International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 12, No. 3, July-Sep 2023 Online ISSN: 2250-3137
Print ISSN: 2977-0122

ORIGINAL RESEARCH

Effect of surgical timing on outcomes after cholecystectomy for mild gallstone pancreatitis

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Received: 11 June, 2023 Accepted: 17 July, 2023

ABSTRACT
Background: Retrospective and single-center studies have demonstrated that early cholecystectomy is associated with shorter length of stay in patients with mild gallstone pancreatitis. However, these studies are not powered to detect differences in adverse events. Using a nationally representative cohort, we evaluated the association of timing for cholecystectomy with clinical outcomes and resource use in patients with gallstone pancreatitis. **Methods:** All adult hospitalizations for gallstone pancreatitis were tabulated from the 2016–2019 Nationwide Readmissions Database. Using International Classification of Disease, 10th Revision codes, patient comorbidities and operative characteristics were determined. Patients with end-organ dysfunction or cholangitis were excluded to isolate those with only mild gallstone pancreatitis. Major adverse events were defined as a composite of 30-day mortality and perioperative (cardiovascular, respiratory, neurologic, infectious, and thromboembolic) complications. Timing of laparoscopic cholecystectomy was divided into Early (within 2 days of admission) and Late (>2 days after admission) cohorts. Multivariable logistic and linear regression were then used to evaluate the association of cholecystectomy timing with major adverse events and secondary outcomes of interest, including postoperative hospital duration of stay, costs, non-home discharge, and readmission rate within 30 days of discharge. **Results:** Of an estimated 129,451 admissions for acute gallstone pancreatitis, 25.6% comprised the Early cohort. Compared to patients in the Early cohort, Late cohort patients were older (56 [40–69] vs 53 [37–66] years, $P < .001$), more likely male (36.6 vs 32.8%, $P < .001$), and more frequently underwent preoperative endoscopic retrograde cholangiopancreatography (22.2 vs 10.9%, $P < .001$). In addition, the Late cohort had higher unadjusted rates of major adverse events and index hospitalization costs, compared to Early. After risk adjustment, late cholecystectomy was associated with higher odds of major adverse events (adjusted odds ratio 1.40, 95% confidence interval 1.29–1.51) and overall adjusted hospitalization costs by $2,700 (95% confidence interval 2,400–2,800). In addition, compared to the Early group, those in the Late cohort had increased odds of 30-day readmission (adjusted odds ratio 1.12, 95% confidence interval 1.03–1.23) and non-home discharge (adjusted odds ratio 1.42, 95% confidence interval 1.31–1.55). **Conclusion:** Cholecystectomy >2 days after admission for mild gallstone pancreatitis was independently associated with increased major adverse events, costs, 30-day readmissions, and non-home discharge. Given the significant clinical and financial consequences, reduced timing to surgery should be prioritized in the overall management of this patient population.

INTRODUCTION

Gallstone pancreatitis (GSP) is a potentially life-threatening condition that accounts for nearly 270,000 emergency department visits in the United States annually.[1] In patients without end-organ damage, laparoscopic cholecystectomy remains the definitive treatment for GSP as it prevents recurrence.[2,3] In the case of mild GSP, same-admission cholecystectomy has been shown to reduce recurrent gallstone-related complications and readmission rates compared to interval intervention.[4,5] Furthermore, early intervention within 48 hours of admission has been repeatedly deemed safe and cost-efficient.6, 7, 8 Chang et al have shown preoperative endoscopic retrograde cholangiopancreatography (ERCP) to unnecessarily delay definitive care for patients with mild GSP.[9] Despite available evidence supporting early cholecystectomy for mild GSP, the proportion of patients who undergo operative intervention during the index admission has been reported to be as low as 40% to 51%.[10] This discrepancy between recommendation and clinical practice warrants further investigation.

Using a nationally representative cohort of patients with mild GSP, we examined the association of cholecystectomy timing with clinical and financial endpoints. In addition, we evaluated the association between hospital caseload volume and outcomes of interest. We hypothesized that cholecystectomy performed within 2 days of admission would be associated with reduced major adverse events (MAE) and decreased rates of 30-day nonelective readmission.

MATERIAL AND METHODS

DATA SOURCE AND STUDY COHORT

This was a retrospective study of all adults (≥18 years) undergoing nonelective cholecystectomy for GSP in the 2016–2019 Nationwide Readmissions Database (NRD). Maintained by the Healthcare Cost and Utilization Project (HCUP), the NRD is an all-payer readmissions database that samples approximately 37 million inpatient hospital discharges annually. Validated algorithms using discharge weights provide accurate quantification for greater than 60% of all hospitalization across the United States while accounting for clustering. In addition, the NRD contains linkage numbers for all sampled patients, thus allowing readmissions within each calendar year to be tracked across participating hospitals. Because of the deidentified nature of the NRD, this study was determined to be exempt from full review by the Institutional Review Board at the University of California, Los Angeles.

STUDY VARIABLES AND OUTCOMES

Patients were identified using the International Classification of Disease, 10th Revision (ICD-10) codes. Baseline patient and hospital characteristics, including age, sex, and income level, were defined using the HCUP data dictionary.[11] Other clinically relevant covariates and complications were tabulated using ICD-10 codes (Supplementary Table S1). Following the Atlanta classification of acute pancreatitis, patients with end-organ dysfunction were considered to have moderate to severe GSP and subsequently were excluded from analysis.[12] The remainder was included in the mild GSP cohort (Figure 1). Records with missing data for age or mortality, as well as those undergoing laparoscopic cholecystectomy after 2 weeks of index hospitalization, were excluded from the analysis (9.5%; Figure 1). Among those undergoing same-admission cholecystectomy, timing to cholecystectomy or ERCP was determined using the “PRDAY” variable, which documents which hospital day a given procedure is performed. The van Walraven modification of the Elixhauser Comorbidity Index was used to quantify the burden of chronic conditions.[13] Hospitalization costs were calculated using cost-to-charge ratios to total hospitalization charges and adjusted for inflation using the 2019 Personal Health Index.

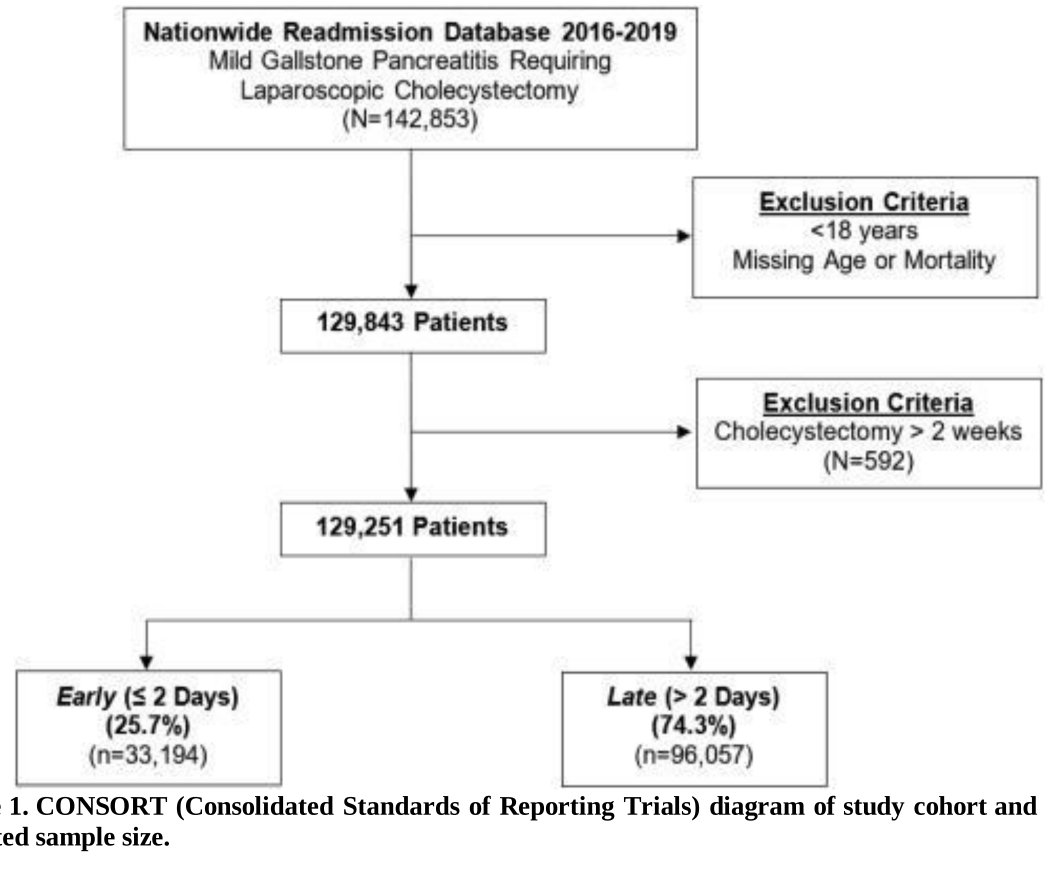

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of study cohort and survey-weighted sample size.

The primary outcome of interest was MAE defined as a composite of 30-day in-hospital mortality and perioperative complications. Perioperative complications comprised cardiovascular (arrest, tamponade, arrhythmia), respiratory (failure, pneumonia, prolonged ventilation), gastrointestinal (biliary leak), and infectious (sepsis surgical site infection) sequelae. Secondary outcomes included timing of ERCP, postoperative length of stay (LOS), hospitalization costs, rates of non-home discharge, and 30-day readmission.

Multivariable regressions were developed using institutional cholecystectomy volume as restricted cubic splines to model MAE and 30-day nonelective readmission as previously described.[14] Based on exploratory analysis, the timing to laparoscopic cholecystectomy corresponding to the inflection point of these models were determined to be at 2 days postadmission (Figure 2). Patients were subsequently stratified into *Early* (within 2 days of admission) and *Late* (more than 2 days after admission) cohorts based on timing to operative intervention. Those undergoing cholecystectomy more than 14 days after admission were excluded to minimize outlier effects in regression models.[15] Using the previously described methodology, hospitals were divided into quintiles based on annual institutional cholecystectomy caseload.[16] Institutions from the lowest volume (LVH) and highest volume quintile (HVH) were compared in our analysis.

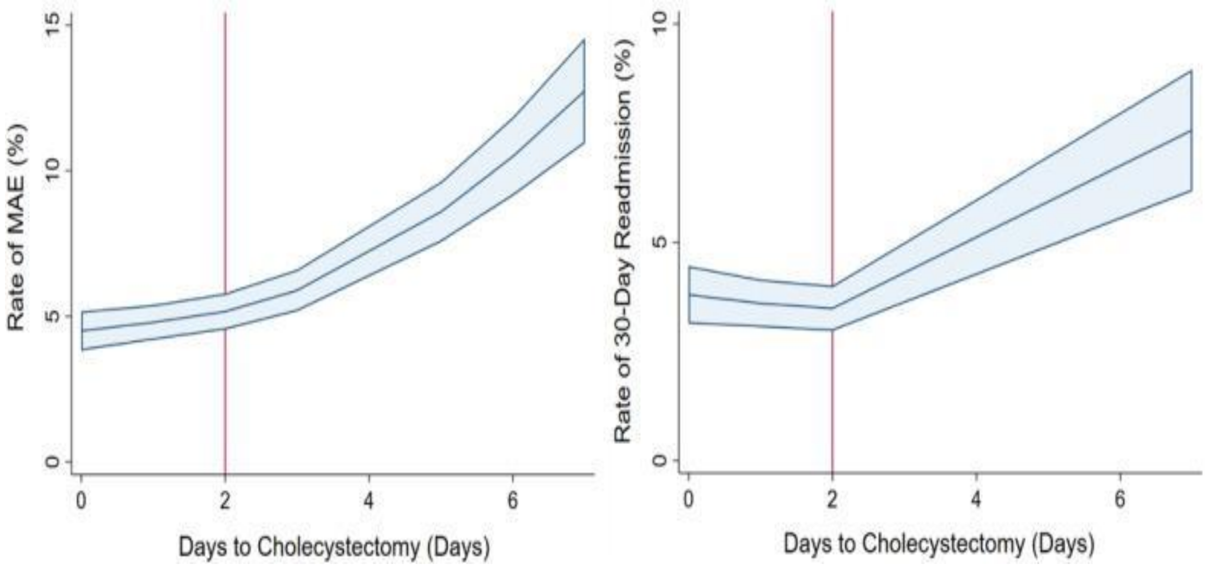

Figure 2. Spline analysis of risk-adjusted major adverse event (MAE) and 30-day readmission by timing of cholecystectomy (Reference: late cholecystectomy threshold). MAE was defined as a composite of 30-day mortality and perioperative (cardiovascular, respiratory, neurologic, infectious, and thromboembolic) complications.

STATISTICAL METHODS

Categorical variables are expressed as group proportions, whereas continuous variables were reported as the median and interquartile range. The significance of intergroup differences was determined using the χ^2 test for categorical and the Student's *t* test for continuous variables. Multivariable logistic and linear regression were then used to evaluate the association of cholecystectomy timing with clinical and financial outcomes of interest. Entropy balancing was used to adjust potential inequalities of the covariate distribution in the study cohorts and reduce bias. This methodology queries for the set of sample weights that satisfy balance constraints while maintaining the entire cohort for analysis.[17,18] Covariate selection was assisted by Elastic Net regularization, which selects variables to improve out-of-sample generalizability.[19] Models were optimized using the receiver operator characteristic and Akaike and Bayesian information criteria to improve the probability of estimation.[20] Regression outputs are reported as adjusted odds ratios (AORs) or beta coefficients (β), as appropriate, with 95% confidence intervals (CI). Significance was set at $\alpha < .05$. To better assess effect size, we employed standardized mean difference (SMD) and considered a value greater than 0.10 as significant.[21] All statistical analyses were performed using Stata 16 (StataCorp, College Station, TX).

RESULTS

Of an estimated 129,251 admissions for mild GSP, 33,194 (25.7%) patients were stratified into the Early cohort, with the remainder comprising the Late cohort. Compared to Early patients, Late patients were older (56 [40–69] vs 53 [37–66] years, $P < .001$), more commonly male (36.6 vs 33.8%, $P < .001$), and had a higher median Elixhauser Comorbidity Index Score (2 [1–3] vs 1 [1–3], $P < .001$). In addition, Late patients were more frequently in the lowest income quartile (27.8 vs 24.9%, $P < .001$), insured by Medicare (34.6 vs 28.7%, $P < .001$), and underwent cholecystectomy at HVH (23.3 vs 22.0%, *P* = .002) (Table I). Compared to the Early cohort, the Late group less frequently underwent postoperative ERCP after cholecystectomy (4.4 vs 7.5%, *P* < .001).

Table I. Demographic of patients with mild gallstone pancreatitis stratified by timing of cholecystectomy (early (<2 days of admission) and late (>2 days of admission) groups)

Empty Cell	**Early (*n* = 33,194)**	**Late (*n* = 96,257)**	***P* value**	**SMD**
Female sex (%)	66.2	63.4	<.001	0.06
Age, (y)	53 [37–66]	56 [40–69]	<.001	0.16
Elixhauser index score	1 [1–3]	2 [1–3]	<.001	0.25
Hospital bed size, (%)			<.001	0.06
Small	19.2	17.3		
Medium	29.4	28.5		
Large	51.4	54.2		
Hospital teach status, (%)			<.001	0.03
Rural	27	25.6		
Metropolitan nonteaching	65.7	67.5		
Metropolitan teaching	7.3	7.0		
Insurance status, (%)			<.001	0.09
Medicare	28.7	34.6		
Medicaid	17.5	16.7		
Private	44.6	38.7		
Self-pay	6	6.2		
Income quartile (%)			<.001	0.08
0–25th	24.9	27.8		
25th–50th	27.0	25.0		
50th–75th	27.6	25.4		
75th–100th	20.5	18.8		
Hospital cholecystectomy volume (%)			.002	0.07
Low	21.0	19.0		
Medium	18.7	18.6		
High	22.0	23.3		

Continuous variables are reported using median and interquartile range.
SMD, standardized mean difference.

On bivariate analysis, the Late cohort faced higher rates of MAE (8.1 vs 4.9%, *P* < .001), shorter postoperative LOS (1 [1–2] vs 2 [1–2] days, *P* < .001), and higher index hospitalization costs ($14,400 [11,100–19,200] vs $11,700 [8,900–15,700], *P* < .001) compared to others. Compared to early, patients undergoing late cholecystectomy had a higher rate of preoperative ERCP (22.2 vs 10.9%, *P* < .001) and shorter postoperative LOS (1 [1–2] vs 2 [1–2] days, *P* < .001). Further, the Late cohort demonstrated increased rates of non-home discharge (7.6 vs 4.4%, *P* < .001) and 30-day readmission (5.6 vs 4.3%, *P* < .001) compared to the Early (Table II).

Table II. Unadjusted outcomes in patients with mild gallstone pancreatitis stratified by timing of cholecystectomy (early, <2 days of admission; late, >2 days of admission groups)

Empty Cell	**Early**	**Late**	***P* value**	**SMD**
Major adverse event (%)	4.9	8.1	<.001	0.13
Cardiovascular complication (%)	0.2	0.4	<.001	0.04
Infectious complication (%)	2.5	4.3	<.001	0.10
Respiratory complication (%)	1.0	1.6	<.001	0.05
Neurological complication (%)	2.1	2.8	<.001	0.04
Thromboembolic complication (%)	0.1	0.2	<.001	0.02
ERCP (%)			<.001	0.22
Pre-cholecystectomy	10.9	22.2		
Post-cholecystectomy	7.5	4.4		
Days until ERCP (d)	1 [0–2]	2 [1–3]	<.001	0.10
Days until cholecystectomy (d)	1 [0–1]	3 [2–4]	<.001	2.20
Postoperative LOS (d)	2 [1–2]	1 [1–2]	<.001	0.11
Cost ($1,000)	11.7 [8.9–15.7]	14.4 [11.1–19.2]	<.001	0.33
Non-home discharge (%)	4.4	7.6	<.001	0.14
Readmission <30 days (%)	4.3	5.6	<.001	0.04

Continuous variables are reported using median and interquartile range.
ERCP, endoscopic retrograde cholangiopancreatography; *LOS*, hospital duration of stay; *d*, days; *SMD*, standardized mean difference.

After risk adjustment, late cholecystectomy was associated with increased odds of MAE (AOR 1.40, 95% CI 1.29–1.51). Compared to the Early, the Late cohort had shorter postoperative LOS by 0.3 days (95% CI 0.3–0.4) and incurred $3,500 incremental hospitalization costs (95% CI 3,200–3,800). As shown in Figure 3, the odds of MAE and hospitalization costs incrementally increased each day until achieving a relative plateau at 7 days (Figure 3). Those undergoing Late cholecystectomy for mild GSP were also noted to have higher adjusted odds of cardiovascular, infectious, and respiratory complications (Table III). Compared to the Early cohort, those in the Late cohort had increased odds of non-home discharge (AOR 1.42, 95% CI 1.33–1.52) and 30-day nonelective readmission (AOR 1.18, 95% CI 1.09–1.27). Subgroup analysis of outcomes by institutional cholecystectomy caseload was notable for decreased odds of MAE at HVH (AOR 0.87, 95% CI 0.77–0.98) compared to LVH. Compared to LVH, HVH additionally had a reduced cost by $3,300 (95% CI 3,000–3,700). However, adjusted odds of non-home discharge and 30-day nonelective readmission were not significantly different between HVH and LVH.

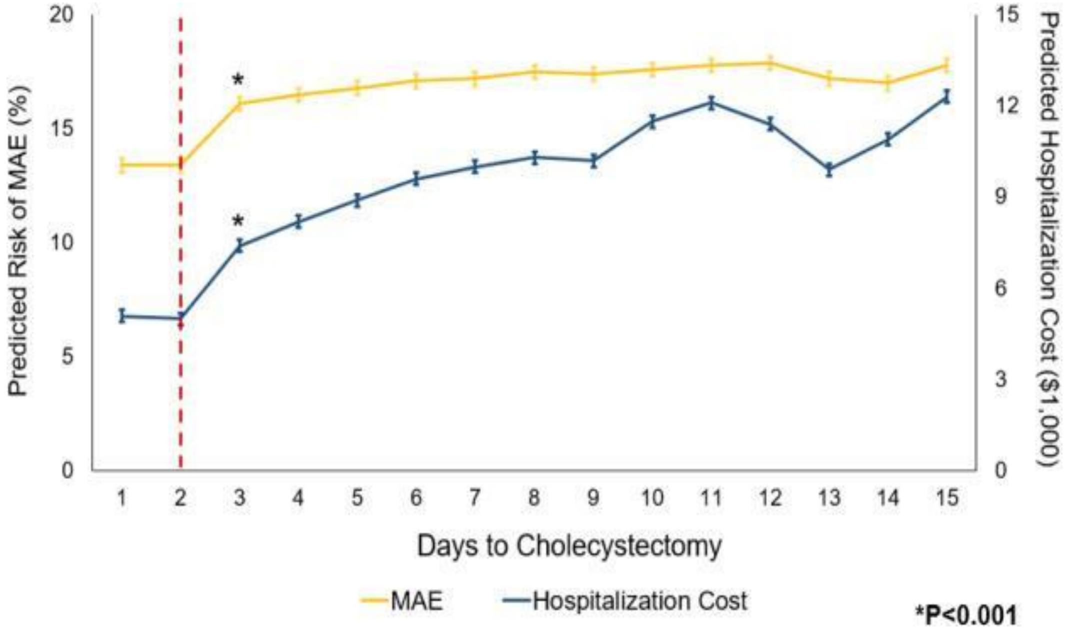

Figure 3. Differential effect of operative timing on major adverse events (MAE) and hospitalization cost in patients with mild GSP undergoing laparoscopic cholecystectomy. Reference line at day 2 indicates the cutoff for early cholecystectomy cohort.

Table III. Adjusted outcomes and resource utilization of late cholecystectomy in patients with mild gallstone pancreatitis (Reference: early cholecystectomy)

Empty Cell	**Estimate**	**95% CI**
Major adverse events	1.40∗	1.24–1.51
Mortality	2.77	0.64–1.11
Cardiovascular	1.70∗	1.16–2.48
Infectious	1.44∗	1.18–1.26
Respiratory	1.33∗	1.13–1.57
Neurologic	1.01	0.89–1.14
Thromboembolic	1.43	0.88–2.34
Post-cholecystectomy ERCP	0.61∗	0.58–0.64
Postoperative LOS (d)	-0.33∗	-0.37–0.30
Cost ($1,000)	2.53∗	2.34–2.70
Non-home discharge	1.41∗	1.29–1.53
Readmission <30 days	1.12∗	1.03–1.23

Estimates are reported as adjusted odds ratio for dichotomous outcomes and β-coefficients for continuous outcomes with corresponding 95% confidence interval for both (Reference: Early cholecystectomy).
Continuous variables are reported using median and interquartile range.
CI, confidence interval; *ERCP*, endoscopic retrograde cholangiopancreatography; *LOS*, hospital duration of stay; *d*, days.

∗Denotes a significant difference (*P*-value < .05) from the reference.

DISCUSSION

GSP is a frequently encountered emergency general surgery diagnosis, with the annual US costs estimated to be ∼$2.2 billion.[22] Optimal timing to laparoscopic cholecystectomy is of particular importance given evidence of worse clinical outcomes with delayed surgical management.[23] In the present study, we demonstrate that, compared to late, early cholecystectomy is associated with reduced MAE and index hospital expenditures. Additional subgroup analysis further illustrated improved outcomes at hospitals with high annual cholecystectomy caseloads regardless of operative timing.

In the present study, we found that early laparoscopic cholecystectomy was associated with lower odds of MAE and index hospitalization costs compared to late intervention in patients with mild GSP. A meta-analysis comparing early and late cholecystectomies likewise showed decreased perioperative complications and readmission rates among those undergoing early intervention.[24] However, prior studies inconsistently defined early intervention as cholecystectomy within 48 hours, 72 hours, or 2 weeks after admission. A consistent definition for early intervention remains unclear, and subsequent nationwide cost analyses are lacking in the literature. Using a restricted cubic spline analysis, we identified that cholecystectomy occurring more than 2 days after admission conferred a significant increase in MAE and 30-day readmission in patients undergoing laparoscopic cholecystectomy. Nonetheless, 74.3% of our study population underwent cholecystectomy beyond the second day of hospitalization.

Despite numerous studies demonstrating the benefit and safety of early cholecystectomy in mild GSP, it is disconcerting that cholecystectomy is still delayed in a majority of patients. There is a myriad of reasons for these delays. In other cases, some physicians still believe that surgery should be delayed until complete resolution of pancreatitis symptoms and full normalization of laboratory values despite randomized studies indicating that this is unnecessary.[25] The timeliness of surgery may also be related to whether the patient is admitted to surgery or medicine. An institutional study by Kulvatunyou et al has shown that patients with mild GSP admitted to a surgical service are more likely to undergo early cholecystectomy.[26] Additionally, the necessity to clear stones from the common bile duct before cholecystectomy has been proposed as a reason to delay the operation. Nonetheless, prior studies indicate that preoperative ERCP in mild gallstone pancreatitis is generally unnecessary and is associated with higher costs and longer hospital stays.[9] Instead of preoperative ERCP, early definitive care via cholecystectomy with optional selective postoperative ERCP was proposed as the standard of care for mild GSP. In the present study, 10.9% of the Early cohort underwent preoperative ERCP compared to 22.2% of the Late cohort. However, even after adjusting for the number of comorbidities and preoperative ERCP, the Early cohort demonstrated significantly improved perioperative outcomes and resource utilization. Although we are unable to assess the individual patient and physician decision-making, we postulate that reducing time to operative intervention should be prioritized in patients with mild GSP.

Previous studies have shown hospital volume to be associated with lower mortality and perioperative complications across a wide spectrum of procedures.[14,27, 28, 29] In the present work, a subgroup analysis revealed that patients at HVH had significantly lower adjusted odds of MAE and hospitalization costs than those at LVH despite similar rates of late cholecystectomy. Compared to LVH, HVH often has greater resources and is equipped with a wide range of specialties and staffing to manage postoperative complications.[30,31] Our results may underscore that the reasons for delayed cholecystectomy may differ between HVH and LVH. While HVH may have advanced diagnostic capabilities or treatment options to more safely delay cholecystectomy, LVH may postpone cholecystectomy due to limited resources leading to reduced prioritization. As more centers adopt Acute Care Surgery models of care, resource allocation to provide timely access to early intervention may benefit patients with mild GSP.[32] Simultaneously, specific processes and care pathways that improve outcomes at HVH should be evaluated in order to provide standardized care.

This retrospective study has several notable limitations due to its use of an administrative database. Our results depend on accurate ICD-10 coding, which is used primarily for billing. More granular data derived from vital signs, laboratory values, and body mass index were unavailable. Thus pancreatitis severity could not be calculated using known scoring systems. Indications for preoperative ERCP also could not be delineated. Furthermore, although we were able to ascertain the association between patient characteristics and operative timing, we could not clearly delineate reasons for delayed cholecystectomy due to a lack of longitudinal data. Although we were able to determine the timing of cholecystectomy based on the hospital day, we could not ascertain hours or minutes to intervention due to the nature of the database. Additionally, factors such as physician expertise or patient-specific factors that may play a role in clinical decision-making are not captured in the NRD. Although we accounted for multiple clinically relevant patient factors, delayed operative intervention may be the result of other objective and subjective clinical information unavailable within the database. Nonetheless, we used statistically valid methodologies to mitigate bias and the effects of these limitations to show the effect of surgical timing on outcomes after cholecystectomy for mild gallstone pancreatitis.

In the present nationwide study, using a restricted cubic spline analysis, we determined cholecystectomy after 2 days to be associated with greater odds of major adverse events and readmission per each incremental day. Furthermore, our findings demonstrate that cholecystectomy performed within 2 days of admission for mild GSP was independently associated with reduced odds of MAE, non-home discharge, and 30-day nonelective readmissions. In most instances, cholecystectomy should not be delayed to perform preoperative ERCP. Delayed cholecystectomy was also associated with higher hospitalization costs. Although operative timing was similar between LVH and HVH, HVH had improved clinical and financial outcomes of cholecystectomy compared to LVH. While the standard of care may be dependent on available resources and patient characteristics, our findings suggest early cholecystectomy should be prioritized in patients with mild GSP. Improved institutional quality metrics to better distribute resources and provide timely access to early intervention may improve patient outcomes. Further randomized control trials to evaluate the operative timing of cholecystectomy are warranted.

FUNDING/SUPPORT
This research did not receive any specific funding from any agencies in the public, commercial, or not-for-profit areas.

CONFLICT OF INTEREST/DISCLOSURE
The authors of have no conflicts of interest or disclosures to report.

SUPPLEMENTARY MATERIALS
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Supplementary Data.

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