

Original Investigation

Optimal Time for Early Laparoscopic Cholecystectomy for Acute Cholecystitis

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IMPORTANCE There is growing evidence in support of performing early laparoscopic cholecystectomy (LC) for acute cholecystitis. However, the definition of *early* LC varies from 0 through 10 days depending on the research protocol. The optimum time to perform early LC is still unclear.

OBJECTIVES To determine whether outcomes after early LC for acute cholecystitis vary depending on time from presentation to surgery and to determine the optimum time to perform LC for acute cholecystitis.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective review of prospectively collected data from the Nationwide Inpatient Sample (NIS) for 2005 through 2009. The population-based sample included 95 523 adults (18 years and older) who underwent LC within 10 days of presentation for acute cholecystitis.


INTERVENTIONS Patients were categorized and analyzed in 2 ways based on length of time from presentation to surgery. First, patients were categorized into 3 groups: 0 through 1 day, 2 through 5 days, and 6 through 10 days. Second, we compared outcomes for each incremental preoperative day (days 0-5).


MAIN OUTCOMES AND MEASURES Outcomes of interest were mortality, length of stay, complications, and cost. Propensity score matching and generalized linear modeling were used. The hypothesis being tested was formulated after data collection was complete.

RESULTS A total of 95 523 patients were selected. After matching the 3 groups based on propensity scores, patients who underwent surgery during days 2 through 5 and days 6 through 10 had increasingly worse outcomes when compared with those undergoing surgery on days 0 through 1. The odds of mortality were 1.26 (95% CI, 1.00-1.58) and 1.93 (95% CI, 1.38-2.68), and the odds of postoperative infections were 0.88 (95% CI, 0.69-1.12) and 1.53 (95% CI, 1.05-2.23) for days 2 through 5 and days 6 through 10, respectively. Adjusted mean hospital cost increased from \$8974 (days 0-1) to \$17 745 (days 6-10). Analysis by each incremental day revealed the optimal time of surgery to be within the first 48 hours of presentation.

CONCLUSIONS AND RELEVANCE Laparoscopic cholecystectomy performed within 2 days of presentation of acute cholecystitis yielded the best outcomes and lowest costs. Although causality could not be established, delaying LC was associated with more complications, higher mortality, and higher costs.

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There is growing evidence in support of early laparoscopic cholecystectomy (LC) for acute cholecystitis.¹⁻⁴ Traditionally, acute cholecystitis has been treated conservatively in the acute phase, with readmission several weeks later for delayed LC. The thought is to allow the initial inflammatory process to subside before surgery and that surgery on inflamed tissue may lead to more complications. However, many studies⁵⁻⁸ have failed to support this notion.

Multiple randomized clinical trials report that early LC is safe, with no difference in complications or mortality when compared with delayed LC.⁵⁻⁸ All studies⁵⁻⁸ found a significant advantage of early LC in reducing hospital stay and lowering cost. One study⁸ even found a lower rate of morbidity with early LC. However, in all these studies, the definition of *early* LC varies significantly, ranging from LC performed within 24 hours to LC performed up to 10 days from presentation. The optimum time for early LC for acute cholecystitis remains elusive.

Studying infrequent outcomes within short intervals requires a large sample size. Laparoscopic cholecystectomy is a relatively safe procedure with low morbidity and mortality, and a meta-analysis⁵ revealed that many studies are underpowered to examine serious outcomes. Multicenter trials with thousands of patients could provide definitive answers but may not be feasible. In lieu, comparative effectiveness research using large administrative databases may provide important insights. A published analysis² of a large database from the Swiss Association of Laparoscopic and Thoracoscopic Surgery found that LC performed within 48 hours was associated with the least amount of complications. However, a major criticism of this study was that patients in whom LC was delayed may have been sicker at presentation, which was not adequately controlled for in the analysis. A similar study⁹ that used data from the National Surgical Quality Improvement Program in the United States found no differences in postoperative morbidity for LC performed within a week of presentation. However, in this analysis, all comparisons were made between procedures performed on day 0 vs other days and not among each other. Therefore, the optimal time for intervention was not clearly established. Furthermore, this study did not examine differences in cost.

Our objective was to use the Nationwide Inpatient Sample (NIS) to perform robust comparative effectiveness research analysis to determine the optimum time for early LC. Use of the NIS provides the benefits of a nationally representative data set with enough power to enable adequate risk adjustment and cost analysis.

Methods

We analyzed the NIS admission years 2005 through 2009. The NIS is the largest all-payer inpatient database.¹⁰ It contains demographic, clinical, and outcome information on a nationally representative sample of hospitals within the United States. Informed consent and institutional review board approval were not required for our analysis. We selected adult patients (18 years and older) who underwent LC (*International Classifica-*

tion of Diseases, Ninth Revision [ICD-9], procedure code 51.23), who had a primary diagnosis of acute cholecystitis (*ICD-9* diagnosis codes 575.0, 575.1, 574.3, and 574.0) and who required urgent admission. Patients were excluded if their LC was performed more than 10 days after admission.

Patients were then categorized into 3 groups depending on the number of days from admission to LC. The first group consisted of patients who had their operation performed on days 0 through 1 of presentation, the second group had their operation performed on days 2 through 5 after presentation, and the third group had their operation performed on days 6 through 10 after presentation. The cutoffs for these groups were decided a priori to the analysis after consensus among the authors. They were arbitrarily chosen to reflect clinically relevant cutoff values. The 0- to 1-day group reflects patients taken to the operating room without any delay. The 2- to 5-day group reflects patients among whom delays commonly occur because of logistical reasons, and the 5- to 10-day group consists of patients further delayed possibly because of severity of disease or comorbidities.

We analyzed frequencies and percentages for demographic- and hospital-level characteristics for each group of patients and tested for differences using the χ^2 test. Outcomes of interest were mortality, length of stay, common bile duct injury, conversion to open surgery, cost, and postoperative complications, including pneumonia, urinary tract infection, and surgical site infections. Bile duct injuries were identified by *ICD-9* procedure codes for bile duct repair (*ICD-9* codes 51.36, 51.37, 51.39, 51.71, 51.72, and 51.79). Conversion from laparoscopic to open surgery was identified by the *ICD-9* code V64.41.

With the understanding that several factors (such as severity of illness) may contribute to delayed LC, we used the propensity score technique to control for these factors.¹¹ To derive propensity scores, we conducted a multinomial logistic regression, with time to LC (categorized into 3 groups as described above) as the dependent variable, adjusting for age, comorbidities (using the Charlson Comorbidity Index¹²), and risk of mortality (as a proxy for severity of illness). Equal weights were applied to each of these factors. The variable for risk of mortality, one of the clinically based severity measurement indexes, is contained in the NIS disease severity subfile and is categorized as minor, moderate, major, and extreme likelihood of death.¹³ The All Patient Refined Diagnosis Related Group is calculated by a health informatics company. It is a grading system in which each patient is assigned a disease severity and mortality risk. Calculations are based on clinical logic that uses disease diagnoses, age, comorbidities, procedures, and other clinically relevant variables.¹⁴

The propensity scores derived from the multinomial logistic regression analysis were further categorized into quintiles. We then used multivariate logistic regression analyses to test for differences in the defined outcomes among the 3 groups. The models were adjusted for demographic differences, including sex, race/ethnicity, primary payer, year of admission, income quartile of patient's residential zip code, and hospital-level characteristics, such as bed size, teaching status, location (rural vs urban), type (government vs private), and propensity score quintiles.

Generalized linear models, with log link (to better achieve linearity through log transformation) and gamma family (given the gamma distribution of the cost data), were used to estimate the adjusted mean costs for the comparison groups. The individual cost of hospitalization was calculated as a product of total charge and hospital-specific cost-charge ratio. Hospital-specific cost-charge ratios are developed using standardized hospital information on all-payer inpatient cost and charge reported by hospitals to the Centers for Medicare & Medicaid Services. By using appropriate Consumer Price Indexes, costs in prior years (2005-2008) were adjusted for inflation and converted to 2009 US dollars. The area wage index was used to control for the influence of local markets on prices. The area wage index is computed by the Centers for Medicare & Medicaid Services to measure relative hospital wage levels by geographic area compared with the national mean.

Given the Poisson distribution of postoperative length-of-stay data, a generalized linear model (with log link and Poisson family) was used to compare adjusted mean postoperative length of stay among the 3 groups. The length-of-stay and cost models were adjusted for complications in addition to the aforementioned variables.

To further delineate the optimum time for LC, we performed 6 separate analyses that dichotomized the data set by days to surgery. Comparisons were made between day 0 vs days 1 through 10, days 0 through 1 vs days 2 through 10, days 0 through 2 vs days 3 through 10, and so on.

Each of these analyses consisted of a 4-step process. First, we performed propensity score matching analysis using multivariable logistic regression to balance the 2 comparison groups on age, comorbidities, and severity of disease and risk of mortality as described above. Second, we performed separate multivariable logistic regression analyses for each outcome variable while adjusting for propensity scores and other covariates. Third, the models were adjusted for sex, race/ethnicity, primary payer, year of admission, income quartile of patient's residential zip code, bed size, teaching status, location (rural vs urban), type (government vs private), and propensity score quintiles. Fourth, we derived adjusted mean cost differences between the 2 comparison groups for each of the day cutoffs using the same methods as described previously.

In addition, we calculated risk-adjusted outcome ratios for each day of surgery. Using the above-mentioned regression model, we predicted the occurrence of the outcome of interest in each patient. This prediction was then used to determine the observed-expected outcome ratio for each day of surgery. Finally, this ratio was multiplied by the mean outcome proportion to determine risk-adjusted outcome ratios for each day. We also derived adjusted mean cost and length-of-stay differences between the 2 comparison groups for each of the day cutoffs using the same methods as described previously.

For all analyses, discharge-level weights were applied to account for the NIS sampling design and provide for nationally representative estimates. All statistical analyses were performed using STATA software, version 12 (StataCorp).

Results

Of the approximately 5 million patient records in the NIS, 217 932 adults had a primary diagnosis of acute cholecystitis. A total of 193 974 patients (89.0%) were admitted through the emergency department. Of these, 130 189 (67.1%) underwent an LC during the same hospital admission, and 95 523 patients (43.8%) had the operation performed within 10 days of presentation and were included in the analysis.

Most LCs ($n = 61\,576$ [64.5%]) were performed within days 0 through 1 of presentation, whereas 30 838 LCs (32.3%) were performed within days 2 through 5 and 3109 (3.3%) within days 6 through 10 of presentation. **Table 1** compares demographic and hospital characteristics among these 3 groups. Patients in the days 0 through 1 group were younger, more likely to be men of white race, and had fewer comorbidities. These patients were more likely to have private insurance and belong to the high-income quartile. They were also less likely to be at large teaching hospitals.

Table 2 gives the outcome proportions among the 3 groups. Almost all outcomes (conversions, complications, and mortality) increased as days to procedure increased. **Table 3** gives the results of the multivariate analyses after propensity score matching on disease severity for each outcome. Compared with operations performed within days 0 through 1, LCs performed later were associated with a higher likelihood of urinary tract infections, pneumonia, surgical site infections, postoperative length of stay, and hospital costs. The overall mortality rate was 0.41%, and the overall rate of complications was 6.9%.

When each day was analyzed separately (**Figure 1**), patients who underwent LCs within days 0 through 2 had the lowest mortality rates. Also noted was a sudden increase in mortality from 0.37% to 0.45% at day 3 ($P < .001$). Risk-adjusted complication rates were lowest (6.4%) when the procedure was performed during the day of presentation (day 0) and steadily increased (to 8.1%) as days to the procedure increased ($P < .001$) (**Figure 2**). An inflection point in the complications curve was noticed after day 3. Because the numbers for bile duct injury and conversions to open surgery were significantly lower than expected, to avoid bias, these factors were removed from the overall complications model. However, a separate sensitivity analysis that included these was performed, and similar results were obtained.

Risk-adjusted mean hospital costs increased almost linearly from \$8974 (days 0-1) to \$17 745 (days 6-10) as days to procedure increased (**Figure 3**). No difference was found in the risk-adjusted postoperative length of hospital stay by days to procedure (**Figure 4**).

Discussion

Our study found that LC performed within 2 days of presentation for acute cholecystitis is not only safe but also associated with better outcomes. To our knowledge, this is the largest population-based analysis of studies on outcome

Table 1. Comparison of Demographic and Hospital Characteristics of Patients by Days From Presentation to Procedure^a

Characteristic	0-1 Day (n = 61 576)	2-5 Days (n = 30 838)	6-10 Days (n = 3109)	P Value
Age, mean (SD), y	48.5 (18.4)	55.2 (19.9)	62.9 (18.8)	<.001
Age group, y				
<25	5323 (8.6)	1928 (6.3)	96 (3.1)	<.001
25-39	16 396 (26.6)	5667 (18.4)	321 (10.3)	
40-59	21 801 (35.4)	9343 (30.3)	768 (24.7)	
60-79	14 319 (23.3)	9978 (32.4)	1237 (39.8)	
≥80	3737 (6.1)	3922 (12.7)	687 (22.1)	
Sex				
Male	21 713 (35.3)	12 054 (39.1)	1365 (43.9)	<.001
Female	39 863 (64.7)	18 784 (60.9)	1744 (56.1)	
Race/ethnicity				
White	35 379 (57.5)	17 382 (56.4)	1703 (54.8)	<.001
Black	3892 (6.3)	2658 (8.6)	383 (12.3)	
Hispanic	10 681 (17.4)	5518 (17.9)	499 (16.1)	
Other	3589 (5.8)	1822 (5.9)	196 (6.3)	
Unknown	8062 (13.1)	3458 (11.2)	328 (10.6)	
Charlson Comorbidity Index				
0	45 164 (73.4)	17 850 (57.9)	1183 (38.1)	<.001
1	11 531 (18.7)	7571 (24.6)	834 (26.8)	
≥2	4881 (7.9)	5417 (17.6)	1092 (35.1)	
Severity of disease and risk of mortality				
Minor	52 709 (85.6)	20 393 (66.1)	1057 (34.0)	<.001
Moderate	6307 (10.2)	6902 (22.4)	1054 (33.9)	
Major	1891 (3.1)	2604 (8.4)	662 (21.3)	
Extreme	669 (1.1)	939 (3.0)	336 (10.8)	
Insurance				
Private	29 364 (47.7)	10 759 (34.9)	670 (21.6)	<.001
Medicare	14 032 (22.8)	11 657 (37.8)	1728 (55.6)	
Medicaid	7977 (12.9)	4035 (13.1)	373 (12.0)	
Self-pay	6915 (11.2)	2748 (8.9)	196 (6.3)	
No charge	3131 (5.1)	1577 (5.1)	140 (4.5)	
Unknown	157 (0.3)	62 (0.2)	2 (0.1)	
Income quartile				
Lowest	13 920 (22.6)	8624 (28.0)	964 (31.0)	<.001
Second	15 610 (25.4)	7857 (25.5)	753 (24.2)	
Third	15 801 (25.7)	7259 (23.5)	733 (23.6)	
Highest	14 960 (24.3)	6406 (20.8)	591 (19.0)	
Unknown	1285 (2.1)	692 (2.2)	68 (2.2)	
Year of admission				
2005	8814 (14.3)	4629 (15.0)	501 (16.1)	<.001
2006	11 760 (19.1)	5907 (19.2)	669 (21.5)	
2007	12 822 (20.8)	6631 (20.8)	641 (20.6)	
2008	14 456 (23.5)	7080 (23.5)	718 (23.1)	
2009	13 724 (22.3)	6591 (22.3)	580 (18.7)	
Hospital bed size				
Small	7732 (12.6)	3408 (11.1)	284 (9.1)	<.001
Medium	16 147 (26.2)	7788 (25.3)	782 (25.2)	
Large	37 697 (61.2)	19 642 (63.7)	2043 (65.7)	
Hospital teaching status				

(continued)

Table 1. Comparison of Demographic and Hospital Characteristics of Patients by Days From Presentation to Procedure^a (continued)

Characteristic	0-1 Day (n = 61 576)	2-5 Days (n = 30 838)	6-10 Days (n = 3109)	P Value
Nonteaching	40 511 (65.8)	19 813 (64.3)	1896 (61.0)	<.001
Teaching	21 065 (34.2)	11 025 (35.8)	1213 (39.0)	
Location				
Rural	7124 (11.6)	3423 (11.1)	328 (10.6)	.04
Urban	54 452 (88.4)	27 415 (88.9)	2781 (89.5)	
Hospital management				
Government, nonfederal	6587 (10.7)	3560 (11.5)	332 (10.7)	<.001
Private	38 959 (63.3)	18 910 (61.3)	1835 (59.0)	
Government, private	16 030 (26.0)	8368 (27.1)	942 (30.3)	
Region				
Northeast	10 924 (17.7)	9021 (19.0)	755 (24.3)	<.001
Midwest	9021 (14.7)	3951 (12.8)	321 (10.3)	
South	25 682 (41.7)	14 889 (48.3)	1470 (47.3)	
West	15 949 (25.9)	6145 (19.9)	563 (18.1)	

^a Data are presented as number (percentage) of patients unless otherwise indicated.

Table 2. Bivariate Analysis for Postoperative Complications, Length of Stay, and Mortality by Days From Presentation to Procedure^a

Complication	Days 0-1 (n = 61 576)	Days 2-5 (n = 30 838)	Days 6-10 (n = 3109)	P Value
Conversion to open surgery	60 (0.1)	43 (0.1)	6 (0.2)	.03
Bile duct injury	11 (0.02)	3 (0.01)	2 (0.1)	.78
Surgical site infection or abscess	178 (0.3)	131 (0.4)	38 (1.2)	<.001
Pneumonia	779 (1.3)	870 (2.8)	252 (8.1)	<.001
UTI	1984 (3.2)	2167 (7.0)	425 (13.7)	<.001
Postoperative LOS, mean (SD), d	2.03 (2.2)	2.63 (3.3)	4.61 (5.3)	<.001
Mortality	131 (0.2)	198 (0.6)	61 (1.7)	<.001

Abbreviations: LOS, length of stay; UTI, urinary tract infection.

^a Data are presented as number (percentage) of patients unless otherwise indicated.

Table 3. Multivariate Outcome Analysis After Propensity Score Matching for Postoperative Complications, Mortality, Hospital Costs, and Postoperative LOS by Days From Presentation to Procedure

Outcome	Odds Ratio (95% CI)		
	Days 0-1	Days 2-5	Days 6-10
Complications			
Bile duct injury	1.0 [Reference]	0.57 (0.16-2.08)	3.24 (0.54-19.5)
Surgical site infection or abscess	1.0 [Reference]	0.88 (0.69-1.12)	1.53 (1.05-2.23)
UTI	1.0 [Reference]	1.71 (1.59-1.83)	2.63 (2.31-2.98)
Conversion to open surgery	1.0 [Reference]	1.24 (0.83-1.87)	1.61 (0.64-4.10)
Pneumonia	1.0 [Reference]	1.19 (1.08-1.32)	2.01 (1.72-2.36)
Mortality	1.0 [Reference]	1.26 (1.00-1.58)	1.93 (1.38-2.68)
Postoperative LOS	1.0 [Reference]	0.99 (0.98-1.01)	1.21 (1.16-1.27)
Relative cost	1.0 [Reference]	1.31 (1.30-1.32)	1.98 (1.93-2.03)

Abbreviations: LOS, length of stay; UTI, urinary tract infection.

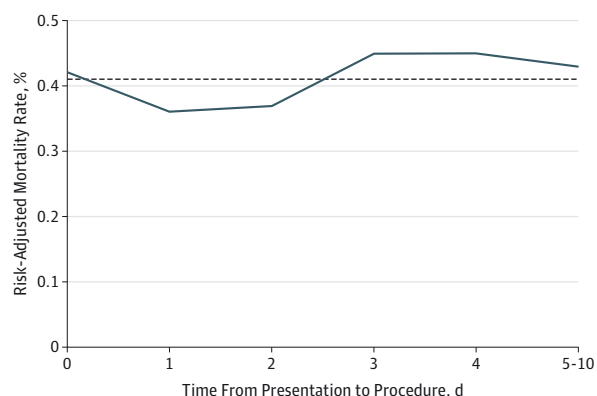
differences by time from presentation to surgery for early LCs performed for acute cholecystitis. In this matched analysis of more than 95 000 patients, we found that operations performed within the first 48 hours of presentation were associated with the lowest rates of complications, length of stay, mortality, and hospital cost. Our analysis adds important and compelling evidence in support of very early LC for acute cholecystitis.

Since the late 1980s, LC for acute cholecystitis has been a controversial topic in general surgery practice. Initially, acute cholecystitis was considered a contraindication to LC when sur-

geons were less experienced with laparoscopic techniques and fearful of operating on inflamed tissue.¹⁵ Subsequently, practices evolved in favor of delayed LC to allow time for the inflammation to “cool off.”¹⁶ This process led to initial management by antibiotics and resuscitation followed by elective LC 4 through 6 weeks after the acute attack. For years, with little evidence, delayed LC remained the preference for many surgeons.¹⁷⁻¹⁹

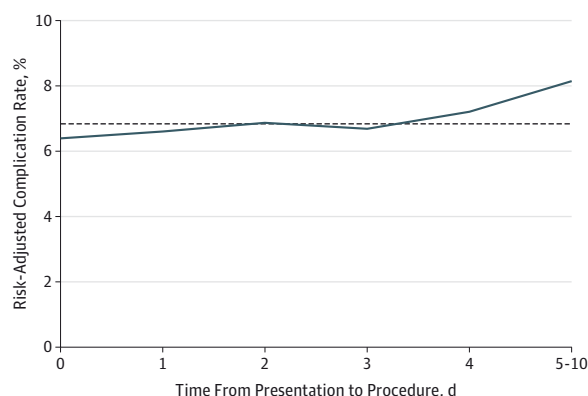
Some studies^{7,20} have found that harmful effects or failure of conservative management directed attention to early LC. Other studies,^{1,8,21,22} including case series, retrospective re-

Figure 1. Risk-Adjusted Mortality Rate by Day Cutoffs



The mean mortality rate, as indicated by the dashed line, was 0.41%.

Figure 2. Risk-Adjusted Complication Rate by Day Cutoffs



The mean complication rate, as indicated by the dashed line, was 6.9%.

Figure 3. Risk-Adjusted Cost by Day Cutoffs

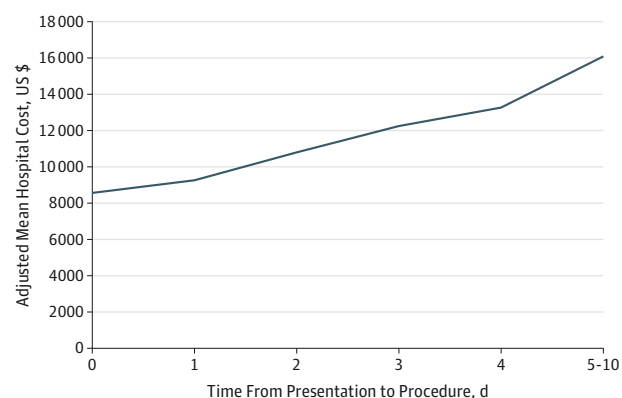
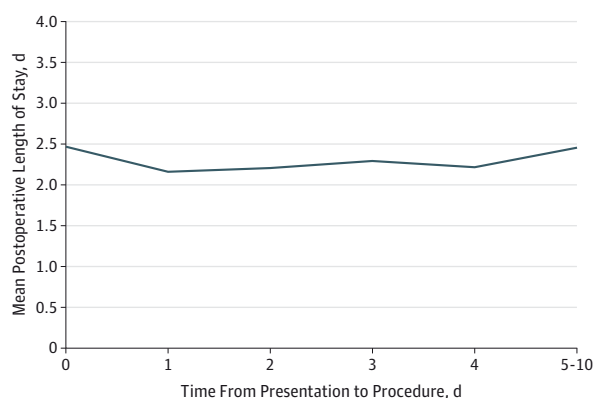


Figure 4. Risk-Adjusted Length of Stay by Day Cutoffs



views, prospective randomized trials, and meta-analyses, have found no advantage in delaying surgery. Furthermore, many of these studies have found early LC to be beneficial with regard to lower hospital costs, decreased length of stay, and fewer complications. However, the definition of *early* LC varies substantially from LC within 24 hours to within 10 days of presentation. A large, multicenter, prospective randomized clinical trial (Acute Cholecystitis-Early Laparoscopic Surgery Versus Antibiotic Therapy and Delayed Elective Cholecystectomy study, $n = 618$ patients) by Gutt et al⁸ compared early LC within 24 hours of presentation of acute cholecystectomy to delayed LC within days 7 through 45 of presentation. Their analysis revealed LC within 24 hours to be safe and superior to delayed LC. Patients who underwent surgery within 24 hours of admission had lower morbidity (11.8% vs 34.4%), lower mean length of hospital day (by 4.6 days), and lower hospital costs (€2919 vs €4262) (all $P < .001$). They found no difference in the rate of conversions to open surgery or mortality (one patient died in each arm).

Currently, the most debated aspect of the surgical management of acute cholecystitis revolves around the optimum timing of early LC. In general, there is a consensus for surgery to be performed during the same admission. The question re-

mains whether there is a difference in outcomes when surgery is performed within 24 hours, within the next few days, or any time during the same admission. In lieu of a very large prospective multicenter trial, evidence to address such questions can only come from large database studies. Our study is the largest to date on this topic, including more than 95 000 patients.

To the best of our knowledge, the only other large database analysis was conducted by Banz et al,² who published data on 4113 patients from the Swiss Association of Laparoscopic and Thoracoscopic Surgery, and by Brooks et al,⁹ who used data from 5268 patients in the National Surgical Quality Improvement Program database. Banz et al² also found that delaying LC for acute cholecystitis beyond 48 hours of presentation resulted in increased conversions to open surgery, more complications, and longer postoperative hospital stay. However, a major criticism of their study was that patients who underwent surgery later may have been more ill from the outset and therefore had worse outcomes. There was no matching or adjustment on degree of illness. In our study, we used propensity score matching techniques to account for differences in severity of illness. We believe that this kind of matching is an integral component of comparative effectiveness research.

Brooks et al⁹ performed risk-adjusted analyses using a variety of preoperative variables. In their analysis, they found no significant difference in morbidity and mortality for LCs performed on day 0 vs other days after presentation. However, there was a definite trend of increasing morbidity from 6% on day 0 to 19% for LCs performed after day 4. The lack of statistical significance may in part be due to small sample size.

Another strength of our analysis is that this study has enough power to determine mortality differences after LC. Mortality after LC is very rare and ranges from 0.3% to 1.1%.^{2,8,9} Mortality after LC in the 2 largest studies^{2,9} was only 0.8% (n = 32 of 4111 patients)² and 1.1% (n = 58 of 5268 patients).⁹ In our nationally representative analysis, the overall mortality rate was 0.41% with 390 deaths. We found the lowest risk-adjusted mortality when LC was performed within 1 day or 2 days of presentation (0.36% and 0.37%, respectively). There was a sudden increase in mortality from day 3 and later (0.45%, $P = .01$). Of interest, mortality for surgery performed on day 0 was higher at 0.42%. This finding may be explained by operations performed on underresuscitated patients. Patients with acute cholecystitis may present severely dehydrated and at times even in shock. Patients should be adequately resuscitated before surgery.

Our study has certain limitations that are worth mentioning. This is a retrospective study of prospectively collected data. Therefore, analysis was limited to available information. For example, we were unable to determine how long patients had symptoms of acute cholecystitis before presentation. Therefore, we did not have a precise measure of duration of disease. As with any national patient database, there are potentially unknown or unreported confounder variables that could not be adjusted for by propensity score matching. While adjusting for severity of illness, we used the All Patient Refined

Diagnosis Related Group severity index. Even though this index is widely used and considered to be very accurate and reliable, it is not perfect, and some degree of residual confounding is expected. The Charlson Comorbidity Index is similarly not 100% accurate and has undergone multiple revisions in the past to improve accuracy.

Another limitation is the variation in accuracy and completeness by the coding health care professional. In our analysis, few patients were found to have bile duct injuries (n = 15 [0.02%]) and conversions to open surgery (n = 109 [0.1%]). It is possible that these events were not being adequately documented or reported. Therefore, no conclusions were made based on bile duct injuries or conversions to open surgery. The NIS is not a surgical outcome database; therefore, no stringent protocols are in place to ensure absolute accuracy of coding of postoperative complications. However, because coding of complications is extremely important for hospital reimbursement, it is believed that these complications were captured accurately. Any errors in coding are thought to be evenly distributed among the patient population and thus should not be a cause of major bias for this study.

Conclusions

The optimal time for surgery for acute cholecystitis is within 2 days of presentation. Even though causal associations could not be determined in this retrospective analysis, delay in surgery was found to be associated with increased morbidity, mortality, length of stay, and higher hospital costs. The practice of unnecessarily delaying cholecystectomy for acute cholecystitis should be discouraged.

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Study concept and design: Zafar, Obirieze, Adesibikan, Fullum, Tran.

Acquisition, analysis, or interpretation of data: Zafar, Obirieze, Cornwell, Tran.

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Critical revision of the manuscript for important intellectual content: Zafar, Adesibikan, Cornwell, Fullum, Tran.

Statistical analysis: Zafar, Obirieze.

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REFERENCES

- Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg*. 2010;97(2):141-150.
- Banz V, Gsponer T, Candinas D, Güller U. Population-based analysis of 4113 patients with acute cholecystitis: defining the optimal time-point for laparoscopic cholecystectomy. *Ann Surg*. 2011;254(6):964-970.
- Papi C, Catarci M, D'Ambrosio L, et al. Timing of cholecystectomy for acute calculous cholecystitis: a meta-analysis. *Am J Gastroenterol*. 2004;99(1):147-155.
- Barcelo M, Cruz-Santamaria DM, Alba-Lopez C, Devesa-Medina MJ, Diaz-Rubio M, Rey E. Advantages of early cholecystectomy in clinical practice of a tertiary care center. *Hepatobiliary Pancreat Dis Int*. 2013;12(1):87-93.
- Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. *Cochrane Database Syst Rev*. 2013;6:CD005440.
- Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L. Management of acute cholecystitis in the laparoscopic era: results of a prospective, randomized clinical trial. *J Gastrointest Surg*. 2003;7(5):642-645.
- Lau H, Lo CY, Patil NG, Yuen WK. Early versus delayed-interval laparoscopic cholecystectomy for acute cholecystitis: a metaanalysis. *Surg Endosc*. 2006;20(1):82-87.
- Gutt CN, Encke J, Königer J, et al. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC study, NCT00447304). *Ann Surg*. 2013;258(3):385-393.
- Brooks KR, Scarborough JE, Vaslef SN, Shapiro ML. No need to wait: an analysis of the timing of cholecystectomy during admission for acute cholecystitis using the American College of Surgeons National Surgical Quality Improvement Program database. *J Trauma Acute Care Surg*. 2013;74(1):167-173, 173-174.
- Overview of the Nationwide Inpatient Sample. Health Cost and Utilization Project website. <http://www.hcup-us.ahrq.gov/nisoverview.jsp>. 2014. Accessed February 17, 2014.
- D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.
- Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251.

13. Overview of disease severity measures disseminated with the Nationwide Inpatient Sample (NIS). Health Cost and Utilization Project website. <http://www.hcup-us.ahrq.gov/db/nation/nis/OverviewofSeveritySystems.pdf>. 2014. Accessed April 24 2014.
14. 3M APR DRG software. 3M website. http://solutions.3m.com/wps/portal/3M/en_US/Health-Information-Systems/HIS/Products-and-Services/Products-List-A-Z/APR-DRG-Software/. Accessed April 24, 2014.
15. Gouma DJ, Obertop H. Acute calculous cholecystitis: what is new in diagnosis and therapy? *HPB Surg*. 1992;6(2):69-78.
16. Kuster GG, Domagk D. Laparoscopic cholecystostomy with delayed cholecystectomy as an alternative to conversion to open procedure. *Surg Endosc*. 1996;10(4):426-428.
17. Lee AY, Carter JJ, Hochberg MS, Stone AM, Cohen SL, Pachter HL. The timing of surgery for cholecystitis: a review of 202 consecutive patients at a large municipal hospital. *Am J Surg*. 2008;195(4):467-470.
18. Senapati PS, Bhattacharya D, Harinath G, Ammori BJ. A survey of the timing and approach to the surgical management of cholelithiasis in patients with acute biliary pancreatitis and acute cholecystitis in the UK. *Ann R Coll Surg Engl*. 2003;85(5):306-312.
19. Yamashita Y, Takada T, Hirata K. A survey of the timing and approach to the surgical management of patients with acute cholecystitis in Japanese hospitals. *J Hepatobiliary Pancreat Surg*. 2006;13(5):409-415.
20. Cameron IC, Chadwick C, Phillips J, Johnson AG. Acute cholecystitis: room for improvement? *Ann R Coll Surg Engl*. 2002;84(1):10-13.
21. Singhal T, Balakrishnan S, Grandy-Smith S, Hunt J, Asante M, El-Hasani S. Gallstones: best served hot. *JSLs*. 2006;10(3):332-335.
22. Casillas RA, Yegiyants S, Collins JC. Early laparoscopic cholecystectomy is the preferred management of acute cholecystitis. *Arch Surg*. 2008;143(6):533-537.