Trends in Early and Late Mortality in Patients With Severe Acute Pancreatitis Admitted to ICUs

Trends in Early and Late Mortality in Patients With Severe Acute Pancreatitis Admitted to ICUs: A Nationwide Cohort Study

OBJECTIVES: To investigate national mortality trends over a 12-year period for patients with severe acute pancreatitis (SAP) admitted to Dutch ICUs. Additionally, an assessment of outcome in SAP was undertaken to differentiate between early (< 14 d of ICU admission) and late (> 14 d of ICU admission) mortality.

DESIGN: Data from the Dutch National Intensive Care Evaluation and health insurance companies' databases were extracted. Outcomes included 14-day, ICU, hospital, and 1-year mortality. Mortality before and after 2010 was compared using mixed logistic regression and mixed Cox proportional-hazards models. Sensitivity analyses, excluding early mortality, were performed to assess trends in late mortality.

SETTING: Not applicable.

PATIENTS: Consecutive adult patients with SAP admitted to all 81 Dutch ICUs between 2007 and 2018.

INTERVENTIONS: Not applicable.

MEASUREMENTS AND MAIN RESULTS: Among 4,160 patients treated in 81 ICUs, 14-day mortality was 17%, ICU mortality 17%, hospital mortality 23%, and 1-year mortality 33%. After 2010 in-hospital mortality adjusted for age, sex, modified Marshall, and Acute Physiology and Chronic Health Evaluation III scores were lower (odds ratio [OR], 0.76; 95% CI, 0.61–0.94) than before 2010. There was no change in ICU and 1-year mortality. Sensitivity analyses excluding patients with early mortality demonstrated a decreased ICU mortality (OR, 0.45; 95% CI, 0.32–0.64), decreased in-hospital (OR, 0.48; 95% CI, 0.36–0.63), and decreased 1-year mortality (hazard ratio, 0.81; 95% CI, 0.68–0.96) after 2010 compared with 2007–2010.

CONCLUSIONS: Over the 12-year period examined, mortality in patients with SAP admitted to Dutch ICUs did not change, although after 2010 late mortality decreased. Novel therapies should focus on preventing early mortality in SAP.

KEY WORDS: intensive care unit; mortality; organ failure; severe acute pancreatitis; trends

Daniel R. J. Wolbrink, MD[1]
Marcel C. G. van de Poll, PhD[2,3,4]
Fabian Termorshuizen, PhD[5,6,7]
Nicolette F. de Keizer, PhD[5,6,7]
Iwan C. C. van der Horst, PhD[2,8]
Ronny Schnabel, MD[2]
Cees H. C. Dejong, PhD[4]
Hjalmar C. van Santvoort, PhD[9,10]
Marc G. Besselink, PhD[11]
Harry van Goor, PhD[1]
Stefan A. W. Bouwense, PhD[4]
Bas C. T. van Bussel, PhD[2,7,12]
for the Dutch Pancreatitis Study Group and the Dutch National Intensive Care Evaluation (NICE) Collaborators

Acute pancreatitis is the most common gastrointestinal disease requiring acute hospitalization in the Western world, and its incidence is rising (1). Approximately 80% of patients with acute pancreatitis experience relatively mild symptoms, which generally resolve within 7 days (2). The other 20% develop a severe form of acute pancreatitis with organ failure and/or necrotizing pancreatitis, classified as severe acute pancreatitis (SAP) (2, 3). The early phase (generally the first 14 d) of SAP is characterized by a systemic inflammatory response syndrome (SIRS). This may result in severe systemic symptoms with single or multiple organ failure requiring admission to an ICU (4). Despite advances in critical care medicine, the mortality remains high (30%)

DOI: 10.1097/CCM.0000000000005629

in these patients (4). After the first phase of the illness, 30% of patients will develop secondary infection of pancreatic collections and pancreatic necrosis with a peak incidence 3 to 4 weeks following the onset. In this second phase, there is a considerable increase in morbidity and "late" mortality with an additional 15% of patients dying (4).

In the early phase of SAP, therapy merely consists of supportive care but if infected pancreatic necrosis occurs, antibiotic treatment, catheter drainage, and necrosectomy are considered (5). In the last decade, a paradigm shift has occurred with emphasis on minimally invasive transgastric or percutaneous catheter drainage and necrosectomy (6). Using this minimally invasive approach has been supported by a number of randomized trials, which have demonstrated a reduction in major complications including pancreatic fistula and organ failure (7–12). Disappointingly despite the reduction in major complications demonstrated in these trials, the anticipated reduction in mortality of SAP was not observed. Indeed recently, it has been shown that immediate drainage of infected necrotizing pancreatitis is associated with a worse outcome and also that antibiotic therapy can be delayed (13).

It remains unclear how the change in clinical practice affects the "early" and "late" mortality among patients with SAP admitted to the ICU. We aimed to investigate whether 14-day, ICU, hospital, and 1-year mortality among these patients had decreased over a 12-year period. To enable us to focus on the impact of improved treatment of infected necrosis, this study additionally assessed early and late (up to 14 d and beyond 15 d after admission to ICU) mortality.

METHODS

The article was written in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (14). Data from both the nationwide Dutch National Intensive Care Evaluation (NICE) registry and an overall national health insurance company database (VEKTIS database) were used (15).

NICE is the national ICU quality registry, which includes data on every ICU admission in participating hospitals in the Netherlands. Since 2016, the NICE registry has reached complete coverage of all 81 Dutch ICUs. Participating hospitals provide demographic, physiologic, diagnostic, and both ICU and hospital outcome data for each ICU admission (16). The medical ethics committee of the Amsterdam Universital Medical Center waived the need for ethical approval for this study under registration number W15-160.

The VEKTIS database is a national health insurance company database. As health insurance is mandatory in the Netherlands, the VEKTIS database provides accurate follow-up on mortality data for every patient in the Netherlands. In order to obtain accurate, long-term mortality data for this study, the NICE registry data, were linked to the VEKTIS database, using hospital, sex, birthdates, and date of admission. After linking the databases, all personal identifiable data were removed to obtain an anonymized research database.

Participants: Acute Pancreatitis

In the present study, all patients with an Acute Physiology and Chronic Health Evaluation (APACHE) IV reason for ICU admission due to "pancreatitis" were included. Data between January 1, 2007, and December 31, 2018, were examined. Patients with nonemergency admission, surgery for pancreatitis (i.e., APACHE IV diagnosis as a proxy for chronic pancreatitis), and those without valid record linkage with the VEKTIS database were excluded (**Supplemental Fig. 1**, http://links.lww.com/CCM/H174).

Outcome

ICU, hospital, 14-day, and 1-year mortality were derived from the ICU admission date in the NICE registry and the date of death in the NICE and VEKTIS databases. Additionally, we determined the time interval between hospital admission date and ICU admission date.

Potential Confounders

For baseline characteristics, the NICE registry includes data on age, sex, comorbidities (i.e., cardiovascular and pulmonary disorders, diabetes mellitus, malignancy, kidney failure, liver cirrhosis, AIDS, and immunological insufficiency), and the APACHE III score (15, 17). The modified Marshall score, a widely recommended score to assess organ failure in acute pancreatitis, at admission, was computed from the NICE database, see **Supplemental Table 1** (http://links.lww.com/CCM/H174) (2, 18).

Statistical Analysis

Data were analyzed using R (Version 3.6.1., R Foundation for Statistical Computing, Vienna, Austria) for Windows. Patient characteristics, disease severity, comorbidities, and mortality during both ICU and hospital admission (including length of stay), 14-day and 1-year mortality were described as mean (± SD), median (with interquartile ranges), or percentages as appropriate. Using mixed logistic and Cox proportional-hazard models, the results were reported as odds ratios (ORs) with their 95% CIs and hazard ratios (HRs) with 95% CI and *p*. The following six models were investigated: Crude model (model 1) is adjusted for sex and age (model 2). Model 2 is then adjusted for Marshall score (model 3), for comorbidities (i.e., diabetes, cirrhosis, malignancy, AIDS, chronic obstructive pulmonary disease, cardiovascular insufficiency, chronic kidney failure/dialysis, immunological insufficiency) (model 4); for APACHE III score (model 5); and for Marshall score, comorbidities, and APACHE III score (model 6). A two-sided *p* value of less than 0.05 was considered statistically significant.

RESULTS

The cohort included 4,160 consecutive patients with SAP admitted to 81 Dutch ICUs between 2007 and 2018 (Supplemental Fig. 1, http://links.lww.com/CCM/H174). The overall population had a mean age of 61 years (± 16 yr). The majority were men (61%) and had relevant comorbidities including diabetes mellitus (18%), chronic obstructive pulmonary disease (9%), and chronic kidney failure (6%) (**Table 1**). The mean APACHE III score was 71 ± 32. The mean modified Marshall score was 4 ± 3. The total number of patients per year increased after 2008 (Table 1), as did the number of ICUs that contributed to the NICE registry (100% coverage in the Netherlands by 2016). In 42% of patients, there was a less than 1-day difference between hospital and ICU admission. Overall, 84% of patients in this cohort were admitted to the ICU within 5 days of hospital admission (**Table 2**).

Overall Mortality

Within 14 days of ICU admission (i.e., early mortality), mortality was 17%. This accounted for more than half of all deaths within 1-year (33%). ICU and hospital

TABLE 1.
Population Characteristics of Patients With Acute Pancreatitis Admitted to the ICUs in the Netherlands

Characteristic	2007–2018
Patients, *n*	4,160
Age, yr	61 ± 15
Women, %	38
Modified Marshall score	4 ± 3
Pao_2/Fio_2	216 ± 127
Serum creatinine, μmol/L (maximum)	152 ± 134
Systolic blood pressure, mm Hg	96 ± 25
Vasoactive drugs, %	42
pH lowest	7.35 ± 0.12
Comorbidities, %	
Diabetes mellitus	18
Cirrhosis	2
Malignancy	2
AIDS	0.1
Chronic obstructive pulmonary disease	9
Cardiovascular insufficiency	2
Chronic kidney failure/dialysis	6
Immunological insufficiency	5
Acute Physiology and Chronic Health Evaluation III score	71 ± 32

Data are *n*, means ± SD, or percentages.
For year-to-year details, see **Supplemental Table 2** (http://links.lww.com/CCM/H174).

TABLE 2.
Time Between Hospital Admission and ICU Admission

Time to ICU Admission	Frequency (*n*)	Percent (%)	Cumulative Percent (%)
Within 1 d	1,748	42.0	42.0
1–5 d	1,730	41.6	83.6
5–10 d	330	7.9	91.5
10–15 d	149	3.6	95.1
15–20 d	69	1.7	96.8
More than 20 d	125	3.0	99.8
Unknown	9	0.2	100.0
Total	4,160	100.0	

mortality were 17% and 23%, respectively, with 6% of patients dying in hospital following ICU discharge (**Table 3** and **Supplemental Fig. 2**, http://links.lww.com/CCM/H174).

Mortality Before and After 2010

The mixed logistic regression model with a random center effect demonstrated no statistically significant difference in ICU mortality between patients admitted before and after 2010, with an OR of 0.94 (95% CI, 0.77–1.14) (**Table 4**). Additional adjustments for sex, age, modified Marshall, and APACHE III scores (model 5) did not alter this result. After left truncation at 14 days of ICU admission, models 1–6 showed significantly lower ORs of ICU death ranging from 0.45 to 0.49 and with 95% CIs below 1.00. This indicated a statistically significantly lower ICU mortality in patients admitted after 2010 compared with before 2010.

Crude hospital mortality did not differ between patients admitted after 2010 compared with those admitted before 2010 with an OR of 0.90 (95% CI, 0.76–1.08). Additional adjustment for sex, age, comorbidities, modified Marshall, and APACHE III scores showed a lower OR of 0.76 (95% CI, 0.61–0.94). This indicates statistically significantly lower hospital mortality in patients admitted after 2010 compared with before 2010. Left truncation at 14 days demonstrated a further reduction of the OR for hospital mortality in patients admitted after 2010, compared with before 2010, with ORs ranging from 0.48 to 0.54 and 95% CIs below 1.00 for all models.

TABLE 3.
Outcomes for Patients Admitted to the ICU With Acute Pancreatitis in the Netherlands

Outcome	2007–2018
14-d mortality, *n* (%)	693 (17)
ICU mortality, *n* (%)	718 (17)
Hospital mortality, *n* (%)	961 (23)
1-yr mortality, *n* (%)	1,372 (33)
ICU length of stay, d	3.5 (1–10)
Hospital length of stay, d	14 (6–30)

Data are *n*, median (interquartile range), or percentages.
For year-to-year details, see **Supplemental Table 3** (http://links.lww.com/CCM/H174).

A mixed Cox proportional-hazards model, with random center effect demonstrated no difference in the 1-year mortality between patients admitted before and after 2010, with an HR of 1.03 (95% CI, 0.91–1.17) (**Table 5**, model 1). Additional adjustments for sex, age, and comorbidities, modified Marshall score, and APACHE III score did not affect this result, whereas left truncation at 14 days demonstrated lower HRs ranging from 0.81 to 0.84 and 95% CI below 1.00 for all models. This indicates a statistically significantly lower 1-year mortality in patients admitted after 2010 compared with those admitted before 2010. The 1-year mortality HR in 14-day survivors for each year apart did not differ significantly (**Supplemental Fig. 3**, http://links.lww.com/CCM/H174).

DISCUSSION

This national analysis of 4,160 patients with SAP admitted to 81 Dutch ICUs demonstrated that overall and early mortality did not decrease over the 12-year period between 2007 and 2018. Neither the crude, nor the adjusted, all-cause 1-year mortality differed between the periods before and after 2010. However, after 2010, patients who survived at least 14 days following their ICU admission (i.e., late mortality) had lower ICU and lower hospital mortality than the comparable group admitted before 2010. This survival benefit remained statistically significant at 1-year following ICU admission. This may imply that novel treatment strategies directed at infected pancreatic necrosis, such as the PANTER trial, did significantly impact the "late mortality" nationally.

The 2010 PANTER trial demonstrated the superiority of a minimally invasive step-up approach compared with direct laparotomy for patients with infected necrotizing pancreatitis (8). As a consequence, the step-up approach has been widely implemented in the Netherlands and internationally. In addition, ongoing refinements of the treatments for infected necrotizing pancreatitis have been studied and implemented, including the endoscopic step-up approach producing a further reduction in morbidity compared with the surgical step-up approach (7, 9). This iterative evolution of the management of SAP and its complications continues to be investigated and change clinical practice (19).

Technical and clinical improvements have developed in parallel with national collaborative initiatives, which have been employed to improve the treatment of

TABLE 4.

Logistic Regression Analyses Comparing Hospital and ICU Mortality Among Acute Pancreatitis Patients on the ICU Between 2007–2010 and 2011–2018

	ICU Mortality (Survivors 3,442, Deaths 718)		ICU Mortality Patients Admitted to the ICU and Alive on Day 14 (Survivors 3,282, Deaths 180)	
Model	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
1) Crude + random center effect	0.94 (0.77–1.14)	0.512	0.49 (0.36–0.68)	< 0.001
2) One + age + sex	0.93 (0.76–1.14)	0.487	0.48 (0.35–0.67)	< 0.001
3) Two + modified Marshall score	0.82 (0.66–1.03)	0.090	0.47 (0.34–0.67)	< 0.001
4) Two + comorbidities[a]	0.90 (0.74–1.11)	0.332	NA	NA
5) Two + APACHE III score	0.80 (0.63–1.02)	0.067	0.44 (0.31–0.63)	< 0.001
6) Two +modified Marshall score + comorbidities + APACHE III score	0.81 (0.64–1.03)	0.087	0.45 (0.32–0.64)	< 0.001
	Hospital Mortality (Survivors 3,199, Deaths 961)		**Hospital Mortality Patients Admitted to the ICU and Alive on Day 14 (Survivors 3,135, Deaths 327)**	
Model	**OR (95% CI)**	*p*	**OR (95% CI)**	*p*
1) Crude + random center effect	0.90 (0.76–1.08)	0.255	0.54 (0.42–0.69)	< 0.001
2) One + age + sex	0.89 (0.74–1.07)	0.220	0.53 (0.41–0.68)	< 0.001
3) Two + modified Marshall score	0.80 (0.66–0.98)	0.029	0.51 (0.39–0.67)	< 0.001
4) Two + comorbidities[a]	0.86 (0.71–1.03)	0.104	0.51 (0.39–0.66)	< 0.001
5) Two + APACHE III score	0.76 (0.62–0.94)	0.011	0.48 (0.36–0.63)	< 0.001
6) Two + modified Marshall score + comorbidities + APACHE III score	0.76 (0.61–0.94)	0.010	0.48 (0.36–0.63)	< 0.001

APACHE = Acute Physiology and Chronic Health Evaluation, NA = not applicable, OR = odds ratio.

[a]Comorbidities: diabetes, cirrhosis, malignancy, AIDS, chronic obstructive pulmonary disease, cardiovascular insufficiency, chronic kidney failure/dialysis, and immunological insufficiency; model 4 no model estimates possible due to low cases (deaths).

Data are ORs with their 95% CIs and *p*, which indicate a survival effect after 2010, with ≤ 2010 as reference.

acute pancreatitis. These include the establishment of a national expert panel that can be consulted for patients with SAP (20). Several randomized trials describing individual elements of the multimodal state-of-the-art treatment of pancreatic necrosis have reduced complications and long-term morbidity, although a significant effect on survival has not yet been demonstrated (8–13). Our study differs from those of other groups that have assessed national trends in overall, early, and late mortality in SAP. The national data from the Netherlands specifically describes the most severely ill patients with acute pancreatitis and differentiates between early and late mortality (21). This makes it possible to evaluate both early mortality, which is likely to be due to inflammation and organ failure, and late mortality, probably caused by infected necrotizing pancreatitis. This identifies the period during which complications resulting in mortality occur and hence those areas where research should be focused. The crude mortality data we describe here are consistent with a cohort of SAP patients reported from Scotland. That cohort consisted of patients admitted to the critical care unit between 2008 and 2010 and showed an overall mortality of 44% after a mean follow-up of 4.4 years, with a mortality of 21% during admission (22).

By using two comprehensive national registries, we were able to create a cohort of patients with SAP requiring ICU treatment that was sufficiently large to demonstrate that hospital mortality, adjusted for relevant confounders, has significantly improved since 2010. A major improvement in survival (crude mortality) for the whole population was not observed, and

TABLE 5.
Cox Proportional-Hazard Analyses to Compare Mortality Among Acute Pancreatitis Patients on the ICU Between 2007–2010 and 2011–2018

	1-yr Mortality (n = 4,160, Events 1,372)		1-yr Mortality, Patients Admitted to the ICU and Alive on Day 14 (n = 3,462, Events 679)	
Model	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
1) Crude + random center effect	1.03 (0.91–1.17)	0.631	0.84 (0.71–0.99)	0.049
2) One + age + sex	1.03 (0.91–1.18)	0.604	0.84 (0.70–0.99)	0.046
3) Two + modified Marshall score	1.02 (0.90–1.16)	0.743	0.83 (0.70–0.99)	0.038
4) Two + comorbidities[a]	1.02 (0.89–1.16)	0.798	0.81 (0.68–0.97)	0.021
5) Two + APACHE III score	1.00 (0.88–1.14)	0.971	0.81 (0.68–0.96)	0.016
6) Two + modified Marshall score + comorbidities + APACHE III score	1.01 (0.89–1.16)	0.832	0.81 (0.68–0.96)	0.018

APACHE = Acute Physiology and Chronic Health Evaluation, HR = hazard ratio.

[a]Comorbidities: diabetes, cirrhosis, malignancy, AIDS, chronic obstructive pulmonary disease, cardiovascular insufficiency, chronic kidney failure/dialysis, and immunological insufficiency.

Data are HRs with their 95% CIs and p, which indicate a survival effect after 2010, with ≤ 2010 as reference.

interestingly, the hospital survival benefit observed for patients treated after 2010 disappeared after 1 year. A number of factors could explain this difference including patients eschewing life-sustaining treatments and therapies and instead choosing to go home in the last phase of their lives. Alternatively, the burden of an episode of SAP in combination with substantial comorbidities may prevent a sufficiently rapid recovery from the initial insult predisposing to late complications. Whether such mechanisms are contributory or solely responsible is speculative as our databases include no information on the reasons for discharge or the cause of death.

To further explore the hypothesis that a potential survival benefit in patients admitted after 2010 could be due to practice changes in the management of infected pancreatic necrosis, we applied left truncation of person time at risk at 14 days after ICU admission. We only left patients in the analysis that were still alive 14 days after ICU admission. This additional analysis is particularly relevant for early mortality in SAP as the majority results from multiple organ failure consequent upon an overwhelming inflammatory response characterizing SAP (23). The treatment of the early phase of pancreatitis consists merely of supportive care and organ replacement therapy, which has not changed significantly over the last 15 years (5). Patients dying within 14 days of ICU admission unfortunately do not benefit from the newer treatments and approaches to infected pancreatic necrosis (8). After left truncation of person time at risk at 14 days, we observed a statistically significant improvement in ICU, hospital, and 1-year survival. This further supports the hypothesis that the introduction of minimally invasive, multimodal management of infected pancreatic necrosis may reduce SAP-associated mortality. Similar results were reported by van Brunschot et al (7), who performed a combined analysis of international cohorts. They found that mortality decreased in patients treated according to the step-up approach compared to open necrosectomy, which is consistent with our present observations. Despite an improved survival in a selected population of patients who survived 14 days of ICU, the substantial anticipated benefit of novel therapies in the whole population of acute pancreatitis patients could not be demonstrated.

Although the observation that survival improved in a selected population after 2010, particularly in those patients admitted to the ICU who survive for at least 14 days, is interesting, the excessive mortality within the first 14 days after ICU admission is potentially more important. This was as high as 17% in the present cohort consistent with the belief that half of SAP deaths occur in the first 14 days (24). The development of SIRS, caused by the release of proteolytic enzymes and cytokines in the early phase of acute pancreatitis,

is most likely the main cause of multiple organ failure and mortality in the early phase of SAP. We can only speculate that a more inflammation prone population with SAP over time populated the ICU. Such a population could have an increased inflammatory response, causing more multiple organ failure and death during the early phase. In line with this hypothesis, several attempts to reduce mortality by modifying inflammation in the early phase have been suggested. Different agents including anti-oxidants, cyclooxygenase-2 inhibitors, and probiotics have been investigated to modulate the inflammatory cascade during acute severe pancreatitis. To date, however, none have proved beneficial, and some were even harmful (12, 25, 26). More recently, a clinical trial and a systematic review on early administration of IV omega-3 fatty acids appear to confirm improvement in the severity of acute pancreatitis, including a nonsignificant decrease in mortality (27, 28). Large, pragmatic, well-designed randomized trials are required to confirm a beneficial effect on anti-inflammatory agents in the setting of early and SAP, such as omega-3 fatty acids.

This study has several limitations. The diagnosis of SAP was not uniformly defined at data entry and a proxy definition to identify potential patients of interest was used. We cannot entirely rule out that a small number of patients with other primary diagnoses such as chronic pancreatitis with superadded acute pancreatitis were included in the dataset and our study is also limited to include inter-hospital transportation. We have no information about the etiology of pancreatitis, the proportion of patients that developed infected pancreatic necrosis (e.g., radiological imaging) or about surgical, radiological, or endoscopic interventions, which limits direct comparisons to evaluate the effects of the step-up approach and other novel treatments. In this study, we used the cutoff of 14 days after ICU admission to divide the cohort into two groups with an "early phase" and "late phase." In the early phase, treatment is predominantly focused on the complications of severe inflammation and early organ failure. In the late phase, the focus of treatment is predominantly on the complications of secondary infections of pancreatic necrosis. The cutoff of 14 days is often inexact in clinical practice. For example, the first invasive intervention for infected pancreatic necrosis in the TENSION trial was after a median of 39 days after disease onset in the endoscopic step-up approach group and 41 days in the surgical step-up approach group. In the present study, the cutoff was after 14 days of ICU admission. This means for the present cohort that the majority of patients are 17–19 days after disease onset (in this cohort > 80% of patients are admitted to the ICU after a median of 2–3 d after hospital admission) (11). We chose ICU admission as the starting point as potential confounders, such as comorbidities, modified Marshall, and APACHE scores were measured at that time point, and these data were not available at hospital admission. Finally, no data on the cause of death were registered, which clearly is a limitation of this study, and we cannot rule out that patients died of other causes.

Despite the potential problems with this study, it has a number of strengths. First, by using the nationwide NICE and VEKTIS registry data, we created a large dataset with clinical data on mortality from two independent sources, which has the advantage of enabling time-to-event analysis. Second, the clinical data allows extensive adjustments for potential confounders, such as comorbidities, pancreatitis specific score for severity of organ failure (modified Marshall score), and ICU disease severity (APACHE III score). Third, the national health insurance company database enables accurate follow-up since health insurance is mandatory in the Netherlands, ensuring complete follow-up data from this registry. This is a large study including 4,160 patients with SAP with data recorded over a period of 12 years. The national coverage by the registries, including comprehensive and complete datasets with extensive analyses addressing potential confounders, increases the internal validity of the results. Furthermore, results are generalizable to the ICU population with SAP.

CONCLUSIONS

This large national cohort study demonstrates that the overall ICU mortality has not decreased in the period from 2007 to 2018 for patients with SAP. Since 2010, in a subgroup of patients who survived the first 14 days of ICU admission, survival has improved. This observation suggests that novel treatments for infected pancreatic necrosis, gradually introduced since 2010 may be responsible for the decreased mortality. Nevertheless, mortality in the early phase of SAP remains unacceptably high and future research should focus on reducing

and treating early organ failure in patients with SAP admitted to ICU.

ACKNOWLEDGMENTS

We would like to acknowledge A. Dennison for reviewing this article as a native speaker.

1 *Department of Surgery, Radboudumc, Nijmegen, The Netherlands.*

2 *Department of Intensive Care Medicine, Maastricht University Medical Centre+, Maastricht, The Netherlands.*

3 *School for Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands.*

4 *Department of Surgery, Maastricht University Medical Centre+, Maastricht, The Netherlands.*

5 *Department of Medical Informatics, Amsterdam Universital Medical Center, Location University of Amsterdam, Amsterdam, The Netherlands.*

6 *Amsterdam Public Health, Amsterdam, The Netherlands.*

7 *National Intensive Care Evaluation (NICE) Foundation, Amsterdam, The Netherlands.*

8 *Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands.*

9 *Department of Surgery, University Medical Centre Utrecht, Utrecht, The Netherlands.*

10 *Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands.*

11 *Department of Surgery, Amsterdam Universital Medical Center, Location University of Amsterdam, Amsterdam, The Netherlands.*

12 *Department of Surgery, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Wolbrink, van de Poll, Termorshuizen, Bouwense, and van Bussel were involved in study concept and design. NICE Collaborators were involved in acquisition of data. Drs. Termorshuizen, de Keizer, and van Bussel were involved in analysis. Drs. Wolbrink, van de Poll, Termorshuizen, de Keizer, and Bouwense were involved in interpretation of data. Drs. Wolbrink, van de Poll, Termorshuizen, Bouwense, and van Bussel were involved in drafting of the article. Drs. de Keizer, van der Horst, Schnabel, Dejong, Besselink, and van Goor were involved in critical revision of the article. Drs. van de Poll, de Keizer, Besselink, Bouwense, and van Bussel were involved in supervision.

Drs. Termorshuizen's and de Keizer's institutions received funding from the National Intensive Care Evaluation Foundation. Dr. Termorshuizen's institution received funding from the Rivierduinen Institute for Mental Health Care. Dr. de Keizer's institution received funding from the Ministry of Health and Welfare. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: bas.van.bussel@mumc.nl; Daan.Wolbrink@radboudumc.nl

REFERENCES

1. Peery AF, Dellon ES, Lund J, et al: Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; 143:1179–1187.e3
2. Banks PA, Bollen TL, Dervenis C, et al; Acute Pancreatitis Classification Working Group: Classification of acute pancreatitis–2012: Revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102–111
3. Bakker OJ, van Santvoort H, Besselink MG, et al; Dutch Pancreatitis Study Group: Extrapancreatic necrosis without pancreatic parenchymal necrosis: A separate entity in necrotising pancreatitis? *Gut* 2013; 62:1475–1480
4. Schepers NJ, Bakker OJ, Besselink MG, et al; Dutch Pancreatitis Study Group: Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. *Gut* 2019; 68:1044–1051
5. Guidelines WGIAAP: IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; 13(4 Suppl 2):e1–e15
6. van Dijk SM, Hallensleben NDL, van Santvoort HC, et al; Dutch Pancreatitis Study Group: Acute pancreatitis: Recent advances through randomised trials. *Gut* 2017; 66:2024–2032
7. van Brunschot S, Hollemans RA, Bakker OJ, et al: Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: A pooled analysis of individual data for 1980 patients. *Gut* 2018; 67:697–706
8. van Santvoort HC, Besselink MG, Bakker OJ, et al; Dutch Pancreatitis Study Group: A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; 362:1491–1502
9. Bakker OJ, van Santvoort HC, van Brunschot S, et al; Dutch Pancreatitis Study Group: Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: A randomized trial. *JAMA* 2012; 307:1053–1061
10. Bakker OJ, van Brunschot S, van Santvoort HC, et al; Dutch Pancreatitis Study Group: Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* 2014; 371:1983–1993
11. van Brunschot S, van Grinsven J, van Santvoort HC, et al; Dutch Pancreatitis Study Group: Endoscopic or surgical step-up approach for infected necrotising pancreatitis: A multicentre randomised trial. *Lancet* 2018; 391:51–58
12. Besselink MG, van Santvoort HC, Buskens E, et al; Dutch Acute Pancreatitis Study Group: Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 371:651–659
13. Boxhoorn L, van Dijk SM, van Grinsven J, et al; Dutch Pancreatitis Study Group: Immediate versus postponed intervention for infected necrotizing pancreatitis. *N Engl J Med* 2021; 385:1372–1381

14. von Elm E, Altman DG, Egger M, et al; STROBE Initiative: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *BMJ* 2007; 335:806–808
15. van de Klundert N, Holman R, Dongelmans DA, et al: Data resource profile: The Dutch National Intensive Care Evaluation (NICE) registry of admissions to adult intensive care units. *Int J Epidemiol* 2015; 44:1850h–50h
16. Zimmerman JE, Kramer AA, McNair DS, et al: Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; 34:1297–1310
17. Knaus WA, Wagner DP, Draper EA, et al: The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100:1619–1636
18. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; 23:1638–1652
19. van Grinsven J, van Dijk SM, Dijkgraaf MG, et al; Dutch Pancreatitis Study Group: Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): Study protocol for a randomized controlled trial. *Trials* 2019; 20:239
20. van Grinsven J, van Brunschot S, van Santvoort HC; Dutch Pancreatitis Study Group: The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis. *Gastroenterology* 2017; 152:685–688.e6
21. Xiao AY, Tan ML, Wu LM, et al: Global incidence and mortality of pancreatic diseases: A systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterol Hepatol* 2016; 1:45–55
22. Ventre C, Nowell S, Graham C, et al: Survival and new-onset morbidity after critical care admission for acute pancreatitis in Scotland: A national electronic healthcare record linkage cohort study. *BMJ Open* 2018; 8:e023853
23. Granger J, Remick D: Acute pancreatitis: Models, markers, and mediators. *Shock* 2005; 24(Suppl 1):45–51
24. Spanier B, Bruno MJ, Dijkgraaf MG: Incidence and mortality of acute and chronic pancreatitis in the Netherlands: A nationwide record-linked cohort study for the years 1995-2005. *World J Gastroenterol* 2013; 19:3018–3026
25. Petrov MS, Shanbhag S, Chakraborty M, et al: Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010; 139:813–820
26. Huang Z, Ma X, Jia X, et al: Prevention of severe acute pancreatitis with cyclooxygenase-2 inhibitors: A randomized controlled clinical trial. *Am J Gastroenterol* 2020; 115:473–480
27. Al-Leswas D, Eltweri AM, Chung WY, et al: Intravenous omega-3 fatty acids are associated with better clinical outcome and less inflammation in patients with predicted severe acute pancreatitis: A randomised double blind controlled trial. *Clin Nutr* 2020; 39:2711–2719
28. Wolbrink DRJ, Grundsell JR, Witteman B, et al; Dutch Pancreatitis Study Group: Are omega-3 fatty acids safe and effective in acute pancreatitis or sepsis? A systematic review and meta-analysis. *Clin Nutr* 2020; 39:2686–2694