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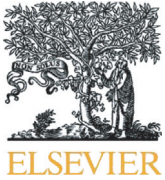
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# Short- and long-term survival after severe acute pancreatitis: A retrospective 17 years' cohort study from a single center

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## ABSTRACT

**Purpose:** To study mortality in severe acute pancreatitis (SAP) and to identify risk factors for mortality.

**Materials and methods:** A retrospective 17-years' cohort study of 435 consecutive adult patients with SAP treated at intensive care unit of a university hospital.

**Results:** Overall, 357 (82.1%) patients survived at 90 days follow-up. Three-hundred six (89.5%) patients under 60 years, 38 (60.3%) patients between 60 and 69 years, and 13 (43.3%) patients over 69 years of age survived at 90 days follow-up. Independent risk factors for death within 90-days were: 60 to 69 years of age (odds ratio [OR] 5.1), >69 years of age (OR 10.4), female sex (OR 2.0), heart disease (OR 2.9), chronic liver failure (OR 12.3), open abdomen treatment (OR 4.4) and sterile necrosectomy within 4 weeks (OR 14.7). The 10-year survival estimate was <70% in patients under 60 years and <30% in patients over 60 years. Underlying cause of death after the initial 90-day follow-up period was alcohol-related in 48 (57.1%) patients, and all of them had suffered from alcoholic SAP.

**Conclusions:** Although younger patients have excellent short-term survival after SAP, the long-term survival estimate is disappointing mostly due to alcohol abuse.

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## 1. Introduction

The definition of severe acute pancreatitis (SAP) according to the revised Atlanta classification (2012) is organ failure (OF) affecting respiratory, renal or cardiovascular system, that does not resolve within 48 h [1]. Severe acute pancreatitis occurs in about 10% of patients with acute pancreatitis [2,3]. Patients with SAP usually require admission to intensive care unit (ICU), where treatment may last for several weeks [3,4]. Management of patients with SAP is supportive, including renal replacement therapy, mechanical ventilation and inotropic medication [1]. Early enteral nutrition is associated with fewer local and distant infectious complications, seems to reduce mortality, and is recommended to be started routinely in the management of SAP [5,6]. Managing secondary infections plays an important part of treatment, and some patients may need surgical treatment for complications such as abdominal compartment syndrome (ACS) or infected pancreatic necrosis (IPN) [7–10]. However, necrosectomy should be postponed to after 4 weeks from symptom start whenever possible [6].

The mortality rate in acute pancreatitis (AP) is about 2.7–7.5%, and increasing age is associated with increased mortality [3,11,12]. About

50% of deaths occur within the first 2 weeks of the disease and early death is usually associated with persistent multiple organ failure (MOF) [11–13]. Organ failure in AP is associated with up to 30% mortality rates [14]. Type 2 diabetes and fatty liver might increase mortality in AP, but to our knowledge there are few studies on the effect of pre-existing comorbidities on mortality using the latest classification system of the severity of acute pancreatitis [15,16]. Furthermore, there is limited information regarding short- and long-term mortality in SAP based on the new classification system.

Severe acute pancreatitis increases the risk for intra-abdominal hypertension and ultimately ACS and a recent systematic review reported as high as 49% mortality rates in patients with ACS related to AP [17–21]. Conservative management of intra-abdominal hypertension consists of optimized fluid management, sedation and analgesia, neuromuscular blockade and evacuation of intraluminal contents and intra-abdominal collections [22]. Abdominal compartment syndrome requiring surgical decompression is associated with severe MOF and high mortality and morbidity rates [8]. Infected pancreatic necrosis is associated with mortality and delaying necrosectomy for IPN, has previously been shown to have survival benefit [14,23]. Current guidelines recommend delaying invasive interventions (i.e. endoscopic transluminal drainage or necrosectomy, minimally invasive or open necrosectomy) whenever possible for 4 weeks after onset of symptoms for the collections to become walled off [6].

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The aim of this study is to report short- and long-term survival rates in patients with SAP according to the revised Atlanta classification (2012). In addition, the aim is to evaluate the impact of pre-existing comorbidities, disease complications and treatment strategies on survival in a large cohort of patients from a single center. The impact of changes in treatment protocols on survival is also reported.

## 2. Material and methods

This is a retrospective analysis of patients with SAP treated at some point of the disease in the ICU at the Helsinki University Hospital (HUU) Meilahti between January 1, 1999 and December 31, 2015. Information was gathered from hospital records including daily ICU-monitoring sheets. The diagnostic criteria for pancreatitis included typical abdominal pain and serum amylase level at least three times the upper limit of normal or pancreatitis verified on CT-scan. Severe acute pancreatitis was defined by persistent organ failure not resolving within the first 48 h according to revised Atlanta classification (2012) [1]. Short- and long-term information on survival was collected from the Finnish civil registry records. Cause of death was gathered from hospital records, and if cause of death was not retrievable from hospital records it was gathered from Statistics Finland (<http://www.stat.fi>). STROBE statement checklist (<http://www.strobe-statement.org>) was followed.

Meilahti Hospital serves as the secondary and tertiary surgical referral center in the area with a catchment population of about 1.4 million. The majority of patients with SAP are treated in the ICU of the Meilahti Hospital, the largest ICU in the area. The initial search in patient database included all patients treated at ICU during the study period with diagnosis of acute pancreatitis ( $n = 610$ ). Data of these 610 patients was systematically reviewed to identify those patients that fulfilled the revised Atlanta classification (2012) criteria for SAP. One-hundred seventy-two patients were excluded from this study because they did not meet the criteria for SAP. Furthermore, three patients were lost to follow up, and consequently these patients were excluded from this study. This resulted in 435 patients meeting the inclusion criteria. Data of surgical necrosectomies were gathered. Indication for surgical necrosectomy was clinical suspicion or verified infected necrosis. Another indication was persistent symptoms due to walled off necrosis without suspicion of infection later than four weeks from symptom onset. Patients were divided into two groups based on the period of treatment (group 1,  $n = 204$ : 1999–2007 and group 2,  $n = 231$ : 2008–2015) to evaluate potential differences in survival and the effect of changes in management strategies.

### 2.1. Statistical analysis

A Kaplan-Meier analysis on survival at 90 days and for the total follow-up time was performed, and survival differences were statistically compared using Log Rank test. Univariate odds ratios with 95% confidence intervals were calculated to identify patient-, disease-, and treatment-related variables affecting survival. All statistically significant univariate analysis results, and other clinically relevant variables were included in a multivariate logistic regression analysis. Differences regarding continuous variables were analysed with Mann-Whitney  $U$  test. Pearson Chi-Square test or Fisher's Exact Test (2-sided) (when comparing sample sizes equal or  $<5$ ) were used in comparison of proportions. All statistical analysis was made with SPSS 24.0 (IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Patient data and characteristics

Patient characteristics are presented in Table 1. Overall, female patients in this study were significantly older ( $P = .002$ ) than male patients, and the median age at disease onset was 54 years (interquartile

**Table 1**  
Patient Characteristics.

Age, median (IQR), y	48 (39–58)
Duration of symptoms before hospital admission, median (IQR), d	1 (0–1)
Hospital length of stay before ICU admission, median (IQR), d	1 (1–3)
Intensive care unit length of stay, median (IQR), d	13 (6–25)
Hospital length of stay, median (IQR), d	25 (15–45)
Sex, n (%)	
Female	80 (18.4)
Male	335 (81.6)
Etiology, n (%)	
Alcohol	335 (77.0)
Biliary	51 (11.7)
Other	49 (11.3)

range [IQR], 44–64 years) for females and 47 years (IQR, 39–56 years) for males, respectively. The etiology of pancreatitis differed significantly between the sexes ( $P < .001$ ): etiology of SAP in 39 (48.8%) female patients was other than alcohol, whereas 294 (82.8%) male patients suffered from alcoholic SAP.

Three-hundred seven (70.6%) patients were managed nonoperatively within the first 90 days; 68 (15.6%) patients required open abdomen treatment mostly due to ACS or to prevent ACS after laparotomy, and 103 (23.7%) patients had open surgical necrosectomy. During the whole follow-up time 110 (25.3%) patients had open surgical necrosectomy at some point of their illness.

### 3.2. 90-day (short-term) survival rate

Overall, 357 (82.1%) patients survived 90 days after hospital admission. Survivors were significantly younger, median 47 years (IQR, 39–55 years) than non-survivors 61 years (IQR, 44–68),  $P < .001$ . Underlying cause of death was acute pancreatitis in 77 (98.7%) patients within 90 days after hospital admission.

The impact of age on survival was evaluated by grouping patients by age at disease onset (Fig. 1). We found, that 306 (89.5%) patients under 60 years of age, 38 (60.3%) patients between 60 and 69 years, and 13 (43.3%) patients aged 70 or more survived at 90-days follow-up (Fig. 2). Patients under 60-years were subcategorized into three groups (under 40 years, 40–49 years and 50–59 years), but there was no difference in 90-day ( $P = .844$ ) between these groups. 98 (89.1%), 109 (90.8%) and 99 (88.4%) patients survived at 90 days follow-up, respectively.

Univariate logistic regression analysis of risk factors for death within 90 days are summarized in Table 2. To consider potential confounding factors, a multivariate logistic regression analysis based on results of univariate analysis and other clinically relevant collected data was performed. The results are summarized in Table 3.

### 3.3. Long-term survival

The median follow-up time of patients in this study was 5.8 years (mean; 6.0 years, IQR; 1.1–9.5 years, range; 0–17.3 years). The long-term survival estimate is presented in Fig. 3. The 10-year survival estimate was 28.3% and 67.9% for patients over and under 60 years, respectively. Survival estimates at 10 years after SAP in patients under 60-years subcategorized into three groups (under 40 years, 40–49 years and 50–59 years) were 65.7%, 68.4% and 69.5%, respectively ( $P = .680$ ). The median age at death was 38.1 years, 47.7 years and 56.2 years, respectively.

Underlying cause of death in patients that died after 90 days from hospital admission was acute pancreatitis in 22 (26.2%). These late deaths occurred due to alcohol-related reasons (any underlying, immediate or contributory alcohol-related disease, alcohol-intoxication or traumatic death related to alcohol-use) in 48 (57.1%) patients, and all of these patients had suffered from alcoholic SAP, whereas alcohol-

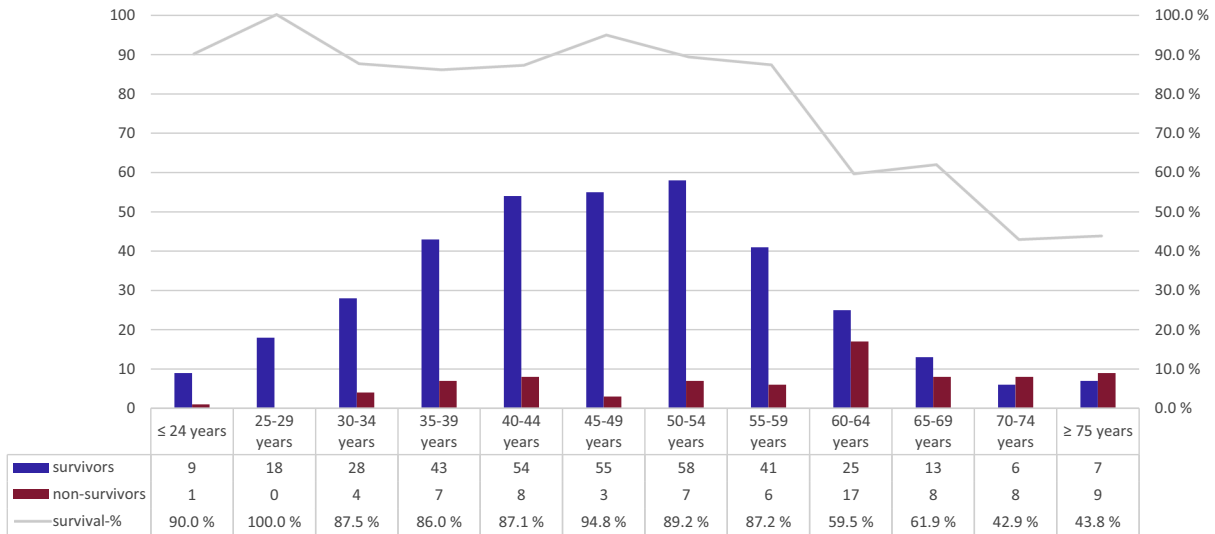


Fig. 1. Age and 90-day Survival.

related deaths did not occur in patients with other SAP etiology ( $P < .001$ ).

3.4. Differences between group 1 (1999–2007,  $n = 231$ ) and group 2 (2008–2015,  $n = 204$ )

In comparison to group 1 there were significantly more patients with pre-existing diabetes and respiratory disease in group 2: 34 (16.7%) vs. 22 (9.5%),  $P = .026$ , and 26 (12.7%) vs. 16 (6.9%),  $P = .040$ , respectively. There were no age ( $P = .291$ ), sex ( $P = .062$ ) or other known significant differences between the groups.

In group 2 compared with group 1, open abdomen was utilized more frequently: 43 (21.1%) vs. 25 (10.8%) patients,  $P = .003$ . Within 90 days from symptom start 54 (26.5%) and 49 (21.2%),  $P = .198$ , patients were treated with surgical necrosectomy in group 2 and group 1, respectively, and the proportion of late (>4 weeks) necrosectomies increased significantly in group 2 21 (38.9%) vs. 9 (18.4%),  $P = .022$ . Additionally, in group 2, the proportion of necrosectomies within 90 days due to sterile

necrosis decreased: 5 (9.3%) vs. 16 (32.7%) patients,  $P = .003$ . The overall number of patients requiring necrosectomies within 90 days due to IPN increased in group 2 compared to group 1: 49 (24.0%) vs. 33 (14.3%),  $P = .010$ . Within the 90-day follow-up period 186 (80.5%) and 171 (83.8%) patients survived during the years 1999–2007 and 2008–2015, respectively, but the difference was not statistically significant ( $P = .373$ ) (Fig. 4).

4. Discussion

This study with a long follow-up time in a large cohort of patients treated in an ICU with SAP demonstrates that patients under 60 years with SAP have excellent 90-day survival. Age had a major impact on 90-day survival even after adjusting for pre-existing co-morbidities, resulting in poor outcome in elderly patients. The majority of patients were managed nonoperatively. Surgical decompression for ACS and necrosectomy for sterile necrosis within the first 4 weeks were associated with increased risk of death within the first 90 days.

Ninety-day survival worsened significantly if patients were over 60-years of age, and survival was even worse in patients over 70-years of age. Our results on the impact of age on survival in SAP are in line with previous results concerning AP [7,11]. Heart disease, including coronary artery disease and cardiac insufficiency, and chronic liver failure worsen survival in SAP. A previous study suggests that diabetes might increase mortality in AP, but our study failed to show a significant effect of diabetes on outcome in SAP [15]. Even if the number of patients in this study was relatively large, the prevalence of some pre-existing co-morbidities was fairly low, making definite conclusions on other co-morbidities' effect on survival in SAP difficult.

In multivariate analysis, female sex was associated with reduced 90-day survival. Intriguingly, female sex was a predictor of mortality in a previous cohort study on open surgical debridement of pancreatic necrosis [9]. Even so, our result may also reflect the two major differences between female and male patients in this cohort: female patients were in general significantly older and alcohol etiology was significantly less frequent in comparison with male patients. Also, during this 17-year study period, only 80 female patients met the inclusion criteria for this study, and this relatively low number of female patients might have influenced the results.

Open abdomen treatment, that is used mostly to reduce intra-abdominal pressure in ACS or to prevent occurrence of ACS after laparotomy, was associated with worse 90-day survival in our study. An earlier study from our institution showed that patients requiring surgical decompression for ACS suffer from MOF, with a median Sequential

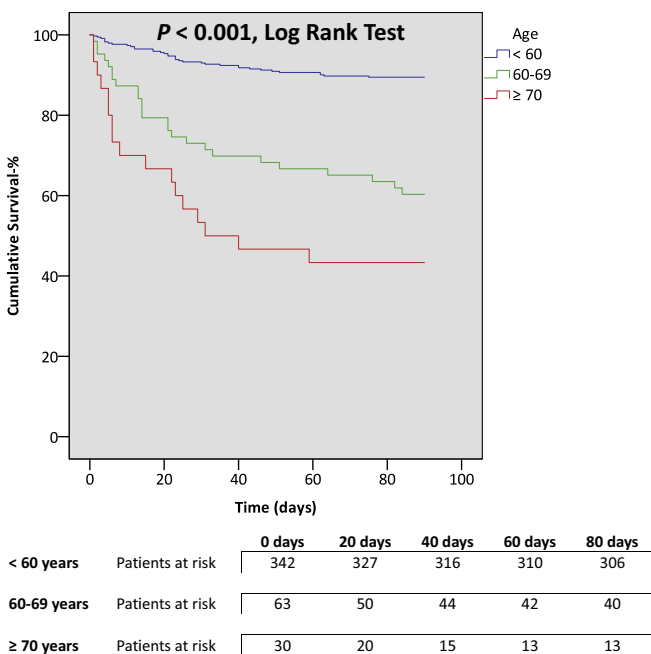


Fig. 2. Kaplan-Meier 90-day Survival Table.

**Table 2**  
90-day survival univariate analysis.

Risk factor	Non-survivors*	Survivors*	All patients†	Odds ratio (95% CI)	P
Sex					
Female	20 (25.0)	60 (75.0)	80 (18.4)	1.707 (0.957–3.046)	0.070
Male	58 (16.3)	297 (83.7)	355 (81.6)	0.586 (0.328–1.045)	0.070
Age, y					
<60	36 (10.5)	306 (89.5)	342 (78.6)	reference	<0.001
60–69	25 (39.7)	38 (60.3)	63 (14.5)	5.592 (3.034–10.308)	<0.001
≥70	17 (56.7)	13 (43.3)	30 (6.9)	11.115 (4.992–24.749)	<0.001
Etiology					
Alcohol	47 (14.0)	288 (86.0)	335 (77.0)	reference	0.001
Biliary	17 (33.3)	34 (66.7)	51 (11.7)	3.064 (1.585–5.921)	0.001
Other	14 (28.6)	35 (71.4)	49 (11.3)	2.451 (1.227–4.898)	0.011
Comorbidities					
None	36 (12.4)	254 (87.6)	290 (66.7)	0.348 (0.211–0.573)	<0.001
Diabetes	17 (30.4)	39 (69.6)	56 (12.9)	2.272 (1.208–4.276)	0.011
Chronic pancreatitis	6 (23.1)	20 (76.9)	26 (6.0)	1.404 (0.545–3.620)	0.482
Heart disease	27 (40.9)	39 (59.1)	66 (15.2)	4.317 (2.434–7.655)	<0.001
Renal disease	5 (35.7)	9 (64.3)	14 (3.2)	2.648 (0.862–8.133)	0.089
Pulmonary disease	10 (23.8)	32 (76.2)	42 (9.7)	1.494 (0.701–3.183)	0.299
Chronic liver failure	5 (71.4)	2 (28.6)	7 (1.6)	12.158 (2.314–63.880)	0.003
Previous pancreatitis					
None	65 (19.3)	271 (80.7)	336 (77.2)	reference	0.368
Once	8 (13.6)	51 (86.4)	59 (13.6)	0.654 (0.296–1.445)	0.294
Twice or more	5 (12.5)	35 (87.5)	40 (9.2)	0.596 (0.225–1.580)	0.298
Infected pancreatic necrosis	22 (21.4)	81 (78.6)	103 (23.7)	1.339 (0.771–2.325)	0.300
Other infection	44 (18.6)	193 (81.4)	237 (54.5)	1.100 (0.671–1.801)	0.706
Group					
1999–2007	45 (19.5)	186 (80.5)	231 (53.1)	1.254 (0.764–2.056)	0.371
2008–2015	33 (16.2)	171 (83.8)	204 (46.9)	0.798 (0.486–1.308)	0.371
Non-operative management	43 (14.0)	264 (86.0)	307 (70.6)	0.433 (0.261–0.717)	0.001
Open abdomen	24 (35.3)	44 (64.7)	68 (15.6)	3.162 (1.779–5.619)	<0.001
Necrosectomy ≤ 90 days‡					
No necrosectomy	51 (15.4)	281 (84.6)	332 (76.3)	reference	<0.001
Sterile necrosis	11 (52.4)	10 (47.6)	21 (4.8)	6.061 (2.447–15.009)	<0.001
Infected necrosis	16 (19.5)	66 (80.5)	82 (18.9)	1.336 (0.717–2.489)	0.362
Necrosectomy ≤ 4 weeks‡					
No necrosectomy	51 (15.4)	281 (84.6)	332 (76.3)	reference	0.001
Necrosectomy on day 0–28	24 (32.9)	49 (67.1)	73 (16.8)	2.699 (1.523–4.783)	0.001
Necrosectomy on day 29–90	3 (10.0)	27 (90.0)	30 (6.9)	0.612 (0.179–2.094)	0.434
Timing of necrosectomy‡					
No necrosectomy	51 (15.4)	281 (84.6)	332 (76.3)	reference	<0.001
≤4 wk, sterile necrosis	11 (64.7)	6 (35.3)	17 (3.9)	10.101 (3.576–28.536)	<0.001
≤4 wk, infected necrosis	13 (23.2)	43 (76.8)	56 (12.9)	1.666 (0.837–3.316)	0.146
>4 wk, sterile necrosis	0 (0.0)	4 (100.0)	4 (0.9)	0.000 (0.000 – NC)	0.999
>4 wk, infected necrosis	3 (11.5)	23 (88.5)	26 (6.0)	0.719 (0.208–2.482)	0.601

CI = confidence interval, NC = not countable.

\* Unless otherwise noted, data is presented as number of patients (% in subgroup of patients with the comorbidity in question).

† Number of patients (% of total number of patients,  $n = 435$ ).

‡ Timing of necrosectomy from the start of symptoms.

Organ Failure Assessment (SOFA) score 12 at the time of decompression, and hence the disease itself might be the reason for poor survival despite surgical efforts [8,21]. Surgical management of ACS is

**Table 3**  
90-day Survival, Multivariate Analysis.

Risk factor	Odds ratio (95% CI)	P
Age, y		
<60	reference	<0.001
60–69	5.095 (2.452–10.588)	<0.001
≥70	10.366 (4.105–26.174)	<0.001
Female sex	2.023 (1.005–4.072)	0.048
Heart disease	2.858 (1.395–5.853)	0.004
Chronic liver failure	12.305 (1.747–86.654)	0.012
Open abdomen	4.413 (2.018–9.650)	<0.001
Necrosectomy		
No necrosectomy	reference	<0.001
Necrosectomy ≤ 4 wk, sterile	14.658 (4.402–48.804)	<0.001
Necrosectomy ≤ 4 wk, infected	1.493 (0.614–3.626)	0.376
Necrosectomy > 4 wk*	0.382 (0.093–1.575)	0.183

\* Necrosectomy due to sterile or infected pancreatic necrosis, and timing of necrosectomy (earlier or later than 4 weeks after onset) were evaluated using a single variable due to otherwise presented redundancies in the equation. CI = confidence interval.

considered a life-saving operation, although the scientific evidence to support this in patients with SAP is limited [24]. Because ACS usually develops early in the course of SAP, a reduction of early mortality would be expected if ACS is managed surgically in a timely manner. However, no such reduction of early or late mortality was observed in this study, although surgical management of ACS with open abdomen became significantly more frequent during latter years of study. Therefore, this study doesn't provide additional information into which patients benefit from surgical open abdomen treatment of ACS in SAP, and further study is needed in this area.

Necrosectomies in the present series were done using the anterior open surgical debridement approach. The indication for necrosectomy was either clinical suspicion of infected necrosis or verified infected necrosis. Only a minority of all patients 103 (23.7%) had necrosectomy within 90 days. In 21 (20.4%) patients infection could not be verified. In line with previously reported results, our data showed that necrosectomy within the first 4 weeks of disease due to sterile necrosis is associated with worse survival [9]. These patients usually present with progressive MOF after the second week, and if worsening is not due to infected necrosis, surgery with high risk of bleeding may be detrimental to the patient. On the other hand, early necrosectomy (within

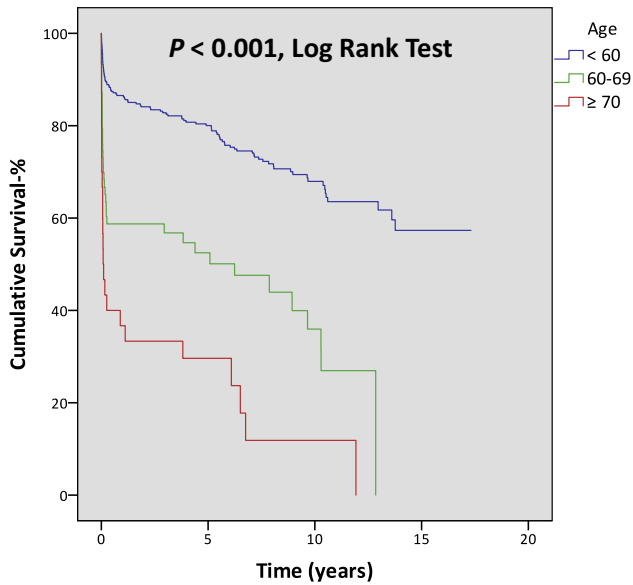


Fig. 3. Kaplan-Meier Long-time Survival Estimate.

4 weeks) in patients with infected necrosis did not significantly affect survival. Furthermore, late necrosectomy (after 4 weeks) regardless of the infection of necrosis did not influence survival. Therefore, it seems very important to determine the possible presence of infected necrosis before surgical intervention, unless intervention is postponed until four weeks has passed from the disease onset. Earlier studies have shown that preoperative verification of IPN (fine-needle aspiration and culture or gas-filled collection on CT-scan) is insufficient, and consequently the diagnostic workup remains a clinical challenge [9]. A

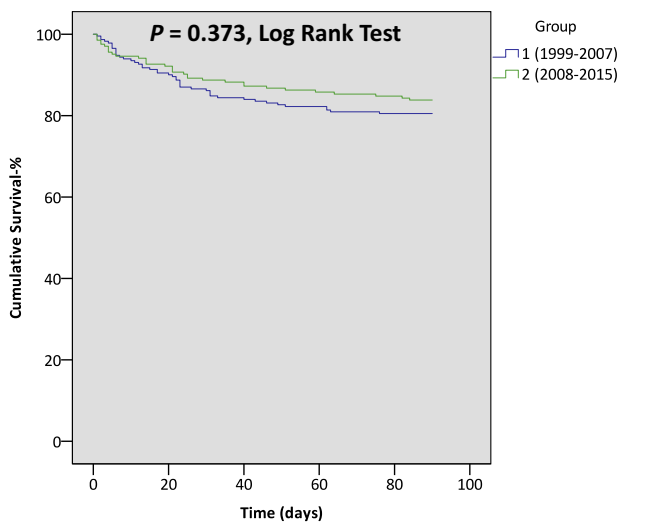


Fig. 4. Kaplan-Meier 90-day Survival Group 1 vs Group 2.

step-up percutaneous drainage with bacterial cultures serves as a method of choice during the first four weeks. During the later study period in this series, fewer patients with sterile necrosis were operated on, which could reflect the change in the diagnostic workup for suspected infected necrosis.

The survival rate after late open necrosectomy was 90%, which is comparable to survival after mini-invasive necrosectomies for walled off necrosis [25–28]. Interestingly, all four patients undergoing late necrosectomy due to sterile pancreatic necrosis survived. Although this scenario is quite rare, the result might indicate that late operative treatment of walled off sterile necrosis can be a safe and feasible option in those patients suffering from symptomatic sterile necrosis after SAP, but further study is needed.

A recent Finnish study in working-age patients, where criteria for SAP might have included some patients with moderately severe acute pancreatitis according to the latest Atlanta classification, showed a 10-year survival estimate of 60% in patients with SAP [29]. In line with these findings, our results in a large cohort of patients treated at ICU with SAP according to the latest Atlanta classification showed a long-time survival of <70% in patients younger than 60 years. Early in the acute course of the disease, significant management resources are invested in these patients, resulting in good primary outcome as shown in this study [4]. However, these significant efforts do not translate into good long-term survival, and our results indicate that ongoing excessive alcohol consumption contributes to shortened life-expectancy in younger patients with SAP. This finding warrants that the medical profession increases their involvement in prevention of alcohol abuse in patients surviving from alcoholic SAP short-termly.

Recent years' changes in the recommendations for the management of SAP were reflected in this study. A shift towards later necrosectomy was observed, and during later years most necrosectomies were done due to infection. In addition, open abdomen treatment became a more common practice during the latter years. Despite these changes in the management the survival did not improve significantly.

One of the limitations of this study is that an index reflecting disease-severity, such as the Sepsis-related Organ Failure Assessment score (SOFA), was not collected from the cohort of patients. Hence, the analysis was not assessed in relation to disease severity or organ-specific failures. Another limitation of study is the retrospective setting, where the patient material itself might have changed during the years, which may reduce the value of the assessment of changes in the treatment. Therefore, it is possible that the spectrum of the disease could have introduced a bias to the results. Also, in contrast to most studies on SAP where biliary etiology is more common than alcohol, the main etiology of SAP in this cohort was alcohol. This difference could mean that the long-term survival results may not be comparable with etiologically differing cohorts. Also, the management of elderly patients with anticipated poor outcome might have been different from younger patients, which could have affected age-related survival differences. Furthermore, although long-term survival records were reported, we did not investigate the quality of life in patients that survived.

### 5. Conclusions

Severe acute pancreatitis can be managed with excellent 90-day survival rate in young and otherwise healthy patients. The majority of patients can be managed non-operatively, which results in excellent short-term survival. Open abdomen treatment and necrosectomy without actual infection within the first 4 weeks of the disease increase the risk of death. The overall survival rate did not change significantly during the study period despite significant changes in indications and timing of surgery. However, the long-term survival estimate is disappointing even in younger patients. Predominantly alcoholic etiology of pancreatitis in younger patients associated with alcohol related death and short life expectancy. Results indicate that successful prevention

of ongoing alcoholic abuse in patients that survive alcoholic SAP could increase their long-term survival.

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### Conflicts of interests

Authors have no personal conflicts of interest to declare.

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