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Identifying risk factors for progression to critical care admission and death among individuals with acute pancreatitis: a record linkage analysis of Scottish healthcare databases.

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Abstract

Objectives

Acute pancreatitis (AP) can initiate systemic complications that require support in critical care (CC). Our objective was to utilize the unified national health record to define the epidemiology of AP in Scotland, with a specific focus on deterministic and prognostic factors for CC admission in AP.

Setting

Health boards in Scotland (n=4).

Participants

We included all individuals in a retrospective observational cohort with at least one episode of AP (ICD10 code K85) occurring in Scotland from 1st April 2009 to 31st March 2012. 3340 individuals were coded as AP.

Methods

Data from sixteen sources, spanning general practice, community prescribing, A&E, hospital in-patient, critical care, and mortality registries were linked by a unique patient identifier in a national safe haven. Logistic regression and gamma models were used to define independent predictive factors for severe AP (sAP) requiring CC admission or leading to death.

Results

2053 individuals (61.5% (95%CI 59.8, 63.2%)) met the definition for true AP (tAP). 368 patients (17.9% of tAP (95%CI 16.2, 19.6%)) were admitted to CC. Predictors of sAP were: pre-existing angina or hypertension, hypocalcaemia, and age 30-39 years, if type 2 diabetes mellitus was present. The risk of sAP was lower in patients with multiple previous episodes of AP. In-hospital mortality in tAP was 5.0% (95%CI 4.1, 5.9%) overall, and 21.7% (95%CI 19.9, 23.5%) in those with tAP necessitating CC admission.

Conclusion

National record-linkage analysis of routinely collected data constitutes a powerful resource to model CC admission and prognosticate death during AP. Mortality in patients with AP who require CC admission remains high.

Strengths and Limitations of this Study

- National record-linkage analysis of routinely collected data constitutes a powerful resource to model critical care admission and prognosticate death during critical illness.

- This project brought together sixteen electronic data sources through a new record-linkage model for Scotland and was at the forefront of the development of the National Data Safe Haven in Scotland

- For individuals with AP who are not severely ill, electronically-formatted routinely recorded clinical data is less comprehensive and this may have led to a negative reporting bias for events not sufficiently severe to need critical care admission.

- Although we specifically conducted a data accuracy pilot, comparing electronic records with hand-written notes in four separate study sites, certain variables are likely to be more accurate, for example automatically-retrieved Wardwatcher™ critical care data, than others for example comorbidity and hospital immediate discharge summaries.

- Although specific risk factors can be identified which increase risk of developing multiple organ dysfunction in AP, it is not pragmatic or straightforward to predict which individual patients are likely to require critical care based on their routinely-collected medical data.

Keywords

Acute pancreatitis; severity stratification; critical care; organ failure; multiple organ dysfunction syndrome; national record linkage; safe haven.

Introduction

Background/rationale

Acute pancreatitis (AP) is an inflammatory disease of the pancreas with potentially devastating consequences for those who suffer a severe attack. Individual estimates of the incidence of AP range from 10 to 78 per 100 000 per year[1-6]. AP was found to be the most common reason for hospitalization with a gastrointestinal disorder in the US in 2012[7]. The estimated financial cost for AP-related care in the US in 2004 was $3.7 billion, with AP resulting in 277 000 hospital admissions and 475 000 ambulatory visits[8]. The financial cost of treating AP in the UK has been estimated at £200 million per year[9].

In approximately 20% of patients with AP, severe complications can develop which may evolve into multiple organ dysfunction syndrome (MODS) requiring critical care (CC) support in high dependency (HDU) or intensive treatment units (ITU)[10][11]. AP-MODS usually occurs rapidly, and features of AP-MODS may be present at the time of presentation to hospital[12]. Between 2008 and 2010, 5% of all available intensive care beds in Scotland were taken up by patients with AP[9]; in tertiary referral centres ITU bed occupancy may reach 9%[13]. The epidemiological risk factors for developing organ dysfunction amongst individuals with AP are not known at present. This knowledge will be important and useful to identify high-risk patients by enhancing the stratification of disease severity, and to influence treatment decisions, plan healthcare, allocate resources and inform trial design. Therefore, there exists a need to understand and identify risk factors for progression to AP-MODS based on laboratory and clinical information leading up to, and at the time of acute presentation to hospital.

The Farr Institute[14] was conceived with the goal of creating a unified healthcare informatics infrastructure to allow interested parties from government, academia, industry, healthcare providers and other related organisations utilise linked electronic healthcare data on a national scale in a secure, confidential and streamlined way for medical research within the UK. Given the substantial healthcare burden of AP, the need for improved understanding and treatment of AP, and the considerable interest in development of novel therapies for AP by us[15] and others, the aim of this study was to

harness the power of the Farr Institute capabilities to elucidate the epidemiology of AP with a focus on defining the risk factors for the development of organ failure in AP.

Objectives

Our specific objectives were to use the Farr Institute infrastructure to:

1. Characterize the epidemiology of AP in Scotland
2. Define the determinants of admission to CC and/or death in AP
3. Describe the morbidity, length of critical care stay, organ support and mortality of patients with AP admitted to CC.

Methods

Study design

We undertook a retrospective observational cohort study of linked healthcare records from sixteen electronic data sources in Scotland.

Project structure and Study management

The collaborative core project team consisted of a project manager (PJ), clinician scientists with expertise in AP (DJM, CS), an epidemiologist and statistician from industry (UG, AL), national healthcare data expertise (CG, ADM, FS), data managers, clinical information governance (HW) and clinical statistics and epidemiology expertise (LC, PTD). A project board (including lay membership) met quarterly to oversee the project. The study protocol and analysis plan were agreed in advance by the project board.

Ethical approval, patient confidentiality and data security

We obtained approvals from: National Services Scotland, Privacy Advisory Committee; National Research Ethics Service; National Research and Development Office; the local Research and Development Office for each Health Board; NHS Board Caldicott Guardians, via the Caldicott Guardians' National Scrutiny Process; Scottish Intensive Care Society Audit Group (SICSAG) Steering Group; and General Practitioners (as Caldicott Guardians). The study adhered to strict information governance and security protocols. All primary data was held within the NHS Scotland Information Services Division (ISD) National Safe Haven with access restricted to two named statisticians

from University of Dundee (LC, PTD). Industry partners did not have sight of patient-level data at any stage.

Setting and data sources

The study cohort consisted of all patients who had a general or acute inpatient or day case record of acute pancreatitis in any coding field, coded as K85 under ICD10 K85 (including K85.0 Idiopathic acute pancreatitis; K85.1 Biliary acute pancreatitis; K85.2 Alcohol induced acute pancreatitis; K85.3 Drug induced acute pancreatitis; K85.8 Other acute pancreatitis; K85.9 Acute pancreatitis, unspecified), occurring in any of four NHS Health Board areas in Scotland between 1st April 2009 and 31st March 2012. The first episode for any one individual occurring in that time period was taken as the index episode. The combined total population of the four Health Boards was 2 063 511 (48.9% of the population of Scotland aged 18 years old and over) at the midpoint of the study, and included large conurbations and rural areas. For each patient, data were collected from Accident and Emergency attendances (A&E2 database), Scottish Morbidity Record 00 (SMR00) Outpatient attendances, SMR01 (General/Acute inpatient and day cases), SMR04 (Mental Health inpatient and day cases), SMR99 (Death registrations), Prescribing Information System (PIS, primary care prescribing and dispensing), SICSAG (critical care), SCI Stores (laboratory test results), and general practice data. Data were linked within the National Safe Haven by an approved indexing process based on a unique patient identifier (the CHI number). There were no exclusion criteria. A pilot study was performed to assess the coding accuracy of AP in SMR01.

Definitions and categories

Acute pancreatitis (AP) was defined as occurring when any elective or emergency admission was coded as ICD10 K85 in any diagnosis field. To account for inaccuracies of coding, True AP (tAP) was predefined as a subset of AP as: upper abdominal pain with or without nausea or vomiting at presentation in the clinical records and a serum amylase or lipase result greater than 3 times the upper limit of the reference range for that laboratory; or CT evidence of AP alone. We predefined severe AP (sAP) as a subset of tAP as: tAP requiring admission to CC as part of the same episode, or tAP resulting in death during that hospital episode. Critical care was defined as either or both Level 2 or Level 3 inpatient care, also known as high-dependency (HDU) and intensive treatment units (ITU) respectively. Aetiology of AP was defined at two levels: 1) in the entire

cohort, AP was attributed to gallstones if this (or a related diagnosis, for example cholecystectomy) was recorded in any coding position; the remainder was regarded as non-gallstone AP; 2) aetiology recorded explicitly in hospital or GP records as gallstones, alcohol or other less common causes. A GP visit was defined as a patient-practice interaction recorded as a visit event in GP records, without being able to differentiate between an actual medical consultation and other, for example obtaining results, visiting the practice nurse or getting a repeat prescription. The day of hospital admission was defined as day zero, and the next day after hospital admission as day 1 and so on. Overall hospital mortality was defined as death during a single episode of AP occurring prior to hospital discharge. Overall 90-day mortality was defined as any death occurring within 90 days of the first day of an episode of AP.

Variables

The primary outcome of interest was the development of sAP (admission to CC, tAP death). Secondary outcomes of interest were: length of hospital stay in days, length of CC stay in hours and days, maximum number of organs supported, renal replacement therapy, ventilator dependence, duration of enteral nutrition, hospital acquired infection and death among those with sAP admitted to CC. Potential risk factors included patient demographics, measures of socioeconomic deprivation (using the Scottish Index of Multiple Deprivation[16], SIMD), aetiology of AP, laboratory and clinical data at the time of presentation to hospital, history of medication use (prior to AP presentation), and clinical/disease history up to the time of AP presentation, the latter two being obtained from patients primary care records in the 12 month period prior to the index episode. Calcium values were corrected for serum albumin concentration.

Record Linkage

Data were linked using established probability and deterministic matching techniques[17] based on the Howard Newcombe principles[18]. Linkage was undertaken by a trusted third party. A population spine, which contained the personal identifiers of all individuals who have been in contact with NHS Scotland, was used as an intermediary linkage tool. The process outlined was based on the principles of data linkage outlined in the Scottish Informatics Programme (SHIP) blueprint[19]. The steps of the process were: the indexing team were supplied the CHI number of each of the cohort members

by a single data provider, for which they generated a different record ID number across the range of datasets. Each data provider received a file back with a list of patient CHI numbers and unique person index ID numbers specific to that dataset, generated by the indexing team. The data provider then attached the received index ID number to the remaining content of the dataset to be provided for linkage and sent this to the research coordinator. The research coordinator sent the file to the linkage agent, which is an automated computer programme. The linkage agent received 2 files - all the datasets including unique person ID numbers, plus a master control file containing a master person ID and unique person index ID numbers for the entire dataset. The linkage agent replaced all the dataset unique person ID numbers with the master person ID number on each of the content data files. The person analyzing the data had access to all the records belonging to an individual across all the datasets without sight of personal identifiers.

Statistical methods

Descriptive analyses were performed according to standard principles using SAS 9.3 and following the STROBE criteria[20]. Categorical variables were reported as counts and percentages of the number of valid cases. Continuous variables were described by either mean and standard deviation (for plausibly Normal data) or medians and quartiles (non-Normal data). Between group comparisons for univariate analyses were by independent samples t-test or Mann-Whitney U-test for Normal data and non-Normal data respectively. Differences in proportions were tested by the χ^2 test. To correct for extreme outliers in an otherwise Normally distributed dataset, the 5% trimmed mean was used where stated; this value is the arithmetic mean of data between the 5th and 95th centile. Time-to-event variables were summarized using medians and quartiles. Factors predicting the development of sAP in the tAP cohort were modeled by logistic regression with sAP as binary dependent variable. Variables were selected on the basis of known clinical importance as well as backward elimination to identify variables significant at the 5% level. The final model was also assessed for goodness-of-fit using Akaike's Information Criterion (AIC). Interactions between variables were entered and assessed by adding interaction terms in the model. Predictive performance of the model was assessed by estimation of the Area under the ROC curve (AUROC) and calibration assessed with the Hosmer-Lemeshow test. The final

model for prediction was based on the largest AUROC. A number of parametric survival models were applied to identify factors that predict death during the CC admission. AIC was used to decide on which model was optimal. Model selection criteria were the same as for the logistic regression model.

Imputation of missing data

For the logistic regression model, where clinically important variables had less than 50% missing values, multiple imputation was used to ensure regression analysis was robust assuming data was missing at random (MAR). In practice, 19% of calcium measures at index admission were imputed along with 35% of the primary care flag for alcohol dependency. All other variables in the models were 100% complete.

Results

Participants and univariate analysis

3340 individuals were identified as having an AP coded hospital admission, of which 2053 (61.5%) met the case definition of tAP and were included in the study. **Figure 1** shows patient flow in the study. The incidence of an AP-coded hospital admission was 54.0 (95% CI 41.1, 70.9) per 100 000 per year; the incidence of tAP was 33.1 (95% CI 24.4, 46.9) per 100 000 per year; and the incidence of sAP requiring CC admission was 5.9 (95% CI 3.4, 15.3) per 100 000 per year. Demographic characteristics of the cohort are shown in **Table 1**. Gender distribution was approximately equal across all categories and only increased marginally towards a male preponderance for those with sAP admitted to critical care. The mean age of those with sAP was significantly higher than those who did not develop severe disease. Gallstones were co-recorded in 43.8% of the entire cohort coded as AP. The proportion of patients with gallstone aetiology AP was higher for females. The BMI of patients admitted to CC was on average 1.1 kg/m^2 higher than the remainder of the tAP cohort. A disproportionate number of tAP admissions (35.3%) were from the most socially deprived quintile; this disproportion was similarly observed in the subset with sAP (35.0%). The proportion of patients with tAP who develop sAP and the proportion of those requiring CC admission were not affected by social deprivation (**Table 1**).

Table 1. Demographics and comorbidity of patients admitted with acute pancreatitis

		Patients coded as ICD10 K85 (acute pancreatitis, AP)	Patients meeting definition of true AP (tAP)	Patients meeting definition of severe AP (sAP)	Patients with sAP admitted to critical care (CC) (a subset of sAP)	Patients with sAP not admitted to critical care (a subset of sAP that died without CC admission)	Patients not meeting definition of sAP (nsAP)	Comparison of nsAP vs sAP (statistical significance, P-value; χ^2 test 1 d.f., unless specified)
Number of cases	**(N, % total cases)**	3340	2053 (61.5%)	390 (11.7%)	368 (11.0%)	22 (0.7%)	1663 (49.8%)	
	(N, % tAP)			390 (19.0%)	368 (17.9%)	22 (1.1%)	1663 (81.0%)	
	(N, % sAP)				368 (94.4%)	22 (5.6%)		
Gender	**(N female, % cases within category)**	1578 (47.2%)	1028 (50.1%)	183 (46.9%)	172 (46.7%)	11 (50%)	845 (50.8%)	0.167
Age in years	**mean (SD)**	54.9 (18.5)	55.8 (18.5)	60.1 (18.0)	59.2 (17.9)	73.5 (13.5)	54.8 (18.5)	**<0.001**
Body mass index (N = 1466)	**median (1st, 3rd quartile)**	26.7 (22.7, 31.6)	27.5 (23.0, 32.3)	28.4 (23.3, 33.1)	28.4 (24.1, 33.1)	22.1 (18.9, 30.7)	27.3 (22.9, 32.0)	0.227
Proxies for lifestyle (from GP records)	**(N for which this recorded, % total cases)**	1657 (49.6%)	1039 (50.6%)	195 (50.0%)	185 (50.3%)	10 (45.6%)	844 (50.8%)	
	Overweight	238 (14.4%)	145 (14.0%)	47 (24.1%)	43 (23.2%)	4 (40.0%)	98 (11.6%)	**<0.001**
	Prior/known alcohol overuse	64 (3.9%)	33 (3.2%)	13 (6.7%)	12 (6.5%)	1 (10.0%)	20 (2.4%)	**0.002**
	Smoking	615 (37.1%)	364 (35.0%)	85 (43.6%)	80 (43.2%)	5 (50.0%)	279 (33.1%)	**0.006**
Aetiology of AP	**(N aetiology recorded, %)**	3340 (100%)	2053 (100%)	390 (100.0%)	368 (100%)	22 (100%)	1663 (100%)	
	gallstones (N, % of recorded)	1482 (44.4%)	919 (44.8%)	171 (43.9%)	165 (44.8%)	6 (27.3%)	748 (45.0%)	0.686
	Alcohol + other non-gallstone* (N, % of recorded)	1877 (55.6%)	1134 (55.3%)	219 (56.1%)	203 (55.2%)	16 (72.7%)	915 (55.0%)	
Social deprivation quintile	**most deprived 1**	1209 (36.4%)	720 (35.3%)	136 (35%)	128 (34.9%)		584 (35.4%)	Between groups
(N, % within category)	**2**	704 (21.2%)	412 (20.2%)	79 (20.3%)	72 (19.6%)		333 (20.2%)	0.971 (χ^2 test 1 d.f. trend)
	3	543 (16.3%)	327 (16%)	66 (17%)	65 (17.7%)		261 (15.8%)	
	4	442 (13.3%)	283 (13.9%)	51 (13.1%)	48 (13.1%)		232 (14.0%)	
	most affluent 5	424 (12.8%)	299 (14.6%)	57 (14.7%)	54 (14.7%)		242 (14.6%)	
`								
Duration of continuous inpatient stay, days	**median (1st, 3rd quartile)**	5 (3, 11)	6 (3, 11)	16 (9, 31)	16 (10, 32)	6 (2, 20)	5 (3, 8)	**<0.001 (Wilcoxon)**

*Exact proportion of alcohol diagnosis not possible for the entire cohort – see text for discussion.

Healthcare in General Practice prior to study episode of AP

The GP consultation rate in the year preceding the index AP episode was higher in the subset of patients that died without being admitted to CC than those patients requiring CC or those that did not develop severe AP (**Table 2**). 25.6% of patients with an episode of tAP had a previous episode of AP recorded in their GP-held record, but a smaller proportion (18.5%) of those with sAP had a previous AP episode documented. Although the aetiology of AP could be attributed to gallstones in 43% of patients, gallstones were only known to be present (in advance of the index episode) in 17.7% of those with tAP. A similar proportion (16.5%) had been admitted to hospital following alcohol misuse prior to the index episode. The proportion with a prior episode of alcohol-related hospital admission was not higher in the sAP group.

There was a greater baseline comorbidity burden amongst patients with sAP compared to the remainder of the cohort. Pre-existing ischemic heart disease (previous MI or IHD/angina) was more prevalent in those with sAP needing CC admission than in the tAP cohort as a whole (**Table 2**). Pre-existing type 2 diabetes mellitus was significantly more prevalent in those with sAP requiring CC compared to the tAP cohort. Similarly, chronic obstructive pulmonary disease, hypertension, and renal failure (acute and chronic) were significantly more prevalent among the sAP cohort requiring CC admission (**Table 2**).

The following classes of drug were prescribed more frequently in those with sAP compared to the nsAP group: antidepressants, calcium-altering drugs, neuroleptic agents, oral corticosteroids and statins. The proportions of patients taking each class of drug are presented in **Table 3.**

Endoscopic retrograde cholangiopancreatography (ERCP) had been undertaken in the preceding year in 5.6% of those admitted with tAP. This proportion was not higher in those with sAP. Coronary artery stenting had been performed in the preceding year more frequently in those with sAP requiring CC (3.0%) compared to the nsAP cohort (1.0%) (**Table 3)**.

Table 2. Healthcare prior to index AP admission

		Patients coded as ICD10 K85 (acute pancreatitis, AP)	Patients meeting definition of true AP (tAP)	Patients meeting definition of severe AP (sAP)	Patients with sAP admitted to critical care (sAP-CC)	Patients with sAP not admitted to critical care	Patients not meeting definition of sAP (nsAP)	Comparison of nsAP vs sAP (statistical significance, P-value; χ² test 1 d.f., unless specified)
Number of cases	(N, % total cases)	3340	2053 (61.5%)	390 (11.7%)	368 (11.0%)	22 (0.7%)	1663 (49.8%)	
Patients attending GP in year prior to admission	(N, % total cases)	618 (18.5%)	317 (15.4%)	48 (12.3%)	42 (11.4%)	6 (27.3%)	269 (16.2%)	
Number of GP visits in year prior to admission (GP attendees only)	median (1st, 3rd quartile)	5 (2, 11)	5 (2, 10)	7 (3, 13)	5 (2, 12)	12 (7, 18)	5 (2, 9)	0.075(Mann-Whitney U-test)
A&E attendances in year prior to admission	median (1st, 3rd quartile)	1 (1, 3)	1 (1, 2)	1 (1, 2)	1 (1, 2)	2 (1, 4)	1 (1, 2)	0.745 (Mann-Whitney U-test)
Hospital inpatient stays in year prior to admission	median (1st, 3rd quartile)	1 (0, 2)	1 (0, 3)	1 (0, 2)	1 (0, 2)	2 (0, 4)	1 (0, 2)	0.119 (Mann-Whitney U-test)
Hospital outpatient visits in year prior to admission	median (1st, 3rd quartile)	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 2)	1 (0, 3)	0.202 (Mann-Whitney U-test)
Number of previous admissions with AP	median (1st, 3rd quartile)	2 (1, 3)	1 (1, 2)	1 (1, 2)	1 (1, 3)	1 (1, 2)	1 (1, 3)	**0.045** (Mann-Whitney U-test)
Previous diagnoses or admissions (N, % within category)	Acute pancreatitis	968 (29.0%)	525 (25.6%)	72 (18.5%)	71 (19.3%)	1 (4.5%)	453 (27.2%)	**<0.001**
	Gallstones	628 (18.8%)	364 (17.7%)	61 (15.6%)	58 (15.8%)	2 (13.6%)	303 (18.2%)	0.230
	Alcohol-related psychiatric admission	757 (22.7%)	338 (16.5%)	59 (15.1%)	56 (15.2%)	3 (13.6%)	279 (16.8%)	0.429
	Hypertension	942 (28.2%)	595 (29.0%)	152 (39.0%)	143 (38.9%)	9 (40.9%)	443 (26.6%)	**<0.001**
	Ischemic heart disease	539 (16.1%)	334 (16.3%)	102 (26.2%)	95 (25.8%)	7 (31.8%)	232 (14.0%)	**<0.001**
	Myocardial infarction	223 (6.7%)	146 (7.1%)	48 (12.3%)	45 (12.2%)	3 (13.6%)	98 (5.9%)	**<0.001**
	Stroke or TIA	226 (6.8%)	139 (6.8%)	41 (10.5%)	38 (10.3%)	3 (13.6%)	98 (5.9%)	**0.001**
	Hypercholesteremia	197 (5.9%)	125 (6.1%)	21 (5.4%)	21 (5.7%)	0	104 (6.3%)	0.518
	DM type 2 not on insulin	471 (14.1%)	267 (13.0%)	79 (20.3%)	79 (21.5%)	0	188 (11.3%)	**<0.001**
	DM type 2 treated with insulin	57 (1.7%)	20 (1.0%)	6 (1.5%)	5 (1.4%)	1 (4.5%)	14 (0.8%)	0.208
	Diabetes mellitus (DM) type 1	113 (3.4%)	45 (2.2%)	9 (2.3%)	9 (2.4%)	0	36 (2.2%)	0.862
	DM (unspecified)	124 (3.7%)	66 (3.2%)	19 (4.9%)	18 (4.9%)	1 (4.5%)	47 (2.8%)	**0.039**
	Asthma	345 (10.3%)	198 (9.6%)	45 (11.5%)	43 (11.7%)	2 (9.1%)	153 (9.2%)	0.159
	COPD	313 (9.4%)	180 (8.8%)	47 (12.1%)	40 (10.9%)	7 (31.8%)	133 (8.0%)	**0.011**
	Chronic kidney disease	247 (7.4%)	150 (7.3%)	49 (12.6%)	45 (12.2%)	4 (18.2%)	101 (6.1%)	**<0.001**
	Acute kidney disease	114 (3.4%)	62 (3.0%)	20 (5.1%)	16 (4.3%)	4 (18.2%)	42 (2.5%)	**0.007**
	Renal Dialysis	16 (0.5%)	7 (0.3%)	3 (0.8%)	3 (0.8%)	0	4 (0.2%)	0.107
	Chronic liver disease	277 (8.3%)	119 (5.8%)	20 (5.1%)	19 (5.2%)	1 (4.5%)	99 (6.0%)	0.530
	Cystic Fibrosis	2 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0	1 (0.1%)	0.628
	Abdominal trauma	5 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0	1 (0.1%)	0.628

Table 3. Prescription medications and procedures

		Patients coded as ICD10 K85 (acute pancreatitis, AP)	Patients meeting definition of true AP (tAP)	Patients meeting definition of severe AP (sAP)	Patients admitted to critical care (a subset of sAP)	Patients with sAP not admitted to critical care (a subset of sAP)	Patients not meeting definition of sAP (nsAP)	X² test of sAP vs. nsAP p-value
Number of cases	(N, % total cases)	3340	2053 (61.5%)	390 (11.7%)	368 (11.0%)	22 (0.7%)	1663 (49.8%)	
Prescribed drugs in year up to and including admission (N, % within category)	paracetamol	1557 (46.6%)	917 (44.7%)	202 (51.8%)	188 (51.1%)	14 (63.6%)	715 (43.0%)	**0.001**
	antidepressants	544 (16.3%)	304 (14.8%)	67 (17.2%)	64 (17.4%)	3 (13.6%)	237 (14.3%)	0.137
	calcium-altering drugs	466 (14%)	283 (13.8%)	78 (20%)	74 (20.1%)	4 (18.2%)	205 (12.3%)	**<0.001**
	azathioprine	26 (0.8%)	17 (0.8%)	4 (1%)	4 (1.1%)	0	13 (0.8%)	0.629
	carbemazepine	51 (1.5%)	26 (1.3%)	3 (0.8%)	3 (0.8%)	0	23 (1.4%)	0.331
	oestrogens	158 (4.7%)	107 (5.2%)	21 (5.4%)	21 (5.7%)	0	86 (5.2%)	0.818
	neuroleptic agents	876 (26.2%)	512 (24.9%)	116 (29.7%)	108 (29.3%)	8 (36.4%)	396 (23.8%)	**0.017**
	oral antidiabetic agents	247 (7.4%)	144 (7%)	33 (8.5%)	32 (8.7%)	1 (4.5%)	111 (6.7%)	0.209
	oral corticosteroids	206 (6.2%)	133 (6.5%)	35 (9%)	28 (7.6%)	7 (31.8%)	98 (5.9%)	0.025
	simvastatin	625 (18.7%)	402 (19.6%)	110 (28.2%)	107 (29.1%)	3 (13.6%)	292 (17.6%)	**<0.001**
	statins (excluding simvastatin)	56 (1.7%)	35 (1.7%)	11 (2.8%)	10 (2.7%)	1 (4.5%)	24 (1.4%)	0.058
Procedures in year up to and including admission (N, % within category)	ERCP	267 (8.0%)	115 (5.6%)	18 (4.6%)	18 (4.9%)	0	97 (5.8%)	0.352
	Cholecystectomy	254 (7.6%)	142 (6.9%)	19 (4.9%)	18 (4.9%)	1 (4.5%)	123 (7.4%)	0.079
	Thyroid/parathyroid surgery	13 (0.4%)	8 (0.4%)	1 (0.3%)	1 (0.3%)	0	7 (0.4%)	0.640
	Coronary artery stent	40 (1.2%)	27 (1.3%)	11 (2.8%)	11 (3.0%)	0	16 (1.0%)	**0.004**
	Heart valve and/or CABG	15 (0.4%)	9 (0.4%)	1 (0.3%)	1 (0.3%)	0	8 (0.5%)	0.547

Critical care admission

368/2053 (17.9%) patients with tAP were admitted to critical care a median of 1 day (IQR 0, 2) after admission to hospital (**Table 4**). The 5% trimmed mean for this time interval was 1.8 days. 27.4% of patients had 2 or more CC admissions in relation to 1 episode of AP and 6.2% had 3 or more CC admissions. Median (IQR) duration of stay for the first CC admission was 68 (27, 139) hours. The duration of CC stay was slightly longer when averaged over all CC admissions (median 72 hours, IQR (29, 156)), and when total (sum) CC stay was calculated for any one individual AP episode (i.e. episodes during which there was more than 1 CC stay), the median (IQR) duration was 107 (45, 221) hours. An individual patient with AP requiring CC admission utilized 6 (3, 11) calendar days of CC care (**Table 5**).

The median (IQR) APACHE-2 score on admission to CC was 19 (14, 24). The number of organ systems requiring support is presented in **Table 4**. A small proportion of sAP patients (24/368 (6.5%)), were admitted for close observation without any recorded organ support. During the initial admission, cardiovascular support with vasopressors was used in 60.3% of sAP patients, but this value rose to 65.5% when all CC admissions were considered. 13.9% required mechanical ventilation on the first admission, rising to 18.1% when all CC admissions for that AP episode were considered. 4.8% required invasive renal replacement therapy at any point during CC admission.

Table 4. Admission to critical care

		First CC admission	All CC admissions
CC admissions during one continuous inpatient stay	**1 or more**		368 (100%)
	2 or more		101 (27.4%)
	3 or more		23 (6.2%)
	4 or more		5 (1.4%)
	5		1 (0.0%)
Days from hospital admission to first CC admission	**mean (95% CI)**	3.03 (2.32, 3.74)	
	5% trimmed mean	1.83	
	median (1st, 3rd quartile)	1 (0, 2)	
APACHE II score at CC admission	**median (1st, 3rd quartile)**	19 (14, 24)	19 (14, 24)
Organs requiring invasive support at CC admission	**0**	123 (33.4%)	139 (27.9%)
	1	124 (33.7%)	162 (32.5%)
	2	96 (26.1%)	157 (31.5%)
	3	22 (6%)	36 (7.2%)
	4	3 (0.8%)	4 (0.8%)
Organ support required at CC admission	**No immediate organ support given**	24 (6.5%)	26 (5.2%)
Respiratory	**Facemask / nasal cannulae**	296 (80.4%)	382 (76.7%)
	O2 less than 50%	206 (56.0%)	254 (51)
	O2 50% or more	77 (20.9%)	111 (22.3%)
	Continuous positive airway pressure	10 (2.7%)	17 (3.4%)
	Endotracheal tube	46 (12.5%)	85 (17.1%)
	Mechanical ventilator	51 (13.9%)	90 (18.1%)
	Tracheostomy	2 (0.5%)	5 (1%)
Cardiovascular	**Central venous catheter**	136 (37.0%)	217 (43.6%)
	Arterial line	186 (50.5%)	276 (55.4%)
	Inotropes/vasopressors	222 (60.3%)	326 (65.5%)
	Single vasoactive/antiarrhythmic drugs	37 (10.5%)	66 (13.3%)
	Multiple vasoactive/antiarrhythmic drugs	15 (4.2%)	21 (4.2%)
	Invasive cardiac output monitoring	10 (2.8%)	16 (3.2%)
	Pulmonary artery catheter	0 (0%)	0 (0%)
	Oesophageal doppler waveform analysis	1 (0.3%)	3 (0.6%)
	Peripheral pulse contour analysis	8 (2.2%)	10 (2)
	other method	1 (0.3%)	3 (0.6%)
Renal	**Haemofiltration / dialysis**	17 (4.6%)	24 (4.8%)
Neurological	**Invasive neurological monitoring**	0 (0%)	0 (0%)

Table 5. Outcomes in critical care

		1st CC period	All CC periods	Sum of CC periods in one continuous inpatient stay
Admitted to critical care (CC)	Number of patients	368	498	368
Died in CC				54 (14.7%)
Hours from CC admission to death	median (1st, 3rd quartile)			70 (25, 371)
	mean			260
Hours from hospital admission to death	median (1st, 3rd quartile)			82 (26,371)
	mean			264
Hours in CC	median (1st, 3rd quartile)	68 (27, 139)	72 (29, 156)	107 (45, 221)
	mean	115	132	179
Days in CC	median (1st, 3rd quartile)	4 (2, 7)	4 (2, 7)	6 (3, 11)
	mean	6.14	6.47	8.76
Ventilator-free days	median (1st, 3rd quartile)	3 (2, 5)	3 (2, 5)	4 (2, 7)
	mean	4.18	4.01	5.43
Haemofiltration/dialysis (days)	median (1st, 3rd quartile)	0 (0, 0)	0 (0, 0)	0 (0, 0) 6 (3, 8) on dialysis
	mean	0.94	0.96	1.30 8.1 on dialysis
Lowest pO_2 on blood gas kPa	median (1st, 3rd quartile)	9.9 (8.1, 11.4)	9.8 (8.2, 11.2)	
Highest pO_2 on blood gas kPa	median (1st, 3rd quartile)	14.5 (11.2, 22.7)	15.4 (11.4, 23.6)	
Lowest pCO_2 on blood gas kPa	median (1st, 3rd quartile)	5.1 (4.4, 6.0)	5.3 (4.5, 6.1)	
Highest pCO_2 on blood gas kPa	median (1st, 3rd quartile)	5.4 (4.8, 6.2)	5.7 (5.0, 6.7)	
Lowest pH on blood gas	median (1st, 3rd quartile)	7.28 (7.15, 7.38)	7.28 (7.20, 7.37)	
Highest pH on blood gas	median (1st, 3rd quartile)	7.37 (7.29, 7.42)	7.36 (7.27, 7.42)	
Highest fiO_2 recorded %O2	median (1st, 3rd quartile)	80 (50, 100)	90 (60, 100)	
Highest creatinine mmol/L	median (1st, 3rd quartile)	139 (91, 243)	144 (80, 272)	
Highest bilirubin mmol/L	median (1st, 3rd quartile)	26 (15, 68)	25 (14, 58)	

Factors predicting sAP (admission to critical care or death)

The results of the logistic model predicting sAP in those with tAP are given in **Table 6**. A lower calcium level (-0.1 mmol/L) at admission significantly increased the odds of developing sAP by 17% (OR = 1.17 95% CI 1.08, 1.26). Patients previously admitted with AP were less likely to need to need CC admission during a subsequent admission (OR = 0.77, 95% CI 0.61, 0.98 for one previous visit). A history of angina or IHD increased odds of sAP (OR = 1.46 95% CI 1.07 to 2.00), as did hypertension (OR = 1.43 95% CI 1.05 to 1.96), in addition to a primary care flag for alcohol dependency (OR = 1.68 95% CI 0.83 to 3.41). There was a significant interaction of age with type 2 diabetes. Generally, younger patients had a lower odds of sAP compared to those aged over 80 years, but for those aged 30-39 years with type 2 diabetes the odds were significantly increased (OR = 18.85 95% CI 1.36 to 90.84). The odds were still higher for those with type 2 diabetes as age increased but lower than for the 30-39 age group. The AUROC = 0.68 and the Hosmer-Lemeshow test was non-significant.

Table 6. Logistic regression of factors predicting development of tAP to sAP (critical care admission or death)

Parameter	Regression Estimate†	Std Error
Intercept	2.499	1.069
T2 DM No Insulin (Y/N)	-0.298	0.442
Simvastatin 12 Months Prior (Y/N)	0.221	0.151
Number of prior AP Emergency adm (+ 1 adm)	-0.259	0.123
Angina or IHD (Y/N)	0.379	0.161
Hypertension (Y/N)	0.360	0.161
Test Result Calcium* at Index Admission (-0.1 mmol/L)	0.156	0.038
Age group (vs 80+)		
18-19	-0.386	0.780
20-29	-0.867	0.630
20-29 * T2 DM (Y/N)	1.235	1.279
30-39	-0.879	0.614
30-39* T2 DM (Y/N)	2.936	0.802
40-49	1.053	0.608
40-49 * T2 (Y/N)	0.643	0.686
50-59	-0.342	0.596
50-59 * T2 (Y/N)	0.292	0.576
60-79	-0.466	0.591
60-79 * T2 (Y/N)	0.890	0.487
Alcohol flag* (Y/N)	0.521	0.360

*19% missing calcium, 35% missing alcohol; 98% relative efficiency of multiple imputations with 10 imputations
†Increase in logodds

Mortality

Overall in-hospital mortality was defined for tAP patients only and was 102/2053 (5.0%). Overall 90-day mortality for the tAP cohort was 127/2053 (6.2%) and for the sAP cohort was 100/390 (25.6%). In-hospital mortality amongst sAP admitted to critical care was 80/368 (21.7%), of whom 54/368 (14.7%) died in CC and 26/368 (7.1%) died in hospital after discharge from CC (**Table 5**).

Patients who died in CC died after a median (1st, 3rd quartile) of 70 (25, 371) hours after CC admission (**Table 5**). The median time from hospital admission to death for those dying in CC was 82 (26,371) hours, from which it can be inferred that the median time between admission to hospital and admission to CC was 12 hours (**Table 5**). Patients who died in hospital after discharge from CC died after a median (1st, 3rd quartile) of 9.9 (5.1, 21.9) days and mean 23.0 days after CC admission.

22 patients with sAP died in hospital without being admitted to critical care after a median (1st, 3rd quartile) of 4.5 (2.0, 18.0) days and mean of 12.0 days. The specific reasons why patients with severe AP in this subgroup were not admitted to CC are not known. None of these patients had advanced malignancy recorded as a cause or contributor on their death certificate. As a surrogate to identify nursing home residents who may not have been suitable for critical care, we examined place of residence. All 22 were admitted from private residence rather than a nursing home and 2/22 lived alone. Because pre-hospital and early mortality in severe AP is greater in rural areas[21], we examined postcodes for this patient subgroup. 20/22 were from urban postcodes. The mean ± SD age of these 22 patients was 74 ± 14 years and median (range) 72 (46 to 92) years. The median BMI (1st, 3rd quartile) for these 22 patients was significantly lower (22.1 (18.9, 30.7)) than the respective measures for the remainder of the tAP cohort.

Risk of death after critical care admission

The results of fitting the parametric Gamma model (lowest AIC) are shown in **Table 7** and **Figure 2**. Generally negative regression coefficients indicate factors that shorten the time to death. The only factor that was positive was T2 DM, which gave a time ratio of 2.99 (95% CI 0.42, 21.28). This indicates that the time to death was three-fold longer in those with T2 DM. There were very significant associations of shortening of time to death with thyroid / parathyroid history (TR = 0.003 95% CI 0.001 to 0.012) and

history of CV stent in previous year (TR = 0.049 95% CI 0.014 to 0.168). For each unit increase in APACHE II score there was a 29% reduction in time to death (TR = 0.71, 95% CI 0.48 to 1.05), while for each additional prior CC admission the time to death reduced by 34% (TR = 0.66 95% CI 0.37 to 1.19). Finally for each increase in age by one year the time to death reduced by 4% (TR = 0.96 95% CI 0.92 to 1.01). Probabilities estimated from the Gamma model were very close to the Kaplan-Meier estimates of survival.

Table 7. Factors that impact on time to death following critical care from a Gamma prediction model

Parameter	Regression Estimate*	Standard Error	95% Confidence Limits		Chi-Square	p-value
Intercept						
	10.006	1.752	6.572	13.440	32.61	**<.0001**
Age at index admission (+1 year)						
	-0.037	0.022	-0.080	0.006	2.83	0.093
T2 DM (Y/N)						
	1.095	1.001	-0.867	3.058	1.20	0.274
Log (APACHE II) (+ 1 unit)						
	-0.345	0.200	-0.736	0.046	2.99	0.084
CV stent within 1year (Y/N)						
	-3.015	0.628	-4.245	-1.785	23.08	**<.0001**
Thyroid/parathyroid (Y/N)						
	-5.875	0.746	-7.336	-4.414	62.10	**<.0001**
Number of CC Stays in previous year (+ 1 CC stay						
	-0.414	0.299	-1.000	0.172	1.92	0.166
Gamma Scale parameter						
	0.326	0.053	0.238	0.448		
Gamma Shape parameter						
	6.816	1.093	4.673	8.958		

*Log of time to death ratio (negative represents a shorter time to death)

Discussion

Acute pancreatitis is associated with a high mortality, shortens overall life expectancy in survivors[22] and constitutes a considerable healthcare resource burden[7-9 13]. Specifically, the evolution of persistent organ dysfunction requiring critical care (CC) support has the most deleterious short and long term consequences in AP. Building on previous work by others[23 24], in this cross-sectional observational study, we have brought together sixteen electronic healthcare records into a single national Safe Haven overseen by the Farr Institute governance structure to conduct a detailed study of the development of organ dysfunction and CC admission in AP.

These data confirm a disproportionately high incidence of AP in the most multiply deprived quintiles of areas, in keeping with previous observations by us and others[25], and that CC admission during an episode of AP has a high (21.7%) mortality compared to that of the overall cohort (5.0%). Patients who require CC admission do so early in the disease course (at a median of 1 day after admission) and experience a median total of 6 days CC support per episode of AP. Factors independently predictive of CC admission or death include a history of angina, pre-existing hypertension, hypocalcaemia, fewer prior emergency admissions with AP, and type 2 diabetes in young patients. The reasons for the association with young persons with type 2 diabetes has not been ascertained from our data, despite our efforts to do so; it is possible that this observation may reflect differences in older persons, or reflect a confounder in our dataset that we have been unable to uncover. Once admitted to CC, factors predictive of death included cardiovascular stenting and thyroid or parathyroid surgery within the previous year.

The overall mortality seen in our study is comparable with that seen in other large epidemiological studies in the UK[26], the US[7 8], Taiwan[2], Japan[4] and South Africa[27]. The mortality in the population of patients with tAP requiring CC in the present cohort is somewhat higher than many other reported studies, and certainly the APACHE-II score on admission to CC was higher than the average for the general ICU population in the Scottish system[28]. Patients admitted to CC who subsequently died were admitted to CC sooner (median 12 hours, mean 14 hours) after hospital admission than the overall 5% trimmed mean for overall sAP-CC cohort of 1.83 days (**Table 4**). Therefore, non-survivors were admitted to CC sooner after hospital admission than eventual survivors.

It is likely that this is a consequence of more severe AP in non-survivors triggering earlier CC admission criteria. A second alternative explanation is that it is possible that a faster evolution variant of AP is more lethal, or that this subgroup of patients is more susceptible to rapid evolution of disease. Lastly, this observation may reflect a delay in presentation to hospital leading to increased mortality in those not presenting promptly for treatment.

Independent predictors of severe disease in tAP included a history of angina and hypertension. It is logical that patients with pre-existing chronic heart disease would be at increased risk of death once they develop organ dysfunction, and this is borne out in our study by the association between coronary stenting in the preceding year and risk of death after CC admission. However, it is not as straightforward to link angina and hypertension with an increased likelihood of needing CC admission in the context of an AP episode. Angina and hypertension in this scenario may be confounders, acting as surrogate markers of other chronic health conditions that directly reduce the threshold for developing organ dysfunction requiring CC, or they may indicate a lack of physiological compensatory reserve in critical illness, such that for a given inflammatory insult there is greater physiological derangement.

Our observation that a higher number of previous admissions with AP reduces the risk for CC admission or death during a subsequent AP episode is novel. It is uncertain whether this is a result of increased individual likelihood of developing systemic organ dysfunction with particular severity of inflammatory insult, or whether frequent A&E attenders, particularly with regard to alcohol overuse represent a different subset of patients.

The relationship between fluctuations in serum calcium and pancreatitis is known[29] and the association between thyroid and parathyroid surgery and death after CC admission, and between hypocalcemia and calcium-altering drugs is not surprising. Hypo- or hypercalcemia is recognized in both the Imrie[30] and Ranson[31] scoring systems, and there is a wealth of preclinical experimental evidence of deranged calcium signaling as a mechanism of pancreatic acinar cell injury[32].

Strengths of study

The main strength of this study is the coalition of multiple electronic data sources linked though a unique identifier on a national basis. Critical to this process was strict

data protection. This was achieved through the use of a centralized protected safe haven and minimizing the number of individuals with access to the non-anonymised primary data. Furthermore, industry partners could be fully involved in the protocol design and processes surrounding the data collection and depository without needing sight of any primary data. Combining detailed inpatient CC information collected at high temporal resolution and integrating this with broad background data derived from community data sources was achieved.

Limitations and Bias

Limitations of this study include an inability to gain information in electronic form on routinely recorded clinical data from those inpatients that did not require CC. This may have led to negative reporting bias for events that might be relevant to this study but not sufficiently severe to necessitate CC admission. In addition, we are unable to ascertain exactly how many individuals might have met criteria for CC admission but not admitted due to advance directives or limited capacity. A further limitation inherent to the study design based on routinely collected data is the relative lack of confirmation of the accuracy of source data entry. Although we specifically conducted a coding accuracy pilot for the diagnosis of AP, comparing electronic records with hand-written notes in four separate study sites, and while certain variables are likely to be highly accurate, for example automatically-retrieved Wardwatcher™ critical care data, laboratory values and date of death on death certificates, certain other fields are impossible to ratify accurately. We include in the latter category comorbidity and clinical information recorded in hospital discharge summaries.

Conclusions

National record-linkage analyses from a wide variety of routinely collected primary and secondary care data sources are feasible and constitute a powerful resource. Factors that predict sAP are distinct from those that prognosticate mortality. Mortality in patients with AP who require CC admission remains high.

Acknowledgements

Tables

Figure legends

Author contributions

Damian J. Mole contributed to the study idea, protocol design, literature search, limited data analysis, drafted manuscript, figures and tables, research in context, cover letter. Usha Gungabissoon contributed to the study idea, protocol design, literature search, limited data analysis, commented and revised drafts of the manuscript, figures and tables, research in context, cover letter. Philip Johnston contributed to the study idea, protocol design, pilot data, safe haven, coordinated the study data linkage and conduct and commented and revised drafts of the manuscript, figures and tables. Lynda Cochrane performed the statistical analysis and contributed to, commented and revised drafts of the manuscript, figures and tables. Leanne Hopkins contributed to the study idea, protocol design, pilot data, contributed to the study data linkage and conduct and commented and revised drafts of the manuscript, figures and tables. Grant M. A. Wyper contributed to the protocol design, study data linkage, safe haven design, and conduct and commented and revised drafts of the manuscript, figures and tables. Christos Skouras contributed to the literature search and revised and commented on the manuscript, figures and tables, research in context, cover letter. Chris Dibben contributed to the study data linkage, safe haven design, and conduct and commented and revised drafts of the manuscript, figures and tables. Frank Sullivan contributed to the study idea, protocol design, pilot data, safe haven, contributed to the design of the study data linkage and conduct and commented and revised drafts of the manuscript, figures and tables. Andrew Morris contributed to the study idea and commented and revised drafts of the manuscript, figures and tables. Hester Ward contributed to the study idea, protocol design, pilot data, safe haven, coordinated the study data linkage and conduct and commented and revised drafts of the manuscript, figures and tables. Andrew M. Lawton contributed to the study idea, protocol design, literature search, commented on data analysis, and contributed to revising the manuscript, figures and tables, research in context, and cover letter. Peter T. Donnan contributed to the study idea, protocol design, performed data analysis and statistical modelling, drafted sections of the manuscript, figures and tables, and commented and revised on all sections and the research in context, cover letter.

Data sharing statement

Applications for data for this study should be made to the Farr Institute/NHS ISD/eDRIS single portal, via an initial approach to the corresponding author. No additional data are available outwith that process.

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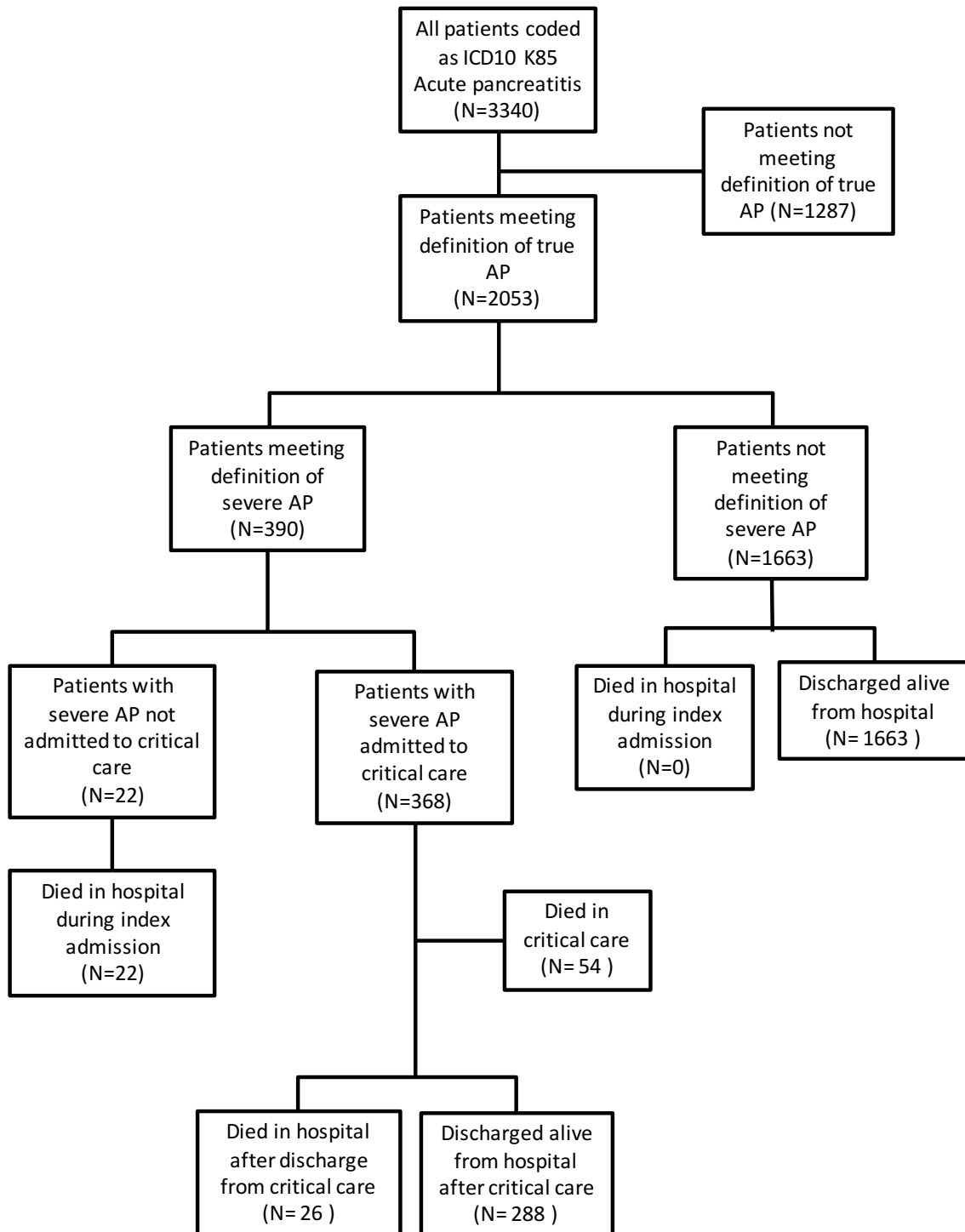
Figure 1. CONSORT flow diagram

Figure 2. Probability (95% CI) plot for the Gamma model