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Structural imaging findings are related to clinical complications in chronic pancreatitis

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Abstract

Background/objectives: Structural pancreatic changes and complications related to chronic pancreatitis are well described, but little is known about their relationship. We aimed to explore the associations between pancreatic morphology and clinical complications in a large chronic pancreatitis cohort.

Abbreviations: BMI, body mass index; CI, confidence interval; CP, chronic pancreatitis; CT, computed tomography; FE, fecal elastase; MPD, main pancreatic duct; OR, odds ratio; PEI, pancreatic exocrine insufficiency; SD, standard deviation; SBPC, the Scandinavian Baltic Pancreatic Club.

Methods: The Scandinavian Baltic Pancreatic Club database collects registrations on patients with definite or probable chronic pancreatitis according to the M-ANNHEIM diagnostic criteria. In this cross-sectional study, we used multivariate logistic regression analyses to evaluate whether imaging-based structural pancreatic changes were associated with common clinical complications. We adjusted for sex, age, disease duration, current alcohol abuse and current smoking.

Results: We included 742 patients with a mean age of 55 years. Among these, 68% were males, 69% had pancreatic exocrine insufficiency, 35% had diabetes, 12% were underweighted and 68% reported abdominal pain. Main pancreatic duct obstruction, severe (i.e. more than 14) calcifications, pancreatic atrophy and parenchymal changes throughout the entire pancreas (continuous organ involvement) were positively associated with pancreatic exocrine insufficiency. Continuous organ involvement and pseudocysts were positively and negatively associated with diabetes, respectively. Pancreatic atrophy and severe calcifications were positively associated with underweight, and severe calcifications were negatively associated with pain.

Conclusions: This study shows independent associations between distinct structural changes on pancreatic imaging and clinical complications in chronic pancreatitis. Pancreatic atrophy, severe calcifications and continuous organ involvement may be of particular clinical relevance, and these findings should motivate monitoring of pancreatic function and nutritional status.

KEYWORDS
diabetes mellitus, exocrine pancreatic insufficiency, pain, pancreas, underweight

INTRODUCTION

Chronic pancreatitis (CP) is a progressive disease where pancreatic inflammation leads to the replacement of normal pancreatic parenchyma with calcified and fibrous connective tissue.[1] Abdominal pain is the most prevalent symptom in the majority of CP patients and is associated with reduced quality of life and increased disability.[2,3] Other frequent symptoms are related to two other common complications; pancreatic exocrine insufficiency (PEI) and diabetes mellitus.[1] Patients may develop malnutrition and metabolic bone disease due to PEI, but dietary habits, alcohol abuse, smoking, chronic inflammation, and postprandial pain are also important factors.[4,5] Less common CP complications include vascular complications such as pseudoaneurysm and venous thrombosis, duodenal obstruction, biliary obstruction, and pancreatic cancer.[1]

CP is a multifaceted disease with variable morphology and presents with different grades and patterns of ductal changes, calcifications, fibrosis, pancreatic atrophy, and pseudocysts.[1] The changes occur either segmentally or throughout the entire pancreas. Pancreatic imaging is a key element in diagnosing and

Key Summary

The established knowledge on this subject:

- Chronic pancreatitis is a complex disease, which may have different presentations with respect to structural pancreatic imaging changes and clinical complications.
- The relationships between structural pancreatic imaging changes and complications in chronic pancreatitis are poorly documented.

The significant and/or new findings of this study:

- Duct obstruction, severe calcifications, atrophy and continuous organ involvement were positively associated with pancreatic exocrine insufficiency.
- Patients with structural imaging changes throughout the pancreas were more likely to have diabetes.
- Patients with pancreatic atrophy or severe calcifications did more frequently suffer from underweight.

detecting disease-related structural changes.[1,6,7] The optimal use of diagnostic imaging for staging, monitoring, and predicting clinical complications in CP warrants further explorations. Understanding the associations between pancreatic morphologic changes and clinical complications is a critical step towards improving the precision of prognostics and disease monitoring in CP. Previous studies report mostly weak associations between pancreatic imaging findings and clinical complications in CP; however, these studies focused on selected structural changes or complications, and some were limited by small sample sizes.[8–11]

We hypothesized that varying patterns of structural pancreatic imaging findings are related to clinical complications. Thus, in this large multicenter study with comprehensive evaluations of clinical data and pancreatic imaging from CP patients in the Scandinavian Baltic Pancreatic Club (SBPC) database, we aimed to explore the associations between pancreatic morphologic changes from diagnostic imaging and the most common clinical complications in CP using multivariate logistic regression models.

METHODS

Study design

The SBPC database is a multicenter database collecting prospective data from CP patients.[12] We have employed a cross-sectional observational study design using baseline registrations collected from 1 February 2016 to 1 July 2019. The study was conducted according to the Helsinki Declarations. Institutional review boards at each participating center approved data collection and sharing. The coordinating center for the database is Aalborg University Hospital, Denmark (200858-0028, project ID 2018-19). The present study is coordinated by Haukeland University Hospital, Norway (Regional Committees for Medical and Health Research Ethics, Western Norway, registration number 2019/1037). Results are reported according to the TRIPOD statement.[13]

Subjects

The SBPC database includes patients ≥18 years with definitive or probable CP according to the M-ANNHEIM diagnostic criteria,[14] who are referred to the participating specialized pancreas referral centers. Registration of data in the imaging module was optional. We performed a center-wise exclusion to obtain consistent and high-quality data, and centers reporting imaging data on <60% of their patients were excluded. Patients from the remaining centers, in whom the imaging module did not include registrations from computed tomography (CT), were also excluded.

Patient characteristics

Clinical data were registered upon inclusion in the database. We extracted information on age, sex, duration since CP diagnosis and first symptom, body mass index (BMI), presence of pain and diabetes, and fecal elastase (FE) results. We also collected information on CP etiology according to the M-ANNEHIM classification,[14] in addition to patient-reported information on smoking habits and alcohol history.

Definition of CP related complications

Diabetes was defined according to the American Diabetes Association's diagnostic criteria,[15] and PEI was defined as FE <200 μg/g. Underweight was defined as BMI <18.5 kg/m^2 and used as a proxy for malnutrition. Pain was reported according to the M-ANNHEIM classification: 1-no pain, 2-intermittent pain, 3-constant pain, and 4-constant pain with acute pain exacerbations.[14] Categories 2–4 were defined as presence of pain.

Pancreatic imaging data

Findings from pancreatic CT imaging were registered. When registrations from more than one CT examination per patient were available, we prioritized the examination closest to the time of inclusion. The recorded pancreatic imaging findings are defined in Table 1 and included: presence of main pancreatic duct (MPD) dilatation, MPD obstruction, pseudocysts, continuous organ involvement, any calcifications, severe (i.e. more than 14) calcifications, pancreatic atrophy, and focal acute pancreatitis. Standardized definitions and instructions for reporting assessments were provided prior to the local review of imaging findings performed at the different sites.[16] We used the definition of pancreatic atrophy as previously suggested by our group,[17] using the sum of the anteroposterior diameters of the pancreatic head and body. Examples of structural pancreatic imaging changes are shown in Figure S1.

Statistical analysis

The statistical analyses were performed in SPSS statistics package version 26.0 (IBM). Normality was assessed using Q–Q plots and Shapiro Wilk test. Continuous variables are presented as mean values with standard deviations (SD) or median values with interquartile range (IQR), as appropriate.

To evaluate the associations between structural pancreatic changes and clinical CP-related complications, we used logistic regression analyses in a four-step, forced-entry process. First, structural features were analyzed against the CP-related complications in

TABLE 1 Definitions

Age: Age at inclusion
Calcifications: Presence of calcifications >1 mm
Continuous organ involvement: Pathological changes observed in all segments of the pancreas
Diabetes: According to the American diabetes Association's diagnostic criteria[15]
Disease duration: Years since first attack of acute pancreatitis or first relevant symptom of chronic pancreatitis
Focal acute pancreatitis: Presence of imaging changes indicative of ongoing pancreatic inflammation
Main pancreatic duct (MPD) dilatation: MPD diameter ≥4 mm in the pancreatic head and/or ≥3 mm in the pancreatic body
MPD obstruction: Abrupt change of MPD caliber with upstream dilatation and small caliber downstream
Pain: Patient reporting pain syndromes with localisation and patterns of suspected pancreas origin any of the categories intermittent pain, continuous pain or continuous pain with exacerbations
Pancreatic atrophy: Sum of anteroposterior diameters in head and body of the pancreas <37 mm for males and <32 mm for females[17]
Pancreatic exocrine insufficiency (PEI): Reported fecal elastase (FE) <200 μg/g
Pseudocyst: Presence of pseudocysts, all sizes
Severe calcifications: >14 calcifications in the pancreas
Underweight: Body mass index <18.5 kg/m^2

univariate analyses. Second, we performed multivariate analyses with all structural features included. Third, we included all structural features with $p \leq 0.1$ in at least one of the previous two steps, plus five predefined key features, in unadjusted multivariate analyses. The predefined key features were presence of MPD dilatation, MPD obstruction, pseudocysts, calcifications, and pancreatic atrophy. In the fourth and final step, the models from the previous step were adjusted for the covariates sex, age, disease duration, current smoking, and current alcohol abuse. We assessed relevant interaction effects and dependencies between the structural features, and the variables any calcifications and severe calcifications were analyzed in separate multivariate analyses due to dependency. We also tested for interaction effects between disease duration and structural features, but found no significant interactions. Results from logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs) and in Forest plots. Missing data were handled using listwise deletion. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient inclusion

Eight pancreas referral centers were included: Denmark (Aalborg, Bispebjerg, Herlev and Hvidovre), Norway (Bergen and Oslo), Lithuania (Kaunas), and Russia (Moscow). As of July 2019, these centers included a total of 1290 CP patients. Imaging module registrations from CT were completed for 742 patients, who were all included in the subsequent analyses (Figure 1). Median time interval between inclusion in the SBPC database and date of imaging examination was 2 (IQR 0, 5) months. Patient demographics and clinical characteristics are presented in Table 2.

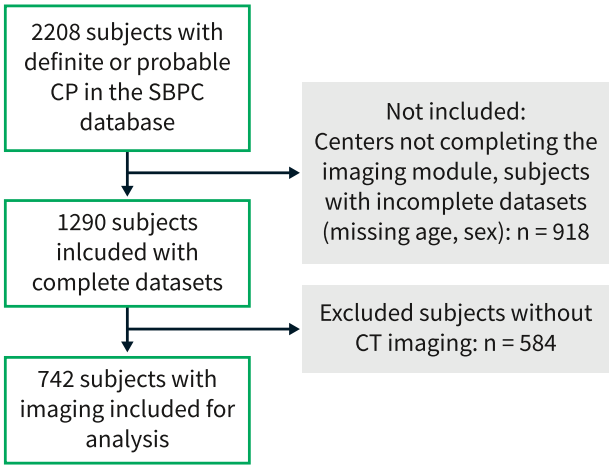

FIGURE 1 Inclusion flow diagram. CP, chronic pancreatitis; SBPC, Scandinavian Baltic Pancreatic Club

Imaging data

Structural pancreatic changes, as defined in Table 1, were observed in 92% of patients. Forty-one percent had parenchymal changes throughout the entire pancreas (continuous organ involvement). Calcifications were the most frequent finding (69%), followed by MPD dilatations (59%) and MPD obstructions (36%). Prevalences of imaging findings in the patient cohort are presented in Table 2.

Structural pancreatic changes are related to CP complications

Results from univariate and multivariate analyses of associations between morphologic pancreatic changes, covariates and clinical complications are presented in Table 3. Results from the final multivariate analyses are also presented as Forest plots in Figure 2. Table S1 presents results from all steps of the analyses.

Pancreatic exocrine insufficiency

We found moderate to strong associations between structural pancreatic changes and presence of PEI. Particularly, patients with pancreatic atrophy were more likely to have PEI compared to patients without atrophy (OR 4.6 [95% CI 1.8, 11.3], $p = 0.001$). Duct

obstruction (OR 2.9 [95% CI 1.3, 6.7], $p = 0.010$), structural involvement of the entire pancreas (OR 2.1 [95% CI 1.1, 4.0], $p = 0.021$), and severe calcifications (OR 2.9 [95% CI 1.3, 6.5], $p = 0.012$) also showed positive associations with PEI.

Diabetes

All CP-related imaging features were associated with diabetes in the univariate model. However, the adjusted multivariate model only showed two significant associations; patients with pseudocysts were less likely to have diabetes compared to those without pseudocysts (OR 0.6 [95% CI 0.4, 1.0], $p = 0.037$), and patients with structural involvement of the entire pancreas were more likely to have diabetes compared to those whose structural changes were focal or not evident on diagnostic imaging (OR 1.5 [95% CI 1.0, 2.3], $p = 0.038$). None of the adjusting covariates were significantly associated with diabetes.

Underweight

Patients with pancreatic atrophy were more frequently underweighted than patients with normal pancreatic size (OR 2.5 [95% CI 1.2, 5.1], $p = 0.015$), and severe calcifications showed a moderate

TABLE 2 Patient characteristics and frequencies of CP-related imaging findings in the 742 patients with definitive or probable CP included from the Scandinavian Baltic Pancreatic Club database

		Analyzed, *n*	Missing, *n*
Age, years, mean (SD)	55 (13)		
Sex, males	68%		
Disease duration since first symptom, years	5 [1, 10]	715 (96%)	27 (4%)
BMI, kg/m^2	23 [20, 26]	719 (97%)	23 (3%)
Frequency of underweight (BMI <18.5 kg/m^2)	12%	719 (97%)	23 (3%)
FE, μg/g	74 [18, 256]	417 (56%)	325 (44%)
Frequency of PEI (FE <200 μg/g)	69%	417 (56%)	325 (44%)
Frequency of diabetes	35%	720 (97%)	22 (3%)
Frequency of pain	68%	726 (98%)	16 (2%)
Frequency of smokers	82%	704 (95%)	38 (5%)
Frequency of >5 years intake of ≥5 standard alcohol units per day	31%	532 (72%)	210 (28%)
Etiology according to M-ANNHEIM[14]			
Alcohol	61%	721 (97%)	21 (3%)
Nicotine/smoking	68%	711 (96%)	31 (4%)
Nutritional	8%	723 (97%)	19 (3%)
Hereditary	8%	679 (92%)	63 (8%)
Efferent duct	12%	714 (96%)	28 (4%)
Immunological	2%	715 (96%)	27 (4%)
Miscellaneous	8%	719 (97%)	23 (3%)
Any structural change	92%	742 (100%)	0
MPD dilatation	59%	703 (95%)	39 (5%)
MPD obstruction	36%	688 (93%)	54 (7%)
Any calcifications	69%	734 (99%)	8 (1%)
Severe calcifications	37%	636 (86%)	106 (14%)
Pancreatic atrophy	19%	627 (85%)	115 (15%)
Pseudocysts	34%	721 (97%)	21 (3%)
Continuous organ involvement	41%	719 (97%)	23 (3%)
Focal acute pancreatitis	19%	719 (97%)	23 (3%)

Note: Data with non-normal distributions are presented as median [interquartile range]. Frequencies are presented percentages of the analyzed proportions. Diabetes is defined according to the American Diabetes Association's diagnostic criteria.[15]

Abbreviations: BMI, body mass index; CP, chronic pancreatitis; FE, fecal elastase; MPD, main pancreatic duct; PEI, pancreatic exocrine insufficiency; SD, standard deviation.

TABLE 3 Associations between structural changes, covariates and complications related to chronic pancreatitis

	Univariate			Multivariate, final model		
	OR	95% CI	*p*	OR	95% CI	*p*
Exocrine insufficiency						
MPD dilatation	2.42	1.56, 3.76	**<0.001**	1.13	0.55, 2.34	0.739
MPD obstruction	3.26	1.93, 5.50	**<0.001**	2.93	1.29, 6.65	**0.010**
Pseudocysts	1.09	0.69, 1.70	0.745	1.09	0.58, 2.06	0.790
Continuous organ invasion	2.56	1.66, 3.95	**<0.001**	2.12	1.12, 4.03	**0.021**
Focal acute pancreatitis	0.79	0.47, 1.32	0.365			
Severe calcifications*	4.41	2.38, 8.17	**<0.001**	2.86	1.26, 6.50	**0.012**
Pancreatic atrophy	4.67	2.16, 10.11	**<0.001**	4.57	1.85, 11.31	**0.001**
Age (per year)				0.99	0.97, 1.01	0.284
Sex (male)				0.95	0.51, 1.75	0.866
Disease duration (per year)				0.98	0.94, 1.02	0.371
Current smoking				1.81	0.97, 3.31	0.056
Current drinking**				0.88	0.33, 2.33	0.789
Diabetes						
MPD dilatation	1.39	1.00, 1.92	**0.048**	0.91	0.54, 1.53	0.725
MPD obstruction	1.55	1.12, 2.15	**0.009**	1.42	0.86, 2.35	0.168
Pseudocysts	0.57	0.40, 0.80	**0.001**	0.62	0.40, 0.97	**0.037**
Continuous organ invasion	1.33	0.97, 1.82	0.073	1.54	1.03, 2.33	**0.038**
Focal acute pancreatitis	0.68	0.45, 1.03	0.068	0.83	0.48, 1.42	0.495
Calcifications	1.89	1.33, 2.68	**<0.001**	1.35	0.83, 2.21	0.225
Pancreatic atrophy	1.57	1.03, 2.39	**0.034**	1.15	0.69, 1.92	0.603
Age (per year)				1.00	0.98, 1.02	0.978
Sex (male)				1.15	0.75, 1.74	0.522
Disease duration (per year)				1.03	1.00, 1.05	0.063
Current smoking				0.85	0.57, 1.28	0.441
Current drinking**				1.35	0.69, 2.61	0.380
Underweight						
MPD dilatation	1.65	1.01, 2.68	**0.046**	1.63	0.75, 3.56	0.222
MPD obstruction	1.11	0.69, 1.80	0.663	0.82	0.41, 1.68	0.593
Pseudocysts	0.94	0.58, 1.52	0.801	0.93	0.48, 1.77	0.818
Continuous organ invasion	1.53	0.97, 2.41	0.066	1.83	0.98, 3.42	0.058
Focal acute pancreatitis	0.73	0.39, 1.36	0.325			
Severe calcifications*	1.93	1.20, 3.11	**0.007**	2.02	1.07, 3.83	**0.030**
Pancreatic atrophy	1.59	0.91, 2.76	0.105	2.48	1.19, 5.13	**0.015**
Age (per year)				1.00	0.98, 1.03	0.898
Sex (male)				0.22	0.12, 0.41	**<0.001**
Disease duration (per year)				0.98	0.94, 1.02	0.242
Current smoking				3.56	1.86, 6.81	**<0.001**
Current drinking**				1.26	0.38, 4.14	0.702

TABLE 3 (Continued)

	Univariate			Multivariate, final model		
	OR	95% CI	*p*	OR	95% CI	*p*
Pain						
MPD dilatation	0.84	0.60, 1.17	0.297	0.99	0.58, 1.69	0.967
MPD obstruction	0.98	0.69, 1.38	0.891	1.36	0.80, 2.33	0.262
Pseudocysts	1.34	0.95, 1.89	0.096	0.98	0.63, 1.55	0.943
Continuous organ invasion	1.04	0.75, 1.44	0.831			
Focal acute pancreatitis	1.36	0.89, 2.07	0.156			
Severe calcifications*	0.65	0.46, 0.93	**0.016**	0.53	0.33, 0.84	**0.006**
Pancreatic atrophy	0.65	0.42, 0.99	**0.044**	0.97	0.55, 1.70	0.920
Age (per year)				0.96	0.94, 0.98	**<0.001**
Sex (male)				0.46	0.29, 0.73	**0.001**
Disease duration (per year)				1.02	0.99, 1.05	0.197
Current smoking				1.40	0.90, 2.16	0.132
Current drinking**				2.05	0.87, 4.85	0.102

Note: This table presents odds ratios (ORs) with 95% confidence intervals (CIs) for associations between structural changes and complications related to chronic pancreatitis. Results from univariate analyses are presented in the left columns, and results from the final multivariate analyses are presented in the right columns. In the final analyses, key features were forced back, and we adjusted for age, sex, disease duration, current drinking and current smoking. Significant *p*-values (<0.05) are marked in bold font.

*If calcifications were not significantly associated to the outcome variable, analyses were redone using severe calcifications.

**Current drinking is defined as drinking five or more alcohol units per day. MPD: main pancreatic duct.

positive association with underweight (OR 2.0 [95% CI 1.1, 3.8], $p = 0.030$) in the adjusted multivariate model. Males were less likely to be underweight compared to females, and current smoking showed a strong, positive association to underweight.

Abdominal pain

The only structural pancreatic change associated with the presence of abdominal pain was severe calcifications, showing a negative association (OR 0.5 [95% CI 0.3, 0.8], $p = 0.06$). The likelihood of reporting pain was reduced with age, and males were less likely to report pain compared to females.

DISCUSSION

In this large cross-sectional multicenter study, we demonstrated associations between pancreatic structural imaging findings and the most common complications in CP. Positive associations between several structural imaging features and PEI were found, including ductal obstruction, severe calcifications, pancreatic atrophy, and continuous organ involvement. While continuous organ involvement showed a positive association with diabetes, pseudocysts showed a negative association. Severe calcifications were negatively associated with pain, and we demonstrated positive associations between underweight and both pancreatic atrophy and severe calcifications. Our study shows that some structural pancreatic imaging findings are distinctly related to the risk of concomitant clinical complications in CP.

Previous studies on CP have shown relationships between and across etiologies, risk factors, clinical outcomes, patient factors, and selected pancreatic imaging features. For instance, smoking, alcohol abuse, diabetes, and pancreaticoduodenectomy have been linked to PEI.[18,19] Furthermore, several factors have been associated with diabetes in patients with CP, including alcohol abuse, pancreatic resection, and common type 2 diabetes risk factors.[18,20,21] Alcohol abuse and smoking have also been linked to underweight and pain.[18,22] Moreover, smoking and alcohol abuse as etiologic risk factors have been associated with different patterns of structural pancreatic imaging findings.[17,18] Apart from calcifications, which have been associated with PEI, diabetes and reduced BMI,[10,11,20] knowledge on the relationship between pancreatic imaging findings and clinical outcome is sparse, particularly concerning the consequences of pancreatic atrophy.

Though many of our findings have not previously been demonstrated, we will discuss how they seem to cohere with current knowledge of CP pathophysiology and other reported associations. In CP, PEI is typically caused by loss of, or damage to, acinar cells, or by obstruction of pancreatic outflow including MPD obstruction.[1] Pancreatic atrophy, continuous organ involvement, and severe calcifications are imaging features indicating severe loss of functional

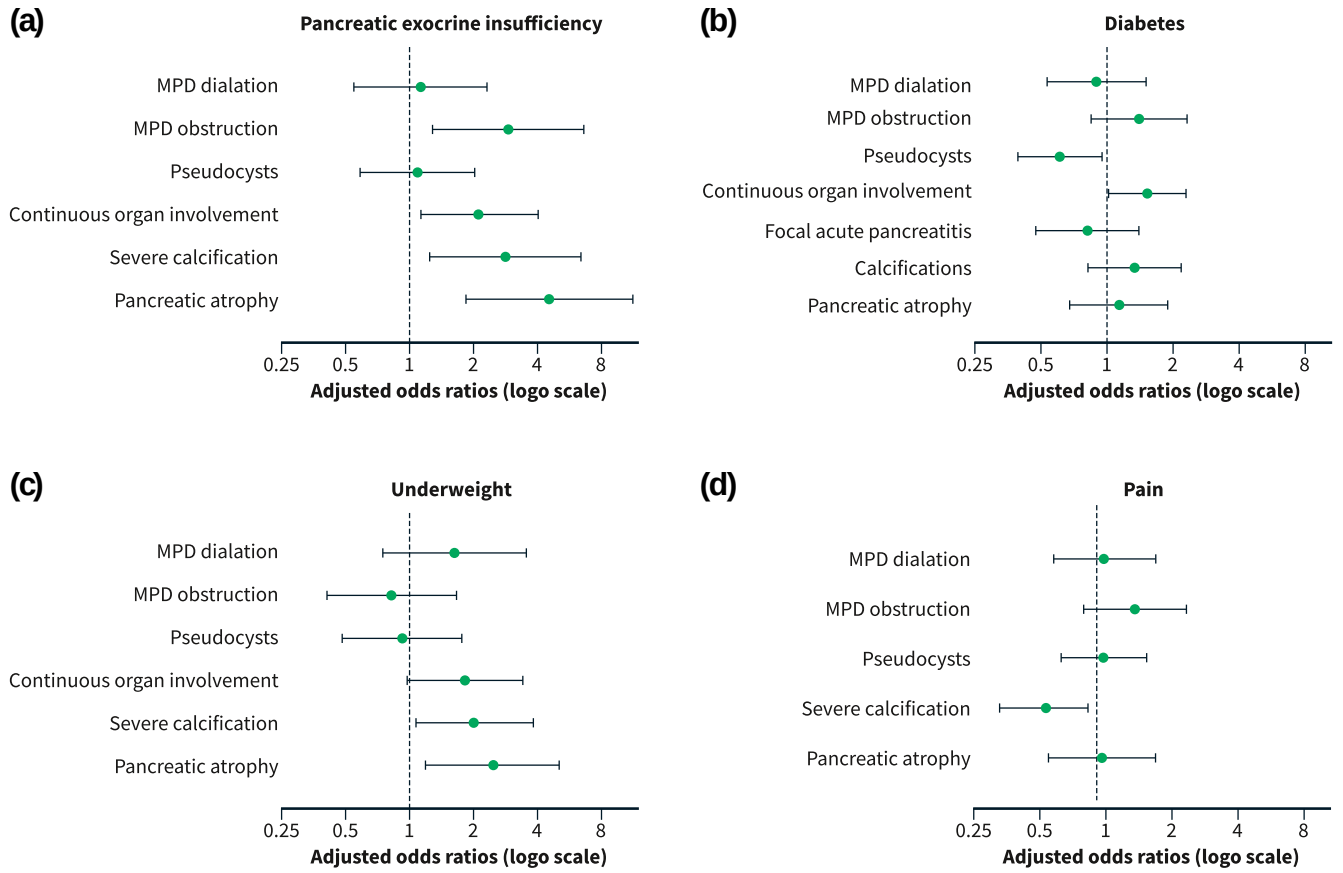

FIGURE 2 Forest plots display the Odds ratios (circles) with 95% confidence intervals (whiskers) from the multivariate analysis of each factor analyzed: pancreatic exocrine insufficiency (a), diabetes (b), underweight (c) and pain (d). Adjusted for age, sex, disease duration, current drinking and current smoking. MPD, main pancreatic duct

tissue, and we found all these features to be strongly associated with presence of PEI. In addition, obstructed ducts cause reduced secretion of pancreatic enzymes, and possibly also lead to loss of healthy tissue following longstanding obstruction.[23] The association between PEI and calcifications was only significant for severe (i.e. more than 14) calcifications, perhaps due to more pronounced damage to the pancreatic parenchyma.[10]

The prevalence of diabetes increases with disease duration and is associated with factors considered indicative of beta cell loss such as calcifications, PEI and pancreatic resections.[21] We found a negative association between diabetes and pseudocysts, possibly because pseudocysts are associated with shorter disease duration.[17] Diabetes was positively associated with structural changes affecting the entire pancreas, which may be related to displacement of healthy endocrine tissue. We found no association between pancreatic atrophy and diabetes in our material, though this has been reported in previous studies.[9,24,25]

Underweight may be caused by a multitude of different factors. In CP, important factors include PEI, chronic inflammation, nutritional habits, alcohol abuse, smoking, pain (especially when postprandial), opioid treatment, and diabetes.[18,22] We found pancreatic atrophy and severe calcifications to be positively associated with underweight, probably explained by the distinct associations between these features and PEI. Similarly and possibly for the same reason, continuous organ involvement tended towards a positive association ($p < 0.1$) with underweight. In addition, pancreatic atrophy and severe calcifications are associated with long disease duration,[17] and are thus likely markers of more advanced disease. A previous study also showed a correlation between the number of calcifications and decreasing BMI.[11] Results may be influenced by factors improving nutritional status, such as pancreatic enzyme replacement therapy, abstinence from smoking/alcohol, and improvement in pain.[22,26]

Ductal obstruction, pseudocysts, and focal acute pancreatitis are structural changes that theoretically could induce pain,[1,8] but similar to previous observations,[8,9,27–32] we found no positive associations between structural pancreatic changes and pain. Still, the lack of significant findings does not rule out the existence of associations for subgroups of patients, exemplified by studies showing pain relief after endoscopic or surgical intervention in patients with obstructive CP.[33] In contrast, we found a negative association between severe calcifications and pain, and one can speculate on whether this may be related to the disputed "burn out" phenomenon, where patients with longstanding CP may experience pain relief with progressive pancreatic insufficiency.[1,7,34] On the other hand, persistence of pain has been observed in a significant fraction of patients after >10 years of disease,[34,35] and recently, a

longitudinal study showed that pain patterns often fluctuate over time.[32] Pursuing registrations on indications for performing the imaging examination and pain registrations at the time of imaging, may provide more detailed knowledge on the roles of acute and possibly reversible structural changes in pancreatic pain. Furthermore, longitudinal data may provide novel information on temporal changes in pancreatic structural pathology and corresponding variations in pain.

The risk of a patient exhibiting structural pancreatic changes increases with prolonged disease duration,[17] and so does the risk of PEI and diabetes.[36] Still, we found that disease duration was not independently associated with complications, and that it did not alter the associations between structural pancreatic changes and complications in CP. This fits the assumption that although structural changes and complications both develop over time, the temporal relationships between structural changes and complications are most important.

Limitations

There are several limitations related to database studies, including missing data causing biased analyses. Excluding centers with low reporting rate for imaging data may have introduced a selection bias. In a previous publication from the same material,[17] we showed that patients excluded due to missing imaging registrations were older and more frequently had PEI and diabetes. Thus, this selection bias may have reduced the proportion of subjects with severe structural changes and complications.

Biased reporting is relevant for both imaging and complications. To reduce the impact of center-related differences in reporting of imaging findings, we distributed predefined guidelines for standardized imaging reporting prior to the registrations.[16] Registrations on FE were missing in a proportion of included subjects, and this may have caused bias, for instance if FE was not measured in patients in whom the clinician evaluated the risk of PEI to be low based on imaging.

All imaging modalities have inherent strengths and limitations.[6] Because CT is not very sensitive for minor ductal changes as compared to endoscopic ultrasound or magnetic resonance imaging, such changes may be underreported. Information on indications for performing the imaging examinations or symptoms at the day of imaging was not available. If a frequent indication was suspicion of CP-related complications, this may have biased our results causing higher frequencies of pathologic changes (ductal obstruction, pseudocysts, or acute pancreatitis).

Underweight in patients with CP can be caused by several different factors, including non-structural factors and factors not directly related to the pancreatic disease. Thus, relevant covariates may not be accounted for in the analyses.

Pain is complex and exposed to a range of biases, and information may have been lost as a result of reducing the presence of pain to a dichotomous variable. Furthermore, associations between structural changes and pain for subgroups of patients may have gone undetected because our analyses did not differentiate between longstanding and newly developed structural changes, and because not all structural changes were scored dependent on severity.

The cross-sectional design limits drawing conclusions regarding causality, and the absence of healthy controls further limits the generalizability to a population with non-CP subjects. Nevertheless, our findings do provide a steppingstone for future studies with longitudinal data.

In CP, the different structural pancreatic changes may to some extent be related. Multivariate regression analyses assume little to no multicollinearity between the included predictors, and complex relationships between structural pancreatic changes in our multivariate models may have affected the results.

Clinical relevance and future directions

Our findings showed that especially the imaging findings pancreatic atrophy, the distribution of morphologic changes (focal vs. continuous), and the extent of calcifications (mild vs. severe) are strongly linked to complications of CP. Although more recently proposed imaging scoring systems include these more specific parenchymal factors,[37,38] they are not included in the systems typically referred to in guidelines, such as the M-ANNHEIM pancreatic imaging criteria,[14] the Rosemont classification,[39] and the Cambridge classification.[40,41] Validated systems for scoring the severity of CP are lacking. We argue that the demonstrated associations between structural changes and complications may indicate which changes should be particularly weighted in future severity scoring systems. Studies validating the newly proposed scoring systems for diagnostic accuracy and benefit in severity scoring in relevant populations are warranted.

CONCLUSIONS

This study demonstrated associations between specific pancreatic morphologic changes and clinical complications in CP, underlining the importance of monitoring pancreatic exocrine and endocrine function and nutritional status in CP patients exhibiting these imaging findings. Furthermore, our results indicate that specific imaging findings such as pancreatic atrophy, extent of pancreatic calcifications and the distribution of structural changes throughout the pancreas are particularly important markers of the fibroinflammatory process and likely relevant for accurate staging and prediction of complications in CP.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

The study was conducted according to the Helsinki Declarations. Institutional review boards at each participating center approved data collection and sharing. The coordinating center for the database is Aalborg University Hospital, Denmark (200858-0028, project ID 2018-19). The present study is coordinated by Haukeland University Hospital, Norway (Regional Committees for Medical and Health Research Ethics, Western Norway, registration number 2019/1037).

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

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