

## Optimal Timing of Laparoscopic Cholecystectomy for Moderate Acute Cholecystitis: A Cohort Study

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## 1. Abstract

### 1.1. Background

Early Laparoscopic Cholecystectomy (ELC) is superior to Delayed Laparoscopic Cholecystectomy (DLC) for Moderate Acute Cholecystitis (MAC) as defined by Tokyo Guidelines 2018, but the optimal timing of ELC for MAC is still controversial. The purpose of this study was to evaluate the outcomes of ELC in patients with delayed management.

### 1.2. Methods

A retrospective analysis was performed of all patients with MAC who underwent LC in Affiliated Hospital of Zunyi Medical University from November 2016 to October 2019. The included patients were classified into three groups according to the time from admission to surgery: within 7 days (G1), beyond 7 days(G2), at least 6 weeks after antibiotic treatment (G3).

### 1.3. Results

A total of 157 patients were included, of which 55 in G1, 43 in G2, and 59 in G3. Conversion rate and perioperative complications were similar in the three groups (G1 3.6% vs G2 11.6% vs G3 6.8%,  $P=0.305$ ) and (G1 5.5% vs G2 9.3% vs

G3 8.5%,  $P=0.804$ ), respectively. G1 had a shorter total length of stay (G1 8 vs G2 14 vs G3 15 days,  $P<0.001$ ) and lower costs (14654 vs 20431 vs 20801¥,  $P<0.001$ ). G2 had a longer oper-

ative time (G1 92 vs G2 110 vs G3 76 min,  $P<0.001$ ). G3 had a shorter postoperative length of stay (G1 4 vs G2 4 vs G3 3 days,  $P=0.016$ ), drainage tube removal time (2 vs 2 vs 2d,  $P=0.002$ ) and postoperative duration of antibiotic therapy (3 vs 3 vs 2d,  $P<0.001$ ). Postoperative duration of antibiotic therapy (OR=2.953, 95%CI:1.944 to 4.486,  $P<0.001$ ) were independent risk factors for postoperative length of stay.

### 1.4. Conclusions

ELC is effective and safe in patients with MAC who can tolerate surgery with over 7 days of admission. In addition, rational and appropriate use of antibiotics should be underscored.

## 2. Introduction

Acute cholecystitis (AC) is a common acute abdominal disorder and can be fatal if not appropriately treated in time [1]. Laparoscopic cholecystectomy (LC) is considered a golden standard treatment for AC [2,3]. Tokyo Guidelines 2013(TG13) [4] have defined a severity grading system, being used unchanged as the TG18 diagnostic criteria [5], which have testified well regarded as a factor predicting vital prognosis [6]. A long-standing dogma has stipulated that patients with moderate AC (MAC) should not undergo early LC (ELC) as severe local inflammation makes LC potentially more dangerous. However, with advances in laparoscopic equipment and technology, offering ELC for patients with MAC was reported, and a randomised controlled trials [7] has shown it

is safe and with similar conversion rate and perioperative complications, shorter total hospital stay and duration of antibiotic therapy compared with delayed laparoscopic cholecystectomy (DLC). This consequence was endorsed in Tokyo Guidelines 2018(TG18) and ELC should be underwent within 3 days or 7 days of admission because data remain weak on the specific management of MAC beyond 1 week.

Therefore, the purpose of this study was assessed the outcomes of patients with MAC in our hospital who performed LC within 7 days of admission, beyond 7 days, and at least 6 weeks after conservative treatment.

### 3. Patients and Methods

We selected a total of 157 patients, associated with biliary stone, were diagnosed with MAC according to the TG18[5] at the Affiliated Hospital of Zunyi Medical University between November 2016 and October 2019. Inclusion criteria were as follows: (1) patients with MAC according to the TG18; (2) the surgeons who performed the LC were professors or associate professors. Patients who were diagnosed with cholangitis, biliary tract tumor, acute pancreatitis or pregnancy were excluded. MAC was diagnosed according to the TG18 with the presence of any one of the following conditions: (1) elevated white blood cell count  $>18 \times 10^9/L$ ; (2) palpable tender mass in the right upper abdominal quadrant; (3) duration of complaints  $>72$  h; and (4) marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). The included patients were classified into three groups according to the time from admission to surgery: group 1 (G1) within the first 7 days, group 2 (G2) beyond 7 days, group 3 (G3) at least 6 weeks after conservative treatment.

Patients diagnosed with MAC were treated with empirical intravenous antibiotic therapy according to the guidelines [3,8]: Cephalosporin or Fluoroquinolone was used.

Our center has advanced laparoscopic equipment and mature laparoscopic technology. All operations used the 3-ports technique, and the 4-ports technique was used if the operation was difficult. For those with gallbladder edema and high tension, puncture and extraction of fluid at the bottom of the gallbladder for decompression and blunt separation of the gallbladder Calot triangle were performed. If there was more exudation in the abdominal cavity, a peritoneal drainage tube was placed near the Winslow hole.

Patient characteristics collected include age, sex, laboratory findings, abdominal ultrasound results, cardiorespiratory co-morbidities, American Society of Anesthesiologists (ASA) score and previous abdominal surgery. Data of surgery include operative time, conversion rate, perioperative complications (bile duct injury, pneumonia, peritonitis, postoperative abdominal bleeding, incision infection). Total length of stay (TLOS), total duration of antibiotic therapy (TDAT), total hospital costs (THC), drainage tube clinicsofsurgery.com

removal time (DTRT), postoperative duration of antibiotic therapy (PDAT), postoperative length of stay (PLOS) were collected and analyzed.

This study was approved by the Research Ethics Board from our centre.

### 4. Statistical Analysis

All statistical analyses were performed using SPSS 18.0. Normal continuous variables were expressed as mean(standard deviation, SD), and compared using the Student's t test or Bonferroni test. Non-normal continuous variables were expressed as median (interquartile range, IQR), and compared using the Mann-Whitney U test or Kruskal-Wallis H test. Categorical variables are shown as frequencies and percentages, and were compared using the Chi-square test or Fisher's exact test. Multivariable logistic regression analysis and receiver operating characteristic (ROC) curves was performed to determine independent predictors of outcomes. A P value  $<0.05$  was considered significant.

### 5. Results

Between November 2016 and October 2019, 157 patients were diagnosed with MAC, included 85 males and 72 females, ranging in age from 18 to 82 years. Median white blood cell count was  $13 \times 10^9/L$ . All cases were thickening of the gallbladder wall on abdominal ultrasound, associated with biliary stone, 55 in G1, 43 in G2, and 59 in G3. (Figure 1)

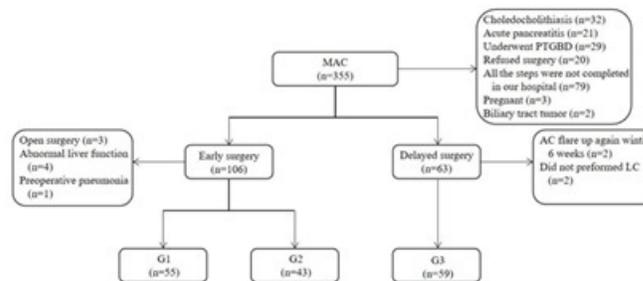


Figure 1: G1: the timing of surgery from admission within 7 days, G2: beyond 7 days, G3: at least 6 weeks after conservative treatment.

**Figure 1:** Patients in the three group. G1: the timing of surgery from admission within 7 days, G2: beyond 7 days, G3: at least 6 weeks after conservative treatment

Compared with G1 and G3, G2 patients were older (G1  $47 \pm 12$  vs G2  $55 \pm 14$  vs G3  $49 \pm 13$ ,  $P=0.005$ ) and a greater number of hypertension (G1 10.9% vs G2 30.2% vs G3 11.9%,  $P=0.018$ ), which may be the reason why it took longer to evaluate surgical tolerance before surgery. However, there was no statistical difference in the American Society of Anesthesiologists (ASA) score among the three groups ( $P=1.000$ ). (Table 1)

Regarding surgery data, three patients in G3 were diagnosed with secondary cholelithiasis received ERCP+LC after re-admission, the operative time was only calculated for the LC. And there was a significant difference in the operative time among the three groups (92 vs 110 vs 76min,  $P<0.001$ ), G2 had longer operative

time than G1 and G3. In G1, 2 patients were converted to open surgery. After surgery, 2 patients had pneumonia, and 1 patient had an incision infection. In G2, 5 patients were converted to laparotomy. After surgery, 2 patients had peritonitis, 1 patient had pneumonia, and 1 patient had an incision infection. In G3, 3 cases were converted to laparotomy. After surgery, 1 case had pneumonia, 1 case had postoperative abdominal bleeding, 1 case had peritonitis, and 2 cases had an incision infection. Conversion rate and perioperative complications were (3.6% in G1 vs 11.6% in G2 vs 6.8% in G3,  $P=0.305$ ) and (5.5% in G1 vs 9.3% in G2 vs 8.5% in G3,  $P=0.804$ ), respectively. No bile duct or intestinal tract injury was found in the three groups. TDAT, TLOS and THC in G3 involved admission and re-admission parameters. In this study, compared with G2 and G3, G1 had shorter TDAT (7 vs 11 vs 9d,  $P<0.001$ ) and TLOS (8 vs 14

vs 15d,  $P<0.001$ ), lower THC (14654 vs 20431 vs 20801¥,  $P<0.001$ ). G3 had shorter postoperative length of stay (PLOS) (4 vs 4 vs 3d,  $P=0.016$ ), postoperative duration of antibiotic therapy (PDAT) (3 vs 3 vs 2d,  $P<0.001$ ) and drainage tube removal time (DTRT) (2 vs 2 vs 2d,  $P=0.002$ ) than G1 and G3. (Table 2)

According to the TG18, there was no difference in PLOS between ELC and DLC. Hence, we analyzed the factors associated with prolonged PLOS and found that age (OR=1.043, 95%CI: 1.003 to 1.084,  $P=0.034$ ), DTRT (OR=2.838, 95%CI: 1.540 to 5.231,  $P=0.001$ ) and PDAT (OR=2.953, 95%CI: 1.944 to 4.486,  $P<0.001$ ) were independent factors for prolonged PLOS (Table 3). Age, DTRT and PDAT had an area under the ROC curve (0.594,  $P=0.041$ ; 0.826,  $P<0.001$ ; 0.906,  $P<0.001$ ; respectively). (Figure 2)

**Table 1:** Patient characteristics

	G1 (n=55)	G2 (n=43)	G3 (n=59)	P
Sex, n(%)				0.632
Male	27(49.1)	25(58.1)	33(55.9)	
Female	28(50.9)	18(41.9)	26(44.1)	
Age(year), mean(SD)	47±12	55±14	49±13	0.005
WBC(10 <sup>9</sup> /L), median(IQR)	13(11, 15)	12(11, 15)	14(12, 17)	0.101
Gallbladder wall(mm), median (IQR)	6(4, 10)	5(4, 8)	5(4, 8)	0.544
Diabetes, n(%)	1(1.8)	4(9.3)	4(6.8)	0.28
Heart disease a, n(%)	0	2(4.7)	2(3.4)	0.318
Hypertension, n(%)	6(10.9)	13(30.2)	7(11.9)	0.018
COPD b, n(%)	1(1.8)	0	0	0.624
Cerebrovascular disease, n(%)	0	2(4.7)	1(1.7)	0.275
ASA I-II, n(%)	55(100)	43(100)	58(98.3)	1
Previous abdominal surgery, n(%)	10(18.2)	3(7.0)	9(15.3)	0.259

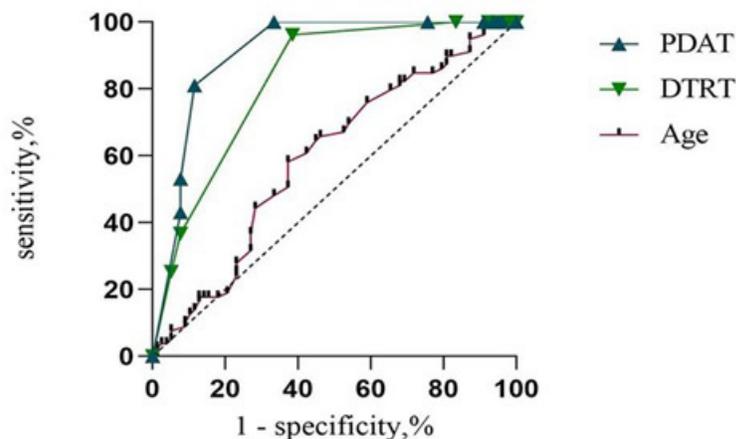
a: arrhythmia, valvulopathy, Ischemic heart disease: chronic obstructive pulmonary disease e;

ASA : American Society of Anesthesiologists

**Table 2:** Surgical and postoperative outcomes between the 3 groups

	G1 (n=55)	G2 (n=43)	G3 (n=59)	P
Operative time (min), median (IQR)	92(75, 118)	110(90, 150)	76(56, 110)	<0.001
Conversion rate, n(%)	2(3.6)	5(11.6)	4(6.8)	0.305
Perioperative complications, n(%)	3(5.5)	4(9.3)	5(8.5)	0.804
Pneumonia	2	1	1	
Peritonitis	0	2	1	
Postoperative abdominal bleeding	0	0	1	
Incision infection	1	1	2	
Bile duct injury	0	0	0	
DTRT (day), median (range)	2(2, 3)	2(1, 3)	2(0, 2)	0.002
PDAT (day), median (range)	3(2, 4)	3(2, 4)	2(0, 3)	<0.001
PLOS (day), median (range)	4(3, 5)	4(3, 5)	3(2, 5)	0.016
TDAT (day), median (range)	7(4, 9)	11(7, 14)	9(7, 13)	<0.001
TLOS (day), median (range)	8(7, 9)	14(12, 16)	15(12, 20)	<0.001
THC (¥), median (range)	14654(12434, 18187)	20431(17085, 25480)	20801(17061, 27546)	<0.001

Abbreviations: DTRT, drainage tube removal time. PDAT, postoperative duration of antibiotic therapy. PLOS, postoperative length of stay. TDAT, total duration of antibiotic therapy. TLOS, total length of stay. THC, total hospital costs.



**Figure 2:** Receiver operating characteristic(ROC) curves for prolonged postoperative length of stay. PDAT, postoperative duration of antibiotic therapy. DTRT, drainage tube removal time

**Table 3:** Results of univariate and multivariate analyses of prolonged PLOS

	Prolonged (n=78)	Non prolonged (n=79)	Univariate P value	Multivariate P value	OR and 95%CI
Sex, n(%)			0.694		
Male	41(52.6)	44(55.7)			
Female	37(47.4)	35(44.3)			
Age(year), mean(SD)	52±14	48±12	0.055	0.034	1.043(1.003 to 1.084)
Operative time (min), median (IQR)	108(76, 146)	80(60, 105)	<0.001	0.58	1.004(0.990 to 1.018)
DTRT(day), median (IQR)	3(2, 3)	2(0, 2)	<0.001	0.001	2.838(1.540 to 5.231)
PDAT(day), median (IQR)	4(3, 4)	1(0, 2)	<0.001	<0.001	2.953(1.944 to 4.486)
Conversion rate, n(%)	10(12.8)	1(1.3)	0.005	0.388	0.161(0.003 to 10.175)
Perioperative complications, n(%)	13(16.7)	2(2.5)	0.003	0.893	1.188(0.098 to 14.415)

Abbreviations: PLOS, postoperative length of stay. DTRT, drainage tube removal time. PDAT, postoperative duration of antibiotic therapy

**6. Discussion**

On the basis of anatomic-pathological observation [9]: cholecystitis symptoms of more than 72 hours results in the development of necrotizing and suppurative cholecystitis making surgery more difficult. According to the TG18 diagnostic criteria, however, those patients are part of MAC. Meanwhile, existing trial have shown ELC to be superior than DLC although necrotizing and suppurative cholecystitis present [7,10]. Nonetheless, the criteria for performing ELC to MAC patients with relatively controversial in current literature.

The TG18 have updated their standpoints and recommendations that ELC should be underwent within 3 days or 7 days of admission for patients with MAC who can tolerate surgery. However, we found that some patients with MAC required a long time to complete tests and evaluation of surgical tolerance after admission, or surgery is considered until conservative treatment fails. Data remain weak on the specific management of those patients. Therefore, we aimed to compare the outcome among G1 (surgery from admission within the first 7 days), G2 (more than 7 days), and G3 (DLC at least 6 weeks after antibiotic treatment), and we found providing ELC for patients with hospitalized beyond 7 days was safe.

There was no statistically significant difference in conversion rate between the three groups, which confirmed that ELC effectively removed suppurative gallbladder. Converting to open laparotomy is associated with significant disadvantages such as increased surgical trauma and hospital costs [13], although it has no effect on the rate of local postoperative complications [11,12]. Several studies have demonstrated AC is closely associated with the conversion rate [14,15], as well as severity grade was an independent predictor of conversion to open surgery [16]. With the aggravation of gallbladder inflammation, theoretically, the risk of conversion is increased. However, we considered that the conversion rate was similar between offering ELC and DLC, it is postulated that decision-making on open conversion may vary greatly between hospitals, in where ELC is the standard treatment for MAC the conversion rate associated with ELC must be lower than those reported rates [17,18].

In addition, it is well known that BDI is the most feared complication during LC, which has a substantial negative impact on patient survival [11,19]. AC is independent factors for BDI. However, a retrospective review based on the Nationwide Inpatient Sample analyzed 95523 patients with AC who underwent LC have shown prolonged hospitalization before surgery the incidence of BDI did

not increased [20], which is consistent with this reports. Because none of the patients with subsequent BDI after LC. We found that most patients with LC-associated BDI were referred from junior hospitals to our center, there are isolated and backward areas in China on the one had easily obtained laparoscopic equipment, on the other hand lagged in offering surgeons with laparoscopic skills, which led more patients with LC-associated BDI transferred to advanced center. Therefore, we deem providing ELC for MAC has a lower risk in advanced center, even if patients are hospitalized for more than a week the conversion rate and BDI did not significantly increased.

In recent years, the proportion of secondary choledocholithiasis increasing in China, and the incidence of secondary choledocholithiasis can be up to 10%-15% in surgically-treated patients [21,22]. In contrast to choledocholithiasis, most cases of secondary choledocholithiasis do not have symptoms and the diagnosis is often missed [23]. Moreover, if stones obstruct the common bile duct and bacteria ascend the biliary tree and infect the sterile bile, acute cholangitis will occur [24]. This is life-threatening in patients with choledocholithiasis secondary to calculous cholecystitis who refuse surgery after conservative treatment. In our study, 3 patients in the DLC group were diagnosed with secondary choledocholithiasis after re-admission and ERCP followed by LC was performed. As a result, providing ELC may decline the incidence of gallstone-related secondary disease and avoidance of excessive testing and high operation costs will reduce the financial burden on the patients.

A reduction in TLOS and its resultant improvement in THC effectiveness remains a major aspect in supporting the use of ELC over DLC. Studies have demonstrated that the THC in the ELC group are lower than those in the DLC group [25,26]. While THC was higher in G2, this was an expected result as those patients had longer preoperative length of hospital stay and PLOS. And PLOS was longer in G1 and G2, seemingly different from previous studies offering ELC which have shown no significant difference between ELC and DLC groups in terms of PLOS [7,27], it is estimated that patients underwent ELC with longer PDAT which with the intent to reduce infectious complications. Antimicrobial therapy is deemed therapeutic for MAC, and antimicrobial therapy may be required until the gallbladder is removed. However, the recommended duration of antimicrobial therapy for MAC in the TG13 is no more than 7 days after cholecystectomy [8], which is disagreed with the TG18 that postoperative antibiotic therapy is not recommended unless bacteremia with Gram-positive bacteria is present [1]. We prolonged PDAT in the most cases according to the TG18, although we strictly followed the anti-infection criteria, which may be the reason why PLOS is higher in ELC groups. In addition, several studies have shown that prolonged antibiotic therapy after LC is not beneficial in reducing surgical site infec-

tion, and which also can cause nausea, allergic reactions and digestive complaints [28,29]. Nevertheless, increasing incidence of multi-drug resistance caused by overuse of antibiotics has become a major threat to global public health, this phenomenon is particularly serious in China. Thus, reducing unnecessary antibiotic therapy such as PDAT is an important countermeasure to avoid infection by multi-drug resistance bacteria. Rational and appropriate use of antibiotics is also likely to reduce not only PLOS and THC, but antibiotic adverse reactions.

Our study had some limitations. Firstly, surgeons' preference affects the timing of surgery; therefore, selection bias could not be fully excluded, and the benefits and harms of ELC and DLC may have been overestimated. Secondly, the popularity of LC results in patients not being confined to a single center for treatment, consequently, this study had a small sample size.

## 7. Conclusions

ELC is effective and safe in patients with MAC who can tolerate surgery with over 7 days of admission. We agree with the recommendation of the TG18 that LC should be performed by experienced surgeons cased by severe local inflammation of gallbladder. Finally, antimicrobial management should be underscored and prudent antimicrobial usage implemented.

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