Surgical Repair of Perforated Peptic Ulcers: Laparoscopic vs. Open Approach

A THESIS
SUBMITTED TO THE FACULTY OF THE
GRADUATE SCHOOL OF THE UNIVERSITY OF MINNESOTA
BY

Victor Vakayil, MBBS

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

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January 2019

Acknowledgements

I would like to thank Dr. James Harmon, for his thoughtfulness, insight, mentorship. and support over the years. Without his help, this thesis would not have been possible. I am fortunate to have collaborated with Dr. Brent Bauman, Dr. Reema Mallick and Mr. Keaton Joppru, and thank them their subject expertise and literary contributions. I thank Dr. John Connett and Dr. Christopher Tignanelli for their methodological and statistical oversight. I am grateful to the members of my dissertation committee Dr. Sayeed Ikramuddin and Dr. Gregory Beilman, who were very kind to agree to be on the advisory board. I thank Mrs. Mary Knatterud for helping me edit this manuscript. This work was supported by William Harmon Surgical Education & Research Fund.

I dedicate this all those who show the courage to take the road less trodden/

Abstract

Perforated peptic ulcers are a surgical emergency that can be repaired using either laparoscopic surgery (LS) or open surgery (OS). No consensus has been reached on the comparative outcomes and safety of each approach.

Using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database, we conducted a 12-year retrospective review (2005 - 2016) and identified 6,260 adult patients who underwent either LS (n = 616) or OS (n = 5,644) to repair perforated peptic ulcers. To mitigate selection bias and adjust for the inherent heterogeneity between groups, we used propensity-score matching with a case (LS):control (OS) ratio of 1:3. We then compared intraoperative outcomes such as operative time, and 30-day postoperative outcomes including infectious and non-infectious complications, and mortality.

Propensity-score matching created a total of 2,462 matched pairs (616 in the LS group, 1,846 in the OS group). Univariate analysis demonstrated successful matching of patient characteristics and baseline clinical variables. We found that OS was associated with a shorter operative time (67.0 ± 28.6 minutes, OS vs. 86.9 ± 57.5 minutes, LS; $P < 0.001$) but a longer hospital stay (8.6 ± 6.2 days, OS vs. 7.8 ± 5.9 days, LS; $P = 0.001$). LS was associated with a lower rate of superficial surgical site infections (1.5%, LS vs. 4.2%, OS; $P = 0.032$), wound dehiscence (0.3%, LS vs. 1.6%, OS; $P = 0.030$), and mortality (3.2%, LS vs. 5.4%, OS; $P = 0.009$).

Fewer than 10% of patients with perforated peptic ulcers underwent LS, which was associated with reduced length of stay, lower rate of superficial surgical site infections, wound dehiscence, and mortality. Given our results, a greater emphasis should be provided to a minimally invasive approach for the surgical repair of perforated peptic ulcers.

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Introduction

Peptic ulcer disease is a common medical condition worldwide with a reported annual incidence between 0.03% to 0.19%.[1] After the introduction of antibiotic therapy and proton-pump inhibitors for *Helicobacter pylori* eradication, the incidence decreased, particularly in Western countries. However, temporal trends associated with hospitalization rates and common complications, such as perforation, hemorrhage, and obstruction have remained relatively stable.[1–5] Morbidity associated with peptic ulcer disease still remains between 10% to 20% ,[6, 7] and although hemorrhage is almost eight times more common than an ulcer perforation, perforation is associated with increased mortality, accounting for 37% of all peptic ulcer-related deaths.[8] In the United States, perforated peptic ulcers were associated with a 5-fold increase in mortality as compared to hemorrhage and was the most important contributor to inpatient mortality from 1993 through 2006 (odds ratio [OR], 12.1; 95% confidence interval [CI], 9.8 to 14.9).[8, 9]

Surgery remains the standard of care for patients with perforated peptic ulcers and surgical delays have consistently been linked to inferior outcomes and higher mortality.[10–12] A number of surgical techniques have been described in the literature[6]: primary closure of the perforation with interrupted sutures; overlay with an omental pedicle after primary closure; occluding the perforation with a pedicled omentoplasty (Cellan-Jones repair)[13]; placing a free omental patch (Graham patch as originally described)[14]; and performing a sutureless repair.[15] Laparoscopic surgery (LS) to repair perforated peptic ulcers was first described in 1990[16, 17] and has since garnered significant interest. However, recent estimates from a U.S. nationwide database[18] suggest that fewer than 3% of such repairs today involve LS, and the ideal approach remains the subject of considerable debate.[19–22] Few randomized clinical trials[15, 23–26] and meta-analyses[27–31] have compared LS to open surgery (OS), evaluating the perioperative and postoperative outcomes, however the results have been contradictory. Nearly all randomized controlled trials had limited samples sizes with considerable heterogeneity between populations, precluding the generalizability of results.[31] Moreover, the majority of trials included in these reviews were carried out prior to 2004. There still exists a knowledge gap; larger studies, and more clinical data are needed to discern the actual difference between LS and OS in this population.

In our study, using a U.S. national surgical outcomes database, we compared intraoperative, and 30 -day postoperative outcomes between LS and OS, among adult patients with perforated peptic ulcers.

Methods

Data Source

Using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database, we conducted a 12-year retrospective review (2005 - 2016). The ACS NSQIP collects data from more than 250 hospitals in 2010 and 600 hospitals in 2015, all within the United States. At each of those hospitals, a trained and certified surgical clinical reviewer collects data on more than 150 variables including preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes, for inpatients and outpatients undergoing major surgical procedures. To reduce sampling bias, ACS NSQIP administrators use a systematic sampling process. Additionally, to ensure the quality of the data collected, they routinely conduct an interrater reliability audit of selected participating hospitals. Those audits have revealed an overall disagreement rate of less than 2.5% for all assessed program variables.[32]

Population of Interest

We identified all adult patients (age > 17) who underwent either LS or OS to repair perforated peptic ulcers from the ACS NSQIP database using the *International Classification of Diseases, Ninth Revision* (ICD-9) [531.1, 531.5, 532.1, 532.5, 533.1, 533.5] and *10th Revision* (ICD-10) [K25.1, K25.5, K26.1, K26.5, K27.1, and K27.5] diagnostic codes.

We excluded patients with hemorrhage and obstruction, as well as patients with gastrojejunal ulcers secondary to gastric bypass surgery. To reduce the inherent heterogeneity between the LS and OS groups, we excluded patients with atypical clinical comorbidities, such as ongoing chemotherapy (n = 78, 0.5%), ongoing radiation therapy (n = 35, 0.5%), quadriplegia or paraplegia (n = 15, 0.2%), central nervous system tumors (n = 16, 0.3%), history of a cerebrovascular accident with concurrent neurologic deficits (n = 16, 0.3%), history of a transient ischemic attack (n = 52, 0.8%), and any additional surgical intervention within the same operative interval. Subsequently, using Current Procedural Terminology (CPT) codes, we stratified patients into either OS (43840, 44602, and 49000) or LS (44238 and 43659).

Missing Data

Fewer than 8% of all variables that were analyzed had missing values; within these variables, pre-operative albumin had the highest percentage of missing data (14%). Our missing data analysis revealed no significant patterns, trends, or clusters, so we characterized all such data as missing at random. To account for the missing data, we used multiple imputation and constructed regression models using the following factors and covariates: patient characteristics, such as age, gender, race, and body mass index (BMI); baseline comorbidities, preoperative laboratory values, type of surgery, class of infected wounds; and American Society of Anesthesiologists (ASA) score. For the parsimony of presentation and subsequent analysis, we created a single imputed dataset. Overall, 11 pre-operative laboratory variables were imputed.

Univariate Analysis of Baseline Variables and Propensity Score Matching

To compare variables between the LS and OS groups, we performed a univariate analysis. We compared clinical comorbidities individually; in addition, we used an ACS NSQIP–specific, validated, modified frailty index (m-FI).[33] To measure the differences between the 2 groups, we used the χ^2 test and the Fisher exact test for categorical variables, the Wilcoxon rank-sum test for nonparametric continuous variables, and the independent-sample *t*-test for parametric continuous variables.

Subsequently, we used propensity-score matching as we have done previously[34], to reduce the heterogeneity among the baseline variables**.** This statistical technique helps estimate the independent treatment effect, irrespective of the treatment option, thereby eliminating the effect of any underlying selection bias.[35] To calculate propensity scores, we used a logistic regression model with a maximum likelihood technique. As independent predictors in that model, we included all variables from our univariate analysis that yielded a *P* value ≤ 0.1. In addition, irrespective of their statistical range, we also included as covariates any potential clinical confounders like gender, ulcer site, preoperative blood transfusion, and coagulation parameters.

After we calculated propensity scores, we stratified our study population by type of surgery (LS vs. OS); then, within this indication, matched each patient who underwent LS to 3 patients who underwent OS (1:3 ratio), according to the closest estimated propensity score. We chose that ratio to maximize power.[36] Using the recommended[37] calipers setting of 0.2, we applied a nearest-neighbor matching technique, without replacement.

Assessment of Balance in the Matched sample

Using analytic methods that accounted for the now-matched (1:3) nature of our data, we assessed the balance of baseline variables between the 2 groups.[35, 38] Because matching can lead to an artificial decrease in baseline variance between the populations of interest, we used repeated-measure analysis to evaluate the balance and then to estimate our final treatment effects. To analyze dichotomous variables, we used the nonparametric Cochran *Q* test. To analyze continuous variables, we used mixed-effects linear regression. To account for the clustered nature of the data, we specified a compound symmetry-repeated covariance structure. In addition to statistical hypothesis testing, as recommended[39] we calculated standardized differences, before and after matching, for all variables with a *P* value ≤ 0.1 per our univariate analysis. Because standardized differences represent the difference in means between 2 groups in standard deviation units, they are an independent value immune to the effect of sample size, and are believed to better estimate the balance of data.[39]

Outcomes of Interest

Our outcomes of interest included mean operative time, hospital length of stay, 30-day mortality, and 30-day morbidity (infectious and noninfectious complications). Each of those variables are defined on the ACS NSQIP website.[40]

Treatment Effects and Adjusting for Residual Bias

After applying generalized estimating equations to control for residual bias, we calculated final adjusted treatment effects. To analyze treatment effects, we modeled multivariable logistic regression equations (for dichotomous variables) and multivariable linear regression equations (for continuous variables). The models incorporated an exchangeable working variance correlation matrix.

In our final model, to reduce residual heterogeneity and to estimate the independent treatment effects, we adjusted for potential clinical confounders, such as age, year of hospital admission, class of infected wound, and ASA score. For each effect, we calculated the OR and 95% CI; all *P* values were 2-tailed, with a significance of 0.05 to detect a difference. To confirm the validity of each multivariable model, we performed appropriate regression diagnostics, including calculating the Hosmer-Lemeshow goodness-of-fit test, testing for outliers, and using classification tables to compare the predicted vs. actual outcomes. For all statistical analysis, we used IBM SPSS software (version 24.0, Armonk, NY) and R software (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 6,260 patients met our initial inclusion criteria: 5,644 underwent OS, and 616 underwent LS.

Patient Characteristics and Clinical Variables

The patient characteristics and clinical variables of the LS and OS groups are summarized in **Table 1** Patients in the OS group tended to be slightly older (60.0 ± 17.9 years, OS vs. 57.0 ± 19.0 years, LS) and had a higher rate of baseline comorbidities, preoperative sepsis, abnormal preoperative laboratory values, as well as higher ASA scores. A lower proportion of African Americans underwent LS.

Table 1. Univariate Analysis of Baseline and Matched Population

	Variable	**Baseline Population**			**Matched Population**		
		Open Surgery (OS) (N=5,644)	**Laparoscopic Surgery (LS) (N=616)**	**P-value**	**Open Surgery (OS) (N=1,842)**	**Laparoscopic Surgery (LS) (N=616)**	**P-value**
Race[a]	American Indian/Alaska Native	1.2%(68)	2.1%(13)	0.059	2.0%(36)	2.1%(13)	0.902
	Asian	4.2%(238)	5.5%(34)	0.132	5.0%(92)	5.5%(34)	0.694
	African American	15.6%(885)	9.7%(60)	<0.001*	9.9%(182)	9.7%(60)	0.996
	Caucasian	69.4%(3918)	71.6%(441)	0.266	73.2%(1349)	71.6%(441)	0.922
	Other	9.5%(535)	11%(68)	0.213	9.9%(183)	11%(68)	0.714
Demographics	Age[b]	60.0 ± 17.9	57.0 ± 19.0	<0.001*	57.0 ± 18.3	57.0 ± 19.0	0.928
	Female[a]	47.1% (2658)	50.2% (309)	0.158	50.7% (934)	50.2% (309)	0.564
	BMI[b]	26.5 ± 7.4	27.4 ± 7.4	0.004*	27.6 ± 7.9	27.4 ± 7.4	0.619
Pre-op Morbidities[a]	Diabetes	13.1%(739)	9.4%(58)	0.009*	10.2%(187)	9.4%(58)	0.835
	Dyspnea						
	At Rest	4.3%(244)	1.0%(6)	<0.001*	1.1%(21)	1.0%(6)	0.759
	On Moderate Exertion	6.0%(339)	5.2%(32)	0.418	5.4%(99)	5.2%(32)	0.908
	Functional Status						

	Partially Dependent	7.4%(420)	5.0%(31)	0.028*	5.9%(108)	5.0%(31)	0.401
	Totally Dependent	3.8%(216)	1.1%(7)	0.001*	1.5%(27)	1.1%(7)	0.771
	Mechanical Ventilation	4.1%(232)	1.1%(7)	<0.001*	1.7%(31)	1.1%(7)	0.203
	Smoker	43.9%(2477)	35.4%(218)	<0.001*	35.3%(651)	35.4%(218)	0.833
	COPD	8.7%(492)	6.3%(39)	0.044*	6.3%(116)	6.3%(39)	0.844
	Ascites	7.1%(401)	4.5%(28)	0.018*	4.9%(90)	4.5%(28)	0.889
	Congestive Heart Failure	2.7%(152)	1.3%(8)	0.037*	1.1%(20)	1.3%(8)	0.572
	Pneumonia	1.1%(60)	0.5%(3)	0.174	0.4%(7)	0.5%(3)	0.716
	Renal Disease	4.6%(257)	3.4%(21)	0.190	3.5%(65)	3.4%(21)	0.890
	Hypertension	43.7%(2467)	37.8%(233)	0.005*	39.4%(725)	37.8%(233)	0.091
	Cancer	2.5%(141)	1.9%(12)	0.401	2.2%(41)	1.9%(12)	0.568
	Open wound	3.8%(217)	1.9%(12)	0.017*	2.5%(46)	1.9%(12)	0.623
	Steroid use	7.1%(403)	5.8%(36)	0.238	6.5%(120)	5.8%(36)	0.907
	Weight loss	3.1%(176)	1.9%(12)	0.106	2.0%(37)	1.9%(12)	0.996
	Bleeding Disorder	7.2%(408)	4.7%(29)	0.020*	4.5%(82)	4.7%(29)	0.939
	Blood Transfusion	2.4%(136)	1.9%(12)	0.474	1.5%(27)	1.9%(12)	0.546
	Modified Frailty Index (mFI-5)	0.16 ± 0.2	0.12 ± 0.2	<0.001	0.12 ± 0.2	0.12 ± 0.2	0.390
Ulcer Site[a]	Gastric Ulcer	44.6%(2517)	47.1(290)	0.213	46.6%(859)	47.1(290)	0.711
	Duodenal Ulcer	51.9(2928)	48.5(299)		49.3%(908)	48.5(299)	
	Peptic Ulcer (Site Unknown)	3.5%(199)	4.4%(27)		4.1%(75)	4.4%(27)	
Preop Sepsis[a]	None	44.7%(2525)	51.3%(316)	<0.001*	51.6%(951)	51.3%(316)	0.910
	Sepsis	27.6%(1557)	30.2%(186)		28.9%(533)	30.2%(186)	
	Septic Shock	9.7%(548)	4.2%(26)		4.7%(87)	4.2%(26)	
	SIRS	18.0%(1014)	14.3%(88)		14.7%(271)	14.3%(88)	
Pre-op Labs[b]	Sodium	136.7 ± 4.6	137.2 ± 4.0	0.006*	137.3 ± 4.2	137.2 ± 4.0	0.597
	BUN	24.6 ± 18.4	20.9 ± 14.2	<0.001*	21.1 ± 14.0	21.0 ± 14.2	0.851
	Creatinine	1.3 ± 0.9	1.2 ± 0.9	<0.001*	1.2 ± 0.8	1.2 ± 0.9	0.969
	Albumin	3.6 ± 0.8	3.7 ± 0.7	<0.001*	3.7 ± 0.7	3.7 ± 0.7	0.901
	Bilirubin	0.9 ± 0.9	0.8 ± 0.6	0.011*	0.8 ± 0.6	0.8 ± 0.6	0.919
	SGOT	24(18, 35)	23(17,33)	0.091	23(18, 32)	23(17,33)	0.696

	ALP	77(60,100)	75(60,99)	0.489	75(60,97)	75(60,99)	0.671
	WBC	12.8 ± 7.1	12.5 ± 6.1	0.206	12.4 ± 6.1	12.5 ± 6.1	0.820
	Hematocrit	39.9 ± 7.3	40.1 ± 6.9	0.421	40.2 ± 6.7	40.1 ± 6.9	0.384
	Platelet Count	290.0 ±120.3	283.8 ± 103.8	0.107	284.3 ±106.1	283.8 ± 103.8	0.916
Wound Class[a]	Clean-I	1.9%(110)	2.4%(15)	0.002*	2.4%(45)	2.4%(15)	0.724
	Clean/Cont-II	13.8%(779)	10.7%(66)		10.4%(192)	10.7%(66)	
	Contaminated-III	18.5%(1044)	14.1%(87)		13.7%(252)	14.1%(87)	
	Infected-IV	65.7%(3711)	72.7%(448)		73.5%(1353)	72.7%(448)	
ASA Score[a]	1	3.3%(185)	7.1%(44)	<0.001*	6.6%(121)	7.1%(44)	0.997
	2	26.5%(1498)	33.4%(206)		34.2%(630)	33.4%(206)	
	3	43.3%(2442)	43.8%(270)		43.6%(804)	43.8%(270)	
	4	24.4%(1377)	14.1%(87)		13.8%(254)	14.1%(87)	
	5	2.5 %(142)	1.5 %(9)		1.8 %(33)	1.5 %(9)	

BMI= Body Mass Index, COPD= Chronic obstructive pulmonary disease, SIRS= Systemic inflammatory response syndrome, BUN= Blood Urea Nitrogen, SGOT= Serum glutamic oxaloacetic transaminase, ALP= Alkaline phosphatase, WBC= White blood cell count, ASA Score = American Society of Anesthesiologists score.

*Two tailed P Value ≤0.05

[a]Categorical variables measured as count and percentages.

[b]Continuous variables as measured in the ACS NSQIP Participant user file[40]

Propensity Score Matching and Balance of Baseline Variables

The median propensity score for the whole cohort was 0.21 (range, 0.02 to 0.3), indicating that the overall probability of undergoing LS was low). The Hosmer-Lemeshow test demonstrated good fit of the data (P = 0.512). After propensity-score matching, statistical testing and standardized difference analysis (**Figures 1A and 1B**) demonstrated successful matching on all baseline patient characteristics, clinical variables, and preoperative laboratory values **(Table 1).** Propensity-score matching created a total of 2,462 matched pairs (616 in the LS group, 1,846 in the OS group).

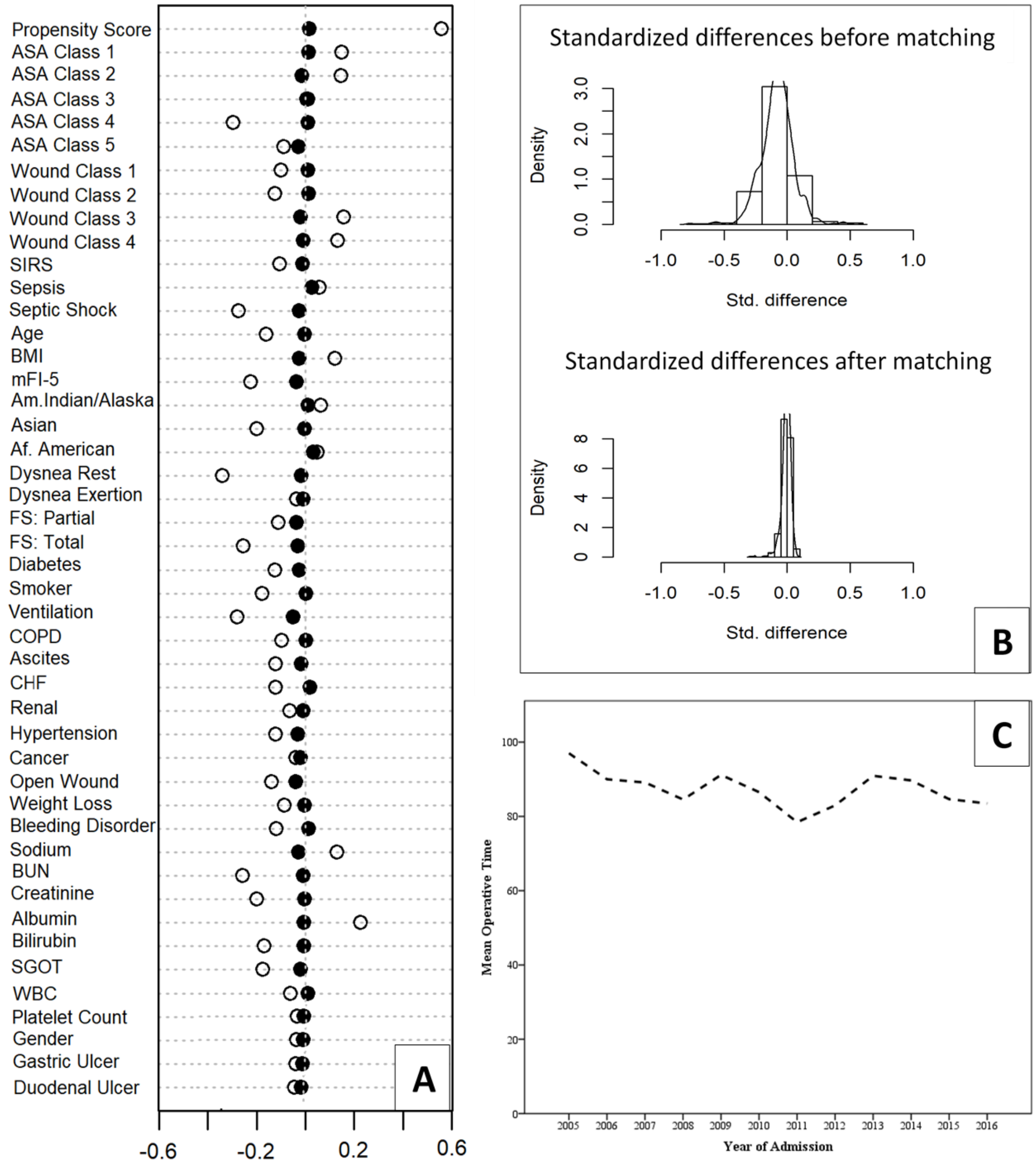
Treatment Effects

Adjusted outcomes are highlighted in **Table 2**. OS was associated with a significantly shorter operative time (OR < 0.1; 95% CI, 0.001 to 0.006, P < 0.001) but a longer hospital stay (OR, 2.3;

95% CI, 1.4 to 3.7, $P < 0.001$). Moreover, the rate of superficial surgical site infections was 2 times higher in the OS group than in the LS group (OR, 2.2; 95% CI, 1.1 to 4.5, $P = 0.032$). The rate of deep incisional infections was also higher in the OS group, but the difference was not statistically significant (OR, 6.9; 95% CI, 0.9 to 15.3, $P = 0.064$). The 2 groups had similar rates of organ space infections (6.0%, LS vs. 6.2%, OS). But the rate of wound dehiscence (OR, 4.9, 95% CI, 1.1 to 7.8, $P = 0.030$) and the rate of prolonged ventilatory support (OR, 1.5; 95% CI, 1.1 to 2.3, $P = 0.018$) were both higher in the OS group.

We found no significant difference between the 2 groups in the rate of other postoperative infectious complications, such as pneumonia, urinary tract infections, sepsis, and septic shock. Also similar were the rate of perioperative blood transfusion and the rate of postoperative morbidity, including reintubation, progressive renal insufficiency, and acute renal failure. As well, the incidence of thromboembolic events (including pulmonary embolism, stroke, deep venous thrombosis, and myocardial infarction) was comparable. The 30-day reoperation rate was similar between the 2 groups (OR, 1.1; 95% CI, 0.7 to 1.7, $P = 0.547$), but the overall 30-day mortality rate was nearly twice as high in the OS group than in the LS group (OR, 1.9 95% CI, 1.1 to 3.3, $P = 0.009$).

Figure 1. A. Forest plot depicting standardized differences before (white dots) and after (black dots) propensity score matching of all variables with a P value ≤0.1 on univariate analysis. **B.** Density distributions of standardized differences before and after matching. **C.** Mean operative time for laparoscopic repair of perforated peptic ulcer repair plotted from 2005- 2016**.**



ASA score = American Society of Anesthesiologists Score, SIRS = Systemic inflammatory response syndrome, BMI =Body mass index, mFI-5= Modified frailty index 5, Am. = American, Af = African, FS= Functional status, COPD = Chronic obstructive pulmonary disease, CHF = Chronic heart failure, BUN = Blood Urea Nitrogen, SGOT = Serum glutamic oxaloacetic transaminase, WBC = White blood cells

Table 2. Adjusted Treatment Effects

Outcome Variable[a]	Open Surgery (OS) (N=1846)	Laparoscopic Surgery (LS) (N=616)	Adjusted OR	Adjusted OR (95% CI)	P-Value
Operative Time(mins)	67.0 ± 28.6	86.9 ± 57.5	<0.1	0.001-0.006	<0.001*
Total Length of Hospital Stay (days)	8.6 ± 6.2	7.8 ± 5.9	2.3	1.4-3.7	0.001*
Postoperative Infectious Complications					
Superficial Surgical Site Infection	4.2% (78)	1.5% (9)	2.2	1.1-4.5	0.032*
Deep Incisional Infection	1.2% (23)	0.2% (1)	6.9	0.9-15.3	0.064
Organ Space Infection	6.2% (115)	6.0% (37)	0.9	0.6-1.4	0.741
Wound Dehiscence	1.6% (29)	0.3% (2)	4.9	1.1-7.8	0.030*
Pneumonia	5.7% (106)	4.9% (30)	1.0	0.7-1.6	0.986
Urinary Tract Infections	1.4% (25)	1.5% (9)	1.1	0.5-2.3	0.844
Sepsis	11.8% (217)	14.4% (89)	0.8	0.6-1.1	0.130
Septic Shock	7.5% (139)	6.8% (42)	1.1	0.8-1.6	0.481
Postoperative Non-Infectious Complications					
Prolonged Ventilation (>48 hours)	8.8% (162)	6.0 (37)	1.5	1.1-2.3	0.018*
Unplanned Re-intubation	5.8% (107)	4.2% (26)	1.1	0.7-1.7	0.666
Progressive Renal Insufficiency	1.1 (9)	0.2% (1)	4.4	0.6-33.5	0.156
Acute Renal Failure	2.3% (9)	1.1% (7)	1.5	0.7-3.5	0.336
Pulmonary Embolism	0.7% (13)	0.8% (5)	0.7	0.2-2.0	0.478
Cardiac arrest requiring CPR	1.6% (30)	0.6% (4)	2.9	0.9-8.4	0.090
Myocardial Infarction	1.0% (18)	0.6% (4)	1.8	0.4-8.7	0.166
DVT requiring therapy	1.6% (29)	1.6% (10)	0.8	0.4-1.7	0.534
Blood Transfusion (Intra/Postoperative period)	7.7% (143)	5.8% (36)	2.1	0.7-6.1	0.255
Re-operation	5.4% (99)	4.7% (29)	1.1	0.7-1.7	0.547
Mortality	5.8% (106)	3.2% (20)	1.9	1.1-3.3	0.009*
***Clavien-Dindo* grading of postoperative compilations**					
Grade I	8.8% (162)	6.0 (37)	1.5	1.1-2.3	0.018*
Grade II	23.4% (1321)	13.3% (82)	1.4	1.1-1.8	0.017*

Grade III	9.7% (178)	9.6% (59)	1.0	0.7-1.4	0.970
Grade IV	22.9% (422)	23.7% (146)	1.1	0.8-1.3	0.639
Grade V	5.4% (100)	3.2% (20)	1.9	1.1-3.3	0.009*

OR= Odds Ratio, CI= Confidence Interval, CPR= Cardio-pulmonary resuscitation.

*Two tailed P Value $\leq$0.05

[a]30 day post-operative outcomes, all categorical variables measured as number of events and percentages, all scale variables measured as mean and standard deviation.

[b]Clavien-Dindo grading: Grade I: Prolonged ventilation(>48hours), Grade II: Superficial surgical site infection + Deep Incisional Infection + Wound dehiscence + Pneumonia +Urinary tract infections + Progressive renal insufficiency + Blood transfusion (Intra/Postoperative period) + DVT requiring therapy, Grade III: Organ space infections + Re-operation, Grade IV: Sepsis + Septic Shock + Unplanned re-intubation +Acute renal failure + Pulmonary embolism + Cardiac arrest requiring CPR + Myocardial Infarction, Grade V: Death

Discussion

In this 12-year study of the ACS NSQIP database focusing on patients with perforated peptic ulcers, we found that LS was associated with a lower rate of infectious complications, wound dehiscence, and postoperative mortality. Given the low incidence of perforated peptic ulcers in the general population, evaluating accurate treatment effects has been challenging.[1, 30] To date, 5 randomized clinical trials[15, 23–26] primarily from Asia and Europe, have been published. These 5 studies had a pooled sample size of 406 patients (n = 208, LS, and n = 198, OS), with rather equivocal results. A few meta-analyses have also compared LS vs. open surgery (OS) and have had contradictory results. The first meta-analysis[27] noted that LS was associated with significantly lower rates of wound infection, as well as reduced postoperative pain and analgesic use, but a longer operating time and a higher rate of reoperation. Another review[28] found that LS was associated with a significant increase in surgical site leakage. But 2 reviews[29, 30] found no statistically significant differences in postoperative morbidity and mortality between LS and OS. Another updated meta-analysis[31] found a lower rate of postoperative complications and reoperation with LS. Most nonrandomized, high-quality studies have had significant heterogeneity among their surgical cohorts, precluding the generalizability of results.[31] To overcome this drawback, we attempted to maximize statistical power using a 1:3 LS:OS matching ratio. Univariate analysis of our original cohort demonstrated potential bias, in that OS was more commonly performed in older and more ill patients; however, our propensity-score matching successfully mitigated this presumed selection bias. This technique not only helped to substantially reduce population variances between both surgical cohorts but also helped us control for numerous clinical confounders. With this we were able to match all patients who underwent LS to patients who underwent OS, as well as adequately control for various demographic and clinical confounders like age, race, gender, and disease severity scores.

We refrained from using traditional comorbidity scores, such as the Charlson Comorbidity Index (CCI)[41] or the modified CCI,[42, 43] as previous studies have disputed their validity and use with the ACS NSQIP database.[44] A substantial proportion of variables that were originally collected by the database, and arguably critical to computation of those indices, have been subsequently discontinued. Therefore, we instead calculated and adjusted for each comorbidity individually; in addition, we used an ACS NSQIP–specific, validated, modified m-FI.[33]

Operative Time

In our study, LS was associated with a longer operative time than OS. With limited operative space and restricted intraabdominal mobility, performing a copious intraabdominal lavage and meticulous surgical closure can be time-consuming. Broad consensus has been reached on the need for peritoneal lavage in the surgical management of perforated peptic ulcers, yet the benefits of generous irrigation are contested.[45] Operative time can be heavily dependent on the quantity of fluid used to irrigate the peritoneum, and additionally, on the caliber of the suction device.[25].However, the advent of high-volume abdominal irrigation systems might limit any such delay.[28]

The precise surgical technique introduces some additional heterogeneity. Simple closure, for example, requires a shorter operative time than either omental patches or overlays.[46] Zhou et al.[31] noted that omental patches offered no additional benefits; their finding were echoed by other studies.[15, 22, 46–48] Furthermore, Zhou et al.[31] noted that, even though LS was associated with a longer operative time, operative time progressively shortened when patients were stratified by the year of surgery. Zhou et al.[31] attributed that trend to increased exposure, over time, to LS, coupled with the rapid technological advancements in equipment and technique. However, in our study, we did not find such an association (**Figure 1C**); instead, operative times remained relatively stable. Still, several recent studies[22, 24, 49] also noted a shorter operative time with LS**,** translating into lower exposure to anesthesia and CO_2 pneumoperitoneum, theoretically improving postoperative outcomes.

Length of Stay

In our study, postoperative hospital length of stay favored LS; clinically, after adjusting for baseline health status using various health indicators, we found that OS doubled hospital length of stay (OR, 2.3; 95% CI, 1.4 to 3.7). A minimally invasive approach can improve pain control, augment gastrointestinal motility and function, promote pulmonary toilet, enhance overall postoperative recovery, and thereby accelerate hospital discharge. Similar trends have been found in several other studies.[24, 31]

Postoperative Morbidity

Infectious Complications

Multiple studies[28, 30] have found that rates of postoperative morbidity favored LS, but most of the differences were not statistically significant, despite strong trends. Given the heterogeneity among studies and a strong concern for selection bias, the authors exercised caution to the broader exposition of their results. In our study, the rate of postoperative wound infections was lower with LS, particularly for superficial surgical site infections. The rate of deep surgical site infections was also low with LS, but the singularity of this event may have precluded the model from accurately delineating treatment effects with confidence limits, resulting in sparse data bias.[50] Organ space infection rates and other infectious complications such as rates of pneumonias, UTI's and sepsis were comparable between groups.

Some authors[51] have been skeptical about LS in patients with prolonged peritonitis, given the higher rates of pneumonia associated with LS. Several experimental animal studies[52, 53] found that increases in intraabdominal pressures, caused by CO_2 pneumoperitoneum, were associated with a higher risk of subsequent bacteremia and sepsis. Pneumoperitoneum can increase bacterial translocation and thereby increase the rate of systemic sepsis. However, there is no clinical evidence to support these experimental animal findings.[54]

Noninfectious Complications

Noninfectious complication rates favored LS, but for most outcomes, the difference was not statistically significant. However, OS *did* significantly increase dependence on mechanical ventilation and the rate of wound dehiscence. A larger incision coupled with a higher rate of wound infection may explain these findings. The views regarding those outcomes are largely contradictory in the literature: a few studies have found no difference,[28, 30, 55] but a few others have found fair evidence in favor of LS.[31] Even though most meta-analyses have found trends in favor of LS, those trends were limited to the few studies that collected those endpoints, once again limiting external validity.

Reoperation Rates and Leakage from the Ulcer Repair Site

In our study, the 30-day reoperation rates were similar in the LS and OS group. Leakage from the perforated ulcer repair site is often deemed a major cause of reoperations,[27, 28, 56] and hence this variable could potentially suffice as a surrogate marker for such leakage. A number of studies have expressed concern about the safety of LS regarding such leaks. A meta-analysis by Lunevicius et al.[28] in 2004 found a higher rate of leakage associated with LS. The friability of tissue, restricted mobility, limited intraoperative space, and need to mobilize and secure the omentum over the perforation with intracorporal knots can all contribute to the complexity of LS. However, with advances in instrumentation, improvement of surgeons' laparoscopic skill, and wider adoption of sutureless and knotless techniques, the rate of leakage and subsequent reoperations may have become more congruent between LS and OS. In fact, more recent studies[31] have found a similar rate for both approaches.

Mortality Rate

Among patients who have undergone surgery for perforated peptic ulcers, the reported mortality rate has varied considerably; the geographic variation in etiology might play a role.[57] Sonnenberg[58] demonstrated a relatively stable mortality rate of 10% in Europe, but the rate reported in the United States has varied from 3% to 15%.[7] The source of data might also contribute to the varied mortality rate. Administrative datasets, such as the National Inpatient Sample[59] of the United States and the Health Insurance Claims Registry in Korea[60], have yielded a lower mortality rate of around 3%. In our study, after performing propensity-score matching for various clinical confounders and then, in our final model, controlling for clinical severity with indices such as the ASA score, we observed that LS was associated with a significantly lower mortality rate than OS. Most other studies analyzing mortality have had several limitations, such as smaller sample sizes, significant heterogeneity between populations, predominant inclusion of patients with low ASA scores of 1 or 2,[61] and very limited sampling of critically ill patients with ASA scores ≥ 3.

The authors of a more recent review[31] noted that, after they excluded studies done before 2004, LS offered a survival benefit. Our study is concordant with their findings. Mortality and morbidity in patients with perforated peptic ulcers are inextricably linked to sepsis and inflammation; we believe that a minimally invasive approach enhances postoperative recovery and thus minimizes the systemic inflammatory response, reducing postoperative mortality.

We acknowledge the limitations of our study, most of which are inherent to a retrospective review of ACS NSQIP data. Because the quality of the data collected depends on the accuracy of the coding, it is possible that an error in coding could have biased our results. In addition, procedural codes for LS may be non-specific, additionally, they do not distinguish between the technique employed, a simple repair or an omentoplasty, nor do they permit identification of patients who converted from LS to OS. Ideally, according to the intention-to-treat principle, to provide conservative estimates of treatment effects, irrespective of the conversion status, patients who received a laparoscopic intervention should be analyzed with the LS group, but we could not discern that information and it is possible that some patients who converted from LS to OS may have been analyzed with the OS group. Despite making efforts to minimize selection bias, we know that our findings are susceptible to the effects of unmeasured covariates, such as the size of the perforation, surgical technique and the surgeon's ability and experience. Several reports have noted that perforations $\geq$ 2cm may benefit from an excision, a distal gastrectomy, a diverting gastrojejunostomy, or placement of a T-tube.[2, 62, 63] Our exclusion of all such procedures from our study might have contributed to some unaccounted bias. Time from diagnosis to surgery has been shown to impact outcomes[11, 64, 65]; scoring systems such as the Boey score[10, 64], that predict mortality using clinical variables such as the time from perforation to surgery, systolic blood pressure, and the presence of comorbidities, have been used to account for this variability. The absence of the variables used to calculate the Boey score from the ACS NSQIP database, precluded its evaluation. Despite this, we were able to adjust for the ASA score, which has previously been validated as a predictor of postoperative mortality and morbidity, with a sensitivity and a specificity similar to that of the Boey score.[66, 67] Moreover, a systematic review by Møller et al[68], that reviewed 37 different pre-operative prognostic factors in 29,782 patients, noted that in an adjusted analysis, delay in surgery, or time from perforation to surgery is a surrogate marker for the underlying propensity to develop sepsis. In our model, in addition to matching for pre-operative sepsis and various clinical grades of sepsis, we estimated our final treatment effects after adjusting for pre-operative sepsis, hence we believe final treatment effects are reliable. Finally, we were unable to evaluate the precise cause for mortality, and other outcomes of interest—such as level and duration of pain control, return of bowel function, and the rate of long-term complications like hernia and bowel obstruction. However, evaluating 30-day surgical outcomes (morbidity and mortality) is common practice in the literature and is an accepted standard. Similarly, mortality outcomes are irrefutably associated, either directly or indirectly, to the underlying surgical intervention and hence drawing temporal and causal associations between them may be permissible.

Despite those limitations, our study has several strengths. To our knowledge, it is the largest retrospective cohort study in the United States on outcomes of perforated peptic ulcer repair over the last decade. The ACS NSQIP dataset encompasses a large, heterogeneous patient population that reflects the general trends of care. Keeping the infrequency of the diagnosis in perspective, it is difficult to perform a well-powered randomized controlled trial; furthermore, the restrictive inclusion criteria of such trials limit the generalizability of outcomes to a larger population. Our statistical approach—using propensity-score matching with several predefined, perioperative variables—provided us with more robust estimates and, after adjusting for residual bias, enabled us to compute final treatment effects. Moreover, we matched 100% of the LS patients in our 12-year study period, maintaining a higher 1:3 LS:OS match ratio that improved our power to detect differences.

In conclusion, in our 12-year study, we found that the patients with perforated peptic ulcers who underwent LS (fewer than 10% of our study population) experienced a lower rate of postoperative morbidity and mortality, as compared with OS. The availability of large, high-quality health care databases, such as the ACS NSQIP database, has clearly enhanced the ability to perform health outcomes research using more sophisticated statistical models. Given our results, and those of another recent inquiry into this subject[31], a greater emphasis should be provided to a minimally invasive approach for the surgical repair of perforated peptic ulcers. Future research should evaluate individual provider-level characteristics and broader hospital-based attributes, this may help in identifying those factors that lower the propensity to perform this procedure laparoscopically. Additionally, this may be particularly useful from an education and intervention point-of-view. Developing high and low fidelity surgical simulators may be quintessential to imparting skill; our initial experience with developing a low fidelity simulator was met with much enthusiasm at our department. In addition to improving patient outcomes, a minimally invasive technique may be a cost-effect solution, improving pain control, augmenting gastrointestinal motility and function, promoting pulmonary toilet and enhancing overall postoperative recovery.

References

1. Sung JJY, Kuipers EJ, El-Serag HB (2009) Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther 29:938–946 . doi: 10.1111/j.1365-2036.2009.03960.x

2. Malfertheiner P, Chan FKL, McColl KEL (2009) Peptic ulcer disease. Lancet (London, England) 374:1449–1461 . doi: 10.1016/S0140-6736(09)60938-7

3. Lau JYW, Barkun A, Fan D, Kuipers EJ, Yang Y, Chan FKL (2013) Challenges in the management of acute peptic ulcer bleeding. Lancet (London, England) 381:2033–2043 . doi: 10.1016/S0140-6736(13)60596-6

4. Paimela H, Paimela L, Myllykangas-Luosujarvi R, Kivilaakso E (2002) Current features of peptic ulcer disease in Finland: incidence of surgery, hospital admissions and mortality for the disease during the past twenty-five years. Scand J Gastroenterol 37:399–403

5. Post PN, Kuipers EJ, Meijer GA (2006) Declining incidence of peptic ulcer but not of its complications: a nation-wide study in The Netherlands. Aliment Pharmacol Ther 23:1587–1593 . doi: 10.1111/j.1365-2036.2006.02918.x

6. Bertleff MJOE, Lange JF (2010) Perforated peptic ulcer disease: a review of history and treatment. Dig Surg 27:161–169 . doi: 10.1159/000264653

7. Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC (2011) Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. Digestion 84:102–113 . doi: 10.1159/000323958

8. Wang YR, Richter JE, Dempsey DT (2010) Trends and outcomes of hospitalizations for peptic ulcer disease in the United States, 1993 to 2006. Ann Surg 251:51–58 . doi: 10.1097/SLA.0b013e3181b975b8

9. Vaira D, Menegatti M, Miglioli M (1997) What is the role of Helicobacter pylori in complicated ulcer disease? Gastroenterology 113:S78-84

10. Boey J, Choi SK, Poon A, Alagaratnam TT (1987) Risk stratification in perforated

duodenal ulcers. A prospective validation of predictive factors. Ann Surg 205:22–26

11. Buck DL, Vester-Andersen M, Moller MH (2013) Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg 100:1045–1049 . doi: 10.1002/bjs.9175

12. Surapaneni S, S R, Reddy A. VB (2013) The perforation-operation time interval; an important mortality indicator in peptic ulcer perforation. J. Clin. Diagn. Res. 7:880–882

13. Cellan-Jones CJ (1929) A rapid method of treatment in perforated duodenal ulcer. Br. Med. J. 1:1076–1077

14. Graham R (1937) The treatment of perforated duodenal ulcers. Surg Gynecol Obs 235–238

15. Lau WY, Leung KL, Kwong KH, Davey IC, Robertson C, Dawson JJ, Chung SC, Li AK (1996) A randomized study comparing laparoscopic versus open repair of perforated peptic ulcer using suture or sutureless technique. Ann Surg 224:131–138

16. Nathanson LK, Easter DW, Cuschieri A (1990) Laparoscopic repair/peritoneal toilet of perforated duodenal ulcer. Surg Endosc 4:232–233

17. Mouret P, Francois Y, Vignal J, Barth X, Lombard-Platet R (1990) Laparoscopic treatment of perforated peptic ulcer. Br J Surg 77:1006

18. Wright GP, Davis AT, Koehler TJ, Scheeres DE (2018) Cost-efficiency and outcomes in the treatment of perforated peptic ulcer disease: Laparoscopic versus open approach. Surgery 156:1003–1008 . doi: 10.1016/j.surg.2014.06.047

19. Bhogal RH, Athwal R, Durkin D, Deakin M, Cheruvu CN V (2008) Comparison between open and laparoscopic repair of perforated peptic ulcer disease. World J Surg 32:2371–2374 . doi: 10.1007/s00268-008-9707-5

20. Khoursheed M, Fuad M, Safar H, Dashti H, Behbehani A (2000) Laparoscopic closure of perforated duodenal ulcer. Surg Endosc 14:56–58

21. Arnaud J-P, Tuech J-J, Bergamaschi R, Pessaux P, Regenet N (2002) Laparoscopic suture closure of perforated duodenal peptic ulcer. Surg Laparosc Endosc Percutan Tech 12:145–147

22. Ates M, Sevil S, Bakircioglu E, Colak C (2007) Laparoscopic repair of peptic ulcer perforation without omental patch versus conventional open repair. J Laparoendosc & Adv Surg Tech Part A 17:615 . doi: 10.1089/lap.2006.0195

23. Lau JY, Lo SY, Ng EK, Lee DW, Lam YH, Chung SC (1998) A randomized comparison of acute phase response and endotoxemia in patients with perforated peptic ulcers receiving laparoscopic or open patch repair. Am J Surg 175:325–327

24. Siu WT, Leong HT, Law BKB, Chau CH, Li ACN, Fung KH, Tai YP, Li MKW (2002) Laparoscopic repair for perforated peptic ulcer: a randomized controlled trial. Ann Surg 235:313–319

25. Bertleff MJOE, Halm JA, Bemelman WA, van der Ham AC, van der Harst E, Oei HI, Smulders JF, Steyerberg EW, Lange JF (2009) Randomized clinical trial of laparoscopic versus open repair of the perforated peptic ulcer: the LAMA Trial. World J Surg 33:1368–1373 . doi: 10.1007/s00268-009-0054-y

26. Schietroma M, Piccione F, Carlei F, Sista F, Cecilia EM, Amicucci G (2013) Peritonitis from perforated peptic ulcer and immune response. J Invest Surg 26:294–304 . doi: 10.3109/08941939.2012.762073

27. Lau H (2004) Laparoscopic repair of perforated peptic ulcer: a meta-analysis. Surg Endosc 18:1013–1021 . doi: 10.1007/s00464-003-8266-y

28. Lunevicius R, Morkevicius M (2005) Systematic review comparing laparoscopic and open repair for perforated peptic ulcer. Br J Surg 92:1195–1207 . doi: 10.1002/bjs.5155

29. Antoniou SA, Antoniou GA, Koch OO, Pointner R, Granderath FA (2013) Meta-analysis of laparoscopic versus open repair of perforated peptic ulcer. JSLS J. Soc. Laparoendosc. Surg. 17:15–22

30. Sanabria A, Villegas MI, Morales Uribe CH (2013) Laparoscopic repair for perforated peptic ulcer disease. Cochrane database Syst Rev CD004778 . doi: 10.1002/14651858.CD004778.pub3

31. Zhou C, Wang W, Wang J, Zhang X, Zhang Q, Li B, Xu Z (2015) An updated meta-analysis of laparoscopic versus open repair for perforated peptic ulcer. Sci Rep 5:13976

32. No Title. https://www.facs.org/quality-programs/acs-nsqip

33. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM (2018) New 5-Factor Modified Frailty Index using American College of Surgeons NSQIP data. J Am Coll Surg 226:173–181.e8 . doi: 10.1016/j.jamcollsurg.2017.11.005

34. Tignanelli CJ, Joseph B, Jakubus JL, Iskander GA, Napolitano LM, Hemmila MR (2018) Variability in management of blunt liver trauma and contribution of level of American College of Surgeons Committee on Trauma verification status on mortality. J Trauma Acute Care Surg 84:273–279 . doi: 10.1097/TA.0000000000001743

35. Austin PC (2008) A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 27:2037–2049 . doi: 10.1002/sim.3150

36. Hennessy S, Bilker WB, Berlin JA, Strom BL (1999) Factors influencing the optimal control-to-case ratio in matched case-control studies. Am J Epidemiol 149:195–197 . doi: 10.1093/oxfordjournals.aje.a009786

37. Austin PC (2011) Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 10:150–161 . doi: 10.1002/pst.433

38. Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083–3107 . doi: 10.1002/sim.3697

39. Imai K, King G, Stuart EA (2008) Misunderstandings between experimentalists and observationalists about causal inference. J R Stat Soc Ser A (Statistics Soc 171:481–502 . doi: 10.1111/j.1467-985X.2007.00527.x

40. ACS NSQIP Participant User File. https://www.facs.org/~/media/files/quality programs/nsqip/nsqip_puf_user_guide_2015.ashx

41. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383

42. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA (2018) New

ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 57:1288–1294 . doi: 10.1016/j.jclinepi.2004.03.012

43. D'Hoore W, Bouckaert A, Tilquin C (2018) Practical considerations on the use of the charlson comorbidity index with administrative data bases. J Clin Epidemiol 49:1429–1433 . doi: 10.1016/S0895-4356(96)00271-5

44. Basques BA, McLynn RP, Fice MP, Samuel AM, Lukasiewicz AM, Bohl DD, Ahn J, Singh K, Grauer JN (2017) Results of database studies in spine surgery can be influenced by missing data. Clin Orthop Relat Res 475:2893–2904 . doi: 10.1007/s11999-016-5175-7

45. Schein M, Gecelter G, Freinkel W, Gerding H, Becker PJ (1990) Peritoneal lavage in abdominal sepsis. A controlled clinical study. Arch Surg 125:1132–1135

46. Lin B-C, Liao C-H, Wang S-Y, Hwang T-L (2017) Laparoscopic repair of perforated peptic ulcer: simple closure versus omentopexy. J Surg Res 220:341–345 . doi: https://doi.org/10.1016/j.jss.2017.07.034

47. Abd Ellatif ME, Salama AF, Elezaby AF, El-Kaffas HF, Hassan A, Magdy A, Abdallah E, El-Morsy G (2013) Laparoscopic repair of perforated peptic ulcer: Patch versus simple closure. Int J Surg 11:948–951 . doi: https://doi.org/10.1016/j.ijsu.2013.06.014

48. Seelig MH, Seelig SK, Behr C, Schönleben K (2003) Comparison between open and laparoscopic technique in the management of perforated gastroduodenal ulcers. J Clin Gastroenterol 37:

49. Golash V (2008) Ten-year retrospective comparative analysis of laparoscopic repair versus open closure of perforated. Oman Med J 23:241–246

50. Greenland S, Mansournia MA, Altman DG (2016) Sparse data bias: a problem hiding in plain sight. BMJ 352: . doi: 10.1136/bmj.i1981

51. Naesgaard JM, Edwin B, Reiertsen O, Trondsen E, Faerden AE, Rosseland AR (1999) Laparoscopic and open operation in patients with perforated peptic ulcer. Eur J Surg 165:209–214 . doi: 10.1080/110241599750007063

52. Gurtner GC, Robertson CS, Chung SC, Ling TK, Ip SM, Li AK (1995) Effect of carbon dioxide pneumoperitoneum on bacteraemia and endotoxaemia in an animal model of

peritonitis. Br J Surg 82:844–848

53. Evasovich MR, Clark TC, Horattas MC, Holda S, Treen L (1996) Does pneumoperitoneum during laparoscopy increase bacterial translocation? Surg Endosc 10:1176–1179 . doi: 10.1007/s004649900273

54. Robertson GS, Wemyss-Holden SA, Maddern GJ (2000) Laparoscopic repair of perforated peptic ulcers. The role of laparoscopy in generalised peritonitis. Ann R Coll Surg Engl 82:6–10

55. Tan S, Wu G, Zhuang Q, Xi Q, Meng Q, Jiang Y, Han Y, Yu C, Yu Z, Li N (2016) Laparoscopic versus open repair for perforated peptic ulcer: A meta analysis of randomized controlled trials. Int J Surg 33 Pt A:124–132 . doi: 10.1016/j.ijsu.2016.07.077

56. Lee FY, Leung KL, Lai PB, Lau JW (2001) Selection of patients for laparoscopic repair of perforated peptic ulcer. Br J Surg 88:133–136 . doi: 10.1046/j.1365-2168.2001.01642.x

57. Søreide K, Thorsen K, Harrison EM, Bingener J, Møller MH, Ohene-Yeboah M, Søreide JA (2018) Perforated peptic ulcer. Lancet 386:1288–1298 . doi: 10.1016/S0140-6736(15)00276-7

58. Sonnenberg A (2007) Time trends of ulcer mortality in Europe. Gastroenterology 132:2320–2327 . doi: 10.1053/j.gastro.2007.03.108

59. Wilhelmsen M, Moller MH, Rosenstock S (2015) Surgical complications after open and laparoscopic surgery for perforated peptic ulcer in a nationwide cohort. Br J Surg 102:382–387 . doi: 10.1002/bjs.9753

60. Bae S, Shim K-N, Kim N, Kang JM, Kim D-S, Kim K-M, Cho YK, Jung SW (2012) Incidence and short-term mortality from perforated peptic ulcer in Korea: a population-based study. J Epidemiol 22:508–516

61. Di Saverio S, Bassi M, Smerieri N, Masetti M, Ferrara F, Fabbri C, Ansaloni L, Ghersi S, Serenari M, Coccolini F, Naidoo N, Sartelli M, Tugnoli G, Catena F, Cennamo V, Jovine E (2014) Diagnosis and treatment of perforated or bleeding peptic ulcers: 2013 WSES position paper. World J Emerg Surg 9:45 . doi: 10.1186/1749-7922-9-45

62. Kumar P, Khan HM, Hasanrabba S (2014) Treatment of perforated giant gastric ulcer in

an emergency setting. World J Gastrointest Surg 6:5–8 . doi: 10.4240/wjgs.v6.i1.5

63. Gupta V, Singh SP, Pandey A, Verma R (2013) Study on the use of T-tube for patients with persistent duodenal fistula: is it useful? World J Surg 37:2542–2545 . doi: 10.1007/s00268-013-2196-1

64. Boey J, Wong J, Ong GB (1982) A prospective study of operative risk factors in perforated duodenal ulcers. Ann Surg 195:265–269

65. Kneebone R (2003) Simulation in surgical training: educational issues and practical implications. Med Educ 37:267–277

66. Lohsiriwat V, Prapasrivorakul S, Lohsiriwat D (2009) Perforated peptic ulcer: clinical presentation, surgical outcomes, and the accuracy of the boey scoring system in predicting postoperative morbidity and mortality. World J Surg 33:80–85 . doi: 10.1007/s00268-008-9796-1

67. Thorsen K, Søreide JA, Søreide K (2014) What is the best predictor of mortality in perforated peptic ulcer disease? a population-based, multivariable regression analysis including three clinical scoring systems. J Gastrointest Surg 18:1261–1268 . doi: 10.1007/s11605-014-2485-5

68. Moller MH, Adamsen S, Thomsen RW, Moller AM (2010) Preoperative prognostic factors for mortality in peptic ulcer perforation: a systematic review. Scand J Gastroenterol 45:785–805 . doi: 10.3109/00365521003783320