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Development of pancreatic diseases during long-term follow-up after acute pancreatitis: a post-hoc analysis of a prospective multicenter cohort

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Key words
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Abstract

Background and Aim: More insight into the incidence of and factors associated with progression following a first episode of acute pancreatitis (AP) would offer opportunities for improvements in disease management and patient counseling.

Methods: A long-term post hoc analysis of a prospective cohort of patients with AP (2008–2015) was performed. Primary endpoints were recurrent acute pancreatitis (RAP), chronic pancreatitis (CP), and pancreatic cancer. Cumulative incidence calculations and risk analyses were performed.

Results: Overall, 1184 patients with a median follow-up of 9 years (IQR: 7–11) were included. RAP and CP occurred in 301 patients (25%) and 72 patients (6%), with the highest incidences observed for alcoholic pancreatitis (40% and 22%). Pancreatic cancer was diagnosed in 14 patients (1%). Predictive factors for RAP were alcoholic and idiopathic pancreatitis (OR 2.70, 95% CI 1.51–4.82 and OR 2.06, 95% CI 1.40–3.02), and no pancreatic interventions (OR 1.82, 95% CI 1.10–3.01). Non-biliary etiology (*alcohol*: OR 5.24, 95% CI 1.94–14.16, *idiopathic*: OR 4.57, 95% CI 2.05–10.16, and *other*: OR 2.97, 95% CI 1.11–7.94), RAP (OR 4.93, 95% CI 2.84–8.58), prior pancreatic interventions (OR 3.10, 95% CI 1.20–8.02), smoking (OR 2.33, 95% CI 1.14–4.78), and male sex (OR 2.06, 95% CI 1.05–4.05) were independently associated with CP.

Conclusion: Disease progression was observed in a quarter of pancreatitis patients. We identified several risk factors that may be helpful to devise personalized strategies with the intention to reduce the impact of disease progression in patients with AP.

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Introduction

Over the years, the incidence of acute pancreatitis (AP) has gradually increased.[1,2] Although most patients fully recover from a first episode of AP, a subset of patients develop recurrent acute pancreatitis (RAP), chronic pancreatitis (CP), or pancreatic cancer.[3–5] RAP exposes patients to new episodes of considerable risks of pancreatitis-related complications.[5] CP is a debilitating and difficult to manage disease, which has a profound impact on patients' quality of life (QoL).[6,7] Furthermore, with pancreatic cancer being one of the most fatal malignancies with an overall actual 5-year survival rate below 5%,[8] it is crucial to gain insight into which patients are at risk for disease progression as preventive measures and a more intensive follow-up could be offered to these patients.

Several previous cohort studies on transition of AP to RAP and CP have been published.[3,5,9–12] However, most of these studies originated from a time when AP and CP were seen as separate diseases. To date, evidence suggests that AP, RAP, and CP represent a disease continuum. The mechanisms and risk factors underlying disease progression, however, are still not properly understood.[13] Furthermore, these previous studies do not consider the association between AP and pancreatic cancer. AP has previously been linked to pancreatic cancer, but it is still unclear whether there is a direct correlation or if this relationship is solely driven by progression to RAP and CP.[14–17] Furthermore, once diagnosed with CP, little is known whether the risk for pancreatic cancer differs for patients with or without a previous diagnosis of RAP.

This long-term follow-up study aims to gain insight into the incidence of and factors associated with transition to RAP, CP, and pancreatic cancer following a first episode of AP.

Methods

Study design and population. This study is a long-term post hoc analysis of a prospective nationwide cohort study to investigate the risk of and factors associated with disease progression. Patients were selected from a nationwide cohort of AP patients who were prospectively registered in a consecutive manner between 2008 and 2015. A subset of these patients were included in previous trials of the Dutch Pancreatitis Study Group.[18–21] For the present study, only patients with a first episode of AP from 17 different hospitals were eligible for inclusion. AP was defined according to the 2012 revised Atlanta classification.[22] An overview of the definitions of the different etiologies is provided in the Supporting Information. Exclusion criteria included no survival of index admission, (suspected) CP or pancreatic cancer prior to the index date, missing baseline data that could not be retrieved, and loss to follow-up. Written informed consent was obtained from each participant prior to registration. Both the registration cohort study and the previous trials were approved by a central medical ethics committee. All authors had access to the study data and reviewed and approved the final manuscript.

Data collection. Demographic and clinical characteristics at index admission were prospectively collected during the patients' inclusion in the various trials. Medical records were checked for disease progression, readmissions, laboratory and imaging reports, endoscopic or surgical pancreatic interventions, and mortality during long-term follow-up by using a standardized case record form. Additionally, a standard follow-up questionnaire regarding alcohol and smoking behavior (including quit dates in the case of smoking or alcohol cessation), medication use, QoL (i.e. SF-36), and pain severity (i.e. Izbicki Pain Questionnaire) was sent via post to patients who were still alive at the end of follow-up. Non-responders received up to two reminders. Data were checked for completeness and verified by the second author (NS). Any discrepancies were resolved by discussion until consensus was reached.

Study outcomes. The primary endpoints were RAP, CP, or pancreatic cancer. RAP was defined as a new episode of AP meeting the revised Atlanta criteria and requiring hospitalization.[22] Definite CP was diagnosed according to the M-ANNHEIM-criteria.[23] Pancreatic cancer was diagnosed based on histopathology or detected on imaging when no histology was obtained. Secondary endpoints included new onset of diabetes mellitus and/or exocrine pancreatic insufficiency (EPI), medication for (potential) pancreatic pain, endoscopic or surgical pancreatic interventions, QoL, pain severity, and mortality due to pancreatic pathology. EPI was defined in case of a fecal elastase-1 test <200 µg/g or use of exogenous pancreatic enzymes. Diabetes mellitus was registered when patients were using oral diabetic medication or insulin therapy. The follow-up period was defined as the time between initial enrolment and the date of data collection or the date of death for non-surviving patients.

Data analysis and statistical methods. Data were analyzed by using SPSS version 28 (IBM Corp: Armonk, NY, USA). Categorical data are presented as frequencies with percentages and continuous variables as medians with interquartile ranges (IQR). Between-group differences were analyzed using the Mann–Whitney *U* test for continuous data and Fisher's exact test or χ^2-test for categorical data. Logistic regression models were performed to identify potential risk factors for disease progression and presented as odds ratios (ORs) with their respective 95% confidence intervals (CI). A subgroup analysis in biliary pancreatitis patients was performed to evaluate the protective role of cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) in preventing RAP. For CP, a subgroup analysis was performed for patients without a history of RAP. In the logistic regression models, missing data were handled by using multiple imputation for variables with less than 20% missing values. Additionally, sensitivity analyses on the original dataset were performed. Cox proportional hazards models were used to calculate the cumulative incidence risk scores for RAP, CP, and pancreatic cancer. Results were stratified by initial etiology and by history of RAP. Furthermore, subgroup analyses were performed for patients in whom preventive measures (i.e. ERCP, cholecystectomy, alcohol and smoking counseling) were taken as proposed in current guidelines to lower the risk for disease progression. A two-sided *P*-value of less than 0.05 was considered significant.

Results

Study population. In total, 1377 patients were prospectively registered, of whom 1184 were included in this long-term follow-up study (Fig. S1). Median follow-up was 9 years (IQR 7–11). Patient and disease characteristics at baseline are provided in Table 1. The median age was 59 years (IQR 45–71) and 56% were male. The most frequent etiology of AP was biliary (63%), followed by alcoholic (13%) and idiopathic (13%). The majority of patients had a mild disease course (70%). In 269 moderately severe AP patients (23%), AP was complicated by transient organ failure and/or local complications. In total, 82 patients (7%) developed persistent organ failure (i.e. severe pancreatitis). The follow-up questionnaire was sent to 917 patients (77%), of whom 370 responded (response rate: 40%).

Study outcomes. RAP occurred in 301 patients (25%), with a median time from the initial pancreatitis episode of 9 months (IQR 2–34) (Table 2). CP was diagnosed in 72 patients (6%) after a median follow-up period of 31 months (IQR 7–61) and was preceded by RAP in 45 patients (63%). Pancreatic cancer was diagnosed in 14 patients (1%), of whom one patient was previously diagnosed with both RAP and CP and five patients with only RAP. Median time to pancreatic cancer diagnosis was 24 months (IQR 4–84). New onset diabetes and EPI was observed in 12% (n = 147) and 9% (n = 105) of patients, respectively. Pancreatic surgery was performed in 37 patients (3%), 60 patients underwent endoscopic pancreatic therapy (5%), and 52 patients (4%) needed medical treatment for pancreatic pain. Overall, 267 patients (23%) died during follow-up. Death was related to pancreatic diseases in 31 patients (3%).

RAP. The risks of RAP for different variables after multiple imputations are summarized in Table 3 (see Table S1 for non-imputed data). In the multivariate model, factors independently associated with development of RAP were alcoholic and idiopathic pancreatitis (OR 2.70, 95% CI 1.51–4.82 and OR 2.06, 95% CI 1.40–3.02), and no pancreatic intervention(s) performed during the initial episode (OR 1.82, 95% CI 1.10–3.01). In the subgroup analysis for biliary pancreatitis patients, independent protective factors for RAP were ERCP ≤3 months after onset of AP (OR 0.37, 95% CI 0.23–0.61) and cholecystectomy when performed prior to or ≤3 months after onset of AP (OR 0.16, 95% CI 0.11–0.25) (Table S2). The cumulative risk for RAP over 9 years was the highest among patients with an initial alcoholic etiology (40%) (Fig. 1a).

Subgroup analyses for biliary interventions, smoking, and alcohol. An overview of the preventive measures taken in our biliary cohort and the recurrence rate is provided in the Supporting Information (Fig. S2a,b). ERCP ≤3 months after hospitalization was performed in 233 patients (31%). In these patients, 10% (24/233) developed RAP after ERCP. The overall recurrence rate within this subgroup was 15% (36/233). This was significantly lower compared to patients who underwent an ERCP >3 months after AP ($P < 0.001$), but not significantly different from those in whom no ERCP was performed ($P = 0.287$). Cholecystectomy was performed before or ≤3 months after the first episode of AP in 61% of biliary patients (n = 446). The lowest recurrence rate (14%) was observed in this subgroup. Cholecystectomy >3 months after hospitalization was not associated with a lower recurrence rate compared to no cholecystectomy. No significant differences in recurrence rates were observed between patients who quit smoking and continued smoking (Table S4) and between patients who stopped drinking alcohol and continued drinking (Table S5a). Within the subgroup of alcoholic pancreatitis patients, alcohol cessation was significantly associated with a lower recurrence rate compared with long-term alcohol consumption ($P = 0.043$) (Table S5b).

CP. Table 4 presents the results of the logistic regression analyses for development of CP (see Table S6 for non-imputed data). In multivariate analysis, non-biliary etiology (*alcohol*: OR 5.24, 95% CI 1.94–14.16, *idiopathic*: OR 4.57, 95% CI 2.05–10.16, and *other*: OR 2.97, 95% CI 1.11–7.94), RAP (OR 4.93, 95% CI 2.84–8.58), pancreatic intervention(s) performed during the initial episode (OR 3.10, 95% CI 1.20–8.02), smoking (OR 2.33, 95% CI 1.14–4.78), and male sex (OR 2.06, 95% CI 1.05–4.05) were independently associated with CP. Multivariate analyses with RAP removed as covariate are presented in Table 4. Patients with alcoholic AP (22%) and a history of RAP (15%) had the highest cumulative risk for developing CP over 9 years (Fig. 1b,c).

Subgroup analyses for smoking and alcohol. No significant differences in progression rates to CP were observed between patients who continued smoking and drinking and patients who reported cessation of smoking and alcohol cessation at long-term follow-up (Tables S7 and S8).

Table 1 Patient and disease characteristics in 1184 patients with a first episode of acute pancreatitis

	n			
Age (year), median (P25–P75)	1184		59 (45–71)	
Male sex, no. (%)	1184		660 (56)	
Body mass index, median (P25–P75)	741		28 (25–31)	
Etiology, no. (%)	1184			
Biliary			740 (63)	
Alcoholic			156 (13)	
Idiopathic			156 (13)	
Other (i.e. ischemic, post-ERCP, genetic or drug-induced)			132 (11)	
Smoking, no. (%)	1029			
Current			276 (23)	
Past			151 (13)	
Never			602 (51)	
Alcohol, no. (%)	1066			
Current[†]			649 (55)	
Heavy users			112 (10)	
Excessive users			49 (4)	
Social users			488 (41)	
Past			35 (3)	
Never			382 (32)	
ASA classification, no. (%)	1184			
I			225 (19)	
II			520 (44)	
III			430 (36)	
IV			9 (1)	
C-reactive protein (CRP) <48 h after admission, median (P25–P75)	1176		162 (73–287)	
Leukocytes <48 h after admission, median (P25–P75)	1178		15 (11–19)	
APACHE score <48 h after admission, median (P25–P75)	1172		7 (4–9)	
IMRIE score <48 h after admission, median (P25–P75)	1173		1 (1–2)	
Severity according to Atlanta, no. (%)		Mild		Moderate/severe
Predicted severity at admission[‡]	1175	506 (43)		669 (57)
Actual severity after admission	1184	833 (70)		269 (23) /82 (7.0)
CT severity index score, median (P25–P75)[§]	215		6 (4–8)	
Necrosis, no. (%)[§]	351		257 (22)	
Extent necrosis, no. (%)[§]	253			
Pancreatic parenchymal			33 (3%)	
Peripancreatic tissue			80 (7%)	
Both			140 (12%)	
Peripancreatic collections, no. (%)[§]	351		305 (26)	
Persistent organ failure, no. (%)	1184		82 (7)	
Pancreatic intervention, no. (%)	1184		119 (10)	
Radiological percutaneous drainage			83 (7)	
Endoscopic procedure[¶]			64 (5)	
Surgical procedure[††]			37 (3)	
Endoscopic retrograde cholangiopancreatography (ERCP) <3 months after onset acute pancreatitis, no. (%)[‡‡]	1182		263 (22)	
Cholecystectomy, no. (%)	1182		689 (58%)	
Prior to first episode of acute pancreatitis			105 (9)	
Performed after first episode of acute pancreatitis			584 (49)	
<3 months after onset acute pancreatitis			400 (34)	
>3 months after onset acute pancreatitis			182 (15)	
Date unknown			2 (2)	
Follow-up questionnaire, no. (%)	1184			
Questionnaire completed			370	
Questionnaire not completed			547	
No reply			414	
Current address unknown			48	
Refused questionnaire			85	
Not available for questionnaire (i.e. no survival)			267 (23%)	

[†]Divided into categories as defined by the National Institute for Public Health and Environment: heavy users = at least once a week ≥4 units/day (women)/≥6 units/day (men), excessive users = > 21 units/week (men)/>14 units/week (woman).
[‡]Predicted severe acute pancreatitis was defined as an Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥8, Imrie score ≥3, or C-reactive protein >150 mg/L.
[§]Only described for the moderately severe and severe acute pancreatitis patients (*n* = 351).
[¶]Endoscopic drainage and/or endoscopic necrosectomy.
[††]Surgical drainage and/or surgical necrosectomy.
[‡‡]Only ERCP procedures that included a sphincterotomy, nettoyage/stone extraction, and/or stenting therapy were included in the evaluation.

Table 2 Primary and secondary study endpoints of 1184 patients with a first episode of acute pancreatitis

	n	
Follow up duration (years), median (P25–P75)	1184	9 (7–11)
Mortality, no. (%)	1184	267 (23)
Due to pancreatic diseases	241	31 (3)
Recurrent pancreatitis	1184	301 (25)
Number of recurrences	301	
1 episode		179 (15)
2 episodes		49 (4)
≥3 episodes		73 (6)
Time to recurrent pancreatitis (months), median (P25–P75)	301	9 (2–34)
Etiology first acute pancreatitis episode, no. (%)	301	
Biliary		153/740 (21)
Alcoholic		62/156 (40)
Idiopathic		52/156 (33)
Other		34/132 (26)
Chronic pancreatitis, no. (%)	1184	72 (6)
Time to chronic pancreatitis (months), median (P25–P75)	71	31 (7–61)
Etiology first acute pancreatitis, no. (%)	72	
Biliary		13/740 (2)
Alcoholic		35/156 (22)
Idiopathic		16/156 (10)
Other		8/132 (6)
History of recurrent pancreatitis	72	45/72 (63)
Pancreatic cancer, no. (%)	1183	14 (1)
Time to pancreatic cancer (months), median (P25–P75)	14	24 (4–84)
Etiology first acute pancreatitis, no. (%)	14	
Biliary		3/740 (0)
Alcoholic		2/156 (1)
Idiopathic		7/155 (5)
Other		2/132 (2)
History of recurrent pancreatitis	14	5/14 (36)
History of chronic pancreatitis	14	0/14 (0)
History of recurrent and chronic pancreatitis	14	1/14 (7)
New-onset diabetes, no. (%)	1184	147 (12)
Exocrine pancreatic insufficiency, no. (%)	1184	105 (9)
Medication for pancreatic pain, no. (%)	1181	52 (4)
Endoscopic therapy during follow-up, no. (%)	1184	60 (5)
Surgery during follow-up, no. (%)	1183	37 (3)
Pancreatic resection		26 (2)
Other surgical procedures[†]		13 (1)

[†]Surgical drainage (*n* = 3), surgical necrosectomy (*n* = 2), bypass surgery because of duodenal obstruction (*n* = 6), and fistulotomy (*n* = 2).

Pancreatic cancer. The number of patients who developed pancreatic cancer was insufficient to perform multivariate analysis. Of the 14 patients who developed pancreatic cancer, seven were diagnosed within 2 years after onset of AP. In 57% of these patients (4/7), the cause of the initial AP episode was unknown. When introducing a 5-year lag period, five patients remained, of whom one patient with idiopathic AP. Pancreatic cancer was preceded by RAP in six patients (43%), of whom one patient was also diagnosed with CP (Fig. 1d).

Table 3 Factors associated with recurrent acute pancreatitis—univariate and multivariate analyses

Variable	*n*/*N* (%)	Univariate analyses		Multivariate analyses	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)		1.00 (0.99–1.00)	0.341		
Gender					
Male	178/660 (27%)	1.20 (0.92–1.57)	0.170		
Female	123/524 (23%)	1			
BMI[†]		0.97 (0.94–1.00)	0.074		
Etiology					
Biliary	153/740 (21%)	1		1	
Alcoholic	62/156 (40%)	2.53 (1.75–3.65)	<0.001	2.70 (1.51–4.82)	<0.001
Idiopathic	52/156 (33%)	1.92 (1.32–2.80)	0.001	2.06 (1.40–3.02)	<0.001
Other	34/132 (26%)	1.33 (0.87–2.04)	0.191	1.40 (0.90–2.17)	0.134
Smoking					
Current	93/316 (29%)	1.46 (1.03–2.05)	0.032	1.12 (0.75–1.70)	0.581
Past	52/173 (30%)	1.48 (0.99–2.20)	0.055	1.39 (0.92–2.11)	0.122
Never	156/695 (22%)	1		1	
Alcohol					
Heavy users	39/114 (34%)	1.57 (1.00–2.47)	0.048	0.71 (0.36–1.40)	0.317
Excessive users	22/64 (34%)	1.60 (0.66–3.90)	0.280	0.97 (0.41–2.30)	0.939
Social users	123/536 (23%)	.90 (0.65–1.25)	0.532	0.81 (0.58–1.14)	0.231
Past	10/40 (25%)	1.08 (0.48–2.43)	0.849	0.92 (0.41–2.10)	0.848
Never	107/430 (25%)	1		1	
ASA classification					
I	47/225 (21%)	1		1	
II	123/520 (24%)	1.17 (0.80–1.72)	0.409	1.05 (0.71–1.57)	0.793
III	128/430 (30%)	1.61 (1.10–2.35)	0.015	1.22 (0.80–1.84)	0.358
IV	3/9 (33%)	1.89 (0.46–7.86)	0.379	1.72 (0.40–7.33)	0.466
CRP <48 h after admission		1.00 (1.00–1.00)	0.740		
Leukocytes <48 h after admission		1.00 (0.99–1.02)	0.919		
APACHE II score		0.98 (0.94–1.01)	0.179		
Modified Glasgow score		0.90 (0.81–1.01)	0.062		
Severity according to Atlanta					
Mild	91/351 (26%)	1.04 (0.78–1.38)	0.796		
Moderate/severe	210/833 (25%)	1			
Pancreatic necrosis					
Yes	44/177 (25%)	0.97 (0.67–1.41)	0.862		
No	257/1007 (26%)	1			
Acute (peripancreatic) fluid collection(s)					
Yes	74/309 (24%)	0.90 (0.66–1.22)	0.503		
No	227/875 (26%)	1			
Local complications[‡]					
Yes	82/332 (25%)	0.95 (0.71–1.28)	0.734		
No	219/852 (26%)	1			
Persistent organ failure					
Yes	17/82 (21%)	0.75 (0.43–1.31)	0.313		
No	284/1102 (26%)	1			
Pancreatic intervention(s) during first episode					
Yes	21/119 (18%)	0.60 (0.37–0.98)	0.042	0.55 (0.33–0.91)	0.020
No	280/1065 (26%)	1		1	
Follow-up (years)		1.04 (1.00–1.09)	0.059		

[†]BMI not imputed since data were only available in 741 patients.

[‡]Local complications: parenchymal necrosis, peripancreatic necrosis, and/or acute (peripancreatic) fluid collection(s).

QoL and pain severity. QoL was not significantly different between patient with and without progression to RAP and CP ($P > 0.05$) (Table S9). Regarding pain severity, both RAP and CP patients reported significantly higher Izbicki Pain scores ($P = 0.004$ and $P < 0.001$) compared to their controls.

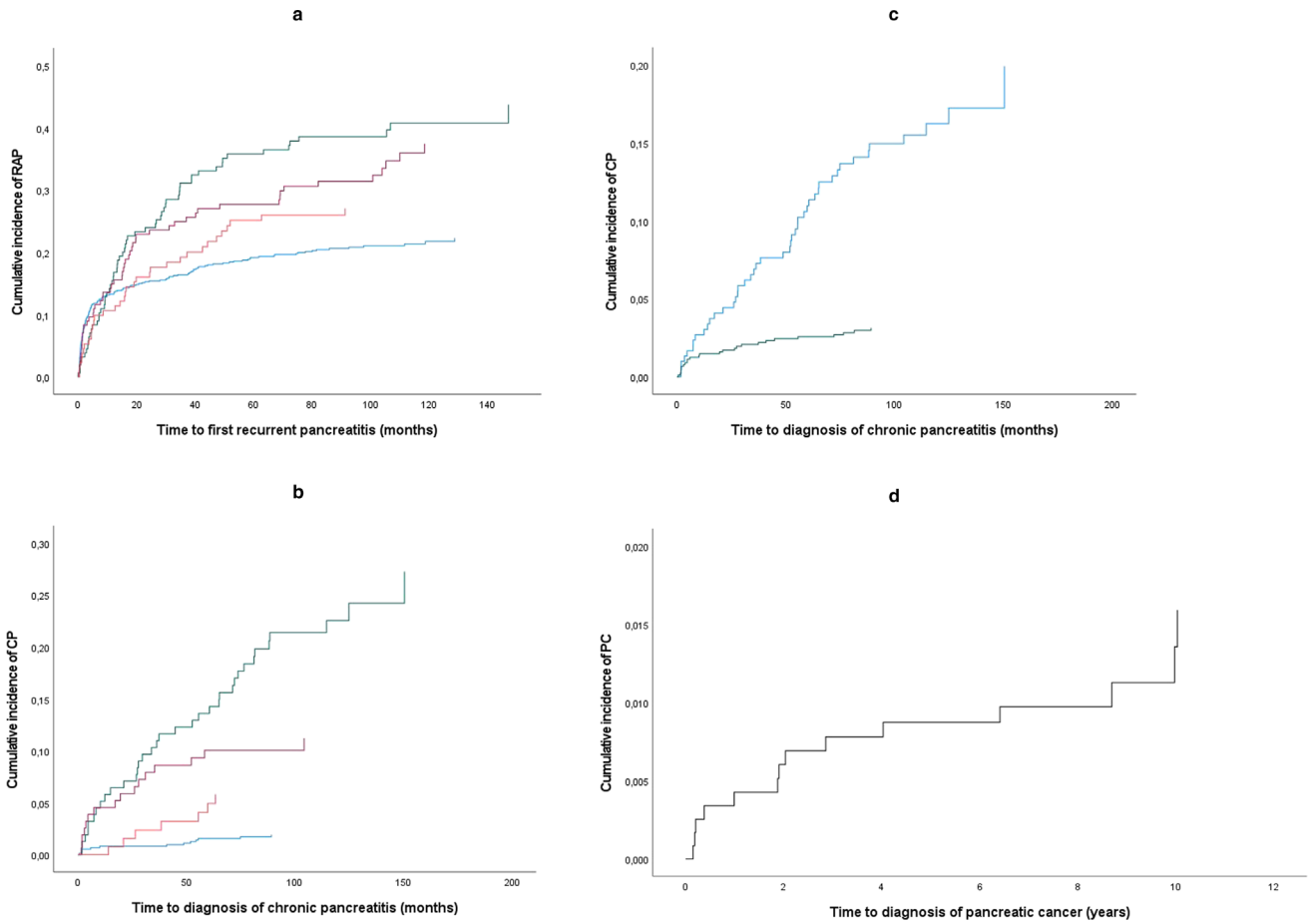

Figure 1 Cumulative incidence over time for disease progression. Cumulative incidence for (a) recurrent acute pancreatitis, (b) chronic pancreatitis when stratified by etiology, (c) chronic pancreatitis when stratified by history of recurrent acute pancreatitis, and (d) for pancreatic cancer. (a) Etiology: ⌐¬, Biliary; ⌐¬, Alcoholic; ⌐¬, Idiopathic; ⌐¬, Other. (b) Etiology: ⌐¬, Biliary; ⌐¬, Alcoholic; ⌐¬, Idiopathic; ⌐¬, Other. (c) History of recurrent pancreatitis: ⌐¬, RAP; ⌐¬, No RAP.

Discussion

This long-term clinical follow-up study showed that 25% of patients developed RAP, 6% of patients progressed to CP, and 1% of patients were diagnosed with pancreatic cancer. Median duration from index admission to RAP, CP, and pancreatic cancer was 9 months (IQR 2–34), 31 months (IQR 7–61), and 24 months (IQR 4–84), respectively. Several independent predictive factors were identified for both RAP and CP.

The reported progression rates after a first episode of AP vary widely among previous studies.[3,5,9–12] The latest meta-analysis, with a median follow-up between 18 and 180 months, reported a pooled prevalence rate of 22% for RAP and 10% for CP.[24] Some of the included studies were population-based matched cohort studies, which allow for a smaller sample size and automatically control for confounding factors by socioeconomic position.[14,15] A drawback of these studies is that the effects of matching factors on disease occurrences of interest (i.e. RAP, CP, and pancreatic cancer) could not be evaluated. Moreover, no adjustments were made for potentially confounding factors such as alcohol and smoking due to the limited data available. Therefore, the incidence of and risk factors associated with transition to these pancreatic diseases following a first episode of AP are best investigated in prospective observational cohort studies. The risk of progression after a first episode of AP has been investigated by our study group in such manner before.[3,4] In this previous study, 17% and 8% of patients developed RAP and CP, respectively.[3] Pancreatic cancer following AP was observed in 1% of patients.[4] In both previous studies, however, patients were followed up for a maximum of 5 years, which is probably too short and may have led to an underestimation of the progression rate. In the present study with a significantly longer follow-up period, 25% of patients were diagnosed with RAP, of whom 33 patients (11%) developed the first recurrent attack after more than 5 years' follow-up. This leaves us with a recurrence rate of 23% within 5 years, which is higher than our previous study, but comparable to the meta-analysis.[24] On the contrary, we found a lower incidence of CP, which can be explained by a smaller proportion of alcoholic pancreatitis patients included in the current study.[25] Furthermore, our incidence rate of pancreatic cancer was comparable to the previous study[4] but significantly higher compared to the 0.2% incidence rate of the Dutch general population between 2008 and

Table 4 Factors associated with chronic pancreatitis—univariate and multivariate analyses

Variable	*n*/*N* (%)	Univariate analyses		Multivariate analyses with RAP as covariate		Multivariate analyses without RAP as covariate	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)		0.98 (0.96–0.99)	<0.001	0.99 (0.97–1.01)	0.378	0.99 (0.97–1.01)	0.167
Gender							
Male	58/660 (8%)	3.51 (1.94–6.37)	<0.001	2.06 (1.05–4.05)	0.035	1.98 (1.02–3.83)	0.044
Female	14/524 (3%)	1		1		1	
BMI[†]		0.86 (0.80–0.92)	<0.001				
Etiology							
Biliary	13/740 (2%)	1		1		1	
Alcoholic	35/156 (22%)	16.18 (8.32–31.46)	<0.001	5.24 (1.94–14.16)	0.001	6.51 (2.47–17.22)	<0.001
Idiopathic	16/156 (10%)	6.39 (3.01–13.58)	<0.001	4.57 (2.05–10.16)	<0.001	5.53 (2.53–12.10)	<0.001
Other	8/132 (6%)	3.61 (1.47–8.88)	0.005	2.97 (1.11–7.94)	0.030	3.06 (1.18–7.98)	0.022
Smoking							
Current	41/316 (13%)	5.02 (2.83–8.88)	<0.001	2.33 (1.14–4.78)	0.021	2.29 (1.17–4.48)	0.016
Past	11/173 (6%)	2.34 (1.09–5.03)	0.030	1.96 (.84–4.61)	0.122	1.93 (.83–4.49)	0.125
Never	20/695 (3%)	1		1		1	
Alcohol							
Heavy users	22/114 (19%)	11.74 (5.11–26.96)	<0.001	2.19 (0.67–7.10)	0.193	1.95 (0.62–6.11)	0.251
Excessive users	10/64 (16%)	9.43 (3.24–27.42)	<0.001	3.12 (0.90–10.86)	0.074	2.91 (0.85–9.98)	0.088
Social users	28/536 (5%)	2.73 (1.23–6.05)	0.014	1.76 (0.75–4.14)	0.195	1.69 (0.72–3.95)	0.227
Past	3/40 (8%)	4.03 (1.02–15.90)	0.046	2.33 (0.50–10.98)	0.284	2.80 (0.63–12.35)	0.175
Never	9/430 (2%)	1		1		1	
ASA classification							
I	10/225 (4%)	1		1		1	
II	22/520 (4%)	0.95 (0.44–2.04)	0.895	0.71 (0.29–1.74)	0.450	0.76 (0.32–1.83)	0.544
III	40/430 (9%)	2.21 (1.08–4.50)	0.030	0.79 (0.29–2.13)	0.644	0.88 (0.33–2.30)	0.786
IV	0/9 (0%)	0.00 (0.00–)	0.999	0.00 (0.00–)	0.999	0.00 (0.00–)	0.999
CRP <48 h after admission		1.00 (1.00–1.00)	0.038	1.00 (1.00–1.00)	0.786	1.00 (1.00–1.00)	0.792
Leukocytes <48 h after admission		1.01 (0.99–1.03)	0.433				
APACHE II score		0.99 (0.92–1.05)	0.661				
Modified Glasgow score		0.91 (0.74–1.11)	0.336				
Severity according to ATLANTA							
Mild	45/833 (5%)	1					
Moderate/severe	27/351 (8%)	1.46 (0.89–2.39)	0.134				
Pancreatic necrosis							
Yes	17/177 (10%)	1.84 (1.04–3.26)	0.036	0.88 (0.36–2.19)	0.788	1.07 (0.44–2.62)	0.882
No	55/1007 (5%)	1		1		1	
Acute (peri-)pancreatic fluid collection(s)							
Yes	26/309 (8%)	1.66 (1.01–2.74)	0.048	1.10 (0.51–2.37)	0.802	0.96 (0.46–2.01)	0.905
No	46/875 (5%)	1		1		1	
Local complications[‡]							

(Continues)

Table 4 (Continued)

Variable	*n*/*N* (%)	Univariate analyses		Multivariate analyses with RAP as covariate		Multivariate analyses without RAP as covariate	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Yes	26/332 (8%)	1.49 (0.91–2.46)	0.117				
No	46/852 (5%)	1					
Persistent organ failure							
Yes	6/82 (7%)	1.24 (0.52–2.95)	0.628				
No	66/1102 (6%)	1					
Pancreatic intervention during first episode							
Yes	14/119 (12%)	2.32 (1.25–4.29)	0.008	3.10 (1.20–8.02)	0.020	2.13 (0.85–5.33)	0.108
No	58/1065 (5%)	1		1		1	
Recurrent acute pancreatitis						Not included	
Yes	45/301 (15%)	5.57 (3.39–9.16)	<0.001	4.93 (2.84–8.58)	<0.001		
No	27/883 (3%)	1		1			
Follow-up (years)		1.06 (0.98–1.16)	0.143				

†BMI not imputed since data were only available in 741 patients.
‡Local complications: parenchymal necrosis, peripancreatic necrosis, and/or acute (peripancreatic) fluid collection(s).

2011.[26] When introducing a lag period of 2 and 5 years, as proposed by previous studies to avoid misdiagnosis of pancreatic cancer as AP,[14,27] our incidence rate was still three and two times higher (0.6% and 0.4%, respectively). In our study, 50% of the pancreatic cancer patients (n = 7) were diagnosed within 2 years after the first pancreatic episode, of whom four were idiopathic pancreatitis patients, indicating a possible diagnostic delay. This may raise the question whether follow-up imaging would allow for an earlier diagnosis in idiopathic pancreatitis patients. As follow-up imaging has previously been proposed for these patients to further investigate etiology and identify the need of a cholecystectomy, screening for pancreatic cancer may be another indication.[28,29]

Several important findings emerged from our data when examining risk factors for disease transition. Consistent with other studies, the highest cumulative incidence of RAP and CP was observed among alcoholic pancreatitis patients.[10,11] Alcoholic pancreatitis was an independent risk factor for both RAP and CP, which resulted in a three and five times higher risk compared with biliary pancreatitis. Independent preventive factors for RAP in biliary patients were an ERCP and cholecystectomy prior to or ≤3 months after onset of AP. As shown in other studies,[30,31] our results emphasize once again the importance of these preventive measures. Although these interventions are already standard of practice for biliary pancreatitis, the timing of an ERCP and cholecystectomy can be challenging, especially in severe AP patients. With respect to ERCP, a conservative treatment strategy is opted for patients without cholangitis or persistent choledocholithiasis. However, in the case of patients who are considered unfit for surgery, an ERCP with sphincterotomy should be considered to reduce the risk of recurrent biliary events.[30] In patients fit for surgery, a cholecystectomy should preferably be performed during index admission in mild pancreatitis patients and within 8 weeks in severe pancreatitis patients in the absence of peripancreatic collections.[32] In our cohort of biliary patients, no significant difference in recurrence rate was observed between patients who underwent ERCP within 3 months after AP and patients in whom ERCP was not performed. However, confounding by indication may have played a role, as ERCP is only indicated in cases of proven choledocholithiasis. In the long term, not all of these patients need to undergo ERCP. However, in the case of choledocholithiasis, our results show that ERCP should preferably be performed <3 months after hospitalization. For cholecystectomy, the protective effect is negligible compared to no cholecystectomy if performed >3 months after the onset of AP. Therefore, to significantly reduce the risk of recurrent gallstone-related complications, cholecystectomy should ideally be performed in all patients with biliary pancreatitis within 3 months after the first episode of AP. Our study shows that there is significant room for improvement in the follow-up of patients with biliary pancreatitis, as cholecystectomy was not performed in one quarter of the patients. Furthermore, we have demonstrated that patients with biliary pancreatitis have the lowest risk of developing CP if the causative factor is appropriately treated.

Interestingly, the risk of RAP was lower in patients who underwent pancreatic interventions during the index episode, but at the expense of a higher risk of developing CP. A possible explanation for this latter being that pancreatic interventions might be prone for causing permanent pancreatic damage and consequently

accelerating chronic inflammation. Confounding by indication could also play a role here as pancreatic interventions are more frequently performed in patients with moderate/severe pancreatitis; in our population, however, disease severity and complications proved not to be associated with disease progression. Furthermore, a recent study showed that one in four necrotizing pancreatitis patients suffer from a disconnected pancreatic duct, which is associated with higher risk of RAP if not treated accordingly.[33] This partly explains the higher risk of RAP for patients not undergoing endoscopic drainage with long-term indwelling of double-pigtail plastic stents. Previous studies on factors associated with disease progression yielded conflicting results for pancreatic necrosis and disease severity.[3,8,24] In this study, disease severity and complications were no determinants of disease progression, which is consistent with the most-recent meta-analysis.[24] To further explore the impact of pancreatic necrosis on progression rate, we have performed additional regression analyses for disease severity and complications within the subgroup of patients with predicted severe pancreatitis, which failed to detect any relevant statistically differences (data not shown). For CP, other independent risk factors than those previously mentioned, were male sex, smoking, and RAP, which is in line with previous studies.[3,25] In the majority of patients, CP was preceded by RAP (63%). Post hoc risk analyses for the impact of lifestyle modifications showed that alcohol cessation significantly reduced the risk of RAP in patients with alcoholic pancreatitis, which was not the case for CP. Associations between smoking cessation and a reduced risk of RAP and CP were also not found. This was presumably due to limited data available on current smoking and alcohol use. Their impact on disease progression may therefore be underestimated. Both smoking and alcohol have, however, previously been identified as important independent risk factors for disease progression and related complications. Therefore, counseling for alcohol and smoking cessation should be standard of follow-up care.[34–37] In our study population, disease progression was not significantly associated with a lower QoL.

This study evaluated the likelihood of developing pancreatic diseases following AP after a median follow up of more than 9 years in a prospective cohort of 1184 patients and therefore provides a more in-depth insight compared to previous studies. Additionally, our study suggests that preventive measures for disease progression are not sufficiently implemented in current practice, which should become a point of attention in future care.

This study has some limitations. First, follow-up data were retrospectively collected, which may have led to information bias. Second, data on current smoking and alcohol consumption were only provided by a limited number of patients. Third, our ability to explore the relation between CP and pancreatic cancer was limited due to a small subset of CP patients.[37] Finally, we have pragmatically chosen a cutoff of 3 months between the first presentation of acute biliary pancreatitis and the performance of biliary procedures, as logistics (i.e. waiting lists) often delay these procedures. Although we acknowledge that this is longer than the recommendations based on the existing literature, we believe that the use of this interval more accurately reflects current clinical practice.[38]

In conclusion, one in four patients with AP will develop RAP, CP, or pancreatic cancer after a first episode of AP. We identified several risk factors that may be helpful to devise personalized strategies, such as lifestyle counseling, biliary interventions, or more intense follow-up for those at risk for disease progression. Our findings should encourage physicians to improve preventive interventions and follow-up care for those patients at risk for pancreatic disease progression.

Data availability statement. Data are available upon reasonable request from the corresponding author.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.