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Evaluating the advantages of treating acute cholecystitis by following the Tokyo Guidelines 2018 (TG18): a study emphasizing clinical outcomes and medical expenditures

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Abstract

Background Acute cholecystitis (AC) is a common surgical emergency. The Tokyo Guidelines 2018 (TG18) provides a reliable algorithm for the treatment of AC patients to achieve optimal outcomes. However, the economic benefits have not been validated. We hypothesize that good outcomes and cost savings can both be achieved if patients are treated according to the TG18.

Method This retrospective study included 275 patients who underwent cholecystectomy in a 15-month span. Patients were divided into three groups (group 1: mild AC; group 2: moderate AC with American Society of Anesthesiologists (ASA) physical status class ≤ 2 and Charlson Comorbidity Index (CCI) score ≤ 5; and group 3: moderate AC with ASA class ≥ 3, CCI score ≥ 6, or severe AC). Each group was further divided into two subgroups according to management (followed or deviated from the TG18). Patient demographics, clinical outcomes, and hospital costs were compared.

Results For group 1 patients, 77 (81%) were treated according to the TG18 and had a significantly higher successful laparoscopic cholecystectomy (LC) rate (100%), lower hospital cost ($1896 vs $2388), and shorter hospital stay (2.9 vs 8 days) than those whose treatment deviated from the TG18. For group 2 patients, 50 (67%) were treated according to the TG18 and had a significantly lower hospital cost ($1926 vs $2856), shorter hospital stay (3.9 vs 9.9 days), and lower complication rate (0% vs 12.5%). For group 3 patients, 62 (58%) were treated according to the TG18 and had a significantly lower intensive care unit (ICU) admission rate (9.7% vs 25%), but a longer hospital stay (12.6 vs 7.8 days). However, their hospital costs were similar. Early LC in group 3 patients did not have economic benefits over gallbladder drainage and delayed LC.

Conclusion The TG18 are the state-of-the-art guidelines for the treatment of AC, achieving both satisfactory outcomes and cost-effectiveness.

Keywords Acute cholecystitis · Tokyo Guidelines · Laparoscopic cholecystectomy · Cost · Cost effectiveness · Outcome

Acute cholecystitis (AC) is an acute inflammation of the gallbladder and is usually caused by obstruction of gallbladder drainage leading to gallbladder distension and wall edema that progresses to ischemia, necrosis, and perforation [1]. Although AC is a common disease, the diagnosis and management of AC continue to evolve and require a multifactorial systemic approach.

Practical diagnostic and grading systems, most notably the Tokyo Guidelines, have been developed to optimize the management of AC. Nonetheless, several controversial areas regarding the treatment of AC, such as the timing of surgical intervention, indications for percutaneous cholecystostomy, and optimal approach for difficult cholecystectomy, have prompted continual revisions of the guidelines based on new investigations [2–4].

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A number of recently published papers proposed a modification to the Tokyo Guidelines for Acute Cholecystitis 2013 (TG13) [5]. These papers suggested that the severity of AC should not be the sole determinant of the timing of laparoscopic cholecystectomy (LC) and that patient comorbidities also impact the treatment pathway. Therefore, unlike the TG13, the recommended treatment strategies for AC in the Tokyo Guidelines 2018 (TG18) are not only based on the severity of cholecystitis but also consider issues such as comorbidities and risk profiles of the patients. Hence, according to the TG18, early LC is feasible for moderate AC patients with low risk profiles if an advanced LC technique is available and is also feasible for severe AC patients who have favorable organ system failure (FOSF) and no negative predictive factors [6].

Nonetheless, clinical studies regarding the impact of the TG18 on the treatment of AC with regard to both outcomes and medical costs are still limited. Furthermore, the differences in patient outcomes and medical costs between those who were treated according to the recommendations in the TG18 or not have rarely been compared before. The aim of this study was to investigate the cost effectiveness and outcome of the treatment of AC according to the TG18.

Materials and methods

Study design

This was a retrospective study approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201700825B0). By reviewing the medical records of all patients with a diagnosis of AC between October 2015 and December 2016, patients ≥ 18 years old who underwent cholecystectomy were identified. Patient demographics, preexisting diseases, length of hospital stay, surgical outcomes, morbidities, in-hospital mortalities, and hospital costs were recorded. Based on the TG18, patients were divided into 3 groups according to the severity of AC (group 1: mild AC; group 2: moderate AC with an American Society of Anesthesiologists (ASA) physical status class ≤ 2 and a Charlson Comorbidity Index (CCI) score ≤ 5; and group 3: moderate AC with an ASA class ≥ 3, a CCI score ≥ 6, or severe AC). Each group was further divided into two subgroups according to the treatment of AC (followed or deviated from the TG18). For groups 1 and 2 patients, those who underwent early LC were defined as following the TG18. For group 3, moderate AC patients who underwent percutaneous gallbladder drainage followed by delayed LC, severe AC patients with good performance status (PS) and FOSF who underwent early LC, and severe AC patients with poor PS and no FOSF who underwent percutaneous gallbladder drainage followed by delayed LC were defined as following the TG18. Patients who were treated conservatively without cholecystectomy, who had concomitant cholangitis, or whose primary diagnosis was not AC during the index admission were excluded.

Patient demographics, such as age, sex, body mass index (BMI), ASA score, and the presence of existing comorbidities, including atrial fibrillation, hypertension, coronary artery disease, history of myocardial infarction (MI), congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes, renal disease, hepatic disease, thyroid disease, a history of pulmonary embolism or deep vein thrombosis, and cancer, were collected. The CCI score was used to represent the complexity of their comorbidities. The results of patients' clinical tests that were taken on admission, including routine hematological and biochemical tests as well as imaging studies, were also collected. Early LC was defined as cholecystectomy that was performed within 72 h of symptom onset, presentation or admission. Delayed LC was defined as cholecystectomy that was performed after 6 weeks.

The time interval between the onset of symptoms and surgery and the details and outcomes of the operation, including the type of surgery, operative time, amount of blood loss and Clavien–Dindo classification of surgical complications, were also collected.

In addition, fees for medical services, including physician fees, ward fees, medication fees, and fees for operations and procedures, were provided by the hospital's financial system. The overall hospital cost was calculated as the sum of all fees from the time of admission to the completion of cholecystectomy and discharge from the hospital.

The primary outcome was the overall hospital cost, and the secondary outcomes were the clinical outcomes, which included the successful LC rate (complete resection of the gallbladder without conversion), surgical complications, total length of hospital stay, length of postoperative hospital stay, length of intensive care unit (ICU) stay and in-hospital mortality rate. The length of hospital stay and the hospital costs for patients who required a hospital readmission for delayed cholecystectomy were calculated as the sum incurred during each admissions until the completion of cholecystectomy.

Statistical analysis

All the statistical analyses were performed using IBM SPSS 22 for Windows.

For continuous variables, independent t-tests were conducted, and the 95% confidence intervals (CIs) were calculated. For categorical variables, Pearson's Chi-square test was used. A two-sided $p < 0.05$ was considered statistically significant. Multiple logistic regression analyses were used to explore the factors that significantly affected the surgeons' treatment decisions.

Results

Overall, 352 patients were diagnosed with AC during the study period. Seventy-one of them were excluded because they did not undergo surgery, and another 6 patients were excluded because of a lack of crucial data. As a result, 275 patients were enrolled in this study. According to the TG18 definition of AC grades, there were 96 mild, 158 moderate, and 21 severe AC patients. Thus, there were 96 patients in group 1 (mild AC), 74 patients in group 2 (moderate AC with an ASA class ≤ 2 and a CCI score ≤ 5), and 106 patients in group 3 (moderate AC with an ASA class ≥ 3, a CCI score ≥ 6, or severe AC) (Fig. 1).

As expected, those patients with more severe disease had worse outcomes, and their hospital costs were higher. Patients with mild AC had a significantly smaller volume of intraoperative blood loss, shorter operative time, shorter total and postoperative lengths of hospital stay and lower hospital costs than patients with moderate and severe AC.

Following a full review of the medical records, among all 275 patients, 189 patients were treated according to the TG18, while the remaining 86 patients were not. In general, those patients who were treated according to the guidelines had a significantly higher successful LC rate, fewer morbidities, a shorter length of hospital stay, lower overall and ICU mortality rates, and lower medical costs than those whose treatment deviated from the TG18.

Among group I patients ($n = 95$), 77 (81%) were treated according to the TG18 and underwent early LC, while the remaining 18 patients underwent delayed operations. Those who were treated according to the TG18 were younger (mean, 49.7 vs 59.9 years, $p = 0.008$) and had lower CCI scores (mean, 1.23 vs 2.61, $p = 0.002$), lower neutrophil ratios (mean, 76.4% vs 82.7%, $p = 0.012$), lower C-reactive protein (CRP) levels (mean 50.7 vs 112.7 mg/L, $p = 0.003$), and more normal prothrombin times than those whose treatment deviated from the TG18 (Table 1). In addition, those who were treated according to the TG18 had a better

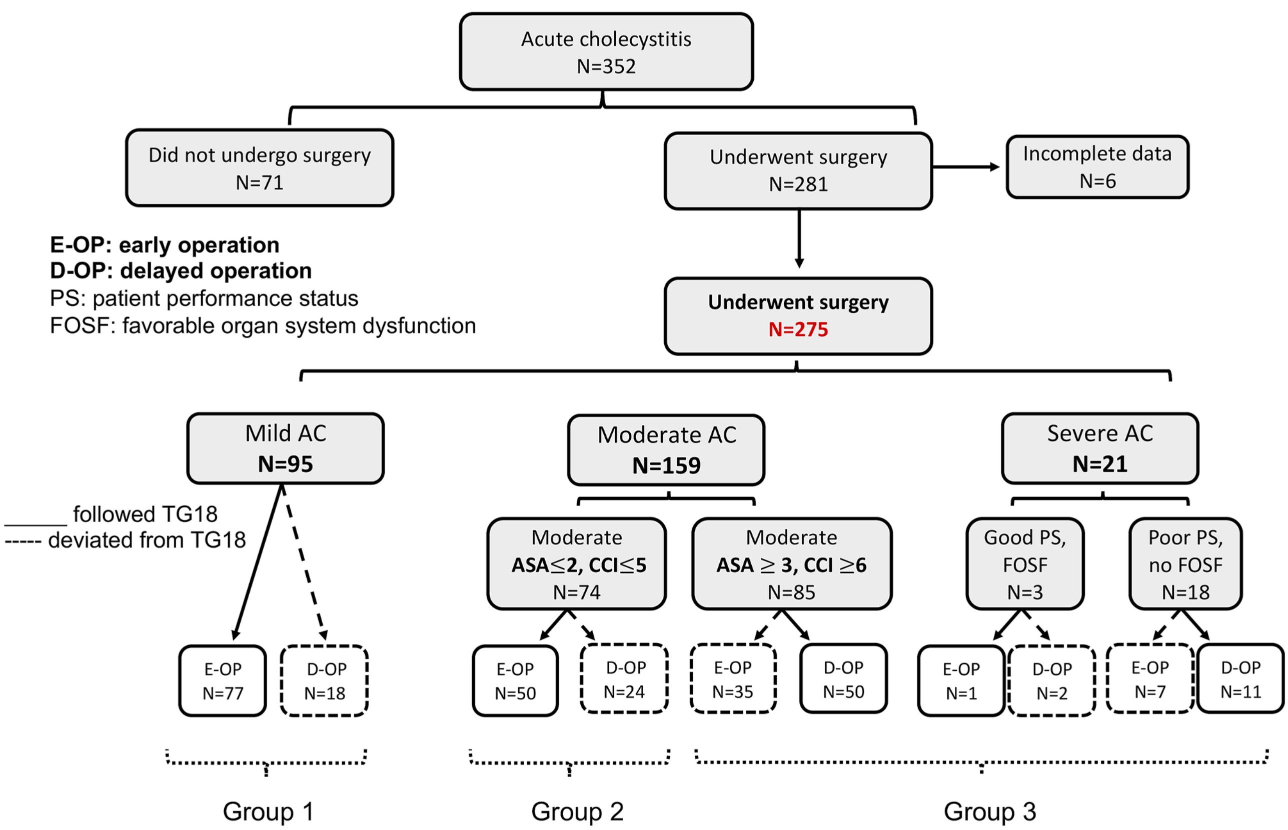

Fig. 1 Flowchart of patient grouping based on TG18. Based on the TG18, patients were divided into 3 groups according to the severity of acute cholecystitis (group 1: mild AC; group 2: moderate AC with American Society of Anesthesiologists (ASA) physical status class ≤ 2 and Charlson comorbidity index (CCI) score ≤ 5; group 3: moderate AC with ASA class ≥ 3, CCI score ≥ 6, or severe AC). Each group was further divided into two subgroups according to the treatment of AC (followed or deviated from the TG18). Those who followed TG18 were indicated by solid arrows and boxes, while those deviated from TG18 were indicated by dash arrows and boxes

Table 1 Comparison of patient demographics for the three groups of patients who were treated following or deviating from the TG18

	Group 1 (Mild AC)			Group 2 (Moderate AC with ASA ≤ 2 and CCI ≤ 5)			Group 3 (Moderate AC with ASA ≥ 3 or CCI ≥ 6 plus Severe AC)		
	Followed TG 18	Deviated from TG18	*p*	Followed TG 18	Deviated from TG18	*p*	Followed TG 18	Deviated from TG18	*p*
	n = 77	*n* = 18		*n* = 50	*n* = 24		*n* = 62	*n* = 44	
Age	49.68 ± 13.74 (49)	59.94 ± 16.09 (62)	0.008	45.94 ± 12.31 (45.5)	54.38 ± 11.65 (53)	0.006	70.4 ± 11.4 (74)	67.3 ± 11.9 (67.5)	0.177
Sex			0.391			0.596			0.846
Male	61% (47)	50% (9)		56% (28)	62.5% (15)		56.5% (35)	54.5% (24)	
Female	39% (30)	50% (9)		44% (22)	37.5% (9)		43.5% (27)	45.5% (20)	
BMI	26.9 ± 4.3 (26.2)	25.3 ± 3.0 (26.4)	0.127	25.78 ± 3.66 (25.7)	25.43 ± 2.16 (25.1)	0.688	26.3 ± 4.3(26.1)	26.7 ± 5.3(26.4)	0.702
Anticoagulant	0% (0)	16.7% (3)	0.000	0% (0)	4.2% (1)	0.146	14.5% (9)	6.8% (3)	0.218
CCI	1.23 ± 1.54 (1)	2.61 ± 2.00 (2.5)	0.002	0.8 ± 1.13 (0)	1.54 ± 1.44 (1)	0.018	4.0 ± 1.7(4)	3.5 ± 1.9(3)	0.125
CCI ≥ 3	22.1% (17)	50% (9)	0.017	10% (5)	29.2% (7)	0.036	87.1% (54)	65.9% (29)	0.009
ASA	2.31 ± 0.57 (2)	2.56 ± 0.51 (3)	0.098	1.94 ± 0.24 (2)	2 ± 0 (2)	0.083	2.95 ± 0.22(3)	3 ± 0.48(3)	
ASA ≥ 3	36.4% (28)	55.6% (10)	0.135	0%	0%		95.2% (59)	93.2% (41)	0.664
WBC count (10^3/mm^3)	11.76 ± 3.02 (12)	12.67 ± 3.20(12.5)	0.263	14.61 ± 4.81 (15)	16.11 ± 4.40 (16.3)	0.199	15.16 ± 7.55(14.45)	14.97 ± 6.38(13.6)	0.888
Neutrophils (%)	76.4 ± 9.5 (77.5)	82.7 ± 8.1 (84.3)	0.012	81.32 ± 9.44 (83.5)	83.67 ± 7.11 (86.3)	0.288	81.73 ± 8.83(83.00)	80.35 ± 8.84(81.70)	0.436
PLT ($\times 10^3$)	238.96 ± 57.63 (240.5)	213.78 ± 60.08 (207.5)	0.102	255.62 ± 64.39 (242.5)	253.79 ± 92.88 (253.5)	0.922	224.15 ± 127.66 (206.5)	223.34 ± 69.48 (213.50)	0.970
Bandemia	3.9% (3)	5.6% (1)	0.752	2% (1)	8.3% (2)	0.196	14(22.6%)	7(15.9%)	0.396
INR	1.07 ± 0.08 (1.05)	1.14 ± 0.13 (1.1)	0.022	1.09 ± 0.09 (1.1)	1.17 ± 0.09 (1.2)	0.004	1.15 ± (1.10)	1.31 ± (1.2)	
CRP (mg/L)	50.7 ± 67.65(19.8)	112.7 ± 88.89 (108.8)	0.003	80.14 ± 79.99 (41.6)	191.47 ± 102.39 (188.1)	0.000	189.91 ± 111.82 (192.85)	139.67 ± 115.39 (125.10)	0.039
Bil-T (mg/dL) ≥ 2	9.5% (7)	17.6% (3)	0.330	8.3% (4)	25% (6)	0.054	8.8% (5)	9.1% (4)	0.956

The data are presented as the mean ± SD (median) or % (number)

AC acute cholecystitis, *TG18* Tokyo Guidelines 2018, *ASA* American Society of Anesthesiologists physical status class, *CCI* Charlson Comorbidity Index, *BMI* body mass index, *WBC* white blood cell, *PLT* platelet count, *INR* international normalized ratio, *CRP* C-reactive protein, *Bil-T* total bilirubin

LC success rate (100%), lower hospital costs ($1896 vs $2388, $p = 0.005$), and a shorter length of hospital stay (2.9 vs 8 days, $p = 0.000$). None of the patients treated according to the TG18 had serious surgical complications (Clavien–Dindo score > 2). No group 1 patients were admitted to the ICU or died in the hospital (Table 2).

Group 2 consisted of 74 patients who had moderate AC, with ASA classes ≤ 2 and CCI scores ≤ 5. Fifty patients in group 2 underwent early LC, as recommended by the TG18, while the remaining 24 patients underwent delayed surgery. Similar to group 1, patients who were treated according to the TG18 recommendations ($n = 50$) were younger (mean: 45.9 vs 54.4 years old, $p = 0.006$) and had a lower average CCI score (0.8 vs 1.54, $p = 0.018$), better international normalized ratio (INR) (1.09 vs 1.17, $p = 0.004$), and lower CRP level (80.1 vs 191.5, $p = 0.000$) than the 24 patients whose treatment deviated from the TG18. Furthermore, the average hospital costs and total length of hospital stay of the 50 patients whose treatment adhered to the TG18 were significantly lower ($1926 vs $2856, $p = 0.000$) and shorter (3.9 vs 9.9 days, $p = 0.000$), respectively, than those of the other 24 patients. The complication rate was also significantly lower (0% vs 12.5%, $p = 0.011$). Overall, no group 2 patients were admitted to the ICU or died in the hospital (Table 2).

Group 3 consisted of 106 patients who either had moderate AC with severe morbidities (ASA class ≥ 3 or CCI score ≥ 6) or had severe AC. Among these patients, 62 were treated according to the TG18, while the other 44 patients were not. Those who were not treated according to the TG18 were significantly less likely to have severe comorbidities (CCI scores ≥ 3) (65.9% vs 87.1%, $p = 0.009$) and had significantly lower CRP levels than those who were treated according to the TG18 (Table 2). Moreover, patients who were not treated according to the TG18 had a higher ICU admission rate (25% vs 9.7%, $p = 0.034$) but a shorter total hospital stay (7.8 vs 12.6, $p = 0.011$) than those who were treated according to the TG18. However, the hospital costs were similar between the 2 groups ($2885 vs $3462, $p = 0.182$). Furthermore, those who were not treated according to the TG18 had a lower LC success rate than those

Table 2 Comparison of patient outcomes for the three groups of patients who were treated following or deviating from the TG18

	ALL			Group 1 (Mild AC)			Group 2 (moderate AC with ASA ≤ 2 and CCI ≤ 5)			Group 3 (moderate AC with ASA ≥ 3 or CCI ≥ 6 plus Severe AC)		
	Followed TG18	Deviated from TG18	*p*	Followed TG18	Deviated from TG18	*p*	followed TG18	Deviated from TG18	p	Followed TG18	Deviated from TG18	p
Number of patients	189	86		77	18		50	24		62	44	
Hospital cost (USD)	2406 ± 1399 (1770)	2773 ± 1572 (2070)	0.035	1896 ± 387 (1618)	2388 ± 377 (2039)	0.005	1926 ± 345 (1689)	2856 ± 1024(2236)	0.000	3426 ± 2044(2604)	2885 ± 2046(1820)	0.182
Blood loss (ml)	55.35 ± 89.88 (30)	74.86 ± 135.40(50)	0.225	43.6 ± 80.6 (25)	44.0 ± 115.5 (10)	0.984	67.0 ± 104.4(50)	44.3 ± 64.8 (25)	0.333	60.65 ± 87.92(40)	104.14 ± 164.07(50)	0.114
Successful LC rate (*n*)	94.2% (178)	83.7% (72)	0.005	100% (77)	94.4% (17)	0.038	92% (46)	87.5% (21)	0.536	90.3% (56)	77.3% (34)	0.064
Length of OP (min)	140 ± 47(133)	140 ± 50 (130)	0.985	128.2 ± 36.1 (123)	123.0 ± 34.9 (116)	0.580	145.7 ± 46.1 (147.5)	134.5 ± 44.6 (126)	0.330	150.4 ± 56.0(135.5)	149.9 ± 56.0(136.5)	0.966
ICU admission rate (*n*)	3.2% (6)	12.6% (11)	0.002	0% (0)	0% (0)		0% (0)	0% (0)		9.7% (6)	25% (11)	0.034
Complication rate (C–D > II)	1.6% (3)	11.5% (10)	0.000	0% (0)	5.6% (1)	0.038	0% (0)	12.5% (3)	0.011	4.8% (3)	13.6% (6)	0.109
Total length of hospital stay(day)	6.4 ± 5.9(4)	8.42 ± 9.3(7)	0.028	2.9 ± 1.1 (3)	8.0 ± 2.8 (8)	0.000	3.9 ± 1.8 (4)	9.9 ± 4.3 (9)	0.000	12.61 ± 6.59 (11.00)	7.75 ± 12.68 (5.00)	0.011
Postop hospital stay (day)	3.5 ± 2.8 (3)	5.2 ± 9.4 (3)	0.103	2.6 ± 0.9 (3)	3.0 ± 2.0 (3)	0.220	3.4 ± 1.6 (3)	4.0 ± 3.6 (2)	0.437	4.6 ± 4.5 (3)	6.73 ± 12.7 (3)	0.266
In-hospital mortality rate (%)	0% (0)	2.3% (2)	0.035	0% (0)	0% (0)		0% (0)	0% (0)		0% (0)	4.5% (2)	0.09

The data are presented as the mean ± SD (median) or % (number)

AC acute cholecystitis, *TG18* Tokyo Guidelines 2018, *ASA* American Society of Anesthesiologists physical status class, *CCI* Charlson Comorbidity Index, *LC* laparoscopic cholecystectomy, *OP* operation, *ICU* intensive care unit, *C–D* Clavien–Dindo classification who were treated according to the TG18 (77.3% vs. 90.3%). There were two in-hospital deaths in the group of patients who were not treated according to the TG18 (Table 2). In addition, for all the high-risk patients in group 3 (high-risk moderate AC and poor performance/no FOSF severe AC), 59.2% (61 out of 103 patients) were treated according to the TG18 by percutaneous gallbladder drainage followed by delayed LC. No mortalities were noted in these 61 patients (Fig. 1).

To analyze the independent factors that might affect the surgeon's decision to not follow the TG18, univariate and multivariate analyses were applied. Patient characteristics, including age ($>55, \leq 55$ years), sex (M, F), BMI ($>25, \leq 25$ kg/m^2), CCI score ($\geq 3, <3$), ASA class ($>3, \leq 3$), white blood cell (WBC) count ($>1.5\times10^4, \leq 1.5\times10^{4/}$μL), neutrophil ratio ($>80\%, \leq 80\%$), INR ($>1.2, \leq 1.2$), bandemia (Y, N), CRP level ($>50, \leq 50$ mg/L), and total bilirubin level ($>1.2, \leq 1.2$ mg/dL), were included in the univariate analysis in 3 groups. Only those items with $p<0.05$ were included in the multivariate analysis.

Among group I patients (mild AC), those patients who were older than 55 years or had a CRP level higher than 50 mg/L tended to be treated with delayed LC, which was a deviation from the TG18. Among group 2 patients (moderate AC with an ASA class ≤ 2 or a CCI score ≤ 5), those who had a CRP level higher than 50 mg/L tended to be treated with delayed LC, contrary to the recommendations in the TG18. Among group 3 patients (who had moderate AC with an ASA class ≥ 3 or a CCI score ≥ 6 or had severe AC), surgeons tended to perform early LC for those who had a CCI score <3 or a CRP level <50 mg/L although such treatment was not recommended by the TG18 (Table 3). The CRP level was the only independent factor for all the 3 groups that significantly affected surgeons' decisions to follow or deviate from the TG18. At a cutoff CRP value of 50 mg/L, the sensitivity and specificity were 79% and 55%, respectively.

Discussion

AC is a common and significant disease worldwide. Evidence-based guidelines according to population-based randomized studies are available to guide the proper management of AC [7, 8]. For the majority of the patients, it has clearly been demonstrated that early LC is the best treatment for AC because LC is usually not a complex procedure, and early LC is associated with a shorter duration of hospital stay and higher patient satisfaction [9–14]. However, straightforward LC might be contraindicated if the inflammation of the gallbladder is too severe and/or the risk of the operation is too high due to complex comorbidities and profound multiple organ failure. Therefore, the TG13 recommended different treatment strategies for the management of AC based on severity. In short, mild AC can be managed by early LC, while severe AC should be managed by drainage first followed by proper antibiotic treatment and delayed LC (TG13). The TG18 are revised guidelines of the TG13 that take risk factors such as the CCI score and organ dysfunction into consideration to enable better patient selection and treatment outcomes. While the TG18 have been widely accepted as the standard guidelines for patients with AC, it is interesting to determine whether treating patients according to these guidelines is also economically beneficial [6, 15, 16].

Eighty-one percent of patients in group 1 were treated according to the TG18, while the proportions were only 62% and 58% in groups 2 and 3, respectively. Treatment for mild AC is usually quite straightforward; therefore, only a small proportion of patients received treatment that deviated from the TG18. On the other hand, patients with moderate and severe AC were more likely to have organ dysfunction or severe comorbidities; thus, it was relatively more difficult to select the proper timing for LC. Since only approximately 60% of the patients in group 2 or 3 were treated according to the TG18, it suggested that there could be some clinical factors affecting surgeons' treatment plans even though these factors were not included in the TG18. Regarding deviations from the TG18, our experience showed that surgeons tended to choose delayed LC for groups 1 and 2 patients if the patients were relatively older, had longer prothrombin times, and had higher CCI scores or CRP levels. One reason for such deviations from the guidelines might be that the risk of conversion could be increased in those patients, as was reported by Mentula et al. [17]. In addition, surgeons also tended to deviate from the guidelines and treat group 3 patients with early LC if those patients had relatively lower CCI scores and CRP levels, partly because some evidence indicated that early LC was still feasible for severe AC [18]. Furthermore, lower CCI scores and CRP levels may suggest less operative risk and surgical difficulty in this group of patients because of the lower risk of gangrenous and phlegmonous changes in the gallbladder [19].

Our results revealed that for groups 1 and 2 patients for whom early LC was the recommended treatment modality, deviating from the TG18 and treating these patients with percutaneous transhepatic gallbladder drainage (PTGBD) and delayed LC resulted in more surgical complications, prolonged hospital stays, and increased hospital costs. These results were consistent with those reported by Felming et al. A propensity score-matched comparison of readmissions and the cost of LC vs. PTGBD for AC showed that PTGBD patients were more frequently readmitted, had longer hospital stays, and had higher hospital costs than those undergoing LC [20]. Therefore, treating groups 1 and 2 AC patients by following the TG18 appears to be the better strategy, even though some patients in these groups are relatively older and ill.

Table 3 Univariate and multivariate analyses for factors affecting surgeons' decision to follow or deviate from the TG18

	Group 1 (Mild AC)								Group 2 (Moderate AC with ASA ≤ 2 and CCI ≤ 5)								Group 3 (Moderate AC with ASA ≥ 3 or CCI ≥ 6 plus Severe AC)							
	Follow	Deviate	UV			MV			Follow	Deviate	UV			MV			Follow	Deviate	UV			MV		
	$n=79$	$n=17$	OR	95% CI	p	OR	95% CI	p	$n=50$	$n=24$	OR	95% CI	p	OR	95% CI	p	$n=62$	$n=44$	OR	95% CI	p	OR	95% CI	p
Age			8.276	2.205–31.058	0.002	5.184	1.091–24.627	0.038			2.333	0.856–6.362	NS						0.395	0.120–1.201	0.127			
> 55	32	15							15	12							57	36						
≤ 55	47	2							35	12							5	8						
CCI			3.529	1.211–10.284	0.021	1.642	0.416–6.481	NS			3.706	1.034–13.277	0.044	2.171	0.549–8.583	NS			0.286	0.109–0.755	0.011	0.314	0.117–0.847	0.022
≥ 3	20	8							5	7							54	29						
< 3	59	9							45	17							8	15						
Neutrophil			3.288	1.067–10.131	0.038	3.112	0.854–11.348	NS			1.207	0.444–3.278	NS						0.53	0.238–1.183	0.121			
> 80%	36	12							29	15							43	24						
≤ 80%	43	5							21	9							19	20						
CRP			6.556	2.154–19.953	0.001	4.986	1.485–16.738	0.009			6.756	2.156–21.163	0.001	5.811	1.800–18.764	0.003			0.381	0.168–0.866	0.021	0.418	0.179–0.972	0.043
> 50	20	10							18	19							46	23						
≤ 50	59	7							32	5							16	21						

Only those items that had $p < 0.05$ in the univariate analysis (UV) were included in the multivariate analysis (MV)

AC acute cholecystitis, *TG18* Tokyo Guidelines 2018, *ASA* American Society of Anesthesiologists physical status class, *CCI* Charlson Comorbidity Index, *CRP* C-reactive protein

Consistent with the results in groups 1 and 2 patients in the current study, a number of studies have demonstrated that early LC is the treatment of choice for AC [21–23]. On the other hand, unlike the results in groups 1 and 2 patients, our study also revealed that early LC did not have any significant advantages in group 3 patients in terms of surgical outcomes and hospital costs. The hospital costs for treating group 3 AC were the highest among all the groups because a significant proportion of the patients in this group required a prolonged hospital stay, ICU admission and, according to the TG18, a drainage procedure before LC. Nonetheless, our results showed that the attempt to shorten the hospital stay and save hospital costs by early LC, namely, by deviating from the TG18, appeared to be ineffective. This was because the rate of ICU admission, which substantially increased hospital costs, was significantly higher for group 3 patients if they were treated by early LC even though the total length of hospital stay could be shortened. Therefore, based on our results, the best strategy for the treatment of patients with severe AC is to follow the TG18 recommendations for delayed LC after adequate resuscitation and resolution of acute inflammation [1].

Another interesting but unresolved issue was the optimal timing of LC after gallbladder drainage, which has been reported to range from days to weeks in the literature [24]. According to our results, compared to early LC, it seems that a gallbladder drainage followed by delayed LC is probably a safe and cost-effective approach for high-risk moderate or severe AC patients because there was no mortality and the cost was not increased. For mild AC patients who were treated initially with gallbladder drainage, earlier LC soon after gallbladder drainage within the same admission might be a feasible approach in terms of cost saving because the total medical cost was significantly increased if mild AC patients were treated with delayed LC.

In the multivariate analysis, our results revealed that the CRP level was the only independent factor that significantly affected surgeons' decisions to follow or deviate from the TG18. At a cutoff CRP value 50 mg/L, the sensitivity and specificity to predict surgeons' decisions to follow or deviate from the TG18 were 79% and 55%, respectively. Although the CRP level is not listed as a biological determining criterion of the severity assessment of AC in the TG18, surgeons tend to treat mild or moderate AC more conservatively, avoiding early LC if patients' CRP levels are relatively high; however, surgeons attempt early LC for severe AC if patients' CRP levels are not extremely high. Similar to our results, Bouassisa et al. demonstrated that among blood cell counts (WBC count), the neutrophil-to-lymphocyte ratio (NLR) and CRP, CRP was the best factor to use to diagnose severe AC. In addition, the CRP level with a cutoff value at 60.5 mg/L had the highest discriminative power to predict conversion with a sensitivity and specificity of 71% and 71.4%, respectively [25]. As a result, they recommended that the CRP level should be considered as a severity criterion for AC in the next revised version of the Tokyo guidelines.

There is no doubt that early LC has become the standard practice for the treatment of AC, based mainly on a shorter hospital stay and thus a presumed economic benefit [16]. From this point of view, the TG18 severity grades have been shown to correlate well with the hospital length of stay, conversion to open cholecystectomy, and morbidity and mortality, providing clinicians with an optimal management strategy to follow [1]. Nonetheless, whether following the TG18 can also be economically beneficial in equivocal cases remains to be validated. For example, although either drainage or early cholecystectomy can be performed for moderate AC, Rice et al. argued that patients presenting with moderate AC developed more complications and incurred higher costs when undergoing early cholecystectomy than when undergoing a delayed approach. Thus, they recommended a careful and selective approach to treating patients with moderate AC; otherwise, the economic benefit of early cholecystectomy would be negated by increased charges for treating complications [26]. Our results provide solid evidence that, according to the TG18, a selective approach of treating patients with moderate AC according to their ASA class and CCI score not only achieves a satisfactory outcome but is also economically beneficial [6].

There are several limitations of this study. First, this was a retrospective observational study. Although a randomized controlled trial would be preferable, such a study is difficult to carry out due to the emergency nature of the disease. In addition, it is unethical to design a study in which one of its arms intentionally deviates from the treatment guidelines. Second, the choice of treatment plan was based on the surgeons' discretion, which was in turn related to their own practical experience and surgical skill. Hence, selection bias was inevitable. Nonetheless, since all these patients were treated between 2015 and 2016 and their outcomes were validated retrospectively according to the TG18, the choice of treatment was to some extent "randomized" because the TG18 did not exist at that time.

Conclusion

In conclusion, our results showed that the TG18 are state-of-the-art guidelines for the treatment of AC and that satisfactory outcomes and cost savings can both be achieved if they are followed. However, deviation from the guidelines is not uncommon, especially if age, CCI score and CRP level are taken into account by clinicians. All these factors might be considered in the next revision to optimize the Tokyo guidelines.

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Compliance with ethical standards

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