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ORIGINAL ARTICLE

Natural History After Acute Necrotizing Pancreatitis: a Large US Tertiary Care Experience

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Abstract

Background Most studies of acute necrotizing pancreatitis (ANP) focus on short-term outcomes. We evaluated long-term survival and outcomes following ANP.

Methods Patients treated for ANP at the University of Pittsburgh Medical Center from 2001 to 2008 were studied. Data on presentation and course during initial hospitalization and follow-up (median 34 months) was extracted.

Results Mean age of patients ($n = 167$) was 53 ± 16 years; 70 % were male, 94 % white, 71 % transfers, 52 % biliary etiology, and 78 % had first-attack of acute pancreatitis. Majority had severe disease with high Acute Physiology and Chronic Health Evaluation II (APACHE-II) score (median 11), length of stay (median 26 days), intensive care unit (ICU) admission (87 %), presence of systemic inflammatory response syndrome (SIRS) (90 %), persistent organ failure (60 %), and infected necrosis (50 %). Intervention was needed in 74 %. Eighteen (10.8 %) patients died during index hospitalization, 9 (5.4 %) during the first year, and 13 (7.8 %) after 1 year. Median survival was significantly shorter when compared with age- and sex-matched US general population (9.1 vs. 26.1 years, $p < 0.001$). Increasing age (HR 1.05), persistent organ failure (HR 4.5), and >50 % necrosis (HR 3.8) were independent predictors of death at 1 year. In eligible patients, new-onset diabetes, oral pancreatic enzyme replacement therapy, and disability were noted in 45, 25, and 53 %, respectively.

Conclusion ANP significantly impacts long-term survival. A high proportion of patients develop functional derangement and disability following ANP.

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Introduction

Acute necrotizing pancreatitis (ANP) develops in 6–40 % of cases of acute pancreatitis (AP), with a higher incidence in the tertiary care setting when compared with community populations.[1–9] Mortality has remained substantial (10–36 %) despite advances in critical care.[2–4,9–15] The two primary determinants of morbidity and mortality in AP are the presence of organ failure (OF) and necrosis.[13,16–20] OF in ANP is associated with the amount of necrosis and the presence of local or systemic infection.[17,21,22] Secondary infection of necrotic tissue occurs in 30–70 % of patients with ANP and is associated with poor outcomes.[16,17] Mortality is highest

among patients with both OF and infected pancreatic necrosis.[15,16]

The role and timing of interventions in ANP have undergone a recent paradigm shift. Open debridement and necrosectomy, especially within the first few weeks of ANP, has fallen out of favor due to high risk of complications and death. Consensus has evolved to delay operative intervention in the first several weeks, particularly for acute peripancreatic fluid collections and walled-off pancreatic necrosis.[12,23–28] If an intervention is deemed necessary, a "step-up approach" is preferred, using an initial endoscopic and/or percutaneous approach to drain the collection, while reserving surgical drainage as a salvage procedure should these approaches fail.[29–33] Although various studies in the past two decades have shed light on the impact of OF and infection on short-term mortality,[13,16,18,34] outcomes of different interventional strategies,[27,29–33,35–39] and the risk of endocrine and/or exocrine insufficiency after ANP,[34,40–45] there is limited information on the long-term survival following an attack of ANP. We hypothesized that ANP impacts the long-term survival of patients even after recovery from the initial period of hospitalization and its related complications.

In this study, we evaluated the natural history in terms of mortality, risk of new-onset endocrine insufficiency, use of oral pancreatic enzyme replacement therapy (PERT), and long-term disability following ANP in a consecutive cohort of patients treated at the University of Pittsburgh Medical Center (UPMC) from 2001 to 2008.

Methods

Study Design and Setting

This is a retrospective cohort study evaluating the natural history of patients treated for ANP at the Presbyterian Hospital of the UPMC. UPMC Presbyterian is an 800-bed, fully accredited level I regional trauma center, and the major teaching hospital of the UPMC health system. The study was approved by the Institutional Review Board of the University of Pittsburgh.

Identification of Patients

We used the Medical Archival Retrieval System (MARS, MARS Inc., Pittsburgh, PA) to identify the patient cohort.[46] MARS was used to screen all radiology, operative, and pathology reports from years 2001–2008 using the following search terms (exact or with variations in spelling): "pancreas necrosis," "pancreatic necrosis," "necrotizing pancreatitis," "phlegmon," "debridement," "necrosectomy," and "pseudocyst drainage." Medical records of these patients were reviewed by the study investigators (CU, AR, SS) under supervision of the senior author (DY) to identify patients with definite evidence of ANP for inclusion. We defined pancreatic necrosis by a lack of enhancement of the pancreas on contrast-enhanced computed tomography (CECT) or detection of necrosis in sample sent from percutaneous drainage or surgery.

Data Collection

The electronic health record of patients with definite evidence of ANP was reviewed to retrieve information on the clinical course during index hospitalization and follow-up. For patients transferred from other institutions, available outside records were also reviewed. The following information was collected—demographics, date of initial admission to UPMC, and to the outside hospital when applicable, date of discharge, death, or last follow-up; clinical presentation and management, intensive care unit (ICU) admission, ICU length of stay, total length of stay, relevant laboratory tests; findings on microbiology, pathology, radiology, endoscopic procedures, and operative notes; medication use, and nutritional interventions (parenteral, enteral). Other variables of interest included etiology of pancreatitis according to physician documentation, risk factors (smoking, alcohol, obesity, etc.), prior history of AP or chronic pancreatitis (CP), pre-existing diabetes, presence of complications (e.g., infection, OF, gastrointestinal bleeding), development of new endocrine insufficiency, use of PERT, and mortality. When feasible, clinical and laboratory parameters were used to calculate severity scores (Ranson, Acute Physiology and Chronic Health Evaluation II [APACHE II], Bedside Index of Severity in AP [BISAP]), systemic inflammatory response syndrome (SIRS) at admission, and at 24 and 48 h from admission. In patients who died, the timing and cause of death were noted.

Definitions

The episode responsible for ANP was considered to be the index admission. OF was defined by the presence of shock (systolic pressure <90 mm Hg or need for vasopressors), pulmonary insufficiency (pO2 <60 mm Hg or O2 saturation <90 % on room air or the need for mechanical ventilation), or renal failure (serum creatinine level ≥2 mg/dl after rehydration or the need for dialysis).[47,48] Persistent OF was defined as OF lasting for ≥48 h.[20,47,49] OF was classified as early (i.e., occurring within 1 week of admission) or delayed (i.e., occurring more than 1 week of admission).[49,50] An intervention was defined as any pancreatic surgery (open/laparoscopic debridement and/or drainage with/without pancreatic resection), endoscopic necrosectomy or drainage, or percutaneous drainage of peripancreatic fluid collections or walled-off necrosis. The timing of intervention was noted.

New-onset endocrine insufficiency was diagnosed using the World Health Organization (WHO) criteria for diabetes mellitus: fasting blood glucose ≥126 mg/dl, 2-h blood glucose ≥200 mg/dl, or HgbA1c ≥6.5.[51] Formal testing for exocrine insufficiency by fecal elastase, chymotrypsin, or quantitative fecal fat was rarely performed ($n = 2$). Therefore, we analyzed documented use of PERT as a surrogate for exocrine insufficiency. The patients were considered to have had long-term disability if they received disability benefits for more than 3 months after recovery from the episode of ANP, as documented during their outpatient follow-up visits. Only the disability attributable to ANP or a complication resulting from it was considered.

Outcomes

The primary outcome of interest was short- and long-term survival after ANP. Since all deaths directly attributable to ANP occurred within 1 year of index admission, we analyzed patient and disease-related factors predicting mortality at 1 year. Secondary outcomes of interest were the risk of new-onset endocrine insufficiency and/or PERT and long-term disability (i.e., ≥3 months) following ANP. The duration of follow-up was the time from the onset of ANP until last follow-up, death, or last contact until December 31, 2013.

Data Analysis

Descriptive information is presented as proportions for categorical data and mean ± SD or median and interquartile range (IQR) for continuous data as applicable. The chi-square test was used to assess association between two categorical variables, and comparison in continuous variables between two groups of patients was conducted using the Student's *t* test or Mann-Whitney *U* test as applicable. For estimating survival, we created a pseudo age- and sex-matched sample from the general population. For each case, we created a pseudosubject with the same age and sex. The death of the pseudosubject was assumed at the expected lifetime of subjects with the same age and sex in the general population, as obtained from the Social Security Administration Actuarial Life Table (http://www.ssa.gov/OACT/STATS/table4c6.html). The Kaplan-Meier curve for the survival of these pseudosubjects was plotted and compared with that of the 167 enrolled patients with ANP. Multivariable Cox regression analysis was used to determine independent predictors of survival. All statistical analyses were performed using the IBM SPSS software version 22 (SPSS, Inc., Chicago, IL, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Two-tailed p values <0.05 were considered significant.

Results

Demographics and Etiology

Of the 227 potential patients identified on initial search, 167 had definitive evidence of ANP on review of medical records and formed the final study cohort. The mean age of patients was 52.7 years, 70 % were male, 94 % were Caucasian, and nearly three fourths were transfers from other hospitals (Table 1). The median time from admission to the outside hospital to transfer was 6 days (IQR 2, 12). The median length of stay during the index admission was 26 days (IQR 15, 48).

Data on etiology of ANP was available for 150 (90 %) patients. Gallstones (77/150, 52 %) or alcohol (35/150, 23 %) was the etiology in three fourths of all cases, while the remaining (38/150, 25 %) had other etiologies (Table 1). A prior history of AP or CP was present in 26 (16 %) and 19 (11 %) patients, respectively, and the remaining 122 patients (73 %) were admitted for their first episode of ANP. A prior history of diabetes was noted in 51 (31 %) patients.

Severity

Overall, 87 % of patients needed ICU admission, of which 96 % required >48 h of ICU care. OF developed in 72 % and persistent OF in 60 % (early 50 %, delayed 9 %; single 20 %, multiple 39 %, unknown 1 %). Median APACHE II score in the first 48 h of admission was 11 (IQR 7, 19), while a BISAP score of ≥3, Ranson score ≥3, and SIRS were present in 53, 88, and 90 % patients, respectively.

Pancreatic Necrosis

Pancreatic necrosis was diagnosed during the index admission in 126 (75 %) patients, while in the remaining 41 (25 %), it was diagnosed only during a readmission for ongoing symptoms or complications related to necrosis. Pancreatic necrosis was diagnosed on CECT in 86 % (142/166) and intraoperatively in 14 % (24/166) patients. Among patients diagnosed intraoperatively, 83 % (20/24) underwent open debridement, performed for suspected infected necrosis (20), pseudocyst (3), and pancreatic cancer (1). Information on the timing of detection of necrosis was available in 92 % (154/167) patients: necrosis was diagnosed within 1–2 weeks of admission in 99 (64 %), 3–4 weeks in 25 (16 %), and >4 weeks in 30 (20 %). Quantification of necrosis on CT scan was mentioned in 69 % (116/167) patients, of whom 65 (56 %) had >50 % necrosis. The majority of patients in whom the amount of necrosis was not quantified were transfers (35/51, 69 %).

Infected necrosis was diagnosed in 86/166 patients (50 %), with nearly two thirds (53/86, 62 %) growing more than one organism on microbiology. The majority of patients had bacterial only infection (59/86, 69 %), followed by combination

Table 1 Characteristics of patients with acute necrotizing pancreatitis, overall and after stratification by survival at 1 year

Variable	Entire cohort ($n = 167$)	Died at 1 year ($n = 27$)	Alive at 1 year ($n = 140$)	P value
Age[c] [mean ± SD]	52.7 ± 16.2	62.7 ± 15.3	50.7 ± 15.7	<0.001
Male (%)	70	78	68	0.31
Caucasian (%)	94	89	95	0.21
Obesity[a] (%)	47	56	46	0.43
Transfers (%)	71	82	69	0.18
First attack of AP (%)	73	82	72	0.28
Etiology of AP[a] (%)				
Gallstones	52	66	48	0.28
Alcohol	23	15	25	
Other[b]	25	19	27	
Necrosis diagnosed during index admission (%)	75	89	73	0.08
ICU admission[a] (%)	87	100	84	0.03
SIRS[a] (%)	90	96	89	0.25
BISAP ≥3[a] (%)	53	85	46	<0.001
APACHE II[d,a] [median (IQR)]	11 (7, 19)	18 (11, 24)	10 (7, 16)	0.01
Any organ failure[a] (%)	72	96	67	0.002
Persistent organ failure[a] (%)	60	85	55	0.004
Early organ failure[a] (%)	50	73	45	0.004
Multiple organ failure[a] (%)	39	69	33	0.004
>50 % necrosis[a] (%)	56	79	51	0.03
Infected necrosis[a] (%)	52	74	48	0.01
Prophylactic antibiotics[a] (%)	71	68	71	0.74
Intervention (%)				
Pancreatic debridement alone	74	67	76	0.33
Percutaneous drainage	55	48	57	
followed by surgery	16	15	17	
Percutaneous drainage alone	2	4	1	
Endoscopic necrosectomy	1	0	1	
Nutrition type (%)				
Enteral	34	30	35	0.14
Parenteral	18	30	15	
Both	41	33	43	
Oral	4	0	5	
Unknown	3	7	2	
Length of stay index admission[d], $n = 161$ [median (IQR)]	26 (15, 48)	45 (18, 63)	25 (15, 44)	<0.05

Details on the number of subjects in each group for these variables (entire cohort, died at 1 year, alive at 1 year) is as follows: obesity—119, 16, 103; etiology of AP—150, 26, 124; ICU admission—158, 27, 131; SIRS—156, 26, 130; BISAP ≥3—147, 26, 121; APACHE II—145, 25, 120; any organ failure—159, 26, 133; persistent organ failure/early organ failure/multiple organ failure—156, 26, 130; >50 % necrosis—116, 19, 97; infected necrosis—166, 27, 139; and prophylactic antibiotics—154, 25, 129. All comparisons were made using the chi-square test unless specified otherwise

[a] These variables had missing information

[b] Other etiologies: medications (5), hypertriglyceridemia (8), hypercalcemia (1), post-ERCP (12), post-surgical (3), pancreas divisum (1), cystic fibrosis (1), pancreatic cancer (1), trauma (1), and idiopathic (5)

[c] Age was compared using the Student's t test

[d] APACHE II and length of stay were compared using the Mann-Whitney U test

of bacterial and fungal infection (19/86, 22 %), fungal only infection (5/86, 6 %), and data was missing in the rest (3/86, 3 %). Prophylactic antibiotics were used in 109/154 (71 %) patients (85/109, 78 % carbapenems) with 72/109 (66 %) receiving a full 14-day course of antibiotics.

Nutrition and Interventions

Nutritional support was needed in 93 % patients (enteral only 34 %, parenteral only 18 %, both 41 %). Some form of intervention was needed in 124/167 (74 %) patients (surgical debridement alone 93, percutaneous drainage followed by surgery 27, percutaneous drainage alone 3, endoscopic necrosectomy 1). Cholecystectomy was performed in 88/162 (54 %) patients—of these 60 had biliary etiology and 28 had other/unknown etiology. Cholecystectomy was performed during the index admission in 33, during follow-up in 54, and the timing was unknown in 1 patient.

Survival

Overall, 24 % ($n = 40$) patients died during the study period—of these 68 % (27/40) deaths occurred during the first year (18 during index hospitalization, 9 during the first year) and 32 % (13/40) after 1 year. Among deaths that occurred during the first year, 89 % (24/27) were directly attributable to ANP (infected necrosis—67 %, persistent OF—83 %, multiple OF—91 %, >50 % necrosis—75 %), while the other 11 % (3/27) were due to sepsis from gunshot wound, urosepsis, and congestive heart failure. The cause of death in 13 patients who died after 1 year included—acute myeloid leukemia (1), cholangitis (1), gram-negative sepsis (1), gunshot wounds (1), rupture of aortic pseudoaneurysm (1), sepsis from bowel perforation (1), septic shock (1), and definite cause of death was not available for 6 patients.

At last contact, 127 patients were alive. The median follow-up time was 3 years (IQR = 1.2, 6.7). When compared with patients who lived beyond 1 year, patients who died within the first year were significantly (all $p < 0.05$) older (median age of 65 vs. 54 years); a higher fraction had necrosis diagnosed during index admission (89 vs. 73 %) and had severe disease as reflected by a higher proportion needing ICU admission (100 vs. 84 %), having higher severity scores (median APACHE II score of 18 vs. 10; BISAP score ≥3 in 85 vs. 46 %) and incidence of OF including persistent OF (85 vs. 55 %) and multi-OF (69 vs. 33 %). These patients also had significantly (all ps < 0.05) more extensive necrosis (>50 % necrosis in 79 vs. 51 %), a higher incidence of infected necrosis (74 vs. 48 %), and longer hospitalization (45 vs. 25 days) when compared with patients who survived beyond the first year (Table 1). When comparing patients who did and did not receive prophylactic antibiotics, there was no difference in overall (22 vs. 24 %) or 1-year mortality (16 vs. 18 %) ($p =$ 0.74). There was no difference in 1-year mortality between patients with primary surgical debridement and those who had percutaneous drainage alone/followed by surgery (step-up approach) (14 vs. 16 %), though the sample size for the latter group was small.

Table 2 Predictors of death at 1 year following acute necrotizing pancreatitis

Variable	Hazard ratio	95 % CI	*P* value
Age (years)	1.048	1.002–1.095	0.039
Persistent organ failure	4.535	1.023–20.106	0.047
>50 % necrosis	3.787	1.086–13.213	0.037

No. of cases included in Cox regression analysis—109

On multivariable Cox-regression analysis (Table 2), the risk of death by the end of year one increased 5.24-fold with every 5 years increase in age (hazard ratio (HR) 5.24, 95 % CI 5.01–5.475, $p = 0.039$), 4.54-fold with persistent OF (HR 4.54, 95 % CI 1.02–20.11, $p = 0.047$), and 3.79-fold with >50 % necrosis (HR 3.79, 95 % CI 1.09-13.21, $p = 0.037$).

Overall, the median survival following ANP was 9.1 years (IQR 4.5,), which was significantly lower when compared with age- and sex-matched US population (26.1 years) (Fig. 1a). When we restricted the analysis to ANP patients who survived at least 1 year, their survival was still significantly lower when compared with age- and sex-matched population controls (log-rank $p < 0.0001$) (Fig. 1b).

Endocrine Insufficiency, PERT, and Disability

Of the 167 patients, after excluding those with pre-existing DM ($n = 51$), a prior history of AP ($n = 15$) or CP ($n = 14$) and those who died during index admission ($n = 14$), there were 73 patients with first attack of AP eligible for evaluation of new-onset endocrine insufficiency (Fig. 2). Of these, 33 (45 %) were diagnosed with new-onset endocrine insufficiency. The majority (70 %, 23/33) of these were diagnosed with diabetes during index admission. Median time from index admission to the diagnosis of diabetes was 1 month (IQR 1, 2). Development of endocrine insufficiency was associated with the extent of necrosis. Of 22/33 patients with new-onset endocrine insufficiency in whom data was available, 15 (68 %) had >50 % necrosis on CT scan. Among patients with new-onset endocrine insufficiency, 15 (45 %) also required PERT following ANP.

After excluding those with prior history of AP ($n =$ 26) or CP ($n = 19$) and those who died during index admission ($n = 16$), 106 patients with a first attack of AP were eligible for evaluation of PERT (Fig. 3). Of these, 30 (28 %) were started on PERT during the observation period. Median time from index admission to

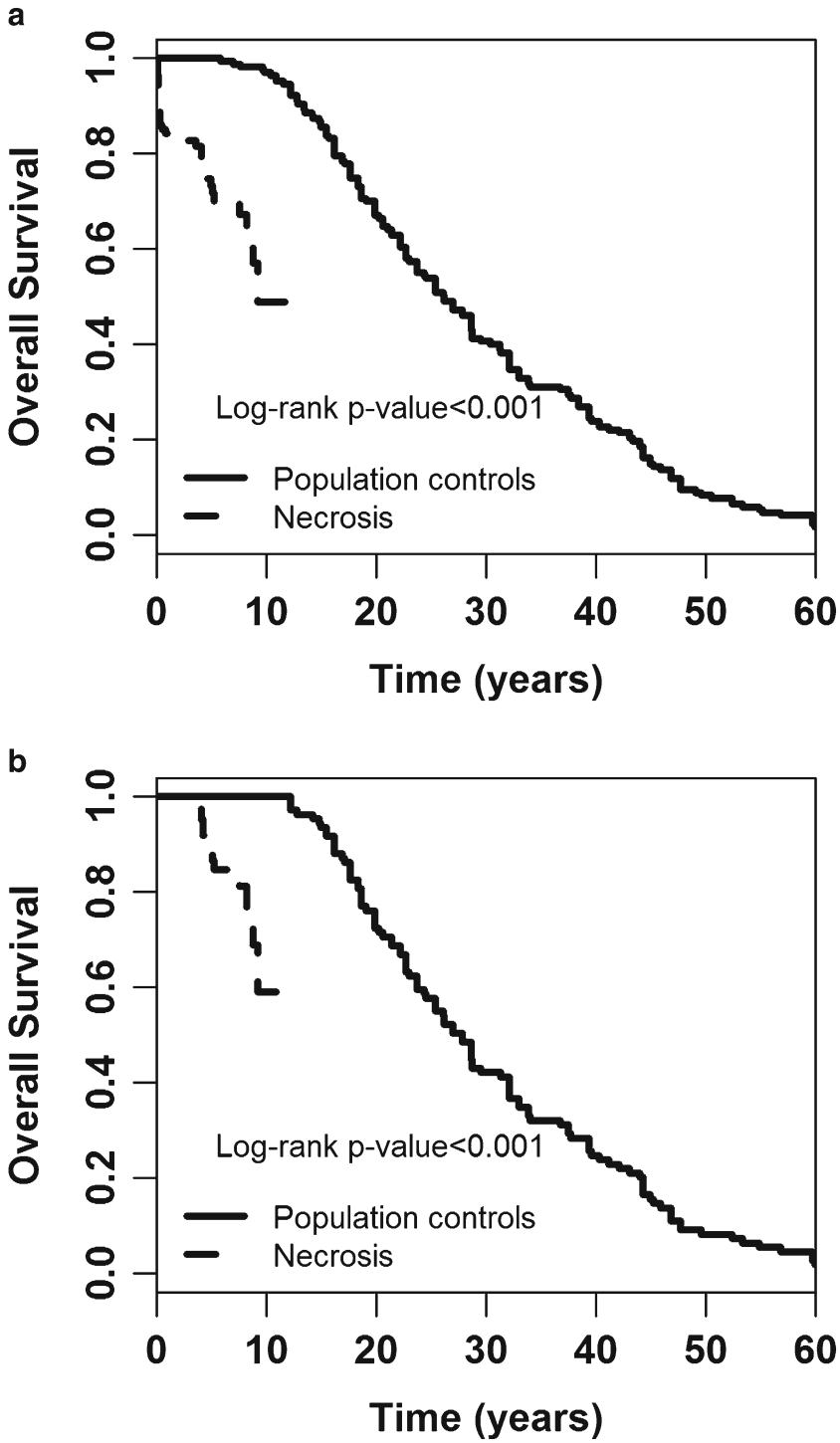

Fig. 1 Long-term survival after acute necrotizing pancreatitis—**a** entire cohort and **b** among those who survived at least 1 year

starting PERT was 2 months (IQR 1, 4). Interestingly, 26/30 (87 %) of these patients had undergone surgical debridement or drainage ($p < 0.05$).

After excluding those who died during or within 1 year ($n = 27$) of index admission, had pre-existing disability ($n = 4$), and those without documented information on disability available in their records ($n = 60$), there were 76 patients who had at least 1 year of follow-up information (Fig. 4). Of these, 42 (55 %) were documented to have long-term disability due to ANP.

Discussion

This report evaluated the natural history of ANP at a major US tertiary care center and revealed that ANP is associated with

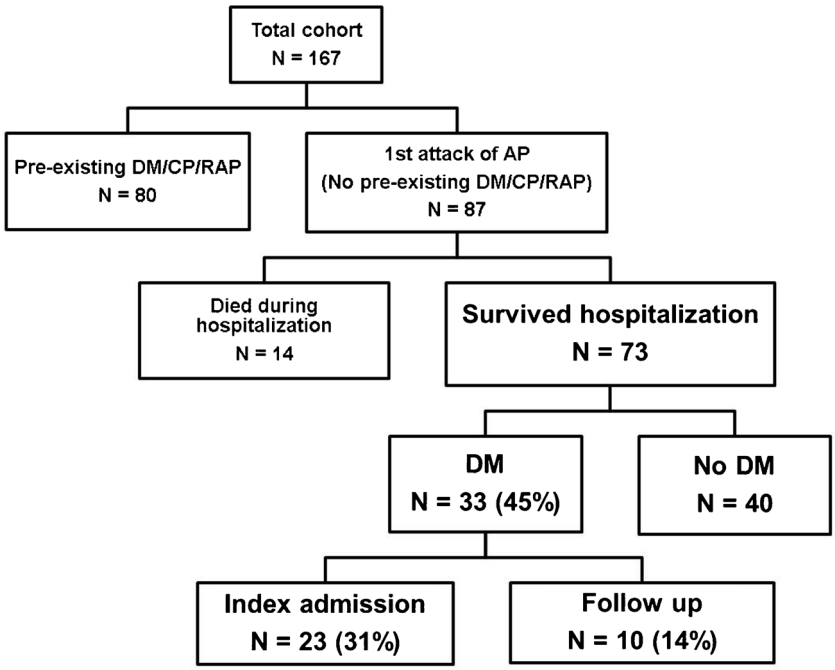

Fig. 2 Risk of new-onset endocrine insufficiency following the first attack of acute pancreatitis in patients with no pre-existing diabetes who survived index hospitalization

substantial short- and long-term morbidity and mortality, high risk of subsequent endocrine insufficiency, use of PERT, and long-term disability. The important determinants of mortality were increasing age, persistent OF, and the amount of necrosis.

The impact of ANP on short-term outcomes has been well documented. Deaths within the first 2–4 weeks are attributable to persistent OF, while infected necrosis or other local or systemic complications are the major causes of death after the first 2–4 weeks. This report confirms these findings. There has been, however, little study on the impact of ANP on long-term survival, i.e., after a patient has survived the initial phase of ANP and its immediate complications. We found that these patients are at an increased risk of dying even beyond 1 year of disease when compared with age- and sex-matched population controls. It is likely that ANP may have played an indirect role on mortality in these patients. Some potential explanations would include complications related to exocrine and endocrine insufficiency such as malnutrition (85 % of these patients had pancreatic surgery, 86 % developed new-onset diabetes, 56 % required PERT), increased risk of infections (sepsis played an important role in patients with

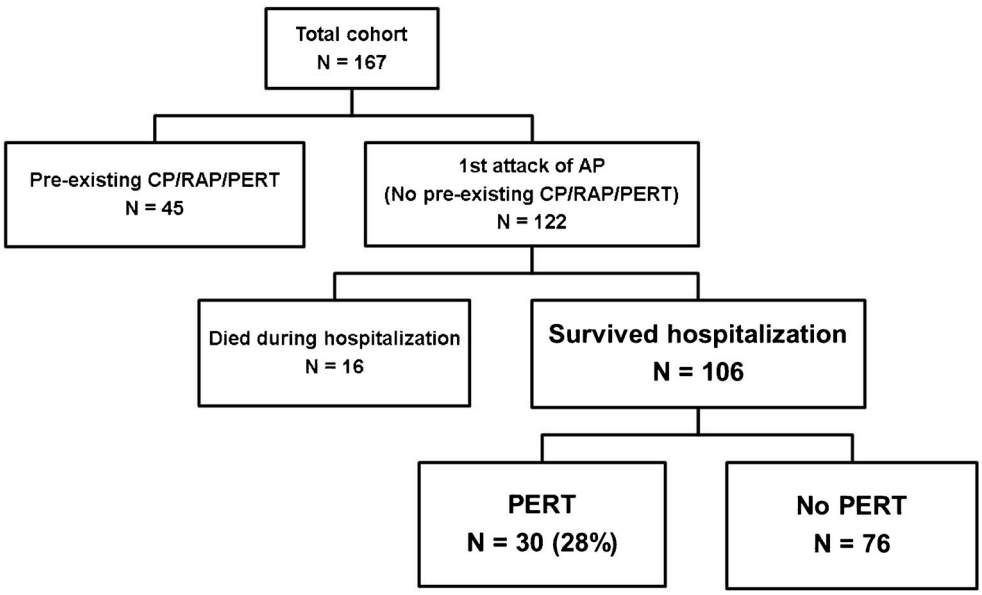

Fig. 3 Use of pancreatic enzyme replacement therapy following the first attack of acute necrotizing pancreatitis in patients with no pre-existing exocrine insufficiency who survived index hospitalization

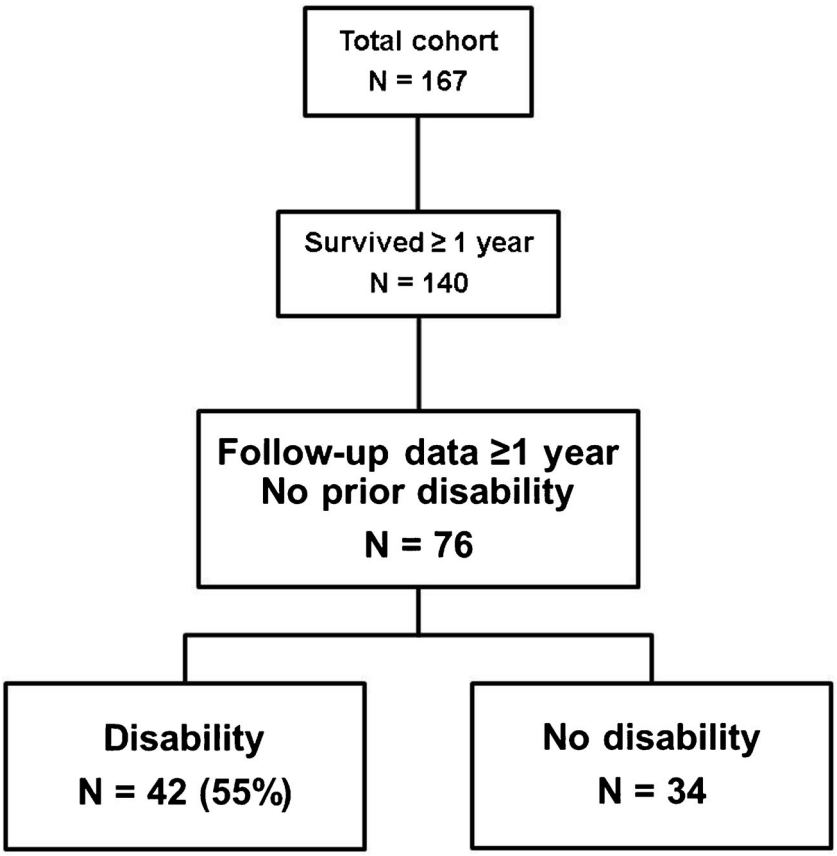

Fig. 4 Risk of disability following the first attack of acute necrotizing pancreatitis in patients who survived at least 1 year and did not have pre-existing disability

available data on the cause of death), exacerbation of underlying comorbid conditions, development of chronic pain syndrome, etc. Future studies need to evaluate the mechanisms responsible for increased long-term mortality after ANP and factors that affect these.

Similar to previous observations, we noted a high frequency of using PERT after ANP. Close correlation of these outcomes with the amount of necrosis and surgical debridement suggests that direct destruction of islets and acinar tissue from pancreatic necrosis to be the major factor for development of pancreatic insufficiency after ANP[29]. The prevalence of diabetes and exocrine insufficiency observed in our analyses is likely an underestimation due to the retrospective nature of our study and a lack of guidelines for systematic evaluation of diabetes and exocrine insufficiency in these patients. This study suggests that a high index of suspicion is needed to screen patients for endocrine and exocrine insufficiencies so that treatment can be initiated at an early stage to prevent malnutrition, fat soluble vitamin deficiencies, and complications of uncontrolled diabetes. Data on the presence and impact of long-term disability after ANP is equivocal. We noted that over half of the patients who had more than 1 year of follow-up were disabled. This high risk is likely multifactorial. In addition to diabetes and exocrine insufficiency, other potential contributors would be deconditioning, weight loss, development of chronic pain, and effects of local complications.

Open necrosectomy was used as the surgical intervention of choice since this was the predominant gold standard for treating ANP-related complications during the study period. This represented 72 % of our cohort. The treatment strategy for ANP has evolved over the years in favor of delays in procedural and operative interventions when possible.[28] Should intervention become necessary, then a step-up approach using percutaneous and endoscopic modalities and eventually, minimally invasive surgery and videoscopic assisted retroperitoneal debridement (VARD) is employed with good outcomes compared to the traditional open surgical necrosectomy.[28–30] Since the primary aim was to evaluate long term survival after ANP, we purposefully limited our study population to years 2001–2008. Consequently, this study cannot assess the impact of the step-up approach on the short-term outcomes following ANP.

This study has a number of limitations, foremost being its retrospective design. While a prospective study design would be ideal, this is difficult due to the fact that ANP is an uncommon disease for which a multicenter study would be required to ensure an adequate sample size. Our tertiary care setting allowed us to achieve a large sample size with a modest follow-up period to evaluate long-term outcomes in this unique population. Second, data regarding amount of necrosis on CT was not available for 30 % of patients, therefore limiting the analysis. Ideally, all cross-sectional imaging should

have been reviewed by the same expert radiologist to minimize the bias involved in assessing and quantifying the amount of necrosis. Another limitation is the fact that this was a single-center study, so the results may not be generalizable to all clinical settings. Finally, we retrospectively diagnosed new-onset endocrine and/or exocrine insufficiency following ANP based on chart review, which likely led to an underestimation of the actual risk of these long-term disabilities.

Conclusions

This study has shown that ANP significantly impacts both short- and long-term survival. Factors affecting short-term outcomes include increasing age, persistent OF and the amount of necrosis. A high fraction of patients develops endocrine insufficiency, requires PERT, and suffers from long-term disability. Future studies should focus on developing guidelines for monitoring and early detection of the long-term consequences of ANP.

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Authorship Criteria and Contributions Study conception and design: Amit Raina, Chandraprakash Umapathy, and Dhiraj Yadav.

Data acquisition: Chandraprakash Umapathy, Amit Raina, and Shreyas Saligram.

Data analysis: Chandraprakash Umapathy and Gong Tang.

Data interpretation: All authors.

Drafting of manuscript: Chandraprakash Umapathy, Gong Tang, and Dhiraj Yadav.

Revising the manuscript and providing important intellectual input and final approval of the version to be published: All authors.

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Conflict of Interest The authors declare that they have no conflict of interest.

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