Predictive factors for developing acute cholangitis and cholecystitis in patients undergoing delayed cholecystectomy: a retrospective study

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Abstract

Background We evaluated the risk of acute cholangitis and cholecystitis while waiting for cholecystectomy for gallstones.

Methods We retrospectively enrolled 168 patients who underwent cholecystectomy for gallstones after a waiting period and conservative therapy between April 2014 and March 2018 at our hospital. We compared the clinical data from 20 patients who developed acute cholangitis and cholecystitis while waiting for cholecystectomy (group A) with data from 148 patients who did not develop cholangitis and cholecystitis (group B). The risk factors for developing acute cholangitis and cholecystitis and all patients' surgical outcomes were investigated.

Results Preoperatively, significant differences in age (68.6 years vs 60.7 years; p= 0.004) and the number of patients with a previous history of acute grade II or III cholecystitis (55.0% vs 10.8%; p< 0.001) and biliary drainage (20.0% vs 2.0%; p= 0.004) were observed between group A and group B, respectively. Preoperative white blood cell counts (13500/μL vs 8155/μL; p< 0.001) and serum C-reactive protein levels (12.6 mg/dL vs 5.1 mg/dL; p< 0.001) were significantly increased, and serum albumin levels (3.2 g/dL vs 4.0 g/dL; p< 0.001) were significantly decreased in group A vs group B, respectively. Gallbladder wall thickening (≥ 5 mm) (45.0% vs 18.9%; p= 0.018), incarcerated gallbladder neck stones (55.0% vs 22.3%; p= 0.005), and abscess around the gallbladder (20.0% vs 1.4%; p= 0.002) were seen significantly more frequently during imaging in group A vs group B, respectively. Furthermore, investigating patients' surgical outcomes revealed a higher conversion rate to open surgery (20.0% vs 2.0%; p= 0.004), longer operation time (137 min vs 102 min; p< 0.001), and a higher incidence of intraoperative complications (10.0% vs 0%; p= 0.014) in group A vs group B, respectively.

Conclusions Our results suggest that a history of severe cholecystitis is a risk factor for developing acute cholangitis and cholecystitis in patients waiting for surgery, and a risk factor for increased surgical difficulty.

Background

The 2018 Tokyo Guidelines [1], the international practice guidelines for acute cholangitis and cholecystitis, have been published as the third edition. Since 2007, when the first edition was released, early laparoscopic cholecystectomy (LC) was revealed as superior to delayed cholecystectomy [1]. However, following the 2018 Tokyo Guidelines is difficult in community medicine, with problems with uneven distribution of doctors, namely, surgeons and anesthesiologists, as well as aging patients [2, 3]. Therefore, many communities have no choice but to perform conservative therapy for patients with acute cholangitis and cholecystitis, even with the disadvantage of LC after conservative therapy of recurrence while waiting for cholecystectomy; the reported recurrence rate is 2.5%–22% [4, 5]. While various studies of LC are being performed, managing cholangitis and cholecystitis in community medicine remains a challenge, and the risk factors for recurrence are poorly documented. Therefore, we investigated the predictive factors for patients with recurrent cholangitis and cholecystitis who initially underwent successful nonoperative management for gallstones with the aim of providing valuable information that may help determine the appropriate management during the first episode of gallstone-related cholangitis and cholecystitis in community medicine.

Methods

Patients

Between April 2014 and March 2018, 223 patients underwent cholecystectomy at the Department of Surgery, Japanese Red Cross Kanazawa Hospital, Kanazawa, Japan. Of these 248 patients, we excluded 80 patients because they underwent emergency surgery for acute cholecystitis within 72 hours (n = 44), were diagnosed with gallbladder polyp (n = 18) or gallbladder cancer (n = 6), or they underwent choledocholithotomy or simultaneous resection of other organs (n = 12). Therefore, the final study group constituted 168 patients treated by cholecystectomy for acute cholangitis and cholecystitis caused by gallstones after conservative therapy of > 72 hours. Preoperative clinical diagnoses were made on the basis of each patient's history of right upper abdominal pain and tenderness, fever, blood examinations such as blood cell counts, and increased C-reactive protein (CRP), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ- glutamyltranspeptidase, and total bilirubin levels. Additionally, positive signs on ultrasonography or computed tomography (CT) of a thickened gallbladder wall and pericholecystic fluid collection were confirmed by expert ultrasonographers and two radiologists. The severity classification of patients' cholangitis and cholecystitis was graded according to the 2018 Tokyo Guidelines [1]. All resected specimens were evaluated histopathologically by the same pathologist. This study was approved by the Institutional Review Board of the Japanese Red Cross Kanazawa Hospital.

Treatment strategy

Because of the lack of full-time anesthesiologists, we performed initial conservative therapy for acute cholecystitis after obtaining patients' consent and after excluding patients who could not be treated conservatively and who required emergency surgery. Conservative treatment was defined as antibacterial therapy, fasting, infusion management, and analgesia. Antibiotics were tazobactam and piperacillin hydrate, and pain management involved nonsteroidal anti-inflammatory drugs or acetaminophen. A single gastroenterologist performed endoscopic retrograde biliary drainage for acute cholangitis. Oral intake resumed when improved abdominal tenderness was observed, and we discharged patients after confirming improvement in their inflammatory response according to blood examination findings. When we discharged patients from the hospital, we discussed the necessity of surgery and scheduled elective LC at least 4 weeks after conservative therapy. We defined preoperative waiting days in this study as from the day the appointment for surgery was scheduled to the day of the elective surgical procedure.

LC was performed using a standard four-trocar technique. Briefly, the anesthetized patient was placed in the standard supine, crucifix, reverse-Trendelenburg position, with the surgeon on the patient's left side. Pneumoperitoneum was achieved by visually-guided, cannular carbon dioxide insufflation. Dissection began at Calot's triangle to confirm a safe surgical field of view, then the cystic duct, common bile duct, and cystic artery were exposed and divided between the clips. Intraoperative cholangiography was not routinely performed. When the anatomy of Calot's triangle was unclear or inflammation in the gallbladder neck was advanced, the bile duct stump was treated at the neck, and cholecystectomy was limited to a partial resection. The gallbladder was carefully mobilized from the liver bed using electrocautery, and an endo-bag was always used to remove the gallbladder to prevent wound infection. The abdominal cavity was irrigated before the trocars were removed, and the fascial defects were closed.

Data collection

The data were retrospectively collected from medical records and operative reports. We divided patients into a recurrent group (group A) and a nonrecurrent group (group B) of acute cholangitis and cholecystitis while waiting for cholecystectomy, and we evaluated the outcomes for each group. We evaluated patients' clinical characteristics on admission, namely, patient's American Society of Anesthesiologists physical status (ASA-PS) score and age-adjusted Charlson comorbidity index (CCI), medical history associated with gallstones, laboratory data before cholecystectomy, abdominal CT, and surgical outcomes. For the analyses, we used the highest values for the laboratory data and CT measurements from the first episode of acute cholangitis and cholecystitis. Evaluated surgical outcomes were the conversion rate, operation time, blood loss (minimal bleeding was defined as 0 mL), operative complications, presence or absence of a drain, and length of hospital stay.

Statistical analysis

Values were expressed as means ± standard deviations, and we used the two-sided Student's t test and the Mann–Whitney U test for continuous data. The cutoff values for the continuous variables were calculated using a receiver operating characteristic curve analysis, and comparisons were made using the Chi-squared test with Yates' correction. Variables considered to have an apparent confounding effect were excluded from the multivariate analysis, even if found to be significant in the univariate analysis. All statistical analyses were performed using the SPSS software package, version 10.0 (IBM Corp., Armonk, NY, USA). Significance was defined as $P < 0.05$.

Results

Patients' characteristics and preoperative findings

The mean age of all patients was 61.6 ± 13.2 years (range, 31–92 years), and the 168 (85 men and 83 women) patients who underwent cholecystectomy were divided into two groups. Patients with recurrent acute cholangitis and cholecystitis while waiting for cholecystectomy constituted group A, and those with no recurrence constituted group B. Data from the two groups are summarized in *Table 1.* We saw no difference for sex ratio, body mass index, ASA-PS, and incidence of a history of abdominal surgery. Age-adjusted CCI (p = 0.063) and the number of preoperative waiting days (p = 0.065) in group A tended to be higher vs group B. Patients in group A were, on average, almost 8 years older than those in group B (p = 0.004). The average period from the first episode to the day of acute cholangitis and cholecystitis recurrence in group A was approximately 39 days (range, 17–80 days).

Medical history associated with gallstones

Table 2 shows that there were no differences in the incidence of a history of cholangitis and the rate of performing endoscopic therapy between the two groups. In contrast, the rate of patients with grade II or III acute cholecystitis was significantly higher in group A (55.0% [11/20]) vs group B (10.8% [16/148]; p< 0.001). We performed preoperative percutaneous transhepatic gallbladder drainage (PTGBD) in 20.0% of patients in group A and 2.0% of patients in group B (p = 0.004).

Laboratory data before cholecystectomy

Preoperative laboratory data (*Table 3)* showed significantly increased white blood cell (WBC) counts (13500 ± 5472/µL vs 8155 ± 4249/µL; p< 0.001) and CRP levels (12.6 ± 8.9 mg/dL vs 5.1 ± 9.9 mg/dL; p< 0.001), and significantly decreased serum albumin levels (3.2 ± 0.9 g/dL vs 4.0 ± 0.6 g/dL; p< 0.001) between group A and group B, respectively. There were no differences in the serum hepatobiliary enzyme levels.

Abdominal CT

Imaging studies (*Table 4)* revealed gallbladder wall thickening (≥ 5 mm) in 45.0% vs 18.9% (p = 0.018), incarcerated gallbladder neck stones in 55.0% vs 22.3% (p = 0.005), and abscess around the gallbladder in 20.0% vs 1.4% (p = 0.002) of the patients in group A vs group B, respectively. There were no differences in gallbladder diameter or gallbladder stone size or number.

Results of univariate and multivariate analyses

Grade II or III acute cholecystitis (p = 0.002, odds ratio (OR): 10.630), albumin values ≤ 4 g/dL (p = 0.020, OR: 8.702), and gallbladder wall thickening (p = 0.047, OR: 4.099) were found by logistic regression analysis to be independent risk factors for recurrence during standby for cholecystectomy (*Table 5)*.. The area under the receiver operating characteristic curve for albumin level between group A and group B was 0.778, and the best cutoff value was 4.0 g/dL. We removed CRP because Pearson's correlation coefficient between CRP and WBC was 0.804.

Surgical outcomes

Blood loss volume did not differ significantly between the two groups (p = 0.247) (*Table 6)*.. However, the mean operation time was 137 min (range, 40–220 min) in group A and 102 min (range, 40–216 min) in group B (p< 0.001). Conversion from LC to open cholecystectomy (OC) was usually implemented to prevent bile duct injury within 30 min of beginning the laparoscopy. The conversion rate was significantly higher in group A (20.0% [4/20]) vs group B (2.0% [3/147], p = 0.004). The total number of operative complications in the two groups did not differ significantly (p = 0.076); however, group A had a significantly higher incidence of intraoperative complications (p = 0.014), with one patient experiencing massive bleeding (> 1000 mL) and one experiencing bile duct injury. There were no differences in postoperative complications between the groups. Wound infection occurred in one patient in group A. In group B, postoperative complications occurred in six patients; three patients experienced wound infection, one patient experienced pneumonia, and one experienced intestinal obstruction; all patients were treated conservatively. A drain was inserted into the liver bed in half of group A patients, but only in approximately 10% of group B patients (p< 0.001). The average length of hospital stay was 7.4 ± 4.1 days (range, 3–20 days) in group A and 5.7 ± 4.2 days (range, 3–45 days) in group B (p = 0.102). Histopathological examination was performed for all patients, with no diagnoses of gallbladder cancer.

Discussion

Acute cholecystitis (AC) is a common surgical diagnosis requiring inpatient admission [6]. Since the 2007 Tokyo Guidelines presented the world's first classification system, the standard treatment for mild and moderate acute cholecystitis is early LC. However, uniformly implementing early LC for AC is difficult because of a lack of experienced surgeons, anesthesiologists, and clinical and management commitments such as support staff, particularly in community medicine [2, 3]. Moreover, the higher risk of postoperative morbidity, particularly in older patients with cardiopulmonary disease or other severe illnesses, makes it difficult to perform early cholecystectomy [7, 8]. However, a disadvantage of conservative treatment is the potential for recurrence [4, 5]. We performed the present study to determine the risk factors associated with recurrence after conservative therapy for acute cholangitis and cholecystitis.

The indications for LC for patients following conservative therapy for acute cholangitis and cholecystitis and the optimal timing for delayed cholecystectomy have not yet been clarified [8, 9]. We schedule elective LC at least 4 weeks after conservative therapy, with an interval of preoperative waiting days as long as 46.7 ± 27.8 days in group A and 35.4 ± 25.8 days in group B, in this study. The average period of recurrence was 38.8 ± 16.9 days, confirming the problem with recurrence while waiting for cholecystectomy.

Significant differences in the number of patients with acute grade II or III cholecystitis requiring preoperative PTGBD were seen in group A vs group B, suggesting that previous cholecystitis with severe inflammation was a risk factor for recurrent acute cholangitis/cholecystitis. This hypothesis was supported by the significantly increased preoperative WBC counts and CRP levels and significantly decreased albumin levels in group A, and the more frequent imaging findings of gallbladder wall thickening (≥ 5 mm) and abscess around the gallbladder in group A. Several reports [10, 11] found that incarcerated gallbladder neck stones was a high risk factor for AC. Our findings also suggested that incarcerated gallbladder neck stones was a risk factor for recurrence while waiting for cholecystectomy. In contrast, acute cholangitis, gallstone-related pancreatitis, endoscopic therapy, and the size and number of gallstones were not risk factors for recurrence of acute cholangitis and cholecystitis, in our study.

A recent meta-analyses of randomized studies showed that the conversion rate from LC to OC ranged from 12.7%–23.6% [12–16], and the frequency of perioperative complications in LC has been reported to be 2.7%–13.1% [17, 18]. However, the rate of conversion and perioperative complications associated with LC for patients after conservative therapy in hospitals where this strategy is the standard treatment for AC is likely lower than reported rates. Sippey et al. used the American College of Surgeons database and found that conversion to open surgery was required in 436/7242 (6.0%) patients who underwent LC for AC [19]. In the present study, we intended to complete LC without conversion to open surgery. The conversion rate was 4.2% for all 168 patients, and in group B, only 2.0% of patients required conversion to OC. Giger et al. reported that the frequency of postoperative complications was 4.0% in 22 953 patients who underwent LC [17]. The postoperative complication rate in our study was 3.6% and in good agreement with previous reports. In contrast, the conversion rate to OC was 20.0% in group A. We emphasize safety in our surgical procedures and convert to OC without hesitation in difficult cases; however, the rate of serious intraoperative complications in group A was significantly higher than that in group B, indicating the need for improvement, in our hospital.

In previous reports, in the late stage, chronic inflammation tended to result in firm adhesion of the gallbladder to the surrounding organs, which led to scarring and contraction of pericystic tissues [20–22] and increased gallbladder wall thickness. Furthermore, increased preoperative leukocytosis was a statistically significant risk factor for conversion to open surgery [23, 24]. It is our firm belief that a recurrent high inflammatory response in a short period leads to changes that make it difficult for surgeons to recognize the layers and extend the dissection, which increases the risk for conversion, prolongs operation time, and increases intraoperative complications.

Our study was not without limitations. First, the study sample size was small, and this was a retrospective study performed at a single institution. Second, patients in group A had a high risk of selection bias because they tended to undergo operation later after the first episode because they were older or potentially critically ill patients with higher surgical risks compared with patients in group B. However, LC was performed by the same method and the same surgeons during the entire study period.

Conclusions

Our results strongly suggest that patients who undergo conservative therapy for grade II or III AC should be carefully followed for recurrence of cholangitis and cholecystitis. Moreover, these patients could have an increased risk of surgical complications, higher conversion rates, and more intraoperative complications.

List Of Abbreviations

LC: laparoscopic cholecystectomy, CRP: C-reactive protein, CT: computed tomography, ASA-PS: American Society of Anesthesiologists physical status, CCI: Charlson comorbidity index, PTGBD: percutaneous transhepatic gallbladder drainage, WBC: white blood cell, OC: open cholecystectomy, AC: Acute cholecystitis

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all patients for publication of this report, and this study was approved by the Institutional Review Board of the Japanese Red Cross Kanazawa Hospital. A copy of the written consent is available for review by the Editor of this journal.

Consent for publication

Not applicable.

Availability of data and material

All data are available without restriction. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors’ contributions

TM, KN, FF, and HT designed the study. TM, YF, HS, DM, YO, and TM performed data acquisition, analysis, and interpretation. TM prepared the manuscript. KN, FF, TN, and HT revised the paper critically. All authors read and approved the final manuscript.

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Tables

Table 1 Results of the analyses of patients' preoperative clinical variables

	Group A (n=20)	Group B (n=148)	p-value
Age (years)			0.004
Mean	68.6±14.6	60.7±12.7	
Range	35–92	31–88	
Sex			0.406
Male	10	75	
Female	10	73	
BMI (kg/m^2)	22.3±3.62	23.2±3.30	0.504
ASA-PS			0.157
1	1 (5%)	30 (20.3%)	
2	15 (75%)	80 (54.1%)	
3	4 (20%)	38 (25.7%)	
Age-adjusted CCI (n)			0.063
0/1/2/3/4/5/6/7/8	1/1/4/1/8/3/0/2/0	10/18/37/29/31/14/6/2/1	
Mean	3.7±1.7	2.9±1.6	
History of abdominal surgery (n)	6 (30%)	58 (39.2%)	0.473
Preoperative waiting days (n)			0.065
Mean	46.7±27.8	35.4±25.8	
Range	12–103	7–180	
Period from the first episode of acute cholangitis and cholecystitis to the day of recurrence (mean, days)	38.8±16.9		

BMI: Body Mass Index

ASA-PS: American Society of Anesthesiologists physical status

CCI: Charlson comorbidity index

Table 2 Results of the analyses of patients with a medical history of gallstones

	Group A (n=20)	Group B (n=148)	p-value
Cholangitis (grade)			
I	3 (10%)	51 (34.5%)	0.124
II	1 (5%)	10 (6.8%)	0.771
III	0 (0%)	2 (1.35%)	0.970
II + III	1 (5%)	12 (8.1%)	0.630
Cholecystitis (grade)			
I	5 (25%)	69 (46.6%)	0.093
II	7 (35%)	13 (8.8%)	0.003
III	4 (20%)	3 (2.0%)	0.004
II + III	11 (55%)	16 (10.8%)	<0.001
Pancreatitis	5 (25%)	19 (12.8%)	0.170
Endoscopic therapy	5 (25%)	37 (25%)	1.000
PTGBD	4 (20%)	3 (2.0%)	0.004

Values are presented as number (%)

PTGBD: percutaneous transhepatic gallbladder drainage

Table 3 Results of the analyses of patients' laboratory data before cholecystectomy

	Group A (n=20)	Group B (n=148)	p-value
WBC (/μL)	13500±5472	8155±4249	<0.001
CRP (mg/dL)	12.6±8.9	5.1±9.9	<0.001
Plt ($\times 10^4$/μL)	22.8±9.6	22.9±7.6	0.863
Albumin (g/dL)	3.2±0.9	4.0±0.6	<0.001
AST (IU/L)	180.8±250.5	127.4±185.4	0.320
ALT (IU/lL)	157.9±256.8	135.2±170.5	0.930
ALP (IU/L)	557.4±453.2	372.5±223.7	0.637
γGT (IU/L)	298.9±368.5	180.4±248.7	0.527
T-Bil (mg/dL)	2.4±1.4	1.8±1.7	0.065
Cre (mg/dL)	0.95±0.37	0.84±0.24	0.464

WBC: white blood cell

CRP: C-reactive protein

Plt: platelet

AST: aspartate aminotransferase

ALT: alanine aminotransferase

ALP: alkaline phosphatase

γGT: γ-glutamyltranspeptidase

T-Bil: total bilirubin

Cre: creatinine

Table 4 Results of the analyses of patients' abdominal computed tomographic imaging findings

	Group A (n=20)	Group B (n=148)	p-value
Short gallbladder diameter (mm)	32.4±8.6	30.6±8.4	0.515
Long gallbladder diameter (mm)	70±16.3	64.1±17.7	0.070
Gallbladder wall thickness (>5mm)	9 (45%)	28 (18.9%)	0.018
Stone size (<5 mm)	9 (45%)	83 (56.1%)	0.619
Multiple stones	17 (85%)	113 (76.4%)	0.615
Stone incarceration	11 (55%)	33 (22.3%)	0.005
Abscess around the gallbladder	4 (20%)	2 (1.4%)	0.002

Table 5 Results of the multivariate analyses

	Multivariate analysis (odds ratio, 95% CI)	p-value
Age (years)	0.977 (0.269, 3.545)	0.972
Cholecystitis grade II + III	10.63 (2.348, 48.135)	0.002
PTGBD	3.082 (0.359, 26.478)	0.305
WBC	3.305 (0.813, 13.434)	0.095
Albumin	8.702 (1.415, 53.516)	0.020
Gallbladder wall thickness	4.099 (1.018, 16.512)	0.047
Stone incarceration	2.500 (0.709, 8.813)	0.154
Abscess around the gallbladder	1.495 (0.209, 10.719)	0.689

CI: confidence interval

PTGBD: percutaneous transhepatic gallbladder drainage

WBC: white blood cell

Table 6 Results of patients' operative findings

	Group A (n=20)	Group B (n=148)	p-value
Procedure			1.000
Open surgery (n)	0	1	
Laparoscopy (n)	20	147	
Conversion to open cholecystectomy (n)	4/20 (20%)	3/147 (2.0%)	0.004
Time (min)	137±40.6	102±30.6	<0.001
Blood loss volume (mL)	96.7±135.2	39.7±186.4	0.247
Drain placement	10 (50%)	16 (10.8%)	<0.001
Complications (n)	3 (15%)	5 (3.4%)	0.076
Intraoperative (n)	2 (10%)	0	0.014
Specifics	massive bleeding (n=1) bile duct injury (n=1)		
Postoperative (n)	1 (5%)	5 (3.4%)	0.538
Specifics	wound infection (n=1)	wound infection (n=3) pneumonia (n=1) ileus (n=1)	
Postoperative hospital stay (days)	7.0±4.1	5.7±4.2	0.102

Values are means ± standard deviations