quantitative imaging protocols.

Conclusion
Medically managed patients with large duct CP have an excess risk of EPI and pancreatic atrophy compared to their counterparts with small duct CP. These findings help expand the understanding of the natural course of CP and may be of importance in future charting of disease progression and treatment.

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