

RESEARCH

Emergent Operation for Perforated Peptic Ulcer Disease – Analysis of the ACS-NSQIP Database from 2005 to 2013.

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Joedd Biggs MD, Stephen Osterlind PhD, Erin Dalton, Linda Hanley, Jacob A. Quick MD, Stephen L. Barnes MD, Salman Ahmad MD

University of Missouri Hospital & Clinics ,Columbia, Missouri

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CORRESPONDENCE AUTHORS: Salman Ahmad, MD

ADDRESS: One Hospital Drive, MC214 ,Columbia, MO 65212, Office: (573) 884-6779,

Home: (207) 332-2541, Fax: (573) 884-4611

E-MAIL: ahmadsa@health.missouri.edu

CONFLICTS OF INTEREST

THERE ARE NO CONFLICTS OF INTEREST FOR ANY OF THE AUTHORS.

ABSTRACT:

Objectives

To evaluate perioperative clinical factors associated with morbidity and mortality in emergency operations for acute perforated peptic ulcer disease (PUD).

Background

While the incidence of hospital admissions for PUD may have changed over the decades, peptic ulcer disease remains a significant cause for mortality, with perforation having a mortality of approximately 11-16%, and morbidity of approximately 30%.

Methods

We utilized the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to study demographic and perioperative variables that may be associated with morbidity and mortality after emergent surgical management of acute perforated PUD. We queried the ACS-NSQIP participant user files (PUF) from 2005 to 2013 and extracted only those cases with a postoperative diagnosis of peptic ulcer disease to include gastric and duodenal perforations. Our study population was then narrowed to emergency operations for perforated PUD. Demographic and perioperative factors were noted and compared for mortality. This study was considered exempt by our IRB as the database does not include any patient identifiers.

Results

5666 cases were extracted between the years of 2005 and 2013 as our study population. There were 723 deaths yielding a 30-day mortality rate of 12.8%. Significant demographic differences between survivors and non-survivors included age (59.4 vs. 72.9, $p < 0.01$), ASA class (2.94 vs. 3.82, $p < 0.01$), female gender (46.5% vs. 55.1%, $p < 0.01$) and white race (75% vs. 85.2%, $p < 0.01$). Average days from hospital admission to surgery were also significant between the groups (0.98 vs. 2.04, $p < 0.05$). The most significant preoperative risk factors for death were preoperative serum albumin less than 3.5 g/dL (OR 6.88, 95% CI 5.45-8.70), disseminated cancer (OR 5.26, 95% CI 3.94-7.09), congestive heart failure (OR 4.9, 95% CI 3.58-6.67), renal failure (OR 4.33, 95% CI 3.25-5.78) and dialysis (OR 4.26, 95% CI 2.91-6.25). A MELD score greater than 30 increased the risk of death by 5.94 (95% CI 3.35-10.53). The most significant postoperative complications associated with mortality included renal failure (OR 12.22, 95% CI 8.90-16.81) and septic shock (OR 8.2, 95% CI 6.80-10.00). Bleeding requiring a transfusion increased the risk of death by 3.33 (95% CI 2.75-

4.02). A multivariate logistic regression model for mortality controlling for age, gender and race predicted the highest risks from the preoperative conditions of disseminated cancer (OR 4.20, 95% CI 2.63-6.71), dialysis (OR 3.94, 95% CI 2.27-6.84), esophageal varices (OR 3.72, 95% CI 1.17-11.84), and a low serum albumin (OR 2.97, 95% CI 2.13-4.14) and the postoperative complications of comatose state (OR 5.85, 95% CI 1.87-18.18), septic shock (OR 5.67, 95% CI 4.06-7.93), acute renal failure (OR 4.35, 95% CI 2.61-7.25) and myocardial infarction (OR 4.00, 95% CI 2.00-8.00).

Conclusion

This is one of the largest databases of emergent operations for perforated PUD. According to the ACS-NSQIP database between 2005 and 2013 the mortality rate for emergent operations in perforated peptic ulcer disease was consistent with prior studies. In addition to expected post-operative complications, age and preexisting comorbidities contributed significantly to outcomes as did timing to operation which also increased the risk for post-operative complications. Our results emphasize the need for early operation, aggressive resuscitation to prevent renal failure, limiting blood loss and the need to transfuse and controlling perioperative infectious events to reduce the risk of sepsis.

INTRODUCTION

While the incidence of hospital admissions for peptic ulcer disease has declined, morbidity and mortality remain unchanged from 11-16 % and 30% respectively¹⁻³. Complications of PUD include obstruction, hemorrhage and perforation as well as increasing the risk for malignant transformation. The most common complications are hemorrhage, accounting for 73% of hospitalizations for PUD, followed by perforation (9.3%) and obstruction (2.9%)^{1,4}. Acute perforated PUD occurs in approximately 4-11 cases per 100,000 annually and is the most common etiology for pneumoperitoneum identified on radiography⁵.

ACS-NSQIP is the first nationally validated, risk-adjusted, outcomes-based program to measure and improve the quality of surgical care. It is designed to help hospitals improve surgical care through the use of risk-adjusted clinical data. There are currently over 600 hospitals participating in ACS-NSQIP with all data being collected by highly trained Surgical Clinical Reviewers (SCR). They extract over 200 demographic and perioperative variables from patient charts including demographics, comorbidities, operations, and 30-day morbidity and mortality data. The annual de-identified participant user files (PUF's) compile this risk- and case-mix-adjusted data from every participating hospital⁶. We utilized the PUF's from 2005 to 2013 to study demographic and perioperative variables that may be associated with morbidity and mortality after emergent surgical management of acute perforated peptic ulcer

disease which included gastric and duodenal ulcers. Our results were then compared to prior studies.

METHODS

Following Institutional Review Board exemption, we queried the adult ACS-NSQIP database participant user files (PUF) from 2005 to 2013 to examine the outcomes of emergent surgical management of acute perforated PUD. We extracted only those cases with a postoperative diagnosis of perforated peptic ulcer disease from PUFs from 2005 to 2013 (ICD-9 codes 531.xx to 533.xx) encompassing gastric and duodenal ulcers. Our study population was then narrowed to emergency operations for perforated peptic ulcer disease. Only those variables that were collected in all years of the PUF from 2005 to 2013 were included. Table 1 includes the clinically relevant variables that were analyzed organized by demographics, preoperative comorbidities, procedures and postoperative complications. The frequency of postoperative complications was determined within the study population. Categorical variables were compared using Pearson's χ^2 test and continuous variables were compared using the Student *t*-test. Statistical power was calculated and found to be above 0.8, an expected result given our large sample size. We also calculated univariate odds ratios for mortality and developed a binomial logistic regression model for multiple variables associated with mortality. All statistical analyses were performed on SPSS for Windows v.23 (IBM, Chicago, IL).

This study was considered exempt by our IRB because the database contains no patient identifiers.

RESULTS

For the years between 2005 and 2013 as our study period we extracted 9292 cases with a postoperative diagnosis of peptic ulcer disease. Of those cases, 5666 were emergent procedures and thus constituted our study population. The mean and median age of the study population was 61 years with 2960 males (52.2%) and 2692 females (47.5%) in the group with 14 cases unspecified. Figure 1 tabulates in decreasing frequency the top 90% of principle procedures. Primary suture repair of stomach lesion (56.5%, 3201); primary repair of small intestine (8.9%, 506); and distal gastrectomy with

gastrojejunostomy (4.2%, 238) accounted for 70% of all principle procedures. Of the 5666 procedures, 245 of the principle procedures were laparoscopic and were included in the analysis. The emergent procedures resulted in 723 deaths yielding a 30-day mortality rate of 12.8% over the study period. Fifteen (2.1% of total deaths) underwent a laparoscopic principle procedure. Table 2 compares non-survivors and survivors based on demographics, ASA classification, days from admission to surgery and operative time (initial procedure). Non-survivors were older, female and white. They also had higher ASA classifications and were taken to the operating room later in their hospital course. There were no pregnant patients in this patient population.

Table 1. Database variables included in our analysis.

Demographics	Comorbidities	Comorbidities	Procedure	Complications
Age	Diabetes	Weight loss > 10%	Principle	Death
Gender	Dyspnea	Bleeding disorder or anticoagulation	Other procedure 1	Surgical Site Infections
Race	Ventilator Dependence	Preoperative blood transfusion	Other procedure 2	Dehiscence
Body Mass Index (Height & Weight)	Chronic Obstructive Pulmonary Disease	Chemotherapy or Radiotherapy	Blood transfusions	Pneumonia
Alcohol use	Concurrent Pneumonia	Sepsis or septic shock	Operative time	Unplanned intubations
Tobacco use	Ascites	Prior operation w/in 30d		Mechanical ventilation > 48 hours
	Esophageal varices	Days from hospital admission to OR		Renal insufficiency
	Renal failure	Preoperative WBC		Renal failure
	Dialysis	Albumin		Urinary Tract Infection
	Impaired sensorium	Chronic steroid use		Cerebrovascular Accident
	Comatose > 24h			Comatose > 24h
	Hemiplegia			Cardiac arrest
	Transient Ischemic Attack or Cerebrovascular Accident			Myocardial infraction
	Central Nervous System tumors			Bleeding requiring blood transfusion
	Para or quadriplegia			Deep Venous Thrombosis / Phlebitis
	Disseminated cancer			Return to the Operating Room.
	Existing open wound infection			

Figure 1. Bar graph of principle emergent procedures performed in decreasing frequency. The most common was simple repair of the gastric perforation. The remaining principle procedures decreased significantly in frequency among the study population. Secondary procedures were also very limited in frequency as discussed in the manuscript.

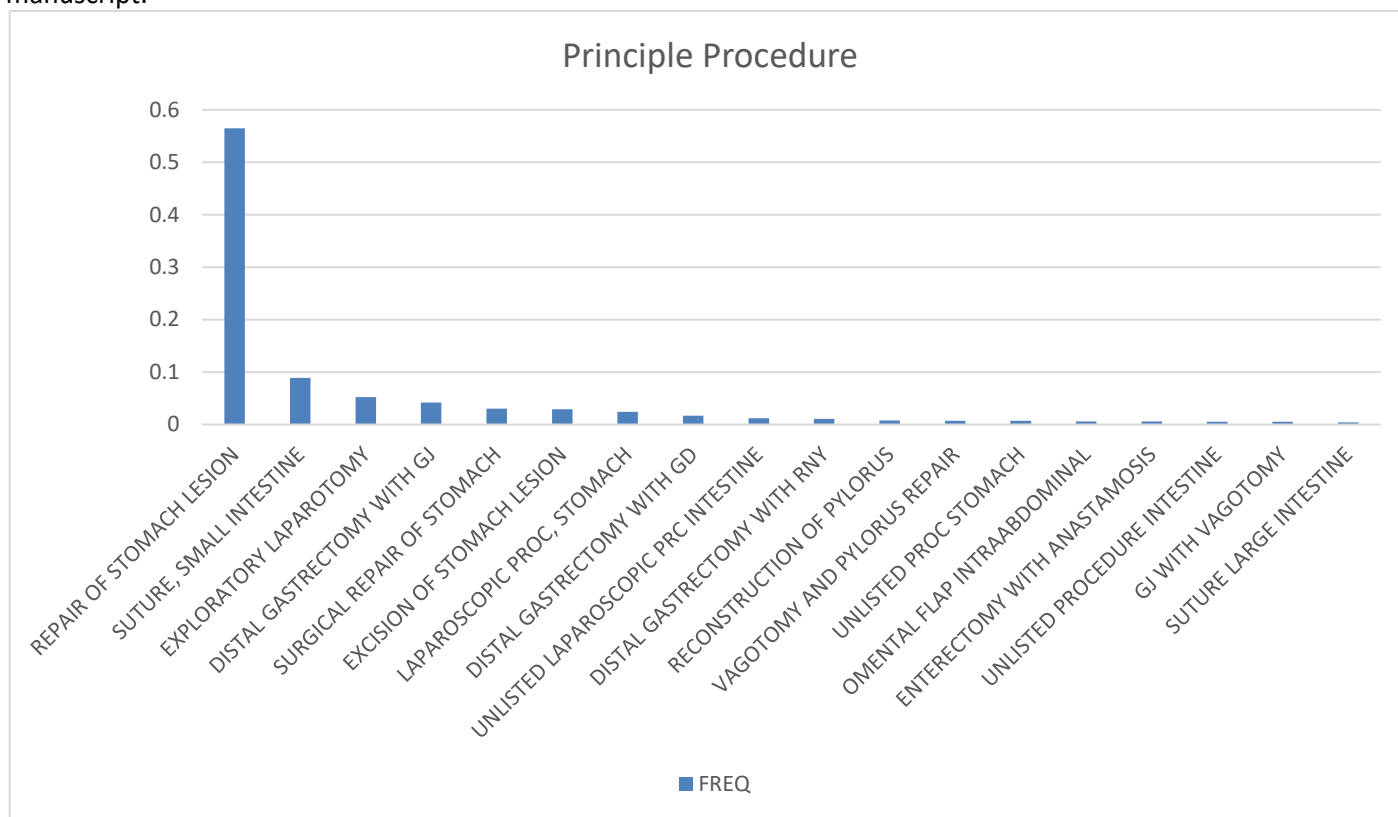


Table 2. Preoperative demographic factors between non-survivors and survivors. Student's t-test and Chi-squared test used for significance.

Factor	Non-Survivors	Survivors	p-value
Age	72.93	59.42	< 0.01 ^a
ASA Classification	3.82	2.94	< 0.01 ^a
Body Mass Index	26.73	26.4	NS ^a
Female	55.1%	46.5%	< 0.01 ^b
White Race	85.2%	75.0%	< 0.01 ^b
Days to Operating Room	2.04	0.98	< 0.01 ^a
Operative Time	99.4 min SD 70.2 min	88.5 min SD 65.1	NS ^a

a) t-test

b) χ^2 test

Univariate Preoperative Variables

Table 3 lists the preoperative demographic characteristics and comorbidities significantly associated with mortality in decreasing odds ratios with their 95% confidence intervals. The preoperative patient variables with the highest odds of death in a univariate analysis included a comatose state (OR 9.8, 95% CI 4.18-23.26) defined as a patient who is unconscious or unresponsive

to stimuli for at least 24 hours prior to the operation, a serum albumin less than 3.5 g/dL (OR 6.88, 95% CI 5.45-8.70) and disseminated cancer (OR 5.26, 95% CI 3.94-7.09) defined as metastatic disease that is widespread, fulminant or near terminal. Other significant preoperative comorbidities included congestive heart failure (OR 4.9, 95% CI 3.58-6.67), esophageal varices (OR 4.48, 95% CI 1.82-10.99), ventilator dependence (OR

4.48, 95% CI 3.61-5.56), impaired sensorium (OR 4.39, 95% CI 3.30-5.81) defined as acute confusion or delirium with response to stimuli in the context of current illness within 48 hours preoperatively, age over 60 years (OR 4.35, 95% CI 3.58-5.29), renal failure (OR 4.33, 95% CI 3.25-5.78) and the need for dialysis (OR 4.26, 95% CI 2.91-6.25). Given the constellation of findings that potentially suggest liver insufficiency (esophageal varices, hypoalbuminemia and dialysis), we also calculated their model for end-stage liver disease (MELD) scores to quantify liver function using preoperative creatinine, bilirubin and international normalized ratio (INR) with this equation,

$$MELD = (9.57 \times \ln(\text{creatinine})) + 3.78 \times \ln(\text{bilirubin}) + 11.2 \times \ln(INR) + 6.43$$

Laboratory values were set to 1.0 if they were less than 1.0 to eliminate negative scores from the natural log of a number less than one. Any patient on dialysis utilized a creatinine of 4.0 mg/dL in this equation⁷. In our study population, a MELD score greater than 30 increased the risk of death by 5.94 (95% CI 3.35-10.53) as did a score between 20 and 29 (OR 5.65, 95% CI 4.49-7.11) while a score between 10 and 19 doubled their risk of death (OR 2.06, 95% CI 1.74-2.44).

Preexisting infectious and immunological conditions increasing the risk of death included open wound infections (OR 3.48, 95% CI 2.66-4.55), pneumonia (OR 3.41, 95% CI 2.31-5.00), sepsis (OR 3.18, 95% CI 2.71-3.75), chemotherapy (OR 2.56, 95% CI 1.72-3.79), steroid use (OR 2.42, 95% CI 1.92-3.05) and a white blood cell count less than $6 \times 10^9/L$ (OR 2.09, 95% CI 1.71-2.54) or greater than $20 \times 10^9/L$ (OR 1.4, 95% CI 1.12-1.75). White race also increased the risk of death (OR 1.92, 95% CI 1.53-2.41). Alcohol use (OR 0.53, 95% CI 0.37-0.76) and smoking (OR 0.45, 95% CI 0.38-0.54) were protective factors against death. Delayed operative intervention beyond 24 hours nearly tripled the risk of death (OR 2.99, 95% CI 2.44-3.66). This delay also significantly increased the odds of incurring these complications with failure to wean from the ventilator (OR 3.59, 95% CI 3.00-4.00) and renal insufficiency (OR 3.53, 95% CI 2.09-5.96) being the most likely (table 4).

Univariate Postoperative Variables

The most frequent postoperative complications listed in table 5 were failure to wean from the ventilator within 48 hours (19.3%), death (12.8%), need for blood transfusion (12.2%), septic shock (9.8%), pneumonia (9.8%), reintubation (9%), abscess (5.1%), and superficial wound infections (4.4%). Table 5 also lists the odds

ratio of death for Cardiac arrest (OR 26.47, 95% CI 17.87-39.20), comatose state (OR 18.62, 95% CI 7.26-47.75), renal failure (OR 12.22, 95% CI 8.90-16.81) and septic shock (OR 8.2, 95% CI 6.80-10.00) were most highly associated with mortality. Failure to wean off of the ventilator within 48h (OR 5.26, 95% CI 4.44-6.21) and reintubation after failed extubation (OR 3.39, 95% CI 2.75-4.18) also contributed to the risk of death. Postoperative bleeding requiring transfusions more than tripled the risk of death (OR 3.33, 95% CI 2.75-4.02) while wound dehiscence almost doubled it (OR 1.86, 95% CI 1.21-2.87). Infections such as pneumonia (OR 2.88, 95% CI 2.34-3.55) and organ space surgical site infections (OR 1.38, 95% CI 1.00-1.90) also increased the risk of mortality. Also significant was the doubling of mortality risk for patients who required an unplanned return to the operating room (OR 2.09, 95% CI 1.67-2.62). Our analysis did not include the follow-up operations performed during those returns.

Multivariate Mortality Model

A multivariate logistic regression model for mortality was developed controlling for age, gender and race with results shown in table 6 in order of decreasing odds ratios. The Pearson goodness of fit was significant with a χ^2 of 931.83 ($p < 0.01$). The model accurately predicted 96.7% of survivors but only 32.5% of non-survivors with an overall accuracy of 87.9%. Cardiac arrest as a postoperative complication was excluded from this model. We also excluded preoperative MELD score as it was a derived variable incorporating several independent variables. The variables most likely to result in death included postoperative comatose state (OR 5.85, 95% CI 1.87-18.18), postoperative septic shock (OR 5.67, 95% CI 4.06-7.93), postoperative renal failure (OR 4.35, 95% CI 2.61-7.25) and myocardial infarction (OR 4.00, 95% CI 2.00-8.00). The remaining significant factors were preoperative conditions of disseminated cancer (OR 4.20, 95% CI 2.63-6.71), dialysis (OR 3.94, 95% CI 2.27-6.84), esophageal varices (OR 3.72, 95% CI 1.17-11.84) and malnutrition quantified by an albumin less than 3.5 g/dL (OR 2.97, 95% CI 2.13-4.14) and a greater than 10% weight loss (OR 1.83, 95% CI 1.14-2.92). Ascites (OR 2.04, 95% CI 1.45-2.86) may suggest either hepatic insufficiency, metastatic disease or a degree of malnutrition. Significant demographic factors included age over 60 years (OR 2.48, 95% CI 1.54-4.02) and white race (OR 1.66, 95% CI 1.16-2.39) while female gender was not significant (OR 1.25, 95% CI 0.96-1.63).

Table 3. Univariate odds of death for demographic characteristics and preoperative comorbidities in descending order of significance.

Variable	OR of DEATH	95% CI
Coma	9.8	4.18-23.26
Albumin < 3.5 g/dL	6.88	5.45-8.70
MELD score > 30	5.94	3.35-10.53
Disseminated cancer	5.26	3.94-7.09
Congestive Heart Failure	4.9	3.58-6.67
Esophageal varices	4.48	1.82-10.99
Ventilated	4.48	3.61-5.56
Impaired sensorium	4.39	3.30-5.81
Age > 60 years	4.35	3.58-5.29
Renal failure	4.33	3.25-5.78
Dialysis	4.26	2.91-6.25
CNS tumor	4.15	1.71-10
Wound infection	3.48	2.66-4.55
Pneumonia	3.41	2.31-5.00
Ascites	3.31	2.69-4.08
Sepsis	3.18	2.71-3.75
Bleeding disorder	3.15	2.55-3.91
Dyspnea	3.08	2.57-3.69
Hospital admission to Surgery > 1d	2.99	2.44-3.66
Chronic Obstructive Pulmonary Disease (COPD)	2.65	2.13-3.29
Prior transfusions	2.62	2.02-3.40
Hypertension treated with medications	2.56	2.16-3.01
Chemotherapy	2.56	1.72-3.79
Peripheral Vascular Disease	2.46	1.40-4.31
Steroids	2.42	1.92-3.05
Weight Loss > 10%	2.37	1.73-3.25
Cerebrovascular Accident	2.35	1.51-3.65
Angina	2.31	1.22-4.37
Transient Ischemic Attack	2.31	1.44-3.70
Myocardial Infarction	2.13	1.23-3.70
WBC < 6x10 ⁹ /L	2.09	1.71-2.54
Prior cardiac catheterization	2.05	1.40-3.02
White race	1.92	1.53-2.41
Diabetic	1.79	1.41-2.27
WBC > 20x10 ⁹ /L	1.4	1.12-1.75
WBC < 10x10 ⁹ /L	1.35	1.15-1.59
Female gender	1.41	1.20-1.65
Prior cardiac surgery	1.08	0.92-1.26
Alcohol use	0.53	0.37-0.76
Tobacco use	0.45	0.38-0.54

Table 4. Odds of postoperative complications if surgical intervention was delayed more than 24 hours from admission in descending order of risk.

Variable	OR	95% CI
Mechanical ventilation > 48h	3.59	3.00-4.30
Renal insufficiency	3.53	2.09-5.96
Coma > 24h	3.31	1.29-8.47
Bleeding requiring transfusion	2.65	2.15-3.26
Pneumonia	2.56	2.04-3.21
Cardiac arrest	2.54	1.70-3.80
Renal failure	2.52	1.73-3.66
Return to Surgery	2.38	1.87-3.01
Deep Venous Thrombosis	2.2	1.45-3.33
Wound dehiscence	2.18	1.40-3.40
Organ space Surgical Site Infection	1.91	1.39-2.62
Septic shock	1.77	1.39-2.27
Reintubation	1.58	1.22-2.06

Table 5. Odds of death with the incidence of postoperative complications in descending order of risk. Percent of patients is incidence of the complication among the study population.

Variable	% of patients (N)	OR	95% CI
Cardiac arrest	2.6% (146)	26.47	17.87-39.20
Coma	0.4% (22)	18.62	7.26-47.75
Renal failure	3.0% (171)	12.22	8.90-16.81
Septic shock	9.7% (554)	8.2	6.80-10.00
Renal insufficiency	1.3% (71)	6.94	4.33-11.11
Cerebrovascular Accident w/ deficits	0.7% (38)	6.29	3.31-11.90
Mechanical ventilation > 48h	19.4% (1099)	5.26	4.44-6.21
Myocardial infarction	1.6% (93)	4.71	3.08-7.18
Reintubation	8.9% (504)	3.39	2.75-4.18
Bleeding requiring blood transfusion	12.3% (697)	3.33	2.75-4.02
Pneumonia	9.7% (553)	2.88	2.34-3.55
Return to Surgery	9% (510)	2.09	1.67-2.62
Deep Venous Thrombosis	2.6% (148)	1.93	1.29-2.87
Wound Dehiscence	2.3% (128)	1.86	1.21-2.87
Organ Space Surgical Site Infection	5.1% (290)	1.38	1.00-1.90

Table 6. Multinomial logistic regression odds ratios of mortality in descending order of risk with p-value for significance.

Variable	OR	95% CI	p-value
Coma Postop	5.85	1.87-18.18	.002
Septic Shock Postop	5.67	4.06-7.93	.000
Acute Renal Failure Postop	4.35	2.61-7.25	.000
Disseminated Cancer	4.20	2.63-6.71	.000
Myocardial Infarction Postop	4.00	2.00-8.00	.000
Dialysis Preop	3.94	2.27-6.84	.000
Esophageal Varices	3.72	1.17-11.84	.026
Albumin < 3.5 g/dL Preop	2.97	2.13-4.14	.000
Congestive Heart Failure history	2.49	1.54-4.02	.000
Age > 60 years	2.48	1.81-3.39	.000
Transient Ischemic Attack history	2.38	1.32-4.29	.004
Impaired Sensorium Preop	2.08	1.42-3.07	.000
Ascites	2.04	1.45-2.86	.000
Cerebrovascular Accident Preop	1.98	1.09-3.58	.025
Weight Loss > 10%	1.83	1.14-2.92	.012
Bleeding Disorder history	1.81	1.29-2.53	.001
White Race	1.66	1.16-2.39	.006
Female Gender	1.25	0.96-1.63	.099
Organ Space Surgical Site Infection Postop	0.40	0.21-0.79	.008

DISCUSSION

The earliest known case of perforated peptic ulcer disease was a duodenal perforation found in a preserved body of 167 BC in China, found by To Cheng in 1984. King Charles I's daughter, Henriette-Anne, died from a perforated gastric ulcer in 1670. Then, Edward Crisp reported the first case series of perforated peptic ulcers in 1843 when he was able to construe an accurate description of the clinical signs and symptoms of perforation⁸. America saw the famous heartthrob Rudolph Valentino die in 1926 after perforation of a peptic ulcer occurred⁹.

In the early 1900's, explanations of causes of perforated peptic ulcers ranged from the ingestion of coarse food to oral sepsis to hemoglobinemia^{10,11}. Based on these explanations, the standard treatment for perforation was suture the opening closed and perform a gastro-enterostomy to prevent further occurrences¹⁰. Surgeons debated whether the most effective method included excision of the ulcer before closure, invagination of the ulcer, or if the gastro-enterostomy was necessary at all¹²⁻¹⁵. For the latter approach a posterior or anterior approach were the options considered (it was eventually decided that a posterior

approach is preferred)¹³. Patients were then recommended to avoid coarse foods and keep their oral cavities clean.

Dr. Graham began the use of gastrocolic omentum to repair these perforations in 1937 by simply inserting a piece of abdominal fat into the enteral opening¹⁶. With this closure technique, which evolved into the modern Graham Patch, he concluded that routine gastro-enterostomy was unnecessary. The omental patch is still used today to repair perforated peptic ulcers. The 1960's and 70's witnessed elective gastro-enterostomies and vagotomies performed on patients with perforated peptic ulcers in order to stem the production of gastric acid thought to be the major contributor to the disease process. This was followed by the first major change in treatment at the end of the 1970's: use of histamine H2 receptor antagonists. Gastric acid suppression was further utilized as a treatment when proton-pump inhibitors (PPI's) use began at the end of the 1980's¹⁷. Treatment of perforated peptic ulcers was once again radically altered in 1982 after Barry J. Marshall and Robin Warren identified the significant role of *Helicobacter pylori* in

the development of peptic ulcers¹⁸. Surgeons could now perform a simple closure of the perforation via plugging the opening with an omentum patch and prevent most recurrences with post-operative administration of PPI's or H2-receptor antagonists and antibiotics. Laparoscopic approach to perforated peptic ulcer closure was first described in 1989¹⁹. Repair through open laparotomy is the gold standard approach, but laparoscopy has become standard procedure in practice. Patients with recurrent severe ulcer disease are still treated more aggressively with parietal cell vagotomy and pyloroplasty or gastro-enterostomy²⁰.

However, the standard of care has clearly transitioned throughout history as our understanding of the disease has evolved, from primary closure with gastro-enterostomy as a routine procedure to today buttressing the repair with a vascularized omental pedicle followed by gastric acid suppression and eradication of *H. pylori* in disease that is refractory to medical management. The management of peptic ulcer disease (PUD) has also evolved from a primarily surgically managed disease to a medically managed one with advances in endoscopic therapies and treatment of *H. pylori* infection^{21,22}.

Our present analysis of the ACS-NSQIP database is the largest sample in the literature of emergent operations for perforated peptic ulcer disease. Overall mortality (12.8%) was similar to previously published studies. Statistically preoperative demographics and comorbidities contributed significantly to mortality; however, more postoperative complications contributed to mortality in our binomial logistic regression model. Non-survivors were older, female and white with worse ASA scores. ASA classification while subjective, is a surrogate for severity of disease at presentation that incorporates patient status and comorbidities. Perhaps alternative classification models could be used such as the SOFA (Sepsis-related Organ Failure Assessment) and APACHE (Acute Physiology and Chronic Health Evaluation) scores. Preexisting malignancy and comatose mental status portended the worst prognoses but almost any other comorbidity increased the odds of death by 2 to 3 times. The degree of immune response to injury as reflected by the inability to mount a WBC $> 5 \times 10^9/L$ also predicted outcome.

Novel findings include the predilection for survival among males, non-whites and tobacco smokers and alcohol drinkers. The clinical significance of these statistical findings are unclear but one could argue that poor preoperative conditional states lead to an increased risk of complications and death; i.e. weight loss and low serum albumin. However, lifestyle choices

such as smoking and drinking alcohol still appear to be protective. This is a caveat of any database analysis where a statistically significant correlation has no clear clinical reasoning and maybe due to undocumented convoluted variables. Additionally, a recent large meta-analysis determined that female gender was a statistically significant predictor of mortality (RR 1.7) while tobacco use (RR 0.6) was predictive of survival²³. Furthermore, the ACS-NSQIP database does not quantify the amount of tobacco smoked or alcoholic drinks consumed, both of which correlate directly with disease severity^{24,25}. Female gender has been shown to significantly increase the risk of mortality in non-emergent AAA repair in a March 2016 NSQIP study. However, this risk was reduced after controlling for aortic size index (aortic diameter/body surface area), implying that unique anatomy rather than gender was the significant predictive variable²⁶. Without more detailed analysis of gender-specific physiologic or surgical differences, we cannot understand completely the differences in mortality risk between men and women in this study. It is also notable that the constellation of preoperative variables that comprise the MELD score were also highly predictive of death in the univariate analysis. The odds of death in our study population at different tiers of the MELD score, however, are higher than that predicted for this population with liver disease⁷. This may validate this scoring system as a global prognostic indicator and suggests that these comorbidities contribute to a higher rate of death in this population. More focused study of these correlations is needed. The increased risk of death for whites in our study may be confounded by the fact that they make up 69% (3927) of the population. A 2013 ACS-NSQIP analysis by Causey et al analyzed the impact of race on outcomes following emergency surgery. Evaluating 75,280 patients over a 4-year time span undergoing emergency abdominal surgery, they demonstrated a 1.25-fold ($p < 0.001$) increase in complications for blacks but no difference in mortality compared to whites ($p = 0.168$). When combining all minority groups in comparison with the white cohort, overall complications were higher (OR 1.059, 95% CI 1.004 - 1.12; $p = 0.034$) for minorities though mortality was reduced by 1.7-fold (95% CI 1.07 to 1.34; $p < 0.01$)²⁷. Taking patients to surgery more than one day after admission predicted a much higher risk of death and was significantly associated with other complications that also predicted death. Expectedly, severe postoperative complications such as cardiac arrest and comatose mental status predicted a poor outcome, but renal complications were some of the most lethal

clinical complications. Infections after operations also contributed significantly to mortality including septic shock, pneumonia and surgical site infections.

Risk factors for mortality previously reported in the literature for this population include advanced age, hypoalbuminemia, hyperbilirubinemia, elevated creatinine, active malignancy, delay to surgery and ASA classification^{1,2,28,23}. Analyses may compare other risk factors with race such as comorbidities and the incidence of postoperative complications. The authors would conclude from our results that early surgical intervention, limiting blood transfusion, controlling infection and aggressive resuscitation in an ICU setting may improve the outcomes for this surgical population.

LIMITATIONS

While the sample size allows for robust statistical analysis, it may lead to type I errors by being overpowered. This analysis did not include the laparoscopic procedures as an alternative approach to surgical repair, however, with less than 200 cases the sample size may have been too small to affect the results. Future studies could perform a separate analysis of laparoscopic procedures only. Procedure classification for this condition was heterogeneous and made procedure-related analyses difficult. This reflects sampling error and not necessarily the incidence of penetration of this approach within the surgical community. The PUF's are not procedure-directed and thus contain limited patient information. There may be other variables that contributed significantly to outcomes that were not recorded in this database such as medications and past surgical history. There may still be coding errors or variance for the same procedure which make exact surgical management difficult to assess in detail. The data only consist of a sample of operations for perforated peptic ulcer disease and cannot be used to track the incidence or predominance of any one procedure. One other criticism of our study is the assumption that postoperative complications are independent events not related to preoperative comorbidities. Previous work with the ACS-NSQIP database have made similar assumptions²⁹. Future analysis could correlate the risk of a specific complication; i.e. renal failure with its preoperative condition of dialysis or renal insufficiency.

CONCLUSION

According to the ACS-NSQIP database between 2005 and 2013 the mortality rate for emergent operations in perforated peptic ulcer disease is consistent with prior studies. Older, white females are at a higher risk of

death. Poor nutritional status, preoperative comorbidities and certain post-operative complications decrease the likelihood of survival. Our results emphasize the need for early operation, aggressive resuscitation, limiting blood loss and need to transfuse and controlling perioperative infectious events.

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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ABBREVIATIONS

ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologists
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
GD	Gastroduodenostomy
GJ	Gastrojejunostomy
ICD	International Classification of Diseases
INR	International Normalized Ratio
MELD	Model for End-Stage Liver Disease
PPI	Proton Pump Inhibitor
PUD	Peptic Ulcer Disease
PUF	Participant User File
SCR	Surgical Clinical Reviewer
SOFA	Sepsis-related Organ Failure Assessment
WBC	White Blood Cell