Prognosis of acute and chronic pancreatitis - a 30-year follow-up of a Danish cohort

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The present thesis is based upon the following papers:

Paper I.
Factors associated with long-term mortality in acute pancreatitis.
Camilla Nøjgaard, Peter Matzen, Flemming Bendtsen, Jens Rikardt Andersen, Erik Christensen, Ulrik Becker. Accepted for publication in Scand J Gastroenterol.

Paper II.
Progression from acute to chronic pancreatitis – prognostic factors, mortality and natural history
Camilla Nøjgaard, Ulrik Becker, Peter Matzen, Jens Rikardt Andersen, Claus Holst, Flemming Bendtsen. Not published yet.

Paper III.
Danish patients with chronic pancreatitis have a 4-fold higher mortality rate than the population
Camilla Nøjgaard, Flemming Bendtsen, Ulrik Becker, Jens Rikardt Andersen, Claus Holst, Peter Matzen. Clin Gas & Hep. 2010 Apr;8(4):384-90. Epub 2009 Dec 29.

ABBREVIATIONS

AP	acute pancreatitis
B-	Blood-
BMI	body mass index
CI	confidence interval
CP	chronic pancreatitis
CPS	Copenhagen Pancreatitis Study
ERCP	endoscopic retrograde cholangio-pancreaticography
HR	Hazard Ratio
ICD	International Classification of Diseases
ICD-8	ICD, 8th edition
ICD-10	ICD, 10th edition
NAP	non-progressive acute pancreatitis
PAP	progressive acute pancreatitis
S-	Serum-
SD	standard deviation
SMR	standardised mortality ratio
WHO	World Health Organization

INTRODUCTION

Biliary stones and alcohol are common causes of acute pancreatitis. Due to the first Opie hypothesis (1901), the mechanism of gallstone-induced acute pancreatitis is thought to be caused by an impacted gallstone in the ampulla of Vater and hereby an impaired flow in the pancreatic duct. The mechanisms of alcoholic pancreatitis are unclear but alcohol might act inappropriate on the sphincter of Oddi, change the composition of the pancreatic juice, and directly injure the acinar cells. An acute exposition to alcohol leads to acute inflammation, while a continuous exposition leads to development of chronic inflammation and fibrosis. In chronic pancreatitis, tobacco also seems to be an important risk factor. However, the aetiology of both acute and chronic pancreatitis often remains unknown[1-4]. Acute pancreatitis (AP) and chronic pancreatitis (CP) are usually considered to be two sides of the same condition[3,5]. It remains to be established, however, why some patients after either a single or a few attacks of AP have an aggressive disabling course leading to CP with permanent structural changes of the gland, chronic abdominal pain and exocrine and endocrine dysfunction[6-12], whereas others have a harmless course without development of fibrosis or dysfunction[12,13].
Because of a great variation in clinical and biochemical presentation, acute and chronic pancreatitis may be difficult to diagnose. 'The gold standard' is histology but it is rarely available. Most frequently, the AP diagnosis is based on the following criteria: a 3-times upper normal level of serum (S-) amylase combined with acute abdominal pain and possibly in combination with positive findings, indicative of AP, at radiological imaging or per-operative findings. These criteria is often called the 'Atlanta criteria' according to the classification system by Bradley et al[14], although, an exact S-amylase level were not stated. The CP diagnosis is often based on clinical scoring systems based on combinations of the different clinical symptoms: exocrine or

endocrine insufficiency, histology, calcifications, abdominal pain, previous AP, loss of weight, and findings at radiological examinations or ERCP[13].

BACKGROUND

The aetiology, incidence and short-term prognosis in acute pancreatitis (AP) have been described in several retrospective studies[15-26], prospective studies[27-31] and in systematic reviews[32-35]. Hereby, prognostic factors with an impact on short-term survival in AP were identified, and scoring systems predicting the severity of AP[35] were developed. Prognostic factors of importance for long-term survival and causes of death, however, are more sparsely described[12,20,30,36-38] and risk factors of importance for the course from AP to CP are hardly ever described[12,36]. The aetiology of AP is thought to have an influence on the course of the disease, since previous studies indicate that a major part of alcohol-induced AP seems to progress to CP[11,36,39-41], whereas this is only rarely the case for biliary-induced AP[11,42]. Necrotising AP, however, can lead to pancreatic insufficiency and permanent ductal lesions[43,44]. Exocrine and endocrine functional impairment has been described even after mild non-alcoholic AP[45].

CP is a complex disease with a high risk of complications. It is frequently caused by a high intake of alcohol and smoking, but often the aetiology is unknown[1-3,46,47]. Knowledge of the natural history, course and prognosis of CP is limited, partly because diagnostic criteria have changed over the years. Furthermore, studies of prognostic factors for patients with CP are often based on selected patients with complicated disease from tertiary centers[48-54] or are based on retrospective materials[48,55]. Only a few prospective cohort studies of non-selected patients have been published[13,56].

AIMS

Aims were to investigate:

1. the mortality of the AP patients and CP patients compared to the background population
2. prognostic factors associated with the mortality of AP and CP or with the progression from AP to CP
3. the frequency and the natural course of progressive AP (PAP)
4. the causes of death in the AP and CP patients.

This phd-thesis is based on the material from the Copenhagen Pancreatitis Study (CPS).

The CPS is a large prospective cohort study of patients in the municipality of Copenhagen admitted with either acute or chronic pancreatitis fulfilling specific diagnostic criteria and enrolled in the study during 1977 to 1982. The CPS has the advantages of a prospective design, large size, geographical demarcation, and a complete 30-year follow-up by means of record linkage to the Danish health registries. Thereby, results on the morbidity, the mortality and the natural course of AP and CP could be achieved.

MATERIALS AND METHODS

The original CPS cohort

Patients resident in the municipality of Copenhagen (population of 417,000) and admitted with a diagnose of AP or CP were consecutively enrolled in the study from November 1977 to August 1982[57]. The inclusion criteria (Table 1) were modified from the 1963 Marseilles classification[58] – the internationally recommended diagnostic criteria at that time – and based on a combination of clinical history, pancreatic function tests, and biochemical, pathoanatomical or radiological findings except for findings from endoscopic retrograde cholangio-pancreaticography (ERCP).

Table 1
The CPS inclusion criteria and distribution of the cohort (n=642)

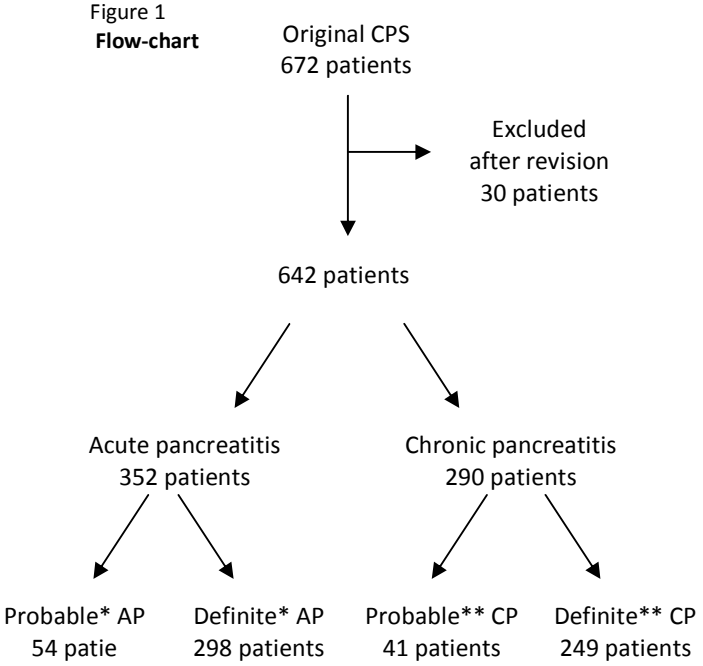
		Clinical criteria	n
Probable AP	CPS-0	Acute abdomen with pain in the upper half of abdomen and S-amylase 300-600 U/L	54
Definite AP	CPS-1	Acute abdomen with pain in the upper half of abdomen and S-amylase >600 U/L	258
	CPS-2	Acute abdomen with pain in the upper half of abdomen and acute inflamed pancreas at surgery for acute abdomen	15
	CPS-3	S-amylase>600 U/L and acute in-flamed pancreas at surgery for acute abdomen	25
Probable CP	CPS-4	At least one earlier attack of AP and recurrent pain in the upper half of abdomen	51
	CPS-5	Diminished exocrine pancreatic secretion (Lundh test): duodenal amylase values<127 U/L	2
	CPS-6	Chronic inflamed pancreas at sur-gery for acute abdomen or at autop-sy	36
Definite CP	CPS-7	Pain in the upper half of abdomen and diminished exocrine pancreatic secretion (Lundh test)	85
	CPS-8	Pain in the upper half of abdomen and pancreatic calcification	50
	CPS-9	Steatorrhea (>7g fat/24h; mean of stool collection for 3 days) and diminished exocrine pancreatic secretion (Lundh test)	66

*Normal reference range of S-amylase 70-300 U/L

Patients were excluded if the pancreas was macroscopically normal at surgery or if pancreatic cancer was diagnosed during the primary admission. A search of the National Patient Registry was made at the end of the inclusion period for patients admitted with a World Health Organization (WHO) International Classification of Diseases (ICD), 8th edition (ICD-8) code for AP or CP (577.00–577.91) in order to complete the inclusion. The original CPS-cohort comprised 672 patients. In 2008, patient hospital records were reviewed retrospectively in order to ensure

correct classification of the patients and for collection of data on smoking habits, previous admissions, and detailed description of ERCP findings when available. ERCP findings were classified using the Cambridge criteria[59]. If pancreatic calcifications were present, the patient had CP, by definition. 30 patients were secondarily excluded for not fulfilling the selection criteria. Thus, the CPS cohort comprised 642 patients (Figure 1). Of these, 262 patients were seen only at inclusion, while the others were followed up in case of a new admission or at scheduled outpatient clinic consultations one to seven times during the inclusion period.

Figure 1
Flow-chart



During 1987–1988, living patients with definite or probable CP (n=167) were asked to complete a mailed questionnaire concerning morbidity (admissions, abdominal pain, use of pain killers, development of diabetes); 71% (119/167) patients answered this questionnaire. All patients fulfilling inclusion criteria CPS-4 to CPS-9 (Table 1) were assessed retrospectively using the CP score developed by Peter Layer et al[13,60,61], referred to as the Layer score (Paper III). This score was chosen as the basis of classification in probable and definite CP (Layer score <4 and ≥4 respectively) replacing the inclusion criteria CPS-4 to CPS-9.

Clinical data of the CPS cohort
At the inclusion and follow-up visits, the following were noted: clinical history, physical signs, treatment, and laboratory tests results. Patients suspected of having CP were subjected to additional examinations, i.e., fasting glucose, glucose tolerance test, ultrasound of the pancreas, ERCP, abdominal x-ray, Lundh test meal with determination of amylase in the duodenal aspirate, and fat excretion in stool (measured by titrimetry), when indicated. Smoking habits were not registered in the original CPS questionnaire. When gallstones were suspected, cholecystography, ultrasound, computed tomography, ERCP or a combination of these was performed. Descriptions of autopsies were obtained for 68 patients with probable or definite AP and for 52 patients with probable or definite CP.

The Danish registries
In August 2008, data from the CPS cohort was linked to the Causes of Death Registry and the National Patient Registry using each patient's unique personal identification number. The Causes of Death Registry contains information from all death certificates in Denmark since 1973. From this registry, date of death and cause of death during the follow-up period (November 1977 to August 2008) were obtained. The National Patient Registry contains information about patients admitted to non-psychiatric hospitals in Denmark since 1977. From this registry, dates of all admissions and discharges during the follow-up period, the diagnoses and dates of discharge and the diagnoses of surgery were obtained. The diagnosis from both the Causes of Death Registry and National Patient Registry were coded using the WHO ICD-8 from 1 January 1977 to 31 December 1993 and the 10th Edition (WHO ICD-10) from 1 January 1994.

Classification of etiologies
In the CPS questionnaire, alcohol intake was divided in the following groups: a) 0 g alcohol per day, b) 10-40 g alcohol per day, c) ≥50 g alcohol per day for <5 years, d) ≥50 g alcohol per day for >5 years. In this context, alcoholic AP or CP was defined as patients with an alcohol consumption of ≥50 g ethanol per day at inclusion irrespective of duration. Non-alcoholic AP or CP as patients with an alcohol consumption of <50 g ethanol per day. Familial AP or CP was defined as patients with first order relatives, who previous to the inclusion date had had AP or CP. Genetic testing was not possible 30 years ago. Idiopathic AP or CP was defined as patients with an alcohol consumption of <50 g ethanol per day combined with no inheritance, no gallstone-induced AP and no other etiologies (e.g., hypercalcemia). Gallstone-induced AP was defined as patients with AP (CPS-0 to CPS-3), and an alcohol intake <50 g ethanol per day combined with one or more of the following findings: gallstones in the biliary duct or gallbladder visualized during ultrasound, computed tomography, ERCP, cholecystography, surgery or autopsy.

Statistical methods
Age- and sex-specific mortality rates for the patient subcohorts were compared with the mortality in a matched background population by calculating standardized mortality ratios (SMR). Cox proportional hazard regression was used to test the association between clinical and social prognostic factors and mortality in both subcohorts, and the development of CP specific in the AP subcohort. For the Kaplan-Meier plots and the log rank test, the time-scale was age at death or censoring. The influence of age was adjusted for by using this time-scale. The student t test, Mann-Whitney and chi-squared tests were used as appropriate to describe the baseline characteristics of the patients. The level of significance was set at 5% ($p<0.05$). SPSS (version 17.0), SAS (version 9.1.3), Stata Version 9.2 (StataCorp, Texas; www.stata.com), and Statistica (version 4.3) software were used.

RESULTS

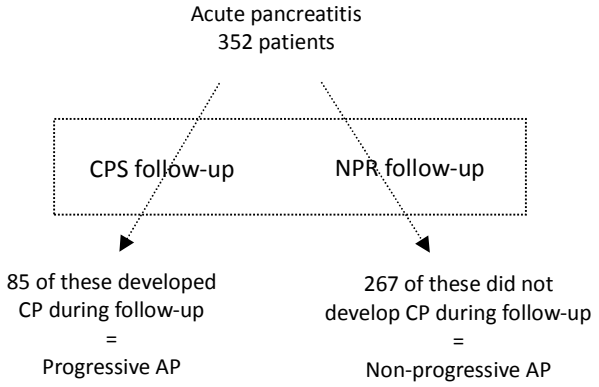
Patients with AP

352 patients with CPS inclusion criteria 0-3 were included in this cohort: 54 patients had probable AP, and 298 definite AP. Table 1 presents the distribution of patients by CPS inclusion criteria.

Patients with PAP

Of 352 patients with probable or definite AP at inclusion, 85 patients (24.1%) subsequently developed verified CP (Figure 2). These patients had PAP. At inclusion, 11 (12.9%) of these patients had probable AP, and 60 (70.6%) had a S-amylase level ≥3 times upper normal limit (≥900 U/L). The CP diagnosis was registered either in the CPS (until 1988) using the cut off level of a Layer score ≥4 or in the National Patient Registry (1978–2008) using the ICD codes for CP (ICD-8: 577.19, 577.90–577.92; ICD-10: K86.0–K86.9).

Figure 2
AP to CP flow-chart



Patients with non-progressive AP

267 patients with probable or definite AP at inclusion did not develop CP during the follow-up registered neither in the CPS (until 1988) using a Layer score <4 nor in the National Patient Registry (until August 2008). These patients thus had non-progressive AP (NAP). At inclusion, 43 (16.1%) of these patients had probable AP, and 169 (63.3%) had a S-amylase level ≥3 times upper normal limit (≥900 U/L). Patients with probable and definite AP were pooled because the survival curve was the same in the two groups (Paper I).

Patients with CP

290 patients were defined as having either probable or definite CP (Table 1). The Layer score was chosen as the basis of classification in probable and definite CP replacing the original inclusion criteria described in Table 1. The validity of the original CPS inclusion criteria according to the Layer score was relatively good and is described in Paper II. Of the CP population, 41 had a Layer score <4 (probable CP), and 249 patients had a Layer score ≥4 (definite CP).

Aetiologies

Table 2 shows the distribution of aetiologies in the different subcohorts. In the AP patients, 48 patients had gallstones verified by ultrasound/computed tomography, cholecystography, ERCP or a combination. Of these, 44 had an alcohol intake <50g per day and categorized to have gallstone-induced AP. The patient with gallstone-induced AP in the PAP subcohort had no prior history of alcohol abuse, had gallstones verified at surgery at inclusion and developed exocrine insufficiency during the follow-up (Layer score=4). 91 of 249 (36.5%) patients with definite CP had previously been hospitalized with an attack of AP.

Table 2
The distribution of aetiologies in the subcohorts, number of patients (%)

Aetiologies	AP patients	PAP patients	CP patients
Alcoholic	129 (36.6%)	41 (48.2%)	128 (44.1%)
Idiopathic	170 (48.3%)	40 (47.0%)	144 (49.8%)
Familial	8 (2.3%)	2 (2.4%)	16 (5.5%)
Hypercalcaemia-induced	1 (0.3%)	1 (1.2%)	1 (0.3%)
Gallstone-induced	44 (12.5%)	1 (1.2%)	1 (0.3%)

Patient characteristics of the AP subcohort

Table 3 shows the characteristics of the patients with definite and probable AP at initial hospitalization. The significant differences between the two groups were linked to their inclusion criteria: S-amylase, B-leukocytes, S-bilirubin, S-alkaline phosphatase, S-aspartate aminotransferase, and S-gammaglutamyltransferase were significantly higher in the definite AP group compared with the probable AP group. Furthermore, patients in the definite AP group were significantly less frequently treated with general analgesics (both opioids and non-opioids), but were more often treated by fasting, with a gastric tube and by surgery than the probable AP group.

Table 3
AP patient characteristics on inclusion in the CPS

	Definite AP (CPS 1-3)	**Probable AP (CPS 0)**
Number of patients	298	54
Gender (male/female)	157/141	33/21
Age, years	55.9 (38.2-72.1)	57.3 (44.7-66.8)
Alcohol intake >50 g per day	112/298 (37.6%)	17/54 (31.5%)
BMI	24.0 (21.6-26.5)	23.6 (20.8-26.5)
Tobacco (g per day)	11.0 (0.1-20.0)	9.0 (0.0-16.4)
B-leukocytes (normal range 3.0-9.0 109/L)	10.2 (7.7-13.9)**	8.5 (6.7-11.2)
S-amylase (normal range 70-300 U/L)	1919 (988-4080)***	413.5 (368-452)
S-bilirubin (normal range 5-17 micromol/L)	14.5 (9.0-28.3)***	9.0 (5.0-12.0)
S-alkaline phosphatase (normal range 51-275 U/L)	240 (180-335)*	198 (147-292)
S-aspartate aminotranspherase (normal range 10-40 U/L)	48 (24-107)***	23.0 (18.0-42.5)

In gender and alcohol intake, values represent number of patients (percentage). Age, tobacco, BMI and biochemistry values are given as median values with 25-75% quartiles in parentheses.
* p<0.05, **p<0.01, and ***p<0.001 in Student's t test, Mann-Whitney or chi-squared tests, as appropriate, comparing definite AP with probable AP.

Clinical characteristics of PAP and NAP patients

Table 4 shows the clinical characteristics of the patients with PAP and NAP. At inclusion, treatment of alcoholism was more frequent (p=0.02), and opioids were more frequently used (p=0.04) in patients with PAP than with NAP, whereas the following were more frequent in patients with NAP than with PAP: non-employment (including unemployment, early retirement, and retirement) (p=0.03), gallstones as cause of pancreatitis (p<0.0001), and abdominal pain in the right upper quadrant (p=0.008).

Table 4
PAP and NAP patient characteristics on inclusion in the CPS

	PAP	NAP
Number of patients	85	267
Age at inclusion, mean (SD)	48.2 (16.7)*	58.2 (18.3)
Gender (male/female)	54/31*	136/131
Daily intake of alcohol (≥50 g/day)	41/85 (48.2%)*	88/267 (33.0%)
Tobacco (g per day), mean (SD)	17.6 (10.9)*	9.0 (10.5)
Gallstone-induced AP; not gallstone-induced AP	1; 84*	43; 224
Employment; non-employment; no data	46; 37; 2*	94; 168; 5

*p<0.05; Student t test, Mann-Whitney and chi-squared tests were used as appropriate comparing the PAP-group with the NAP- group.

Patient characteristics of the CP subcohort

Table 5 shows the characteristics of the patients with probable (n=41) and definite (n=249) CP on inclusion in the CPS. Probable CP patients had a significantly higher intake of alcohol up to admission than patients with definite CP (27/242 vs 14/41; p=0.01), while ERCP investigations (144/209 vs 8/28; p<0.0001), and use of general analgesics (both opioids and non-opioids) in the treatment (96/210 vs 5/41; p=0.01) were more frequent in the definite CP patients. Of the 174 patients with painful definite CP at inclusion, the following percentages were painless at follow up: 8.3% (13/156) at the second visit, 21.4% (24/112) at the third visit, and 28.6% (12/42) at the questionnaire 1987/1988.

Table 5
Patient characteristics of the CP patients on inclusion in the CPS

	Definite CP#	Probable CP#
Number of patients	249	41
Age, mean (SD)	51.0 (12.4)*	46.4 (13.6)
Gender, male/female	179/70	30/11
Daily intake of alcohol ≥50g per day	143/249 (57.4%)	23/41 (56.1%)
Tobacco g per day, mean (SD)	16.5 (9.9)	15.1 (15.2)
BMI, mean (SD)	21.5 (3.7)	22.9 (4.7)
Calcification	75/249 (30.1%)*	0
Exocrine insufficiency	150/249 (60.2%)*	3/41 (2.4%)
Diabetes	46/249 (18.5%)	4/41 (9.8%)
Pancreatic surgery before or at inclusion	74/249 (29.7%)*	1/41 (2.4%)+

Values represent number of patients (percentage) unless otherwise indicated.
Defined using the Layer score and not the original inclusion criteria.
* p<0.05 in Student t test, Mann-Whitney or chi-squared tests, as appropriate, comparing definite CP with probable CP.
+ This patient had drainage of a pseudocyst because of previous AP without signs of CP.

Surgical procedures

Table 6 describes the surgical procedures for AP (17.6%) and CP (25.5%) at inclusion. Surgical procedures during the follow-up are described in Paper I and III.

Table 5
Surgical procedures in the AP and CP subcohorts

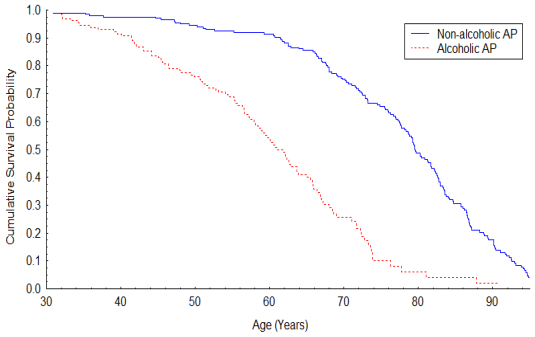
Surgical procedures	Number of procedures in the AP subcohort (n=67) in 62 individuals	Number of procedures in the CP subcohort, n=81 in 74 individuals
Peritoneal drainage with/without necrosectomy	12	2
Peritoneal dialysis	1	
Biliary drainage	31	
Subtotal pancreatectomy (including Whipple)	5	8
Pancreatico-gastrostomy or -jejunostomy		12
Combinations/other procedures		5
Drainage of pseudocyst	8	18
Drainage of pancreatic abscess	2	1
Biliary bypass		11
Gastroenteroanastomosis		3
Combinations/other procedures	4	3
Explorative laparotomy	4	16
Operated for other reasons (cholecystectomy)		2

Survival and prognostic factors for the AP patients

The Kaplan-Meier survival curves for the probable and definite AP groups showed no significant difference (p=0.14, HR 1.22, 95% CI 0.85–1.74). The survival curves for the alcoholic and non-alcoholic

AP groups showed a significantly higher mortality in the alcoholic group (Figure 3, p<0.0001, HR 3.16, 95% CI 2.32–4.29).

Figure 3
The cumulative survival of alcoholic and non-alcoholic AP



The multivariate Cox regression model (Table 7) shows that age, alcohol, and diabetes were all significantly associated with higher mortality, whereas female gender, co-living and employment were associated with better survival. The following factors had no influence on survival (p>0.05): S-amylase level, CPS inclusion criteria (probable or definite AP), gender, BMI, smoking, surgery for AP at inclusion, and inheritance as cause. Gallstones as cause were significant in the univariate model (Paper I) but not in the multivariate model. S-amylase level was also included in the analysis logarithmically transformed and scored in different categories by level, but still had no influence on survival.

Table 7
Multivariate Cox regression analysis of factors with impact on mortality in the AP subcohort

Variable	Scoring	Beta	SE	p-value
Age	Age in years	0.042	0.005	<0.001
Gender	0: woman; 1: man	-0.384	0.128	0.004
Alcohol	0: 0 g/day; 1: 10-40 g/day; 2: ≥50 g/day <5 years; 3: ≥50 g/day ≥5 years	0.074	0.024	0.003
Diabetes vs no diabetes	0: no diabetes; 1: diabetes	0.697	0.274	0.017
Single vs co-living	0: single living; 1: co-living	-0.515	0.137	<0.001
Employment vs non-employment	0: non-employment; 1: employment	-0.323	0.165	<0.05

Prognostic factors for the progression from AP to CP
The risk of progression to CP decreased with increasing age in a dose-dependent manner with 2% less risk per year of age. Therefore, the Cox regression analyses in table 8 were performed with age included as a co-variate. These analysis showed that only smoking had a significant impact on the progression to CP in a consumption-dependent manner, while no signs of gallstones showed a trend towards significance. Gender and employment showed non-proportionality. The risk seemed higher in men and the employed, but it could not be documented by a HR because of the non-proportionality. Necrosectomy for AP at inclusion was not a significant prognostic factor. Smoking habits were not registered at inclusion but could be retrieved retrospectively in 120 of 152 accessible AP patient records.

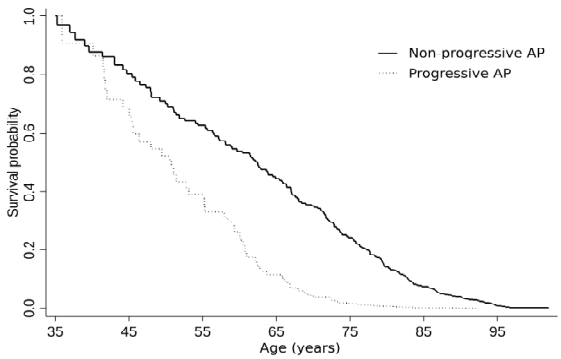
Table 8
Cox regression analysis of factors with impact on the development from AP to CP corrected for age

	HR	95% CI	p-Value	Proportionality* p-Value
Gender (females vs males)	0.81	0.51-1.27	0.35	0.007
Tobacco 1-19 g per day vs non-smoking	2.62	0.86-7.93	0.089	0.18
Tobacco ≥20 g per day vs non-smoking	3.18	1.06-9.55	0.039	0.16
Alcohol 10-40 g per day vs 0 g per day	1.40	0.75-2.60	0.291	0.26
Alcohol ≥50 g per day vs <50 g per day	1.34	0.63-2.86	0.444	0.14
Alcohol ≥50 g per day for >5 years vs <50 g per day for <5 years	1.22	0.68-2.17	0.506	0.04
Employment vs non-employment	1.00	0.60-1.67	0.986	0.008
Signs of gallstones vs no signs of gallstones	0.50	0.25-1.01	0.054	0.52
BMI 20-25 vs BMI <20	0.86	0.44-1.68	0.650	0.97
BMI >25 vs BMI <20	0.56	0.26-1.18	0.127	0.13

*If the test of proportional hazards assumption was highly significant (p<0.01), the Hazard model was neglected (written with italics). vs=versus

The natural course and mortality of PAP
The time from AP to a diagnosis of CP in PAP was mean 3.5 years (SD 4.3 years). The time from AP to development of various clinical presentations of CP is described in Paper II. The mortality in patients with PAP was significantly higher than the mortality in patients with NAP: HR 2.65, 95% CI 1.98-3.56 p<0.0001 (Figure 4).

Figure 4
Kaplan Meier survival curves for the PAP and NAP groups (HR 2.65, p<0.0001)



The SMR for patients with PAP was increased by a factor of 5.3–6.5 compared with the background population, whereas the mortality rate for patients with NAP was 1.6–1.7 times the expected mortality rate in the background population (Table 9).

Table 9
SMR – a comparison between the AP and CP subcohorts and the normal population[62]

	Gender	Observed death	Expected death	SMR	95% CI
PAP	male	49	9.28	5.28	3.99-6.99
	female	28	4.32	6.48	4.47-9.38
NAP	male	101	61.48	1.64	1.35-2.00
	female	101	62.42	1.62	1.33-1.97
Probable CP	male	22	8.01	2.75	1.81 - 4.17
	female	9	4.31	2.09	1.09 - 4.01
Definite CP	male	166	38.85	4.27	3.67 - 4.98
	female	67	14.85	4.51	3.55 - 5.73

Survival and prognostic factors for CP patients
The standardized mortality ratio (SMR) for patients with definite CP was increased by a factor of 4.3–4.5 compared with the background population, whereas the mortality rate for patients with probable CP was 2.1–2.8 times the expected mortality rate in the background population (Table 9).
Cox regression analysis confirmed that the probable CP group had a significantly better survival rate than the definite CP group: p=0.003, HR 1.77, 95% confidence interval (CI) 1.21–2.57 (Paper III). Therefore, probable CP patients were excluded from the following survival analysis.
Cox regression analysis showed a significantly better survival rate for definite CP patients who were employed compared with patients without job (p=0.015; HR 0.70, 95% CI 0.53–0.93), which was even more pronounced by exclusion of patients older than 60 years at entry: p=0.0003; HR 0.48, 95% CI 0.33–0.71. Definite CP patients who were overweight (body mass index, BMI≥25) had a significantly better survival rate than underweight patients (BMI<20) (p=0.016, HR 0.60, 95% CI 0.39–0.91).The analysis were repeated on the 169 CP patients who were diagnosed at inclusion as having identical significant prognostic factors as mentioned above (data not shown). The following factors had no influence on survival in definite CP patients (p>0.05): gender, alcohol, smoking, single/co-living, exocrine insufficiency, diabetes, pancreatic calcification, CP inheritance, painless CP, acute exacerbation in CP, and surgery for CP. Smoking habits were not registered at inclusion but could be retrieved in 133 of 147 accessible CP patient records.

Causes of death
291 patients (82.7%) in the AP cohort died during the 30-year follow-up. Table 10 summarizes the cause of death for these patients. Most patients died from cardiovascular diseases (21.6%), digestive diseases (17.9%) or malignancy (17.2%) – among these two (0.7%) with pancreatic cancer; 4.1% committed suicide, and 4.8% died of an accident.

Table 10
Causes of death for the AP and CP cohort

Causes of death	Number of deaths in the AC population, n=291	Number of deaths in the CP population, n=266	Percentage of deaths in the total Danish population in 2006, n=55,213
Digestive diseases	52 (17.9%)	52 (19.5%)	5.3%
AP	1 (0.3%)		
CP	23 (7.9%)	21 (7.9%)	
Alcoholic liver diseases	16 (5.5%)	24 (9.0%)	1.6%
Malignancy	50 (17.2%)	52 (19.5%)	28.3%
Pancreatic cancer	2 (0.7%)	10 (3.8%)	1.5%
Cardiovascular diseases	63 (21.6%)	30 (11.3%)	19.1%
Diabetes	10 (3.4%)	20 (7.5%)	2.3%
Respiratory diseases	15 (5.2%)	19 (7.1%)	9.6%
Senile decay including stroke and dementia	28 (9.6%)	17 (6.3%)	
Mental illness	7 (2.4%)	16 (6.0%)	
Accident	14 (4.8%)	13 (4.9%)	3.6%
Infectious diseases (including TB)	2 (0.7%)	7 (2.6%)	1.4%
Suicide	12 (4.1%)	2 (0.8%)	1.2%
Diseases in the urinary tract or gynecological diseases	2 (0.7%)	4 (1.5%)	1.9%
Other not clearly defined causes	26 (8.9%)	31 (11.7%)	3.2%
Patients died within the last 2 years*	10 (3.4%)	3 (1.1%)	

*The Danish National Health Service has not yet received information on the cause of death for patients

During the 30-year follow-up, 266 patients (91.7%) in the CP cohort died. Table 10 summarizes the cause of death for these patients. Most patients died from digestive diseases (19.5%), malignancies (19.5%), and cardiovascular diseases (11.3%); 0.8% committed suicide, and 10 patients (3.8%) died of pancreatic cancer. Cause-specific analysis of patients with definite CP who died from digestive diseases showed abdominal pain (p=0.009; HR 0.47, 95%CI 0.27-0.83), and non-employment for patients <60 years of age (p=0.018; HR 0.42, 95% CI 0.20-0.86) as significant prognostic factors. For patients with definite CP who died from cardiovascular diseases, there was a trend towards inheritance of CP as a prognostic factor (p=0.054; HR 2.42, 95%CI 0.99-5.92). For patients who died from malignancies, no factors were identified as significant.

DISCUSSION

Prognostic factors of mortality

This prospective study showed that alcohol is an important prognostic factor of mortality for patients with AP, but in contrast to CP[23,52,54,61,63,64] smoking is not a prognostic factor. Our results agree with the findings of Kristiansen et al[65], although their study was based on the Danish National registries alone and the patient population had a mixture of AP and CP. In this context, the varying validity of the ICD codes from the National Patient Registry concerning CP (varies from 63 to 78%) and AP (varies from 51 to 73%) should be taken into account[66,67]. Other follow-up studies seem to be based on more selected patient populations and do not describe prognostic factors associated with long-term mortality[16,36-38]. We found a significantly higher mortality in alcoholic AP patients compared with non-alcoholic patients. This is not in agreement with Renner et al[26] who found a similar long-term survival in patients with alcohol-induced AP compared with non-alcoholic AP. This difference between the studies may be explained by difference in design: the study of Renner et al was retrospective whereas our study was prospective and thereby more reliable. Our finding of diabetes as a prognostic factor is in aggreement with Renner et al[26] who described a significantly higher prevalence of established diabetes in AP than observed in the control series, and it is not surprising considering the high co-morbidity of these patients. Diabetes was considered, therefore, as an additional risk factor influencing survival in AP. We also found that single living, male gender and non-employment were significantly associated with higher mortality in these patients. Thus, we confirm that social factors influence survival in these patients as in the general population[68].

The mortality in patients with PAP was 2.7 times higher compared with NAP, and compared with the background population, the mortality in patients with PAP was 5.3-6.5 times higher during the 30-year follow-up. There was a trend towards a higher mortality in females. We found no other studies that published long-term mortality data in patients with AP progressing to CP. This finding of a much greater mortality in these patients indicates that AP patients with risk factors of CP should be followed and treated for alcohol[69] and tobacco dependency.

In a retrospective study, Levy et al[55] observed a higher mortality in CP patients compared with a matched French population. Miyake et al[70] found a higher mortality in alcoholic CP patients compared with an age- and sex-matched population but no difference in non-alcoholics. Overall, we found a 2-3-fold higher mortality in probable CP patients, and a 4-fold higher mortality in definite CP patients compared with the mortality in a standardized background population. For definite CP patients, a Cox regression analysis showed that non-employment and low BMI were the only factors having a significant association with mortality. Alcohol and smoking had no individual prognostic influence on mortality; this is surprising as both have been shown to be important etiological factors for the development of CP[1,52,54,61,63,64,71,72]. The strength of this statement may be hampered, however, as smoking habits were not registered in the original CPS questionnaire. At the time the CPS was initiated, smoking habits were not thought to be important, but we compensated for this by adding retrospective information from patient records. Some of the patients in this study were diagnosed with CP several years before inclusion, and they may have changed their life-style, e.g., reducing their alcohol intake[63], thereby confounding the prognostic analysis. However, the lack of prognostic information for alcohol intake, when exclusively analyzing patients who were included in the study on diagnosis of CP, confirms that alcohol had no prognostic influence in this study. Non-employment as a prognostic factor is well known in social medicine[68] and in other diseases[73]. Only Lankisch et al[56] have described the socioeconomic factors in CP patients; they found an increase in unemployment and retirement after CP diagnosis, but the association with mortality has not previously been explored. In patients <60 years at entry, non-employment led to a significantly higher mortality that could not be explained by any other factor such as gender, alcohol consumption, smoking habits, presence of pain, exocrine insufficiency, endocrine insufficiency or pancreatic surgery. Non-employment in these patients may be caused by the severity and duration of their disease, and thereby, absence from work; it may also be attributable, however, to other individual risk factors such as level of education, level of income or psychiatric co-morbidity[68], factors that were not recorded in this study. A higher mortality observed in underweight patients (BMI<20) may hypothetically be caused by the severity of the disease. It seems important, therefore, to focus on social support and nutritional treatment in these patients, as well as alcohol.

Progression from AP to CP

In 1965, Henri Sarles claimed that AP and CP were two different diseases as the patients with AP at initial presentation were older generally than the patients with CP and therefore, it would be unlikely that CP develops after an initial episode of AP[42]. One explanation of the development of CP after AP is the necrosis–fibrosis hypothesis[74]. It has also been hypothesised that the clinical picture of AP is the first manifestation of CP, and that CP always underlies AP[39]. Unfortunately, these hypotheses can only be confirmed by biopsy, which is seldom used. Therefore, we chose a more pragmatic approach using specific clinical definitions of AP and CP. In 1973 and 1997, Ammann et al[39,49] concluded that gallstone-induced AP never leads to CP, while nearly all alcoholic AP will become chronic. In 2009, Lankisch et al[36] observed that alcoholic AP progressed to CP, while idiopathic AP seemed not to. In the present study, 48.2% progressed from alcoholic AP, while 47.0% progressed from idiopathic AP, and only one patient developed CP after gallstone-induced AP. It cannot be excluded that some of the patients in the actual study who were classified as having idiopathic AP may have been undisclosed alcoholics; this could blur the association. The present study, however, was prospective and each patient was specifically questioned about alcohol use and habits at entrance to the study, so minimising the risk of misclassification. According to the low cut-off criteria of S-amylase, one might speculate whether the AP patients in this study had ‘certain AP’. But actually we found that the distribution of etiologies was not affected by a change in the cut-off criteria (≥3 times upper normal limit) for S-amylase (results not shown).

Recently, Symersky et al[45] reported that a large proportion of patients with biliary AP and post-ERCP pancreatitis developed either exocrine insufficiency (65%) or endocrine insufficiency (35%) during a long-term follow-up. Whether this is ‘classic CP’ or insufficiency caused by loss of functional pancreatic tissue is debatable, but in an autopsy study[26] of 405 patients who died

of AP, 47% of the alcoholic AP and 32% of the biliary-induced AP simultaneously had morphological changes consistent with CP. The present studies (Paper II and III), however, does confirm that gallstone-induced AP only infrequently progresses to CP.
We found that CP developed within a mean interval of 3.5 years (SD 4.3 years) from the first attack of AP. This is in aggrement with Ammann et al[38] who found a mean interval of 5.1 years (SD 4.3 years) from alcoholic AP to CP, and also in agreement with Lankisch et al[24,36] that suggested a progression within a time frame of 10 years.
Comparing patients with PAP with a non-progressive control group, risk factors for CP were: male gender, age below 50 years, and thereby association with the labour market, no clinical or imaging signs of gallstone-induced AP, high alcohol consumption, and high tobacco use. In the Cox regression analysis corrected for the influence of age, tobacco (≥20g/day) was the only significant factor in a dose-dependent manner; this is in agreement with the findings of Lankisch et al[36] in a small cohort of patients (n=19) developing CP after AP. Although, smoking habits were not registered in the original CPS questionnaire, it was retrieved by adding retrospective information from the accessible patient records. Hereby, smoking habits were described in 34% of the AP patients. Well knowing the considerations of retrospective data, smoking were still a significant factor despite the reduced amount of material. Several studies on CP patients have shown that tobacco is an important prognostic factor for CP[1,2,54,63,75]; this may be due to the effect of tobacco on inhibition of pancreatic bicarbonate secretion and reduction of both serum trypsin inhibitory capacity and alfa-1-antitrypsin levels[5]. The progression from AP to CP, however, is influenced by multiple factors and should be treated accordingly, for example, with treatment for smoking and alcohol dependency[69], and also nutritional and social support.

Causes of death

We found a high incidence of digestive diseases as the cause of death in both AP patients (17.9%) and CP patients (19.5%) compared with the Danish total population (5.3%). The high incidence in AP patients may be due to the fact that 24% developed CP during follow-up (Paper II); most of these patients died during follow-up, and in some, death cause was CP (7.9%). In addition, 37% of the AP patients had a high alcohol intake and therefore, a high risk of developing alcoholic cirrhosis, which 5.5% of the patients died from compared with 1.6% of the Danish population.
In the CP subcohort, we also observed a high frequency of liver diseases including cirrhosis. This is in agreement with the findings of Apte et al[76], who found a frequency of synchronous cirrhosis and alcoholic CP of 40-50% at autopsy, and with Pitchumoni et al[77], who found that 92% of patients with alcoholic cirrhosis in addition had diffuse pancreatic fibrosis. However, Aparisi et al[78] and Ammann et al[52] found the coincidence of alcoholic CP and liver cirrhosis to be rare.
We found a high incidence of suicide as the cause of death in the AP patient subcohort. This may be due partly to the high frequency of high alcohol intake in this patient cohort as patients with alcohol dependency have a significantly higher suicide rate[79]. In 1982, Thorsgaard et al[48] found a high frequency of suicide in CP patients (2/26=7.7%). Also Müllhaupt et al[51] described a high incidence of suicide, especially in idiopathic juvenile CP (14.3%), while in alcoholic CP the frequency was 2.2%. In this CP subcohort, the frequency of suicide was surprisingly low (0.8%) and actually lower than in the Danish non-matched background population (1985: 2.4%; 2006: 1.2%; source: Danish National Health Service, public statistics, 2006). This may be explained partly by CP being less severe in this cohort compared with other selected patient cohorts[48,51].
The incidence of pancreatic cancer in the CP subcohort (3.8%) was almost equal to the findings in the multicenter study by Lowenfels et al in 1993[80] (56/2015=2.8%), of which the present data were a part, and higher than that observed by Pedrazzoli et al[81] (1.2%) and Talamini et al[72] (1.9%). Pancreatic cancer is also a more frequent cause of death in CP patients compared with the Danish background population (1.5%; source: Danish National Health Service, public statistics, 2006). This confirms the carcinogenic effect of CP, while the difference between the studies can be explained by the difference in follow-up time. Moreover, we could not confirm the high incidence of extra-pancreatic cancer caused death, previously found by other studies[48,70,82].

S-amylase and its usefulness in diagnosing AP

This study showed no difference in survival between patients with S-amylase values 1-2-times the upper normal limit compared with patients with S-amylase values >2 times the upper normal limit. Also, we found no association between S-amylase value and survival, no matter the level of S-amylase and with or without logarithmic transformation. This finding points to the cohort being a homogenous population and disagrees with the so-called 'Atlanta criteria' of S-amylase values >3 times the upper normal limit as the only criterion to diagnose AP, which in agreement with Lankisch et al[83]. When diagnosing AP, we suggest focusing more on the elimination of differential diagnoses than on the level of S-amylase. Thus, the diagnosis of AP is most likely correct when the patient has abdominal pain and increased S-amylase (no matter the level), possibly in combination with positive radiological or per-operative findings, if other causes of abdominal pain are eliminated.

Surgical procedures

In the AP subcohort, 18% had surgery for AP at inclusion and in the CP subcohort, 26% had surgery for CP before or at inclusion. The present study is 30 years old but the treatment of AP and CP has not dramatically changed. In Denmark, surgical procedures for pancreatitis is seldom used and primarily prioritized for patients with pancreatic cancer[84]. Two previous randomised studies have shown that surgical drainage of the pancreatic duct is more effective for pain relief than endoscopic treatment in patients with obstruction of the pancreatic duct due to CP[85,86]. As we found no significant difference in overall survival between CP patients who underwent pancreatic surgery compared to CP patients who did not, one might speculate if surgery should be considered more often in these patients.

Strengths and limitations

The CPS represents the longest follow-up of AP patients to date and the 30 years follow-up in the Danish registries is complete. Patients were prospectively included from a well-defined geographical area and reflected a broad spectrum of patients well characterized clinically from five secondary centers in Copenhagen. Unfortunately, severity according to either the Ranson or Imrie score was not measured at inclusion and was not

possible retrospectively. Therefore, severity as a prognostic factor was not examined. During the inclusion period for the CPS, radiological diagnosis of gallstones was not as good as today, therefore, some gallstone-induced AP may have been missed. Although, ERCP was at the same standard as today, the ultrasound equipment was not as sensitive; cholecystography was often used unlike today; computed tomography was sparsely used, and MRCP and endoscopic ultrasound was not an option. In Denmark, Sweden, Norway and Germany, gallstones is now the most frequent cause of AP in contrast to three decades ago when alcohol was the most frequent cause[4,28,30,67]. The more frequent usage of more sensitive diagnostic radiological tools for the diagnosis of gallstones – including endoscopic ultrasonography - during the last three decades has most likely contributed to this increase in biliary AP[67]. According to the guidelines of Norton et al[87], only 20-25% of all AP should be classified as idiopathic. Some of the 47% idiopathic AP in this study may have been misclassified because of relatively insensitive gallstone diagnostics a quarter of a century ago and maybe also because of a low level of alcohol intake self-reporting. Unfortunately, we did not have informations about alcohol consume and tobacco use during the follow-up period 1982-2008, which can contribute to a misclassification. Also, the percentage of idiopathic CP was high in this study (49.8%). In previous large cohorts of CP the percentage of idiopathic CP is lower (Ammann[52]: 24%; Lankisch[24]: 28%) and the frequency of initial AP was lower (Ammann[49]: 28%; Paper III: 36.5%). These differences in frequency might partly be caused by national variation or misclassified patients because of undisclosed alcoholics in the non-alcoholic group but actually it is in accordance with the latest cohort studies[88,89].
The risk to develop CP after AP was analysed by a pragmatic approach. We included all patients with AP, who at any time developed CP and thereby also patients with synchronous AP and CP, and patients who were screened for CP shortly after their first AP attack were included. This classification is in aggreement with the study of Ammann et al in 1986[12] and 1994[11] and with the statement of Bradley 3rd et al in 1993[14], that AP in patients subsequently shown to harbour underlying CP should be classified as AP until the diagnosis of CP has been clearly established. The cut-off level of S-amylase in this study was lower than that ascribed to the 'Atlanta-criteria' described above. The study was initiated 30 years ago and therefore based on the best diagnostic knowledge at that time[90]. According to the CP subcohort, the CPS inclusion criteria from 1977 did not include ERCP findings, but were primarily based on clinical data and thereby more practically useful compared with any other classification system at that time. The Layer score was applied in the present study to validate the diagnostic accuracy and to classify into probable or definite CP; 25% of patients with an inclusion criterion of CPS-4 and all patients with CPS-6 would have been misclassified as having probable CP if the Layer score had not been used (Paper II), but overall was the validity of the original CPS criteria good.
Necrosectomy in severe AP has previously been claimed to be followed by exocrine and endocrine pancreatic insufficiency in up to 50% of patients[44,91,92]; in addition the severity of AP is an important risk factor for development of pancreatic insufficiency[11]. Whether this is consistent with 'classic CP' or due to necrosis with loss of pancreatic tissue and subsequent loss of pancreatic function is an important discussion point, but beyond the purpose of this thesis. In this study, necrosectomy was infrequent and unfortunately, the extent of pancreatic necrosis and necrosectomy was not precisely registered because whole body computed tomography was not available at the time of inclusion. This may explain why this factor had no significant impact on the development of CP.
It is documented[66,67] that ICD codes from the National Patient Registry concerning CP have a validity that varies from 63 to 78%. In the study of the development of CP after AP, however, only 17 patients (20%) had a CP diagnosis based exclusively on information from the National Patient Registry, and the risk of an important bias from incorrect coding is, therefore, less likely.

CONCLUSIONS

Significant factors associated with mortality in AP patients were high age, alcohol and diabetes, whereas female gender, employment, and co-living were associated with better survival. Level of S-amylase had no impact on mortality. When diagnosing AP, we suggest focusing more on the elimination of differential diagnosis than on the level of S-amylase.

AP can progress to CP not only from alcoholic but also from idiopathic AP within a mean interval of 3.5 years. The mortality was 5–7 times higher compared with the background population, indicating that patients with risk factors for CP should be followed. As the disease is multifaceted, treatment for smoking dependency, and alcohol dependency is encouraged together with nutritional support.

Patients with definite CP had a 4-fold higher mortality than the background population and patients with a suspicion of CP had twice the mortality compared with the background population. Unlike alcohol and smoking, both non-employment and being underweight had a significant negative impact on survival in these patients. In the future, more attention should be given to social support and nutritional treatment in CP patients.

SUMMARY

Acute and chronic pancreatitis are most frequently caused by a high consumption of alcohol and tobacco but often the aetiology is unknown. The diseases have a high risk of complications, but the long-term prognosis and the natural course of the diseases are only sparsely described. The aims of the study were to investigate the long-term prognosis of acute pancreatitis (AP) and chronic pancreatitis (CP), the risk of progression to CP, and the natural course of progressive acute pancreatitis. Hereby, describe the prognostic factors associated with mortality and the causes of death in these patients.
The study was based on the large prospective cohort study – Copenhagen Pancreatitis Study – of patients in the Copenhagen Municipality admitted with either AP or CP fulfilling specific diagnostic criteria and enrolled in the study during 1977 to 1982 and in 2008 followed up by linkage to the Danish registries.
Factors associated with mortality in AP patients were high age, alcohol and diabetes, whereas female gender, employment, and co-living were associated with better survival. Level of S-amylase had no impact on the mortality. AP can progress to CP not only from alcoholic but also from idiopathic AP within a mean interval

of 3.5 years. The mortality of progressive AP was 5–7 times higher compared with the background population. Patients with definite CP had a 4-fold higher mortality than the background population and patients with a suspicion of CP had twice the mortality compared with the background population. Unlike alcohol and smoking, both non-employment and being underweight had a significant impact on survival in CP patients.

In the future, when diagnosing AP, we suggest focusing more on the elimination of differential diagnosis than on the level of S-amylase. The high mortality in progressive AP indicates that patients with risk factors for CP should be followed up. As both AP and CP are multifaceted, treatment for smoking dependency, alcohol dependency, and social and nutritional support is encouraged. More knowledge could be provided by interventional treatment of these four focus areas in patients with AP and CP.

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