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Clinical Course of Medically Managed Patients With Large and Small Duct Chronic Pancreatitis

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INTRODUCTION: **Pancreatic duct obstruction is the primary indication for endoscopic and/or surgical therapy in patients with chronic pancreatitis (CP). However, the clinical course of medically managed patients in relation to pancreatic duct obstruction is largely unknown.**

METHODS: **This was a retrospective cohort study of medically managed patients with CP. We classified patients based on pancreatic duct obstruction from a stricture or stone using cross-sectional imaging (i.e., large vs small duct CP). We compared prevalence of diabetes and exocrine insufficiency (EPI) between subgroups at inclusion and investigated risk of new-onset diabetes, EPI, and all-cause mortality over a follow-up period of 5 years. Changes in pancreatic morphology were studied in patients who underwent follow-up imaging.**

RESULTS: **A total of 198 patients (mean age 58 ± 12 years, 70% male, 60% alcoholic etiology, 38% large duct CP) were evaluated. At inclusion, patients with large vs small duct CP had a higher prevalence of both diabetes (43% vs 24%, $P = 0.004$) and EPI (47% vs 28%, $P = 0.007$). There was an increased risk of new-onset EPI in patients with large duct CP (hazard ratio 1.72; 95% confidence interval [1.05–2.80], $P = 0.031$) and higher rates of pancreatic atrophy ($P < 0.001$). No differences between groups were observed for new-onset diabetes and all-cause mortality. Conversion from small to large duct CP or *vice versa* during follow-up was observed in 14% of patients.**

DISCUSSION: **In a medically managed cohort of patients, large duct CP was associated with increased risk of EPI and pancreatic atrophy compared with small duct CP.**

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INTRODUCTION

Chronic pancreatitis (CP) is a fibroinflammatory disease characterized by sustained pancreatic inflammation with excess risk of comorbidity and mortality (1,2). Most patients present with a primary symptom of abdominal pain and, as the disease progresses, develop exocrine pancreatic insufficiency (EPI) and pancreatogenic diabetes mellitus (1,3). However, there is great variability in symptom severity and the rate of disease progression between patients. This is probably related to differences in exposure to etiological risk factors, genetic factors, and hitherto undetermined disease modifiers (4,5).

The clinical course of CP has mostly been studied in relation to etiology. Accordingly, in a landmark study from 1994, Layer et al. (6) investigated the clinical course of alcoholic vs early-onset and late-onset idiopathic CP and reported a worse prognosis for patients with alcoholic etiology. The findings corroborated earlier observations and were subsequently replicated in multicenter-based and population-based studies using updated classifications of etiological risk factors including alcohol, smoking, and genetics (4,7–13). However, in addition to these established risk factors, additional mediators may be of relevance for disease progression and the clinical course of CP (8).

In most patients with CP, decisions on management are guided by the presence of pancreatic duct obstruction from a stricture or stone on cross-sectional imaging (3). According to most guidelines, patients with large duct disease due to a pancreatic duct stricture and/or stone(s) should be referred for endoscopic or surgical decompression to relieve pain when medical therapy is unsuccessful (14–17). By contrast, patients with small duct disease (i.e., no signs of pancreatic duct obstruction on cross-sectional imaging) are mostly managed medically or by surgical resection procedures in select cases (15–17). As such, pancreatic duct morphology is a defining feature for CP management and may also be associated with disease progression. However, this has only been scarcely investigated, and it remains largely unknown whether the prognosis and risk of disease progression differ between patients with large and small duct disease. In

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addition, the natural evolution of pancreatic duct morphology (i.e., change from small to large duct disease or *vice versa*) is unknown.

We investigated the clinical course of medically managed patients with CP in relation to pancreatic duct morphology. We hypothesized that CP patients with large duct disease have a worse prognosis, including increased risk of EPI, diabetes, and morphological progression, compared with patients with small duct disease. The aims of this study were (i) to compare the prevalence of EPI and diabetes between subgroups at inclusion (cross-sectional study) and (ii) to compare risk of new-onset EPI, new-onset diabetes, and death between subgroups (follow-up study). In patients with available imaging at follow-up, we also compared morphological progression between subgroups and investigated the rate of transition between large and small duct disease (imaging substudy).

METHODS

Study design and approval for data acquisition

This was a retrospective cohort study conducted at the Center for Pancreatic Diseases, Department of Gastroenterology, Aalborg University Hospital, Denmark. The Institutional Review Board at Aalborg University Hospital granted permission to perform this study, and approval for medical record review and registration of patient and disease characteristics was provided by the Danish Patient Safety Authority (study ID 2020-038989). Owing to the observational nature of our study, approval from an ethics committee and written informed consent were not required according to the Danish legislation.

Inclusion and exclusion criteria

The study cohort comprised consecutive adult patients with CP (18 years and older) who visited the outpatient clinic between June 2011 and March 2020. All patients had a definitive diagnosis of CP according to M-ANNHEIM diagnostic criteria and a cross-sectional imaging examination (computed tomography and/or magnetic resonance imaging) within a maximum of 12 months before or after the date of the outpatient visit (18). Patients with a history of pancreatic surgery or procedures directed at the pancreatic duct (endoscopic or surgical decompression) were excluded to conduct an unbiased assessment of pancreatic duct morphology and its relation to clinical outcomes. This approach was chosen because invasively treated patients comprised a heterogenous group including (i) patients who had undergone pancreatic duct decompression before referral to our institution, (ii) patients referred for endoscopic treatment after the primary visit in our clinic, and (iii) patients undergoing pancreatic duct decompression at a later point during follow-up. Consequently, analysis of outcomes for these patients was not straightforward and prone to different sources of bias including immortal time bias (endoscopic treatment conducted before initiation of follow-up). Therefore, we decided to focus our analysis on medically managed patients. Patients with incomplete clinical data at inclusion or follow-up, patients with autoimmune pancreatitis (without evidence of definitive CP), and patients developing pancreatic cancer during follow-up were also excluded from the study cohort.

Data acquisition

Patient's medical records were reviewed at inclusion (date of cross-sectional imaging) and followed until November 1, 2021, (administrative censoring) or the development of new-onset EPI, new-onset diabetes, or death (whichever came first). In the analyses of EPI and diabetes, patients who died before the end of this study (November 1, 2021) were censored at the date of death because we did not consider competing risk to be a major source of bias because of proportionate death rates between patients with large and small duct disease. Patients with available cross-sectional imaging during the follow-up period were included in a nested imaging substudy to investigate changes in pancreatic morphology.

Patient characteristics

Information on demographics and clinical characteristics were derived from patients' medical records and a prospectively maintained database (19). The classification of etiology was based on the TIGAR-O system and reported as alcoholic, idiopathic, or other (20). Smoking habits were defined as current smoking status and categorized as never, past, or current smoker (19). Alcohol consumption was reported as weekly consumption of alcohol units, classified as abstainers, light-to-moderate use, heavy use, or very heavy use (21). Clinical pain patterns at the time of study inclusion were defined as no pain, intermittent pain, or constant pain (22).

Outcomes

Evaluation of exocrine and endocrine pancreatic functions. Exocrine and endocrine functions at inclusion and follow-up were derived from patients' medical records and laboratory data. A diagnosis of clinically relevant EPI was based on the prescription of pancreatic enzyme replacement therapy. In Denmark, reimbursement for pancreatic enzyme replacement therapy depends on an abnormal pancreatic function test result (fecal elastase test or fat absorption coefficient). Therefore, patients with an enzyme prescription are most likely to have an abnormal pancreatic function test and symptoms relevant for enzyme prescription. The date of new-onset EPI was indicated by the first prescription date of pancreatic enzyme replacement therapy during follow-up.

Diabetes was defined by an HbA1c (International Federation of Clinical Chemistry) of $>$ 48 mmol/L ($>$6.5% mmol/L) or prescription of glucose-lowering therapies (23). During follow-up, the date of new-onset diabetes was based on the earliest HbA1c of $>$ 48 mmol/L ($>$6.5% mmol/L) or prescription date of glucose-lowering therapy (23).

Cross-sectional imaging. Pancreatic morphology was evaluated on T2-weighted or balanced steady-state gradient echo sequence (Fast Imaging Employing Steady-state Acquisition) images for magnetic resonance imaging and axial computed tomography images using the Picture Archiving and Communication System. The same imaging modality (magnetic resonance imaging or computed tomography) was used for inclusion and follow-up examinations within patients. The anteroposterior (AP) gland diameter was measured in standardized positions in the pancreatic head and body to obtain a proxy of pancreatic parenchymal volume as recommended in international guidelines (24–26). Measurement points at baseline and follow-up images were placed side by side to harmonize measurement positions. Two-point measurements were positioned on the image with the widest parenchymal diameter while avoiding cystic lesions, but no correction for pancreatic duct dilation was performed. The

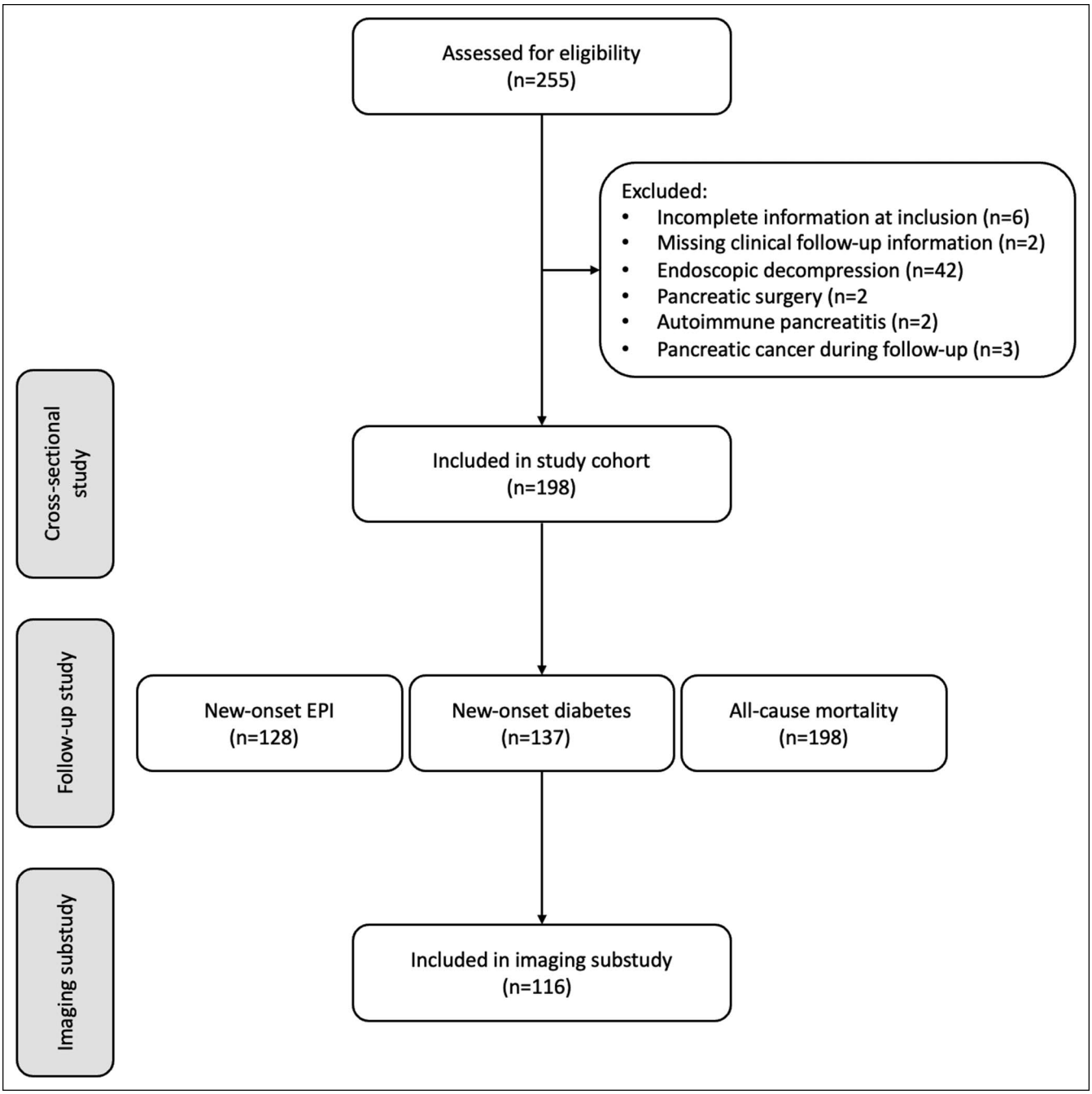

Figure 1. Flow diagram of the patient inclusion process. EPI, exocrine pancreatic insufficiency.

presence of pancreatic duct obstruction (i.e., large duct CP) was indicated by abrupt pancreatic duct caliber change, with upstream dilatation supported by the presence of obstructing intraductal strictures and/or stone(s) (24). This definition was chosen because it has a stronger association with clinical symptoms than definitions based on pancreatic duct diameters (27).

Statistical analysis

Data are expressed as means ± SDs for continuous variables and numbers (percentages) for categorical variables unless otherwise indicated. Demographic and clinical characteristics between patients with large vs small duct CP at inclusion were compared using the Fisher exact test or Student *t* test. Follow-up time was reported as median (interquartile range [IQR]). 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 (large vs small duct CP) and new-onset EPI, new-onset diabetes, and all-cause mortality. Models were adjusted for age, sex, and duration of CP. Effect sizes were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Changes in AP diameter of the pancreatic head and body between baseline and follow-up were analyzed using univariable and multivariable linear regression analyses adjusted for age,

Table 1. Demographic and clinical characteristics of the study cohort at inclusion

	All patients with CP (n = 198)	Small duct CP (n = 123)	Large duct CP (n = 75)	*P* value[a]
Mean age, yr (SD)	58.2 (12.0)	57.0 (12.4)	60.3 (11.2)	0.061
Male sex, n (%)	138 (70)	78 (63)	60 (80)	0.010
Median duration of CP, yr (IQR)	1 (0–5)	1 (0–3)	2 (0–8)	0.021
Etiology, n (%)				
Alcohol	119 (60)	71 (58)	48 (64)	0.468
Idiopathic	55 (28)	38 (31)	17 (23)	
Other	24 (12)	14 (11)	10 (13)	
Smoking, n (%)				
Never smoker	26 (13)	16 (13)	10 (13)	0.874
Former smoker	45 (23)	26 (21)	19 (25)	
Current smoker	115 (58)	74 (60)	41 (55)	
Not reported	12 (6)	7 (6)	5 (7)	
Alcohol consumption, n (%)				
Abstainer	115 (58)	77 (63)	38 (51)	0.111
Light-to-moderate use	38 (19)	20 (16)	18 (24)	
Heavy use	12 (6)	9 (7)	3 (4)	
Very heavy use	15 (8)	10 (8)	5 (7)	
Not reported	18 (9)	7 (6)	11 (15)	
Recurring acute pancreatitis, n (%)				
Yes	81 (41)	50 (41)	31 (41)	0.85
No	90 (45)	57 (46)	33 (44)	
Not reported	27 (14)	16 (13)	11 (15)	
Pain pattern, n (%)				
No pain	69 (35)	39 (32)	30 (40)	0.137
Intermittent pain	71 (36)	48 (39)	23 (31)	
Constant pain	47 (24)	32 (26)	15 (20)	
Not reported	11 (6)	4 (3)	7 (9)	
Diabetes mellitus, n (%)	61 (31)	29 (24)	32 (43)	0.004
EPI, n (%)	70 (35)	35 (28)	35 (47)	0.007

CP, chronic pancreatitis; EPI, exocrine pancreatic insufficiency.
[a]Large vs small duct CP.

sex, and time between imaging studies. Effect sizes were expressed as mean differences with 95% CIs. Statistical significance was defined as a 2-tailed P value of < 0.05. The software package STATA/MP 17.0 (StataCorp LP, College Station, TX) was used.

RESULTS

A total of 255 consecutive patients were initially screened for inclusion, of whom 57 were excluded as illustrated in Figure 1. Three patients were excluded because of pancreatic cancer during follow-up, of whom 1 patient was diagnosed with pancreatic cancer within 3 months from CP diagnosis and, thus, was likely misclassified as CP. The 2 other patients developed pancreatic cancer after 62 and 67 months, respectively; 1 had large duct CP and 1 had small duct CP at index cross-sectional imaging. The final study cohort comprised 198 patients; 75 (38%) had large duct CP, and 123 (62%) had small duct CP. The mean age of included patients was 58 ± 12 years; 70% were male; and 62% had an alcoholic etiology (Table 1).

Patient characteristics in small vs large duct CP

Demographic and disease characteristics stratified by pancreatic duct morphology (small vs large duct CP) at inclusion are summarized in Table 1. A male predominance was observed in patients with large vs small duct CP (80% vs 63%, $P = 0.01$), and patients with large duct CP tended to be older than their counterparts with small duct CP (mean age 60 vs 57 years, $P = 0.06$) and had CP for a longer period (median duration of CP 2 vs 1 year, $P = 0.021$). In addition, patients with large duct CP had a higher prevalence of diabetes (43% vs 24%, $P = 0.004$) and EPI (47% vs 28%, $P = 0.007$) at inclusion while the distribution of pain patterns was similar between groups ($P = 0.13$). Distributions of etiology, smoking status, and quantity of alcohol consumption were not associated with pancreatic duct morphology (Table 1).

Outcomes in small vs large duct CP

New-onset exocrine pancreatic insufficiency. The presence of new-onset EPI during the follow-up period was evaluated in 128 patients without EPI at inclusion (Figure 1). The median observation time was 2.2 years (IQR 0.3–5.0). After 5 years, 75% of patients with large duct CP developed new-onset EPI compared with 52% of patients with small duct CP (HR 1.72; 95% CI [1.05–2.80], $P = 0.031$) (Figure 2a and Table 2).

New-onset diabetes. The presence of new-onset diabetes during the follow-up period was evaluated in 137 patients without diabetes at inclusion (Figure 1). The median observation time was 5.0 years (IQR 3.0–5.0). After 5 years, 40% of patients with large duct disease developed new-onset diabetes compared with 26% of patients with small duct disease (HR 1.69; 95 CI [0.80–3.55], $P = 0.163$) (Figure 2b and Table 2).

All-cause mortality. Mortality was assessed in the full study cohort (n = 198) (Figure 1). The median observation time was 5.0 years (IQR 3.2–5.0). After 5 years, 21% of patients with large duct disease had died compared with 19% of patients with small duct disease (HR 0.96; 95% CI [0.49–1.88], $P = 0.90$) (Figure 2c and Table 2).

Morphological progression in small vs large duct disease

Follow-up imaging studies were available for 116 patients (Figure 1). The median follow-up time between imaging examinations was 2.7 years (IQR 1.6–4.7). The mean change in AP diameter of the pancreatic head was −2.7 ± 3.7 mm in the large duct group compared with −0.1 ± 2.6 mm in the small

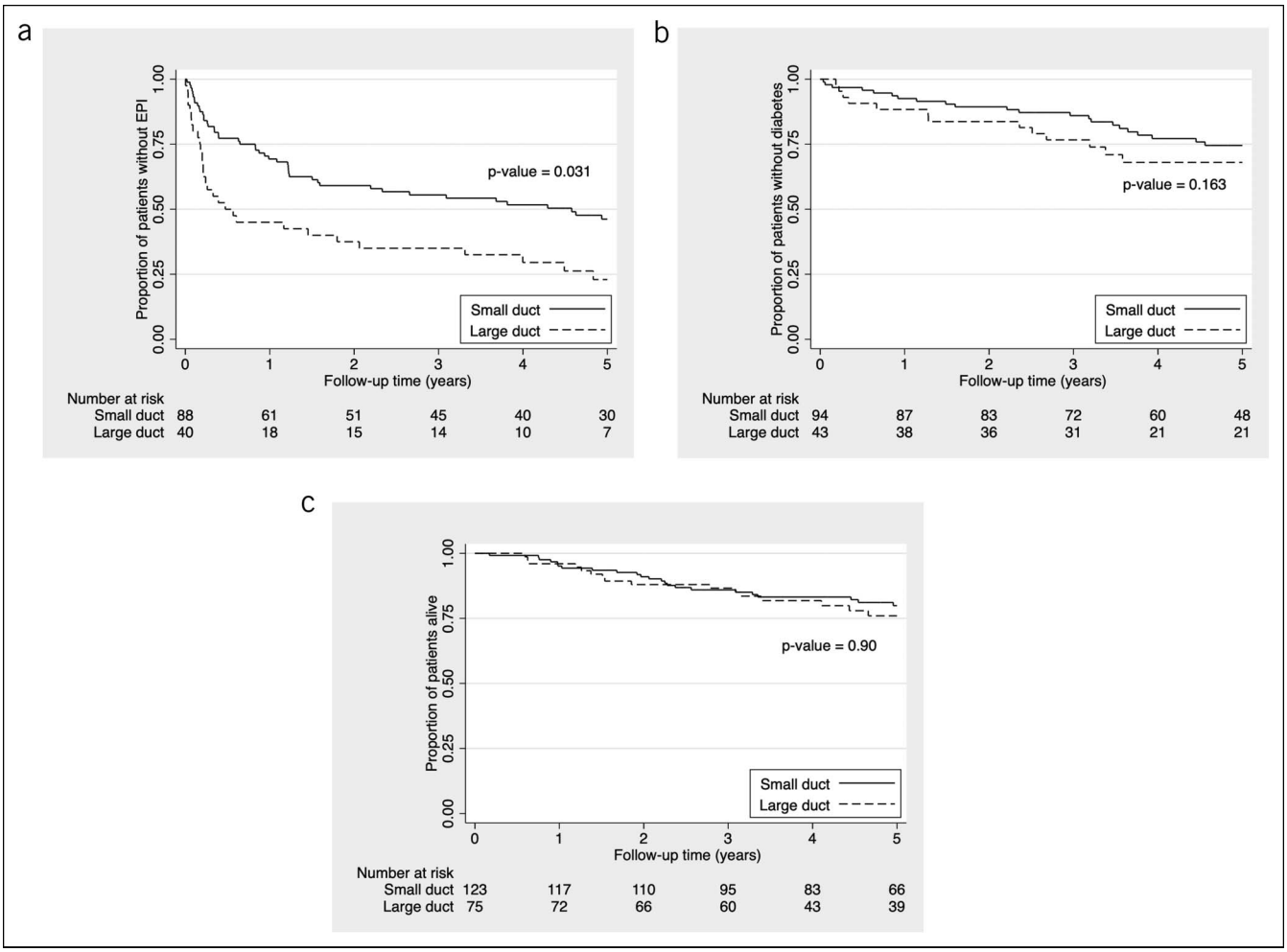

Figure 2. A Kaplan-Meier plot illustrating the proportion of patients (**a**) without exocrine pancreatic insufficiency, (**b**) without diabetes, and (**c**) alive. CP, chronic pancreatitis.

duct group (adjusted mean difference −2.7 mm; 95% CI [−4.0 to −1.5]; $P < 0.001$). The mean change in AP diameter of the pancreatic body was −1.9 ± 2.5 mm in the large duct group compared with −1.1 ± 3.1 mm in the small duct group (adjusted mean difference −0.9 mm; 95% CI [−2.1 to 0.4], $P = 0.17$) (Figure 3 and Table 3). From inclusion to follow-up, 17 of 116 patients (14%) changed their pancreatic duct morphology, of whom 14 progressed from small to large duct disease and 3 regressed from large to small duct disease (Figure 4).

DISCUSSION

This study is the first to evaluate the clinical course of medically managed patients with CP based on pancreatic duct morphology (i.e., large vs small duct CP). Compared with patients with small duct CP, patients with large duct CP had a higher prevalence of EPI and diabetes at inclusion and an approximately 2-fold increased risk of new-onset EPI and increased pancreatic atrophy over a median follow-up time of 2.2 and 2.7 years. Most of the patients (86%) had an unchanged pancreatic duct morphology

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

	Small duct CP			Large duct CP			Hazard ratio (95% CI)	
Outcome	Events	Patients at risk	Follow-up (mo)	Events	Patients at risk	Follow-up (mo)	Crude	Adjusted[a]
New-onset EPI	46	88	3,015	30	40	887	2.00 (1.26–3.18)	1.72 (1.05–2.80)[b]
New-onset diabetes	24	94	4,479	17	43	1,865	1.42 (0.72–2.82)	1.69 (0.80–3.55)
All-cause mortality	23	123	6,030	16	75	3,538	1.18 (0.62–2.24)	0.96 (0.49–1.88)

CI, confidence interval; CP, chronic pancreatitis; EPI, exocrine pancreatic insufficiency.
[a]Adjusted for age, sex, and duration of CP.
[b]*P* value = 0.031.

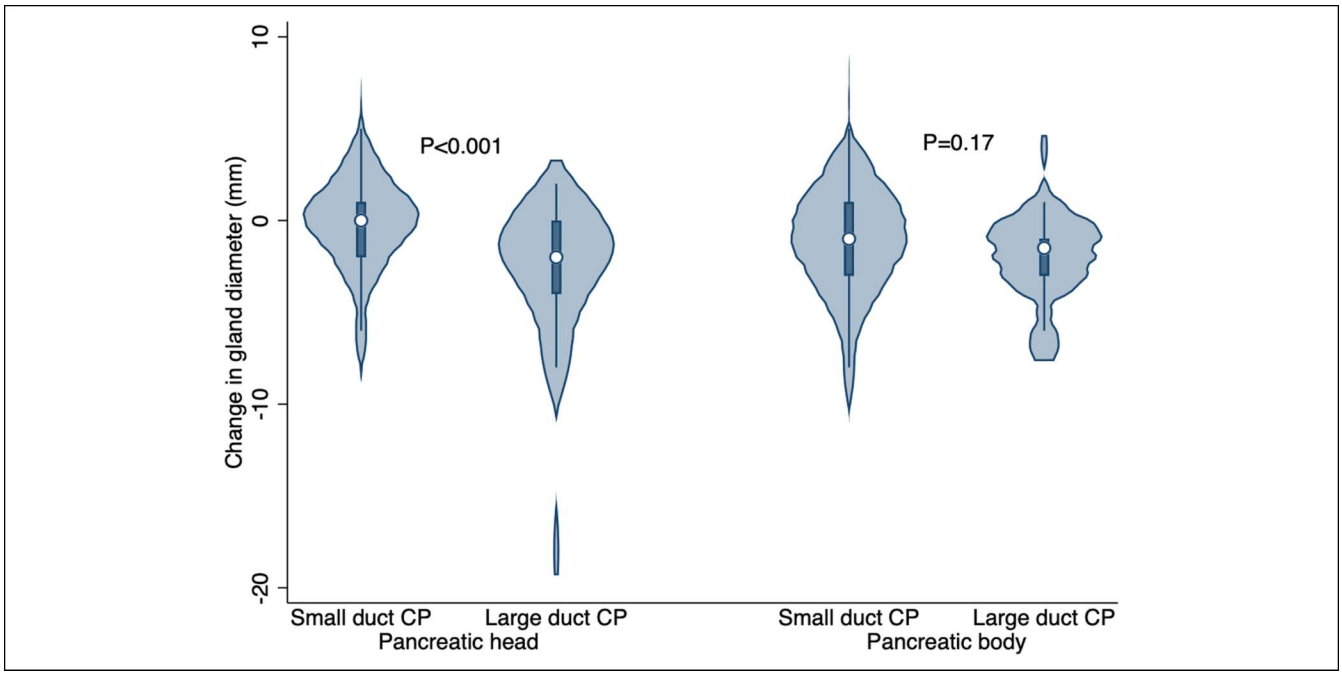

Figure 3. Mean change (millimeters) in anteroposterior (AP) diameter of the pancreatic head and body in patients with large and small duct CP. CP, chronic pancreatitis.

over the follow-up period. Altogether, these findings suggest that medically managed patients with large duct CP have increased risk of functional and morphological progression compared with patients with small duct CP. Furthermore, pancreatic duct morphology rarely changes in the absence of endoscopic or surgical intervention. The findings may have implications for prognostication and management.

Clinical course of large and small duct CP

The prevalence of EPI at inclusion and risk of new-onset EPI during follow-up were increased in patients with large duct CP compared with patients with small duct CP. In addition to pancreatic duct obstruction hindering pancreatic secretory outflow, this finding may also be related to accelerated ductal and acinar cell death as indicated by the excess pancreatic atrophy observed in patients with large duct CP. Accelerated pancreatic atrophy is also observed in other pancreatic disease leading to pancreatic duct obstruction including pancreatic ductal adenocarcinoma and intraductal papillary mucinous neoplasia (20,28).

The prevalence of diabetes was increased in patients with large duct disease at inclusion while the risk of new-onset diabetes was comparable between groups during follow-up. These findings may be explained by the longer duration of CP in the large vs small duct group at study inclusion. However, we adjusted multivariable models to account for disease duration as a putative confounding factor, and as such, we do not expect that disease duration is the main reason for the lack of association between pancreatic duct morphology and risk of new-onset diabetes. Indeed, our findings may indicate that diabetes is less dependent on pancreatic morphology, as opposed to EPI. In line with this, we recently demonstrated that patients with pancreatogenic diabetes were characterized by EPI and pancreatic atrophy, but approximately half of the patients without diabetes had similar exocrine pancreatic function and morphology as their diabetic counterparts, thus indicating additional mediators of diabetes (29). These findings underline the complexity and multiple pathophysiological mechanism underlying diabetes in patients with CP (30,31).

Change in pancreatic duct morphology

A unique feature of this study was the investigation of a large group of patients with medically managed CP, which allowed us

Table 3. Mean change in anterior-posterior diameters from inclusion to follow-up in chronic pancreatitis patients with available imaging studies (n = 116)

Imaging parameter	Small duct CP n = 82	Large duct CP n = 34	Difference (95% CI)	
			Crude	Adjusted[a]
Pancreatic head, mm (SD)	−0.1 ± 2.6	−2.7 ± 3.7	−2.6 (−3.7 to −1.4)	−2.7 (−4.0 to −1.5)[b]
Pancreatic body, mm (SD)	−1.1 ± 3.1	−1.9 ± 2.5	−0.9 (−2.0 to 0.3)	−0.8 (−2.01 to 0.4)

CI, confidence interval; CP, chronic pancreatitis.
[a]Multivariable models were adjusted for age, sex, duration of CP, and duration between imaging studies.
[b]*P* value < 0.001.

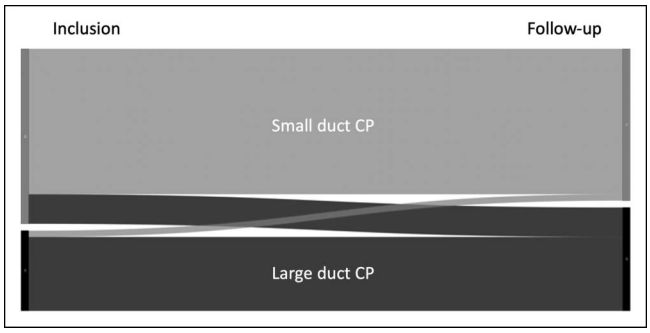

Figure 4. A Sankey diagram illustrating changes in pancreatic duct morphology in patients with large and small duct CP (n = 116) from inclusion (left side) to follow-up (right side). It was more common for patients to convert from small to large duct disease (n = 14) than large to small duct disease (n = 3). CP, chronic pancreatitis.

to study variations in pancreatic duct morphology over time in the absence of interventional procedures. Only a small fraction of patients (14%) changed their pancreatic duct morphology during follow-up. We are not aware of any serial investigations of pancreatic duct morphology over time to compare this finding with. Anecdotal evidence suggests that pancreatic duct obstruction may resolve spontaneously (32). However, according to our observations, this is a relatively rare event, and as such, pancreatic duct morphology does not change in most medically managed patients with CP.

Clinical implications

The finding that medically managed patients with large duct CP have increased risk of EPI and accelerated the development of pancreatic atrophy have implications for monitoring and possibly treatment strategies. Accordingly, medically managed patients with large duct disease may need an intensified clinical follow-up including regular assessment of nutritional status and pancreatic exocrine function (and the presence of diabetes). Earlier diagnosis of EPI is important because it provides a window of opportunity to improve patients' nutritional status before the development of severe nutritional deficits and, thus, possibly improve quality of life and prevent associated comorbidities such as sarcopenia, osteoporosis, and low trauma fractures (33–37). The poorer prognosis associated with large duct CP may also have relevance for prognostication and prediction of disease outcome. As such, pancreatic duct morphology could be a useful parameter to improve the accuracy of severity scores in CP, and importantly, it will be straightforward to implement this parameter in a clinical setting (38).

Pancreatic duct obstruction is the primary indication for endoscopic and/or surgical therapy in patients with CP according to recent guidelines (3,14). However, the pain-relieving effect of pancreatic duct decompression is debated and currently under evaluation in a sham-controlled trial (39,40). The effect of pancreatic duct decompression on pancreatic functional parameters and morphology is difficult to comprehend because this requires long-term follow-up (for several years), which will hardly be feasible in a sham-controlled study (39). As such, observational studies provide an important information source in this context. Although our study was not designed to evaluate the effect of pancreatic duct decompression on pancreatic function, the finding that patients with large duct CP had increased risk of EPI and atrophy may suggest that decompression could decelerate disease progression. Findings from previous observational studies have been mixed with some studies reporting a beneficial effect of decompression on pancreatic functional parameters, whereas others did not find support for a beneficial effect (41–44).

Study strengths and limitations

A strength and unique aspect of this study is the collection of a large group of patients with CP who are being managed medically only. In many countries, the predilection for invasive therapy in patients with large duct CP is very strong, which hinders the conduct of such studies. Indeed, inclusion of a patient population in a country with a single-payer healthcare system where there are high levels of interpersonal trust and trust in the government has been associated with improved health outcomes (45). This may explain the more restricted use of invasive therapies for CP management in the Scandinavian countries where medical treatment including analgesics and neuromodulators are frequently used with success, thus limiting the necessity to proceed to invasive therapies (3,19).

Owing to the retrospective nature of our study, it was not possible to define the reasons for withholding from pancreatic duct interventions in the group of patients with large duct CP. However, this was most likely explained by various reasons including patients' preference and satisfactory response to medical therapy as mentioned above. Indeed, in our study, only 20% in the group of patients with large duct CP reported a constant pain pattern at inclusion, which is lower than that reported in other cohorts (46,47). As such, the generalizability of our findings outside the Scandinavian countries may be questioned. Contrarily, population-based data suggest that the prevalence of severe painful CP (requiring interventional therapy) is much lower than that reported in studies in specialized referral centers (13). Because our clinic serves as a primary referral center for the North Denmark region (approximately 500,000 inhabitants), it is likely that our patient populations more closely reflect a general population-based sample, which again would explain the lower prevalence of constant pain compared with other cohorts (46,47). The diagnosis of EPI was based on a surrogate measure (prescription of pancreatic enzyme replacement therapy) rather than testing of the pancreatic function. However, in the absence of a highly accurate diagnostic test for EPI, the initial administration and continuation of pancreatic enzyme replacement therapy could be considered a more clinically relevant outcome. Monitoring for new-onset diabetes was not standardized at fixed time points, which may introduce a surveillance bias, because symptomatic patients may have been more frequently monitored. This is also a limitation of the imaging substudy. Altogether, these biases warrant prospective cohort studies with fixed time points for functional and imaging assessments (48,49). Finally, assessments of the anterior-posterior gland diameters were not corrected for pancreatic duct dilation. However, as a higher rate of pancreatic atrophy was observed in patients with large duct disease, subtraction of pancreatic duct diameter would most likely have strengthened this finding.

Patients with large duct CP have an increased risk of EPI and pancreatic atrophy compared with those with small duct CP. These findings attest to the understanding of the clinical course of CP and may have implications for management and prognostication.

CONFLICTS OF INTEREST

Guarantor of the article: Søren S. Olesen, MD, PhD.

Specific author contributions: M.B.M.: drafting of the manuscript and acquisition of data; E.S.: acquisition of data, imaging analyses, and critical revision of the manuscript for important intellectual content; V.K.S.: study design and critical revision of the manuscript for important intellectual content; A.M.D.: study design and critical revision of the manuscript for important intellectual content; J.B.F.: imaging analyses and critical revision of the manuscript for important intellectual content; S.S.O.: study design, statistical analysis, analysis and interpretation of data, and drafting and critical revision of the manuscript for important intellectual content. All authors approved of the final version of the manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Pain is the primary indication for endoscopic and/or surgical therapy in patients with large duct chronic pancreatitis.
- ✓ The clinical course of medically managed patients with large and small duct chronic pancreatitis is largely unknown.

WHAT IS NEW HERE

- ✓ Patients with medically managed large duct chronic pancreatitis have increased risk of exocrine pancreatic insufficiency and atrophy compared with those with small duct chronic pancreatitis.
- ✓ Pancreatic duct morphology rarely changes in the absence of endoscopic or surgical intervention.

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