Pancreatology 23 (2023) 341–349

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Mortality and costs related to severe acute pancreatitis in the intensive care units of Australia and New Zealand (ANZ), 2003–2020

Savio George Barreto [a, b, *], Billingsley Kaambwa [b], Karthik Venkatesh [c, d], Sarah C. Sasson [d, e], Christopher Andersen [c, d, f, g], Anthony Delaney [c, f], Shailesh Bihari [b, h], David Pilcher [i, j, k], the P-ANZICS Collaborative

[a] Division of Surgery and Perioperative Medicine, Flinders Medical Center, Bedford Park, Adelaide, South Australia, Australia
[b] College of Medicine and Public Health, Flinders University, South Australia, Australia
[c] Malcolm Fisher Department of Intensive Care, The Royal North Shore Hospital, St Leonards, NSW, 2065, Australia
[d] The Kirby Institute, UNSW, Sydney, Australia
[e] NSW Health Pathology I.C.P.M.R, Westmead Hospital, Sydney, Australia
[f] Northern Clinical School, University of Sydney, Sydney, NSW, Australia
[g] The George Institute for Global Health, King Street, Newtown, NSW, 2042, Australia
[h] Department of ICCU, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia
[i] Department of Intensive Care, The Alfred Hospital, Commercial Road, Prahran, Melbourne, Victoria, 3004, Australia
[j] The Australian and New Zealand Intensive Care-Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, 3004, Australia
[k] The Australian and New Zealand Intensive Care Society (ANZICS), Centre for Outcome and Resource Evaluation (CORE), 277 Camberwell Road, Camberwell, Victoria, 3124, Australia

ARTICLE INFO

Article history:
Received 7 February 2023
Received in revised form
21 March 2023
Accepted 17 April 2023
Available online 21 April 2023

Keywords:
Morbidity
Mortality
Demography

ABSTRACT

Background and objective: Comprehensive data on the burden of severe acute pancreatitis (SAP) in global intensive care units (ICUs) and trends over time are lacking. Our objective was to compare trends in hospital and ICU mortality, in-hospital and ICU length of stay, and costs related to ICU admission in Australia and New Zealand (ANZ) for SAP.

Methods: We performed a retrospective, observational, cohort study of ICU admissions reported to the ANZ Intensive Care Society Adult Patient Database over three consecutive six-year time periods from 2003 to 2020.

Results: 12,635 patients with SAP from 189 ICUs in ANZ were analysed. No difference in adjusted hospital mortality (11.4% vs 11.5% vs 11.0%, $p = 0.85$) and ICU mortality rates (7.5% vs 8.0% vs 8.1%, $p = 0.73$) were noted over the study period. Median length of hospital admission reduced over time (13.9 days in 2003-08, 13.1 days in 2009-14 and 12.5 days in 2015-20; $p < 0.01$). No difference in length of ICU stay was noted over the study period ($p = 0.13$). The cost of managing SAP in ANZ ICUs remained constant over the three time periods.

Conclusions: In critically-ill SAP patients in ANZ, no change in mortality has been noted over nearly two decades. There was a slight reduction in hospital stay (1 day), while the length of ICU stay remained unchanged. Given the significant costs related to care of patients with SAP in ICU, these findings highlight the need to prioritise resource allocation for healthcare delivery and targeted clinical research to identify treatments aimed at reducing mortality.

1. Introduction

In high income countries, the incidence of acute pancreatitis has been rising over the last ~60 years [1], with mortality rates fluctuating between 6.9 and 11.7/million persons/year [2]. Although the disease is self-limiting in nearly 80% of individuals, those that

* Corresponding author. Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia.
E-mail addresses: georgebarreto@yahoo.com, savio.barreto@flinders.edu.au (S.G. Barreto).

https://doi.org/10.1016/j.pan.2023.04.006
1424-3903/

Abbreviations

ANZ	Australia and New Zealand
ANZICS	Australia and New Zealand Intensive Care Society
APACHE	Acute Physiology and Chronic Health Evaluation
APD	Adult Patient Database
BMI	body mass index
CI	Confidence interval
GCS	Glasgow Coma Scale
GDP	Gross domestic product
HDU	High dependency unit
ICU	Intensive care unit
IQR	Interquartile range
MAR	missing at random
MM-GLM	multilevel mixed-effects generalised linear models
SAP	Severe acute pancreatitis
SE	standard error
SOFA	Sequential Organ Failure Assessment

progress to more severe forms, characterized by persistent organ failure, experience mortality rates up to 40% [3]. The impact of severe acute pancreatitis (SAP)-associated organ dysfunction is significant. SAP is associated with prolonged stay in both the hospital as well as intensive care units (ICUs) [4,5]. Thus, not only does SAP result in considerable utilization of health-care resources imposing an economic strain on the health care system, the resultant long-term disability from admissions to ICU [6] with attendant loss of productivity [7] means that there are significant economic implications [8].

Although resource utilization is high in patients with SAP, many survive and have a good long-term quality of life [5]. Thus, efforts aimed at reducing the incidence of SAP, understanding modifiable factors influencing mortality, and developing effective treatments that prevent the progression of disease from mild to severe will not result only in a better outcome for the patient, but also a reduction in health care expenditure [4]. Comprehensive data on the burden of SAP in ICUs world-wide are limited [9,10]. Despite SAP being a common disease worldwide, there is insufficient population-based data [11], especially regarding trends in hospital and ICU length of stay and mortality rates. As the present manuscript was to be submitted for publication, the first data on trends in mortality were published from the Netherlands [12]. These data are needed to prioritise resource allocation for both healthcare delivery and targeted clinical research strategies.

Accordingly, we sought to estimate trends in hospital and ICU mortality as well as length of stay (hospital and ICU), and attendant ICU costs in a large cohort of patients with SAP admitted to ICUs in ANZ from 2003 to 2020. We hypothesized that mortality rates have decreased significantly over the period of analysis.

2. Methods

We performed a retrospective observational, cohort study of data from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD). The ANZICS APD is a clinical quality registry dataset collected by the ANZICS Centre for Outcome and Resources Evaluation. It contains information regarding 3 million ICU admissions and presently covers 98% of ICUs in Australia and 67% of ICUs in New Zealand. The information collected by the dataset includes baseline demographics and co-morbidity data, admission biochemical and clinical data, and interventions and outcomes from the ICU and hospital admission. We analysed data on all adult (≥18 years) patients admitted with a primary diagnosis of acute pancreatitis (coded based on the ANZICS modification of the APACHE diagnostic coding system reflecting the primary cause of admission to ICU) to 174 Australian and 15 New Zealand ICUs (Appendix A) between May 2003 to December 2020. Every admission to hospital was considered as a separate hospitalization episode for each patient. Exclusion criteria included patients <18 years of age, readmission episodes to ICU (to avoid double counting mortality outcomes), and patients where the primary outcome, mortality, was not reported. We did not account for inter-hospital transfers. Ethics approval for the study was obtained from The Alfred Hospital human research ethics committee (HREC number 286/21).

2.1. Statistical analysis

The following information was extracted:

a) ***Patient factors***, including, patients' age, gender, Indigenous status (denoting First Nations Australians and First Nations New Zealanders), body mass index (BMI), organ system scores, *e.g.* Glasgow Coma Scale (GCS) scores, illness severity scores, *e.g.* APACHE III score, comorbidities (immune-suppressive disease, lymphoma, leukemia, metastatic cancer, cardiovascular disease, renal disease), treatment goals on admission to ICU, therapies (renal replacement therapy, tracheostomy, inotropes, invasive and non-invasive ventilation) received in ICU (where available), time in hospital prior to ICU admission, and source of admission to ICU and to hospital.
b) Outcomes

Primary outcome: in-hospital mortality.

Secondary outcomes: mortality in ICU, length of stay in hospital and in ICU (in days) and costs related to ICU admission. We also analysed factors predictive of trends in hospital and ICU mortality.

As patients in the study were nested within 189 study sites with their characteristics, for the most part, measured annually from 2003 to 2020, we used multilevel mixed-effects generalised linear regression models (MM-GLMs) to estimate trends in hospital and ICU mortality as well as the length of stay (hospital and ICU), and attendant ICU costs. MM-GLMs were chosen because they:

1) Allowed us to recognise that there were different hospitals in different sites in Australia and New Zealand.
2) Enabled us to draw valid conclusions even when there was missing data [13–16].
3) Recognised that data for each site were collected at different time points (i.e., annually from 2003 to 2020).

Two analyses were conducted in the MM-GLMs. The first analysis calculated adjusted estimates of the trends in selected indicators. Adjusted estimates controlled for the effect or influence other factors in the data had on how these estimates were computed. For instance, adjusted mortality estimates took away the effects or influence that factors such as patient characteristics (e.g., age, BMI, gender and indigenous status) had on these estimates. This was done by including patient characteristics as independent variables in the model that estimated mortality trends. In the second analysis, patient characteristics that explained trends in mortality were assessed (Supplementary Fig. 1). All analyses were conducted in Stata version 17.1 (College Station, TX: StataCorp LP) [17].

For purposes of reporting, parametric data is represented as mean (± SE) and non-parametric data as median (IQR). Length of stay in hospital was truncated to one year. Mean and median costs associated with ICU admission were calculated by respectively multiplying the mean and median length of stay by published 2013/14 estimates [18]. To reflect current prices, 2013/14 costs were converted to 2021 prices using the Australian consumer price index (CPI) for health [19]. A significance level threshold of 5% (0.05) was assumed to determine statistical significance in all analyses [20]. All analyses were conducted in Stata version 17.1 (College Station, TX: StataCorp LP) [17].

3. Results

3.1. Sample characteristics (Table 1)

Over the entire study period, a total of 12,635 patients (1646 in 2003-08, 4417 in 2009-14 and 6572 in 2015-20) were analysed (Fig. 1 & Supplementary Fig. 2). A total of 5150 (40.8%) and 982 (7.8%) of the included patients, were classified as female and Indigenous peoples, respectively. The mean patient age was 59.0 (Standard error = 0.2) with a mean BMI of 30.2 (S E. = 0.2) and a GCS score of 14.3 (S E. = 0.0), and an APACHE III score of 55.1

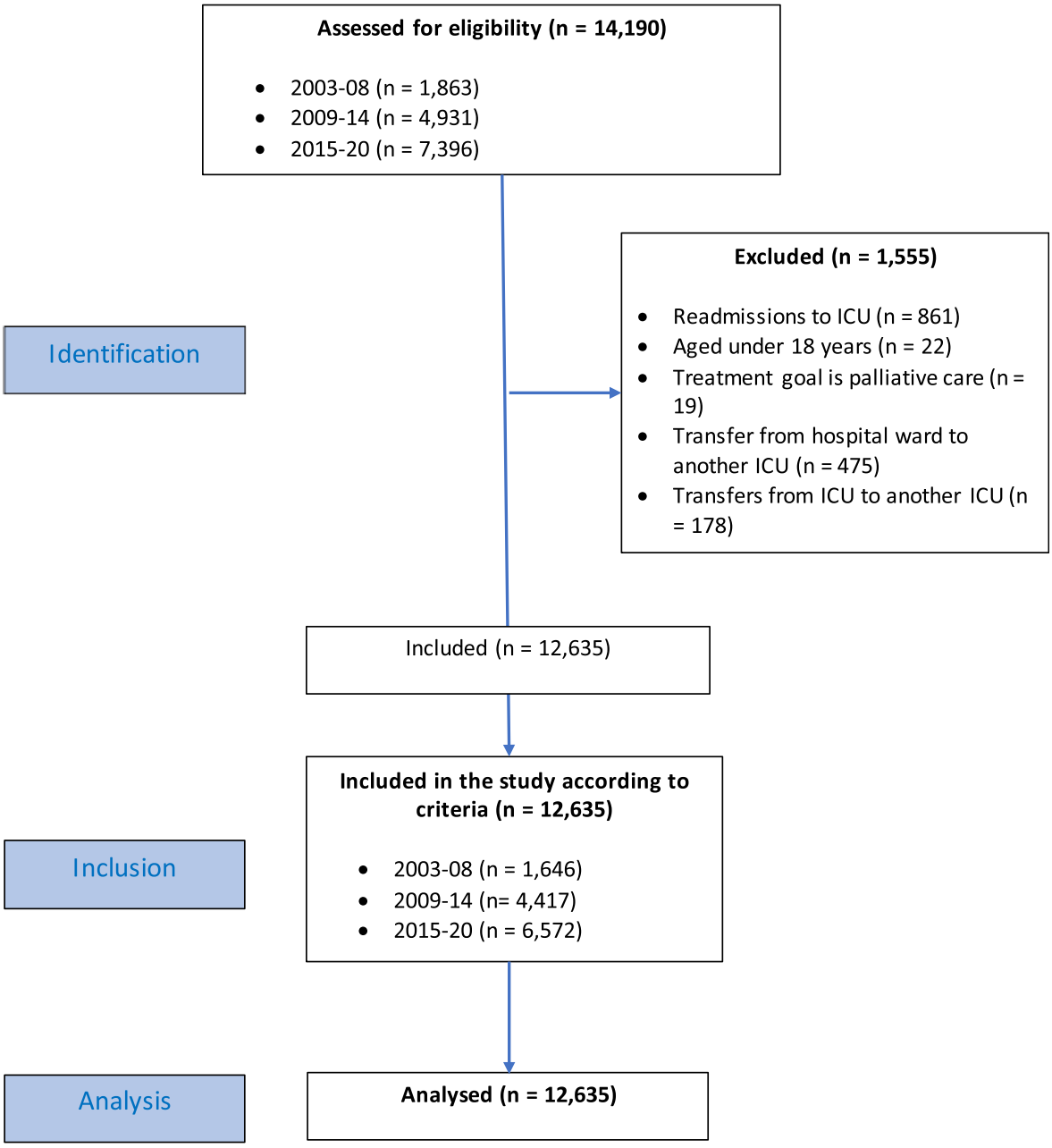

Fig. 1. STROBE flow chart.

Table 1
Characteristics and outcomes in severe acute pancreatitis over the entire study period (Abbreviations: SE – standard error; APACHE - Acute Physiology and Chronic Health Evaluation; ICU – intensive care unit; ED – emergency department; HDU – high-dependency unit; SOFA - Sequential Organ Failure Assessment).

	Total (n = 12,635)
Demographic Characteristics	
	Mean (SE)
Age in years	59.0 (0.2)
Body mass index (BMI)	30.2 (0.2)
Glasgow Coma Scale (GCS) scores	14.3 (0.0)
APACHE III score	55.1 (0.2)
SOFA score [median, (IQR)]	4.0 (2.0, 6.0)
	n (%)
Gender - Female	5150 (40.8)
Indigenous	982 (7.8)
Medical conditions	
Dialysis-dependent renal patients	345 (2.7)
Severe chronic liver disease	302 (2.4)
Immunosuppressed	302 (2.4)
Receiving immune suppressive therapy	321 (2.5)
Chronic Cardiovascular condition	880 (7.0)
Chronic Respiratory condition	302 (2.4)
Insulin dependent diabetes	635 (5.0)
Lymphoma	560 (4.4)
Leukemia	54 (0.4)
Metastatic cancer	43 (0.3)
Treatments/Interventions received	
Renal replacement therapy[b]	353 (13.3)
Tracheostomy[b]	106 (4.0)
Inotropes[b]	843 (30.8)
Invasive ventilation[b]	657 (22.4)
Non-invasive ventilation[b]	461 (16.5)
Day 1 ventilation	2511 (19.9)
	Mean (SE)
Duration of invasive ventilation (hours)[a]	94.1 (8.4)
Duration of non-invasive ventilation (hours)[a]	8.4 (1.1)
Treatment goals	**n (%)**
Full active management (w/o treatment limitation)	10,531 (83.3)
Treatment limitation order	497 (3.9)
Unknown	1607 (12.7)
Admission source, hospital types and patient outcomes	
	Median (IQR)
Length of Stay, days	
Pre ICU	1.0 (1.0, 2.0)
ICU	3.0 (2.0, 7.0)
Hospital	12.0 (7.0, 22.0)
	n (%)
Readmission rates	1119 (8.9)
Hospital Classification	
Metropolitan	3573 (28.3)
Private	1330 (10.5)
Rural/Regional	2971 (23.5)
Tertiary	4761 (37.7)
Source of hospital admission	
Home	9210 (72.9)
Other acute hospital (not ICU/ED)	2683 (21.2)
Nursing home/Chronic care/Palliative care	112 (0.9)
Other hospital – ICU	308 (2.4)
Other hospital – ED	321 (2.6)
Source of intensive care unit (ICU) admission	
Outpatient ward/Recovery	1466 (11.6)
Emergency department	5100 (40.4)
Ward/Coronary care/other HDU	4524 (35.8)
ICU, same hospital	32 (0.3)
Other hospital	1248 (9.9)
Other	261 (2.1)
ICU Outcomes	
Died	1017 (8.0)
Home/Other/Ward	11,254 (89.1)
Other hospital–normal ward	364 (2.9)
Hospital Outcomes	
Died	1463 (11.6)
Home	9142 (72.4)
Nursing Home/Palliative Care	495 (3.9)
Other acute hospital	1368 (10.8)
Other	167 (1.3)

[a] Entire study period.
[b] Data on Renal replacement therapy (n = 2649), Tracheostomies (n = 2646), Inotropes (n = 2739), Invasive ventilation after day 1 (n = 2927) and non-invasive ventilation (n = 2792) were only available from 2017 onwards and so were not analysed for trend.

(S E. = 0.2) and a median SOFA score of 4.0 (IQR = 2–6) (Table 1). The majority of hospital admissions were from home (72.9%) with most patients treated in tertiary hospitals (37.7%). The majority of patients (90%) were managed in public hospitals, compared to private hospitals. Most patients (72.4%) were discharged to their homes after hospital admission.

3.2. Trends in patient characteristics over time (Table 2)

3.2.1. Patient factors

The mean age of patients was 60 (S E. = 1.0) years in 2003-08, 60 (0.0) years in 2009-14 and 58 (0.0) years in 2015-20 and these differences were statistically significant ($p < 0.01$). The proportion of Indigenous patients was also statistically higher ($p < 0.01$) in 2009-14 and 2015–20 (9.3% in both periods) compared to 2003–08 (4.5%). There were no statistically significant changes in APACHE III scores over the years.

3.2.2. Co-morbidities

The proportion of patients with cardiovascular disease decreased from 11.3% in 2003-08 to 6.2% in 2015-20; $p < 0.01$), while the proportion of insulin-dependent diabetics increased from 4.4% in 2009-14 to 6.4% in 2015-20 ($p < 0.02$). A changing trend in dialysis-dependent renal patients was noted over time (3.4% in 2009-14 compared to 2.5% at other times, $p < 0.01$).

3.2.3. Treatment goals and therapies received

The proportion of patients receiving mechanical ventilation was 20.4% in 2003-08, 20.8% in 2009-14 and 16.6% for 2015–20 ($p < 0.01$). The proportion of patients opting for full active management increased between 2009-14 and 2015–20 (i.e., from 88.5% to 94.8%) while that of patients following treatment limitation orders (complete data for the period 2003–2008 was not available) and other treatment goals declined over the study period. Data on some therapies were only available from 2017 onwards (Table 1), due to which we were unable to calculate trends. These data, however, showed that the proportion of patients that received these therapies ranged from 4.0% (tracheostomies) to 30.8% (inotropes). The mean duration of invasive ventilation was 94.1 (8.4) hours.

3.3. Outcomes (Table 2)

The overall hospital mortality rate for SAP over the entire study period was 11.6% (1463 patients). The unadjusted mortality rates were 12.8% (2003–08), 12.1% (2009–14) and 11.0 (2015–20) and these differences were statistically significant ($p < 0.05$). However,

Table 2
Trends in patient characteristics over the study period (Abbreviations: SE – standard error; ICU – intensive care unit).

VARIABLES		Period			
	Statistic[a]	**2003–08 (n = 1646)**[b]	**2009–14 (n = 4417)**[b]	**2015–20 (n = 6572)**[b]	***p*-value**[c]
DEMOGRAPHIC CHARACTERISTICS					
Age in years	n; Mean (SE)	1188; 60 (1.0)	3433; 60 (0.0)	5490; 58 (0.0)	<0.01
Indigenous Status (Yes)	n (%)	51 (4.5)	273 (9.3)	451 (9.3)	<0.01
Gender (Female)	n (%)	490 (41.5)	1446 (42.4)	2208 (40.0)	0.08
Body mass index (BMI)	n; Mean (SE)	13; 31 (2.0)	429; 29 (0.0)	2135; 30 (0.0)	0.09
PERFORMANCE OF ORGAN AND BODY SYSTEMS					
Glasgow Coma Scale (GCS) scores	n; Mean (SE)	1120; 14 (0.0)	3339; 14 (0.0)	5377; 14 (0.0)	<0.01
APACHE III Score	n; Mean (SE)	1158; 54 (1.0)	3422; 55 (0.0)	5486; 55 (0.0)	0.10
MEDICAL CONDITIONS					
Immunosuppressed	n (%)	24 (2.0)	74 (2.2)	145 (2.7)	0.34
Severe chronic liver disease	n (%)	23 (2.3)	73 (2.4)	141 (2.3)	0.74
Cardiovascular disease	n (%)	122 (11.3)	301 (8.2)	316 (6.2)	<0.01
Respiratory disease	n (%)	58 (4.9)	164 (4.4)	229 (4.4)	0.86
Insulin-dependent diabetes	n (%)	54 (5.4)	117 (4.4)	115 (6.4)	0.02
Lymphoma	n (%)	5 (0.3)	16 (0.5)	29 (0.5)	0.73
Leukemia	n (%)	3 (0.3)	14 (0.6)	13 (0.3)	0.27
Metastatic cancer	n (%)	10 (1.0)	27 (0.9)	55 (0.9)	0.88
Dialysis dependent renal patients	n (%)	29 (1.8)	123 (3.4)	123 (2.5)	0.01
TREATMENTS OR INTERVENTIONS AND TREATMENT GOALS					
Day 1 ventilation	n (%)	252 (20.4)	750 (20.8)	886 (16.6)	<0.01
Treatment goals					
Full active management	n (%)	392 (26.5)[d]	3092 (88.5)	5159 (94.8)	
Treatment limitation order	n (%)	17 (12.6)	106 (5.1)	311 (2.5)	<0.01
Unknown/missing/not stated	n (%)	779 (60.9)	235 (6.4)	20 (2.7)	
DESCRIPTORS OF HOSPITAL ADMISSIONS					
Days in hospital prior to admission ICU	n; Mean (SE)	1186; 2.8 (0.3)	3421; 2.7 (0.2)	5480; 2.2 (0.1)	0.02
	Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	
Days spent in intensive care unit	n; Mean (SE)	1187; 7.0 (0.5)	3433; 7.0 (0.2)	5485; 6.5 (0.2)	0.13
	Median (IQR)	3.0 (2.0, 7.0)	3.0 (2.0, 7.0)	3.0 (2.0, 6.0)	
Days spent in Hospital	n; Mean (SE)	1169; 22.5 (1.1)	3363; 20.7 (0.6)	5463; 19.0 (0.5)	<0.01
	Median (IQR)	13.9 (8.1, 26.3)	13.1 (7.7, 23.9)	12.5 (7.3, 21.5)	
PATIENT OUTCOMES					
ICU Mortality	n (%)	97 (7.5)	275 (8.0)	431 (8.1)	0.73
Hospital Mortality	n (%)	142 (11.4)	394 (11.5)	594 (11.0)	0.85
Readmission rates	n (%)	109 (9.8)	287 (8.3)	483 (8.6)	0.52

[a] n; Mean (SE) = sample size; mean value (standard error), n (%) = frequency and percentage, Median (IQR) = median value (interquartile range).
[b] The sample sizes (n) for the variables in this table may not always add up to these totals as they correspond to adjusted mean or probability values are derived from two-level multilevel mixed-effects generalised linear models (MM-GLMs) regression models. In these models, when a particular variable or characteristic was modelled as the dependent variable, the MM-GLMs controlled for the effect that the rest of the characteristics (independent or explanatory variables) had on the regression and some of these explanatory variables had missing values, hence the reduced sample size.
[c] p-value obtained from Wald test assessing whether marginal effects of the patient characteristics differed between time point.
[d] Complete data for the first time period was not available.

there was no difference in adjusted hospital mortality (11.4% vs 11.5% vs 11.0%, p = 0.85; Fig. 2) over the study period. A higher probability of dying in hospital (Table 3) was associated with being older, female, having a treatment limitation order on admission to ICU, being admitted to a tertiary hospital, as well as being admitted to ICU from another hospital.

The overall ICU mortality rate for SAP over the entire study period was 8.0% (1013 patients). The unadjusted mortality rates were 8.6% (2003–08), 8.2 (2009–14) and 7.8% (2015–20) and these differences were not statistically different (p = 0.50). There was no difference in adjusted ICU mortality rates (7.5% vs 8.0% vs 8.1%, p = 0.73; Table 2). However, a higher probability of dying in ICU was associated with being older, female, of Indigenous status, dialysis-dependent, receiving immunosuppressive therapy, having a treatment limitation order, and being admitted to a tertiary hospital.

The adjusted median (IQR) length of stay in hospital reduced over the 3 time periods [13.9 (8.1, 26.3) days in 2003-08, 13.1 (7.7, 23.9) days in 2009-14 and 12.5 (7.3, 21.5) days in 2015-20; p < 0.01] (Fig. 3). There was no difference in the length of stay in ICU over the study period (P = 0.13), nor in the proportion of patients who had at least one readmission (9.8% vs 8.3% vs 8.6%, p = 0.52; Table 2).

3.3.1. Costs related to ICU admission

The mean (95% CI) ICU costs (per patient) were $39,110 ($33,736 - $44,483) for 2003–08, $39,139 ($36,451 - $41,828) for 2009-14 and $36,148 ($33,814 - $38,482) for 2015–20. The corresponding median (IQR) costs were $19,916 ($10,587, $401,098), $21,939 ($11,376 - $43,188) and $19,306 ($10,981 - $37,658). None of these differences were significantly different.

4. Discussion

SAP, and attendant organ failure, are associated with a significantly increased risk of death, despite which there is insufficient

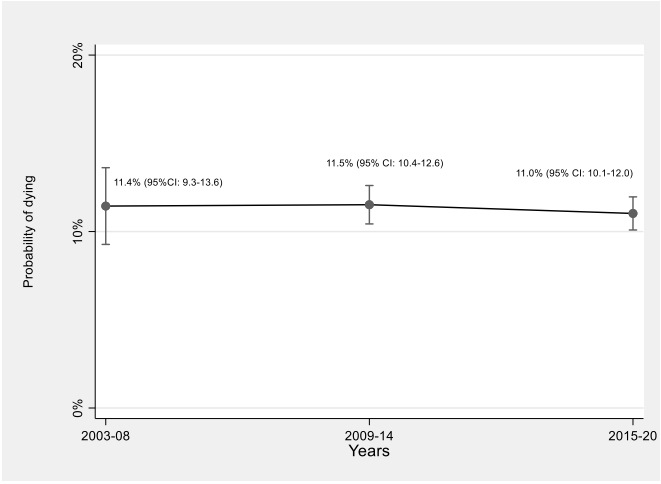

Fig. 2. Trends in adjusted probability of dying in hospital (hospital mortality) of severe acute pancreatitis (SAP) patients with the y-axis reflecting a true probability of dying derived from regressions.

population-based data [11] regarding trends in hospital and ICU length of stay and mortality rates. While the number of patients admitted to the ICU with SAP, who have been reported to the ANZICS APD, has steadily risen over time, in-hospital, as well as, ICU mortality rates have remained unchanged throughout the study period. Although the length of hospital stay reduced over time, there was no change in the length of ICU stay. The majority of patients with SAP treated in ANZ ICUs are middle-aged, obese, non-Indigenous males. The proportions of younger patients, Indigenous peoples, higher GCS scores at admission, and insulin-dependent diabetics [21], have significantly increased over time. A higher probability of dying in hospital was associated with being older, female, having a treatment limitation order, being admitted to a tertiary hospital, as well as being admitted to ICU from another hospital. The costs of managing SAP in ANZ ICUs remained constant over the study periods.

The most compelling finding in this study has been the unchanged mortality (in-hospital and ICU) over the 18 years of the study period. Most reports on critical health conditions being managed in ICU have noted a reduction in mortality of varying proportions [22], including sepsis [23] and secondary infections in cirrhotic patients [24]. The lack of improvement in mortality in patients with SAP remains a cause for concern and warrants further investigation. The severity of illness, too, has not changed over time. One of the most relevant considerations in SAP is the absence of specific, targeted therapies [11], with current management revolving around the supportive principles of early fluid resuscitation [25], pain relief [26], and nutrition [27]. The other issue with acute pancreatitis is that while only 20% will progress to develop SAP, current models for the early prediction of disease severity lack the desired sensitivity [28].

The demography of SAP patients admitted to ANZ ICUs is similar to other global reports. The mean age of 59.0 years and male predominance (59.2%) noted in our study reflects the experience from SAP in the ICUs of Japan [29], China [9], Scotland [10], the EPAMI International study [30], and the United States [31]. This also corroborates the findings of a previous study from New Zealand [32]. The lower likelihood of females presenting with SAP has been previously reported in Australia [33] and New Zealand [34]. The proportion of Indigenous patients with SAP being admitted to ICU has been significantly increasing over the study period. This finding, too, is consistent with a recent international study exploring pancreatic diseases in Indigenous peoples worldwide. The Maori were found to have the highest incidence rate of acute pancreatitis of 93.6 per 100,000 general population per year [95% CI 83.1–105.1] [35].

In-hospital and ICU mortality following the development of SAP has been reported to be as high as 42% and 31% in the United Kingdom [36], respectively. The recent Nation-wide study from the Netherlands [12] provides an interesting comparative model. The study by Wolbrink et al. [12] which included the data from 4160 patients treated in 81 Dutch ICUs as compared to 12,635 patients with SAP from 189 ICUs in ANZ, noted an overall hospital mortality rate of 23% and ICU mortality rate of 17%, compared to 11.6% and 8% in ANZ, respectively. The median length of hospital stay was 14 days compared to 20 in ANZ. Unlike the ANZ experience, in which we noted no change in in-hospital and ICU mortality over the entire time period, in the Netherlands, since 2010 the hospital mortality and mortality at 1-year reduced significantly. The Dutch experience confirms an unchanged ICU mortality rate as noted in ANZ. The hospital and ICU mortality rates in ANZ correspond to the lower end of the spectrum of global mortality rates for SAP [9,10,30,31]. We surmise from the Dutch experience that this is possibly due to patients being shifted to ICU earlier in ANZ as compared to the rest of the world. The comparison of mean APACHE III scores of 71 in the Netherlands, compared to 55 in our study supports this. Factors predictive of a higher risk of mortality in ICU, include advancing age, a known contributor to an increased likelihood of SAP, as well as an increased risk of mortality [10]. While previous studies have noted a higher mortality amongst males for acute pancreatitis [37] and following SAP [38], the finding of female sex being a risk factor for SAP-related mortality, noted in our study, is a novel finding that requires independent validation. The increased risk of mortality related to being admitted to a tertiary hospital has been previously noted in a cohort of patients analysed in the United States [39]. The authors' perception was this reflected an increasing severity of disease amongst those transferred from another hospital to ICU as a result of proving challenging to manage thereby increasing their risk of mortality [22]. Dialysis-dependent renal disease, noted to correlate with a higher risk of mortality in our study, has also been reported by Kothari et al. [40]. It has been postulated that immunosuppressive therapies offset the systemic inflammatory response syndrome (SIRS) encountered in acute pancreatitis [41] that drives the disease pathogenesis, and its progression [11]. Previously, Simons-Linares et al. [41] found no effect of immunosuppressants on the risk of mortality in a cohort of 819 patients with acute pancreatitis. Our results demonstrating increased mortality in our cohort associated with immunosuppressive therapy is in contrast to this, suggesting further delineation is required.

In Australia [42], SAP contributes to 1% of ICU admissions. Australia currently spends US$6140 per capita, or 9.1% of its GDP, on health care [43]. ICU stays in the United States cost three times the amount of general hospital stays [44]. A study from Finland [4] found the mean hospital cost per patient with SAP in Helsinki to be €86,856. The cost of managing a patient with SAP in the United Kingdom in 2014 was estimated to be €50,000 [45]. Significantly increased costs for managing SAP patients, as compared to mild acute pancreatitis, have been reported from Sweden [46]. This prompted the authors to suggest the need for optimising early care in order to decrease the onset of organ dysfunction, as well as the development of better prognostic models that would result in savings in health care expenditure [4]. This study, thus, provides important information on the burden of SAP in ICU from two developed countries with a representative Indigenous population.

To our knowledge, this study is one of the largest of its kind, spanning 2 countries and 18 years, providing a compelling trend in outcomes of SAP in ICUs. It must be borne in mind that definitions

Table 3
Factors predicting trends in hospital mortality related to severe acute pancreatitis (SAP) using Multilevel Mixed effects Generalised Linear Model (MM-GLM) Regression Results (Abbreviations: ED – emergency department; ICU – intensive care unit; OT – operating theatre).

Independent variables	Dependent variables			
	Hospital Mortality Coefficient (standard error)	*p*-value	ICU Mortality Coefficient (standard error)	p-value
Time				
2003–08 (reference)				
2009–14	0.007 (0.011)	0.524	0.002 (0.013)	0.856
2015–20	0.001 (0.012)	0.910	−0.009 (0.014)	0.502
Demographic characteristics				
Age (years)	0.003 (0.000)***	<0.001	0.004 (0.000)***	<0.001
Gender (Female)	0.010 (0.005)*	0.054	0.012 (0.006)**	0.047
Is respondent indigenous? Yes	0.016 (0.011)	0.131	0.023 (0.012)*	0.062
Does respondent have any of the following medical conditions?				
Diseases associated with impaired immune function	0.029 (0.026)	0.261	0.038 (0.029)	0.196
Lymphoma	−0.022 (0.043)	0.605	0.053 (0.037)	0.149
Leukemia	0.015 (0.041)	0.713	0.047 (0.043)	0.281
Metastatic cancer	−0.025 (0.028)	0.371	0.004 (0.028)	0.874
Cardiovascular disease	−0.012 (0.010)	0.235	−0.001 (0.011)	0.927
Dialysis dependent	0.015 (0.014)	0.259	0.045 (0.015)***	0.002
Respiratory disease	0.010 (0.011)	0.405	0.009 (0.013)	0.497
Receiving immunosuppressive therapy	0.010 (0.016)	0.521	0.028 (0.017)*	0.097
Treatment goals				
Full active management (w/o treatment limitation) (reference)				
Treatment limitation order	0.110 (0.017)***	<0.001	0.148 (0.019)***	<0.001
Unknown	−0.001 (0.015)	0.959	0.002 (0.018)	0.918
Hospital classification				
Metropolitan (reference)				
Private	−0.028 (0.011)**	0.011	−0.031 (0.013)**	0.019
Rural/Regional	−0.020 (0.010)**	0.042	−0.026 (0.012)**	0.024
Tertiary	0.026 (0.012)**	0.024	0.049 (0.014)***	0.001
Descriptors of hospital admissions				
Was this an emergency response admission?				
No (reference)				
Yes	−0.019 (0.009)**	0.026	−0.015 (0.010)	0.122
Unknown	0.002 (0.018)	0.931	−0.001 (0.020)	0.945
Was this an elective admission? Yes	−0.038 (0.015)**	0.013	−0.036 (0.016)**	0.026
Source of intensive care unit (ICU) admission				
OT/Recovery (reference)				
Emergency department	−0.004 (0.012)	0.727	−0.011 (0.014)	0.443
Ward/Coronary care/other HDU	0.012 (0.013)	0.321	0.020 (0.015)	0.171
ICU, same hospital	0.086 (0.064)	0.181	0.080 (0.067)	0.236
Other hospital	0.027 (0.016)*	0.087	0.021 (0.017)	0.227
Other	−0.065 (0.014)***	<0.001	−0.085 (0.017)***	0.000
Source of hospital admission				
Home (reference)				
Other acute hospital (not ICU/ED)	0.008 (0.008)	0.330	0.008 (0.009)	0.390
Nursing home/Chronic care/Palliative care	−0.008 (0.023)	0.721	−0.005 (0.028)	0.866
Other hospital – ICU	0.026 (0.020)	0.190	0.033 (0.023)	0.148
Rehabilitation	–	–	–	–
Other hospital – ED	−0.012 (0.014)	0.393	−0.004 (0.017)	0.818
Observations	10,082		10,060	
Standard errors in parentheses				

***p < 0.01, **p < 0.05, *p < 0.1.

of SAP have evolved from the initial Atlanta classification [47] in 1993 to the determinant-based classification in 2012 [48] and revised Atlanta classification in 2013 [49]. However, similar to the recently published study by Wolbrink et al. [12], the inclusion of patients in our study was based on the ANZICS modification of the APACHE diagnostic coding system to recognise the SAP. Using the Sepsis-3 convention [50] for organ dysfunction, 84% of our patients had a SOFA score of ≥2 confirming organ failure. It must be acknowledged that a SOFA score of <2 does not rule out the presence of organ failure. Additionally, while not captured in this dataset, surgical management of acute pancreatitis has steadily transformed from early surgical intervention towards the step-up approach [51]. We retrieved data from a database that, by 2012, included more than 90% of all ICU admission in the binational area of ANZ. The data were collected prospectively for routine quality surveillance purposes. Such data, therefore, are unlikely to be biased, or affected by changing diagnostic criteria. However, the impact of variation in contribution to the registry over the time of the study cannot be entirely excluded. Third, the size of the study cohort enabled robust analysis of mortality rates. Fourth, the findings were consistent in subgroups and consistent with existing literature.

Our findings are limited by the fact that the diagnosis of SAP was only applied to patient characteristics during the first 24 h in ICU.

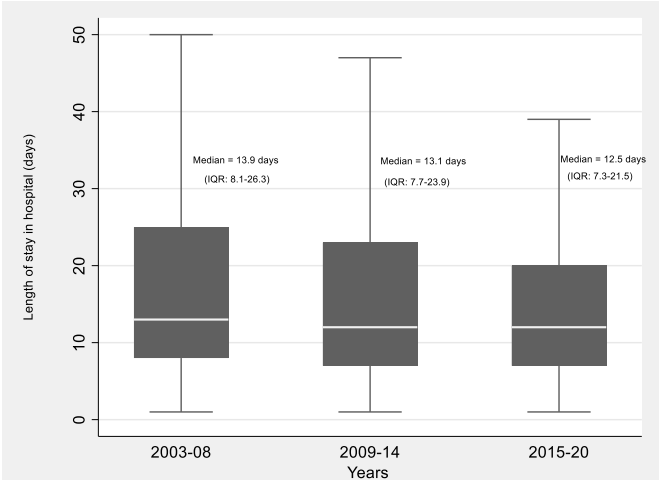

Fig. 3. Trends in hospital length of stay (in days) for severe acute pancreatitis (SAP) patients over the three time periods expressed as the raw median with the interquartile range (IQR).

Thus, patients who developed SAP later, while in the ICU, were not analysed. The accuracy of SAP diagnosis was not monitored, but trained collectors collected the data, and we used physiological coding for systemic inflammatory response syndrome and organ failure, which are less subject to the coding artifact. There remains a likelihood of inaccuracy in the coding of Indigenous status prior to 2007 as this has not been validated. In addition, although the diagnostic criteria for SAP reported in the literature have evolved, our use of the ICU admission diagnosis represents a practical and recently validated method to identify this cohort [12]. Additionally, the criteria used encompass roughly the same elements enabling us to detect changes in mortality over time in an unbiased way. Finally, the aetiological factor(s) underlying the development of the episode of SAP as well as information on supportive treatments such as feeding practice, antibiotics, necrosectomy, etc. are not recorded and, hence, we are unable to comment on their contribution to the overall observations. Also, the impact of variation in contribution to the registry or changes in data quality over the time of the study cannot be determined.

5. Conclusions

In critically-ill SAP patients in ANZ, no change in mortality has been noted over nearly two decades. Despite a reduction in hospital stay, the length of stay in ICU has remained unchanged. Early admission to ICU (based on a lower mean APACHE III score compared to the Netherlands) may help achieve lower hospital and ICU mortality rates. Given the significant costs related to the care of patients with SAP in ICU, these findings highlight the need to prioritise resource allocation for healthcare delivery and targeted clinical research to identify treatments aimed at reducing mortality.

Contributor statement

SGB: Conceptualization and design of study, literature search, data interpretation, drafting the manuscript, final approval.

BK: Data analysis, drafting the manuscript, critical revision of manuscript, final approval.

SB: Design of study, data interpretation, critical revision of manuscript, final approval.

DP: Design of study, data interpretation, critical revision of manuscript, final approval.

KV, SS, AD: critical revision of manuscript, final approval.

Declaration of competing interest

None to declare.

Acknowledgements

Prof. Andrew Bersten for advice regarding the conceptualization of the study.

Our research was supported as follows:
Pankind, grant: 21.R7.INV.CB.UOSA.6.2
SGBsupport -Flinders Foundation grant: 49358025.
NHMRC Ideas Grant: GNT2021009.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2023.04.006.

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