Early versus delayed laparoscopic cholecystectomy for gallbladder perforation

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BACKGROUND:	Gallbladder perforation occurs in 2% to 11% of patients with acute cholecystitis, with associated mortality estimated to be at 12% to 42%. Because of its low incidence, the data on management remain sparse. There is a lack of evidence to suggest whether early or delayed cholecystectomy is superior in the treatment of perforated cholecystitis. We hypothesize that an early definitive operation is associated with decreased total hospital length of stay (THLOS).
METHODS:	Using the National Surgical Quality Improvement Program database from the American College of Surgery, we identified patients who underwent laparoscopic cholecystectomy for gallbladder perforation on an urgent or emergent basis from 2012 to 2021. We divided them into those who underwent early (<2 days from the date of admission to the date of operation) and delayed cholecystectomy (≥2 days from the date of admission to the date of operation). Our primary outcome was the THLOS. We created multivariate regression models to assess for the association of early versus delayed operation and THLOS.
RESULTS:	The THLOS was found to be 2.94 days longer in the delayed group compared with the early group ($p < 0.05$). In those who did not present with sepsis on admission, the THLOS was noted to be 4.71 days longer in the delayed group compared with the early group ($p < 0.05$). Early versus delayed operation was not associated with a difference in the postoperative length of stay, 30-day postoperative complications, rate of readmission, and reoperation, regardless of preoperative sepsis status.
CONCLUSION:	Early laparoscopic cholecystectomy for gallbladder perforation is associated with decreased THLOS, and there were no other differences in outcomes compared with delayed laparoscopic cholecystectomy. Patients with gallbladder perforation would likely benefit from an early operation within 2 days of admission. (*J Trauma Acute Care Surg.* 2025;98: 642–648. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)
LEVEL OF EVIDENCE:	Therapeutic/Care management; Level IV.
KEY WORDS:	Perforated cholecystitis; gallbladder perforation; cholecystitis; laparoscopic cholecystectomy.

Gallbladder disease affects approximately 20 million people in the United States. Of those who are estimated to have cholelithiasis, approximately 20% will eventually develop gallstone-related complications.[1] In acute cholecystitis, the progression of inflammation may lead to ischemia and necrosis, resulting in gallbladder perforation in 2% to 11% of patients.[2,3] The mortality associated with gallbladder perforation is estimated to be 12% to 42%, making it one of the most severe complications of cholecystitis.[4] The current guidelines recommend early cholecystectomy for acute cholecystitis based on findings from multiple randomized control trials, observational studies, and systematic reviews.[5–8] However, there is lack of evidence to suggest whether early or delayed cholecystectomy is superior in the treatment of perforated cholecystitis.[7] Given that gallbladder perforation is the most severe complication of cholecystitis, it is critical to understand the optimal timing for a definitive operation.

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Because of the low incidence of perforated cholecystitis, the data on its management remain sparse and consist primarily of case studies, case series, and single-centered studies. While some studies have found that an early operation for perforated cholecystitis is associated with decreased postoperative complications,[9] others showed decreased mortality, postoperative complications, and rate of prolonged hospitalization with delayed cholecystectomy.[10,11] A recent systematic review found no difference in complications or need for further interventions between groups that underwent early versus delayed cholecystectomy.[12] Existing studies suggest that there is a wide variety of practice patterns for perforated cholecystitis, ranging from treatment with early cholecystectomy during the index hospitalization,[13–16] percutaneous gallbladder drainage,[10,17] or antibiotics and interval cholecystectomy at a later date.[18,19]

In this study, we sought to use the National Surgical Quality Improvement Program (NSQIP) database from the American College of Surgery (ACS) to compare the outcomes associated with laparoscopic cholecystectomy for gallbladder perforation. We hypothesize that an early definitive operation is associated with decreased total hospital length of stay (THLOS), postoperative complications, rate of readmission, and rate of reoperation.

PATIENTS AND METHODS

Study Population

The ACS NSQIP database, which contains risk-adjusted 30-day surgical outcomes from more than 600 hospitals was

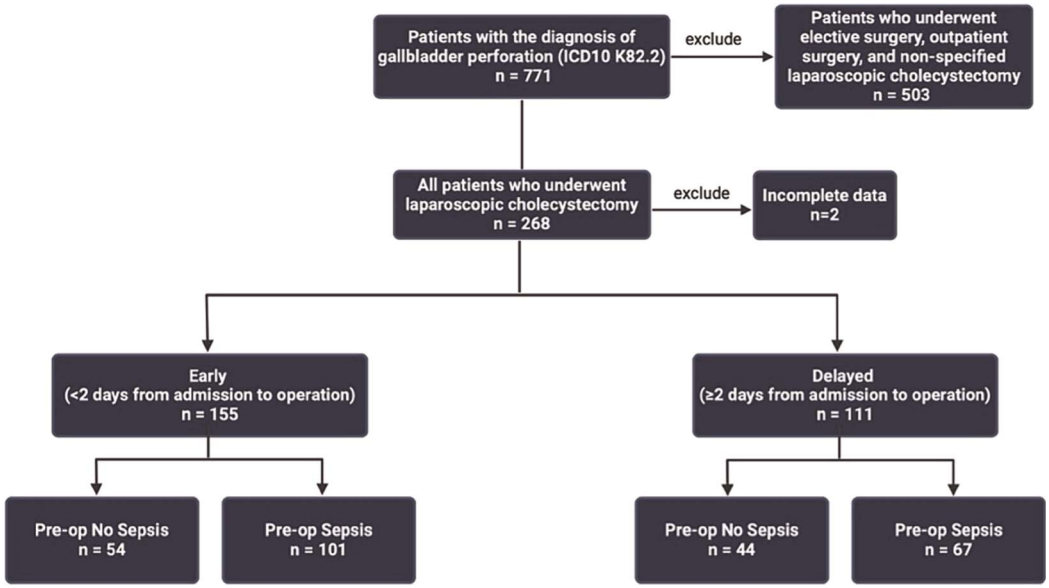

Figure 1. Flow diagram of patients with the diagnosis of gallbladder perforation using ICD10 code of K82.2 from the ACS NSQIP database from 2012 to 2021.

used for this cohort study according to STROBE guidelines (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/E103). The participant user file of this database is a Health Insurance Portability and Accountability Act of 1996 compliant deidentified data file.[20] Therefore, our study was deemed exempt from review from our institutional review board. Patients with a primary diagnosis of gallbladder perforation (ICD.10 code of K82.2) who underwent laparoscopic cholecystectomy on an urgent or emergent basis from 2012 to 2021 were included in this study (Fig. 1). Those who underwent outpatient and elective surgeries were excluded from this study, as patients presenting with perforated cholecystitis typically do so in an emergent or urgent setting. Those with nonspecified "cholecystectomy" as their primary procedure were also excluded from the study, as this Current Procedural Terminology code was not sufficient in differentiating primary laparoscopic cholecystectomy from primary open cholecystectomy. Therefore, since the most common management for gallbladder disease is laparoscopic surgery, we limited our study population to only those who underwent primary laparoscopic cholecystectomy to avoid inconsistencies in coding and confounding our primary outcome of THLOS. We did not specifically examine the outcomes associated with nonoperative management of gallbladder perforation in this study, as this patient population could not be clearly identified within the ACS NSQIP database.

Data Collection

The primary outcome was the THLOS. Secondary outcomes included 30-day postoperative complications, reoperation, and readmission. We divided the patients into two groups —early and delayed laparoscopic cholecystectomy. The early group consisted of those who underwent an operation <2 days from the date of admission to the date of operation, and the delayed group consisted of those who underwent an operation ≥2 days from the date of admission to the date of operation. We chose 2 days as a cutoff for the early versus delayed group because, based on our experience, urgent surgeries are usually completed within 24 hours of admission. However, at institutions with limited resources, such as ours, delays can occur. We aimed to capture those who elected to operate urgently versus those who elected to wait with this cutoff.

Statistical Analysis

We performed Student's *t* tests and χ^2 tests to compare the patient demographics between the early and delayed groups. We performed Mann-Whitney rank-sum test to compare the medians of THLOS, postoperative length of stay, operative times, and 30-day postoperative complications. We then created multiple linear regression models with THLOS and total number of 30-day postoperative complications as dependent variables. Multiple logistical regression models were used to examine the odds ratio of reoperation and readmission. We adjusted for preoperative sepsis status and preoperative estimated probability of morbidity and mortality in these regression models. Because the preoperative risk of morbidity and mortality was calculated based on each preoperative comorbidity, we did not include them individually again in our regression analyses. We then stratified the patients based on their sepsis status on presentation and repeated the aforementioned analyses. Preoperative estimated probability of morbidity and mortality was determined by the ACS based on a logistical regression analysis using the patient's preoperative characteristics as the independent or predictive variables. p values of <0.05 were considered statistically significant. All tests were performed using R version 4.3.0 (R Core Team 2023, Vienna, Austria) and GraphPad Prism version 10.1.1 (GraphPad Software, LLC 2023, La Jolla, CA).

RESULTS

Study Population Demographics

We identified a total of 771 patients with the diagnosis of gallbladder perforation, of which 268 patients underwent an

urgent or emergent laparoscopic cholecystectomy as inpatients (34.76%). Two patients were excluded because of incomplete data. One hundred fifty-five patients underwent an early operation (58.27%), while 111 patients underwent a delayed operation (41.73%) (Fig. 1). Most cholecystectomies in the delayed group were performed within 10 days of admission. The remainders were outliers. Table 1 demonstrates the demographics of the patients included in the study. There were no statistically significant differences in age in quantiles or sex of the patients between the early and the delayed groups. However, the estimated probabilities of morbidity and mortality, calculated based on the ACS logistical regression analyses, were significantly higher in the delayed group compared with the early group ($p = 0.02$ and $p = 0.03$, respectively). The body mass index could not be reliably calculated because of significant amounts of missing data.

Univariate Analyses of Early Versus Delayed Groups

The median THLOS was 4 days in the early group compared with 7 days in the delayed group ($p < 0.05$, Table 2). The median postoperative length of stay was 3 days for the early group, compared with 4 days in the delayed group. The median operative times were 97 minutes and 99 minutes in the early and

TABLE 1. Demographics of Patients Who Underwent Early Versus Delayed Cholecystectomy for Gallbladder Perforation Demonstrated as Means With Standard Deviation Where Applicable

	Total (N = 266)	Early (n = 155)	Delayed (n = 111)	*p*
Age, n (%)				0.21
21–56	72 (27.07)	47 (17.67)	25 (9.40)	
57–78	136 (51.13)	79 (29.70)	57 (21.43)	
>79	58 (21.80)	29 (10.90)	29 (10.90)	
Sex, n (%)				0.65
Female	87 (32.71)	49 (18.42)	38 (14.29)	
Male	179 (67.29)	106 (39.85)	73 (27.44)	
Estimated probabilities*				
Morbidity, mean ± SD, %	**6.73 ± 4.20**	**6.22 ± 3.71**	**7.44 ± 4.73**	**<0.05**
Mortality, mean ± SD, %	**2.37 ± 4.24**	**1.90 ± 3.75**	**3.01 ± 4.79**	**<0.05**
Comorbidities				
Diabetes	71 (26.69)	43 (27.74)	28 (25.23)	0.65
Smoke	36 (13.53)	25 (16.13)	11 (9.91)	0.14
Functional partial or total dependence	**15 (5.64)**	**5 (3.23)**	**10 (9.01)**	**<0.05**
Ventilator dependence	2 (0.75)	1 (0.65)	1 (0.90)	0.81
COPD	12 (4.51)	7 (4.52)	5 (4.50)	1.00
Ascites	4 (1.50)	1 (0.65)	3 (2.70)	0.17
CHF	5 (1.88)	1 (0.65)	4 (3.60)	0.08
Hypertension requiring medications	150 (56.39)	83 (53.55)	67 (60.36)	0.27
Dialysis	4 (1.50)	1 (0.65)	3 (2.70)	0.17
Disseminated cancer	**6 (2.26)**	**1 (0.65)**	**5 (4.50)**	**<0.05**
Steroid use	**13 (4.89)**	**4 (2.58)**	**9 (8.11)**	**<0.05**
Bleeding disorders	**23 (8.65)**	**8 (5.16)**	**15 (13.51)**	**<0.05**
Preoperative transfusion	**6 (2.26)**	**1 (0.65)**	**5 (4.50)**	**<0.05**
Race, n (%)				0.09
American Indian or Alaska Native	2 (0.75)	2 (0.75)	0 (0)	
Asian	11 (4.14)	3 (1.13)	8 (3.01)	
Black or African American	18 (6.77)	14 (5.26)	4 (1.50)	
Unknown	88 (33.08)	50 (18.80)	38 (14.29)	
White	146 (54.89)	85 (31.95)	61 (22.93)	
Other	1 (0.38)	1 (0.38)	0 (0)	
Ethnicity				0.29
Hispanic	34 (12.78)	16 (6.02)	18 (6.77)	
Not Hispanic	146 (54.89)	85 (31.95)	61 (22.93)	
Unknown	86 (32.33)	54 (20.30)	32 (12.03)	

Statistically significant values in bold.

*Estimated probabilities of morbidity and mortality were determined by the ACS based on a logistical regression analysis using the patient's preoperative characteristics as the independent or predictive variables.

COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

TABLE 2. Outcomes of Patients Who Underwent Early Versus Delayed Cholecystectomy for Gallbladder Perforation Demonstrated as Median and Interquartile Range

	Total (N = 266)	Early (n = 155)	Delayed (n = 111)	*p*
THLOS, median (IQR), d	**5 (3–9)**	**4 (3–7)**	**7 (5–12)**	**<0.05**
Postoperative length of stay, median (IQR), d	3 (2–6.25)	3 (2–6)	4 (2–7)	0.32
Operative time, median (IQR), min	99 (76–126)	97 (75–127)	99 (77–126)	0.76
30-d Postoperative complications, median (IQR)	0 (0–1)	0 (0–1)	0 (1–1)	0.68

IQR, interquartile range.

the delayed groups, respectively. The median number of 30-day postoperative complications was zero in both the early and the delayed groups. When analyzed with the Mann-Whitney rank-sum test, there were no statistically significant differences in the postoperative length of stay, operative times, and 30-day postoperative complications between the early and the delayed groups ($p = 0.32$, $p = 0.76$, and $p = 0.68$, respectively). However, the THLOS was significantly longer in the delayed group compared with the early group ($p < 0.05$).

Multivariate Regression Analyses of Early Versus Delayed Groups

To address the significant differences between the estimated preoperative probabilities of morbidity and mortality between the early and the delayed groups, we created regression models with these variables, as well as preoperative sepsis status as independent predictors. As shown in Table 3, the THLOS was found to be 2.94 days longer in the delayed group compared with the early group ($p < 0.05$). When stratified for preoperative sepsis status, this difference was no longer observed in those who presented with sepsis on admission ($p = 0.06$). However, in those who did not present with sepsis on admission, the THLOS was noted to be 4.71 days longer in the delayed group compared with the early group ($p < 0.05$) (Table 3, Fig. 2*A*). Early versus delayed operation was not associated with a difference in the postoperative length of stay ($p = 0.69$). When stratified for preoperative sepsis status, there was no significant association between early versus delayed operation and the postoperative length of stay in those who presented with sepsis preoperatively ($p = 0.12$) and those who did not ($p = 0.36$) (Table 3, Fig. 2*B*). Finally, there was no association between early versus delayed operation and the number of postoperative complications ($p = 0.20$). When stratified for preoperative sepsis status, no significant association was observed between early versus delayed operation and the number of postoperative complications in those who presented with sepsis preoperatively ($p = 0.20$) and those who did not ($p = 0.59$) (Table 3, Fig. 2*C*). There was no significant association between early versus delayed operation and the rate of readmission when we examined the entire study population ($p = 0.28$), in those who presented with sepsis preoperatively ($p = 0.08$), and in those who did not ($p = 0.58$) (Table 4, Fig. 3*A*). Similarly, there was no significant association between early versus delayed operation and the rate of reoperation when we examined the entire study population ($p = 0.09$), in those who presented with sepsis preoperatively ($p = 0.08$), and in those who did not present with sepsis preoperatively ($p = 0.76$) (Table 4, Fig. 3*B*).

DISCUSSION

Using the ACS NSQIP database, we found that, in patients who presented with gallbladder perforation, the THLOS was significantly shorter in those who underwent an early operation compared with those who underwent a delayed operation, although this difference was not seen in the group who presented with sepsis on admission. There were no significant differences in the postoperative length of stay, 30-day postoperative complications, rate of readmission, or reoperation between the two groups. These findings were consistent for patients who presented with sepsis on admission and those who did not. These results suggest that there are no benefits to delaying cholecystectomy for the treatment of gallbladder perforation.

It is important to note that Krecko et al.[11] also used the ACS NSQIP database to compare outcomes between those who underwent index versus interval cholecystectomy for the diagnosis of gallbladder perforation. They found that those who underwent cholecystectomy during their index hospitalization had longer postoperative hospital lengths of stay and higher 30-day major morbidity and mortality. Whereas the findings

TABLE 3. β Estimates From Multivariable Linear Regression Models Predicting the Difference in THLOS, Postoperative Length of Stay, and Total Number of 30-Day Complications in the Group That Underwent Early Cholecystectomy Versus Delayed Cholecystectomy for Gallbladder Perforation

	β Estimates/Odds Ratio (95% CI)	*p*
THLOS		
All	**2.94 (1.44–4.44)**	**<0.05**
Sepsis	1.60 (−0.08 to 3.28)	0.06
No sepsis	**4.71 (2.07–7.34)**	**<0.05**
Postoperative length of stay		
All	−0.26 (−1.52 to 1.01)	0.69
Sepsis	−1.21 (−2.74 to 0.32)	0.12
No sepsis	0.9474 (−1.09 to 2.98)	0.36
30-d Postoperative complications		
All	−0.15 (−0.39 to 0.08)	0.20
Sepsis	−0.18 (−0.48 to 0.11)	0.22
No sepsis	−0.11 (−0.49 to 0.28)	0.59

Statistically significant values in bold.
CI, confidence interval.

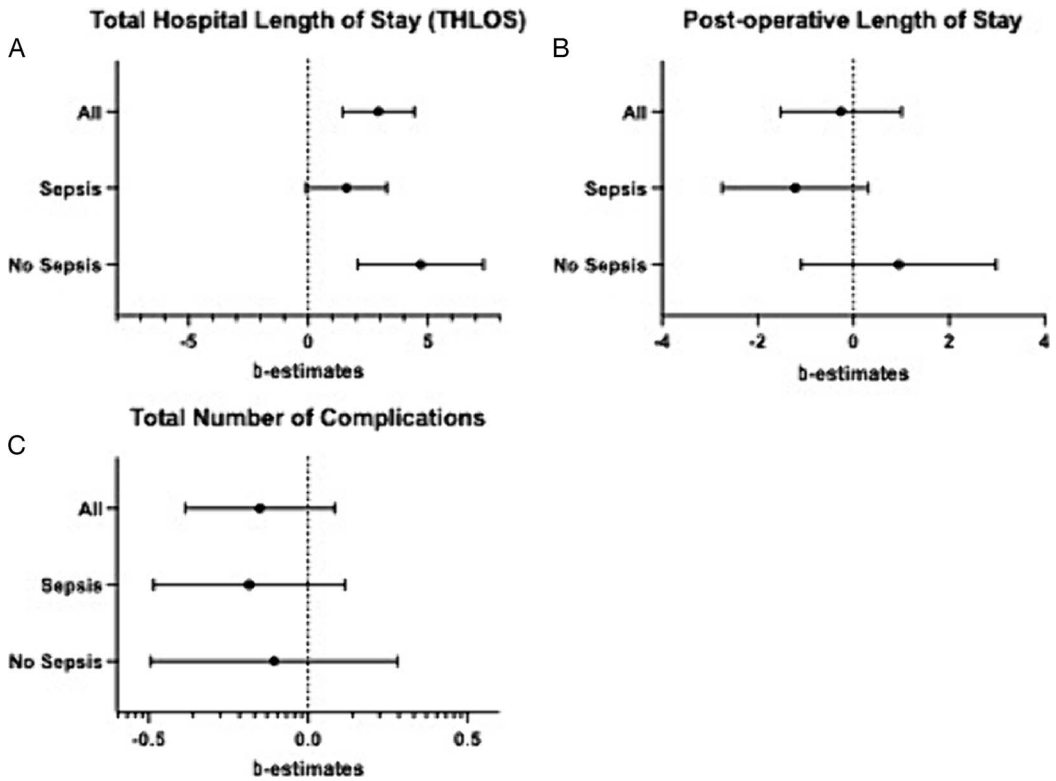

Figure 2. Forest plot of regression models created to evaluate associations between early versus delayed cholecystectomy in (*A*) THLOS, (*B*) postoperative length of stay, and (*C*) total number of 30-day complications. Bars that cross odds ratio of 1 are not statistically significant.

from our study suggest that there is no difference in these outcomes between patients who underwent an early versus delayed cholecystectomy. However, the NSQIP database does not directly indicate whether patients underwent an interval cholecystectomy for perforated gallbladder during a separate admission. Krecko et al.[11] inferred that patients underwent interval operations based on the absence of preoperative sepsis, surgeries classified as nonemergent, and surgeries performed on the initial day of hospitalization. While information on the outcomes associated with interval cholecystectomy would provide guidance for the management of perforated cholecystitis, it is not possible to confirm if patients in the interval group did undergo interval cholecystectomy based on these inferences by Krecko et al. Furthermore, Krecko et al.[11] did not stratify patients who underwent laparoscopic versus open cholecystectomy or specify whether the patients who underwent an interval cholecystectomy received a cholecystostomy tube prior. A prospective study is therefore needed to truly identify patients who underwent early, delayed, or interval cholecystectomy for perforated gallbladder.

The current literature suggests that there is a variety of practices for the management of gallbladder perforation. Gupta et al.[19] described a "step up" approach with initial management consisting of fluid resuscitation and IV antibiotics, followed by percutaneous drainage, biliary drainage if necessary, or surgery. Of the 151 patients in their single-center retrospective study, 106 patients underwent definitive operative management at an average of 57 days after their initial diagnosis.[19] Conversely, Ausania et al.[13] described 137 patients with gallbladder perforation at their institution who all underwent emergency cholecystectomy, with the median number of days from admission to surgery being 1.4. The use of percutaneous transhepatic gallbladder drainage as a temporizing measure and, in some cases, as the definitive treatment has also been described by Huang et al.[10] Our study confirms that there is indeed heterogeneity in the timing of operation for the treatment of gallbladder perforation, with the number of days between admission to operation ranging from 0 to 110 days.

Because of the low prevalence of the disease, most of the existing studies on gallbladder perforation remain single-center retrospective analyses with small sample sizes. Derici et al.,[2]

TABLE 4. Odds Ratio From Multivariable Logistical Regression Models Predicting the Difference in Likelihood of Readmission and Return to the Operating Room in the Group That Underwent Early Cholecystectomy Versus Delayed Cholecystectomy for Gallbladder Perforation

	Odds Ratio (95% CI)	*p*
Readmission		
All	1.79 (0.63–5.26)	0.28
Sepsis	3.59 (0.93–17.59)	0.08
No sepsis	0.61 (0.08–3.34)	0.58
Return to OR		
All	2.99 (0.88–11.76)	0.09
Sepsis	3.59 (0.93–17.59)	0.08
No sepsis	1.55 (0.06–40.60)	0.76

CI, confidence interval.

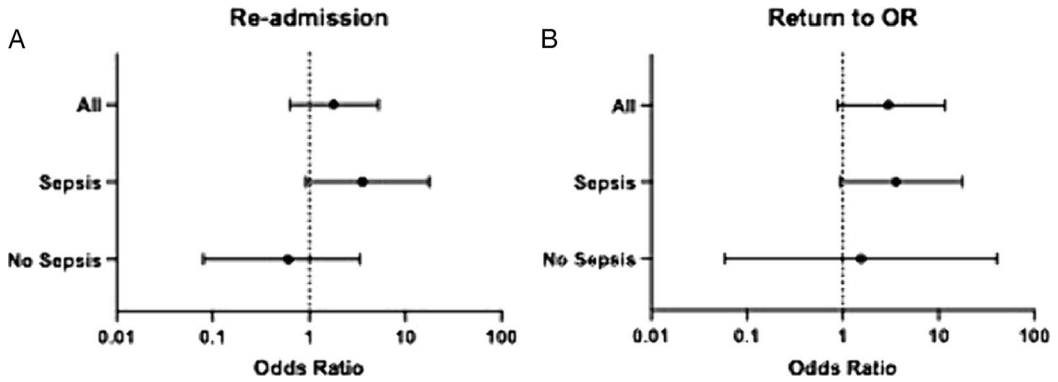

Figure 3. Forest plot of regression models created to evaluate associations between early versus delayed cholecystectomy in (*A*) rate of readmission and (*B*) rate of return to the operating room. Bars that cross odds ratio of 1 are not statistically significant.

Jansen et al.,[3] Gunasekaran et al.,[18] and Rajput et al.[21] all reported on their centers' experiences, with sample sizes of 16, 40, 50, and 32, respectively. None of the aforementioned studies specifically examined the outcomes associated with early compared with delayed cholecystectomy. Furthermore, many of these studies included open cholecystectomy and exploratory laparotomy as the operation of choice in the management of perforated cholecystitis. This serves as a major confounder when examining outcomes, such as the THLOS, as well as 30-day postoperative complications. Our study not only examined a study population based on a large national database but also it specifically examined the outcomes associated with laparoscopic treatment for gallbladder perforation.

The fundus of the gallbladder, which is the most distal portion from its blood supply, has been found to be the most common location of perforation.[2] Therefore, it is possible that perforation per se, especially acutely, may not affect the dissection of the cystic triangle. We speculate that the lack of differences in the postoperative length of stay, postoperative complications, readmission, and reoperation between the early and the delayed groups may be due to the location of the gallbladder perforation and its effects on the critical portion of the dissection. This may explain the lack of significant difference in operative times as well.

The estimated preoperative probability of mortality, calculated based on logistical regression analyses using the patient's preoperative characteristics as predictor variables, was found to be different between the early and delayed groups. Patients with more severe comorbidities, hence higher estimated preoperative risk of mortality, may require more time between admission and operation for suspension of anticoagulation and correction of coagulopathy. This can be seen in the significant differences in preoperative bleeding disorder and requirement of preoperative transfusions between the early and delayed groups. Furthermore, the delayed group could include patients who were diagnosed with gallbladder perforation during their admission for another medical condition; the estimated preoperative probability of mortality may be elevated because of their state of acute illness. We speculate that a surgeon's hesitance to operate on a high-risk patient could also contribute to the delay. For example, one may delay an operation until forced to because of a patient's hemodynamically instability and need for source control.

Our study has several limitations. First, we identified patients who presented with gallbladder perforation by searching for the postoperative diagnosis of gallbladder perforation, with ICD10 code of K82.2. By doing so, we assumed that patients who experienced iatrogenic perforations, which occur regularly, were not included in this group. The postoperative diagnosis does not make the distinction between those who were diagnosed with gallbladder perforation preoperatively and those who were diagnosed intraoperatively. Therefore, the decision to go to the operating room within 2 days of admission or to wait greater than 2 days may not have been based on the diagnosis of gallbladder perforation, rather than logistical reasons, such as surgeon and operative room availability. Second, the NSQIP database does not distinguish between those patients who underwent cholecystectomy on the index admission, during which they were diagnosed with gallbladder perforation, and those who underwent cholecystectomy on an interval admission after they were first diagnosed with gallbladder perforation. Along the same lines, we were not able to gather information on the treatment of this group of patients during their index admission, such as antibiotic choice and duration, as well as cholecystostomy tube placement or endoscopic retrograde cholangiopancreatography. Third, because endoscopic retrograde cholangiopancreatography or percutaneous drain placement is often procedures performed by gastroenterologists and interventional radiologists, respectively, the NSQIP database did not provide reliable information on the rate of these procedures performed postoperatively. Fourth, we excluded patients who were categorized as outpatient and those who underwent elective surgeries. We based this on the assumption that patients with perforated cholecystitis typically present to the emergency room, rather than for surgery on a scheduled or outpatient basis. Moreover, only patients with the principal treatment specified as laparoscopic were included in the study. Patients with principal treatment and/or additional procedures not specified as laparoscopic were excluded from the study. While conversion from laparoscopic cholecystectomy to open cholecystectomy is an important outcome worth examining, the ACS NSQIP database does not offer sufficient information to separate laparoscopic converted to open cholecystectomy from primary open cholecystectomy. Furthermore, patients with primary procedures not specified as laparoscopic often also underwent additional procedures such as hepatectomy, colectomy, repair of abdominal wall hernia, and

enteroenterostomy. To include these patients in our study sample would greatly confound our primary outcome. As a result, only 34.76% of patients with the diagnosis of gallbladder perforation were included in the study. Lastly, because of the lack of Current Procedural Terminology code for subtotal cholecystectomy, we were not able to examine the specific surgical techniques used in treating perforated cholecystitis.

CONCLUSION

Early laparoscopic cholecystectomy for gallbladder perforation is associated with a decreased THLOS compared with delayed laparoscopic cholecystectomy. The postoperative length of stay, 30-day postoperative complication, readmission, and reoperation rates showed no difference between groups. Considering a shorter THLOS, we recommend that patients with gallbladder perforation would benefit from an early operation, within 2 days of admission.

Future directions will focus on comparing outcomes associated with early, delayed, and interval cholecystectomy with cholecystostomy tube placement with data from multiple institutions. In addition, it may be beneficial to examine the common surgical techniques used in the management of gallbladder perforation, such as laparoscopic subtotal cholecystectomy or open cholecystectomy, and to compare their respective outcomes.

AUTHORSHIP

R.W. contributed in the literature search, study design, data collection, data analysis, data interpretation, and writing. R.D. contributed in the critical revision. V.N. contributed in the study design, data interpretation, writing, and critical revision.

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DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E104).
Disclaimer: 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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