Validation of the Tokyo guideline 2018 treatment proposal for acute cholecystitis from a single-center retrospective analysis

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Abstract

Background Based on the revised Tokyo guideline 2018 (TG18), early laparoscopic cholecystectomy (LC) is recommended in patients who satisfy the Charlson Comorbidity Index (CCI) criteria and the American Society of Anesthesiologists Physical Status Classification (ASA-PS). Our study aims to determine the efficacy of TG18 treatment strategy.

Methods We enrolled 324 patients with acute cholecystitis (AC) diagnosed by TG18 who underwent cholecystectomy between 2010 and 2018. Perioperative variables and surgical outcomes were analyzed according to the TG18 treatment strategy and severity grading.

Results ASA-PS scores and CCI were significantly higher in patients with Grade II (GII) and GIII AC. Higher severity grading resulted in failed LC, requiring blood transfusion and bailout surgery. The TG18 within group showed a higher proportion of GI and GII AC and their ASA-PS scores were also significantly lower. TG18 within group demonstrated significant differences in the achievement of LC, bailout surgery, postoperative hospital stays, and 90-day mortality rates. Intraoperative blood loss and blood transfusion were significantly higher in the TG18 outside group than that in the TG18 within group.

Conclusions Our study shows that the TG18 treatment strategy is well-designed and efficacious. Novel findings Our study established the feasibility and efficacy of TG18. The usefulness of performing aggressive surgery beyond the TG18 strategy requires further study.

Background

Acute cholecystitis (AC) is one of the most common gastrointestinal diseases requiring definitive management (1). Laparoscopic cholecystectomy (LC) is the gold-standard treatment for AC, and remains one of the most frequently performed surgical procedures (2–4). Since the establishment of the Tokyo guideline 2007 (TG07), AC has been treated appropriately based on the severity grading (5). The revised Tokyo guideline 2013 (TG13) suggested that 72 hours from symptom onset is the optimal timing for surgery and several reports were in line with the TG13 (6–8). Multiple studies have demonstrated that early cholecystectomy had a stronger impact on the outcomes than delayed cholecystectomy did (9–11).

There has been no evaluation of the TG18 treatment recommendations, and the following guidelines have been revised from TG13 to TG18. One of the recommendations is that LC may be performed in Grade III (GIII) AC under strict conditions, especially in institutions with advanced laparoscopic expertise. The other recommendation is that percutaneous cholecystostomy (PC) may be performed in GIII AC under specific conditions, including failure of antibiotics, and with general supportive care. The efficacy of severity grading in AC has been proven in a previous report (12). TG18 emphasizes that the elevated Charlson Comorbidity Index (CCI) and the low body mass index (BMI) are independent risk factors for 30-day mortality in GI and GII AC. Endo et al. reported that jaundice, neurological dysfunction, and respiratory dysfunction defined by the CCI were significantly associated with 30-day mortality in GIII AC (13). The CCI was originally developed to predict 1-year mortality in those who underwent surgical treatment (14).

Some reports showed that a higher CCI was effective for predicting dismal postoperative outcomes (15, 16). Further investigation is required to ascertain whether the CCI and the American Society of Anesthesiologists Physical Status (ASA-PS) classification are effective in determining treatment strategy for AC (17).

We conducted a retrospective study to address these clinical issues and to clarify the feasibility of aggressive surgical strategy for AC.

Methods

Patients

A retrospective study spanning a 9-year period from June 2010 to June 2018 was performed, and a total of 324 patients, who were diagnosed with AC at Onomichi General Hospital, were enrolled. Our strategy for AC was to perform aggressive surgery when patients were able to tolerate general anesthesia in GI & GII, even if the ASA-PS and the CCI were over the TG18 treatment strategy. In GIII, surgical intervention was preferred in patients with proposed PC according to our institutional policy. These patients were mainly classified in the TG18 outside group. All of the AC cases that we treated met the TG18 criteria when re-classified accordingly, and the severity of these cases was determined by the severity standards of TG18. The measured variables were sex, age, body mass index (BMI), and comorbidity (diabetes mellitus, hypertension, cardiovascular disease, pulmonary disease, and renal failure). Murphy's sign at admission was documented on physical examination by a physician. CT images were checked by at least one physician and one radiologist. Laboratory data were collected prior to the operation. Following the guidelines of the Declaration of Helsinki (Fortaleza, Brazil, October 2013), this study was authorized in advance by the institutional review board of the Onomichi General Hospital (approval number, OJH201849).

Surgical procedures and perioperative management

The first choice of surgical approach was the four-port LC. Deciding the surgical strategy and perioperative management have been described elsewhere (18). Bailout surgery is selected in case of difficulty in dissecting the Calot's triangle and in severe acute gangrenous cases (19).

Morbidity and complications

Major bile duct injury was defined as any injury to the main biliary tree. Biliary leakage was defined as the presence of bile in the drainage fluid or intra-abdominal fluid collection as determined by postoperative CT and ultrasonography. Our definition of complications was determined according to the method described by Clavien et al. (20). Postoperative complications were defined as those that were Clavien-Dindo (CD) classification GIIIa or greater in our study.

Statistical analysis

Values for continuous variables are presented as the median and range. Nominal variables are expressed as the number (%). Non-parametric quantitative data were analyzed using Mann-Whitney *U*-test. Bonferroni correction was performed among the analysis of the three groups. Chi-square test was performed for nominal variables. *P*-values < 0.05 were regarded as significant. Calculations were performed using SPSS software (version 22; IBM Corp., Armonk, NY, USA).

Results

Comparison of patient characteristics and surgical outcomes in each grade of AC.

Table 1 demonstrates the patient characteristics and postoperative outcomes in the three AC severity grades according to TG18. There were 148 (45.7%) patients classified as GI, 154 (47.5%) patients classified as GII, and 22 (6.8%) patients classified as GIII. There were significant differences in age, ASA-PS, CCI score, proportion of TG18 strategy, white blood cell (WBC) count, and C- reactive protein (CRP) levels among the three groups. Patients with GIII AC were older, with higher ASA-PS and CCI scores than those in the other two groups. The incidences of open conversion and bailout surgery, and intraoperative blood loss were lower in patients with GI AC when compared with that in GII and GIII AC patients. There were significant differences in postoperative hospital stays and blood transfusion among the three groups. Postoperative complications (CD ≧IIIa) did not significantly differ among these three groups.

Comparison of patient characteristics and pre-operative examination of TG18 within and outside groups.

According to the TG18 treatment strategy, patients were subdivided into two groups as those within TG18 and those outside TG18 strategy. The main reasons for patients being defined as outside TG18 strategy were as follows (Figure 1): 37 patients (55%) had an ASA-PS score more than 3, and 23 (34%) underwent early surgery without PC. Table 2 shows the pre-operative comparison between the TG18 within and outside groups. There were significant differences in age, ASA-PS, CCI severity grading, preoperative comorbidities, and CRP levels. Other than the presence of ascites, CT findings were comparable between the two groups. The incidences of GII and GIII AC were significantly higher in the TG outside group. Comorbidities such as diabetes mellitus, cardiovascular dysfunction, hypertension, hepatic dysfunction, and renal dysfunction were higher in the TG18 outside group compared with that in the TG18 within group.

Surgical outcomes comparison between TG18 within and outside groups.

Table 3 shows that there were significant differences in the rate of bailout surgery, volume of intraoperative blood loss, requirement of blood transfusion, length of postoperative stay, and occurrence of gangrenous cholecystitis between the two groups. There was no 90-day mortality in the TG18 within group, although 2 patients died. One patient sustained septic shock, while the other patient had severe comorbidities such as chronic renal failure needing dialysis and cardiovascular disease.

Post-operative comparison with timing of surgery from onset and admission in TG18 outside group

As shown in Table 4, patients in the TG18 outside group were subdivided into four groups based on the timing of surgery: Group I underwent surgery within 48 h from the time of admission; Group II, 2 days after the admission; Group III, within 48 h from the onset of symptoms; and Group IV, 2 days after the onset of symptoms. There were no significant differences in open conversion, intraoperative blood loss, blood transfusion, CD ≥IIIa, 90-day mortality, and severity of AC between Group I and Group II, Group III, and Group IV. The incidence of bailout surgery was significantly higher and operative time longer in Group I than that in Group II.

Discussion

This is the first study to validate the efficacy and feasibility of the TG18 treatment strategy from a single-institute retrospective analysis. Our results reflected those of the TG18 proposal, and showed that under the strict conditions defined by ASA-PS and CCI, aggressive surgical strategy would be beneficial in decreasing the conversion rate and the length of hospital stay. There was no difference with regard to postoperative complications between the TG18 within and outside groups; however, 90-day mortality did not occur in patients who were operated within the TG18 strategy. The efficacy of the TG18 treatment strategy was validated in our study. In addition, our treatment strategy involved performing aggressive surgical interventions within 7 days from symptom onset instead of PC in GII & III of AC. This would be acceptable considering the relatively low complication rates even in patients who were defined as TG18 outside.

Clarification of the treatment strategy for GIII AC is one of the most important changes in TG18 from TG13 (17). Endo et al. showed that GIII patients who underwent subsequent cholecystectomy after PC had the lowest mortality (5). On the other hand, Davis CA et al. reported good surgical outcomes in high-risk surgical patients who underwent PC following elective cholecystectomy (21). In our study, high LC completeness was obtained as around 60% of the patients presented with GIII AC. Considering the postoperative mortality, our result showed that 90-day mortality was 4.5 %, which was compatible with results in previous reports (12, 13). These results make aggressive surgical intervention acceptable within 7days from symptom onset.

With regard to the grading of severity, our study proved that longer hospital stays, higher rates of conversion from laparoscopic to open cholecystectomy, and a high rate of bailout surgery were associated with higher severity grading. Paul et al. demonstrated that there was increased morbidity of around 10% associated with GIII AC following LC in contrast to less than 5% with GI and GII (22). On the other hand, S-W Lee et al. reported no significant benefit of the application of the TG13 in surgical outcomes, including survival rates, in their study (23). From our previous study, we know that precise grading is important, especially in clinical situations where several factors including renal failure and anti-coagulant therapy could be impediments to the outcome (24). The TG18 grading was validated as the higher the grading of AC, the higher the rate of postoperative complications.

The optimum timing of PC in the AC setting is difficult to determine. Moreover, the supremacy of PC over early cholecystectomy still remains unclear. There has been a previous report that PC followed by an early cholecystectomy could be safely performed in high-surgical-risk patients once sepsis and acute infection resolved rather than PC followed by a delayed cholecystectomy (25). Whereas some studies have shown that PC followed by delayed LC in critically ill patients was a safe and effective treatment strategy with a lower conversion rate and lower mortality (26, 27). In addition, operation after elective PC had a good prognosis in low-risk patients who presented to the hospital >72 h after symptom onset and did not respond to nonoperative treatment for 48 h (28). Thus, the optimal timing for PC or the optimal timing for subsequent LC in patients initially treated by PC remains controversial. There have been some reports advocating that PC would reduce postoperative complications and prevent intraoperative biliary injury (29, 30). Contrarily, Anderson JE et al. reported that patients who received PC had increased odds of death, longer hospital stay, and higher total charges (29). Our results showed that conversion rate was higher, which reached up to 16% in the TG18 outside group, but the 90-day mortality of 3% in our study was lower than that reported in previous studies (13,29).

This study has several limitations. This was a retrospectively observed, single-center study with a limited sample size. It is necessary to design prospective cohort studies involving multiple institutions for confirming our results. A single-hospital analysis is not enough to accurately evaluate the TG18. However, our strategy was to follow aggressive surgical treatment in patients who were stable enough to receive general anesthesia. Only 8 patients underwent cholecystostomy instead of early cholecystectomy in this study interval.

Conclusion

In conclusion, our study established the feasibility and efficacy of TG18. The usefulness of performing aggressive surgery beyond the TG18 strategy requires further study.

Abbreviations

TG18, Tokyo guideline 2018; LC, laparoscopic cholecystectomy; CCI, Charlson Comorbidity Index; ASA-PS, American Society of Anesthesiologists Physical Status Classification; AC, acute cholecystitis; GII, Grade II; GIII, Grade III; GI, Grade I; TG07, Tokyo guideline 2007; TG13, Tokyo guideline 2013; PC, percutaneous cholecystostomy; BMI, body mass index; CD, Clavien-Dindo; WBC, white blood cell; CRP, C- reactive protein

Declarations

Ethics approval and consent to participate

This study was authorized in advance by the institutional review board of the Onomichi General Hospital (approval number, OJH201849). Written informed consent was obtained from all participants.

Consent for publication

All patients consented to the reporting of this case in a scientific publication.

Availability of data and materials

No applicable.

Competing interests

None of the authors has any financial conflict of interest related to this manuscript.

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Authors' contributions

T. B., T. A., and H. A. wrote the manuscript. All the authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of patients with acute cholecystitis by grade according to the TG18 severity grading system

	Grade I (n=148)	Grade II (n=154)	Grade III (n=22)	*P*-value
Male:Female	91:57	100:54	15:7	0.732
Age (years)	66.4 (9-95)	72.4 (33-99)	79.4 (60-91)	**0.030**
BMI (kg/m^2)	24.4 (15.8-37.3)	23.9 (15.7-40.9)	22.8 (14.6-30.8)	0.243
ASA-PS				**<0.001**
≥3	17 (11.5%)	31 (20.1%)	10 (45.5%)	
CCI score				**0.042**
≥5	1 (0.7%)	4 (0.3%)	2 (9.1%)	
Beyond TG18 strategy	12 (8.1%)	38 (24.7%)	18 (81.8%)	**<0.001**
Comorbid with acute cholangitis	45 (30.4%)	57 (37.0%)	12 (54.5%)	0.069
Laboratory date				
WBC (×10^3/L)	10814 (3602-17900)	15531 (2000-30700)	13758 (4120-23570)	**<0.001**
CRP (mg/dL)	5.2 (0.0-28.7)	14.3 (0.1-44.8)	18.5 (3.4-34.5)	**<0.001**
Lap-C	141 (95.3%)	104 (67.5%)	13 (59.1%)	**<0.001**
Open conversion	2 (0.1%)	27 (17.5%)	2 (9.1%)	**<0.001**
Bailout surgery	16 (10.8%)	65 (42.2%)	6 (27.3%)	**<0.001**
Intraoperative blood loss	49.0 (0-486)	141.2 (0-1337)	189 (0-1200)	**<0.001**
Operative time	146.8 (59-269)	151.3 (71-291)	129.4 (63-199)	0.473
Postoperative hospital stays	7 (2-21)	13 (3-111)	18 (6-49)	**<0.001**
Blood transfusion	2 (0.1%)	5 (3.2%)	3 (13.6%)	**0.013**
CD ≥IIIa	8 (5.4%)	13 (8.4%)	2 (9.1%)	0.615
90-day mortality	0	1 (1.3%)	1 (4.5%)	0.101

Variables in bold are statistically significant (P□0.05). Continuous variables are expressed as median (range). Qualitative variables are expressed as number (%). Abbreviations: BDI, biliary duct injury; BMI, body mass index; BUN, blood urea nitrogen; CD, clavien-dindo; CRP, c-reactive protein; CT, computed tomography; Lap-C, laparoscopic cholecystectomy; PT-INR, prothrombin time-international normalized ratio; the TG18, the 2018 Tokyo Guidelines; WBC, white blood cell count

Table 2. Pre-operative TG18 comparison within and outside groups.

	TG18 within (n=256)	TG18 outside (n=68)	*P*-value
Male:Female	161:95	45:23	0.672
Age (years)	68 (9-99)	77 (47-96)	**<0.001**
BMI (kg/m^2)	24.1 (14.6-40.9)	23.6 (17.5-37.3)	0.464
ASA-PS			**<0.001**
≤2	247 (96.5%)	19 (28%)	
≥3	9 (3.5%)	49 (72.1%)	
CCI score			**<0.001**
≤4	256 (100%)	61 (89.7%)	
≥5	0	7 (10.3%)	
Acute cholecystitis grade 1/2/3	135/116/4	12/38/18	**<0.001**
Laboratory date			
WBC (×10^3/L)	13215 (2970-30700)	13378 (2000-27400)	0.936
CRP (mg/dL)	9.6 (0.0-35.6)	13.5 (0.0-44.8)	**0.002**
Imaging study of CT			
Wall thickness	218 (85.2%)	60 (88.2%)	0.566
Gallstones	178 (66.9%)	44 (64.7%)	0.465
Enhanced surrounding tissue	185 (72.3%)	57 (83.8%)	0.060
Effusion around gallbladder	74 (28.9%)	34 (50%)	0.459
Ascites	34 (13.3%)	20 (29.4%)	**0.002**
Liver abscess	11 (4.3%)	4 (5.9%)	0.745
Abscess around gallbladder	14 (5.5%)	8 (11.8%)	0.099
Emphysematous cholecystitis	5 (2.0%)	2 (2.9%)	0.641
Diabetes mellitus	54 (21.1%)	23 (33.8%)	**0.037**
Respiratory dysfunction	25 (9.8%)	7 (10.3%)	1.000
Cardiovascular dysfunction	28 (10.9%)	27 (39.7%)	**<0.001**
Hypertension	94 (36.7%)	40 (58.8%)	**0.001**
Hepatic dysfunction	4 (1.6%)	6 (8.8%)	**0.007**
Renal dysfunction	9 (3.5%)	12 (17.6%)	**<0.001**

Variables in bold are statistically significant (P<0.05). Continuous variables are expressed as median (range). Qualitative variables are expressed as number (%). Abbreviations: CRP, c-reactive protein; the TG18, the 2018 Tokyo Guidelines; WBC, white blood cell count

Table 3. Post-operative TG18 comparison within and outside groups.

	TG18 within (n=256)	TG18 outside (n=68)	*P*-value
Lap-C	213 (83.2%)	45 (66%)	**0.003**
Open conversion	20 (7.8%)	11 (16.2%)	**0.060**
Primary open cholecystectomy	23 (9.0%)	11 (16.2%)	
Bailout surgery	59 (23%)	28 (41.2%)	**0.004**
Intraoperative blood loss	76 (0.0-1116)	203 (0.0-1337)	**<0.001**
Blood transfusion	3 (1.2%)	7 (10.3%)	**<0.001**
Operative time	148 (59-291)	148 (63-255)	0.970
Postoperative hospital stays	9.0 (2.0-111)	15 (3-78)	**<0.001**
BDI	0	0	1.000
CD≥IIIa	17 (6.6%)	6 (8.8%)	0.595
Postoperative biliary leakage	4 (1.6%)	1 (1.5%)	1.000
90-day mortality	0	2 (2.9%)	**0.044**
Gangrenous cholecystitis	53 (20.7%)	24 (35.3%)	**0.016**

Variables in bold are statistically significant (P<0.05). Continuous variables are expressed as median (range). Qualitative variables are expressed as number (%). Abbreviations: BDI, biliary duct injury; BMI, body mass index; BUN, blood urea nitrogen; CD, clavien-dindo; Lap-C, laparoscopic cholecystectomy; the TG18, the 2018 Tokyo Guidelines

Table 4. Post-operative timing of surgery comparison, from onset to admission, by group

	Group I ~48hour (n=48)	Group II 2~7day (n=20)	*P*-value	Group III ~48hour (n=26)	Group IV 2~7day (n=42)	*P*-value
Reasons for TG18 outside						
ASA≥3	27 (56%)	9 (45%)	0.435	19 (73%)	17 (41%)	**0.012**
Early op for GIII	12 (25%)	4 (20%)	0.762	3 (8%)	13 (33%)	0.083
Open conversion	9 (19%)	2 (10%)	0.487	2 (7.7%)	9 (21%)	0.487
Bailout surgery	24 (50%)	4 (20%)	**0.030**	8 (31%)	20 (48%)	0.210
Intraoperative blood loss	229 (0-1337)	139 (0-700)	0.317	187 (0-1337)	212 (0-1200)	0.589
Blood transfusion	4 (8.3%)	3 (15%)	0.691	5 (19%)	2 (4.8%)	0.097
Operative time	156 (81-255)	129 (63-189)	**0.016**	149 (87-255)	147 (63-250)	0.940
Postoperative hospital stays	15 (3-78)	14 (4-31)	0.109	18 (3-78)	13 (3-49)	0.082
BDI	0	0	1.000	0	0	1.000
CD≥IIIa	6 (12.5%)	0 (0%)	0.169	2 (7.7%)	4 (9.5%)	1.000
Postoperative biliary leakage	1 (2%)	0	1.000	0	1 (2.4%)	1.000
90-day mortality	2 (4.2%)	0	0.354	1 (3.8%)	1 (2.4%)	1.000
Acute cholecystitis grade1/2/3	11/24/13	1/14/5	0.169	8/13/5	4/25/13	0.089
Gangrenous cholecystitis	15 (31%)	9 (45%)	0.796	8 (31%)	16 (38%)	0.608

Variables in bold are statistically significant (P<0.05). Continuous variables are expressed as median (range). Qualitative variables are expressed as number (%). Abbreviations: BDI, biliary duct injury; CD, clavien-dindo

Figures

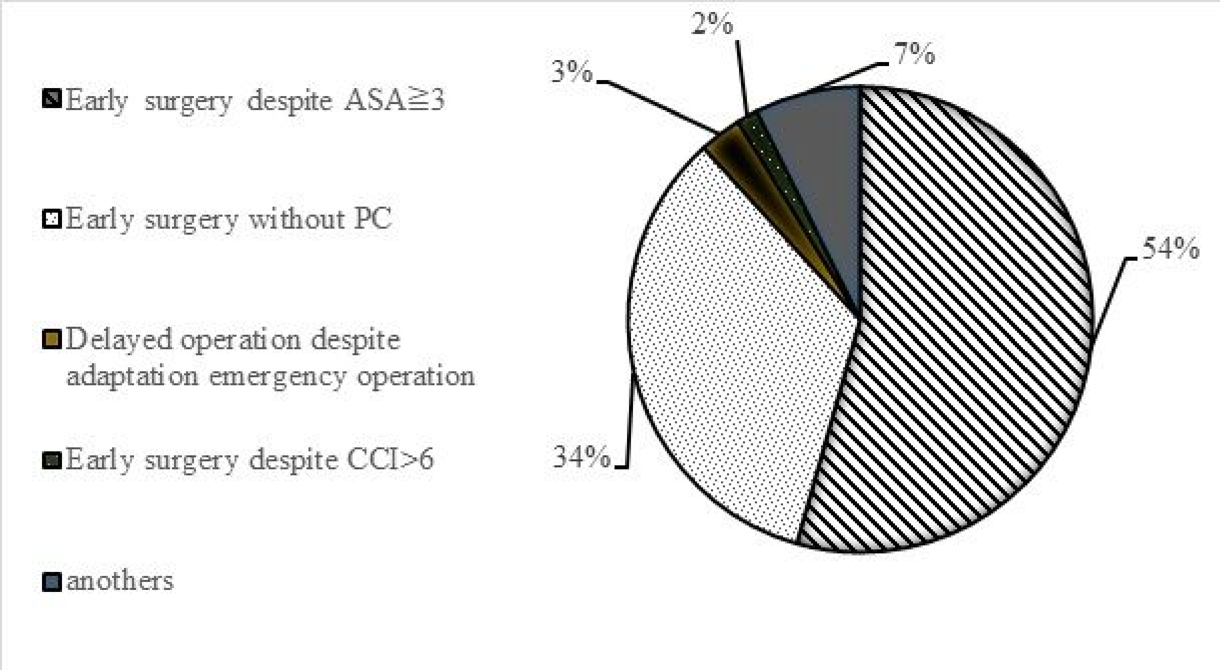

Figure 1

The reasons for exclusion from the TG18 group.