Chronic Pancreatitis Is Characterized by Distinct Complication Clusters That Associate With Etiological Risk Factors

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OBJECTIVES: **Chronic pancreatitis (CP) is characterized by several disease-related complications and multiple etiological risk factors. Past studies of associations between complications and risk factors have mostly been limited to single complications or highly focused on single etiologies. Using an objective data-driven approach (cluster analysis), we characterized complication clusters and their associations with etiological risk factors in a large cohort of patients with CP.**

METHODS: **This was a multicenter, cross-sectional study including 1,071 patients with CP from the Scandinavian and Baltic countries. Complications to CP were classified according to the M-ANNHEIM system, and treelet transform was used to derive complication clusters. Cluster complication frequencies were analyzed for their association with main etiological risk factors (smoking and alcohol).**

RESULTS: **The mean age of participants was 57 years and 66% were men. Alcohol (55%) and smoking (53%) were the most common etiological risk factors and seen in combination in 36% of patients. Cluster analysis identified 3 distinct complication clusters characterized by inflammation, fibrosis, and pancreatic insufficiencies. An independent association between inflammatory complications and alcoholic etiology was seen (odds ratio [OR] 2.00 [95% CI [confidence interval], 1.38–2.90], $P < 0.001$), whereas smoking was associated with fibrosis-related complications (OR 2.23 [95% CI, 1.56–2.3.20], $P < 0.001$) and pancreatic insufficiencies (OR 1.42 [95% CI, 1.00–2.01], $P = 0.046$).**

DISCUSSION: **Three distinctive clusters of complications to CP were identified. Their differing associations with alcoholic and smoking etiology indicate distinct underlying disease mechanisms.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A63.

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INTRODUCTION

Chronic pancreatitis (CP) is a complex fibro-inflammatory disease characterized by pancreatic inflammation with fibrotic replacement of normal exocrine and endocrine tissue (1). The clinical presentation is highly variable and determined by the presence of pancreatic and extrapancreatic complications that occur with varying prevalence and severity (1). Multiple etiological risk factors have been associated with CP; the most common are alcohol and smoking identified as significant and independent risk factors with documented dose-risk

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relationships (2–4). Smoking and alcohol have also been shown to accelerate the progression of acute pancreatitis to CP (5–7) and are associated with an increased risk of developing exocrine pancreatic insufficiency (EPI), diabetes, and calcifications (8,9).

Past studies of associations between CP-related complications and etiological risk factors have mostly been limited to single complications or focused on single etiologies such as alcohol (4,8,9). However, most patients with CP present with a plethora of complications, and multiple risk factors (environmental and genetic) can often be identified in the individual patient. These factors interact in complex patterns and ultimately determine the clinical phenotype. In large-scale studies involving many variables with complex interrelations, analysis of each variable in an independent fashion may lead to statistical bias and often provides an incomplete picture (10). Objective data-driven cluster analysis provides a means to characterize such complex data and has proven valuable to delineate distinct clinical phenotypes in various diseases and setting, for example, in functional gastrointestinal disorders, type II diabetes, and studies of dietary intake (10–12). This approach, however, has not previously been employed in the context of CP.

We hypothesized that cluster analysis focused on CP-related complications would delineate distinct complication clusters that may show diverse associations with etiological risk factors. The aims of the study were: (i) to describe the prevalence of complications in a large cohort of patients with CP using the M-ANNHEIM classification, (ii) to investigate clustering of complications, and (iii) to investigate associations between cluster complication frequencies and etiological risk factors (alcohol and smoking).

METHODS

Data for this cross-sectional, multicenter study were derived from the Scandinavian Baltic Pancreatic Club (SBPC) database. The SBPC database is an ongoing multicenter prospective study initiated in 2016 (13). Data for the present study were derived from the database as of November 1, 2017 and included data from 10 centers in 6 countries in the Scandinavian-Baltic region. The detailed study protocol and methodology of the SBPC database has previously been published (13). CP was defined according to the M-ANNHEIM classification system and both patients with definitive and probable CP were included to cover the full spectrum of the disease (14,15). The study was approved by the Institutional Review Board at each participating center and by National Data Security Agencies.

Patient assessment parameters

Information on patients' demographics (sex and age) and disease characteristics including duration and etiology of CP as well as a preceding history of recurrent acute pancreatitis were recorded based on patient interviews and review of medical records. The most likely etiological risk factor(s) was designated by the treating physician, but no strict risk thresholds were adopted in this process. Complications to CP were characterized according to the M-ANNHEIM system (15). According to this, reversible complications were defined as pseudocysts, common bile duct stenosis, duodenal stenosis, pancreatic fistula, ascites, pleural effusion, pseudoaneurysm, and gastrointestinal bleeding. Irreversible complications were defined as EPI, diabetes (type IIIc), moderate-to-severe pancreatic duct lesions according to the modified Cambridge classification and portal or splenic vein thrombosis (15,16). In addition, the presence of current or past history of pancreatic cancer was noted, but because of a very limited number of patients with this complication (n = 10, <1% of study population) these data were not considered for further analysis. Likewise, pain was not considered as a complication *per se*, because many of the aforementioned complications may give rise to pain and, as such, in many patients, pain can be considered as a symptom of an underlying complication. Exocrine pancreatic function was characterized by the fecal elastase concentration test, C13 mixed triglyceride breath test, or fecal fat collection according to local practice at the individual sites, and EPI was defined according to previously published criteria (17). Review of imaging studies was performed as part of routine clinical practice at the individual sites by expert radiologists or endoscopic ultrasonographers, and relevant information from the radiological reports was registered in the database. Information on past and current endoscopic and surgical treatment was obtained from review of medical records. A limited number of patients had undergone surgical treatment (2%–3% for specific surgical procedures—Table 1) and consequently data on surgical treatments were not considered for further analysis.

Cluster analysis

Treelet transform (TT) was applied to characterize the interrelations of CP-related complications. The TT analysis is a statistical data reduction method that can be used to study clustering in large data studies (10,18); it combines the quantitative pattern extraction capabilities of principal component analysis with the interpretational advantages of hierarchical cluster analysis. As such, the TT can be used to reduce a multidimensional dataset (for example, individual complication profiles of patients with CP) to a small number of components (complication clusters) that characterize complications with a high degree of interrelation (10). In contrast to principal component analysis, the TT produces sparse components, which simplify interpretation and allows for a data-driven derivation of clusters reducing the need for subjective interpretation.

The TT method has three steps: First, the number of clusters to retain for analysis was guided by cluster variances and their graphical representation was displayed as screen-plots. A cluster variance >1.0 together with a well-defined "elbow" in the screen-plot was used as criteria to determine the number of clusters to retain (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/AJG/A63) (18). Second, the cut-level for the TT was determined using 10-fold cross-validation. Data were split randomly into 10 equally sized subsets, the highest-variance clusters were calculated for each cut-level using data from 9 of 10 subsets. The sum of variances of scores based on these clusters was calculated using the omitted subset. This procedure was repeated 10 times, each time leaving out a different data subset, and the cross-validation score at a specific cut-level was calculated by averaging the resulting sums of variances of the 10 repetitions. A graph of cross-validation scores against cut-level was constructed and the optimal cut-level for the TT was determined by locating a "knee" in this graph, where increasing the cut-level did not substantially increase the cross-validation score (see Figure 2, Supplemental Digital Content, http://links.lww.com/AJG/A63). Third, the stability of the TT factors was investigated using subsampling. Sign patterns were determined for each of the retained clusters with TT performed on a random sample of 80% of the original data and sign patterns determined among the new highest-variance factors. This procedure was repeated 100 times, and the frequencies

Table 1. Demographic and clinical characteristics of the study cohort (n = 1,071)

Demographic characteristics	
Gender, n (%)	
Female	362 (34)
Male	709 (66)
Age, yr	57.3 ± 14.1
Age distribution, n (%)	
<30 yr	38 (4)
30–40 yr	86 (8)
40–50 yr	180 (17)
50–60 yr	265 (25)
60–70 yr	282 (26)
>70 yr	220 (21)
Disease characteristics	
Aetiological risk factors, n (%)[a]	
Alcohol	593 (55)
Nicotine	568 (53)
Nutritional	15 (1)
Hereditary	107 (10)
Efferent	87 (8)
Immunological	62 (6)
Miscellaneous	127 (12)
Duration of pancreatitis, yr	4.6 ± 6.1
Duration of pancreatitis, n (%)	
<1 yr	443 (41)
1–5 yr	320 (30)
5–10 yr	169 (16)
>10 yr	139 (13)
Pancreatic calcifications, n (%)	664 (62)
History of recurrent acute pancreatitis, n (%)	
Yes	445 (42)
No	473 (44)
Undetermined	153 (14)
Treatment	
Endoscopic drainage procedure, n (%)	84 (9)
Common bile duct stenting, n (%)	121 (11)
Pancreatic duct stenting, n (%)	167 (16)
Surgical drainage procedure, n (%)	32 (3)
Combined drainage and resection, n (%)	23 (2)
Pancreatic resection, n (%)	36 (3)

[a]Patients may have more than 1 etiological risk factor according to the M-ANNHEIM classification. Concomitant alcoholic and smoking etiology were seen in 373 (36%) patients.

of each of the original sign patterns were used as a measure of stability. The STATA implementation of TT was used for cluster analysis (19).

Statistical analysis

Data are presented as numbers of patients (%) or means ± s.d. unless otherwise indicated. Prevalence estimates were calculated for all complications and reported with 95% confidence intervals (CIs). Complication frequencies were calculated for each of the main complication clusters. In order to control for a small number of patients in the subgroups with highest complication burden, the complication frequencies were reorganized: inflammatory- and fibrosis-related clusters (number of complications; none, 1, or ≥2), pancreatic insufficiency cluster (number of pancreatic insufficiencies; none, 1, or 2). Fisher's exact test was used to analyze the associations between complication frequencies of the different complication clusters as well as the associations between cluster complication frequencies and etiological risk factors (univariable analysis). An extension of the Kruskal-Wallis rank-sum test was used to analyze the effects of concomitant risk factors (smoking and alcohol) compared with single risk factors (20). Multivariable ordinal logistic regression models, incorporating an interaction between smoking and alcoholic etiology, were employed and included the following covariates: age, sex (21), and duration of CP (9). The latter was reorganized and included in the multivariate analysis as a categorical variable (duration of CP; <1 year, 1–5 years, 5–10 years, or >10 years). The proportional odds assumption was checked by the Brant test. Logistic regression models were used to study the association between cluster complication frequencies and risk of endoscopic treatment. Results of regression models were reported as odds ratios (ORs) with 95% CIs. A significance threshold of $P < 0.05$ was used. The software package STATA version 15.1 (StataCorp LP, College Station, TX) was used for statistical calculations.

RESULTS

A total of 1,240 patients with CP were enrolled. Among these patients, a complete characterization of complication profiles and etiological risk factors was available in 1,071 patients (86% complete data). A definitive diagnosis of CP was established in 962 (90%) patients, and 109 (10%) had a diagnosis of probable CP. The baseline demographic and clinical characteristics for these patients are outlined in Table 1. Patients had a mean age of 57.3 ± 14.1 years and were predominantly men (66%). According to the treating physician's designation, alcohol was considered as an etiological risk factor in 593 (55%) patients and smoking in 568 (53%) patients. In 373 (36%) patients, smoking and alcohol was considered concurrent risk factors. Pancreatic calcifications were seen in 664 (62%) patients.

Prevalence of complications

Prevalence estimates for the complications associated with CP are reported in Figure 1. The most prevalent complications were EPI (53%), moderate-to-severe pancreatic duct lesions (53%), pseudocysts (42%), and diabetes (38%). Common bile duct stenosis was seen in 15% of patients, whereas the remaining complications were relatively infrequent with prevalence estimates between 1% and 6%.

Complication clusters

A 3-cluster solution was optimal to characterize the interrelations of complications (see Figures 1 and 2, Supplemental Digital Content, http://links.lww.com/AJG/A63). The cluster tree (dendrogram) is shown in Figure 2, with the 3 clusters indicated by numbered nodes. The first cluster was characterized by *inflammatory*-related complications (pseudocysts, ascites, pleural

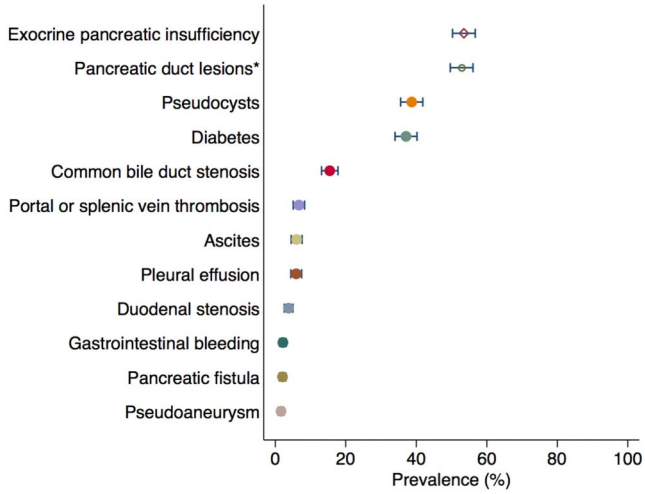

Figure 1. Prevalence estimates of complications to chronic pancreatitis (n = 1,071). Whiskers show 95% confidence intervals. *Moderate-to-severe ductal lesions according to the modified Cambridge classification.

effusion, pancreatic fistula, and portal or splenic vein thrombosis), the second cluster by *fibrosis*-related complications (pancreatic duct lesions, common bile duct stenosis, and duodenal stenosis), and the third cluster by pancreatic exocrine and endocrine *insufficiency*. The cumulative variance explained by the 3 clusters was 36%. Corresponding cluster stabilities were 90% for the inflammatory cluster, 90% for the fibrosis-related cluster and 99% for the pancreatic insufficiency cluster, thus confirming a high degree of internal validity of the retrieved cluster sign patterns.

Complication frequencies and their associations between clusters

Six-hundred three (56%) patients had no inflammatory complications, 349 (33%) had 1 inflammatory complication, and 119 (11%) had 2 or more inflammatory complications. Four-hundred sixty (43%) patients had no fibrotic complications, 474 (44%) had 1 fibrotic complication, and 137 (13%) had 2 or more fibrotic complications. Three-hundred eighty-one (36%) patients had no evidence of pancreatic insufficiency, 407 (38%) had either EPI or diabetes, and 283 (26%) patients had both EPI and diabetes.

The frequencies of inflammatory- and fibrosis-related complications were significantly associated ($P < 0.001$)—Figure 3a. Also, the frequencies of fibrosis-related complications and pancreatic insufficiencies were significantly associated ($P = 0.03$)—Figure 3b. There was no association between the frequencies of inflammatory complications and pancreatic insufficiencies ($P = 0.46$).

Cluster complication frequencies and associations with etiological risk factors

Inflammatory complications. More inflammatory complications were observed in patients with alcoholic etiology compared with patients without alcohol or smoking as etiological risk factor ($P < 0.001$), whereas smoking etiology was not associated with inflammatory complications ($P = 0.38$)—Figure 4a. Patients with concomitant risk factors (smoking and alcohol) had an increased frequency of inflammatory complications compared with patients with single etiological risk factors ($P < 0.001$)—Figure 4a. Multivariable analysis confirmed the independence and significance of the association for alcoholic etiology and frequency of inflammatory complications (OR 2.0 [95% CI, 1.4–2.9], $P < 0.001$)—Table 2.

Fibrotic complications. Compared with patients without alcohol or smoking as risk factors, more fibrosis-related complications were observed in patients with smoking ($P < 0.001$) and alcohol ($P = 0.02$) as etiology—Figure 4b. Patients with concomitant risk factors (smoking and alcohol) had fibrotic complication frequencies comparable to those observed in patients with single risk factors ($P = 0.85$)—Figure 4b. Multivariable analysis confirmed

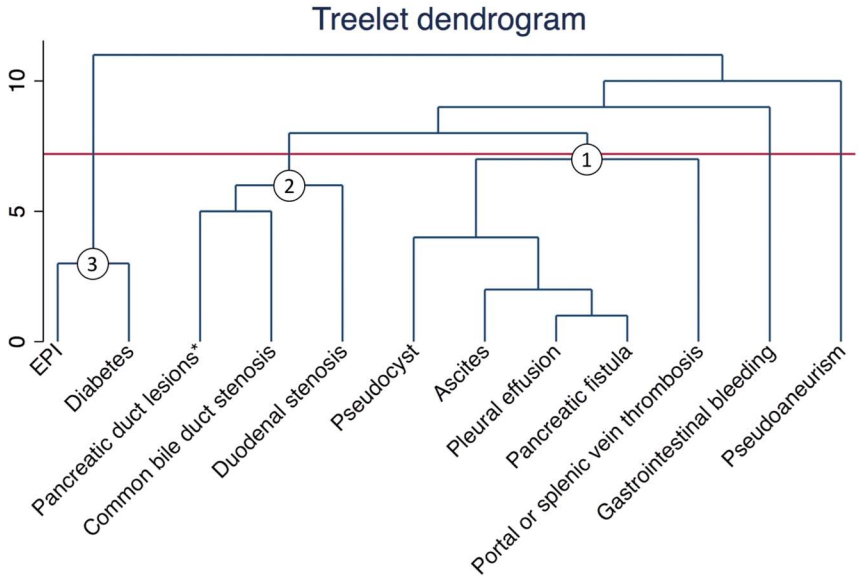

Figure 2. Cluster tree (dendrogram) of complications to chronic pancreatitis defined using treelet transform analysis. The three significant clusters are designated by numbered nodes: Cluster 1 is comprised of inflammatory-related complications, cluster 2 by fibrosis-related complications, and cluster 3 by exocrine- and endocrine pancreatic insufficiency. The dashed line represents the cut-level of the cluster tree derived from the cross-validation procedures (level 7). *Indicates moderate-to-severe ductal lesions according to the modified Cambridge classification.

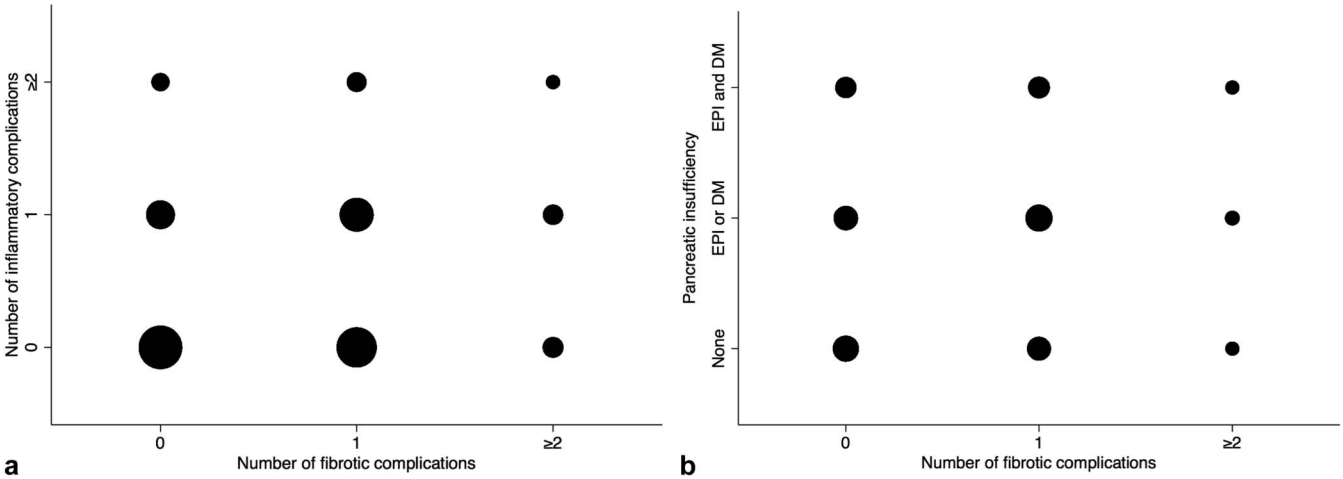

Figure 3. Bubble charts illustrating associations of complication frequencies between the 3 main complication subgroups (inflammatory-related complications, fibrosis-related complications, and pancreatic insufficiencies). The size of the bubbles represents the number of patients in the different subgroups. Significant associations were seen (**a**) between the frequencies of inflammatory- and fibrosis-related complications ($P < 0.001$) and (**b**) between the frequencies of fibrosis-related complications and pancreatic insufficiencies ($P = 0.03$). DM, diabetes mellitus; EPI, exocrine pancreatic insufficiency.

the independence and significance of the association for smoking etiology and fibrosis-related complications (OR 2.2 [95% CI, 1.6–3.2], $P < 0.001$). In addition, a gradual increasing risk of fibrotic complications was seen with prolonged disease duration (all $P \leq 0.003$)—Table 2.

EPI and diabetes. Increased frequencies of pancreatic insufficiencies (EPI and/or diabetes) were observed in patients with smoking as etiological risk factors compared with patients without alcohol or smoking etiology ($P = 0.02$), whereas no difference was seen for alcoholic etiology ($P = 0.36$)—Figure 4c. Patients with concomitant risk factors (smoking and alcohol) had frequencies of pancreatic insufficiencies comparable to those observed in the subgroups with single risk factors ($P = 0.90$)—Figure 4c. Multivariate analysis confirmed the independence and significance of the association for smoking etiology and pancreatic insufficiencies (OR 1.4 [95% CI, 1.0–2.0], $P = 0.046$). In addition, a gradual increasing risk of EPI and/or diabetes was associated with prolonged disease duration (all $P \leq 0.001$). Likewise, age was independently associated with pancreatic insufficiencies, with an increased risk of EPI and/or diabetes associated with advanced age ($P < 0.001$)—Table 2.

Cluster complication frequencies and risk of endoscopic treatment

Associations between cluster complication frequencies and endoscopic treatment are reported in Table 3. The most noticeable associations were seen for patients with high frequencies of inflammatory complications who were more likely to have undergone endoscopic drainage procedures (OR 18.8 [95% CI, 8.2–43.0]; $P < 0.001$) compared with their counterparts with no inflammatory complications. Likewise, patients with high frequencies of fibrosis-related complications were more likely to have undergone endoscopic stenting of the common bile duct (OR 27.8 [95% CI, 15.2–50.6]; $P < 0.001$) or pancreatic duct (OR 3.2 [95% CI, 1.9–5.2]; $P < 0.001$) compared with their counterparts with no fibrosis-related complications. No associations were observed between pancreatic insufficiencies and endoscopic treatment—Table 3.

DISCUSSION

In a large cohort of patients with CP, the prevalence and clustering of disease-related complications was investigated. The most prevalent complications were EPI and diabetes, followed by pseudocysts and pancreatic duct lesions. Complications fell into 3 well-defined clusters characterized by inflammation, fibrosis, or pancreatic insufficiencies (EPI and diabetes). An independent association was seen between complication frequencies of the inflammatory cluster and alcoholic etiology, whereas smoking was associated with fibrosis-related complications, EPI, and diabetes. These findings expand previous investigations and indicate that alcohol and smoking may be associated with distinct complication profiles that possibly reflect different underlying disease mechanisms.

Prevalence of complications to CP

In our cohort, EPI, diabetes, and pancreatic duct lesions (moderate to severe according to the Cambridge classification) were among the most prevalent complications, which underlines that most of our patients had definitive CP and were characterized by end-stage disease features. This is in contrast to the North American Pancreatitis Study II cohort where the patient population represented a wider spectrum of disease including patients with recurrent acute pancreatitis (22). Consequently, our findings must be interpreted in this context and future studies are needed to validate our findings in patients with less progressive disease stages.

Complication clusters

The present study focused on characterization of the interrelations of complications rather than patient subgroups based on disease etiology, the latter being the focus of previous investigations (8,9). Using a data-driven cluster analysis, we identified 3 distinct complication clusters that fell into clinical plausible subgroups comprising inflammatory-related complications, fibrosis-related complications, and pancreatic insufficiencies. This is in agreement with the long-standing understanding of CP

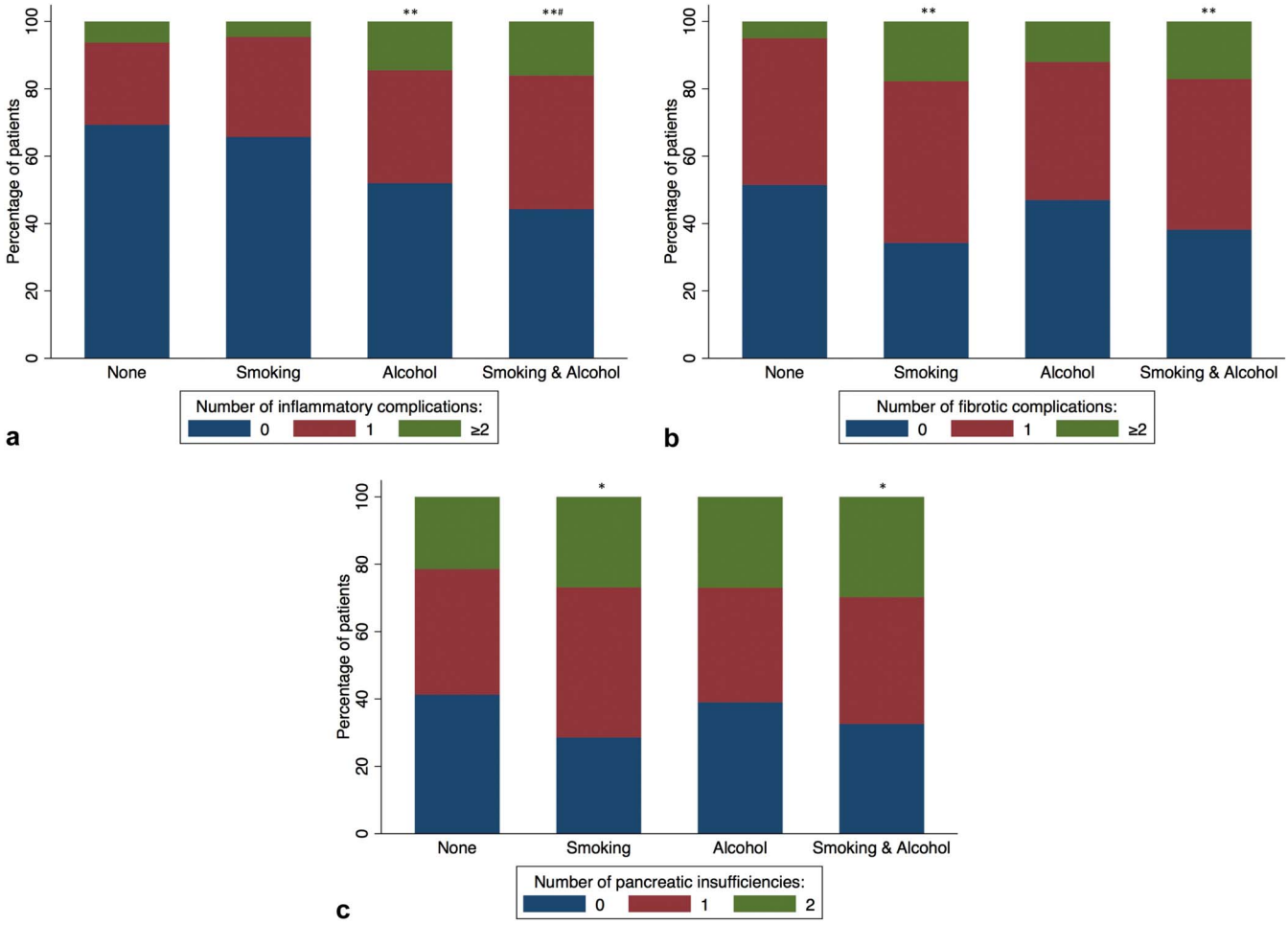

Figure 4. Associations of cluster complication frequencies and etiological risk factors for (**a**) the inflammatory-related complication cluster, (**b**) fibrosis-related complication cluster, and (**c**) pancreatic insufficiency cluster. Significance of the difference compared with patients without alcohol and smoking etiology: $^{*}P < 0.05$, $^{**}P < 0.001$. Significance of the difference compared with patients with single etiological risk factors: $^{\#}P < 0.001$.

as a fibro-inflammatory disease that ultimately leads to pancreatic insufficiency (23).

The complication frequencies were associated for most clusters, thus emphasizing that complications from differing clusters can occur in individual patients at the same time. For example, a typical patient with end-stage CP may present with marked pancreatic duct lesions in combination with a pseudocyst and evidence of EPI. On the other hand, the associations of cluster complication frequencies between clusters were not absolute and large numbers of patients presented with either inflammatory- or fibrosis-related complications. This implies that different pathophysiological disease mechanisms may be responsible for the development of differing complications, which is likely to be determined by complex gene-gene and gene-environmental interactions, as supported by recent clinical and basic studies (14,24,25).

Associations of cluster complication frequencies and etiological risk factors

An important finding of our study was the differing associations between cluster complication frequencies and etiological risk factors. Alcohol was the main driver of inflammatory complications, which is in keeping with previous studies (4). As such, alcohol has for long been known to be an independent risk factor for acute pancreatitis, and excessive alcohol intake (>5 drinks per day) is associated with an increased risk of recurrent acute pancreatitis and development of CP (2,3,5,6). The underlying mechanisms for these associations are complex and involve several mechanisms targeting acinar, ductal, and pancreatic stellate cells (24). In contrast to previous clinical studies, we were not able to demonstrate any association between exocrine and endocrine pancreatic insufficiency and alcoholic disease etiology (9). However, in past studies of disease progression and complications, alcohol and smoking effects were not isolated and consequently the observed effects of alcohol on the development of EPI and diabetes may partly be explained by residual confounding driven by smoking (9).

Smoking was a strong risk factor for fibrosis-related complications and was also associated with an increased risk of EPI and diabetes. Many studies have identified smoking as an independent risk factor for CP, and smoking is known to increase the risk of developing CP in the context of acute and recurrent acute pancreatitis (2–4,7). However, only few studies have explored the influence of smoking on the risk for developing complications to CP, and these studies have been focused on single complications such as diabetes and calcifications (8). The

Table 2. Multivariable analysis of associations between complication frequencies in the 3 clusters and etiological risk factors

	Cluster 1			Cluster 2			Cluster 3		
	Inflammation-related complications			Fibrosis-related complications			Pancreatic insufficiencies		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Gender: Male	1.29	1.00–1.68	0.06	0.98	0.78–1.28	0.98	0.92	0.73–1.17	0.51
Age	0.99	0.98–1.00	0.10	1.00	0.99–1.00	0.75	1.01	1.01–1.02	<0.001
Alcohol	2.00	1.38–2.90	<0.001	1.26	0.89–1.80	0.19	1.20	0.85–1.70	0.29
Smoking	1.15	0.78–1.71	0.49	2.23	1.56–3.20	<0.001	1.42	1.00–2.01	0.046
Alcohol-smoking interaction term	1.18	0.70–1.97	0.53	0.67	0.41–1.08	0.10	0.86	0.54–1.38	0.54
Duration of CP									
<1 yr	Reference	—	—	Reference	—	—	Reference	—	—
1–5 yr	0.87	0.66–1.17	0.36	1.52	1.15–2.00	0.003	1.55	1.19–2.03	0.001
5–10 yr	1.09	0.77–1.54	0.65	1.89	1.34–2.67	<0.001	2.03	1.46–2.83	<0.001
>10 yr	0.94	0.63–1.38	0.74	1.91	1.32–2.77	0.001	3.15	2.19–4.53	<0.001

CI, confidence interval; CP, chronic pancreatitis; OR, odds ratio.

effects of smoking on the cellular and molecular level have been characterized in recent basic studies where nicotine and aryl hydrocarbon receptor ligands, some of the many substances found in cigarette smoke, were shown to promote pancreatic fibrosis in cell and murine models of CP (26,27). In keeping with these findings, smoking is also known to accelerate disease activity and fibrosis in other fibro-inflammatory diseases such as Crohn's disease and chronic obstructive pulmonary disease (28,29).

No significant interactions between etiological risk factors and complication frequencies were observed for any of the clusters on multivariate analysis, thus supporting the notion that differing etiological risk factors modulate disease phenotypes through different mechanisms.

Study limitations

Despite the large number of patients and the novel analytic approach, our study has some limitations. First, the study cohort comprised mostly of patients with established CP at advanced disease stages and, as such, results may not be generalizable to early CP (30). Second, the cross-sectional nature of the study precludes any conclusions on causality of the observed associations between etiological risk factors and CP-related complications. However, most of our findings are supported by previous epidemiological and basic studies. Third, a detailed characterization of smoking and drinking habits was not available for the full study cohort and, as such, risk thresholds could not be identified for the complication clusters (2). However, this is a topic of some uncertainty and until now only few studies have investigated risk thresholds in the context of CP (2). Although a risk threshold of 5 alcohol units per day was found in the North American Pancreatitis Study II study cohort, these findings are mainly valid on a population level. Individual risk thresholds likely vary considerably between patients because these will also be dependent on concomitant risk factors including smoking habits and genetic predisposition as well as other and possible hitherto unidentified factors (2,15). Likewise, to the best of our knowledge, no studies have established risk thresholds for smoking and CP, although a dose-risk relationship has been observed in the

Table 3. Risk of endoscopic treatment by complication frequencies in the 3 clusters

		Endoscopic drainage procedure		Common bile duct stenting		Pancreatic duct stenting	
Complication cluster	No. of complications	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Inflammatory complications	0	Ref		Ref		Ref	
	1	13.1 (6.1–27.9)	<0.001	1.4 (0.9–2.1)	0.12	1.5 (1.0–2.2)	0.03
	≥2	18.8 (8.2–43.0)	<0.001	2.4 (1.4–4.1	0.001	2.0 (1.2–3.3)	0.006
Fibrosis-related complications	0	Ref		Ref		Ref	
	1	1.8 (1.0–3.0)	0.037	2.3 (1.3–4.3)	0.005	2.1 (1.4–3.0)	<0.001
	≥2	3.4 (1.8–6.4)	<0.001	27.8 (15.2–50.6)	<0.001	3.2 (1.9–5.2)	<0.001
Pancreatic insufficiencies	0	Ref		Ref		Ref	
	1	1.5 (0.8–2.5)	0.17	1.1 (0.7–1.7)	0.71	1.1 (0.8–1.7)	0.49
	2	1.6 (0.9–2.8)	0.13	1.3 (0.8–2.1)	0.25	1.2 (0.8–1.9)	0.31

CI, confidence interval; OR, odds ratio.

aforementioned study (2). Finally, although careful adjustments for the effects of age and disease duration were applied in the multivariable analysis, longitudinal studies are needed to confirm the validity of our findings and to better characterize disease progression and its relation to etiological risk factors.

Clinical implications and suggestions for future research

The key finding of the study suggests that alcohol and smoking are not only risk factors of CP but also define the clinical presentation of disease (phenotype). As such, patients with an alcoholic etiology are more likely to develop inflammatory complications, whereas smoking increases the risk of fibrosis-related complications and pancreatic insufficiency. This information can be used to individualize monitoring strategies and underlines the importance of risk factor counseling as a key element in patient management.

Future studies focusing on clustering of patients rather than complications may shed further light on the complexity of disease presentation and its association with environmental and genetic risk factors. This may help to better characterize individual patient trajectories and thus provide a framework for personalized treatment (31).

CONCLUSIONS

Three distinct clusters of complications to CP, characterized by inflammation, fibrosis, and pancreatic insufficiencies, were identified in this large multicenter study including more than 1,000 patients. The differing associations of clusters with alcoholic and smoking etiology may indicate distinct underlying disease mechanisms and support recent preclinical findings.

CONFLICTS OF INTEREST

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Specific author contributions: Study design and data collection: S.S.O., C.N., J.L.P., S.L.H., M.V., M.L., B.L., L.B., A.G., E.K., M.E., F.E., T.E., S.R., S.N., T.H., A.W., J.L., M.P., A.P., I.O.-Z., and A.M.D. Data management and statistical analysis: S.S.O. and J.L.P. Drafting of the manuscript: S.S.O., C.N., and A.M.D. Data interpretation, review of manuscript for important intellectual content, and final approval of the manuscript: all authors.

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Study Highlights

WHAT IS KNOWN

- ✓ CP is a complex disease characterized by several disease-related complications and multiple etiological risk factors
- ✓ Characterization of complications and their association with etiological risk factors (smoking and alcohol) is poorly documented

WHAT IS NEW HERE

- ✓ Cluster analysis identified 3 distinct complication clusters characterized by inflammation, fibrosis, and pancreatic insufficiencies
- ✓ Alcoholic etiology was associated with an increased risk of inflammatory complications, whereas smoking was associated with fibrosis-related complications and pancreatic insufficiencies.
- ✓ The differing associations between complications and disease etiology indicate different underlying disease mechanisms

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