

Predictors of Clavien 4 Complications and Mortality After Necrosectomy: Analysis of the NSQIP Database

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Received: 18 December 2014 / Accepted: 29 March 2015 / Published online: 11 April 2015
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Abstract

Background Acute severe pancreatitis is one of the most common gastrointestinal reasons for admission to hospitals in the USA. Up to 20 % of these patients will progress to necrotizing pancreatitis requiring intervention. The aim of this study is to identify specific preoperative factors for the development of Clavien 4 complications and mortality in patients undergoing pancreatic necrosectomy.

Methods The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) participant use files were reviewed from 2007 to 2012 to identify patients who underwent a pancreatic necrosectomy. Postoperative complications were stratified into Clavien 4 (ICU level complications) and Clavien 5 (mortality). Univariate and multivariate analyses were performed.

Results A total of 1156 patients underwent a pancreatic necrosectomy from 2007 to 2012. Overall, 42 % of patients experienced a Clavien 4 complication. Mortality rate was 9.5 %. Nonindependent functional status and ASA class were highly significant ($p < 0.001$) in univariate analysis. Frailty and emergency surgery status ($p < 0.001$), as well as increased blood urea nitrogen (BUN) and alkaline phosphatase and decreased albumin ($p < 0.05$) demonstrated independent significance of Clavien 4 complications and mortality in multivariate analysis.

Conclusion This study identified specific preoperative variables that place patients at increased risk of Clavien 4 complications and mortality after necrosectomy. Identification of high-risk patients can aid in selection of appropriate treatment strategies and allow for informed preoperative discussion regarding surgical risk.

Keywords Pancreatic necrosectomy · Debridement · Clavien 4 · Complications · Mortality · NSQIP

Introduction

Acute pancreatitis accounts for nearly 270,000 admissions to US hospitals annually and is the top-ranking reason for hospitalization among gastrointestinal complaints.¹ One large retrospective review evaluated over 1000 cases of acute pancre-

atitis in a 5-year period, with 99 patients, or 9 %, developing pancreatic necrosis. Of those 99 patients, 37 % developed infected pancreatic necrosis.² Other series quote an infected necrosis rate up to 63 %.³

The criteria for radiologic or CT diagnosis of pancreatic necrosis includes well-marginated zones of nonenhanced pancreatic parenchyma involving approximately 30 % of the pancreas or an area 3 cm in size.⁴ In the original study by Balthazar and colleagues,⁵ CT findings in acute pancreatitis were used in a prognostic manner, demonstrating patients with a greater than 30 % necrosis experienced over 90 % morbidity and nearly 30 % mortality. Differentiating infected pancreatic necrosis from sterile peripancreatic fluid collections is a diagnostic challenge. The general systemic inflammatory response syndrome (SIRS) of acute pancreatitis, including tachycardia, fever, leukocytosis, or tachypnea, makes it difficult to discern between SIRS and true infection. Diagnostic clues such as air

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in peripancreatic fluid collections and/or positive fluid samples guide the diagnosis and treatment plan towards management of infected necrosis.⁶ One caveat, however, is a false-negative rate up to 20 % from aspirate samples.³

A “step-up” approach to the management of necrotizing pancreatitis was proposed by the Dutch Pancreatitis Study Group in 2010 which compared a minimally invasive approach to open necrosectomy for necrotizing pancreatitis. Less morbidity was present in the minimally invasive approach group, but there was no difference in mortality.⁷ A significant trend toward less-invasive procedures for necrotizing pancreatitis was also observed in a large national database sample of 1783 patients undergoing pancreatic debridement. In this sample, the mortality rate for pancreatic debridement was 15 %.⁸ A recent 2014 single-center study evaluating open debridement of necrotizing pancreatitis demonstrated 8.8 % in-hospital mortality.³ Compared to mortality using a step-up approach, open debridement may yield similar outcomes. As with any surgical technique, adequate patient selection and physician experience are crucial to patient outcome.

Using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), a large national database registry for surgery and postoperative outcomes, we sought to identify preoperative indicators for the development of Clavien 4 complications (intensive-care-level complications) and mortality in patients who underwent open necrosectomy.

Methods

The ACS-NSQIP is a large nationally validated, risk-adjusted outcomes-based database, with approximately 400 hospitals reporting data.⁹ Over 135 variables are collected and data is reported for 30 days postoperatively. The ACS-NSQIP participant use files were reviewed from 2005 to 2012 to identify patients who underwent a pancreatic necrosectomy using current procedural terminology code (CPT) 48105. CPT code 48105 was not available until 2007, so the data set is inclusive for January 1, 2007, through December 31, 2012. Preoperative variables assessed include sex, smoking history, history of congestive heart failure, functional status, alcohol use, history of myocardial infarction, steroid use, and American Society of Anesthesiologists (ASA) class, modified frailty index, and emergency surgery status. Laboratory variables analyzed were sodium, white blood cell count (WBC), blood urea nitrogen (BUN), creatinine, albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), hematocrit (Hct), platelets, partial thromboplastin time (PTT), international normalized ratio (INR), and prothrombin time (PT). Data from the ACS-NSQIP was obtained under the supervision of our institutional review board and in compliance with the NSQIP data user agreement.

The modified frailty index (mFI) was created for use with variables readily available in the NSQIP database.¹⁰ The mFI

has been shown in multiple studies to correlate with postoperative outcomes.^{11–14} The mFI includes 11 variables: (1) nonindependent functional status; (2) history of diabetes mellitus; (3) history of chronic obstructive pulmonary disease or pneumonia; (4) history of congestive heart failure; (5) history of myocardial infarction; (6) history of percutaneous coronary intervention, stenting, or angina; (7) history of hypertension requiring medication; (8) history of peripheral vascular disease or ischemic rest pain; (9) history of transient ischemic attack or cerebrovascular event; (10) history of cerebrovascular accident with neurologic deficit; and (11) history of impaired sensorium. The mFI acts much like a comorbidity index with the addition of functional status. The mFI cannot be validated against other risk stratification indices such as the Charlson comorbidity index due to different variables and limitations of data gathering within the NSQIP database.

Functional status refers to the patient’s ability and independence in performing activities of daily living (ADLs) 30 days preceding surgery. Functional status 1 refers to an independent patient without need for assistance to perform ADLs. Functional status 2 is partial dependence with assistance from another person. Functional status 3 is a completely dependent person for ADLs.

Primary outcomes assessed were Clavien 4 complications (organ dysfunction with need for intensive care unit management) and Clavien 5 complications or mortality.¹⁵ The Clavien-Dindo classification system was first devised in 2004 to rank surgical complications in an objective manner. The Clavien 4 complications are those related to organ dysfunction with need for intensive care unit management and Clavien 5 being mortality. The Clavien 4 complications chosen were first described in 2012 as these variables are contained within the NSQIP data set and are consistent with organ dysfunction and need for ICU-level care¹⁶ including septic shock, need for dialysis, pulmonary embolism, myocardial infarction, cardiac arrest, mechanical ventilation, and reintubation.

Statistical analysis of variables associated with Clavien 4 complications and mortality were performed using the R Project for Statistical Computing (www.rproject.org, Vienna, Austria). $p < 0.5$ was considered statistically significant. Categorical variables were reported as a percentage of the total group and analyzed using Pearson’s chi-square and Fisher’s exact tests. Nonparametric testing for significance of ordinal and continuous variables was confirmed with the Wilcoxon rank sum test.

Results

A total of 1156 patients underwent pancreatic necrosectomy from January 1, 2007, through December 31, 2012. Of the patients included in our analysis 71 % were male and 29 %

female. The number of cases per year fluctuated over the 6-year period (Fig. 1). Of the total 1156 patients, 946 had alcohol (ETOH) as a recorded variable. Of these 946, 81 patients (8.6 %) had a positive ETOH history and 865 had a negative ETOH history. NSQIP defines a positive ETOH history as >2 drinks per day in 2 weeks prior to admission. Over three quarters (76 %) of the patients were nonsmokers. The majority of the patients reported an independent functional status (functional status 1) at the time of surgery, $n=697$ (60 %). Functional status 2 was reported on 162 patients (14 %) and 290 patients were functional status 3 (25 %). Prior to undergoing necrosectomy, ASA class 3 had the highest percentage of patients (51 %). The other ASA class percentages were ASA 1 (0.1 %), ASA 2 (9 %), ASA 4 (37 %), and ASA 5 (3.4 %). The morbidity and mortality rates did increase significantly with an increasing ASA class (Fig. 2).

For open necrosectomy, the overall rate of Clavien 4 complications was 42 % and the mortality rate was 9.5 %. Patient demographics with frequencies of Clavien 4 complications and mortality amongst each variable are described in Table 1. Each laboratory value analyzed between patients experiencing Clavien 4 complications and mortality is demonstrated in Table 2. Functional status and ASA class were both significant ($p<0.001$) in univariate analysis. Specifically looking at Clavien 4 complications, failure to wean from the ventilator was the most common in 37 % of patients. Table 3 describes the frequencies of other Clavien 4 complications.

The rates of both Clavien 4 complications and mortality significantly increase, $p<0.001$, with a higher frailty index, as illustrated in Fig. 3. Using a total of 11 variables to calculate the modified frailty index, the rate of Clavien 4 complications reaches over 70 % and mortality over 20 % for a patient with 4 or more variables. Because the number of patients reported in the NSQIP drastically decreases when the mFI reaches 0.36 or 4/11 variables, a cohort of patients was created for an mFI of 0.36–1.

A total of 234 patients (20 %) returned to the operating room (OR) within 30 days postoperatively from their original index necrosectomy operation. The NSQIP only tracks return to OR and not further interventions such as percutaneous drain placement. One previous NSQIP study¹⁷ cited approximately 64 % mortality rate of those patients returning to OR. Our study has a lower mortality rate of 26 % for those returning to OR and an 80 % Clavien 4 complication rate for those returning to OR. Postoperative wound classification [(1) clean; (2) clean contaminated; (3) contaminated; (4) dirty/infected] had no bearing on mortality, $p=0.7$.

Using multivariate logistic regression analysis, we compared frailty index, Hct, BUN, alkaline phosphatase (alk phos), albumin, and emergency surgery status as independent predictors of both Clavien 4 complications and mortality (Table 4). Frailty index had the highest odds ratio for both Clavien 4 complications (odds ratio (OR) 59; confidence interval (CI) 17–206) and mortality (OR 13; CI 2.5–68), followed by emergency surgery status. The laboratory values of BUN, alk phos, and Hct all have an odds ratio of approximately 1. All values achieved statistical significance except hematocrit for mortality. The frailty index was chosen due to its predictive ability for increased Clavien 4 and 5 complications.^{11–14}

Discussion

This study analyzed reported 30-day outcomes of pancreatic necrosectomy in 1156 patients utilizing the ACS-NSQIP database and sought to identify preoperative predictors of postoperative Clavien 4 complications and mortality. An overall 9.5 % mortality rate is consistent, though on the lower end, with outcomes of pancreatic necrosectomy from studies over the last decade, with a reported mortality rate ranging from 6.8 to 69 %.^{3,6,7,17–19} The one previous study with the lowest

Fig. 1 The number of cases, deaths, and Clavien 4 complications fluctuated from 2007 to 2012 with no discernible trend. The Clavien 4 complications ranged from 38 to 46 % per year and mortality ranged from 6.8 to 12 % per year

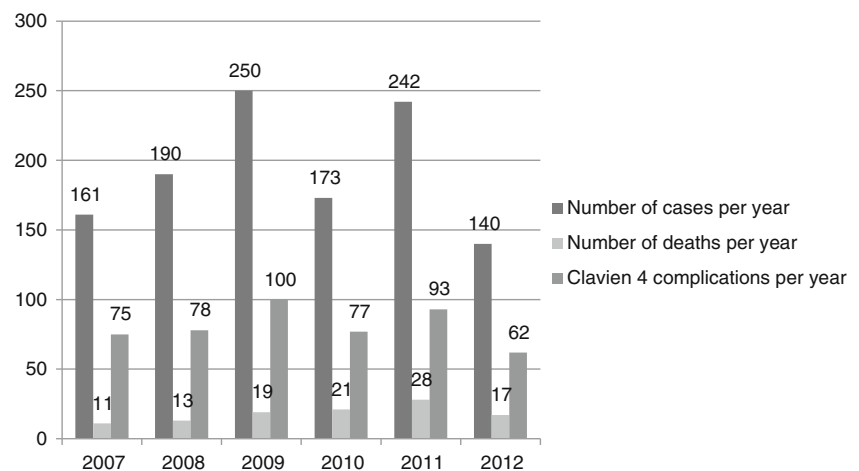
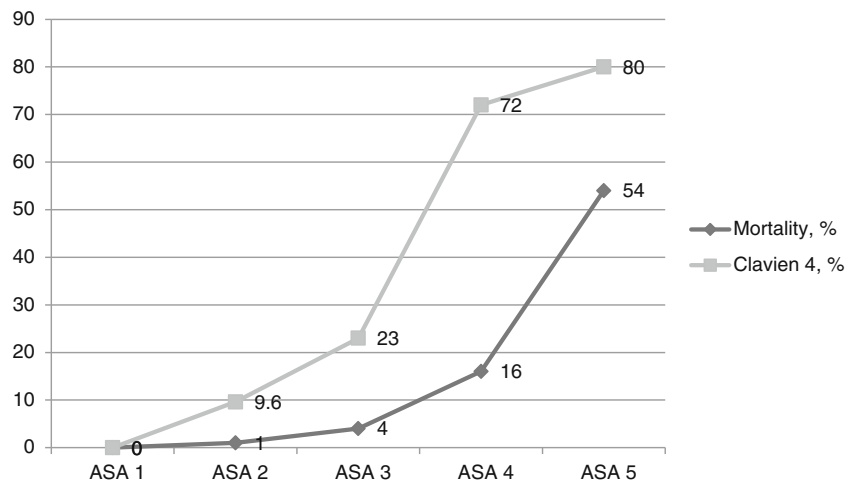


Fig. 2 There was a significant, $p < 0.001$, increase in Clavien 4 complications and mortality with an increasing ASA class



mortality rate (6.8 %) was also an ACS-NSQIP study examining necrosectomy over a 1-year period.¹⁷ With this study, as well as our study, there may be selection bias in the patients that do undergo necrosectomy and the fact that a large percentage of these hospitals are tertiary-care referral centers.

There is also no way to track, in the NSQIP database, procedures patients undergo prior to the operating room. In the “step-up” approach study to the management of pancreatitis by van Santvoort et al.,⁶ patients were randomized into either primary open necrosectomy or a minimally invasive step-up approach utilizing either percutaneous or endoscopic

transgastric drainage, followed by a second drainage procedure if the initial one failed after 72 h, then video-assisted retroperitoneal debridement (VARD) with postoperative lavage if still no improvement after an additional 72 h. In the minimally invasive group, 26 out of 43 (60 %) ended up with a necrosectomy after percutaneous drainage, 24 patients via the VARD route and 2 with an open necrosectomy. Thirty-three percent of these patients required an additional procedure. In the necrosectomy group, 42 % required additional laparotomies for further necrosectomy and 33 % required additional percutaneous drainage procedures. In our study, 20 % of patients made a return to the operating room for whatever reason not clarified within the NSQIP database. In the “step-up” study, 42 % of patients required one or more additional trips to the operating room for further debridement for ongoing sepsis. Whether these patients underwent percutaneous drainage or VARD procedures initially, followed by the index necrosectomy case recorded as their final debridement could account for the lower percentage of return to OR.

There was no specific trend in the number of necrosectomies reported from 2007 to 2012. The rates of Clavien 4 complications ranged from 38 to 47 % throughout the 6-year period, and the mortality rate ranged from 6.8 to 15 %. The majority of the patients in this sample were of the male gender, but the morbidity (male 43 % vs female 40 %) and mortality (male 9.5 % vs female 9.2 %) rates within each gender did not differ significantly.

Only 8.6 % of patients had an alcohol component to their history, and approximately two thirds of those patients experienced a Clavien 4 complication. In a recent study looking at outcomes of pancreatic debridement using a large inpatient sample, Wormer et al.⁸ classified pancreatitis by etiology based on ICD-9 coding. ETOH use was present in only 9.4 % of patients undergoing pancreatic debridement. The most common etiology of patients undergoing pancreatic debridement was idiopathic (50 %) followed by biliary (25 %). ETOH abuse was also only documented as 11 % in the

Table 1 Patient demographics and comorbidities

Variable	Clavien 4	Mortality	Total
<i>n</i> (%)	485 (42)	109 (9.5)	1156
Gender (%)			
Male	43	9.5	71
Female	40	9.2	29
ETOH use (%)	68	8.6	8.6
Functional status (%)			
1	25	5.3	60
2	46	8	14
3	78	14	25
Smoking (%)	43	7.8	23
History of CHF (%)	78	1.7	4.1
History of MI (%)	42	33	1.9
Steroid use (%)	42	25	3.7
ASA class (%)			
1	0	0	0.1
2	9.6	1	9
3	23	3.6	51
4	72	16	37
5	80	53	3.4

ETOH alcohol, CHF congestive heart failure, MI myocardial infarction, ASA American Society of Anesthesiologists

Table 2 Laboratory values

Laboratory value (mean±SD)	Clavien 4 complication			Mortality		
	Yes	No	<i>p</i> value	Yes	No	<i>p</i> value
Sodium	139±5.3*	137±4	<0.001	139±5*	137±4	<0.001
WBC	15±7.5*	11±7	<0.001	16±8*	12±7	<0.001
BUN	32±24*	16±15	<0.001	41±26*	21±19	<0.001
Creatinine	1.6±1.5*	0.9±0.7	<0.001	1.9±1.3*	1.1±1.1	<0.001
Albumin	2±0.7*	2.6±0.8	<0.001	1.9±0.7*	2.4±0.8	<0.001
Bilirubin	1.6±1.9*	1±1.3	<0.001	2.6±3*	1.1±1.4	<0.001
AST	56±86*	38±45	<0.001	70±70*	43±65	<0.001
Alk phos	147±156	166±126	0.27	178±189.5	156±139	0.14
Hct	27±5*	30±5.6	<0.001	28±5*	30±5	<0.005
Platelets	293±152*	319±145	<0.003	226±134*	317±147	<0.001
PTT	35±10*	33±9	<0.001	37±12†	33±9	<0.001
INR	1.4±0.3*	1.3±0.2	<0.001	1.4±0.3*	1.3±0.2	<0.001
PT	16±3*	15±3	<0.002	16±3.5**	15±3	<0.007

WBC white blood cell, AST aspartate aminotransferase, Alk phos alkaline phosphatase, Hct hematocrit, PTT partial thromboplastin time, INR international normalized ratio, PT prothrombin time

p*<0.001 confirmed by Wilcoxon rank sum test; †*p*=0.2 confirmed by Wilcoxon rank sum test; *p*=0.01 confirmed by Wilcoxon rank sum test

previous NSQIP study by Parikh et al.¹⁷ but up to 38 % in one recent single-center study.³ This may be due to the fact that ETOH is just underrepresented as a risk factor in the NSQIP database, or that other etiologies such as idiopathic or biliary pancreatitis precede necrosis more frequently. A Mayo Clinic study looking at moderately severe acute pancreatitis demonstrated gallstone etiology in the majority (40 %) of patients with severe acute pancreatitis.²⁰ Furthermore, a series assessing debridement for necrotizing pancreatitis in 167 patients²¹ demonstrated gallstones as the number one etiology (44 %) and alcohol as the second most frequent etiology (15 %), affirming that biliary pancreatitis may more frequently lead to necrosis of the pancreas rather than ETOH.

When specifically looking at the type of Clavien 4 complications, by far the most common was failure to wean from the

Table 3 The rate of Clavien 4 complications among necrosectomy patients

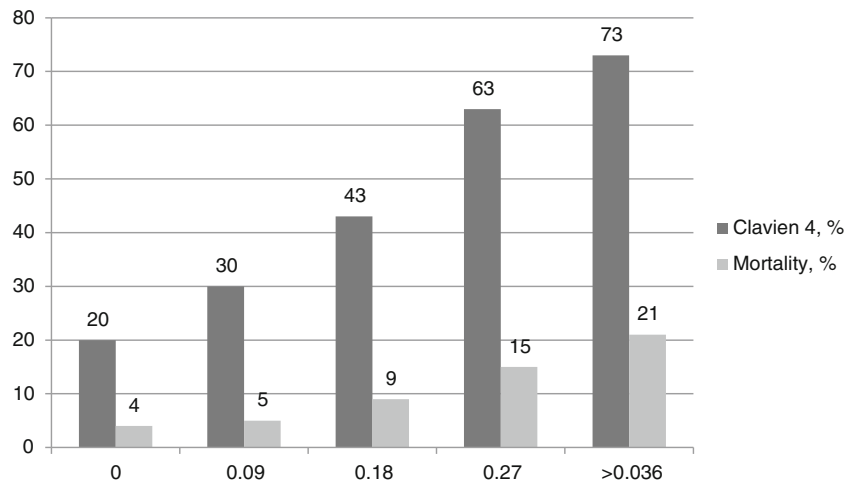
Clavien 4 complication	Frequency (%)
Failure to wean from the ventilator >48 h	37
Septic shock	10
Reintubation	7
Renal failure	3
Pulmonary embolism	2
Cardiac arrest	2
Myocardial infarction	1

Clavien 4 complications are listed in order of frequency, with the most common being failure to wean from the ventilator.

ventilator in 48 h (37 %). Lung injury in severe acute pancreatitis, more specifically acute respiratory distress syndrome, is present in up to 25 % of patients with severe acute pancreatitis^{22–25} making respiratory failure the most common complication in our study plausible. Whether the patient was ventilated prior to the operating room is not elicited in our study, nor is the timing of intubation or reason for intubation. Septic shock (10 %) and reintubation (7 %) were also frequent complications. Septic shock and SIRS response from pancreatic necrosis may be difficult to discern, but by definition in the NSQIP database, septic shock patients are classified as having a positive blood culture or any clinical documentation of purulence from a site thought to be causative. The definition of septic shock is reported in patients having sepsis plus associated end organ injury and circulatory dysfunction. Much less common were renal failure (3 %), pulmonary embolism (2 %), cardiac arrest (2 %), and myocardial infarction (1 %). Renal failure, as we used with Clavien 4 complications, was the need for new-onset hemodialysis, thus possibly skewing the percentage of patients on the lower end.

The stepwise logistic regression was used to analyzed frailty, emergency surgery status, BUN, alk phos, Hct, and albumin. Frailty was by far the greatest predictor of both Clavien 4 complications (OR 59; CI 17–206) and mortality (OR 13; CI 2.5–68). The modified frailty index used in this analysis has been previously retrospectively validated as a predictor of surgical outcomes.^{11–14} The modified frailty index does act like a comorbidity index in that all of the variables except functional status are comorbid conditions 30 days preceding surgery, and functional status is the only potentially

Fig. 3 The rate of Clavien 4 complications and mortality increased significantly, $p < 0.001$, as the modified frailty index increased



modifiable variable. When taking into account management strategies for infected pancreatic necrosis, frailty can be a useful tool. Using the modified frailty index, patients with 4 or more of 11 variables had a mortality rate of 21 % and a Clavien 4 complication rate of 73 %. Patients with a high frailty index on admission may be more suitable candidates for percutaneous drainage first rather than open necrosectomy.

Preoperatively, the majority of patients (60 %) were classified as independent functional status. These patients had the lowest morbidity (26 vs 46 % functional status 2 and 78 % functional status 3) and mortality (5.3 vs 8 and 14 %, respectively), as would be expected. In the future, preoperative functional status and more specifically the modified frailty index can aid in the selection of appropriate treatment strategies and allow for more informed preoperative discussion regarding

perioperative surgical risk. Patients with a high frailty index may be considered for a percutaneous drainage procedure vs an open necrosectomy if anatomically amenable, transfer to a tertiary hospital for increased level of care, or upgrade to intensive care unit level of care. Other lab values analyzed were indicative of end-organ dysfunction, as elevated BUN, elevated Hct, elevated alkaline phosphatase, and low albumin were all significant in Clavien 4 complications, and all were significant except Hct to correlate with mortality.

There are a number of limitations to our study. First, data such as the character of necrosis (sterile vs infected), specific preoperative indications for surgery, whether the patient underwent procedures such as percutaneous or endoscopic drainage prior to necrosectomy, and the timing of operation (immediate vs delayed) from the onset of pancreatitis is not available. The etiology of pancreatitis is not recorded. Next, the indication for reoperation and specific procedure when undergoing reoperation is not reported. Almost half of the patients undergoing open necrosectomy require further operations, either for ongoing sepsis or further drainage.^{7,17} The need for postoperative percutaneous intervention is also not in the data set. Additionally, certain outcomes such as pancreatic fistula, incisional hernia, new-onset diabetes, use of pancreatic enzymes, postoperative enteral vs parenteral nutrition, and ICU length of stay, which were all reported outcomes in previous studies, are not available as reported variables in the NSQIP.^{3,6}

However, despite these limitations, this updated ACS-NSQIP study gives an accurate cross-sectional analysis of 1156 patients undergoing pancreatic necrosectomy across the USA, Canada, UK, Australia, Europe, and other countries with hospitals participating in the NSQIP database. Despite the limitations of a retrospective analysis, an advantage of using a large, multicenter data set is heterogeneity of the patient population and the elimination of potential single-institution bias. We identified frailty, specifically the modified frailty index, as the greatest predictor of Clavien 4 complications and mortality in necrosectomy patients. Other significant

Table 4 Multivariate analysis

Variable	Odds ratio (CI 2.5–97.5 %)	<i>p</i> value
Clavien 4		
Modified frailty index	59 (17–206)	<0.001
Emergency status	3.3 (2.4–4.7)	<0.001
BUN	1 (1.02–1.04)	<0.001
Alk phos	1 (0.99–1)	0.02
Hct	0.95 (0.93–0.99)	0.01
Albumin	0.5 (0.4–0.6)	<0.001
Mortality		
Modified frailty index	13 (2.5–68)	<0.002
Emergency status	2.5 (1.6–4)	<0.001
BUN	1 (1.02–1.03)	<0.001
Alk phos	1 (1–1.01)	0.04
Hct	1 (0.95–1.04)	0.99
Albumin	0.6 (0.4–0.8)	<0.004

Multivariate analysis demonstrated the modified frailty index to have the most significant association for both Clavien 4 complications and mortality

variables in multivariate analysis associated with increased odds of morbidity and mortality were emergency surgery status, BUN, Hct, alk phos, and albumin.

Acknowledgments The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS-NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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