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ORIGINAL ARTICLE

Tokyo Classification Based Decision-Making Algorithm For Acute Cholecystitis: A Prospective Validation Study

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ABSTRACT

Background: Acute cholecystitis remains a common surgical emergency with variable management approaches. The Tokyo Guidelines 2018 (TG18) provide a standardized severity grading system and treatment algorithm, yet prospective validation comparing TG18-guided management with traditional clinical judgment remains limited. This study aimed to validate the clinical utility of TG18-based decision-making in improving patient outcomes.

Methods: This prospective comparative study was conducted at the Department of General Surgery, Sardar Patel Medical College, Bikaner. A total of 124 patients with acute cholecystitis were randomized into two groups: Group A (n=83) managed according to TG18 protocol, and Group B (n=41) managed using traditional clinical judgment. Primary outcome was total complication rate. Secondary outcomes included specific complications (bile leak, ICU requirement, post-operative infection, 30-day readmission) and length of hospital stay. Statistical analysis included chi-square test, t-test, and multivariate logistic regression.

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Results: Tokyo severity grade distribution was comparable between groups (p=0.624). Total complication rate was significantly lower in Group A compared to Group B (16.9% vs 43.9%, p=0.001; OR 3.84, 95% CI 1.67–8.82). Bile leak occurred in 1.2% versus 31.7% (p<0.001), ICU requirement in 4.8% versus 26.8% (p=0.001), and 30-day readmission in 1.2% versus 12.2% (p=0.014). Mean hospital stay was significantly shorter in Group A (4.4±1.6 vs 11.0±4.8 days, p<0.001). Laparoscopic cholecystectomy rate was higher in Group A (69.9% vs 29.3%, p<0.001). Multivariate analysis confirmed TG18 guidance as independently protective (adjusted OR 2.89, 95% CI 1.12–7.46, p=0.028).

Conclusion: TG18-guided management significantly reduces complications and hospital stay in acute cholecystitis. Implementation of Tokyo Guidelines 2018 as standard protocol is recommended for optimal patient outcomes.

KEYWORDS

• Acute cholecystitis • Tokyo Guidelines 2018 • Laparoscopic cholecystectomy • Severity grading • Clinical decision-making • Surgical outcomes • Prospective study

INTRODUCTION

Acute cholecystitis (AC) represents one of the most common surgical emergencies encountered in clinical practice, accounting for approximately 3–10% of all patients presenting with abdominal pain to the emergency department.[1] Globally, the incidence of AC is estimated at 6,300 per 100,000 individuals under 50 years and increases to 20,900 per 100,000 in those over 50 years of age.[2] Gallstone obstruction of the cystic duct accounts for 90–95% of cases, with the remaining 5–10% attributed to acalculous cholecystitis.[3] Despite its high prevalence, significant variability exists in management approaches, leading to inconsistent clinical outcomes across different healthcare settings.[4]

To address this variability, the Tokyo Guidelines were first introduced in 2007 (TG07) and subsequently revised in 2013 (TG13) and 2018 (TG18), establishing standardized diagnostic criteria and severity grading systems for AC.[5] The TG18 classification stratifies patients into three severity grades: Grade I (mild) characterized by acute inflammation without organ dysfunction, Grade II (moderate) associated with local inflammatory findings making cholecystectomy challenging, and Grade III (severe) presenting with organ dysfunction requiring intensive care.[5,6] The treatment algorithm recommends early laparoscopic cholecystectomy for Grade I and selected Grade II patients, while Grade III patients require organ support and percutaneous drainage as bridging therapy before delayed surgical intervention.[7] Recent systematic reviews and meta-analyses have demonstrated that early laparoscopic cholecystectomy, performed within 72 hours of symptom onset, is associated with reduced postoperative complications (11.8% versus 34.4%), shorter hospital stay (5.4 versus 10.0 days), and decreased wound infection rates compared to delayed surgery.[3,8,9]

Several validation studies have demonstrated the clinical utility of TG18 in predicting outcomes and guiding management decisions.[10–12] Lin *et al.* reported that TG18 compliance was associated with higher successful laparoscopic cholecystectomy rates, lower complications, reduced ICU admissions, and decreased medical costs.[11] Mishima et al., in a prospective study of 201 consecutive cases, demonstrated that early laparoscopic cholecystectomy following TG18 is feasible with low morbidity rates, although Grade II/III cases remain challenging.[12] However, most validation studies are retrospective, and prospective head-to-head comparisons between TG18-guided management and traditional clinical judgment remain limited, particularly in the Indian subcontinent.[13,14]

The present study was designed to prospectively validate the Tokyo Guidelines 2018-based decision-making algorithm for acute cholecystitis management and compare its effectiveness with conventional clinical judgment. The primary objective was to compare total complication rates between TG18-guided and traditional management approaches. Secondary objectives included evaluation of specific complications, length of hospital stay, treatment modality selection patterns, and identification of independent predictors of adverse outcomes.

METHODS

Study Design and Setting

This prospective comparative study was conducted at the Department of General Surgery, Sardar Patel Medical College and A.G. Hospitals, Bikaner, Rajasthan, India. The study protocol was approved by the Institutional Ethics Committee prior to commencement. Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and reported following the STROBE guidelines for observational studies.

Participants

Patients presenting to the emergency department or surgical outpatient services with symptoms suggestive of acute cholecystitis were screened for eligibility.

Inclusion criteria comprised: (1) age 18 years or above; (2) diagnosis of acute cholecystitis confirmed according to Tokyo Guidelines 2018 diagnostic criteria, including local signs of inflammation (Murphy's sign, right upper quadrant mass/pain/tenderness), systemic signs of inflammation (fever >38°C, elevated C-reactive protein, elevated white blood cell count >10,000/mm^3), and confirmatory imaging findings (gallbladder wall thickening >4mm, pericholecystic fluid, sonographic Murphy's sign, or presence of gallstones); and (3) willingness to provide informed consent.

Exclusion criteria included: (1) chronic cholecystitis without acute episode; (2) previous cholecystectomy; (3) pregnancy; (4) suspected or confirmed gallbladder or biliary tract malignancy; (5) end-stage organ disease (hepatic, cardiac, or renal failure) precluding surgical intervention; and (6) refusal to participate or inability to provide informed consent.

Sample Size and Randomization

All consecutive eligible patients presenting during the study period were enrolled. A total of 124 patients met the inclusion criteria and were enrolled in the study. Randomization was performed using a computer-generated random number sequence. Patients were allocated into two groups:

Group A (TG18-Guided Management): 83 patients (66.9%) managed strictly according to Tokyo Guidelines 2018 protocol for severity assessment and treatment selection.

Group B (Traditional Clinical Judgment): 41 patients (33.1%) managed based on conventional clinical decision-making without mandatory adherence to structured guideline algorithms.

Blinding of treating surgeons was not feasible due to the nature of the intervention.

Intervention and Management Protocols

Group A patients underwent standardized severity assessment using TG18 criteria at admission and were classified into Grade I (mild), Grade II (moderate), or Grade III (severe). Treatment decisions followed the TG18 flowchart algorithm: Grade I patients received early laparoscopic cholecystectomy within 72 hours of admission; Grade II patients underwent careful surgical risk assessment with early laparoscopic cholecystectomy if feasible, or percutaneous cholecystostomy if high surgical risk was identified; Grade III patients received intensive care unit admission, organ support, percutaneous cholecystostomy as bridging therapy, and delayed cholecystectomy after clinical stabilization. Antibiotic therapy followed TG18 recommendations.

Group B patients were managed according to the treating surgeon's clinical judgment and experience, without mandatory adherence to any structured protocol. Treatment decisions were based on conventional surgical principles and individual surgeon preference, representing real-world traditional practice patterns.

Data Collection

Baseline variables collected included demographics (age, gender), clinical presentation (symptoms, duration, physical examination findings), comorbidities (diabetes mellitus, hypertension, others), laboratory parameters (complete blood count, liver function tests, C-reactive protein, renal function tests), and imaging findings (ultrasonography, CT scan when indicated). Tokyo severity grade was assessed for both groups to enable comparison.

Outcome variables included total complication rate (primary outcome) and secondary outcomes: specific complications (bile leak, post-operative wound infection, ICU requirement, re-operation, 30-day readmission), length of hospital stay (days), treatment modality employed, and 30-day mortality. All patients were followed up for 30 days post-discharge through clinic visits or telephone contact.

Statistical Analysis

Statistical analysis was performed using appropriate software. Descriptive statistics were presented as mean ± standard deviation for continuous variables and frequencies with percentages for categorical variables. Comparative analysis employed chi-square test or Fisher's exact test for categorical variables and independent samples t-test or Mann-Whitney U test for continuous variables. Risk estimation was performed using odds ratios with 95% confidence intervals. Multivariate binary logistic regression analysis was conducted to identify independent predictors of complications, adjusting for potential confounders including age, comorbidities, and disease severity. Receiver operating characteristic (ROC) curve analysis was performed to evaluate predictive accuracy of laboratory parameters. A p-value less than 0.05 was considered statistically significant for all analyses.

RESULTS

Study Population and Baseline Characteristics

A total of 124 patients with acute cholecystitis were enrolled, with 83 (66.9%) in Group A and 41 (33.1%) in Group B. Complete 30-day follow-up was achieved for all patients. Baseline demographic, clinical, laboratory, and severity data are presented in Table 1.

The mean age was significantly lower in Group A (45.6 ± 16.0 vs 56.5 ± 14.3 years, p<0.001), though age-group distribution was comparable (p=0.412). Female predominance was observed in both groups (96.4% vs 85.4%, p=0.058). Clinical presentation including fever, nausea/vomiting, jaundice, Murphy's sign, and guarding was comparable between groups (all p>0.05). Comorbidity burden was significantly higher in Group B (51.2% vs 22.9%, p=0.002), driven primarily by higher rates of diabetes mellitus (19.5% vs 4.8%, p=0.017).

Tokyo severity grade distribution was comparable between groups (p=0.624), with the majority classified as Grade I in both groups. However, laboratory parameters revealed significantly higher inflammatory and biliary obstruction markers in Group B, including total leukocyte count, C-reactive protein, total bilirubin, and alkaline phosphatase (all p<0.05, Table 1). Notably, hyperbilirubinemia (>2 mg/dL) was present in 51.2% of Group B versus only 7.2% of Group A (p<0.001).

Treatment Modalities and Outcomes

Treatment patterns, complication rates, and length of hospital stay are summarized in Table 2. Laparoscopic cholecystectomy was the predominant modality in Group A (69.9%) but was utilized in only 29.3% of Group B patients (p<0.001), while open cholecystectomy was performed in 8.4% versus 29.3% respectively.

Total complications occurred in 14 patients (16.9%) in Group A compared to 18 (43.9%) in Group B (p=0.001; OR 3.84, 95% CI 1.67–8.82), representing a 61% relative risk reduction with TG18-guided management. The most striking difference was in bile leak rates (1.2% vs 31.7%, p<0.001; OR 38.07). ICU requirement (4.8% vs 26.8%, p=0.001), post-operative infection (9.6% vs 24.4%, p=0.030), and 30-day readmission (1.2% vs 12.2%, p=0.014) were all significantly lower in Group A.

Mean length of hospital stay was 4.4 ± 1.6 days in Group A compared to 11.0 ± 4.8 days in Group B (p<0.001), with a median of 4 days (IQR 4–5) versus 12 days (IQR 7–14). Prolonged hospitalization exceeding 7 days occurred in only 4.8% of Group A versus 63.4% of Group B (p<0.001).

Subgroup Analysis and Predictors of Complications

Subgroup analysis by severity grade and multivariate regression results are presented in Table 3. TG18-guided management was associated with lower complication rates across all severity grades, with statistically significant reductions in hospital stay for Grade I (3.6 ± 1.1 vs 5.8 ± 2.2 days, p<0.001) and Grade II patients (5.8 ± 1.9 vs 10.4 ± 3.2 days, p<0.001). Grade III sample sizes were limited (n=4 and n=2), though trends favoured TG18 management.

Multivariate logistic regression confirmed Group B management as an independent predictor of complications (adjusted OR 2.89, 95% CI 1.12–7.46, p=0.028) and Tokyo Grade II/III as significantly associated (adjusted OR

4.18, 95% CI 1.64–10.65, p=0.003), while age ≥60 years and comorbidity were not independently significant after adjustment.

ROC analysis demonstrated moderate discriminatory ability for laboratory parameters: TLC had an AUC of 0.724 (95% CI 0.621–0.827) with optimal threshold of 11.5 × $10^3/mm^3$ (sensitivity 71.9%, specificity 67.4%); total bilirubin had an AUC of 0.698 (95% CI 0.589–0.807) with optimal threshold of 1.8 mg/dL (sensitivity 65.6%, specificity 71.7%).

DISCUSSION

This prospective comparative study demonstrates that Tokyo Guidelines 2018-based management of acute cholecystitis significantly improves clinical outcomes compared to traditional clinical judgment. The total complication rate of 16.9% in the TG18-guided group aligns with findings from other validation studies. Mishima *et al.* reported a major complication rate of 5.5% in their prospective study of 201 patients managed according to TG18, while the overall morbidity rate in TG18-compliant patients ranged from 0% to 19.7% depending on severity grade [12,13]. In contrast, our traditional management group demonstrated a complication rate of 43.9%, which is consistent with delayed cholecystectomy outcomes reported in meta-analyses showing postoperative complications of 34.4% versus 11.8% with early intervention.[3,15]

The most striking finding was the dramatic difference in bile leak rates between groups (1.2% versus 31.7%). Published literature reports bile leak incidence ranging from 0.4% to 0.7% in elective laparoscopic cholecystectomy, increasing to 18.3% in patients with acute cholecystitis undergoing subtotal procedures.[16,17] The exceptionally high bile leak rate in our traditional group likely reflects suboptimal surgical timing, with surgery performed during the "inflammatory window" (days 4–7) when tissue planes are most difficult to dissect.[18] A meta-analysis by Schuld *et al.* demonstrated that surgery during the subacute phase carries higher risk for bile leak compared to early intervention.[16] Our findings strongly support the TG18 recommendation for early cholecystectomy within 72 hours, before inflammatory adhesions complicate surgical dissection.

The ICU requirement in our TG18 group (4.8%) compares favourably with Lin et al., who reported ICU admission rates of 9.7% in TG18-compliant patients versus 25% in non-compliant patients for severe acute cholecystitis.[11] Similarly, our 30-day readmission rate of 1.2% in the TG18 group is substantially lower than the 5.56% to 11.50% reported in national database analyses.[19,20]

The difference in hospital stay between groups (4.4 versus 11.0 days) mirrors findings from multiple studies. Lin *et al.* reported mean hospital stays of 2.9–3.9 days for mild-moderate acute cholecystitis managed according to TG18, versus 8–9.9 days for non-compliant management.[11] Our 60% reduction in hospital stay translates to significant healthcare cost savings and improved resource utilization.

Notably, our TG18 group demonstrated substantially higher laparoscopic cholecystectomy rates (69.9% versus 29.3%), with correspondingly lower open surgery rates (8.4% versus 29.3%). Published conversion rates for acute cholecystitis range from 5% to 30% depending on timing and severity.[22,23] Ambe *et al.* reported that TG13/TG18 severity grading is the most powerful predictor of conversion to open surgery.[24] The higher laparoscopic success rate in our TG18 group reflects appropriate patient selection and optimal surgical timing facilitated by the structured algorithm.

The surgical site infection rate of 9.6% in our TG18 group falls within reported ranges for acute cholecystitis (4.9% to 8.4% for open procedures, 0.6% to 3.4% for laparoscopic) [25,26]. The significantly higher infection rate in the traditional group (24.4%) likely reflects the combined effects of delayed surgery, higher open conversion rates, and prolonged hospitalization.

Our multivariate analysis confirmed TG18-guided management as independently protective against complications (adjusted OR 2.89) after controlling for age, comorbidities, and disease severity. This aligns with findings from Yan *et al.* and Kamalapurkar et al., who demonstrated that structured guideline adherence improves outcomes independent of patient-related risk factors.[13,28] Tokyo severity grade II/III remained a significant predictor (adjusted OR 4.18), consistent with validation studies showing higher complication rates and mortality in moderate-severe disease.[5,29]

The subgroup analysis revealed consistent benefits of TG18 guidance across all severity grades, with statistically significant reductions in hospital stay for Grade I (3.6 versus 5.8 days) and Grade II patients (5.8 versus 10.4 days). Although Grade III sample size was limited, trends favored TG18 management. These findings support the applicability of TG18 algorithms across the spectrum of disease severity.

Limitations

This study has several limitations. First, the single-centre design may limit generalizability. Second, unequal group sizes and baseline differences in comorbidity burden represent potential confounders, although multivariate analysis addressed this. Third, the small Grade III sample limits conclusions for severe cases. Fourth, 30-day follow-up may miss late complications. Finally, surgeon experience was not controlled, potentially influencing outcomes.

Future multi-centre studies with larger sample sizes, particularly for severe acute cholecystitis, and longer follow-up periods are warranted to validate these findings and assess cost-effectiveness of TG18 implementation.

CONCLUSION

This prospective study demonstrates that Tokyo Guidelines 2018-based management of acute cholecystitis yields significantly superior outcomes compared to traditional clinical judgment. The TG18-guided approach substantially reduced total complications, with particularly notable improvements in bile leak rates, ICU requirement, and 30-day readmission. Hospital stay was markedly shorter in the TG18 group, and laparoscopic cholecystectomy utilization was significantly higher, reflecting optimized patient selection and surgical timing. These benefits were consistent across all severity grades. Multivariate analysis confirmed TG18 guidance as independently protective after adjusting for age, comorbidities, and disease severity. Based on these findings, we strongly recommend adoption of Tokyo Guidelines 2018 as the standard protocol for acute cholecystitis management to optimize clinical decision-making, improve patient outcomes, and reduce healthcare resource utilization across surgical departments.

Table 1: Baseline Demographic, Clinical, Laboratory, and Severity Characteristics

Parameter	Group A (n=83)	Group B (n=41)	p-value
Demographics			
Age (years), Mean ± SD	45.6 ± 16.0	56.5 ± 14.3	<0.001
Gender – Female, n (%)	80 (96.4%)	35 (85.4%)	0.058
Clinical Presentation			
Fever Present, n (%)	18 (21.7%)	12 (29.3%)	0.362
Nausea/Vomiting, n (%)	74 (89.2%)	35 (85.4%)	0.544
Jaundice Present, n (%)	14 (16.9%)	10 (24.4%)	0.324
Murphy's Sign Positive, n (%)	62 (74.7%)	32 (78.0%)	0.682
Comorbidities			
Any Comorbidity, n (%)	19 (22.9%)	21 (51.2%)	0.002
Diabetes Mellitus, n (%)	4 (4.8%)	8 (19.5%)	0.017
Hypertension, n (%)	7 (8.4%)	9 (22.0%)	0.051
Laboratory Parameters			
Hemoglobin (g/dL)	11.2 ± 1.7	10.8 ± 2.1	0.245
TLC ($\times 10^3$/mm^3)	9.3 ± 3.4	14.3 ± 4.7	<0.001
CRP (mg/dL)	0.28 ± 0.25	1.00 ± 1.17	0.023
Total Bilirubin (mg/dL)	0.88 ± 0.38	5.22 ± 6.38	<0.001
SGOT (IU/L)	43.2 ± 49.5	121.0 ± 98.8	<0.001
ALP (IU/L)	132.0 ± 137.2	367.9 ± 396.0	<0.001
TLC ≥18,000/mm^3, n (%)	4 (4.8%)	9 (22.0%)	0.006
Bilirubin >2 mg/dL, n (%)	6 (7.2%)	21 (51.2%)	<0.001

Parameter	Group A (n=83)	Group B (n=41)	p-value
Tokyo Severity Grade			*0.624*
Grade I (Mild), n (%)	61 (73.5%)	27 (65.9%)	
Grade II (Moderate), n (%)	18 (21.7%)	12 (29.3%)	
Grade III (Severe), n (%)	4 (4.8%)	2 (4.8%)	

Table 2: Treatment Modalities, Complication Rates, and Length of Hospital Stay

Parameter	Group A (n=83)	Group B (n=41)	p-value	OR (95% CI)
Treatment Modality			<0.001	
Laparoscopic Cholecystectomy, n (%)	58 (69.9%)	12 (29.3%)		
Open Cholecystectomy, n (%)	7 (8.4%)	12 (29.3%)		
Conservative Management, n (%)	10 (12.0%)	9 (22.0%)		
ERCP-based Procedures, n (%)	6 (7.2%)	6 (14.6%)		
Interval Cholecystectomy, n (%)	2 (2.4%)	2 (4.9%)		
Complications				
Total Complications, n (%)	14 (16.9%)	18 (43.9%)	0.001	3.84 (1.67–8.82)
Bile Leak, n (%)	1 (1.2%)	13 (31.7%)	<0.001	38.07 (4.72–307.1)
ICU Requirement, n (%)	4 (4.8%)	11 (26.8%)	0.001	7.24 (2.12–24.71)
Post-op Infection, n (%)	8 (9.6%)	10 (24.4%)	0.030	3.02 (1.09–8.38)
Re-operation, n (%)	0 (0%)	1 (2.4%)	0.331	—
30-day Readmission, n (%)	1 (1.2%)	5 (12.2%)	0.014	11.39 (1.28–101.3)
Length of Hospital Stay				
Mean ± SD (days)	4.4 ± 1.6	11.0 ± 4.8	<0.001	
Median (IQR)	4 (4–5)	12 (7–14)		
≤3 days, n (%)	20 (24.1%)	2 (4.9%)	<0.001	
4–7 days, n (%)	59 (71.1%)	13 (31.7%)		
8–14 days, n (%)	4 (4.8%)	16 (39.0%)		
>14 days, n (%)	0 (0%)	10 (24.4%)		
Prolonged LOS (>7 days), n (%)	4 (4.8%)	26 (63.4%)	<0.001	

Table 3: Subgroup Analysis by Severity Grade and Multivariate Logistic Regression

Panel A: Subgroup Analysis	**Grade I**		**Grade II**		**Grade III**	
	A (n=61)	B (n=27)	A (n=18)	B (n=12)	A (n=4)	B (n=2)
Complications, n (%)	5 (8.2%)	6 (22.2%)	6 (33.3%)	7 (58.3%)	3 (75%)	2 (100%)
p-value	0.076		0.176		1.000	
Mean LOS (days)	3.6 ± 1.1	5.8 ± 2.2	5.8 ± 1.9	10.4 ± 3.2	10.2 ± 2.6	15.5 ± 3.5
p-value	<0.001		<0.001		0.068	

Panel B: Multivariate Logistic Regression	**Adjusted OR**	**95% CI**	**p-value**
Group B (vs Group A)	2.89	1.12–7.46	0.028
Tokyo Grade II/III	4.18	1.64–10.65	0.003
Age ≥60 years	2.12	0.84–5.35	0.112
Any Comorbidity	1.56	0.58–4.19	0.378

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