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Predictors of mortality in the elderly after open repair for perforated peptic ulcer disease

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Abstract

Background: As the U.S. population ages and the number of emergent surgical repairs for perforated peptic ulcer disease (PUD) rise, contemporary national data evaluating operative outcomes for open surgical repair for perforated PUD among the elderly are lacking.

Materials and methods: The National Surgical Quality Improvement Program (2007-2014) was queried for patients ≥ 65 y who underwent open surgical repair for perforated PUD. The primary outcome was 30-d mortality. Secondary outcomes included 30-d postoperative complications. Univariate and multivariable regression analyses were performed.

Results: Overall, 2131 patients underwent open surgical repair for perforated PUD. Among those who died, more used steroids preoperatively (15% *versus* 9%, $P = 0.001$) and fewer were independent preoperatively (55% *versus* 83%, $P < 0.0001$) compared to those who were alive 30-d postoperatively. Common postoperative complications were septic shock (15%) and pneumonia (12%). The overall 30-d mortality rate was 17.7%, with more deaths in subsequent decades of life (65-75 y 13% *versus* 75-84 y 18% *versus* >85 y 24%, $P < 0.0001$). After adjustment for other factors, mortality was significantly associated with older age (85+ *versus* 65-74 y) (odds ratio [OR], 1.5; 95% confidence interval [CI], 0.8, 1.7), dependent functional status preoperatively ([OR], 0.2; 95% CI, 0.2, 0.3), and American Society of Anesthesiologist classification 4 (OR, 3.2; 95% CI, 2.4, 4.3).

Conclusions: At U.S. hospitals, open surgical repair, the accepted treatment of perforated PUD, among the elderly is associated with significant 30-d morbidity and mortality rates that are

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Supplementary data

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Disclosure

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unacceptably high in our contemporary era. Furthermore, mortality rates are associated with older age. Therefore, as the elderly population continues to increase in the United States, preoperative, perioperative, and postoperative measures must be taken to reduce this high morbidity and mortality rates.

Keywords

Peptic ulcer disease; Elderly; Outcomes; Surgical repair

Introduction

The management of peptic ulcer disease (PUD) has drastically evolved in the last 50 y due to the advent of H₂ blockers, proton pump inhibitors, and *Helicobacter pylori* discovery and eradication.^{1–6} Due to these advances in medical treatment, the incidence of PUD and elective surgeries for PUD have decreased⁷; however, the rates of emergent surgical repair of perforated PUD, a dangerous complication of PUD, have surprisingly increased.^{7–11} Perforation occurs in up to 10% of patients with PUD.¹² The reasons for this alarming increase in rates of operation for perforated PUD remain unclear. Perforated PUD is a devastating complication associated with high morbidity and accounts for more than 70% of deaths associated with PUD.¹² Different studies have reported death rates ranging from as low as 1% to as high as 24% after surgical repair of perforated PUD.^{7,9,12–14} However, mortality among elderly patients treated for perforated PUD remains unknown.

Overall, as the U.S. population ages and an unprecedented growth of the elderly population, there has been a shift in the overall population of emergency repair for perforated PUD to a more elderly cohort. Compared to the 1990s, patients currently hospitalized for PUD are now significantly older.^{7,12,13,15} The high mortality among elderly patients with perforated PUD was well described prior to the advent of PPIs and marked reduction of open (elective and emergent) procedures for perforated PUD^{16–18}; however, in an era where patients are living longer and fewer surgeons are facile in operations for PUD, outcomes are less known.

Importantly, despite the widespread uptake of laparoscopy for treatment of various emergency general surgery conditions (e.g., appendicitis, cholecystitis) during the same time frame as the exponential demographic shift of our nation's population toward older ages and medical advances in the treatment of PUD, it appears that laparoscopy is still relatively uncommon for perforated PUD. Byrge et al.,⁹ theorized that laparoscopic repair of perforated PUD has been slow to be adopted over the last 2 decades due to longer operating times, equivocal postoperative benefits, and unclear cost-effectiveness.⁹ Therefore, open repair for perforated PUD continues to be the most widely accepted treatment for perforated PUD and frequent surgical repair, as evidenced by the study by Byrge comparing open surgical repair ($n = 477$) to laparoscopic repair ($n = 50$) of perforated PUD.⁹

Therefore, given the growing elderly population in the United States as well as increasing rates of operation, the widely accepted treatment, for perforated PUD in the contemporary era, the operative outcomes of the elderly population undergoing open surgical repair of perforated PUD are critical. We hypothesized that among the elderly, older patients will have increased morbidity and mortality associated with open surgical repair for perforated PUD.

We aimed to evaluate 30-d mortality and other operative outcomes of open surgical repair of perforated PUD among the elderly by use of a comprehensive, national data set.

Methods

Database

After obtaining institutional review board approval from our institution, the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) Participant Use File from 2007 to 2014 was analyzed for this study. NSQIP is a national, multi-institutional clinical quality improvement program that prospectively collects risk-adjusted data to facilitate review of outcomes and quality improvement targeting institutional observed to expected outcomes ratios. These processes have been described in detail,¹⁹ and data validity has been previously shown.¹⁹ The NSQIP database has grown considerably since the conclusion of its pilot study in 2004, and 2014 data include 323 variables on 750,397 cases from 517 participating sites.¹⁹ Deidentified data from these sites are available to researchers in the Participant Use File.

Cohort

The cohort was first limited to patients greater than or equal to 65 y old, given that the elderly have been previously defined with this cutoff age.²⁰ Patients undergoing open surgical repair of perforated gastric or duodenal ulcers were then identified from the NSQIP data sets by use of the primary Current Procedural Terminology (American Medical Association, Chicago, Ill) code for the procedure (<http://www.sciencedirect.com.ezp-prod1.hul.harvard.edu/science/article/pii/S074152141302288X> Appendix A). The cohort was then further limited, by use of International Classification of Diseases, Ninth and Tenth Revision codes, to exclusively select those patients who had a primary discharge diagnosis related to gastric or duodenal ulcer (<http://www.sciencedirect.com.ezp-prod1.hul.harvard.edu/science/article/pii/S074152141302288X> Appendix B). Only primary discharge diagnosis was used to exclude secondary stress ulcers. Preoperative data included demographics (age, sex, race) and comorbid conditions. Comorbid conditions included smoking, diabetes, hypertension, pneumonia, steroid use for chronic condition, preoperative cancer, history of severe chronic obstructive pulmonary disease, and history of congestive heart failure. Other patient characteristics analyzed by NSQIP variables were preoperative functional status and American Society of Anesthesiologists (ASAs) physical status classification.

Outcomes

The primary outcome measure was 30-d mortality. Secondary outcomes were 30-d postoperative complications, including superficial and deep surgical site infection, organ space abscess and fascial dehiscence, pneumonia, septic shock, deep venous thrombosis, and pulmonary embolism. Hospital length of stay was also analyzed.

Statistical analysis

SAS 9.4 statistical software (SAS Institute, Cary, NC) was used to perform all statistical analyses. Categorical variables are presented as absolute numbers and percentage

frequencies, with continuous data presented as mean values $\pm$ standard deviation (SD). Categorical variables were analyzed by χ^2 or the Fisher exact test, as appropriate. Continuous variables were analyzed by the Wilcoxon rank sum test or two-tailed independent samples t-test, as appropriate. Failure to rescue (FTR) was defined as the probability of operative mortality after suffering a complication.²¹ For FTR analysis, major complications were defined as postoperative myocardial infarction, postoperative deep venous thrombosis, postoperative pulmonary embolism, postoperative acute renal failure, postoperative ventilator dependence, postoperative pneumonia, postoperative surgical site infection (superficial, deep), postoperative wound complication (organ space abscess, fascial dehiscence), and postoperative septic shock. Multivariable logistic regression modeling was determined with a backward elimination approach. Regardless of univariate association, age, as a categorical variable (65-74 y, 74-85 y, and >85 y), was forced into the multivariable model as the primary exposure variable of interest. One model was created to assess predictors of morbidity, specifically a composite outcome of sepsis and septic shock, based on baseline characteristics and postoperative complications. Given that this emergent procedure among the elderly has been previously associated with high morbidity, specifically associated with varying severity of systemic inflammatory response to infection, a model with the composite outcome of sepsis and septic shock was created to better understand the predictors of this morbidity. A second model was created to assess predictors of 30-d mortality based only on baseline patient characteristics. A third model was created to assess predictors of 30-d mortality based on patient characteristics and postoperative complications. Statistical significance was defined as $P < 0.05$.

Results

Baseline patient characteristics

We identified 2131 patients with 65 y old and greater who underwent open surgical repair for perforated PUD from 2007 to 2014 in NSQIP participating hospitals. Patients were predominantly Caucasian (83%) and females (58%) with a mean age ($\pm$ SD) of 78 ($\pm$ 8) y. (Table A.1). 21% of the patients were current smokers (within 1 y) and 10% were taking steroids preoperatively for a chronic condition. Most common comorbidities in the overall cohort included hypertension (66 %), diabetes (20%), and history of severe chronic obstructive pulmonary disorder (COPD) (12%). Although 42% of elderly patients had ASA classification of 4, 78% were functionally independent preoperatively. Mean preoperative white blood cell count ($\pm$ SD) was 12 ($\pm$ 7). Among those who died, more used steroids preoperatively (15% *versus* 9%, $P = 0.001$), more had preoperative cancer (11% *versus* 4%, $P < 0.0001$), more had an ASA classification of 4 (70% *versus* 35%, $P < 0.0001$), and fewer were independent preoperatively (55% *versus* 83%, $P < 0.0001$) compared to those who were alive 30-d postoperatively.

Postoperative outcomes

Overall, the 30-d mortality rate of the cohort was 18% (Table A.2). Mean ($\pm$ SD) total hospital length of stay was 13 d ($\pm$ 15). Common postoperative complications were ventilator dependence >48 h (22%), septic shock (15%), requirement of intraoperative or postoperative blood transfusions (15%), pneumonia (12%), and sepsis (10%); 30-d readmission rates were

10%, and the rate of return to the operating room within 30 d was 7%. Less common postoperative complications were deep venous thrombosis (3%), pulmonary embolism (1%), and stroke (1%). Outcomes were also analyzed by age group (65-74 y, 75-84 y, and >85 y). There were more deaths with subsequent decades of life (65-74 y, 13% *versus* 75-84 y, 18% *versus* >85 y, 24%, $P < 0.0001$). Unadjusted rates of FTR were 32% for the overall group. The rate of FTR among each advancing group was the following: 65-74 y, 25% *versus* 75-84 y, 32%, *versus* >85 y, 43%, $P < 0.0001$.

Multivariable analysis of sepsis/septic shock

After adjustment for baseline patient factors and postoperative complications, overall predictors of combined composite outcome of sepsis and septic shock included male sex (odds ratio [OR], 1.3 [95% confidence interval {CI}, 1.01, 1.6]), postoperative renal failure (OR, 2.8 [95% CI, 1.7, 4.9]), postoperative myocardial infarction (OR, 3.6 [95% CI, 1.9, 6.8]), intraoperative or postoperative blood transfusions (OR, 1.5 [95% CI, 1.1, 2]), and postoperative ventilator dependence >48h (OR, 4.1 [95% CI, 3.2, 5.3]). Age (75-84y *versus* 65-74 y, 85-94 y *versus* 65-74 y) did not remain a significant predictor of composite outcome of sepsis and septic shock associated with open repair for perforated PUD.

Multivariable analysis of in-hospital mortality

After adjustment for baseline patient factors, overall predictors of mortality included older age (85 y *versus* 65-74 y) (OR, 1.5 [95% CI, 1.1, 2.1]), hypertension (OR, 1.5 [95% CI, 1.1, 2]), preoperative cancer (OR, 3 [95% CI, 1.8, 4.8]), dependent functional status preoperatively (OR, 0.3 [95% CI, 0.2, 0.4]), and ASA classification 4 (OR, 3.7 [95% CI, 2.8, 4.9]) (Table A.4). After adjustment for all factors, including baseline patient factors and postoperative complications, predictors of mortality included older age (85 y *versus* 65-74 y) (OR, 1.5 [95% CI, 1.0, 2.2]), preoperative steroid use (OR, 1.7 [95% CI, 1.1, 2.5]), preoperative cancer (OR, 2.6 [95% CI, 1.5, 4.4]), dependent functional status preoperatively (OR, 0.2 [95% CI, 0.2, 0.3]), ASA classification 4 (OR, 3.2 [95% CI, 2.4, 4.3]), postoperative pneumonia (OR, 2.4 [95% CI, 1.6, 3.6]), postoperative renal failure (OR, 8.6 [95% CI, 4.5, 17.0]), and postoperative septic shock (OR, 4.1 [95% CI, 2.9, 5.9]) (Table A. 5).

Discussion

Our national study demonstrated that PUD is a highly morbid disease among elderly Americans. We found a 30-d mortality rate of 18% in our cohort of elderly who underwent open surgical repair for perforated PUD at NSQIP hospitals. This rate is markedly higher than that reported by Bertleff and Lange¹² in review of 100 studies on perforated PUD from 1929 to 2009 citing an overall mortality of 5%-11% and more recently by Wang et al.⁷ and Byrge et al.⁹ who reported mortality rates of 3% and 6%, respectively. One reason for higher mortality among our cohort may be that we focused on elderly patients with a mean age of 78 y compared to a mean age of 48 y in the study by Bertleff et al.¹² Although mortality associated with perforated PUD surgical repair has been cited as high as 24%,¹⁴ this previous study was analyzing pre- and post-1950 outcome trends. Our study's mortality rate was likely lower given the advances in critical care and anesthesia over the last 50 y.

While the U.S. population is aging, it is important to highlight that 42% of our cohort had an ASA classification of 4. Therefore, our population's higher mortality may also be related to a higher baseline prevalence of comorbidities than prior studies with younger and overall healthier patients.^{9,13} Based on an exploratory analysis using NSQIP (2007-2014) that demonstrated that only 107 laparoscopic repairs were performed nationwide for perforated PUD among the elderly, we chose to study only patients undergoing open surgery, the most prevalent surgical repair, for perforated PUD. Furthermore, a previous Cochrane review combining three randomized controlled studies concluded that it is not clear whether laparoscopic repair offers advantages to open repair.²² It is possible that surgeons capable of both open and laparoscopic approaches might have chosen an open approach due to perceived or measured frailty, performance status, and comorbidities; this may also explain why our overall mortality is higher than previous studies combining laparoscopic and open techniques.

In terms of postoperative complications, open surgical repair for perforated PUD among the elderly was associated with significant 30-d morbidity. A review by Bertleff and Lange¹² analyzing 100 studies from 1929-2009 demonstrated similar complications associated with surgical repair for perforated PUD such as pneumonia (4%-30%) and abscess formation (0%-9%). Not surprisingly, with advances of anesthesia and critical care over time, our results fall into the low-mid range of previously reported complications. However, complications (namely septic shock and pneumonia) were predictive of mortality as well. Others have also identified these predictors of mortality associated with surgical repair of perforated ulcer disease.²³ Our study found that when outcomes were analyzed by age group, there were more deaths with each subsequent decade of life. Furthermore, our unadjusted analysis demonstrated increasing rates of FTR with advancing age. Given that elderly surgical patients experience more FTR events compared to their younger counterparts,^{24,25} understanding these FTRs in the setting of a highly morbid disease may provide an opportunity to reduce mortality in this high-risk group of elderly patients with perforated PUD.

After adjustment for baseline patient factors, overall predictors of mortality included older age (85 y *versus* 65-74 y), hypertension, preoperative cancer, dependent functional status preoperatively, and ASA classification 4. One explanation of 85 y *versus* 65-74 y being a predictor of mortality associated with open surgical repair for perforated PUD, but not 75-84 y *versus* 65-74 y being a predictor of mortality may be the greater physiologic differences and less functional reserve between a 90 y old and 65 y old. There may be more similarities between a 75 y old and 65 y old, in terms of physiology and functional reserve. Preoperative functional status, specifically frailty status which has been assessed through various methods, has been shown to predict mortality at 6 mo or later after major cardiac surgical procedures.²⁴ In addition, it has been suggested that frailty predicts postoperative mortality and morbidity more than age alone.²⁶ Based on the overall predictors of mortality, preoperative risk stratification including preoperative functional status should be assessed at the time of presentation of the patient to the emergency department. Algorithms including ASA classification and preoperative functional status are needed for surgical repair for perforated PUD in the elderly. Given that operative repair is the accepted treatment for perforated PUD, even among the elderly, risk stratification cannot be used in a traditional

manner to decide who to operate on; rather risk stratification can provide clinicians with more realistic and true numbers when counseling a patient and family preoperatively as well as during the informed consent process. In addition, based on our second multivariable regression model adjusting for baseline factors and postoperative complications, patients who experience postoperative pneumonia, postoperative renal failure, and postoperative septic shock are even more likely to die within 30 d of surgery.

A 30-d mortality rate associated with open repair of perforated peptic ulcer is unacceptably high in our contemporary era. Given that open operative repair, even among the elderly, is the generally accepted treatment of perforated PUD, we are not recommending against open operative repair; however, we are recommending the following preoperative, perioperative, and postoperative strategies to reduce the mortality of the elderly, a population that has recently had an unprecedented growth in the United States. First, preoperatively, there has not been sufficient attention given to prevention of PUD in all populations, but specifically in the elderly. Given the high national prevalence of hospitalizations (156,108) for PUD,⁷ the projected 83.7 million people who are ≥65 y by 2050,²⁷ and the high mortality found in our study associated with treatment of perforated PUD in the elderly, it is imperative that greater public health attention be given to prevention of PUD, similar to other diseases with high mortality rates, such as vascular and heart disease and colon cancer in the elderly. Primary care physicians need to first ensure all the appropriate elderly patients are on proton pump inhibitors, and possibly even a checklist must be created for primary care physician practices to ensure no elderly patient who should be on acid suppression medication is missed. Second, both perioperative and postoperative critical care among the elderly must be improved, given that a large percentage of reported deaths among elderly surgical patients are FTR as we mentioned previously. For example, early ambulation after the surgery among the elderly may be necessary to return to baseline functional status.²⁸ Based on our results, opportunities exist to change clinical microsystem processes, such as improving safety culture, communication, and teamwork to promote early identification of clinical deterioration and timely rescue. Timely rescue, which may reduce the high mortality rate found in this study, may also involve increased nursing surveillance and training, as well as hospital clinical resources, such as critical care, as suggested by previous literature.²⁹ Finally, our results of 18% mortality among the elderly can be used to realistically counsel the patient and patient's family regarding the risks of the surgery. Although a strict preoperative risk stratification cannot be used traditionally in an emergent setting to stratify those who are too high risk to operate on given that open operative repair is standard of practice treatment for perforated PUD, our findings of 18% mortality rate among elderly who undergo open operative repair for PUD in addition to other baseline patient factors of mortality, such as older age, functional status preoperatively, and ASA classification of ≥4 must be used during the high-risk informed consent process prior to operative intervention. Again, we are not advocating against open operative repair for the elderly, but recommending to use our results to practice better high-risk informed consent.³⁰

Our findings of the study must be interpreted within the context of a number of limitations. First, NSQIP does not capture the amount of time between perforation and operation. Given that the increase of time between perforation and operation could potentially be associated with their level of severity at hospital presentation and therefore associated with mortality,

we attempted to mitigate this limitation by including preoperative white blood cell count in the univariate analysis and adjusting for preoperative white blood cell count in the multivariable regression model. Preoperative white blood cell count was not a significant predictor of mortality in the multivariable regression model. Second, NSQIP participant hospitals are participants of a voluntary quality program; therefore, our results may not be generalizable to elderly patients undergoing surgery for perforated PUD at non-NSQIP participating hospitals. Importantly, during the time of our study, there were only 107 cases performed laparoscopically for perforated PUD. Therefore, to reduce the impact of clinical selection bias, we focused our study on only open surgical repair and believe that a more narrow open surgery cohort was appropriate. Finally, a limitation of our data source is that NSQIP only captures 30-d postoperative outcomes. With more than 25% of Medicare expenditures occurring in the last year of life,³¹ it would be important in our age group of interest to better understand longer term mortality to aid in decision-making for surgical intervention and goals-of-care discussions with the family.

Conclusions

Our study demonstrates that at U.S. hospitals, open surgical repair, the predominant definitive, as well as most widely accepted treatment for perforated PUD among the elderly, is associated with unacceptably high 30-d morbidity and mortality rates in our contemporary era. Therefore, as the elderly population continues to increase in the United States, preoperative, perioperative, and postoperative measures must be taken to reduce this high morbidity and mortality rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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