

# Aggressive Laparoscopic Cholecystectomy in Accordance with the Tokyo Guideline 2018

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## ABSTRACT

**Objectives:** The Tokyo Guidelines 2018 have been widely adopted since their publication. However, the few reports on clinical outcomes following laparoscopic cholecystectomy have not taken into account the severity of the acute cholecystitis and the patient's general condition, as estimated by the Charlson comorbidity index. This study aimed to assess the relationships between severity, Charlson comorbidity index, and clinical outcomes subsequent to laparoscopic cholecystectomy.

**Methods:** We extracted the retrospective data for 370 Japanese patients who underwent emergency or scheduled early laparoscopic cholecystectomy within 72 hours from onset between February 2015 and August 2018. We compared postoperative factors in relationship to severity (grade I versus grade II/III). Then, we made a similar comparison between those with low ( $< 4$ ) and high Charlson comorbidity index ( $\geq 4$ ).

**Results:** According to the Tokyo guideline 2018 levels of severity, there were 282 (76.2%), 61 (16.5%), and 27 (7.3%) patients in grades I, II, and III, respectively. With regards to surgical outcomes, the mean operating time was 62.3 minutes and the mean blood loss was 24.4 mL.

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The mean hospital stay was 3.6 days, with no mortalities. Blood loss was the only factor affected by severity (20.9 mL versus 60.1 mL,  $P = 0.0164$ ), and operating time was the only factor affected by high Charlson comorbidity index (53.4 versus 67.8 minutes,  $P = 0.0153$ ).

**Conclusion:** Our aggressive strategy is acceptable, and severity and Charlson comorbidity index are not critical factors suggesting the disqualification of early laparoscopic cholecystectomy in patients with any grade acute cholecystitis.

**Key Words:** Acute Cholecystitis, Laparoscopic Cholecystectomy, Tokyo Guideline 2018, Charlson Comorbidity Index, Comprehensive Complication Index.

## INTRODUCTION

Acute cholecystitis (AC) is the most frequent complication of cholelithiasis, and laparoscopic cholecystectomy (LC) is the gold-standard procedure for AC.<sup>1</sup> Some studies have demonstrated that early LC brings better clinical outcomes than delayed LC, especially if performed within 72 hours of AC onset.<sup>2,3</sup>

The 2013 Tokyo Guidelines for the management of acute cholangitis and cholecystitis were revised and republished in 2018 (TG18) and now include treatment recommendations for AC.<sup>4,5</sup> In these guidelines, LC for grade III (GIII) AC may be performed only under strict conditions, in particular, it must be done in an institution with expert laparoscopic surgeons who are equipped to deal not only with severe LC but also with bail-out procedures.<sup>6</sup> The TG18 states that a Charlson Comorbidity Index (CCI)  $\geq 6$  and an American Society of Anesthesiologists-physical status (ASA-PS)  $\geq 3$  are to be considered surgical risk factors in GI and GII AC patients. For the GIII AC patients, some indicative risk factors make them candidates for negative prognostic factors, and currently, patients with a CCI  $\geq 4$  or/and an ASA-PS  $\geq 3$  may not undergo surgery.

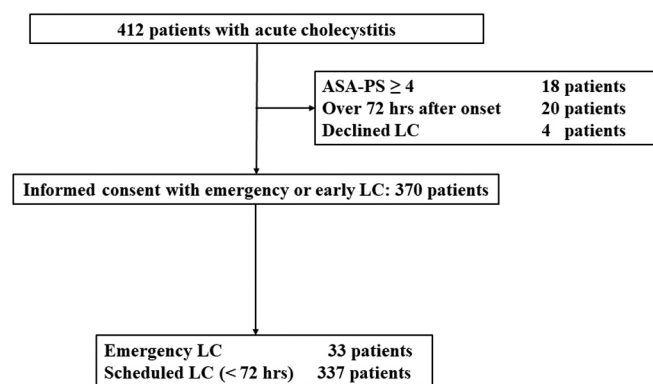
In this study, we conducted a retrospective study to evaluate the safety and feasibility of LC for GII and GIII AC from the viewpoint of the relationship between the patients' general condition and their surgical outcomes.

## METHODS

We extracted the data for 370 Japanese patients with AC who underwent LC at our hospital between February 2015 and August 2018. The hospital policy was to perform LC in patients with GI-GIII AC who could tolerate general anesthesia and a pneumoperitoneum. All the patients enrolled in the study underwent emergency or early scheduled LC within 72 hours of onset. We did not routinely use the CCI and ASA-PS to exclude surgical intervention in this study because the gastroenterologists had already evaluated operative tolerance, and if ASA-PS  $\geq 4$ , the patient was treated by conservative therapy or percutaneous transhepatic gallbladder drainage (PTGBD). A flow chart of the enrolled patients is shown in **Figure 1**.

### Ethical approval

All procedures performed in this study that involved human patients were in accord with the ethical standards of the institutional review board and in accord with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients included in the study.



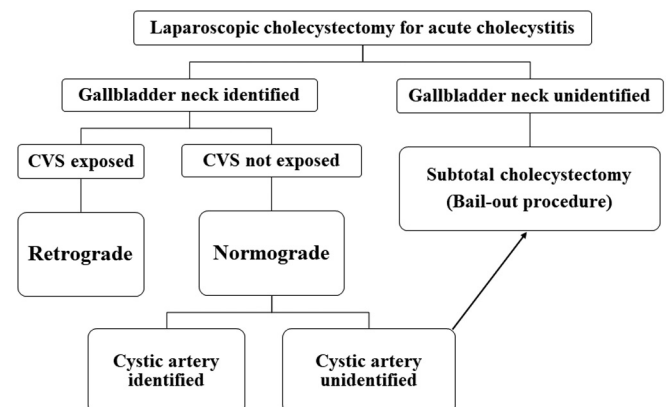
**Figure 1.** Flow chart of enrolled patients. Forty-two patients were excluded due to high ASA-PS, long-interval after onset, and declined to undergo LC. Finally, 370 patients underwent emergency or early scheduled LC.

## Surgical procedure

Following the Tokyo Guideline 2013 (TG13), LC was performed using a 3-port (one 12-mm trocar and two 5-mm trocar) technique. All operations were performed by endoscopic surgical skill qualification system: qualified surgeons by the Japan Society for Endoscopic Surgery (JSES). The retrograde manner was the routine procedure, provided a critical view of safety was confirmed. When, due to severe inflammation, a critical view of safety could not be confirmed, we converted to the normograde manner. When it was still too difficult to achieve in the normograde manner without confirming cystic artery, we finally performed laparoscopic subtotal cholecystectomy as a bail-out procedure and positioned an information drain tube for bile leakage and postoperative bleeding. All the surgical procedures about LC are shown in **Figure 2**.

### Data collection

The preoperative clinical data and surgical outcomes were collected for all patients enrolled in the study. The preoperative data collected and quantified included total bilirubin (T-Bil), direct bilirubin (D-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP),  $\gamma$ -glutamyl transpeptidase (GGT), albumin (Alb), blood urea nitrogen (BUN), creatinine (Cre), amylase (Amy), C-reactive protein (CRP), white blood cell count (WBC), platelet count (Plt), prothrombin time-international normalized ratio (PT-INR), partial pressure of oxygen in arterial blood (PaO<sub>2</sub>), CCI, and ASA-PS. The parameters for



**Figure 2.** Surgical strategy in LC for acute cholecystitis. Our surgical strategy in LC is shown. Cholecystectomy is defined as transection of both cystic artery and cystic duct. Therefore, if we cannot expose gallbladder neck, we perform subtotal cholecystectomy without ligating cystic artery.

surgical outcomes, which were also quantified, included operating time, blood loss, conversion to open surgery, comprehensive complication index,<sup>7</sup> mortality, and postoperative hospital stay. Postoperative complications were evaluated according to Clavien-Dindo classification.<sup>8</sup>

### Statistical analysis

Data are presented as numbers and percentages for categorical variables and as mean  $\pm$  standard deviations for continuous variables. Statistical analysis was performed using  $\chi$ -square tests for categorical variables and Student's *t* tests or Mann-Whitney U tests for continuous variables. Furthermore, using the confounding factors of age, sex, BMI, and CCI, we performed case-matched analyses between the mild group (GI) and the severe group (GII/III), and examined the differences between the groups after matching. In addition, assigning CCI of 0 to 3 to a low-risk group and assigning CCI of 4 or more to a high-risk group, we performed trend matching based on confounding factors such as age, sex, body mass index (BMI), and cholecystitis severity, and the differences between groups after matching were calculated. All statistical analyses were performed using JMP Pro version 15 (SAS Institute Inc., Cary, NC, USA). A *P* value  $<$  .05 was evaluated as significant difference.

## RESULTS

Patient characteristics and surgical outcomes are shown in **Table 1**. There was no mortality and no conversion to open surgery among all the patients enrolled. In the severe group, the mean age of patients, the T-Bil, D-Bil, AST, ALT, LDH, ALP, Alb, CRP, WBC, PT-INR, PaO<sub>2</sub>, CCI, and ASA-PS were all significantly higher in the preoperative data. In relationship to surgical outcomes, operating time was significantly longer (60.2 versus 68.8 minutes, *P* = .037) and blood loss was also significantly higher (13.3 versus 59.9 mL, *P*  $<$  .0001) in the severe group. There was no conversion to open surgery in either group, however, seven cases (2.5%) in the mild group underwent subtotal cholecystectomy as a bail-out procedure. There was no significant difference in conversion rate of bail-out procedure (2.4% versus 0.0%, *P* = .3064). The comprehensive complication index was significantly higher in the severe group (0.6 versus 3.3, *P* = .0006), and the rate of all postoperative complications was higher in the severe group (4.6% versus 10.2%, *P* = .0002). However, 15 cases of postoperative complications occurred within grade II of the Clavien-Dindo classification. There were another

seven postoperative complication cases with higher than grade IIIa of the Clavien-Dindo classification (three cases in the mild group and four cases in the severe group). Of these, three cases were cholangitis due to the passage of an intraoperative stone to the common bile duct, two cases involved bile leakage, and two cases involved postoperative intra-abdominal abscesses. All these were treated by endoscopic or percutaneous drainage. Duration of postoperative hospital stay was significantly longer in the severe group (4.4 versus 3.4 days, *P* = .0035), but there was no mortality in either group. There were not any delayed or recurrent postoperative complications required interventions during six months after discharge.

In this population, the LC for GII/III AC required significantly longer operating time compared to the LC for GI AC (62.3 versus 68.8 minutes, *P* = 0.037). Against this background, case matching was performed for the mild and severe groups by confounding factors such as age, sex, BMI, and CCI to compare the difficulty of LC according to operating time. There were 87 matched cases in the groups where the patients had similar backgrounds, as shown in **Table 2**. With regards to surgical outcomes, blood loss was the only factor affected by AC severity (20.9 versus 60.1 mL, *P* = .0164), and there were no other significant differences in the outcomes.

The TG18 has emphasized that patients with high CCI are at risk for perioperative complications, and it therefore does not recommend LC for GIII AC patients with high CCI except at high-volume centers with expert surgeons. Against this background, we also performed a case-matched analysis between the low-risk and high-risk groups. In this analysis, various factors such as age, sex, BMI, ASA-PS, and AC severity were confounded. A significant difference was found only in CCI (2.9 versus 4.5, *P*  $<$  .0001). With regards to the surgical outcomes, the operating time was the only factor affected by the high CCI (53.4 versus 67.8 minutes, *P* = .0153), and there were no significant differences in postoperative complication rate or comprehensive complication index.

## DISCUSSION

We often encounter difficult AC cases in the course of the LC procedure due to severe inflammation and adhesions, some of which require conversion to open surgery because the patient's safety will take precedence.<sup>9</sup> Factors associated with severe AC have previously been reported as age, male, high CRP levels, cardiovascular disease,

**Table 1.**  
Patients Characteristics and Surgical Outcomes

	All	Mild (GI)	Severe (GII/GIII)	P value (Mild versus Severe)
Number (n)	370	282	88	
Gender (Male/Female)	189/181	145/137	44/44	0.8163
Age (years)	63.0 ± 15.0 <sup>a</sup>	61.6 ± 14.1	68.1 ± 14.9	0.0002
BMI (kg/m <sup>2</sup> )	24.4 ± 3.6	24.5 ± 3.6	24.1 ± 3.6	0.3571
T-Bil (mg/dL)	1.07 ± 0.92	1.0 ± 0.9	1.3 ± 0.9	0.0106
D-Bil (mg/dL)	0.5 ± 0.7	0.5 ± 0.7	0.6 ± 0.3	0.0253
AST (IU/L)	71.0 ± 170.0	54.4 ± 105.9	124.3 ± 288.4	0.0018
ALT (IU/L)	82.0 ± 170.0	70.7 ± 112.9	118.2 ± 282.0	0.0323
LDH (IU/L)	222.0 ± 114.0	206.4 ± 73.1	271.3 ± 185.1	< 0.0001
ALP (IU/L)	322.0 ± 206.0	303.8 ± 192.0	379.1 ± 237.6	0.0045
GGT (IU/L)	154.0 ± 217.0	141.6 ± 184.5	193.4 ± 295.7	0.0617
Alb (g/dL)	4.2 ± 1.3	4.3 ± 1.4	3.8 ± 0.8	< 0.0001
BUN (mg/dL)	15.2 ± 11.0	14.6 ± 11.4	16.9 ± 9.8	0.1147
Cre (mg/dL)	0.9 ± 1.2	0.8 ± 1.1	1.0 ± 1.4	0.2685
Amy (IU/L)	106.0 ± 173.0	97.7 ± 126.8	127.8 ± 257.0	0.2681
CRP (mg/dL)	4.1 ± 7.9	1.9 ± 4.9	9.1 ± 10.6	< 0.0001
WBC (/μL)	7389.0 ± 4177.0	6327.5 ± 2527.8	10792.3 ± 6165.0	< 0.0001
Plt (10 <sup>4</sup> /μL)	23.6 ± 7.5	24.0 ± 6.8	22.6 ± 9.4	0.1333
PT-INR (no unit)	1.04 ± 0.6	0.98 ± 0.08	1.21 ± 1.1	< 0.0001
PaO <sub>2</sub> (mmHg)	82.4 ± 16.6	83.9 ± 13.5	78.6 ± 22.42	0.0305
CCI (points)	3.6 ± 1.9	3.4 ± 1.8	4.2 ± 2.0	0.0309
ASA-PS (n, %)				
I	137, 37.0	120, 42.6	17, 19.3	< 0.0001
II	196, 53.0	143, 50.7	53, 60.2	
III	37, 10.0	19, 6.7	18, 20.5	
Operating time (min)	62.3 ± 23.7	60.2 ± 22.3	68.8 ± 26.8	0.0037
Blood loss (mL)	24.4 ± 68.6	13.3 ± 40.1	59.9 ± 114.5	< 0.0001
Conversion to open (n)	0	0	0	1.0000
Conversion to bail-out procedure (n)	7	7	0	0.3064
Comprehensive complication index	0.7 ± 0.9	0.6 ± 3.9	3.3 ± 9.3	0.0006
Postoperative complication (n, %)	22, 5.9	13, 4.6	9, 10.2	0.0002
Mortality (n)	0	0	0	1.0000
Postoperative hospital stay (days)	3.6 ± 3.0	3.4 ± 1.7	4.4 ± 5.2	0.0035

<sup>a</sup>Continuous data were expressed as mean ± standard deviation.

diabetes, and delayed surgery. Furthermore, increased patient age and more frequent complications with systemic diseases raises the mean CCI of the population. However, these background factors may be associated

with high incidence of AC and rapid progression to a severe condition.<sup>10</sup> As a result, they may also lead to delayed surgery with perioperative risks. In this study, LC was performed in all cases of AC except under severe

**Table 2.**  
Case Matched Analyses Based on AC Severity

	Mild (GI)	Severe (GII/GIII)	P value (Mild versus Severe)
Number (n)	87	87	-
Gender (Male/Female)	46/41	44/43	0.7616
Age (years)	67.9 ± 13.9 <sup>a</sup>	67.8 ± 14.7	0.9701
BMI (kg/m <sup>2</sup> )	24.3 ± 4.3	24.1 ± 3.6	0.7302
CCI (points)	4.2 ± 2.0	4.0 ± 2.0	0.6791
ASA-PS (n, %)			
Group I	26, 29.9	17, 19.5	0.0770
Group II	53, 60.9	53, 60.9	
Group III	8, 9.2	17, 19.5	
Operating time (min)	62.1 ± 24.5	68.9 ± 26.9	0.0861
Blood loss (mL)	20.9 ± 63.0	60.1 ± 27.0	0.0164
Conversion to open (n)	0	0	1.0000
Comprehensive complication index	1.3 ± 5.5	3.3 ± 9.3	0.0961
Postoperative complication (n, %)	5, 5.7	13, 14.9	0.0531
Mortality (n)	0	0	1.0000
Postoperative hospital stay (days)	3.6 ± 2.9	4.4 ± 5.3	0.2667

<sup>a</sup>Continuous data were expressed as mean ± standard deviation.

conditions (ASA-PS ≥ 4), and no cases were converted to open surgery, and no mortality was observed. Therefore, the surgical outcomes and postoperative course of LC treatment were not changed according to the severity of AC.

In the current situation, the optimal timing for PTGBD in AC has not been strictly determined due to some controversial matters and because the supremacy of PTGBD for severe AC has not yet been confirmed. Previous reports have suggested that PTGBD followed by delayed LC in critically ill patients, rather than early LC, may be an acceptable strategy, giving a lower conversion to open surgery and lower mortality.<sup>11,12</sup> Loozen et al.<sup>13</sup> recently reported the results of a randomized clinical trial named the CHOCOLATE study. In this study, LC was found to be superior to PTGBD in the treatment of high-risk patients with AC: LC significantly reduced the major complication rate, the utilization of healthcare resources, and medical costs.<sup>13</sup> From this clinical evidence and from the TG13 and TG18 statements, we have, in principle, applied emergency or scheduled early LC for all AC patients.

Due to the selection criteria for our population, the preoperative data was poorer in the severe group than in the

mild group. The TG18 proposes three negative predictors and two risk factors as warning signs, and recommends that patients with these factors should be considered for elective surgery. In our study, the negative predictors applied in 185 cases (65.6%) of the mild group (ASA-PS 19 cases, and CCI 183 cases) and in 73/88 cases (82.9%) of the severe group (neurological dysfunction eight cases, respiratory dysfunction five cases, jaundice four cases, ASA-PS 17 cases, and CCI 66 cases). Therefore, surgical outcomes were worse in the severe group than in the mild group. This is the result of having a case group that includes all ages, BMI, CCI, ASA-PS, and it is possible that the cases in the severely ill group were overestimated. Accordingly, we re-evaluated our results by matching these confounding factors. With the case matched analysis, only blood loss significantly increased in the severe group. The amount of blood loss cannot be measured separately from the bile juice aspirated following gallbladder puncture or perforation of the gallbladder wall, and from the ascites volume. Furthermore, in our group, we have endoscopic surgical skill qualifications from our domestic society and are experienced with bail-out procedures.<sup>14</sup> From the above results, it is considered that acute phase LC is acceptable even in the severe group.

**Table 3.**  
Case Matched Analyses Based on CCI

	Low-risk (CCI 0-3)	High-risk (CCI ≥ 4)	P value
Number (n)	55	55	-
Gender (Male /Female)	32/23	33/22	0.8462
Age (years)	64.5 ± 4.2 <sup>a</sup>	64.8 ± 4.6	0.7428
BMI (kg/m <sup>2</sup> )	23.7 ± 3.7	24.3 ± 3.3	0.4185
CCI (points)	2.9 ± 0.3	4.5 ± 0.6	<0.0001
AC severity (n, %)			
Group I	40, 72.7	42, 76.4	0.8709
Group II	13, 23.6	8, 14.5	
Group III	2, 3.6	5, 9.1	
ASA-PS (n, %)			
Group I	21, 38.2	14, 25.5	0.3150
Group II	31, 56.4	38, 69.1	
Group III	3, 5.5	3, 5.5	
Operating time (min)	53.4 ± 16.8	67.8 ± 28.2	0.0153
Blood loss (mL)	15.7 ± 44.6	25.8 ± 71.7	0.3885
Conversion to open (n)	0	0	1.0000
Comprehensive complication index	1.5 ± 6.6	1.1 ± 4.2	0.6995
Postoperative complication (n, %)	3, 5.5	4, 7.3	0.6967
Mortality (n)	0	0	1.0000
Postoperative hospital stay (days)	3.5 ± 1.7	3.3 ± 0.9	0.2667

<sup>a</sup>Continuous data were expressed as mean ± standard deviation.

Some cohort studies have demonstrated that CCI ≥ 6 can predict high in-hospital complication rates and mortality, especially in GI/II AC.<sup>15</sup> As described above, higher CCI was the most important factor when considering elective surgery. From these patients' properties, we also re-evaluated the influence of higher CCI on surgical outcomes. In these analyses, there were no significant differences in postoperative complications, including the comprehensive complication index. Higher CCI may not increase the perioperative complication rate when expert endoscopic surgeons perform early LC for AC patients with higher CCI.

However, it has been widely reported that the complication rate and surgical outcomes are usually strongly associated with severity of AC and comorbidity factors.<sup>4,5</sup> Regards to the intraoperative complications, bile duct and artery injury are also associated with the severity of AC; therefore, the severity of AC and CCI are still important factors affecting perioperative outcomes. We have demonstrated that there was no conversion to open surgery in

370 AC cases, however, the top priority is to decide the ideal approach for each individual and to perform safely based on both the patient's factors and the surgeon's experience. To strengthen the surgeon's experience, it is mandatory to acquire all technical nuances of LC and bail-out procedures for surgically difficult AC cases.

This study had several limitations. First, this was a retrospective, single-institute study and we gathered only 370 AC cases. In our institute, three surgeons have endoscopic surgical skill qualifications from the JSES, and all LCs were performed by these three surgeons; therefore, conversion to open surgery and various perioperative complications were dramatically reduced compared with other studies.

## CONCLUSION

Our aggressive strategy for AC was acceptable, and we also demonstrated that AC severity and CCI are not critical factors suggesting disqualification for early LC in patients

with AC. In our institute, PTGBD for patients with ASA-PS  $\leq 3$  and any CCI has little benefit in reducing mortality; however, as the TG18 states, AC patients with ASA-PS  $\geq 4$  or/and CCI  $\geq 6$  are still super high-risk. The TG18 plays an important role in controlling the quality of clinical practice in AC worldwide, however, when LC is performed by endoscopic surgical skill qualification systems: qualified surgeons by JSES, aggressive early LC for AC of any severity is acceptable.

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