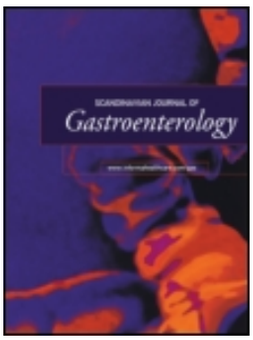

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ORIGINAL ARTICLE

Factors associated with long-term mortality in acute pancreatitis

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Abstract

Background and aims. Knowledge of the long-term prognosis of acute pancreatitis (AP) is limited. The aims were to investigate: (1) prognostic factors associated with long-term mortality in patients with AP; (2) whether or not the level of serum (S-)amylase at admission had an impact on the prognosis; (3) causes of death in these patients. ***Methods.*** During 1977–1982, patients who were admitted to the five main hospitals in Copenhagen with a diagnosis of AP or chronic pancreatitis (CP) were included in a prospective cohort, the Copenhagen Pancreatitis Study (CPS); in 2008, they were followed up by linkage to the Danish Registries. The analyzed subcohort consisted of 352 patients with probable AP (n = 54) or definite AP (n = 298). ***Results.*** Multivariate Cox regression analysis showed that significant factors associated with mortality were age, alcohol, and diabetes, whereas female gender, co-living and employment were associated with better survival. The S-amylase level had no impact on mortality. The most frequent causes of death were cardiovascular diseases, digestive diseases, and malignancies. ***Conclusions.*** Age, alcohol and diabetes had a significant impact on survival whereas the S-amylase level did not.

Key Words: *Acute pancreatitis, cohort, long-term prognosis, prognostic factors, prospective*

Introduction

The etiology, incidence and short-term prognosis in acute pancreatitis (AP) are described in several retrospective studies [1–12], prospective studies [13–17] and in systematic reviews [18–21]. Hereby, prognostic factors with an impact on short-term survival in AP have been identified in order to predict a fatal outcome from AP, and scoring systems predicting the severity of AP [21] have also been developed. Prognostic factors for long-term survival and causes of death, however, are more sparsely described [16,22–24].

To diagnose AP may be difficult because of great variability in the clinical and biochemical presentation. Most often, the diagnosis is based on the "so-called" Atlanta criteria [25]: a three-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. However, in AP, measurement of S-amylase is neither sufficiently sensitive nor specific. In a retrospective study in 1999, Lankisch et al. [26] disputed these criteria and hypothesized that the severity of AP is independent of the level of S-amylase.

The Copenhagen Pancreatitis Study (CPS) is a large prospective cohort study of patients in the Copenhagen Municipality admitted with either AP or chronic pancreatitis (CP) fulfilling specific diagnostic criteria [27,28]. The CPS has the advantages of a prospective design, large size, geographical

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demarcation, and a complete 30-year follow-up by means of record linkage to the Danish health registries [29].

The aims of this study were to investigate: (1) prognostic factors associated with long-term mortality in patients with AP; (2) whether or not the level of S-amylase at admission had an impact on the prognosis; (3) causes of death in these patients.

Material and methods

The original CPS cohort

A total of 672 patients, resident in Copenhagen (population of 417,000) and admitted with diagnosed AP or CP according to the inclusion criteria, were consecutively enrolled in the study from November 1977 to August 1982 [27]. The CPS cohort was followed up until August 2008. Thirty patients were secondarily excluded for not fulfilling the inclusion criteria or fulfilling one of the exclusion criteria. The inclusion criteria were modified from the 1963 Marseilles classification [30] and based on a combination of clinical history, and biochemical, pathoanatomical or radiological findings (Table I). Descriptions of autopsies were obtained for 68 patients with probable or definite AP. At inclusion, clinical history, physical signs, treatment, and laboratory tests were noted. Smoking habits were not registered at inclusion but could be retrieved in 124 of 152 accessible AP patient records. When gallstones were suspected, cholecystography, abdominal ultrasound, computer tomography, endoscopic retrograde cholangio-pancreaticography (ERCP) or a combination of these were performed.

AP cohort

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

Classification of etiologies

Alcoholic AP was defined as patients with CPS inclusion criteria 0–3 and an alcohol consumption of ≥50 g ethanol per day at inclusion, and non-alcoholic AP as patients with CPS inclusion criteria 0–3 and an alcohol consumption of <50 g ethanol per day. Patients with familial pancreatitis were those with first order relatives, who previous to the inclusion date had had AP or CP. Idiopathic AP was defined as patients with CPS inclusion criteria 0–3 and an alcohol consumption of <50 g ethanol per day combined with no inheritance, no gallstone-induced AP and no other etiologies (e.g. hypercalcemia). Patients with gallstone-related AP were those with CPS inclusion criteria 0–3, 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 at ultrasound, computed tomography, ERCP, cholecystography, surgery or autopsy.

The Danish registries

In August 2008, data from the CPS cohort were linked to the Causes of Death Registry and the National Patient Registry using a 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 causes 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

Table I. Copenhagen Pancreatitis Study inclusion criteria and distribution of the acute pancreatitis (AP) cohort.

		Clinical criteria	AP cohort (n = 352)
Probable AP	0	Acute abdomen with pain in the upper half of abdomen and S-amylase 300–600 U/L*	54
Definite AP	1	Acute abdomen with pain in the upper half of abdomen and S-amylase >600 U/L*	258
	2	Acute abdomen with pain in the upper half of abdomen and acute inflamed pancreas at surgery for acute abdomen	15
	3	S-amylase >600 U/L* and acute inflamed pancreas at surgery for acute abdomen	25

*Normal range of S-amylase was 70–300 U/L.

the diagnoses of surgery were obtained. The diagnoses in both the Causes of Death Registry and the National Patient Registry were coded using the World Health Organization International Classification of Diseases, 8th Edition (ICD-8) from 1 January 1977 to 31 December 1993 and from 1 January 1994 using the 10th Edition (ICD-10).

Ethics

The original CPS protocol was approved by the local ethics committees at the five main hospitals in the city of Copenhagen as no formal Regional Ethics Committee was established at that time. The CPS follow-up during 1987–1988 was approved by the Ethics Committee for Medical Research in Copenhagen (number V.100.1239/88 b9). The register-based follow-up was approved by the Regional Committee for Biomedical-Research Ethics in Copenhagen in May 2008 (number 18483) and by the Danish Data Protection Agency (2007–41–0749). Informed consent was not required because the current follow-up was based on registries alone.

Statistical methods

Cox proportional hazard regression was used to test the association between clinical and social prognostic factors, and mortality in the patients with AP. Using Cox proportional hazards models, patients were followed from entry in the CPS until date of death or censoring. Variables that showed indication of prognostic influence in univariate Cox regression analysis ($p < 0.20$) were included in multivariate Cox regression analysis using the backward elimination method. Censoring was because of loss from follow-up, emigration or end of follow-up. 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 by using this time-scale. Student's *t*-test, Mann–Whitney and chi-square 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), and Statistica (version 4.3) were used as software.

Results

Etiology

AP was supposed to be alcoholic in 129 patients (36.6%), familial in eight (2.3%), due to hypercalcemia/hyperparathyroidism in one (0.3%), and gallstones in 44 (12.5%), leaving 170 (48.3%) to be characterized as idiopathic. In 48 patients, gallstones were verified by ultrasound and/or computed tomography, cholecystography, ERCP or a combination. Of these, 44 had an alcohol intake <50 g per day and categorized, therefore, as having gallstone-induced AP.

Patient characteristics at initial hospitalization

Definite AP compared with probable AP. Table II shows the characteristics of the patients with definite and

Table II. Patient characteristics at initial hospitalization.

	Definite AP	Probable AP	Alcoholic AP[#]	Non-alcoholic AP
n	298	54	129	199
Age, years	55.9 (38.2–72.1)	57.3 (44.7–66.8)	40.7 (23.3–77.9)***	65.7 (48.7–76.8)
Gender (male/female)	157/141	33/21	23/106***	119/80
BMI	24.0 (21.6–26.5)	23.6 (20.8–26.5)	23.7 (16.0–34.1)	24.0 (21.5–26.4)
Alcohol intake >50 g per day	112/298 (37.6%)	17/54 (31.5%)	100%***	0%
Tobacco (g per day)	11.0 (0.1–20.0)	9.0 (0.0–16.4)	20.0 (0–40)***	4.0 (0.0–16.0)
B-hemoglobin (normal range 8.1–10.9 mmol/L)	8.9 (8.0–9.8)	9.0 (7.8–9.5)	9.3 (6.0–12.0)***	8.7 (7.9–9.4)
B-leukocytes (normal range 3.0–9.0 10^9/L)	10.2 (7.7–13.9)**	8.5 (6.7–11.2)	10.5 (4.0–33.0)	9.5 (7.7–13.1)
S-amylase (normal range 70–300 U/L)	1919 (988–4080)***	413.5 (368–452)	1189 (29–13020)**	1846 (680–4081)
S-bilirubin (normal range 5–17 μmol/L)	14.5 (9.0–28.3)***	9.0 (5.0–12.0)	11 (3–225)	13.0 (8.5–28.5)
S-alkaline phosphatase (normal range 51–275 U/L)	240 (180–335)*	198 (147–292)	222 (43–1176)	242 (169–402)
S-aspartate aminotransferase (normal range 10–40 U/L)	48 (24–107)***	23.0 (18.0–42.5)	45 (5–500)	36.0 (21.0–111.0)
S-gamma-glutamyltransferase (normal range 6–28 U/L)	112 (46–250)*	51.0 (28.0–126.8)	145 (19–740)	74.5 (32.0–256.3)
S-creatinine (normal range 49–121 μmol/L)	91.0 (78.3–109.0)	93.0 (79.5–113.0)	91 (18–491)	91.5 (79.0–109.0)
S-albumin (normal range 540–800 μmol/L)	518 (449–585)	564 (461–610)	506 (243–691)*	536 (477–591)
P-coagulation factor 2, 7, 10 (normal range 0.7–1.3)	1.03 (0.85–1.30)	1.10 (0.91–1.30)	1.1 (0.0–2.0)	1.05 (0.86–1.30)
S-calcium (normal range 2.19–2.71 mmol/L)	2.23 (2.09–2.35)**	2.35 (2.23–2.45)	2.2 (1.0–3.0)**	2.29 (2.14–2.39)

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.
[#]Alcohol intake data were missing for 24 patients.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ in Student's *t*-test, Mann–Whitney or chi-squared tests, as appropriate, comparing definite AP with probable AP or alcoholic AP compared with non-alcoholic AP.

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-gamma-glutamyltransferase 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. Of all 352 AP patients, 62 patients underwent 67 surgical procedures for AP at inclusion: peritoneal drainage with or without necrosectomy in 12; biliary drainage in 31; subtotal pancreatectomy in five; drainage of a pseudocyst or pancreatic abscess in 10; explorative laparotomy in four; peritoneal dialysis in one; a combination in four. During the follow-up, 20 surgical procedures were done in 17 individuals: subtotal pancreatectomy, pancreaticogastrostomy, pancreaticojejunostomy or pancreatic lithotomy. During the follow-up, 85 (24.1%) patients developed CP [31].

Alcoholic and non-alcoholic AP. Table II also shows the characteristics of alcoholic (n = 129) and non-alcoholic (n = 199) AP patients at initial hospitalization. In 24 patients, alcohol intake information was missing. Alcoholic AP patients were more frequently divorced, whereas unemployment caused by retirement was more frequent in non-alcoholics. These findings were almost unaffected by whether alcoholic pancreatitis was defined as an alcohol consumption of ≥10 g alcohol per day or a value of ≥50 g alcohol per day for ≥5 years.

Survival and prognostic factors

The Kaplan–Meier survival curves for the probable and definite AP groups showed no significant difference (Figure 1: $p = 0.14$, hazard ratio (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 2: $p < 0.0001$, HR 3.16, 95% CI 2.32–4.29).

Table III summarizes the univariate Cox regression analysis corrected for age in AP patients, and Table IV summarizes the multivariate Cox regression analysis. In the final model, 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, body mass index (BMI), smoking, surgery for AP at inclusion, and inheritance as the cause. Gallstones as the cause were significant in the univariate model 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.

Causes of death

291 patients (82.7%) in the AP cohort died during the 30-year follow-up. Table V 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.

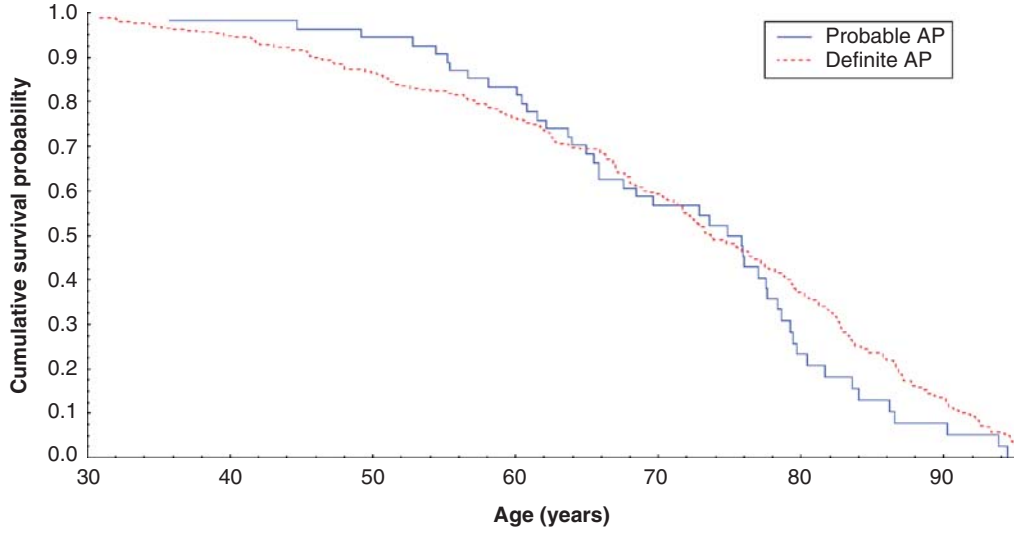

Figure 1. The cumulative survival for definite and probable acute pancreatitis (AP).

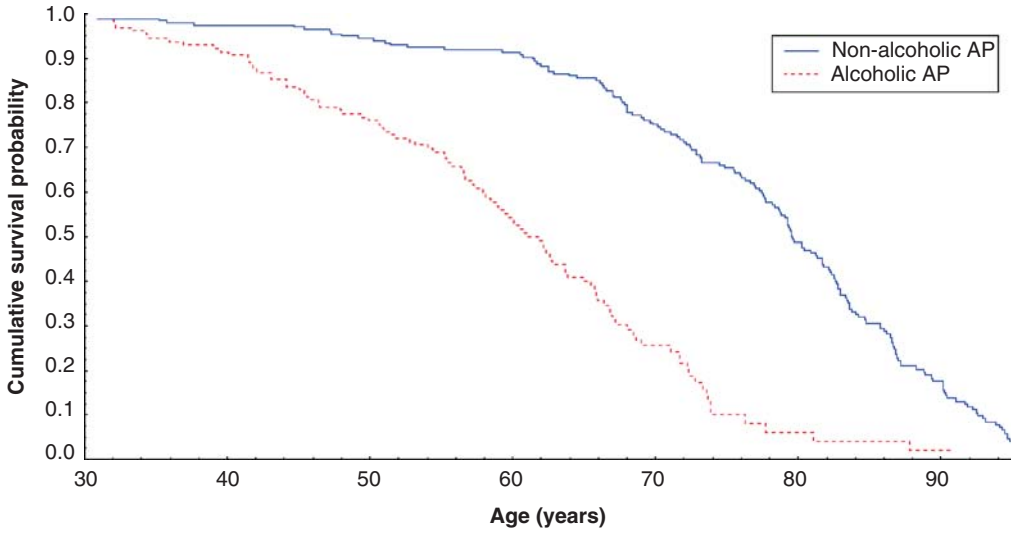

Figure 2. The cumulative survival of alcoholic and non-alcoholic acute pancreatitis (AP).

Discussion

Prognostic factors

This prospective study of a cohort of patients with AP from a well-defined geographical area with complete follow-up showed that alcohol is an important prognostic factor for patients with AP, but in contrast, to CP smoking is not a prognostic factor [9,32–35]. The mechanisms of alcoholic pancreatitis are unclear but alcohol may: act inappropriately on the sphincter of Oddi, change the composition of the pancreatic juice, and directly damage the acinar cells leading to acute inflammation [36]. Our results agree with the findings of Kristiansen et al. [37], 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 for CP (varies from 63% to 78%) and AP (varies from 51% to 73%) should be taken into account [29,38]. Other long-term follow-up studies include a more selected patient population and do not describe prognostic factors associated with long-term mortality [2,22–24]. We found a significantly higher mortality in alcoholic AP patients compared with non-alcoholic patients. This is not in agreement with Renner et al. [12] who found similar long-term survival in patients with alcohol-induced AP

Table III. Univariate Cox regression analysis corrected for age in acute pancreatitis (AP) patients.

Variable	Scoring	Beta	Standard error	*p*-Value
Age	Age in years	0.0424	0.0038	<0.00001
Gender	1: woman; 0: man	−0.2572	0.1213	0.034
Alcohol	0: 0 g/day ; 1: >0 g/day	0.6155	0.1523	<0.0001
Alcohol	0: 0 g/day; 1: 10–40 g/day; 2: ≥50 g/day <5 years; 3: ≥50 g/day ≥5 years	0.0644	0.0224	0.004
Smoking	0: 0 g/day; 1: 10–19 g/day, ≥20 g/day	0.1951	0.1980	0.324
Smoking	Smoking in g/day	0.0133	0.0105	0.204
S-amylase	S-amylase as quantitative variable	−0.00003	0.00002	0.218
Inclusion criteria 0 vs. 1–3	0: S-amylase 300–600; 1: S-amylase >600	0.0182	0.1616	0.910
Inclusion criteria 0–3	See Table I	0.0164	0.0866	0.850
BMI	BMI as quantitative variable	−0.0279	0.0165	0.090
BMI, categories	1: BMI <20; 2: BMI 20–25; 3: BMI >25	−0.1221	0.1046	0.243
Diabetes vs. no diabetes	0: no diabetes; 1: diabetes	0.5740	0.2698	0.033
Familial vs. non-familial	0: no inheritance; 1: inheritance	−0.3311	0.3803	0.384
Single vs. co-living	0: single living; 1: co-living	−0.4144	0.1311	0.002
Employment vs. non-employment	0: non-employment; 1: employment	−0.2423	0.1604	0.131
Surgery for AP vs. no surgery	0: no surgery at inclusion; 1: surgery for AP at inclusion	−0.3362	0.1637	0.040
Gallstone-induced vs. not gallstone-induced	0: not gallstone-induced; 1: gallstone-induced	0.5075	0.1820	0.005

Table IV. Multivariate Cox regression analysis in acute pancreatitis patients.

Variable	Scoring	Beta	Standard error	*p*-Value
Age	Age in years	0.0418	0.0048	<0.00001
Gender	0: woman; 1: man	−0.3841	0.1281	0.0041
Alcohol	0: 0 g/day; 1: 10–40 g/day; 2: ≥50 g/day <5 years; 3: ≥50 g/day ≥5 years	0.0740	0.0236	0.0026
Diabetes vs. no diabetes	0: no diabetes; 1: diabetes	0.6969	0.2743	0.0166
Single vs. co-living	0: single living; 1: co-living	−0.5145	0.1369	0.0003
Employment vs. non-employment	0: non-employment; 1: employment	−0.3233	0.1647	0.0497

compared with non-alcoholic AP. This difference between the studies may be explained by the 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 not surprising considering the high co-morbidity of these patients. It is also in accordance with Renner et al. [12], who described a significantly higher prevalence of established diabetes in AP than observed in the control series; 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 [39].

This study used specific clinical inclusion criteria and all causes of AP were included, but unfortunately, a scoring system for AP severity was not used. From the rather low mortality at the start of the study, we presume that most of the AP was mild or moderate.

Causes of death

We found a high incidence of digestive diseases (17.9%) as the cause of death compared with the total Danish population (5.3%). This may be due to the fact that 24.1% developed CP during follow-up [31]; most of these patients died during follow-up; some of them died of CP alone (7.9%). In a previous study [31], we found that the mortality for patients who developed CP after AP was 2.7 times higher than the mortality in patients who did not develop CP, and 5.3–6.5 times higher than the mortality in the background population. 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 total Danish population. We found a high incidence of suicide as the cause of death in this patient population. This may be due partly to the high frequency of high alcohol intake in this patient cohort as patients with alcohol as an etiology may have a significantly higher suicide rate [40].

Table V. Causes of death in the acute pancreatitis (AP) cohort.

Causes of death	Number of deaths in the AP population, $n = 291$	Percentages of deaths in the total Danish population in 2006, $n = 55{,}213$
Cardiovascular diseases	63 (21.6%)	19.1%
Digestive diseases	52 (17.9%)	5.3%
AP	1 (0.3%)	
CP	23 (7.9%)	
Alcoholic liver diseases and cirrhosis	16 (5.5%)	1.6%
Malignancy	50 (17.2%)	28.3%
Pancreatic cancer	2 (0.7%)	1.5%
Senile decay including stroke and dementia	28 (9.6%)	
Respiratory diseases	15 (5.2%)	9.6%
Accident	14 (4.8%)	3.6%
Suicide	12 (4.1%)	1.2%
Diabetes	10 (3.4%)	2.3%
Mental illness (not dementia)	7 (2.4%)	
Infectious diseases (including tuberculosis)	2 (0.7%)	1.4%
Diseases in the urinary tract or gynecological diseases	2 (0.7%)	1.9%
Other not clearly defined causes	26 (8.9%)	3.2%
Patients died within the last 2 years*	10 (3.4%)	

*The National Health Service has not yet received information about the cause of death for these 10 patients.

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 as being a homogenous population and disagrees with the "Atlanta criteria" of S-amylase values >3 times the upper normal limit as the only criterion to diagnose AP. This opinion agrees with Lankisch et al. [26]. 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.

Strengths and limitations

The CPS represents the longest follow-up of AP patients to date and the follow-up in the Danish registries is complete. Patients were prospectively included from a well-defined geographical area and were well characterized clinically. 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 and, therefore, some gallstone-induced AP may have been missed. Although ERCP was at the same standard, the ultrasound equipment was not as sensitive; cholecystography was often used unlike today; computed tomography was sparsely used, and endoscopic ultrasound and MRCP were not an option. In Denmark, Sweden, Norway and Germany, gallstones are now the most frequent cause of AP in contrast to three decades ago when alcohol was the most frequent cause [14,16,38,41]. The increased use of more sensitive diagnostic radiological tools for the diagnosis of gallstones during the last three decades has most likely contributed to this increase in biliary AP [38]. According to the guidelines of Norton et al. [42], 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, lack of genetic testing, and maybe also because of a low level of alcohol intake self-reporting.

Conclusion

Significant factors associated with mortality in AP patients were high age, alcohol and diabetes, whereas female gender, employment, and single 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.

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