Acute pancreatitis: from treatment to prevention

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PART III

Prevention of recurrent acute pancreatitis

CHAPTER 6

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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ABSTRACT

Background and objective: 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, 1,184 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.

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 (DPSG) (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 Supplementary Appendix. 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 enrollment 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 counselling) 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, 1,377 patients were prospectively registered of whom 1,184 were included in this long-term follow-up study (Figure 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%).

Table 1. Patient and disease characteristics in 1,184 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		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 hours after admission, median (P25 – P75)	1176	162 (73 – 287)	
Leukocytes < 48 hours after admission, median (P25 – P75)	1178	15 (11 – 19)	
APACHE-score < 48 hours after admission, median (P25 – P75)	1172	7 (4 – 9)	
IMRIE score < 48 hours 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)
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)	

Table 1. Patient and disease characteristics in 1,184 patients with a first episode of acute pancreatitis (*continued*)

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)
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. Abbreviations: ASA American Society of Anesthesiologists, ERCP endoscopic retrograde cholangiopancreatography.*

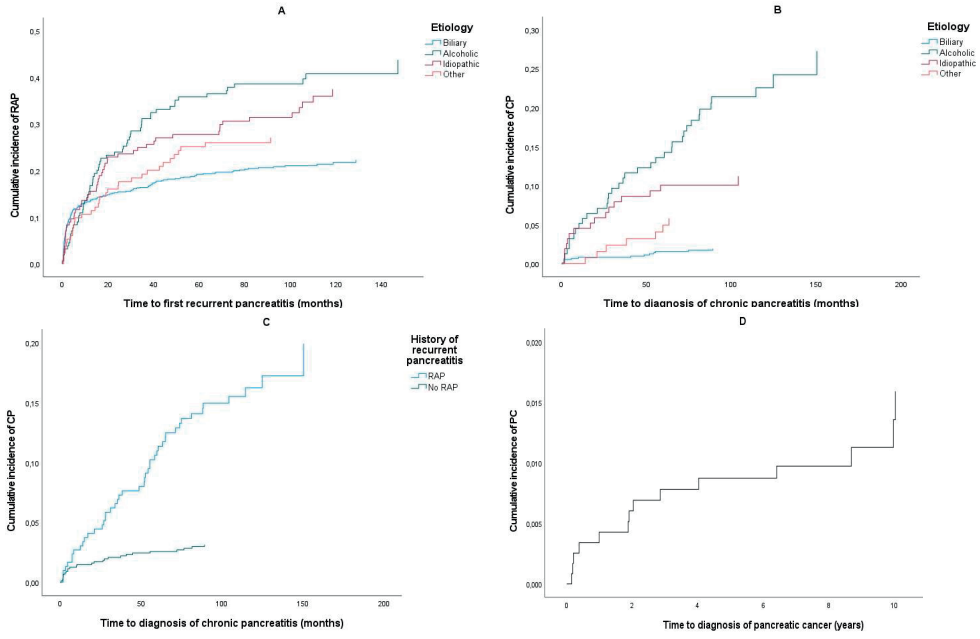
Table 2. Primary and secondary study endpoints of 1,184 patients with a first episode of acute pancreatitis

	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).*

Recurrent acute pancreatitis

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%) (Figure 1A).



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.

Figure 1. Cumulative incidence over time for disease progression.

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

		Univariate analyses		Multivariate analyses	
Variable	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)		1.00 (.99 – 1.00)	.341		
Gender					
Male	178/660 (27%)	1.20 (.92 – 1.57)	.170		
Female	123/524 (23%)	1			
BMI*		.97 (.94 – 1.00)	.074		
Etiology					
Biliary	153/740 (21%)	1		1	
Alcoholic	62/156 (40%)	2.53 (1.75 – 3.65)	<.001	2.70 (1.51 – 4.82)	<.001
Idiopathic	52/156 (33%)	1.92 (1.32 – 2.80)	.001	2.06 (1.40 – 3.02)	<.001
Other	34/132 (26%)	1.33 (.87 – 2.04)	.191	1.40 (.90 – 2.17)	.134
Smoking					
Current	93/316 (29%)	1.46 (1.03 – 2.05)	.032	1.12 (.75 – 1.70)	.581
Past	52/173 (30%)	1.48 (.99 – 2.20)	.055	1.39 (.92 – 2.11)	.122
Never	156/695 (22%)	1		1	
Alcohol					
Heavy users	39/114 (34%)	1.57 (1.00 – 2.47)	.048	.71 (.36 – 1.40)	.317
Excessive users	22/64 (34%)	1.60 (.66 – 3.90)	.280	.97 (.41 – 2.30)	.939
Social users	123/536 (23%)	.90 (.65 – 1.25)	.532	.81 (.58 – 1.14)	.231
Past	10/40 (25%)	1.08 (.48 – 2.43)	.849	.92 (.41 – 2.10)	.848
Never	107/430 (25%)	1		1	
ASA-classification					
I	47/225 (21%)	1		1	
II	123/520 (24%)	1.17 (.80 – 1.72)	.409	1.05 (.71 – 1.57)	.793

III	128/430 (30%)	1.61 (1.10 – 2.35)	.015	1.22 (.80 – 1.84)	.358
IV	3/9 (33%)	1.89 (.46– 7.86)	.379	1.72 (.40 – 7.33)	.466
CRP < 48 hours after admission		1.00 (1.00 – 1.00)	.740		
Leukocytes < 48 hours after admission		1.00 (.99 – 1.02)	.919		
APACHE II score		.98 (.94 – 1.01)	.179		
Modified Glasgow score		.90 (.81 – 1.01)	.062		
Severity according to Atlanta					
Mild	91/351 (26%)	1.04 (.78 – 1.38)	.796		
Moderate/severe	210/833 (25%)	1			
Pancreatic necrosis					
Yes	44/177 (25%)	.97 (.67 – 1.41)	.862		
No	257/1007 (26%)	1			
Acute (peripancreatic) fluid collection(s)					
Yes	74/309 (24%)	.90 (.66 – 1.22)	.503		
No	227/875 (26%)	1			
Local complications[a]					
Yes	82/332 (25%)	.95 (.71 – 1.28)	.734		
No	219/852 (26%)	1			
Persistent organ failure					
Yes	17/82 (21%)	.75 (.43 – 1.31)	.313		
No	284/1102 (26%)	1			
Pancreatic intervention(s) during first episode					
Yes	21/119 (18%)	.60 (.37 – .98)	.042	.55 (.33 – .91)	.020
No	280/1065 (26%)	1		1	
Follow-up (years)		1.04 (1.00 – 1.09)	.059		

**BMI not imputed as data were only available in 741 patients. aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).*

Table 4. Factors associated with chronic pancreatitis – univariate and multivariate analyses

	Univariate analyses			Multivariate analyses with RAP as covariate		Multivariate analyses without RAP as covariate	
Variable	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)		.98 (.96 – .99)	<.001	.99 (.97 – 1.01)	.378	.99 (.97 – 1.01)	.167
Gender							
Male	58/660 (8%)	3.51 (1.94 – 6.37)	<.001	2.06 (1.05 – 4.05)	.035	1.98 (1.02 – 3.83)	.044
Female	14/524 (3%)	1		1		1	
BMI*		.86 (.80 – .92)	<.001				
Etiology							
Biliary	13/740 (2%)	1		1		1	
Alcoholic	35/156 (22%)	16.18 (8.32 – 31.46)	<.001	5.24 (1.94 – 14.16)	.001	6.51 (2.47 – 17.22)	<.001
Idiopathic	16/156 (10%)	6.39 (3.01 – 13.58)	<.001	4.57 (2.05 – 10.16)	<.001	5.53 (2.53 – 12.10)	<.001
Other	8/132 (6%)	3.61 (1.47 – 8.88)	.005	2.97 (1.11 – 7.94)	.030	3.06 (1.18 – 7.98)	.022
Smoking							
Current	41/316 (13%)	5.02 (2.83 – 8.88)	<.001	2.33 (1.14 – 4.78)	.021	2.29 (1.17 – 4.48)	.016
Past	11/173 (6%)	2.34 (1.09 – 5.03)	.030	1.96 (.84 – 4.61)	.122	1.93 (.83 – 4.49)	.125
Never	20/695 (3%)	1		1		1	
Alcohol							
Heavy users	22/114 (19%)	11.74 (5.11 – 26.96)	<.001	2.19 (.67 – 7.10)	.193	1.95 (.62 – 6.11)	.251
Excessive users	10/64 (16%)	9.43 (3.24 – 27.42)	<.001	3.12 (.90 – 10.86)	.074	2.91 (.85 – 9.98)	.088
Social users	28/536 (5%)	2.73 (1.23 – 6.05)	.014	1.76 (.75 – 4.14)	.195	1.69 (.72 – 3.95)	.227
Past	3/40 (8%)	4.03 (1.02 – 15.90)	.046	2.33 (.50 – 10.98)	.284	2.80 (.63 – 12.35)	.175
Never	9/430 (2%)	1		1		1	
ASA-classification							
I	10/225 (4%)	1		1		1	
II	22/520 (4%)	.95 (.44 – 2.04)	.895	.71 (.29 – 1.74)	.450	.76 (.32 – 1.83)	.544
III	40/430 (9%)	2.21 (1.08 – 4.50)	.030	.79 (.29 – 2.13)	.644	.88 (.33 – 2.30)	.786

IV	0/9 (0%)	.00 (.00 –)	.999	.00 (.00 –)	.999	.00 (.00 –)	.999
CRP < 48 hours after admission		1.00 (1.00 – 1.00)	.038	1.00 (1.00 – 1.00)	.786	1.00 (1.00 – 1.00)	.792
Leukocytes < 48 hours after admission		1.01 (.99 – 1.03)	.433				
APACHE II score		.99 (.92 – 1.05)	.661				
Modified Glasgow score		.91 (.74 – 1.11)	.336				
Severity according to Atlanta							
Mild	45/833 (5%)	1					
Moderate/severe	27/351 (8%)	1.46 (.89 – 2.39)	.134				
Pancreatic necrosis							
Yes	17/177 (10%)	1.84 (1.04 – 3.26)	.036	.88 (.36 – 2.19)	.788	1.07 (.44 – 2.62)	.882
No	55/1007 (5%)	1		1		1	
Acute (peri-)pancreatic fluid collection(s)							
Yes	26/309 (8%)	1.66 (1.01 – 2.74)	.048	1.10 (.51 – 2.37)	.802	.96 (.46 – 2.01)	.905
No	46/875 (5%)	1		1		1	
Local complications[a]							
Yes	26/332 (8%)	1.49 (.91 – 2.46)	.117				
No	46/852 (5%)	1					
Persistent organ failure							
Yes	6/82 (7%)	1.24 (.52 – 2.95)	.628				
No	66/1102 (6%)	1					
Pancreatic intervention during first episode							
Yes	14/119 (12%)	2.32 (1.25 – 4.29)	.008	3.10 (1.20 – 8.02)	.020	2.13 (.85 – 5.33)	.108
No	58/1065 (5%)	1		1		1	
Recurrent acute pancreatitis						*Not included*	
Yes	45/301 (15%)	5.57 (3.39 – 9.16)	<.001	4.93 (2.84 – 8.58)	<.001		
No	27/883 (3%)	1		1			
Follow-up (years)		1.06 (.98 – 1.16)	.143				

**BMI not imputed as data were only available in 741 patients. aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).*

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 Supplementary Appendix (Figure 2A and 2B). 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<.001), but not significantly different from those in whom no ERCP was performed (P=.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 versus continued smoking (Table S4) and between patients who stopped drinking alcohol versus 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=.043) (Table S5B).

Chronic pancreatitis

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 (Figure 1B and 1C).

Subgroup analyses for smoking and alcohol

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

Pancreatic cancer

The number of patients who developed pancreatic cancer was insufficient to perform multivariate analysis. Of the 14 patients who developed pancreatic cancer, 7 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-years lag period, 5 patients

remained of whom 1 patient with idiopathic AP. Pancreatic cancer was preceded by RAP in 6 patients (43%) of whom 1 patient was also diagnosed with CP (Figure 1D).

Quality of life and pain severity

QoL was not significantly different between patient with and without progression to RAP and CP (p>.05) (Table S9). Regarding pain severity, both RAP and CP patients reported significantly higher Izbicki Pain scores (P=.004 and p<.001) compared to their controls.

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 18-180 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 adjustment 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 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 4 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 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, counselling 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 1,184 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 cut-off 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).

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 counselling, 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.

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Supplementary file S1. Diagnostic criteria for the different etiologies

Alcoholic etiology
>3 units/day or >4 units 48hrs prior to the start of acute pancreatitis, in absence of gallstones and/or CBD dilatation

Biliary etiology
In the case of one of the following criteria
1. Gallstones and/or sludge diagnosed on imaging (transabdominal or endoscopic ultrasound or computed tomography);
2. A dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old);
3. Alanine aminotransferase (ALAT) level >2 times higher than normal values

And in the absence of alcohol abuse or evidence of other etiology (high risk medication/genetic factors etc.)

Hypertriglyceridemia as etiology
Fasting serum triglyceride >1000 mg/dl (11.2 mmol/l), in absence of criteria for a biliary etiology

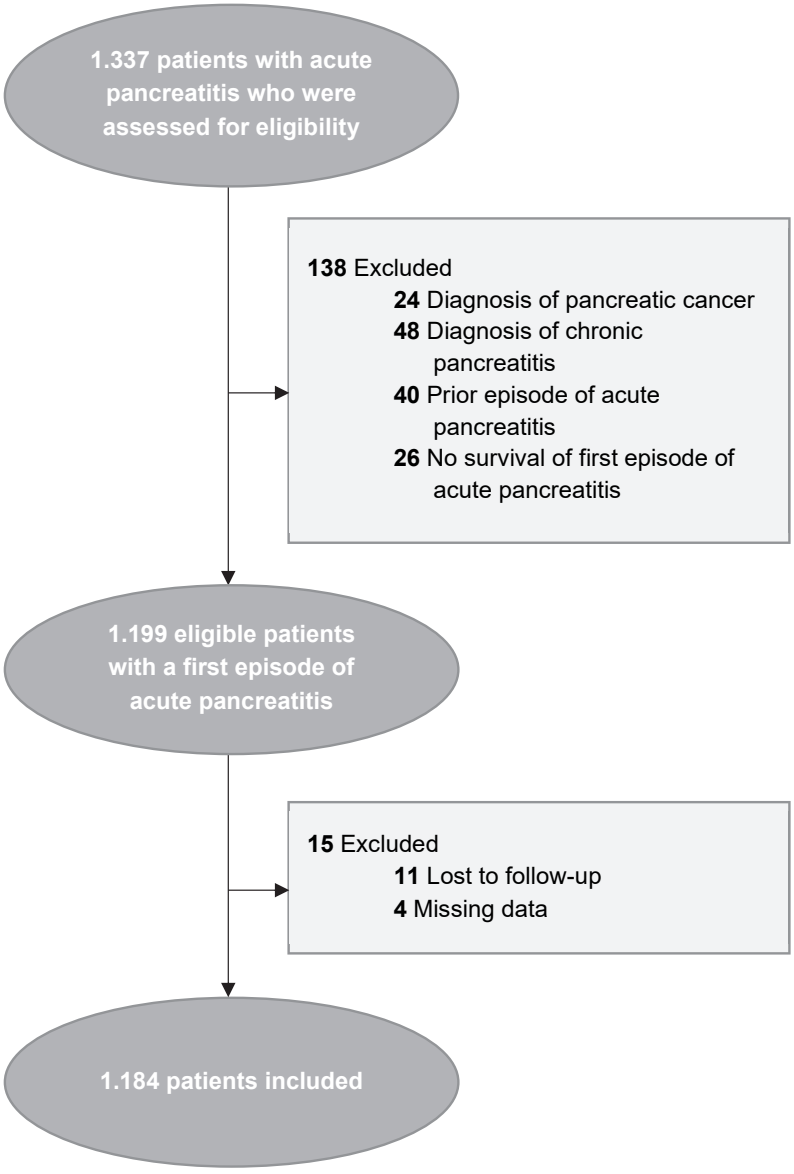
Hypercalcemia as etiology
Serum calcium >12 mg/dl or 3 mmol/l, in absence of criteria for a biliary etiology

Post-ERCP as etiology (Coton criteria, 4 of 4)
(1) Upper abdominal pain;
(2) Serum lipase or amylase levels above three times the upper level of normal;
(3) Timeframe: 24hrs after ERCP
(4) At least 2 days of hospitalization after ERCP

Medication as etiology
Use of 1 or more drugs with a known association with AP, in absence of criteria for a biliary etiology. Definite association: Acetaminophen, asparaginase, azathioprine, bortezomib, capecitabine, carbamazepine, cimetidine, cisplatin, cytarabine, didanosine, enalapril, erythromycin, oestrogens, furosemide, hydrochlorothiazide, i erferon alfa, itraconazole, lamivudine, mercaptopurine, mesalazine, olsalazine, methyldopa, metronidazole, octreotide, olanzapine, opiates, oxyphenbutazone, pentamidine, pentavalent antimony compounds, phenformin, simvastatin, steroids, sulfasalazine, co-trimoxazole

Idiopathic etiology

Patients lacking any of the above-mentioned criteria and with no recent history of surgery/abdominal trauma of any evidence of familial/genetic cause of pancreatitis were classified as idiopathic



Supplementary figure S1. Flowchart patient inclusion

Supplementary table S1. Factors associated with recurrent acute pancreatitis – univariate and multivariate analyses (original dataset)

			Univariate analyses		Multivariate analyses (n = 1009)	
Variable	**N**	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)	1184		1.00 (.99 – 1.00)	.341		
Gender	1184					
Male		178/660 (27%)	1.20 (.92 – 1.57)	.170		
Female		123/524 (23%)	1			
BMI*	741		.97 (.94 – 1.00)	.074		
Etiology	1184			<.001		<.001
Biliary		153/740 (21%)	1		1	
Alcoholic		62/156 (40%)	2.53 (1.75 – 3.65)	<.001	2.50 (1.38 – 4.54)	.003
Idiopathic		52/156 (33%)	1.92 (1.32 – 2.80)	.001	2.23 (1.48 – 3.36)	<.001
Other		34/132 (26%)	1.33 (.87 – 2.04)	.191	1.71 (1.08 – 2.70)	.022
Smoking	1029			.018		.284
Current		87/276 (32%)	1.53 (1.12 – 2.11)	.008	1.20 (.84 – 1.72)	.312
Past		45/151 (30%)	1.41 (.95 – 2.10)	.087	1.37 (.90 – 2.09)	.142
Never		139/602 (23%)	1		1	
Alcohol	1066			.018		.550
Heavy users		39/112 (35%)	1.51 (.96 – 2.37)	.075	.76 (.39 – 1.50)	.432
Excessive users		21/49 (43%)	2.12 (1.15 – 3.89)	.016	1.08 (.50 – 2.31)	.853
Social users		117/488 (24%)	.89 (.65 – 1.21)	.456	.79 (.57 – 1.09)	.151
Past		10/35 (29%)	1.13 (.52 – 2.43)	.759	1.04 (.47 – 2.32)	.918
Never		100/382 (26%)	1		1	
ASA-classification	1184			.050		.962
I		47/225 (21%)	1		1	

II		123/520 (24%)	1.17 (.80 – 1.72)	.409	.97 (.64 – 1.47)	.881
III		128/430 (30%)	1.61 (1.10 – 2.35)	.015	1.06 (.68 – 1.66)	.788
IV		3/9 (33%)	1.89 (.46– 7.86)	.379	1.07 (.19 – 5.88)	.942
CRP < 48 hours after admission	1176		1.00 (1.00 – 1.00)	.653		
Leukocytes < 48 hours after admission	1178		1.00 (.99 – 1.02)	.867		
APACHE II score	1172		.98 (.94 – 1.01)	.227		
Modified Glasgow score	1173		.91 (.82 – 1.01)	.088		
Severity according to Atlanta	1184					
Mild		91/351 (26%)	1.04 (.78 – 1.38)	.796		
Moderate/severe		210/833 (25%)	1			
Pancreatic necrosis	1174					
Yes		44/173 (25%)	.99 (.69 – 1.44)	.969		
No		256/1001 (26%)	1			
Acute (peripancreatic) fluid collection(s)	1176					
Yes		74/305 (24%)	.91 (.67 – 1.23)	.535		
No		227/871 (26%)	1			
Local complications[a]	1176					
Yes		82/326 (25%)	.97 (.72 – 1.30)	.830		
No		219/850 (26%)	1			
Persistent organ failure	1184					
Yes		17/82 (21%)	.75 (.43 – 1.31)	.313		
No		284/1102 (26%)	1			
Pancreatic intervention(s) during first episode	1184					
Yes		21/119 (18%)	.60 (.37 – .98)	.042	.52 (.31 – .89)	.017
No		280/1065 (26%)	1		1	
Follow-up (years)	1184		1.04 (1.00 – 1.09)	.059		

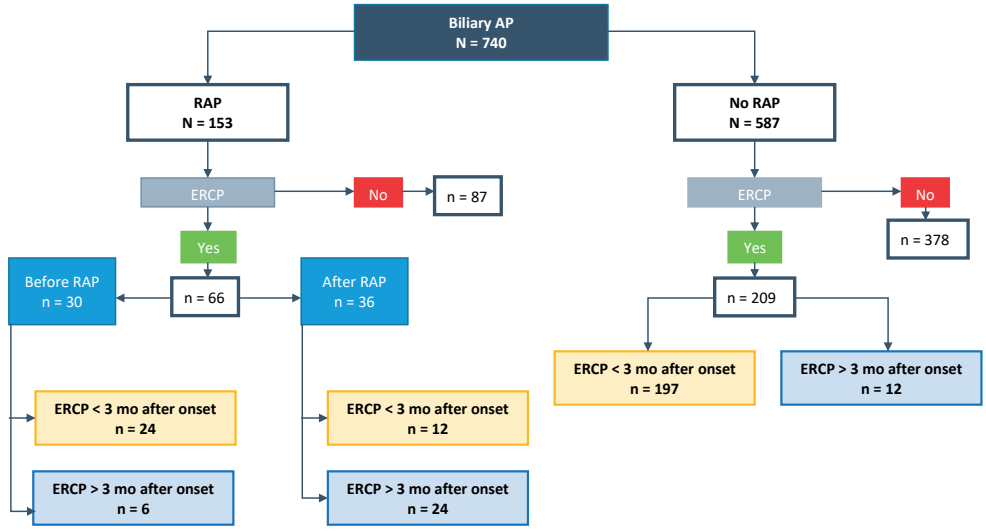
aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).

Supplementary table S2. Factors associated with recurrent acute pancreatitis in biliary pancreatitis patients – univariate and multivariate analyses (imputed dataset)

		Univariate analyses			Multivariate analyses (n = 740)	
Variable	**N**	**n/N (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years)	740		1.01 (1.00 – 1.02)	.220		
Gender	740					
Male		77/367 (21%)	1.04 (.73 – 1.48)	.839		
Female		76/373 (20%)	1			
BMI	479		.99 (.95 – 1.03)	.693		
Smoking	740					
Current		28/137 (20%)	1.09 (.62 – 1.93)	.758	1.06 (.58 – 1.91)	.854
Past		34/113 (30%)	1.83 (1.11– 3.03)	.018	1.63 (.94 – 2.82)	.083
Never		92/490 (19%)	1		1	
Alcohol	740					
Heavy users		2/13 (15%)	.58 (.12 – 2.71)	.486		
Excessive users		8/28 (29%)	1.47 (.25 – 8.57)	.633		
Social users		65/355 (18%)	.73 (.47 – 1.12)	.149		
Past		5/31 (16%)	.64 (.23 – 1.78)	.389	.	
Never		73/313 (23%)	1			
ASA-classification	740					
I		33/173 (19%)	1			
II		60/333 (18%)	.93 (.58 – 1.49)	.771		
III		57/228 (25%)	1.41 (.87 – 2.29)	.160		
IV		3/6 (50%)	4.24 (.82– 21.97)	.085		
CRP < 48 hours after admission	740		1.00 (1.00 – 1.00)	.613		
Leukocytes < 48 hours after admission	740		1.00 (.99 – 1.02)	.683		
APACHE II score	740		1.01 (.96 – 1.05)	.794		

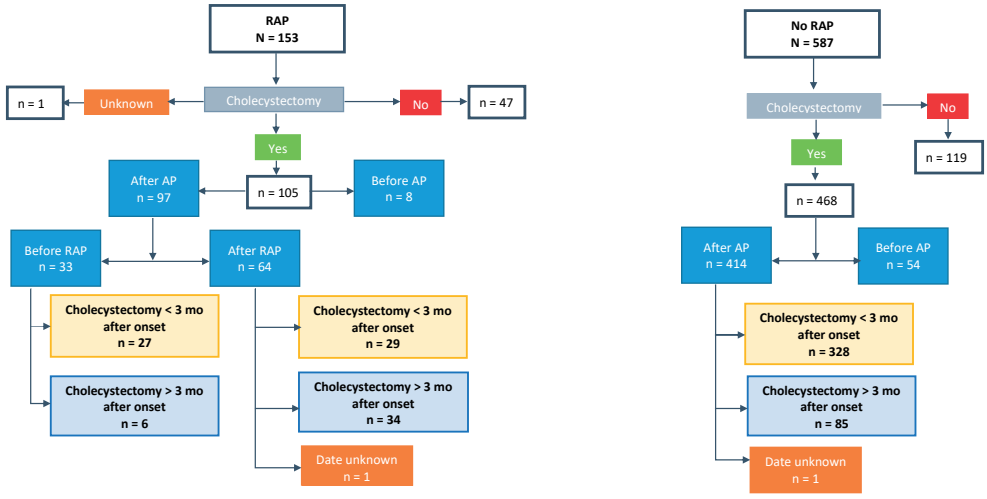
Modified Glasgow score	740		1.01 (.87 – 1.16)	.926		
Severity according to Atlanta	740					
Mild		116/574 (20%)	.88 (.58 – 1.34)	.560		
Moderate/severe		37/166 (22%)	1			
Pancreatic necrosis	740					
Yes		16/84 (19%)	.89 (.50 – 1.60)	.694		
No		137/656 (21%)	1			
Acute (peripancreatic) fluid collection(s)	740					
Yes		28/142 (20%)	.93 (.59 – 1.48)	.771		
No		125/598 (21%)	1			
Local complications[a]	740					
Yes		31/152 (20%)	.98 (.63 – 1.53)	.939		
No		122/588 (21%)	1			
Persistent organ failure	740					
Yes		8/38 (21%)	1.02 (.46 – 2.28)	.953		
No		145/702 (21%)	1			
Pancreatic intervention(s) during first episode	740					
Yes		11/53 (21%)	1.01 (.51 – 2.00)	.988		
No		142/687 (21%)	1			
ERCP ≤ 3 months after onset AP (and before RAP)	740					
Yes		24/221 (11%)	.37 (.23 – .59)	<.001	.37 (.23 – .61)	<.001
No		129/519 (25%)	1		1	
Cholecystectomy prior to or ≤ 3 months after onset of AP (and before RAP)	740					
Yes		35/418 (8%)	.16 (.11 – .24)	<.001	.16 (.11 – .25)	<.001
No		118/322 (37%)	1		1	
Follow-up (years)	740		.99 (.93 – 1.05)	.735		

aLocal complications: parenchymal necrosis, peripancreatic necrosis and/or acute (peripancreatic) fluid collection(s).



Supplementary figure 2A. Preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence – ERCP

Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, ERCP endoscopic retrograde cholangio-pancreatography, mo months



Supplementary figure 2B. Preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence – cholecystectomy

Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, mo months

Supplementary table S3A. Subgroup analysis of preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence - ERCP

	Total (n=740)	**No ERCP (n=465)**	**ERCP < 3 mo after AP (n=233)**	**ERCP > 3 mo after AP (n=42)**	**A vs B**	**A vs C**	**B vs C**
No RAP	587 (79%)	378 (81%)	197 (85%)	12 (29%)	P = .287	P < .001	P < .001
RAP	153 (21%)	87 (19%)	36 (15%)	30 (71%)			
RAP before ERCP	N/A	N/A	12 (5%)	24 (57%)			
RAP after ERCP	N/A	N/A	24 (10%)	6 (14%)			

Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, ERCP endoscopic retrograde cholangiopancreatography, mo months.

Supplementary table S3B. Subgroup analysis of preventive measures taken in biliary pancreatitis patients to reduce the risk of recurrence - cholecystectomy

	Total (n=737)*	**No cholx (n=166)**	**Cholx before or < 3 mo after AP (n=446)**	**Cholx > 3 mo after AP (n=125)**	**A vs B**	**A vs C**	**B vs C**
No RAP	586 (80%)	119 (72%)	382 (86%)	85 (68%)	P < .001	P = .548	P < .001
RAP	151 (20%)	48 (28%)	64 (14%)	40 (32%)			
RAP before cholx	N/A	N/A	29 (7%)	34 (27%)			
RAP after cholx	N/A	N/A	35 (8%)**	6 (5%)			

**Data on cholecystectomy were missing for 3 patients. **Including 8 patients who underwent cholecystectomy prior to their first episode of acute pancreatitis. Abbreviations: AP acute pancreatitis, RAP recurrent acute pancreatitis, cholx cholecystectomy, mo months.*

Supplementary table S4. Subgroup analysis of the effect of smoking on progression to recurrent pancreatitis*

	No RAP	**RAP**	**Total**
Patients who quit smoking	14 (88%)	2 (13%)	16
Patients who continued smoking	15 (58%)	11 (42%)	26
Total	29 (69%)	13 (31%)	42
P = .084			

**Data on smoking were available in 15% (42/276) of the patients who reported current smoking at inclusion.*

Supplementary table S5A. Subgroup analysis of the effect of alcohol consumption on progression to recurrent pancreatitis*

	No RAP	RAP	Total
Alcohol cessation	38 (84%)	7 (16%)	45
No alcohol cessation	102 (76%)	32 (24%)	134
Total	140 (78%)	39 (22%)	179
P = .242			

**Data on alcohol consumption were available in 28% (179/649) of the patients who reported alcohol consumption at inclusion.*

Supplementary table S5B. Subgroup analysis of the effect of alcohol consumption on progression to recurrent pancreatitis stratified for alcoholic etiology

		No RAP	RAP	Total
Alcoholic AP P = .043	Alcohol cessation	8 (89%)	1 (11%)	9
	No alcohol cessation	9 (45%)	11 (55%)	20
	Total	17 (59%)	12 (41%)	29
Non-alcoholic AP P = 1.000	Alcohol cessation	30 (83%)	6 (17%)	36
	No alcohol cessation	93 (82%)	21 (18%)	114
	Total	123 (82%)	27 (18%)	150

Supplementary table S6. Factors associated with chronic pancreatitis – univariate and multivariate analyses (original dataset)

		Univariate analyses			Multivariate analyses with RAP as covariate (n=990)		Multivariate analyses without RAP as covariate (n=990)	
Variable	N	n/N (%)	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1184		.98 (.96 – .99)	<.001	.99 (.97 – 1.02)	.605	.99 (.97 – 1.01)	.306
Gender	1184							
Male		58/660 (8%)	3.51 (1.94 – 6.37)	<.001	1.97 (.97 – 4.00)	.062	1.89 (.94 – 3.79)	.074
Female		14/524 (3%)	1		1		1	
BMI*	741		.86 (.80 – .92)	<.001				
Etiology	1184			<.001		<.001		<.001
Biliary		13/740 (2%)	1		1		1	
Alcoholic		35/156 (22%)	16.18 (8.32 – 31.46)	<.001	6.46 (2.22 – 18.78)	<.001	7.35 (2.60 – 20.76)	<.001
Idiopathic		16/156 (10%)	6.39 (3.01 – 13.58)	<.001	6.09 (2.57 – 14.41)	<.001	7.15 (3.08 – 16.59)	<.001
Other		8/132 (6%)	3.61 (1.47 – 8.88)	.005	3.08 (1.05 – 9.04)	.040	3.21 (1.12 – 9.16)	.029
Smoking	1029			<.001		.026		.019
Current		40/276 (14%)	5.50 (3.09 – 9.79)	<.001	2.54 (1.23 – 5.27)	.012	2.57 (1.29 – 5.12)	.007
Past		11/151 (7%)	2.55 (1.18 – 5.52)	.018	2.40 (1.02 – 5.66)	.046	2.33 (1.00 – 5.41)	.049
Never		18/602 (3%)	1		1		1	
Alcohol	1066			<.001		.468		.412
Heavy users		22/112 (20%)	11.43 (4.93 – 26.51)	<.001	2.33 (.68 – 7.96)	.178	2.08 (.64 – 6.78)	.226
Excessive users		10/49 (20%)	11.99 (4.47 – 32.15)	<.001	3.47 (.92 – 13.13)	.066	3.24 (.89 – 11.81)	.075
Social users		28/488 (6%)	2.85 (1.28 – 6.32)	.010	1.59 (.66 – 3.81)	.304	1.47 (.62 – 3.50)	.385
Past		3/35 (9%)	4.38 (1.11 – 17.34)	.035	2.29 (.47 – 11.18)	.306	2.86 (.63 – 12.96)	.173
Never		8/382 (2%)	1		1		1	
ASA-classification	1184			.010		0.968		0.988
I		10/225 (4%)	1		1		1	
II		22/520 (4%)	.95 (.44 – 2.04)	.895	.86 (.32 – 2.27)	.755	.91 (.35 – 2.32)	.839

III		40/430 (9%)	2.21 (1.08 – 4.50)	.030	.76 (.25 – 2.27)	.618	.83 (.29 – 2.40)	.724
IV		0/9 (0%)	.00 (.00 –)	.999	.00 (.00 –)	.999	.00 (.00 –)	.999
CRP < 48 hours after admission	1176		1.00 (1.00 – 1.00)	.037	1.00 (1.00 – 1.00)	.915	1.00 (1.00 – 1.00)	.926
Leukocytes < 48 hours after admission	1178		1.01 (.99 – 1.03)	.494				
APACHE II score	1172		.99 (.92 – 1.05)	.647				
Modified Glasgow score	1173		.89 (.73 – 1.10)	.278				
Severity according to Atlanta	1184							
Mild		45/833 (5%)	1					
Moderate/severe		27/351 (8%)	1.46 (.89 – 2.39)	.134				
Pancreatic necrosis	1174							
Yes		17/173 (9%)	1.87 (1.06 – 3.31)	.031	.68 (.25 – 1.82)	.443	.87 (.33 – 2.28)	.776
No		55/1001 (5%)	1		1		1	
Acute (peri-)pancreatic fluid collection(s)	1184							
Yes		26/305 (9%)	1.67 (1.01 – 2.76)	.044	1.14 (.52 – 2.52)	.744	1.02 (.48 – 2.20)	.955
No		46/871 (5%)	1		1		1	
Local complications[a]	1176							
Yes		26/326 (8%)	1.52 (.92 – 2.50)	.103				
No		46/850 (5%)	1					
Persistent organ failure	1184							
Yes		6/82 (7%)	1.24 (.52 – 2.95)	.628				
No		66/1102 (6%)	1					
Pancreatic intervention during first episode	1184							
Yes		14/119 (12%)	2.32 (1.25 – 4.29)	.008	3.02 (1.07 – 8.58)	.038	1.92 (.71 – 5.19)	.201
No		58/1065 (5%)	1		1		1	
Recurrent acute pancreatitis	1184						*Not included*	
Yes		45/301 (15%)	5.57 (3.39 – 9.16)	<.001	5.17 (2.89 – 9.27)	<.001		
No		27/883 (3%)	1		1			
Follow-up (years)	1184		1.06 (.98 – 1.16)	.143				

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

Supplementary table S7. Subgroup analysis of the effect of smoking on progression to chronic pancreatitis*

	No CP	**CP**	**Total**
Patients who quit smoking	19 (100%)	0 (0%)	19
Patients who continued smoking	18 (78%)	5 (22%)	23
Total	37 (88%)	5 (12%)	42
P = .530			

**Data on smoking were available in 15% (42/276) of the patients who reported current smoking at inclusion.*

Supplementary table S8A. Subgroup analysis of the effect of alcohol consumption on progression to chronic pancreatitis*

	No CP	CP	Total
Alcohol cessation	46 (90%)	5 (10%)	51
No alcohol cessation	122 (95%)	6 (5%)	128
Total	168 (94%)	11 (6%)	179
P = .298			

**Data on alcohol consumption were available in 28% (179/649) of the patients who reported current alcohol consumption at inclusion.*

Supplementary table S8B. Subgroup analysis of the effect of alcohol consumption on progression to chronic pancreatitis stratified for alcoholic etiology

		No CP	CP	Total
Alcoholic AP P = .633	Alcohol cessation	7 (70%)	3 (30%)	10
	No alcohol cessation	16 (84%)	3 (16%)	19
	Total	23 (79%)	6 (21%)	29
Non-alcoholic AP P = .614	Alcohol cessation	39 (95%)	2 (5%)	41
	No alcohol cessation	106 (97%)	3 (3%)	109
	Total	145 (97%)	5 (3%)	150

Supplementary table S9. Cross-sectional analysis of long-term quality of life and Izbicki Pain Scores in acute pancreatitis patients*

		Recurrent pancreatitis (RAP)			Chronic pancreatitis (CP)		
	Overall (n=370)	**RAP[a] (n=66)**	**No RAP (n=293)**	**P-value**	**CP (n=21)**	**No CP (n=349)**	**P-value**
PCS+ Mean ± SD	49.1 ± 10.3	48.4 ± 10.1	49.3 ± 10.4	.489	48.2 ± 9.3	49.2 ± 10.3	.364
MCS+ Mean ± SD	48.8 ± 10.3	48.0 ± 10.9	49.0 ± 10.2	.760	45.5 ± 12.2	49.0 ± 10.1	.125
	Overall (n=347)	**RAP[a] (n=60)**	**No RAP (n=278)**		**CP (n=18)**	**No CP (n=329)**	
Izbicki Pain score++ Mean ± SD	10.3 ± 16.0	16.2 ± 20.2	8.4 ± 13.5	.004	30.5 ± 28.2	9.2 ± 14.3	<.001

**Data on quality of life were obtained for 370 patients (31%) of whom 77 patients had developed RAP and 21 patients were diagnosed with CP. a11 recurrent pancreatitis patients were not included in these analyses because they have further transited to chronic pancreatitis. +Regression weights derived from normative data of the Dutch general population were used to compute the physical and mental component summaries (PCS and MCS) of the SF-12 (range 0 – 100). Higher scores indicate a better quality of life, whereas a score of 50 represents the mean in the general population.++Scale ranges from 0 to 100 points (increasing scores indicating more pain severity). Questions consist of 4 items: frequency of pain, intensity of pain, use of pain medication and disease-related inability to work.*