CANCER DIAGNOSIS & PROGNOSIS
3: 571-576 (2023) doi: 10.21873/cdp.10256

Optimal Timing of Laparoscopic Cholecystectomy After Conservative Therapy for Acute Cholecystitis

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Abstract. *Background/Aim: According to the Tokyo Guidelines 2018, the operation for acute cholecystitis is recommended to be performed as early as possible. However, there are cases in which early surgeries cannot be performed due to complications of patients or facility conditions, resulting in elective surgery. Hence, we retrospectively analyzed elective surgery cases in this study. Patients and Methods: There were 345 patients who were underwent laparoscopic cholecystectomy (LC) at our hospital from January 2019 to December 2020 in this retrospective study. A total of 83 patients underwent LC more than 3 days after conservative treatment. The elective LC patients were divided into the Early group (4-90 days after onset, n=36) and the Delayed group [91 days or more (13 weeks or more) after onset, n=31], excluding 16 patients who underwent percutaneous transhepatic gallbladder drainage. Results: As for operative time, there was a significant difference between the Delayed and Early groups (91.2 vs. 117 minutes, p=0.0108). And also, there was a significant difference in the postoperative hospital stay, which was significantly shorter in the Delayed group than in the Early group (3.4 vs. 5.9 days, p=0.0436). Although there were no significant differences in either conversion rates or complication rates, both of these were decreasing in the Delayed group. In particular, there were no complications in the Delayed group. Conclusion: When the conservative treatment for acute cholecystitis precedes and precludes urgent/early LC within 3 days, delaying LC for at least 91 days (13 weeks or more) after onset could reduce operative time and postoperative hospital stay. Moreover, there would be no complications after LC, and the rates of conversion during LC may be kept low.*

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Key Words: Cholecystitis, conservative treatment, delayed surgery, laparoscopic cholecystectomy, optimal timing.

Cholecystitis is one of the more common diseases. Laparoscopic cholecystectomy (LC) is a common treatment for benign gallbladder disease. Laparoscopic cholecystectomy was first performed in 1987 (1) and has become widely used worldwide (2). At the time, it was generally considered that conservative treatment would be administrated first for acute cholecystitis to prevent complications associated with inflammation, and then LC would be performed 6-8 weeks after the onset (3). However, recent meta-analyses have reported that early LC for acute cholecystitis results in shorter hospital stays and no significant difference in complications compared to delayed LC (4-6)

More than 38,000 cholecystectomy procedures are performed annually in Japan (7). According to Tokyo Guidelines 2018 (8), early surgery (within three days) is recommended for acute cholecystitis, even if the inflammation is severe. However, depending on the patient's complications or the condition of the facility, it may be necessary to carry out selective LC for four days or more. In addition, many patients come to the hospital for LC after undergoing conservative treatment at another hospital. There are very few reports on the optimal time of LC for patients undergoing conservative treatment without percutaneous transhepatic gallbladder drainage (PTGBD), although there are some reports on the optimal time for elective surgery for acute cholecystitis after PTGBD (9-13).

Table I. *Patient characteristics*.

	Early n=36	Delayed n=31	*p*-Value
Male/Female	20/16	18/13	1.0000
Age (y)	60.6±17.4	64.9±12.1	0.2323
Height (cm)	161.4±10.5	162.6±9.9	0.6151
Body weight (kg)	66.5±13.9	64.2±13.4	0.4952
BMI (kg/m^2)	25.4±4.4	24.1±3.9	0.2071
Days between diagnosis (onset) and surgery (day)	38.5 (19.5-72.25)	110 (96-143)	<0.0001

BMI: Body mass index. Mean±standard deviation: sex, age, height, body weight, and BMI; Median (inter-quartile range): days between diagnosis (onset) and surgery.

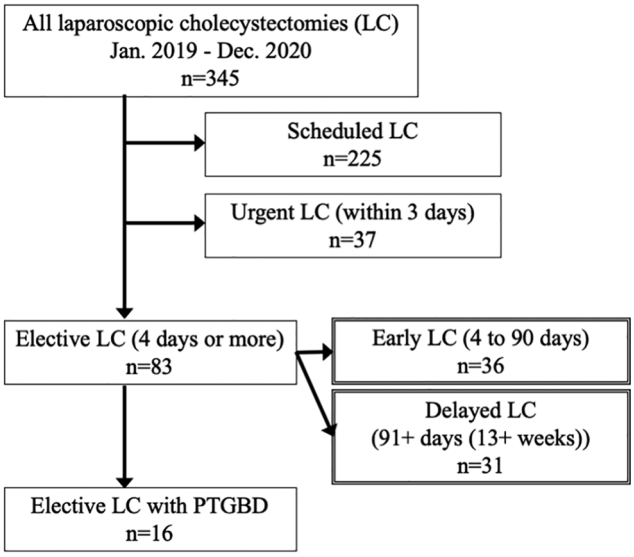

Figure 1. *Flow chart of this study. PTGBD: Percutaneous transhepatic gallbladder drainage.*

This study retrospectively examined the cases in which surgery was performed four days or more after the conservative treatment for acute cholecystitis.

Patients and Methods

This is retrospective study of patients who underwent LC at Showa University Northern Yokohama Hospital from January 2019 to December 2020. We began to conduct this study February 24th 2022. A total of 345 LCs were performed. Thirty-seven patients underwent urgent LC within three days due to acute cholecystitis, and 83 cases who underwent LC four days or more days after conservative treatment were included. The elective LC cases were divided into two groups: the Early group (4-90 days after onset, n=36) and the Delayed group [91+ days (13+ weeks) after onset, n=31] (Table I).

The rationale for surgery, in this study of two groups of patients, was the presence or history of acute cholecystitis. The standard for elective LC was surgery after four days or more of acute cholecystitis onset during or after conservative therapy. There was no difference in postoperative management.

Due to the nature of our hospital, the majority of both groups were referrals. These patients received conservative treatment at another hospital and were referred after discharge. PTGBD cases (n=16) were excluded (Figure 1).

Patient characteristics included sex, age, height, body weight, and body mass index (BMI). Preoperative data included laboratory data, American society of anesthetists-physical status (ASA), and previous abdominal surgery. Operative factors included total operative time and estimated amount of blood loss. Operative outcomes, including conversion rate, postoperative hospital stay, and postoperative complications were compared between the two groups retrospectively. For standardization purposes, complications were classified according to the Clavien-Dindo classification system (14, 15). Postoperative complications were identified by reviewing patient charts retrospectively, and Clavien-Dindo Grade 3 or higher patients were deemed to have a complication. All LCs were performed for symptomatic gallstone disease or cholecystitis. We excluded LCs for suspicious malignant diseases or operations with PTGBD.

All LCs were performed using the conventional 4-port technique in the supine position under general anesthesia and followed the technique previously reported (16). Multiple surgeons performed the procedures. A transumbilical vertical incision was made for the 12mm trocar using the open technique in the umbilicus to achieve carbon dioxide insufflation. Intraoperative cholangiography was not performed routinely.

The data analysis was performed using JMP®Pro 14 (SAS Institute Inc., Cary, NC, USA). For comparisons between the groups, the Fisher's exact test was used for categorical variables, and the Student's *t*-test or Welch's *t*-test was used for quantitative variables. The results are expressed as the mean±standard deviation. Probability *p*-values were considered statistically significant at the <0.05 level.

The study was conducted in accordance with the Declaration of Helsinki. Moreover, the Committee on Ethics of Showa University Medical School and IRB (Institutional Review Board) reviewed and approved the study protocols (The approval code: No. 19H064). As a retrospective cohort study, the Committee on Ethics of Showa University Medical School and IRB directed that the opt-out method to obtain patient consent was utilized and waived the need for informed consent.

Results

The elective LC cases were divided into two groups: the Early group (LC performed within 4-90 days after onset, n=36) and the Delayed group [91+ days (13+ weeks), n=31]. No significant differences in the patient characteristics, including sex, age, height, body weight and BMI were found between the two groups. The median and inter-quartile range between diagnosis (onset) and surgery for Early and Delayed groups were 38.5 days (19.5-72.25) and 110 days (96-143),

Table II. *Preoperative laboratory data.*

	Early n=36	Delayed n=31	*p*-Value
WBC (/μl)	7,302±2,511	5,462±1,481	**0.0005**
PL ($\times 10^4$/μl)	26.7±9.3	23.2±5.9	0.0726
CRP (mg/dl)	2.00±3.41	0.35±0.66	**0.0073**
T-Bil (mg/dl)	0.65±0.31	0.64±0.22	0.8723
AST (IU/l)	30.4±26.3	24.3±9.2	0.1973
ALT (IU/l)	50.1±86.3	26.9±22.2	0.1272
PT (%)	93.3±11.5	96.9±6.2	0.1304

WBC: White blood cell; PL: platelet; CRP: C-reactive protein; T-Bil: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time.

Table III. *Preoperative factors.*

	Early n=36	Delayed n=31	*p*-Value
ASA score			0.7966
1	10 (27.8%)	11 (35.5%)	
2	25 (69.4%)	19 (61.3%)	
3	1 (2.8%)	1(3.2%)	
Previous abdominal surgery	9 (25.0%)	8 (26.7%)	1.0000

ASA: American Society of Anesthetists-physical status.

Table IV. *Operative factors.*

	Early n=36	Delayed n=31	*p*-Value
Operative time (min)	117.0±43.4	91.2±36.3	**0.0108**
Blood loss (ml)	38.4±133.7	6.4±21.6	0.1653

Table V. *Operative outcomes.*

	Early n=36	Delayed n=31	*p*-Value
Conversion, n (%)	3 (8.3%)	1 (3.2%)	0.6178
Postoperative hospital stay (day)	5.9±7.3	3.4±1.3	**0.0436**
Postoperative complications, n (%)	3 (8.3%)	0 (0%)	0.2429

Clavien-Dindo classification ≥3.

Table VI. *Postoperative complications.*

	Early n=36	Delayed n=31
Intestinal injury	1	0
Ileus	1	0
Bleeding	1*	0
Bile leakage	1*	0
Mortality	0	0

*Same patient.

respectively (Table I). The preoperative data showed a significant increase in white blood cell count (p=0.0005) and C-reactive protein (CRP) value (p=0.0073) in the Early group (Table II). However, there were no significant differences in other values, including platelet, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time (PT). Table III shows preoperative factors, including ASA score and previous abdominal surgery; however, there were no significant differences between the two groups. The operative time was significantly shorter in the Delayed group (91.2 min, p=0.0108) (Table IV).

Moreover, blood loss was less in the Delayed group, although this did not reach significance (6.4 g, p=0.1653) (Table IV). Furthermore, the length of postoperative hospital stay was significantly shorter in the Delayed group (3.4 days, p=0.0436) than the Early group (5.9 days). There were no significant differences in the incidence of complications or the rate of conversion; however, the rates of these two factors were reduced in the Delayed group compared to the Early group (Table V).

No postoperative complications were observed in the Delayed group, however, in the Early group, three patients exhibited complications such as intestinal injury, ileus, bleeding, and bile leakage. A patient with postoperative ileus had a long tube inserted, and another patient with postoperative bleeding was managed by surgical hemostasis. Moreover, bleeding and bile leakage were seen in the same patient (Table VI).

Next, univariate and the multivariate analyzes were performed for the rate of conversion and the incidence of postoperative complications using WBC, CRP, operative time, and postoperative hospital stay, as those four factors were significantly different between the Early and Delayed groups. The cut-off values were obtained by constructing receiver operating characteristic curves for each factor.

In the univariate analysis of the rate of conversion, WBC (p=0.0263) and CRP (p=0.0016) levels were considered significant risk factors (Table VII). Furthermore, when a multivariate analysis was performed using these two variables, only the CRP value was extracted as a significantly independent risk factor (Table VIII).

Table VII. *Univariate analysis of factors associated with conversion.*

Variables	OR	95%CI	*p*-Value
WBC (<9,190 *vs.* ≥9,190)	11.6	1.19-116.24	**0.0263**
CRP (<6.0 *vs.* ≥6.0)	60	5.88-1,453.53	**0.0016**

OR: Odds ratio; WBC: white blood cells; CRP: C-reactive protein; CI: confidence interval.

Table VIII. *Multivariate analysis of factors associated with conversion.*

Variables	OR	95%CI	*p*-Value
WBC (<9,190 *vs.* ≥9,190)	0.878	0.024-19.408	0.9362
CRP (<6.0 *vs.* ≥6.0)	65.063	3.153-3,058.197	**0.0065**

Moreover, the univariate and multivariate analyzes of postoperative complications were performed, but none of these four factors were extracted as significant risk factors.

Discussion

Regarding the optimal timing of cholecystectomy, there have been some reports about patients after percutaneous transhepatic gallbladder drainage (PTGBD) (9-13), but there are very few reports on the optimal timing of surgery for cases after hospitalization and conservative treatment. However, this study does not deny the benefit of conducting urgent cholecystectomy within 72 hours for acute cholecystitis. Instead, we examined the second-best timing of cholecystectomy for patients who had missed the best opportunity for surgery due to preoperative condition, complications, or re-hospitalization from other hospitals.

As for a comparison between within three days and four days or more after onset, Ota *et al*. (17) reported no significant differences in conversion rate, operative time, blood loss, postoperative morbidity, or postoperative hospital stay. Therefore, they concluded that cholecystectomy for acute cholecystitis should be performed as soon as possible, even if delayed. Moreover, recent meta-analyses have reported that early LC (24 to 72 hours) for acute cholecystitis results in shorter hospital stays and no significant difference in complications compared to delayed LC (6 to 12 weeks) (4-6).

Hence, we conducted our study simply in two groups, 4-90 days and 91+ days (13+ weeks), focusing on the timing of surgery after conservative treatment. The results of this study showed significant reductions in operative times and postoperative hospital stays in the Delayed group (91+ days). In addition, the amount of blood loss, conversion rate, and incidence of postoperative complications were also lower in the Delayed group (91+ days), although the differences were not significant.

There were no significant differences in patient age, sex, height, body weight, or BMI, but preoperative data showed that the WBC and the value of CRP were significantly higher in the Early group (4-90 days), and the inflammatory response remained when the laparoscopic cholecystectomy was performed. Whereas there were no significant differences in total bilirubin, AST, ALT, PT, or preoperative liver function. Moreover, there were no significant differences in preoperative conditions or complications.

However, regarding surgical factors, our data showed that the operative time was significantly longer in the Early group. Furthermore, there was no significant difference in the amount of bleeding, but it tended to be higher in the Early group. These seemed to indicate the difficulty of surgery in early cases where inflammation remained. The same tendency was observed in the literature of cases in which PTGBD was inserted (12, 18). Furthermore, the conversion rate, length of postoperative hospital stay, and postoperative complications, tended to be more in the early group, especially the length of postoperative hospital stay was significantly longer. Similarly, these also seemed to indicate the difficulty of surgery in early cases where inflammation remains. In addition, as the structure of the inner and outer layers in the gallbladder wall disappeared due to progressive fibrosis, it could make LC more difficult after severe cholecystitis (19).

Several previous reports indicated that early surgery for acute cholecystitis shortened the length of hospital stay (20-22). However, our data revealed a significant reduction in hospital stay length in the Delayed group, specifically "postoperative" hospital stays. Our data indicates that most patients were readmitted, including from other hospitals. Therefore, the calculation of postoperative hospital stay was the same as for the first hospitalization, and the inflammation was sufficiently relieved.

For postoperative complications, multivariate analysis did not extract independent risk factors. However, its analysis revealed high levels of CRP as independent risk factors for conversion. This fact could indicate that in early cases where the inflammatory reaction persists or prolongs, the difficulty of adhesion detachment and the risk of bleeding increases, resulting in a conversion.

In patients with cholecystitis who had undergone conservative treatment and missed the opportunity for cholecystectomy within three days, it is recommended that laparoscopic cholecystectomy is performed after 91 days (13+ weeks) or more.

The limitations of our study are sample size, single institution, and the retrospective design. Further analysis and more patients are needed to confirm our conclusion.

Conclusion

When the conservative treatment for acute cholecystitis precedes and precludes urgent/early LC within 3 days, delaying LC for at least 91 days (13+ weeks) after onset could reduce operative time and postoperative hospital stay, moreover, there would not be complications after LC, and the rates of conversion may be kept low during LC.

Conflicts of Interest

All Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Y.E. contributed to the writing of the article and preparing of the figure and tables. Y.E., K.T., T.H., H.S., K.S., S.N., Y.T., J.S., S.S., K.N., Y.T., and S.M. contributed to the surgeries and the analysis of the data. T.A., N.S., F.I., and S.K. contributed to the design and implementation of this study. All Authors have read and approved the article.

Acknowledgements

We are pleased to inform our readers that a portion of this article has been posted as a preprint on Research Square (https://www.researchsquare.com/article/rs-1615264/v1).

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Received June 15, 2023
Revised August 3, 2023
Accepted August 4, 2023