**THE CURRENT TOKYO GUIDELINES ARE NOT CLINICALLY RELEVANT
FOR THE DIAGNOSIS AND MANAGEMENT OF CHOLECYSTITIS**

Short Title: “Tokyo Guidelines Are Not Clinically Relevant”

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Abstract

Background: The Tokyo Guidelines (TG13) is used to diagnose, grade severity, and guide management of acute cholecystitis (AC). Aim of our study was to verify the diagnostic criteria, severity assessment, and management protocols based on TG13.

Study Design: Our prospectively maintained Emergency General Surgery registry was utilized to review patients who had a surgical consultation for RUQ pain (2013-2015). Diagnosis and severity were graded based on TG13 and compared with pathology report. Our institutional management protocols were compared to TG13.

Results: 952 patients were analyzed, of which 857 had biliary diseases. Mean age was 42 ± 18 y and 67% were female. 779 had a cholecystectomy, 15 underwent cholecystostomy-tube placement, and 63 patients were managed conservatively. Only 4% were febrile on presentation and 51% of patients had leukocytosis. 59% patients did not have any signs of AC on ultrasonography. TG13 criteria had a sensitivity of 53% for diagnosing AC (definitive: 27%, suspected 26%, undiagnosed: 47%) when compared with the final pathology report. 92.5% of patients with grade-I, 93% grade-II and even 64% of grade-III safely underwent cholecystectomy at our institute. There was no difference between the complications (3.7% vs. 4.7%, $p=0.81$), return to the OR (0.6% vs. 0.7%, $p=0.95$) and mortality (0.3% vs. 0%, $p=0.96$) between grade-I and grade-II who underwent early cholecystectomy.

Conclusions: The TG13 diagnostic criterion lacks sensitivity and missed more than half of the patients with AC, as many patients lack clinical signs (fever and leukocytosis). The TG13 recommendations for conservative management and delayed cholecystectomy in grades II and III diseases are not warranted.

Key words: Acute cholecystitis; Tokyo guidelines; Diagnosis; Severity grading.

INTRODUCTION:

Acute cholecystitis is a common manifestation of cholelithiasis and is one of the most common causes of emergency admissions to the acute care service (1). With an estimated 2.2 million visits to the hospital, cholelithiasis and complications are the leading cause of hospital admissions related to gastrointestinal problems. Acute calculous cholecystitis is diagnosed in over a 20 million people in the United States annually and results in a direct cost of more than \$9.3 billion (2, 3). Due to the changing dynamics of the population, the rise in the incidence of obesity, diabetes and increasing use of cholesterol-lowering medications, the incidence of gallstones and related complications have further increased in the past two decades (3, 4). It is estimated that the frequency of acute cholecystitis-related discharges has increased by 44% between 1997 and 2013 (3).

The diagnosis of acute cholecystitis is made on the basis of a constellation of clinical features such as right upper quadrant pain/tenderness, fever, and leukocytosis and is supported by relevant findings from imaging studies (5). Once the diagnosis is made, treatment is primarily surgical and laparoscopic cholecystectomy is considered to have the optimal outcomes (6). An estimated 503,000 laparoscopic cholecystectomies were performed in 2006 (7). Despite the high incidence of acute cholecystitis, significant controversies remain in the diagnosis, grading, and management of acute cholecystitis (8, 9). There is still a considerable debate on the reliability of physical signs and the diagnostic value of ultrasound and laboratory tests. Although, the controversy regarding the timing of surgery has somewhat resolved in favor of early cholecystectomy, the concept of conservative management followed by delayed/elective cholecystectomy particularly in high-risk patients is still debated (10).

A number of algorithms have been devised for the diagnosis and management of acute cholecystitis; however, none of them have been validated or widely adopted. One such effort was the development of Tokyo Guidelines (TG). The first set of these guidelines were developed in 2007 and were later updated in 2013 (9, 11). However, the literature regarding validation of the Tokyo Guidelines 2013 (TG13) and its applicability to U.S. population is scarce. The aim of our study was to evaluate the diagnostic criteria, severity assessment, and management protocols based on TG13. We hypothesized that the TG13 diagnostic criteria lack sensitivity for the diagnosis of acute cholecystitis and patients with moderate to severe acute cholecystitis can be safely managed with early cholecystectomy.

METHODS:

We performed a 3-year analysis of our prospectively maintained emergency general surgery (EGS) database. The database contains patients managed both operatively and non-operatively. We reviewed the records of consecutive patients who underwent surgical consultation for right upper quadrant pain or suspicion for acute cholecystitis from 2013–2015 at our Level-1 Trauma Center. Our center provides 24-hour emergency surgery services in keeping with a dedicated acute care surgery (ACS) model. The institutional review board at the University of Arizona, College of Medicine, approved this study.

Inclusion and Exclusion Criteria:

We analyzed all adult (>18 years) patients admitted to the acute care surgery (ACS) service for which the ACS team was consulted for upper quadrant pain or a suspicion for acute cholecystitis. We excluded patients with acalculous cholecystitis, those transferred from other hospitals, and those with an alternate diagnosis.

Data Points and Definitions:

We collected the following baseline patient characteristics to describe the cohort as well as to examine factors in the Tokyo Guidelines (TGs): Demographics (age, gender, race); admission vitals (heart rate [HR], systolic blood pressure [SBP], temperature); laboratory values (white blood cell count [WBC], C reactive protein [CRP]); physical examination details (murphy's sign, right upper quadrant mass/pain/tenderness); ultra-sonographic finding; CT scan findings; and final pathology result. We also identified the following organ system dysfunctions: Cardiovascular (hypotension requiring treatment with dopamine ≥ 5 ug/kg/min or any dose of norepinephrine); Neurological (decreased level of consciousness); Respiratory ($\text{PaO}_2/\text{FIO}_2$ ratio < 300); Renal dysfunction (Oliguria, creatinine > 2.0 mg/dl); Hepatic dysfunction (PT-INR > 1.5); and hematological dysfunction (platelet dysfunction $< 100,000/\text{mm}^3$).

Patients were stratified based on the Tokyo guidelines 2013 into either a suspected or definite diagnosis (**Supplemental Table 1.**) (9). If the patient did not fulfill criteria for suspected or definite diagnosis, it was considered as no acute cholecystitis. In addition, patients were stratified into Grade I (mild), Grade II (moderate), or Grade III (severe) AC based on the TG13 (**Supplemental Table 2.**) (9).

The hospital and intensive care unit (ICU) length of stay (LOS), complications and mortality were also extracted from the patient charts.

Outcome Measures:

Our primary outcome measure was to calculate the sensitivity of Tokyo guidelines for the diagnosis of acute cholecystitis, and compare the management recommendation of TG13 with our institution protocols. Secondary outcome measures were hospital length of stay, postoperative complications, return to operating room and mortality among this cohort.

Data Analysis:

Data are presented as a mean $\pm$ standard deviation, for continuous variables, as medians [with interquartile range] for ordinal variables, and as proportions for categorical variables. The relationships between measured variables and mortality were tested using Chi-squared tests for categorical variables and student's t-test and Wilcoxon rank-sum tests for continuous variables. The sensitivity was calculated using the standard formula. For data analysis, we used the statistical package for social sciences software (SPSS, V24; IBM Inc.). A p-value <0.05 was considered statistically significant.

Results:

We analyzed 952 consecutive patients who underwent surgical consultation for right upper quadrant pain and had suspicion for acute cholecystitis. Ninety-five patients were excluded due to diagnosis other than cholecystitis. Of 857 patients with the biliary disease, 63 were managed conservatively, and 15 had cholecystostomy tube placement. Overall, 779 patients underwent emergent cholecystectomy within 24 hours of admission. Mean age was 42 ± 18 years, 67% were females, and 75% were whites. Overall, 4% of the patients were febrile on admission, 52% had leukocytosis, 72% had a positive murphy's sign and 92% had right upper quadrant tenderness. The demographics and admission characteristics of the study population are demonstrated in **Table 1**. A total 34% of the patients had delayed presentation (>72 hours of onset of symptoms). Most common organ system dysfunction was renal (2.3%) followed by hepatic (2%).

On the final pathology report, 9.8% of the patients had acute gangrenous/necrotizing cholecystitis, 28.8% had acute cholecystitis and 61.3% had acute on chronic cholecystitis. When the TG13 diagnostic criteria were applied to our cohort, 46.6% of the patients were undiagnosed

while 27.4% had suspected and 26% had a definitive diagnosis for acute cholecystitis. The sensitivity of TG13 for diagnosing acute cholecystitis was 53.4%.

When compared the definitive diagnosis on pathology vs. diagnosis based on TG13 guidelines, 13% patients with acute gangrenous/necrotizing cholecystitis and 36% patients with acute cholecystitis on final pathology were not diagnosed by TG13 criteria. The comparison of diagnosis based on TG13 criteria and final pathology report findings are demonstrated in **Table 2**. Based on TG13 classification for severity of illness, 48.3% of the patients had Grade-I, 46.7% had Grade-II and only 5% (43) had Grade-III disease. When compared the severity of illness and diagnosis based on TG13; 28% of the Grade-III patients and 45% of Grade-II were not diagnosed by the TGI3 diagnosis criteria as shown in **Table 3**. Most of the patients with Grade-III severity had acute necrotizing/gangrenous cholecystitis on final pathology (**Table 4**).

Overall, 91% of the patients underwent emergent cholecystectomy (lap: 85.5%, lap to open: 3.3%, and open: 2.1%) while 7.4% were managed conservatively and 1.8% received c-tube as shown in **Table 5**. Of 43 patients with Grade-III severity, 27 (63%) patients underwent emergent cholecystectomy (Lap: 51%, Lap to open: 5% and open: 7%) while 11 patients were managed with cholecystostomy tube. The outcomes of our study group are demonstrated in **Table 6**. Overall complications rate was 5.7%, and the mortality rate was 1.6%. There was no difference between the complications (3.7% vs. 4.7%, $p=0.81$), return to the OR (0.6% vs. 0.7%, $p=0.95$) and mortality (0.3% vs. 0%, $p=0.96$) between grade-I and grade-II who underwent early cholecystectomy.

Discussion:

Our study results suggest that the TG13 criteria lack sensitivity for diagnosing acute cholecystitis as it misses half of the patients. The lower sensitivity could be attributed to the lack of fever and leukocytosis early on in most of these patients. In our study, the most sensitive findings for acute cholecystitis were right upper quadrant tenderness and Murphy's sign. In addition, most patients with Grade I, Grade II and half of the patients with Grade III underwent early cholecystectomy.

Different diagnostic criteria have been proposed for the diagnosis of acute cholecystitis, however, none of them have been validated or implemented widespread. While the TG13 have improved the understanding of acute cholecystitis to some extent, its applicability in other population has been questioned (12, 13). In contrast to our study which demonstrated a sensitivity of only 53%, the TG13 guidelines claim to have an improved sensitivity of up to 91.8% (9). The lack of sensitivity of the TG13 in our patient population was largely attributed to the absence of clinical signs like fever and leukocytosis. The World Society of Emergency Surgery in their consensus guidelines stated that no single clinical sign or laboratory test finding can establish or exclude the diagnosis of acute cholecystitis (10). The most sensitive findings for our acute cholecystitis in our study were right upper quadrant tenderness and a positive Murphy's sign. A meta-analysis which evaluated the role of different clinical signs and tests in the diagnosis of acute cholecystitis demonstrated that Murphy's sign had the highest positive likelihood ratio among all (14).

The TG13 recommends early cholecystectomy for Grade I; antibiotics and supportive care followed by delayed/elective laparoscopic cholecystectomy for Grade II, and urgent biliary drainage followed by delayed/elective cholecystectomy for Grade III acute cholecystitis. Our

study results showed that more than 90% Grade I and Grade II while half of the patients with even Grade III disease were managed via early cholecystectomy. When compared the outcomes between Grade I and Grade II, there was no difference in the complications, conversion to open, hospital length of stay and mortality between the two groups. Similar results have been demonstrated by Lee et al. (12) from Taiwan. They demonstrated no significant difference in complications, and mortality based on the application of the Tokyo guidelines in the management of different grades of acute cholecystitis. Although no randomized trial has explored the optimal surgical management for the different severity grades of acute cholecystitis, however, a number of studies have shown the benefit of early cholecystectomy compared to delayed/elective cholecystectomy (15-17). The TG13 suggests early gallbladder drainage in Grade II patients, with local severe inflammation, however, a systemic review found no evidence to support drainage over early cholecystectomy even in critically ill patients. Their data showed cholecystectomy to be actually a better option in the elderly or critically ill (18). Similarly, another meta-analysis on the use of laparoscopic cholecystectomy for severe acute cholecystitis did not show any increase in local postoperative complications (19). In addition, delaying surgery increases the risks for further gall-stone related complications. De Mestral et al. (20) demonstrated in their study that in patients discharged home without cholecystectomy after acute cholecystitis, the probability of gallstone-related events is 14% 6-weeks and up to 29% at 1 year with biliary colic in 70 % while biliary tract obstruction occurs in 24 % and pancreatitis in 6 % . We think that the decision to decide between surgery and percutaneous drainage should be based on the general condition, comorbidities, and fitness for anesthesia, rather than the grading and acute disease process itself. If the general conditions of the patients allow to safely undergoing

surgery, acute cholecystitis should be managed via definitive early laparoscopy after stabilization of patients even in moderate to severe disease (21-23).

It is noteworthy to mention here that the TG13 have recently been revised and a new version named the Tokyo guidelines 2018 (TG18) has recently been published (24). They have revised their management algorithm for the different grades which is mostly in line with the results of our study. They have also included the Charlson comorbidity index and the American Society of Anesthesiologist physical status classification (ASA score) in deciding the management option. However, the diagnostic criteria and severity grading in the TG13 has been carried forward, without any modifications in the TG18.

Our study has certain limitations. It is based on retrospective, single-center data that may lack generalizability. In addition, the physical exam findings were extracted from the patient charts, and there may be lack of uniformity. Nonetheless, this is the largest study to date to evaluate the sensitivity of the TG13 in a U.S. population as well as comparing the management of different severity grades of cholecystitis based on the TG13 criteria.

Conclusion:

The TG13 diagnostic criterion lacks sensitivity and missed more than half of the patients with acute cholecystitis, as many patients lack clinical signs (fever and leukocytosis). The TG13 recommendations for conservative management and delayed cholecystectomy in grades II and III diseases are not warranted and our data suggests that the vast majority can be managed with early cholecystectomy. Revision of the Tokyo guidelines or constructing a better algorithm to improve clinical utility is necessary.

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Table 1. Demographic and Admission Characteristic Of The Study Population.

Characteristics	(n=857)
Age, y, Mean $\pm$ SD	42 $\pm$ 18
Females, % (n)	67.2% (576)
White, % (n)	75.1%(643)
Physical Exam, %	
RUQ pain	98.1% (841)
RUQ tenderness	91.5% (784)
Murphy's sign positive	28.8% (247)
RUQ Mass	0.4% (3)
Admission Vitals, % (n)	
Fever	4% (34)
Leukocytosis	51.8% (444)
Elevated CRP	38%(325)
Imaging suggestive of Acute Cholecystitis, % (n)	
Ultrasonography	41% (351)
CT	10.4% (89)
MRI	7.2% (62)
Severity	
Moderate, % (n)	
WBC > 18000	7.5% (64)
Palpable tender mass	0.1% (1)
Duration of complaints > 72 hours	34.1% (292)
Marked Local inflammation	19.4% (166)
Severe, % (n)	
Cardiovascular dysfunction	0.6% (5)
Neurological dysfunction	0.6% (5)
Respiratory dysfunction	0.8% (8)
Renal dysfunction	2.3% (20)
Hepatic dysfunction	2.0% (17)
Hematological dysfunction	0.8% (7)

RUQ= Right Upper Quadrant, CRP= C-Reactive Protein, WBC= White Blood Cell Count,

Table 2. Comparison of Diagnosis based on Tokyo Guidelines Criteria and Final Pathology.

Diagnosis based on TG 13, % (n)	Acute necrotizing/gangrenous cholecystitis (n=76)	Acute cholecystitis (n=225)	Acute on chronic cholecystitis (n=478)	<i>p</i>-value
No Diagnosis	13% (10)	36% (83)	57% (270)	<0.001
Suspected	22% (17)	25% (58)	28% (138)	0.01
Definitive	65% (49)	39% (84)	15% (70)	<0.001

Table 3. Comparison of Diagnosis and Severity based on Tokyo Guidelines Criteria.

Diagnosis based on TG 13, % (n)	Grade-I (n=414)	Grade-II (n=400)	Grade-III (n=43)	<i>p-value</i>
No Diagnosis	53% (217)	45% (180)	28% (12)	<0.01
Suspected	29% (121)	22% (89)	23% (10)	0.02
Definitive	18% (76)	33% (131)	49% (21)	<0.001

Table 4. Comparison of Severity based on Tokyo Guidelines Criteria and Final Pathology.

Severity based on TG 13	Acute nec./gangrenous cholecystitis (n=76)	Acute cholecystitis (n=225)	Acute on chronic cholecystitis (n=478)	<i>p</i> -value
Grade-I	28% (22)	45.5% (102)	53% (255)	<0.001
Grade-II	57% (44)	49.1% (110)	46% (220)	<0.001
Grade-III	15% (12)	5.4% (12)	1% (3)	<0.001

Table 5. Management based on severity of illness

Management	Grade-I (n=414)	Grade-II (n=400)	Grade-III (n=43)	<i>p-value</i>
Cholecystectomy, % (n)				
Laparoscopic	88.6% (367)	86% (344)	51.2% (22)	<0.001
Laparoscopic to Open	2.2% (9)	4.3% (17)	4.7% (2)	0.21
Open	0.7% (3)	3% (13)	7% (3)	<0.01
Conservative, % (n)	7.7% (32)	6.5% (25)	12% (5)	0.43
C-Tube, % (n)	0.7% (3)	0.3% (1)	26% (11)	<0.001

Table 6. Outcomes

	Grade-I (n=414)	Grade-II (n=400)	Grade-III (n=43)	<i>p-value</i>
Hospital LOS, median [IQR]	1 [1-2]	1 [1-2]	3 [2-4]	0.03
Complications, % (n)	3.7% (15)	4.7% (19)	35% (15)	<0.001
Return to OR, % (n)	0.6% (3)	0.7% (3)	5% (2)	0.03
Mortality, % (n)	0% (0)	2% (8)	14% (6)	<0.001

LOS=Length of Stay, IQR=Interquartile Range OR=Operating Room

Supplemental Table 1. TG13 diagnostic criteria for acute cholecystitis
<p>A. Local signs of inflammation etc.</p> <p>(1) Murphy's sign, (2) RUQ mass/pain/tenderness</p> <p>B. Systemic signs of inflammation etc.</p> <p>1) Fever, (2) elevated CRP, (3) elevated WBC count</p> <p>C. Imaging findings</p> <p>Imaging findings characteristic of acute cholecystitis</p> <p>Suspected diagnosis: One item in A + one item in B</p> <p>Definite diagnosis: One item in A + one item in B + C</p>

Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded.

RUQ= Right Upper Quadrant, CRP= C-Reactive Protein, WBC= White Blood Cell.

Supplemental Table 2. TG13 severity grading for acute cholecystitis

Grade III (severe) acute cholecystitis

Associated with dysfunction of any one of the following organs/systems:

1. Cardiovascular dysfunction	Hypotension requiring treatment with dopamine ≥ 5 $\mu\text{g/kg}$ per min, or any dose of norepinephrine
2. Neurological dysfunction	Decreased level of consciousness
3. Respiratory dysfunction	PaO ₂ /FiO ₂ ratio <300
4. Renal dysfunction	Oliguria, creatinine >2.0 mg/dl
5. Hepatic dysfunction	PT-INR >1.5
6. Hematological dysfunction	Platelet count <100,000/mm ³

Grade II (moderate) acute cholecystitis

Associated with any one of the following conditions:

1. Elevated white blood cell count (>18,000/mm³)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complaints >72 h
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

Grade I (mild) acute cholecystitis

Does not meet the criteria of “Grade III” or “Grade II” acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure