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Time from drainage to surgery is an independent predictor of morbidity for moderate-to-severe acute cholecystitis: a multivarirble analysis of 259 patients

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Abstract

Background Acute cholecystitis (AC) is an acute inflammatory disease of the gallbladder and one of the most frequent causes of acute abdominal pain. Early cholecystectomy is recommended for mild cholecystitis. However, the optimal surgical timing for moderate-to-severe cholecystitis requiring percutaneous transhepatic gallbladder drainage (PTGBD) remains unclear. We hypothesized that early elective surgery after PTGBD would reduce surgical morbidity.

Methods A retrospective analysis was performed on adult patients who underwent elective surgery for AC after PTGBD at our hospital between January 2011 and December 2020. Patient demographics, perioperative findings, and postoperative morbidity and mortality rates were also investigated. The patients were divided into two groups based on postoperative morbidity, and univariable analysis was performed for preoperative factors. Multivariable logistic regression analysis was performed for the potential independent variables.

Results A total of 891 patients were screened for eligibility, and 259 were included in the analysis. Among these patients, 32 developed postoperative morbidity; however, there was no postoperative mortality. Multivariable analysis revealed that the time from PTGBD to surgery was an independent predictor of surgical morbidity (odds ratio, 1.05; 95% confidence interval: 1.01–1.10).

Conclusion In early elective surgery for moderate-to-severe AC requiring PTGBD, a shorter interval from biliary drainage to surgery may decrease surgical morbidity.

Keywords Cholecystostomy, Cholecystitis, Gallbladder, Abdominal pain, Laparoscopic cholecystectomy

Background

Acute cholecystitis (AC) is an inflammatory disease of the gallbladder and one of the most frequent causes of acute abdominal pain. Approximately 3–10% of abdominal pain cases are caused by AC, and the incidence increases with age [1].

Early laparoscopic cholecystectomy (LC) is considered safe and effective in patients with acute mild AC [2]. In contrast, biliary drainage is recommended when

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inflammation is severe or when the patient is clinically unstable according to the recent Tokyo Guidelines (TG18) [3]. Percutaneous transhepatic gallbladder drainage (PTGBD), also known as percutaneous cholecystostomy tube placement, is frequently performed in patients with severe cholecystitis or high surgical risk. PTGBD results in rapid improvement of symptoms in approximately 90% of patients [4] and is recommended as a standard drainage method in the TG18 [5]. Furthermore, it acts as a bridge to surgery and a definitive therapy for AC. A recent randomized trial failed to prove that percutaneous cholecystostomy was a safer definitive therapy than emergency LC (within 24 h) for severe AC; significantly more patients needed additional intervention in the group that underwent PTGBD [6]. Therefore, PTGBD should be considered a bridge to surgery unless the patient is extremely ill and not a candidate for surgery. Emergency LCs are not always feasible due to factors such as the availability of surgeons, anesthesiologists, and operating rooms. Moreover, emergency surgery carries considerable risks; there is no proven method for assessing the safety of surgery in emergency situations [7]. Recently, promising new scoring system called Chole-Risk score is developed [8], however, this score is based on the patients with all severity of acute cholecystitis patients without PTGBD. These issues are predominantly related to emergency LC strategies, and interval surgery for severe cholecystitis has been traditionally recommended 4–8 weeks after the onset of symptoms, as the inflammatory chages would be settled by this period and the risk of biliary injuries may decrease. Therefore, early elective surgery (surgey between 24 hous to 4 weeks from onset of symptom) was not recommended. However, this practice is not based on strong evidence, despite the early recovery from septic conditions within a few days after biliary drainage. To date, the optimal timing of surgical intervention for moderate-to-severe cholecystitis after drainage remains uncertain [3, 7]. Although several researchers have investigated this question [9–12], no definitive consensus has been reached. This could partially be due to methodological limitations such as a lack of adjustment for potential confounding factors. A small randomized trial suggested that early LC after PTGBD can be safely performed in patients at high surgical risk, which reduces hospital costs [13]. We hypothesized that early elective surgery after PTGBD may decrease surgical complications and that the time from PTGBD to surgery may affect the outcome.

Methods

Study design

A retrospective chart review was performed for patients with AC who underwent post-PTGBD surgery at Saiseikai Utsunomiya Hospital, Tochigi Prefecture, Japan, from January 2011 to December 2020. Adult patients who underwent early elective cholecystectomy for AC after PTGBD during the same hospital stay were included in the study. The exclusion criteria were as follows: patients aged < 18 years, who had a preoperative diagnosis other than AC, pregnant women, those who had planned major abdominal surgery at the same time, those who underwent interval cholecystectomy (surgery during a separate hospital stay after PTGBD), and those who underwent PTGBD at another hospital.

The patients' baseline characteristics, perioperative findings, and postoperative outcomes were collected from the electronic medical records. The age-adjusted Charlson comorbidity index [14] was used to compare the severity of comorbidity in each patient. Cholecystitis was diagnosed and classified based on TG18 severity grading [15]. They were also classified as calculous or acalculous according to the presence of gallstones or sludge on perioperative imaging; biliary sludge and microlithiasis progress to gallstones and cause similar complications [16]. We excluded abnormal severity grading findings that were derived from the patient's underlying conditions, such as hematologic malignancy, chronic obstructive pulmonary disease, chronic kidney disease, dementia, and antithrombotic use. PTGBD was performed aseptically by a gastrointestinal surgeon or physician under sonographic and radiographic guidance. Candidates for PTGBD were patients with TG18 grade II or III cholecystitis, high surgical risk, or worsening symptoms after the initiation of antibiotic therapy. The patients were screened for malignant diseases, and the presence of risk factors was assessed. Thereafter, laparoscopic or open cholecystectomy was planned according to the attending surgeon's preference. Our study differentiated between emergency, early elective, and interval surgeries. Early elective surgeries were defined as nonemergency surgeries performed during the same hospital stay. Interval surgeries, defined as nonemergency surgeries performed during a separate hospital stay, were excluded from our analysis. Postoperative morbidities were defined as any undesired outcome reported after surgery, with the exclusion of hematological, biochemical, physiological, or patient-reported outcomes [17]. Surgical site infections were defined as infection which occured near or at the incision site and/or deeper underlying tissue spaces and organs within 30 days of a surgical procedure (or up to 90 days for implanted prosthetics) [18]. Biliary injury were defined as bile duct injuries detected intraoperavely or postoperatively. These morbidities were classified according to the Clavien–Dindo classification [19]; major complications were defined as Clavien–Dindo grade III or greater.

Statistical analysis

Patients were categorized into the morbidity group or nonmorbidity group according to the development of postoperative morbidity, and multivariable logistic regression analysis was performed using potential predictive factors for surgical morbidity.

Continuous variables were presented as mean and standard deviation if they followed a normal distribution, as determined by the Shapiro–Wilk test, and as median and interquartile range (IQR) if they did not. Categorical variables are presented as numbers and percentages. Missing values were counted; if they were < 20%, multiple imputations were performed. Between-group differences were compared using Fisher's exact test or the Wilcoxon rank-sum test, as appropriate. Variables with P values < 0.10 in the univariable analysis were included in the multivariable analysis. Stepwise logistic regression was performed using Akaike's information criterion. Multicollinearity was screened using the variance inflation factor. A two-sided P value < 0.05 was considered to indicate statistical significance. All the statistical analyses were performed using EZR [20] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (version 3.4.1; The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 891 patients with AC were treated at our department during the study period. Of these, 690 patients underwent cholecystectomy for AC. After excluding 431 patients (including six who underwent interval cholecystectomy and 12 who underwent simultaneous major abdominal surgery), 259 patients were included in this study (Fig. 1). Among these patients, 32 developed surgical complications, and none of the patients died postoperatively.

Patient characteristics are shown in Table 1. Patients in the morbidity group were significantly older, had a greater comorbidity index, and had a lower white blood cell count on admission than did those in the nonmorbidity group. The time from PTGBD to surgery and from admission to surgery was significantly longer in the morbidity group than in the nonmorbidity group. The perioperative findings are shown in Table 2. Open cholecystectomy was more frequently planned in the morbidity group than in the nonmorbidity group; furthermore, the operative time, estimated blood loss, and postoperative stay were significantly different between the groups. There were only four (1.5%) missing values for C-reactive protein levels; therefore, multiple imputations were performed. Postoperative results are shown in Table 3.

According to the multivariable logistic regression analysis, male sex and the time from PTGBD to surgery were significant predictors of surgical morbidity (Table 4). A sensitivity analysis using complete data showed similar results.

Discussion

In our study, we found a significant association between the time from PTGBD to surgery and overall morbidity. This association can be explained by the fact that the sooner the operative intervention is performed, the less severe the fibrous changes around the gallbladder are. However, early surgical intervention for patients with

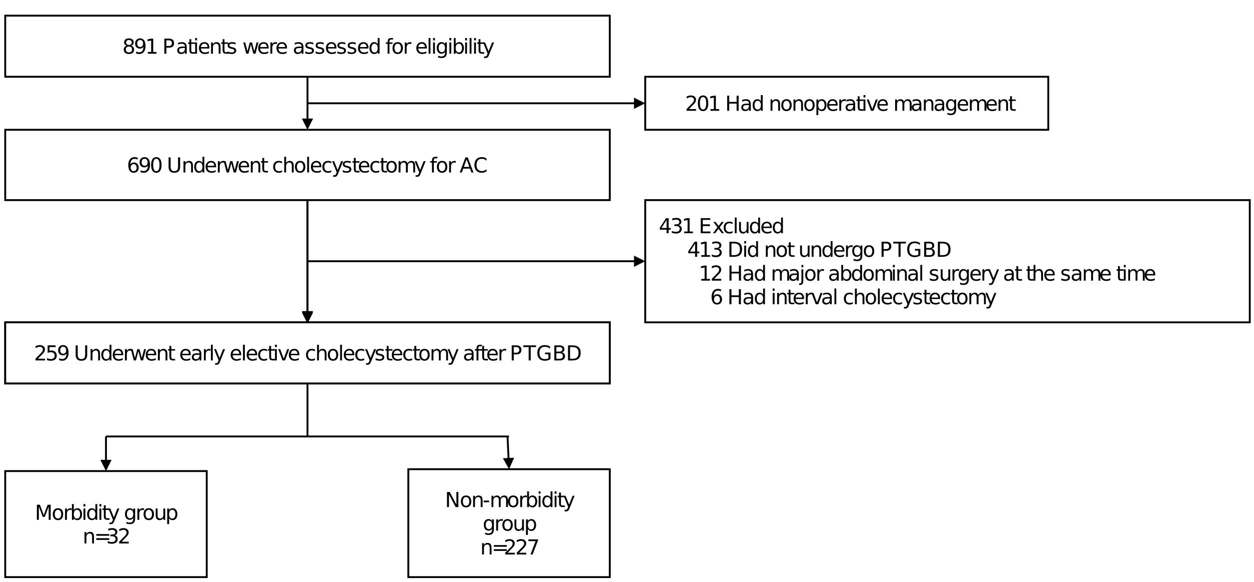

Fig. 1 Flow diagram of patient selection

Table 1 Patient characteristics

Variables		All patients (*n* = 259)	Morbidity group (*n* = 32)	Non-morbidity group (*n* = 227)	*P* value
Age (years), median (IQR)		70 (62–78)	76 (70–80)	69 (61–78)	0.012
Male sex (%)		187 (72.2)	28 (87.5)	159 (70.0)	0.056
Age-adjusted Charlson comorbidity index, median (IQR)		3 (2–4)	4 (3–5)	3 (2–4)	0.010
Calculus cholecystitis (%)		251 (96.9)	29 (90.6)	222 (97.8)	0.062
Concomitant choledocholithiasis (%)		51 (19.8)	8 (25.0)	43 (19.0)	0.476
Severity grading on admission (%)	I	120 (46.3)	13 (40.6)	107 (47.1)	0.785
	II	115 (44.4)	16 (50.0)	99 (43.6)	
	III	24 (9.3)	3 (9.4)	21 (9.3)	
White blood cell count (×10^9/L), median (IQR)		130 (102–162)	106 (91–143)	133 (105–165)	0.022
C-reactive protein (mg/dL), median (IQR)		8.87 (1.87–18.73)	11.90 (1.92–23.14)	8.83 (1.87–17.98)	0.717
Time from symptom to PTGBD (days), median (IQR)		2 (1–3)	3 (2–3)	2 (1–3)	0.122
Time from PTGBD to surgery (days), median (IQR)		8 (6–11)	9 (6–14)	8 (5–10)	0.030
Time from admission to surgery (days), median (IQR)		8 (6–12)	12 (7–14)	8 (6–10)	0.015

PTGBD Percutaneous transhepatic gallbladder drainage, *IQR* interquartile range

Table 2 Perioperative outcome

Variables		All patients (*n* = 259)	Morbidity group (*n* = 32)	Non-morbidity group (*n* = 227)	*P* value
Planned procedure	LC (%)	220 (84.9)	23 (71.9)	197 (86.8)	0.036
	OC (%)	39 (15.1)	9 (28.1)	30 (13.2)	
Operative time (min), median (IQR)		121 (94–156)	152 (111–173)	117 (91–153)	0.004
Estimated blood loss (mL), median (IQR)		50 (10–197)	100 (38–401)	50 (6–170)	0.004
Conversion to laparotomy (%)		40 (17.7)	7 (30.4)	33 (16.2)	0.143
Postoperative stay (days), median (IQR)		6 (4–10)	12 (10–20)	5 (3–8)	< 0.001

LC Laparoscopic cholecystectomy, *OC* Open cholecystectomy, *IQR* interquartile range

Table 3 Severity of postoperative morbidity in the morbidity group

		Morbidity group (*n* = 32)
Clavien-Dindo clas-sificasion (%)	I	8 (25.0)
	II	10 (31.2)
	IIIa	10 (31.2)
	IIIb	2 (6.2)
	IVa	1 (3.1)
	IVb	1 (3.1)
Severe morbidity (%)		14 (43.8)
Surgical site infection (%)		10 (31.2)
Biliary injury (%)		4 (12.5)
Mortality (%)		0

severe cholecystitis may result in a worse postoperative outcome. Therefore, performing PTGBD as a bridge to surgery is rational for soothing both local inflammatory reactions and stabilizing the patient's condition.

Although the surgical timing of AC has long been discussed, the best timing has yet to be determined, especially for moderate-to-severe AC. In some guidelines, early LC is recommended within 7 days of admission [21] and 10 days from symptom onset for all severities of AC [7, 21]. However, the recent TG18 recommends early/urgent LC only for patients with AC grade II or III with no definite operative interval [3]. An important limitation of this global problem is that various terms and definitions for the timing of cholecystectomy exist and are used interchangeably. We believe that the surgical timing of AC should be classified into three categories: emergency (within 24 h of admission), early elective (24 h to 4 weeks from symptom onset), and delayed elective (4 weeks or more from symptom onset). When determining surgical timing after drainage, early elective surgery should be compared with delayed elective surgery because emergency PTGBD tubes are not mandatory if emergency surgery can be performed within 24 h. However, emergency LC is not always possible; furthermore, early elective LC is a practical strategy for moderate-to-severe AC. Despite

Table 4 Univariate and multivariate logistic regression analysis for surgical morbidities

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (years)	1.02 (0.96–1.08)	0.510		
Male sex	3.18 (1.01–10.1)	0.049	3.51 (1.14–10.8)	0.008
Age-adjusted CCI	1.27 (0.89–1.79)	0.184	1.38 (1.09–1.76)	0.143
Calculous cholecystitis	0.30 (0.06–1.48)	0.141		
White blood cell count (10^9/L)	0.99 (0.98–1.00)	0.089	0.99 (0.98–1.00)	0.077
Time from PTGBD to surgery (days)	1.05 (1.00–1.09)	0.044	1.05 (1.01–1.10)	0.022
Planned procedure (OC vs LC)	1.75 (0.67–4.62)	0.256		

CCI Charlson comorbidity index, *PTGBD* Percutaneous transhepatic gallbladder drainage, *OC* Open cholecystectomy, *LC* Laparoscopic cholecystectomy

these unresolved issues, early LC after PTGBD seems comparable to delayed LC in terms of important outcomes (mortality, postoperative complications, or biliary leakage) [22]. A well-designed prospective trial comparing early elective LC with emergency or delayed elective LC is warranted. Our study revealed a very low mortality rate and acceptable morbidity rate for early elective cholecystectomy.

Our study has several limitations. First, owing to its nature as a single-center retrospective study, patient selection bias should be considered. We did not have a strict protocol for the management of AC; each attending surgeon decided the indication and timing of the PTGBD tube and surgical procedure based on their experience. However, previous studies have also had similar limitations regarding the number of included patients and selection biases [12, 23, 24]. Furthermore, our study had a relatively larger real-world sample size than did previous studies that used large databases [25–28], which frequently lacked detailed procedural information regarding the timing and procedure of drainage. Second, the initial AC severity was grade I in approximately 40% of patients in both groups. These patients were initially not critically ill, refractory to antibiotics, and became candidates for PTGBD, which might have affected the outcome. Third, we could not separate the time from PTGBD to surgery from the time from admission to surgery due to the risk of multicollinearity in the multivariable logistic regression analysis. These variables were highly correlated (variance inflation factor > 5), as most of the drainage procedures were performed on the first or second day of admission in our study. Fourth, due to the low occurrence of severe morbidity and mortality, we could not investigate the associations between PTGBD and severe morbidity and mortality. Further prospective studies focusing on this topic are warranted.

Conclusion

In early elective surgery for moderate-to-severe AC requiring PTGBD, a shorter interval from biliary drainage to definitive surgery may decrease surgical morbidity.

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Authors' contributions
Design, data collection, and manuscript preparation: D. K. Conception, revision, and final approval of the manuscript: All authors.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Saiseikai Utsunomiya Hospital's Institutional Review Board (No: 2020–78; July 27, 2020), and the requirement for written informed consent was waived due to the retrospective nature of the study. The research was performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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