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MEDICINE

Early Versus Late Laparoscopic Cholecystectomy in Patients with Acute Gallstone Pancreatitis

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Abstract

The laparoscopic cholecystectomy is the definite treatment of acute gallstone pancreatitis, but the timing remains controversial. We aimed to evaluate trends, prevalence, and outcomes of laparoscopic cholecystectomy amongst patients with acute gallstone pancreatitis in index hospitalization done at different time intervals. We performed a retrospective study using Nationwide Inpatient Sample (years 2003–2014) with adult hospitalizations with acute gallstone pancreatitis who underwent laparoscopic cholecystectomy using ICD-9-CM codes and divided them into subgroups of those who underwent immediately (72 h), early (1 week), and delayed (> 1 week) laparoscopic cholecystectomy. The weighted analysis using chi-square, paired Wilcoxon-rank-sum test, Cochran-Armitage trend test, and multivariable survey logistic regression analysis was performed to evaluate prevalence and outcomes. There was a total of 582,406 acute gallstone pancreatitis admissions of which 291,701 (50.09%) patients had laparoscopic cholecystectomy ($p < 0.0001$). Prevalence of immediate laparoscopic cholecystectomy 114,629 (40.55%) showed incremental trend (32.61 to 49.82%) compared to early 149,931 (53.03%) (57.83 to 46.59%), and late laparoscopic cholecystectomy 18,158 (6.42%) (9.56 to 3.59%) from 2003 to 2014. Immediate and early laparoscopic cholecystectomy had lower prevalence and odds of mortality [0.24% versus 0.37% versus 2.46%; aOR-immediate: 0.614; aOR-early: 0.615; $p < 0.0001$], morbidity [1.36% versus 3.64% versus 27.57%; aOR-immediate: 0.088; aOR-early:0.161; $p < 0.0001$], disability [62.47% versus 70.15% versus 84.26%; aOR-immediate: 0.584; aOR-early: 0.68; $p < 0.0001$], discharge to non-home [7.07% versus 13.04% versus 31.84%; %; aOR-immediate: 0.346; aOR-early: 0.473; $p < 0.0001$], hospital cost $39,466 versus $52,018 versus $129,317 ($p < 0.0001$) and stay 3 days versus 6 days versus 19 days ($p < 0.0001$) than delayed laparoscopic cholecystectomy. The immediate laparoscopic cholecystectomy showed better outcomes; more prospective studies with large numbers of patients should be planned to evaluate the beneficial effects of immediate cholecystectomy in severe acute pancreatitis hospitalizations.

Keywords Acute pancreatitis management · Gallstone pancreatitis · Biliary pancreatitis · Laparoscopic cholecystectomy trend and prevalence · Gallstone pancreatitis guideline · Acute pancreatitis management guideline

This article is part of the Topical Collection on *Medicine*

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Introduction

The annual incidence rate for acute pancreatitis is 4.9 to 35 per 100,000 cases. Acute gallstone pancreatitis is the most common etiology for acute pancreatitis and accounts for 40–70% of the total case, but only 3 to 7% of patients with gallstones develop acute pancreatitis [1, 2]. Acute pancreatitis incidence is increasing with an increasing rate of obesity and gallstone [3]. Small gallstone less than 5 mm has shown to be associated with a higher risk of acute gallstone pancreatitis [4]. Treatment for acute gallstone pancreatitis includes initially conservative and supportive treatment and then definite treatment of underlying cause in the form of either laparoscopic cholecystectomy or endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy if cholecystectomy cannot be performed for any reason. Laparoscopic cholecystectomy is a well-known and proven definitive treatment for acute gallstone pancreatitis in the absence of which there is 25–30% risk of recurrent acute pancreatitis, cholecystitis, cholangitis, and other gallstone-related complication such as biliary colic within 6 to 18 weeks [5, 6]. Multiple studies including randomized control trial and systematic review with meta-analysis have observed that early cholecystectomy (EC) in patients is feasible, safe, and effective with low risk of complications in carefully selected patients with mild acute biliary pancreatitis based on different clinical severity prediction risk tools such as Ranson criteria, Acute Physiology and Chronic Health Evaluation (APACHE II), Bedside severity index in pancreatitis (BISAP), and Modified CT Severity Index (MCTSI). Most studies also observed decreased hospital length of stay, decrease rate of readmissions, and recurrent gallstone-related complications in patients with mild acute gallstone pancreatitis who had early and index admission cholecystectomy [7–10]. American College of Gastroenterology Guideline recommends cholecystectomy before discharge to prevent recurrence in mild biliary pancreatitis [11]. UK Guidelines for the Management of Acute Pancreatitis 2005 recommends doing cholecystectomy in the same admission [12].

Similarly, the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA) evidence-based guidelines for the management of acute pancreatitis recommend cholecystectomy during index admission for mild biliary pancreatitis and further states high risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis with interval cholecystectomy (GRADE 1C, strong agreement) [7]. Most gastroenterology society guidelines around the world acknowledge the benefit of endorsed EC. However, the ideal timeline of intervention has not been established in guidelines because of various definitions of early cholecystectomy in clinical studies. The guidelines differ on the timeline for cholecystectomy and range from as early as 24 to 48 h of admission to a few weeks. Most guidelines agree and strongly recommend early cholecystectomy in index admission; lack of clear consensus on cholecystectomy's timing is also one of the reasons for poor adherence to guidelines. In this paper, we aim to study the trends, prevalence, and outcomes of different timeline interventions classified as immediate, early, and delayed laparoscopic cholecystectomy amongst patients with acute gallstone pancreatitis.

Methods

We gathered the national inpatient sample data from January 2003 to December 2014 from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP). It is the largest publicly available all-payer inpatient care database in the USA and contains discharge-level data provided by states that participate in the HCUP. This administrative dataset contains data on approximately 8 million hospitalizations in 1000 hospitals that are chosen to approximate a 20% stratified sample of all the US community hospitals, representing more than 95% of the national population. Detailed information on NIS is available at http://www.hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp.

Study Population

We used the 9th revision of the International Classification of Diseases, clinical modification (ICD-9-CM) code to identify adult patients admitted to hospital with a primary diagnosis of acute gallstone pancreatitis (ICD-9-CM code 577.8). Similarly, patients who underwent laparoscopic cholecystectomy were identified using ICD-9 procedure code 51.23 and divided them into subgroups of who underwent immediate (within 72 h), early (within a week), and delayed (> 1 week) laparoscopic cholecystectomy. We used ICD-9-CM codes to identify independent predictors (covariates), including the comorbidities of hypertension, diabetes mellitus, obesity, hypercholesterolemia, acquired immunodeficiency syndrome, ischemic heart disease, end-stage renal disease, chronic kidney disease, drug abuse, alcohol abuse/dependence and withdrawal, smoker (current/past), and chronic pancreatitis. Similarly, we identified complications like hypercalcemia, acute renal failure, shock, systemic inflammatory response syndrome, ascites, pleural effusion, respiratory distress/failure, and portal vein thrombosis. We also recognized the procedures like ERCP, abdominal ultrasound, CT scan of the abdomen, cholecystostomy, blood transfusions, and total parenteral nutrition done. Age < 18 years and admissions with missing data for age, gender, and race were excluded. The sample size was based on the available data.

Patient and Hospital Characteristics

Patient characteristics of interest were gender, age, race, insurance status, and concomitant diagnoses, as mentioned above. The race was defined by White (referent), African-American, Hispanic, Asian or Pacific Islander, and Native American. Insurance status was defined by Medicare (referent), Medicaid, private insurance, and other/self-pay/no charge. We defined the severity of comorbid conditions using Deyo's modification of the Charlson Comorbidity Index (Supplementary Table 1). Facilities were considered to be teaching hospitals if they have an American Medical Association–approved residency program, are a member of the Council of Teaching Hospitals, or have full-time equivalent interns and residents to a patient's ratio ≥ 0.25. The HCUP NIS contains data on total charges for each hospital in the databases, which represents the amount that hospitals billed for services.

Outcomes

The primary aim of this study was to evaluate the characteristics of acute gallstone pancreatitis patients who underwent immediate, early, and delayed laparoscopic cholecystectomy and the prevalence of its complications. The secondary aim was to evaluate the outcomes like morbidity, mortality, disability (loss of function), discharge disposition, length of stay (LoS), and cost of hospitalization associated with immediate laparoscopic cholecystectomy (years 2003–2014). The comparison of disability/loss of function was investigated by All Patient Refined Diagnosis Related Groups (APR-DRGs) severity [28, 29]. APR-DRGs were assigned using software developed by 3M Health Information Systems, where score 1 indicates minor loss of function, 2—moderate, 3—major, 4—extreme loss of function. Morbidity defined as the length of stay > 11 days (90th percentile) and discharge other than home (short-term hospital, skilled nursing facility, or intermediate care facility). Discharge disposition was defined by discharge to home versus non-home.

Statistical Analysis

All statistical analyses were performed using the weighted survey methods in SAS (version 9.4). The p values < 0.05 were considered significant. Univariate analysis of differences between categorical variables was tested using the chi-square test, and analysis of differences between continuous variables (age, LoS, and cost of hospitalization) was tested using paired Student's t test. Mixed-effects survey logistic regression models with weighted analysis were used to evaluate the predictors of immediate laparoscopic cholecystectomy in the acute gallstone pancreatitis hospitalization during 2003–2014. We included demographics (age, gender, race), patient-level hospitalization variables (admission day, primary payer, admission type, Median Household Income Category), hospital-level variables (hospital region, teaching versus non-teaching hospital, hospital bed size), comorbidities and concurrent conditions, complications, and Charlson's Comorbidity Index (CCI). The goodness of fit of the model was evaluated by the c-value.

Results

Disease Hospitalizations

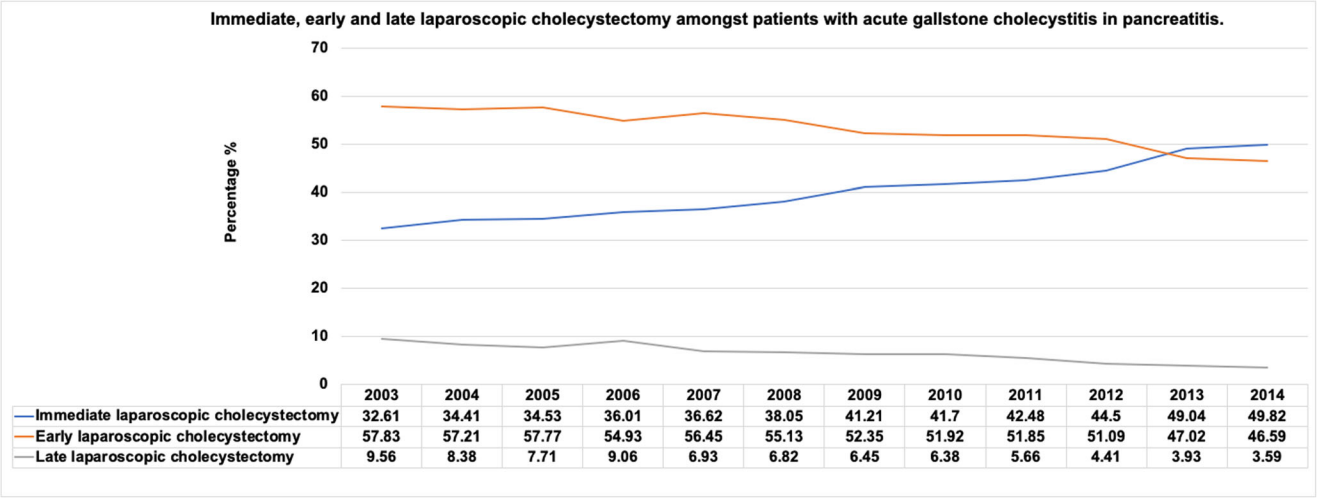
We found a total of 582,406 acute pancreatitis hospitalizations due to gallstone pancreatitis from 2003 to 2014 after excluding patients with missing data for age, race, sex, and outcomes. Out of 582,406 hospitalizations, 291,701 (50.09%) patients had laparoscopic cholecystectomy during the same hospitalization. Out of the same hospitalization cholecystectomy, the prevalence of immediate (within 72 h), early (within one week), and late (> 1 week) laparoscopic cholecystectomy was 114,629 (40.55%), 149,931 (53.03%), and 18,158 (6.42%), respectively.

Prevalence Trend

We analyzed the trend of immediate, early, and late laparoscopic cholecystectomy in acute gallstone pancreatitis. As shown in Fig. 1, the trend of immediate laparoscopic cholecystectomy has increased, and early and late laparoscopic cholecystectomy has decreased from 2003 to 2014 (immediate laparoscopic cholecystectomy, 32.61% in 2003 to 49.82% in 2014; early laparoscopic cholecystectomy, 57.83% in 2003 to 46.59% in 2014; and late laparoscopic cholecystectomy, 9.56% in 2003 to 3.59% in 2014; pTrend<0.0001).

Demographics, Patient and Hospital Characteristics, and Comorbidities

Patients with the age group of 18–55 years have higher prevalence of immediate laparoscopic cholecystectomy utilization (56.47%; $p < 0.0001$) as compared to early and late laparoscopic cholecystectomy (46.30% versus 41.00%; $p < 0.0001$). Whereas patients with age group > 55 years have higher prevalence of late laparoscopic cholecystectomy (59.00%; $p < 0.0001$) as compared to immediate and early laparoscopic cholecystectomy (43.53% versus 53.70%; $p < 0.0001$). In females, the prevalence of immediate laparoscopic cholecystectomy (67.06%) was higher in comparison to early (61.59%) and late laparoscopic cholecystectomy (54.62%) ($p < 0.0001$). Whereas in males, prevalence of late laparoscopic cholecystectomy (45.38%) was more than immediate (32.94%) and early laparoscopic cholecystectomy (38.41%) ($p < 0.0001$).



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Immediate laparoscopic cholecystectomy	32.61	34.41	34.53	36.01	36.62	38.05	41.21	41.7	42.48	44.5	49.04	49.82
Early laparoscopic cholecystectomy	57.83	57.21	57.77	54.93	56.45	55.13	52.35	51.92	51.85	51.09	47.02	46.59
Late laparoscopic cholecystectomy	9.56	8.38	7.71	9.06	6.93	6.82	6.45	6.38	5.66	4.41	3.93	3.59

Fig. 1 Immediate, early, and late laparoscopic cholecystectomy among patients with acute gallstone cholecystitis in pancreatitis

Immediate laparoscopic cholecystectomy was more commonly performed in Native American [(48.85%) versus whites (40.71%), African-American (34.35%), Hispanic (42.67%), and Asian/Pacific Islander (41.49%) ($p < 0.0001$)], in patients with private insurance [(46.01%) versus Medicare (33.70%), Medicaid (42.49%), and other/self-pay/no charge (41.22%) ($p < 0.0001$)], having elective admissions [(54.51%) versus emergency admissions (39.74%) ($p < 0.0001$)], weekday admissions [(41.76%) versus weekends (37.32%) ($p < 0.0001$)], in rural hospitals [(44.49%) versus urban non-teaching (41.19%), and urban teaching hospital location (38.84%) ($p < 0.0001$)], and in west region [(49.98%) versus northeast (29.65%), Midwest (42.88), and south region (38.65%) ($p < 0.0001$)].

Patients with comorbidities like obesity (immediate, 18.68% versus early, 18.13%; late, 16.44%; $p < 0.0001$) and current or past smoker (immediate, 19.19% versus early, 17.82%; late, 15.21%; $p < 0.0001$) were having higher prevalence of immediate laparoscopic cholecystectomy as compared to early and late laparoscopic cholecystectomy. Patients with comorbidities like hypertension (immediate, 39.65% versus early, 49.17%; late, 54.50%; $p < 0.0001$), diabetes (immediate, 16.53% versus early, 20.61%, late, 26.43%; $p < 0.0001$), hypercholesterolemia (immediate, 6.21% versus early, 7.35%; late, 7.54%; $p < 0.0001$), drug abuse (immediate, 1.12% versus early, 1.43%; late, 2.14%; $p < 0.0001$), alcohol abuse (immediate, 2.89% versus early, 4.47%; late, 8.46%; $p < 0.0001$), acquired immunodeficiency syndrome (immediate, 0.10%; versus early, 0.13%; late, 0.48%; $p < 0.0001$), ischemic heart disease (immediate, 9.20% versus early, 13.78%; late, 16.74%; $p < 0.0001$), end-stage renal disease (immediate, 0.62% versus early, 1.05%; late, 2.13%; $p < 0.0001$), chronic kidney disease (immediate, 2.83% versus early, 3.69%; late, 5.89%; $p < 0.0001$), alcohol withdrawal (immediate, 0.09% versus early, 0.24%; late, 0.85%; $p < 0.0001$), and chronic pancreatitis (immediate, 0.72% versus early, 1.20%; late, 3.04%; $p < 0.0001$) were having lower prevalence of immediate laparoscopic cholecystectomy as compared to early and late laparoscopic cholecystectomy. Prevalence of need of blood transfusion (immediate, 2.68%; versus early, 4.46%; late, 14.57%; $p < 0.0001$) and total parenteral transfusion (immediate, 0.92%; versus early, 2.39%; late, 19.29%; $p < 0.0001$) were lower in patients undergoing immediate laparoscopic cholecystectomy as compared to early and late laparoscopic cholecystectomy.

Prevalence of complications like hypercalcemia (immediate, 0.18%; versus early, 0.27%; late, 0.53%; $p < 0.0001$), acute renal failure (immediate, 3.07%; versus early, 5.78%; late, 17.51%; $p < 0.0001$), shock (immediate, 0.27%; versus early, 0.37%; late, 3.59%; $p < 0.0001$), systemic inflammatory response syndrome (immediate, 1.33%; versus early, 2.34%; late, 10.35%; $p < 0.0001$), ascites (immediate, 1.14%; versus early, 1.94%; late, 6.50%; $p < 0.0001$), pleural effusion (immediate, 0.04%, versus early, 0.08%; late, 0.54%; $p < 0.0001$), respiratory distress and failure (immediate, 1.27%; versus early, 2.09%; late, 11.39%; $p < 0.0001$), and portal vein thrombosis (immediate, 0.04%, versus early, 0.07%; late, 0.60%; $p < 0.0001$) were lower in patients undergoing immediate laparoscopic cholecystectomy as compared to early and late laparoscopic cholecystectomy (Table 1).

The Outcomes

Table 2 has mentioned the outcomes of immediate, early, and late laparoscopic cholecystectomy in patients with acute gallstone pancreatitis. The patients who underwent immediate laparoscopic cholecystectomy had lower prevalence of morbidity (immediate, 1.36%; versus early, 3.64%; late, 27.57%; $p < 0.0001$), mortality (immediate, 0.24%; versus early, 0.37%; late, 2.46%; $p < 0.0001$), major/extreme disability (immediate, 62.47%; versus early, 70.15%; late, 84.26%; p

Table 1 Outcomes and healthcare burden of immediate, early, and late laparoscopic cholecystectomy in patients with acute gallstone pancreatitis

	Immediate (within 72 h) laparoscopic cholecystectomy	Early (within 1 week) laparoscopic cholecystectomy	Late (> 1 week) laparoscopic cholecystectomy	Total	*p* value
Acute gallstone pancreatitis-weighted (%)	114,629 (40.55)	149,931 (53.03)	18,158 (6.42)	282,718 (100)	< 0.0001
Demographics of patients					
Age mean (SD) (years)	51 ± 19	56 ± 19	58 ± 18		< 0.0001
Age group (years)					< 0.0001
18–55 years	64,734 (56.47)	69,425 (46.30)	7445 (41.00)	141,604 (50.09)	
> 55 years	49,895 (43.53)	80,506 (53.70)	10,713 (59.00)	141,114 (49.91)	
Gender (%)					< 0.0001
Male	37,755 (32.94)	57,578 (38.41)	8241 (45.38)	103,574 (36.64)	
Female	76,874 (67.06)	92,343 (61.59)	9918 (54.62)	179,135 (63.36)	
Race (%)					< 0.0001
White	73,319 (66.37)	95,877 (66.31)	10,898 (62.83)	180,094 (66.12)	
African-American	9398 (8.51)	15,382 (10.64)	2579 (14.87)	27,359 (10.04)	
Hispanic	24,313 (22.01)	29,277 (20.25)	3394 (19.57)	56,984 (20.92)	
Asian or Pacific Islander	2557 (2.31)	3201 (2.21)	405 (2.34)	6163 (2.26)	
Native American	876 (0.79)	848 (0.59)	69 (0.40)	1793 (0.66)	
Characteristics of patients					
Median household income category for patient's zip code (%)					< 0.0001
0–25th percentile	29,905 (26.72)	43,245 (29.50)	5756 (32.50)	78,906 (28.57)	
26–50th percentile	29,155 (26.05)	37,182 (25.36)	4299 (24.27)	70,636 (25.57)	
51–75th percentile	28,227 (25.22)	35,134 (23.97)	4035 (22.78)	67,396 (24.40)	
76–100th percentile	24,620 (22.00)	31,036 (21.17)	3623 (20.45)	59,279 (21.46)	
Primary payer (%)					< 0.0001
Medicare	32,901 (28.77)	56,938 (38.05)	7796 (43.05)	97,635 (34.61)	
Medicaid	16,360 (14.31)	19,653 (13.13)	2494 (13.77)	38,507 (13.65)	
Private insurance	47,432 (41.47)	50,673 (33.86)	4991 (27.56)	103,096 (36.55)	
Other/self-pay/no charge	17,670 (15.45)	22,369 (14.95)	2829 (15.62)	42,868 (15.20)	
Admission type (%)					< 0.0001
Non-elective	106,185 (92.76)	143,630 (95.91)	17,364 (95.68)	267,179 (94.62)	
Elective	8285 (7.24)	6131 (4.09)	785 (4.32)	15,201 (5.38)	
Admission day (%)					< 0.0001
Weekday	85,770 (74.82)	106,779 (71.22)	12,844 (70.73)	205,393 (72.65)	
Weekend	28,860 (25.18)	43,152 (28.78)	5314 (29.27)	77,326 (27.35)	
Characteristics of hospitals					
Bed size of hospital (%)*					< 0.0001
Small	15,051 (13.19)	17,926 (12.02)	1607 (8.90)	34,584 (12.30)	
Medium	32,047 (28.09)	41,382 (27.74)	4757 (26.36)	78,186 (27.80)	
Large	66,970 (58.71)	89,848 (60.24)	11,683 (64.74)	168,501 (59.91)	
Hospital location and teaching status (%)					< 0.0001
Rural	12,966 (11.37)	14,784 (9.91)	1396 (7.73)	29,146 (10.36)	
Urban non-teaching	55,684 (48.82)	71,708 (48.08)	7809 (43.27)	135,201 (48.07)	
Urban teaching	45,419 (39.82)	62,663 (42.01)	8842 (49.00)	116,924 (41.57)	
Hospital region (%)					< 0.0001
Northeast	14,716 (12.84)	30,123 (20.09)	4789 (26.38)	49,628 (17.55)	
Midwest	18,427 (16.08)	22,215 (14.82)	2332 (12.84)	42,974 (15.20)	
South	46,197 (40.30)	65,775 (43.87)	7543 (41.54)	119,515 (42.27)	
West	35,289 (30.79)	31,818 (21.22)	3494 (19.24)	70,601 (24.97)	

Table 1 (continued)

	Immediate (within 72 h) laparoscopic cholecystectomy	Early (within 1 week) laparoscopic cholecystectomy	Late (> 1 week) laparoscopic cholecystectomy	Total	*p* value
Comorbidities of patients (%)					
Hypertension	45,448 (39.65)	73,719 (49.17)	9897 (54.50)	129,064 (45.65)	< 0.0001
Diabetes	18,946 (16.53)	30,897 (20.61)	4799 (26.43)	54,642 (19.33)	< 0.0001
Obesity	21,410 (18.68)	27,190 (18.13)	2985 (16.44)	51,585 (18.25)	< 0.0001
Hypercholesterolemia	7117 (6.21)	11,018 (7.35)	1368 (7.54)	19,503 (6.90)	< 0.0001
Drug abuse	1284 (1.12)	2139 (1.43)	388 (2.14)	3811 (1.35)	< 0.0001
Alcohol abuse	3307 (2.89)	6705 (4.47)	1537 (8.46)	11,549 (4.09)	< 0.0001
Current or past smoker	21,997 (19.19)	26,716 (17.82)	2762 (15.21)	51,475 (18.21)	< 0.0001
Acquired immunodeficiency syndrome (AIDS)	116 (0.10)	202 (0.13)	86 (0.48)	404 (0.14)	< 0.0001
Ischemic heart disease	10,540 (9.20)	20,657 (13.78)	3040 (16.74)	34,237 (12.11)	< 0.0001
End-stage renal disease	707 (0.62)	1577 (1.05)	387 (2.13)	2671 (0.95)	< 0.0001
Chronic kidney disease	3249 (2.83)	5538 (3.69)	1070 (5.89)	9857(3.49)	< 0.0001
Alcohol withdrawal	108 (0.09)	366 (0.24)	153 (0.85)	627(0.22)	< 0.0001
Chronic pancreatitis	826 (0.72)	1793 (1.20)	553 (3.04)	3172 (1.12)	< 0.0001
Complications (%)					
Hypercalcemia	211 (0.18)	402 (0.27)	96 (0.53)	709 (0.25)	< 0.0001
Acute renal failure	3525 (3.07)	8670 (5.78)	3179 (17.51)	15,374 (5.44)	< 0.0001
Shock	304 (0.27)	554 (0.37)	653 (3.59)	1511 (0.53)	< 0.0001
Systemic inflammatory response syndrome	1523 (1.33)	3501 (2.34)	1879 (10.35)	6903 (2.44)	< 0.0001
Ascites	1308 (1.14)	2902 (1.94)	1179 (6.50)	5389 (1.91)	< 0.0001
Pleural effusion	45 (0.04)	125 (0.08)	99 (0.54)	269 (0.10)	< 0.0001
Respiratory distress and respiratory failure	1453 (1.27)	3140 (2.09)	2068 (11.39)	6661 (2.36)	< 0.0001
Portal vein thrombosis	45 (0.04)	104 (0.07)	109 (0.60)	258 (0.09)	< 0.0001
Procedures (%)					
Endoscopic retrograde cholangiopancreatography	3329 (2.90)	8952 (5.97)	1587 (8.74)	13,868 (4.91)	< 0.0001
Abdominal ultrasonography	1935 (1.69)	3536 (2.36)	681 (3.75)	6152 (2.18)	< 0.0001
Computed tomography scan of abdomen	1534 (1.34)	3985 (2.66)	1023 (5.64)	6542 (2.31)	< 0.0001
Cholecystostomy	117 (0.10)	156 (0.10)	218 (1.20)	491(0.17)	< 0.0001
Blood transfusion	3067 (2.68)	6693 (4.46)	2646 (14.57)	12,406 (4.39)	< 0.0001
Total parenteral nutrition	1056 (0.92)	3587 (2.39)	3503 (19.29)	8146 (2.88)	< 0.0001
Deyo's Charlson's Comorbidity Index (CCI)					< 0.0001
0	78,598 (68.57)	90,632 (60.45)	8574 (47.22)	177,804 (62.89)	
1	23,152 (20.20)	35,088 (23.40)	4833 (26.61)	63,073 (22.31)	
2	7267 (6.34)	13,128 (8.76)	2473 (13.62)	22,868 (8.09)	
3	3021 (2.64)	5866 (3.91)	1202 (6.62)	10,089 (3.57)	
4	1336 (1.17)	2837 (1.89)	522 (2.88)	4695 (1.66)	
5	1254 (1.09)	2380 (1.59)	554 (3.05)	4188 (1.48)	

Percentage in brackets are column % indicating direct comparison between immediate, early, and late laparoscopic cholecystectomy in patients with acute gallstone pancreatitis

*Bed size of hospital indicates number of hospital beds which varies depends on hospital location (rural/urban), teaching status (teaching/non-teaching), and region (Northeast/Midwest/Southern/Western)

< 0.0001), discharge other than home (immediate, 7.07%; versus early, 13.04%; late, 31.84%; $p < 0.0001$), length of stay (immediate, 4 days; versus early, 6 days; late, 19 days; $p < 0.0001$), and cost of hospitalization (immediate, $39,466;

Table 2 Outcomes of immediate, early, and late laparoscopic cholecystectomy in patients with acute gallstone pancreatitis

	Immediate (within 72 h) laparoscopic cholecystectomy	Early (within 1 week) laparoscopic cholecystectomy	Late (> 1 week) laparoscopic cholecystectomy	Total	*p* value
Acute gallstone pancreatitis-weighted (%)	114,629 (40.55)	149,931 (53.03)	18,158 (6.42)	282,718 (100)	< 0.0001
Morbidity*	1555 (1.36)	5455 (3.64)	5006 (27.57)	12,016 (4.25)	< 0.0001
Mortality	271 (0.24)	559 (0.37)	446 (2.46)	1276 (0.45)	< 0.0001
Disability					< 0.0001
Minor/moderate disability	42,815 (37.53)	44,347 (29.85)	2769 (15.74)	89,931 (32.09)	
Major/extreme disability	71,259 (62.47)	104,242 (70.15)	14,828 (84.26)	190,329 (67.91)	
Discharge disposition					< 0.0001
Discharge to home	8072 (7.07)	19,443 (13.04)	5627 (31.84)	33,142 (11.80)	
Discharge other than home[#]	106,090 (92.93)	129,619 (86.96)	12,048 (68.16)	247,757 (88.20)	
Length of stay ± SE (days)	4 ± 0.02	6 ± 0.02	19 ± 0.26		< 0.0001
Cost of hospitalization ± SE ($)	39,466 ± 276	52,018 ± 271	129,317 ± 2678		< 0.0001

*Morbidity: length of stay ≥ 11 days (90th percentile) + discharge other than home

[#] Discharge other than home: discharge to short-term hospital, skilled nursing facility, or intermediate care facility

versus early, $52,018; late, $129,317; $p < 0.0001$) than early and late laparoscopic cholecystectomy (Table 3).

Regression Model Derivation

We have noticed lower chances of morbidity (immediate, aOR: 0.09; 95%CI: 0.07–0.10; $p < 0.0001$; early, aOR: 0.16; 95%CI: 0.14–0.18; $p < 0.0001$), mortality (immediate, aOR: 0.61; 95%CI: 0.38–0.99; $p < 0.0001$; early, aOR: 0.61; 95%CI: 0.41–0.93; $p < 0.0001$), disability (immediate, aOR: 0.58; 95%CI: 0.52–0.65; $p < 0.0001$; early, aOR: 0.68; 95%CI: 0.61–0.76; $p < 0.0001$), and discharge predisposition (immediate, aOR: 0.35; 95%CI: 0.31–0.39; $p < 0.0001$; early, aOR: 0.47; 95%CI: 0.42–0.53; $p < 0.0001$) in immediate and early laparoscopic cholecystectomy as compared to late laparoscopic cholecystectomy. The *c*-statistic which is used to validate the accuracy of the regressions was > 0.5 which indicates a good model (morbidity, 0.92; mortality, 0.94; disability, 0.75; and discharge predisposition, 0.87) (Table 2).

Discussion

In our study, we analyzed national inpatient trend and the prevalence of immediate (within 72 h), early (within 1 week), and late (after 1 week) laparoscopic cholecystectomy in acute gallstone

Table 3 Outcomes associated with immediate, early, and late laparoscopic cholecystectomy in patients with acute gallstone pancreatitis

	Morbidity* Odds ratio (confidence interval) (*p* value)	Mortality Odds ratio (confidence interval) (*p* value)	Disability Odds ratio (confidence interval) (*p* value)	Discharge disposition Odds ratio (confidence interval) (*p* value)
Late (> 1 week) laparoscopic cholecystectomy	Reference			
Immediate (within 72 h) laparoscopic cholecystectomy	0.09 (0.07–0.10) ($p < 0.0001$)	0.61 (0.38–0.99) ($p < 0.0001$)	0.58 (0.52–0.65) ($p < 0.0001$)	0.35(0.31–0.39) ($p < 0.0001$)
Early (within 1 week) laparoscopic cholecystectomy	0.16 (0.14–0.18) ($p < 0.0001$)	0.61 (0.41–0.93) ($p < 0.0001$)	0.68 (0.61–0.76) ($p < 0.0001$)	0.47 (0.42–0.53) ($p < 0.0001$)
Area under the ROC curve/*c*-index	0.92	0.94	0.75	0.87

Models are adjusted for patients' demographics (age, sex, race, income category, primary payer, and procedure days and type), hospital-level characteristics (hospital size, location, region, and teaching status), patients' comorbidity (hypertension, diabetes, obesity, hypercholesterolemia, drug, alcohol and tobacco abuse, alcohol withdrawal, HIV, renal dysfunction, ischemic heart disease, and chronic pancreatitis), complications (hypercalcemia, acute renal failure, shock, SIRS, ascites, pleural effusion, respiratory failure, and portal vein thrombosis), other procedures (ERCP, USG abdomen, CT abdomen, cholecystostomy, blood transfusion, parenteral nutrition), and Charlson's Comorbidity Index

UL, upper limit; *LL*, lower limit

*Morbidity: length of stay > 11 days (90th percentile) + discharge other than home

[#] Discharge other than home: discharge to short-term hospital, skilled nursing facility, or intermediate care facility

pancreatitis patients from the years 2003 to 2014 and associated factors such as outcomes (morbidity and mortality), cost of hospitalization, and other factors affecting it. In our knowledge, this is the first study that has studied and compared the effect of cholecystectomy done on a different time scale for index admission. Several national guidelines suggest that definitive treatment for gallstone pancreatitis is cholecystectomy within the same admission to the first few weeks to decrease the risk of recurrent biliary events [3, 12, 13]. However, nationwide audits from the USA and Europe have shown that most patients undergo cholecystectomy weeks or sometimes months after discharge from the hospital for mild biliary pancreatitis [14–16]. Sanjay et al. and Tyler et al. in their study discussed the difficulties in the implementation of treatment guidelines [17, 18]. Data analysis of our study showed that 50.09% of total patients with gallstone pancreatitis had index admission laparoscopic cholecystectomy. Further analysis showed that the prevalence trend of immediate cholecystectomy increased from 32.6 to 49.8%, and early and late cholecystectomy has decreased from (57.8 to 46.5%) and (9.5 to 3.5%), respectively.

Younger patients (age 18–55) found to be having a higher prevalence of immediate laparoscopic cholecystectomy compared to older patients (age > 55 years), which could be because of greater prevalence of comorbidities in older patients, in general, making them less suitable for surgery or more severe presentation with gallstone pancreatitis. Marc et al. observed that adherence to the current guidelines for the management of mild gallstone pancreatitis was lower in older adults with higher readmission rates. In his study, 33% of readmitted patients eventually required cholecystectomy. The author concluded that 40% of the patients who did not undergo the same admission (versus readmission interval) cholecystectomy would have benefited from definitive therapy in index admission [19]. The highest prevalence of immediate laparoscopic cholecystectomy is observed in Native Americans (48.8%), and the least is seen in African-Americans (34.3%). Interestingly, immediate cholecystectomy utilization prevalence is found to be higher in elective cholecystectomy admissions (7.24 versus 4.32) compared to non-elective cholecystectomy admission (92.76 versus 95.68). A weekend effect is also observed during analysis, in weekday's admission utilization prevalence of immediate cholecystectomy found to be higher (74.82 versus 70.73) compared to weekend admission (25.18 versus 29.27). The effect could be explained by a lack of available resource provisions such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP), and inadequate specialist coverage and trained staff at weekends in many low resource institutes [20, 21].

Patients with comorbidities, including ischemic heart disease, CKD, diabetes, and hypertension, are observed to have a lower prevalence of immediate laparoscopic cholecystectomy compared to late laparoscopic cholecystectomy. Complication rates were lower in patients with an immediate index laparoscopic cholecystectomy group. Immediate cholecystectomy group patients had lower odds of mortality and morbidity and lower odds of requiring a short-term hospital, skilled nursing facility, or intermediate care facility at the time of discharge. The findings on low mortality are similar to the multicenter randomized controlled trial (PONCHO trial) by David da Costa et al., of 266 patients who underwent the same admission cholecystectomy within 3 days versus interval cholecystectomy in 25–30 days [22]. Lower prevalence of disability, length of stay, and cost of hospital utilization are seen in patients with immediate laparoscopic cholecystectomy as compared to patients with early and late laparoscopic cholecystectomy, which concur with multiple other clinical studies [23]. The cost of hospitalization is about three times higher in patients with late laparoscopic cholecystectomy compared to patients with immediate laparoscopic cholecystectomy. The cost-effective benefit of immediate cholecystectomy in acute gallstone pancreatitis has been illustrated in other studies as well [24, 25].

These findings do not establish any causative relationship between complications and the exact timing of surgery or related to the severity of pancreatitis because of the nature of the study. For a severe presentation of gallstone pancreatitis while almost always is a reason to delay the surgery, few studies have also observed some other limitations as well. A British study found only 70% compliance with the guideline's adherence because of inadequate imaging or inappropriate delay in diagnosis and noticed an increased risk of a recurrent biliary event. Delayed or non-availability of timely imaging test and intervention such as MRCP in low suspicion for common bile duct (CBD) stone or ERCP for high suspicion for CBD stone has also been factored in as a reason for delayed cholecystectomy [18, 26, 27]. Our study is one of the largest population-based studies to report the trends, outcomes, and complication profile of acute gallstone pancreatitis patients who underwent laparoscopic cholecystectomy in the same index hospitalization at different times. Though the NIS data is the largest national inpatient database with good statistical power, this study has limitations. This administrative database is obtained retrospectively by chart abstractions based on the discharge diagnosis codes and billing codes, and is susceptible to coding errors. Complications and outcomes depend on the severity of the disease. Our study as being based on the NIS data also has limitation of determining clinical disease severity difference between all the groups which may have affected the decision for timing of surgery. We have not followed up on the patient's post-hospitalization to evaluate the disability.

Conclusion

In our study, we found immediate laparoscopic cholecystectomy is better than early or delayed laparoscopic cholecystectomy, even in the same index admission. An inclusion of a

definite timeline recommendation for immediate laparoscopic cholecystectomy (within 22 h) in societal guidelines for management of acute biliary pancreatitis can provide further clarity and help improve adherence to guideline recommendations. Our study findings showed favorable outcome of immediate cholecystectomy, the study has many limitations as described in the "Discussion" section, and more prospective studies with large numbers of patients should be planned to evaluate the beneficial effects of immediate cholecystectomy in severe acute pancreatitis hospitalizations.

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Code Availability Yes

Author Contribution AS conceptualized the idea. AS, AM, and JR reviewed the literature and collected the data with the help of SS and AJ. JR, AM, and SS formulated the tables. AS, SS, JR, and AJ wrote the main draft of the manuscript. AS supervised the project.

Data Availability Files for the raw analysis can be made available upon request.

Compliance with ethical standards

Ethics Approval We have read and have abided by the statement of ethical standards for manuscript submitted to the *European Journal of Gastroenterology and Hepatology*. The data has been taken from Nationwide Inpatient Sample, which is a deidentified database from the "Healthcare Utilization Project (HCUP)" sponsored by the Agency for Healthcare Research and Quality, so informed consent or IRB approval was not needed for the study. The relevant ethical oversight and HCUP Data Use Agreement were obtained for the study.

Conflict of Interest The authors declare no conflict of interest.

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