



# THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### **New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo guidelines**

**Citation for published version:**

Yokoe, M, Takada, T, Strasberg, SM, Solomkin, JS, Mayumi, T, Gomi, H, Pitt, HA, Gouma, DJ, Garden, OJ, Buechler, MW, Kiriyaama, S, Kimura, Y, Tsuyuguchi, T, Itoi, T, Yoshida, M, Miura, F, Yamashita, Y, Okamoto, K, Gabata, T, Hata, J, Higuchi, R, Windsor, JA, Bornman, PC, Fan, S-T, Singh, H, de Santibanes, E, Kusachi, S, Murata, A, Chen, X-P, Jagannath, P, Lee, S, Padbury, R & Chen, M-F 2012, 'New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo guidelines' *Journal of Hepato-Biliary-Pancreatic Sciences*, vol 19, no. 5, pp. 578-585. DOI: 10.1007/s00534-012-0548-0

**Digital Object Identifier (DOI):**

[10.1007/s00534-012-0548-0](https://doi.org/10.1007/s00534-012-0548-0)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher's PDF, also known as Version of record

**Published In:**

*Journal of Hepato-Biliary-Pancreatic Sciences*

**Publisher Rights Statement:**

This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



## New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo guidelines

Masamichi Yokoe · Tadahiro Takada · Steven M. Strasberg · Joseph S. Solomkin · Toshihiko Mayumi · Harumi Gomi · Henry A. Pitt · Dirk J. Gouma · O. James Garden · Markus W. Büchler · Seiki Kiriyama · Yasutoshi Kimura · Toshio Tsuyuguchi · Takao Itoi · Masahiro Yoshida · Fumihiko Miura · Yuichi Yamashita · Kohji Okamoto · Toshifumi Gabata · Jiro Hata · Ryota Higuchi · John A. Windsor · Philippus C. Bornman · Sheung-Tat Fan · Harijt Singh · Eduardo de Santibanes · Shinya Kusachi · Atsuhiko Murata · Xiao-Ping Chen · Palepu Jagannath · SungGyu Lee · Robert Padbury · Miin-Fu Chen

Published online: 8 August 2012

© The Author(s) 2012. This article is published with open access at Springerlink.com

### Abstract

**Background** The Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) were published in 2007 as the world's first guidelines for acute cholangitis and cholecystitis. The diagnostic criteria and severity assessment of acute cholecystitis have since been widely used all over the world. A validation study of TG07 has shown that the

diagnostic criteria for acute cholecystitis are highly reliable but that the definition of definite diagnosis is ambiguous. In addition, considerable new evidence referring to acute cholecystitis as well as evaluations of TG07 have been published. Consequently, we organized the Tokyo Guidelines Revision Committee to evaluate TG07, recognize new evidence, and conduct a multi-center analysis to revise the guidelines (TG13).

M. Yokoe (✉)

General Internal Medicine, Nagoya Daini Red Cross Hospital, 2-9 Myoken-cho, Showa-ku, Nagoya, Aichi 466-8650, Japan  
e-mail: masa45a@gmail.com; yokoe@nagoya2.jrc.or.jp

T. Takada · F. Miura

Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

S. M. Strasberg

Section of Hepatobiliary and Pancreatic Surgery, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA

J. S. Solomkin

Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

T. Mayumi

Department of Emergency and Critical Care Medicine, Ichinomiya Municipal Hospital, Ichinomiya, Japan

H. Gomi

Center for Clinical Infectious Diseases, Jichi Medical University, Tochigi, Japan

H. A. Pitt

Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

D. J. Gouma

Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands

O. J. Garden

Clinical Surgery, The University of Edinburgh, Edinburgh, UK

M. W. Büchler

Department of Surgery, University of Heidelberg, Heidelberg, Germany

S. Kiriyama

Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

Y. Kimura

Department of Surgical Oncology and Gastroenterological Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan

T. Tsuyuguchi

Department of Medicine and Clinical Oncology, Graduate School of Medicine Chiba University, Chiba, Japan

T. Itoi

Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan

M. Yoshida

Clinical Research Center Kaken Hospital, International University of Health and Welfare, Ichikawa, Japan

Y. Yamashita

Department of Gastroenterological Surgery, Fukuoka University School of Medicine, Fukuoka, Japan

**Methods and materials** We retrospectively analyzed 451 patients with acute cholecystitis from multiple tertiary care centers in Japan. All 451 patients were first evaluated using the criteria in TG07. The “gold standard” for acute cholecystitis in this study was a diagnosis by pathology. The validity of TG07 diagnostic criteria was investigated by comparing clinical with pathological diagnosis.

**Results** Of 451 patients evaluated, a total of 227 patients were given a diagnosis of acute cholecystitis by pathological examination (prevalence 50.3 %). TG07 criteria provided a definite diagnosis of acute cholecystitis in 224 patients. The sensitivity of TG07 diagnostic criteria for acute cholecystitis was 92.1 %, and the specificity was 93.3 %. Based on the preliminary results, new diagnostic criteria for acute cholecystitis were proposed. Using the new criteria, the sensitivity of definite diagnosis was 91.2 %, and the specificity was 96.9 %. The accuracy rate was improved from 92.7 to 94.0 %. In regard to severity grading among 227 patients, 111 patients were classified as Mild (Grade I), 104 as Moderate (Grade II), and 12 as Severe (Grade III).

**Conclusion** The proposed new diagnostic criteria achieved better performance than the diagnostic criteria in TG07. Therefore, the proposed criteria have been adopted

as new diagnostic criteria for acute cholecystitis and are referred to as the 2013 Tokyo Guidelines (TG13). Regarding severity assessment, no new evidence was found to suggest that the criteria in TG07 needed major adjustment. As a result, TG07 severity assessment criteria have been adopted in TG13 with minor changes.

**Keywords** Acute cholecystitis · Murphy’s sign · Diagnostic criteria · Severity assessment · Guidelines

## Introduction

Acute cholecystitis is a very common complication of cholelithiasis, and as such is frequently encountered in surgical practice [1–4]. There were no diagnostic criteria or severity assessment criteria for this common disease until 2007. In 2006, we conducted a systematic review and sponsored an international consensus conference in Tokyo, Japan. This meeting resulted in the development of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07). These guidelines were the world’s first guidelines to include diagnostic criteria and severity assessment of acute cholecystitis [5] (Tables 1, 2).

K. Okamoto

Department of Surgery, Kitakyushu Municipal Yahata Hospital, Kitakyushu, Japan

T. Gabata

Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

J. Hata

Department of Endoscopy and Ultrasound, Kawasaki Medical School, Okayama, Japan

R. Higuchi

Department of Surgery, Institute of Gastroenterology, Tokyo Women’s Medical University, Tokyo, Japan

J. A. Windsor

Department of Surgery, The University of Auckland, Auckland, New Zealand

P. C. Bornman

Division of General Surgery, Health Sciences, University of Cape Town, Cape Town, South Africa

S.-T. Fan

Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

H. Singh

Department of Hepato-Pancreato-Biliary Surgery, Hospital Selayang, Kuala Lumpur, Malaysia

E. de Santibanes

Department of Surgery, Hospital Italiano, University of Buenos Aires, Buenos Aires, Argentina

S. Kusachi

Department of Surgery, Toho University Medical Center Ohashi Hospital, Tokyo, Japan

A. Murata

Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

X.-P. Chen

Hepatic Surgery Centre, Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

P. Jagannath

Department of Surgical Oncology, Lilavati Hospital and Research Centre, Mumbai, India

S. Lee

HepatoBiliary Surgery and Liver Transplantation, Asan Medical Center, Ulsan University, Ulsan, Korea

R. Padbury

Division of Surgical and Specialty Services, Flinders Medical Centre, Adelaide, Australia

M.-F. Chen

Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan

Diagnostic and severity assessment criteria need to be updated periodically based on new information, criticisms, and suggestions for improvement. The diagnostic criteria in TG07 have been set to achieve high sensitivity in order to provide medical care suitable for a large number of patients. The sensitivity of TG07 diagnostic criteria has been reported to be 84.9 % [6] and TG07 diagnostic criteria are recognized as those to be recommended in current care for acute cholecystitis [1]. However, since its publication, we and others have found potential shortcomings in TG07 in clinical practice [6].

To update the Tokyo Guidelines for the management of acute cholangitis and cholecystitis, we organized the Tokyo Guidelines Revision Committee to evaluate TG07, recognize new evidence, and conduct a multi-center analysis to revise the guidelines (TG13). In the present study, we

investigated the validity of the TG07 diagnostic criteria and severity assessment criteria by multi-center analysis. The limitations of TG07 were also investigated to develop tentative new diagnostic criteria and severity assessment criteria.

## Methods and materials

We retrospectively analyzed 451 patients from six tertiary care centers in Japan between November 2005 and November 2011: Sapporo Medical University, Tokyo Medical University, Tokyo Women's Medical University, Nagoya Daini Red Cross Hospital, Ogaki Municipal Hospital, and Fukuoka University School of Medicine. Consecutive patients who were operated on for cholecystectomy were included during the study period. The "gold standard" for acute cholecystitis in this study was pathological diagnosis using standard gross and histological criteria. We therefore confirmed the final diagnosis by pathological examination of excised gallbladders after operation. If the pathological findings were chronic cholecystitis or other, those cases were considered to be "negative."

All 451 patients were evaluated using TG07 criteria. The validity of the diagnostic criteria of TG07 was investigated by analyzing their sensitivity and specificity. The severity grading system of TG07 was evaluated by determining the distribution of severity among these patients. Through these data, the Tokyo Guidelines Revision Committee members discussed the quality of diagnostic criteria and severity assessment of acute cholecystitis in TG07 to reassess TG and propose new guidelines.

**Table 1** TG07 diagnostic criteria for acute cholecystitis

A. Local signs of inflammation, etc.:	
(1) Murphy's sign, (2) RUQ mass/pain/tenderness	
B. Systemic signs of inflammation, etc.:	
(1) Fever, (2) elevated CRP, (3) abnormal WBC count	
C. Imaging findings: imaging findings characteristic of acute cholecystitis	
Definite diagnosis	
(1) One item in A + one item in B are positive	
(2) C confirms the diagnosis when acute cholecystitis is suspected clinically	
Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded	
WBC white blood cell, RUQ right upper quadrant, CRP C-reactive protein	

**Table 2** TG07 severity assessment criteria for acute cholecystitis

"Severe" (Grade III) acute cholecystitis is accompanied by dysfunctions in any one of the following organs/systems:	
1. Cardiovascular dysfunction	Hypotension requiring treatment with dopamine $\geq 5$ $\mu\text{g}/\text{kg}$ per min, or any dose of dobutamine
2. Neurological dysfunction	Decreased level of consciousness
3. Respiratory dysfunction	$\text{PaO}_2/\text{FiO}_2$ ratio $< 300$
4. Renal dysfunction	Oliguria, creatinine $> 2.0$ mg/dl
5. Hepatic dysfunction	PT-INR $> 1.5$
6. Hematological dysfunction	Platelet count $< 100,000/\text{mm}^3$
"Moderate" (Grade II) acute cholecystitis is accompanied by any one of the following conditions:	
1. Elevated WBC count ( $> 18,000/\text{mm}^3$ )	
2. Palpable tender mass in the right upper abdominal quadrant	
3. Duration of complaints $> 72$ h <sup>a</sup>	
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)	
"Mild" (Grade I) acute cholecystitis does not meet the criteria of "Severe (Grade III)" or "Moderate (Grade II)" acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and only mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.	

<sup>a</sup> Laparoscopic surgery in acute cholecystitis should be performed within 96 h after the onset

WBC white blood cell

The literature was selected as follows: using “Tokyo Guidelines” AND “acute cholecystitis[MeSH]”, only 3 items were selected in PubMed since the publication of TG07 (1 April 2007 – 31 March 2012). These articles were screened with “human” and “English”. However, using “acute cholecystitis[MeSH]” AND “prognosis[MeSH]”, a total of 119 items were selected in PubMed over the same length of time. From these articles, the prognostic factors of acute cholecystitis to be utilized for the revision of TG07 were screened by the Tokyo Guidelines Revision Committee members. In addition, the distribution of severity grading was aggregated from the literature which reported the data based on the severity assessment of TG07.

The Tokyo Guidelines Revision Committee discussed the modification of TG07 diagnostic criteria and severity assessment of acute cholecystitis by analyzing the results of the present study and integrating the literature evidence.

**Results**

Assessment of TG07 diagnostic criteria and severity assessment criteria for acute cholecystitis

The 451 patients who were operated on for cholecystectomy comprised 255 male patients and 196 female patients with a mean age of  $63.9 \pm 14.0$  years. 227 of the 451 patients enrolled were given a final pathological diagnosis of acute cholecystitis. The prevalence of acute cholecystitis in the cohort was 50.3 %. Based on the diagnostic criteria in TG07, a definite diagnosis of acute cholecystitis was made in 224 patients. Diagnostic criteria were not met in the remaining 227 patients.

We constructed  $2 \times 2$  contingency tables between pathologically proven acute cholecystitis and acute cholecystitis diagnosed by TG07 criteria. There were 209 true-positive cases, 15 false-positive cases, 18 false-negative cases, and 209 true-negative cases (Table 3). The diagnostic sensitivity and specificity of TG07 were 92.1 % (209/227) and 93.3 % (209/224), respectively; the false-negative and false-positive rates were 7.9 % (18/227) and 6.7 % (15/224), respectively. The positive and negative predictive values were 93.3 and 92.1 %, respectively, and

the positive and negative likelihood ratios were 13.75 and 0.08, respectively. The diagnostic accuracy was 92.7 %.

In terms of severity assessment, a total of 227 patients who were given a final pathological diagnosis of acute cholecystitis were retrospectively examined with TG07 severity assessment criteria for acute cholecystitis. Of them, 111 patients were classified as Grade I (48.9 %), 104 patients as Grade II (45.8 %), and 12 patients as Grade III (5.3 %), respectively.

Revision of TG07 diagnostic criteria and severity assessment criteria for acute cholecystitis

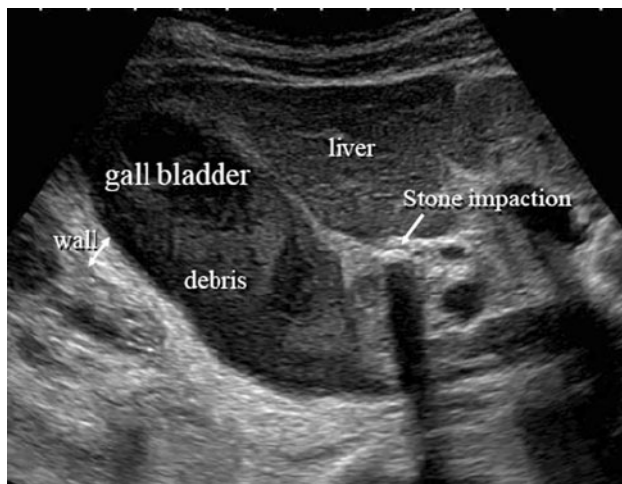
Several problems regarding the TG07 diagnostic criteria and severity assessment system were found during the analysis. The most important problem in TG07 was that the criteria for definite diagnosis were ambiguous and difficult to use. In TG07, there were two categories determining the definite diagnosis of acute cholecystitis (Table 1). Definite diagnosis 1: To obtain a definite diagnosis one item in A and one item in B had to be positive. Definite diagnosis 2: Imaging findings (Criterion C) confirmed the diagnosis when acute cholecystitis was suspected clinically. The Tokyo Guidelines Revision Committee concluded that the term “definite diagnosis” could not be supported in current practice without positive diagnostic imaging studies.

For acute cholecystitis, abdominal ultrasonography, computed tomography (CT), and hepatobiliary scintigraphy (HIDA scan) are the imaging studies most commonly used in diagnosis. In particular, ultrasonography is a test that should be performed first of all in every case for which acute cholecystectomy is suspected. Sonography should be the screening test of choice in acute cholecystitis because it is cost-effective, prospectively highly accurate and fast [7]. The sensitivity of ultrasonography in detecting acute inflammation of the gallbladder has been reported to be 90–95 % [8]. Therefore, emergency room clinicians and surgeons currently prefer ultrasonography for the initial evaluation of suspected acute cholecystitis, because it is a simple, safe, fast and cost-effective tool [9–11]. Acute calculous cholecystitis is diagnosed radiologically by the concomitant presence of thickening of the gallbladder wall (5 mm or greater), pericholecystic fluid, or direct tenderness when the probe is pushed against the gallbladder (ultrasonographic Murphy’s sign) [1] (Fig. 1). CT findings of acute cholecystitis were reported as gallbladder distention (41 %), gallbladder wall thickening (59 %), pericholecystic fat density (52 %), pericholecystic fluid collection (31 %), subserosal edema (31 %) and high-attenuation gallbladder bile (24 %) [12].

As a result, the importance of diagnostic imaging was emphasized for the diagnosis of acute cholecystitis by the Committee, and new criteria were proposed (Table 4). In

**Table 3**  $2 \times 2$  contingency tables of multi-center analysis for diagnostic criteria of TG07

		Acute cholecystitis by pathology		Total
		Yes	No	
TG07 definite diagnosis	Yes	209	15	224
	No	18	209	227
Total		227	224	451



**Fig. 1** Typical US image of acute cholecystitis, demonstrating gallbladder swelling, wall thickening with sonolucent layers, massive debris, and the stone impaction in the cystic duct

**Table 4** TG13 diagnostic criteria for acute cholecystitis

A. Local signs of inflammation, etc.:
(1) Murphy's sign, (2) RUQ mass/pain/tenderness
B. Systemic signs of inflammation, etc.:
(1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings:
Imaging findings characteristic of acute cholecystitis
Suspected diagnosis: One item in A + one item in B
Definite diagnosis: One item in A + one item in B + C
Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded
RUQ right upper quadrant, CRP C-reactive protein, WBC white blood cell

the proposed criteria a “suspected” diagnosis is achieved when one item from section A and one item from section B are present. A “definite” diagnosis is achieved when imaging findings characteristic of acute cholecystitis (Item C) are also present.

Regarding severity assessment criteria, a thorough literature search was performed and variables reported in the literature as predictive of poor prognosis in acute cholecystitis were summarized [13–25] (Table 5). The Tokyo Guidelines Revision Committee discussed whether these newly reported severity or prognostic factors such as diabetes mellitus, old age, and male sex should be adopted for revision. However, the Committee concluded that these factors were not supported by sufficient levels of evidence and so the factors were not adopted as assessment criteria. However, minor changes were made to the description of Grade III severity, i.e. dopamine and nor-epinephrine were both considered as evidence of

cardiovascular dysfunction consistent with the SOFA score system [26] (Table 6).

#### Assessment of TG13 diagnostic criteria and severity assessment for acute cholecystitis

Of 227 patients with a definite diagnosis of acute cholecystitis based on the proposed new diagnostic criteria, a final diagnosis of acute cholecystitis by pathology was made in 207 patients. We constructed  $2 \times 2$  contingency tables between patients with acute cholecystitis by pathology and the cases with definite diagnosis using the proposed new diagnostic criteria, with 207 true-positive cases, 7 false-positive cases, 20 false-negative cases, and 217 true-negative cases (Table 7).

The diagnostic sensitivity and specificity of definite diagnosis were 91.2 % (207/227) and 96.9 % (217/224), respectively. The false-negative and false-positive rates were 8.8 % (20/227) and 3.1 % (7/224), respectively. The positive and negative predictive values were 96.7 and 91.6 %, respectively. The positive and negative likelihood ratios were 29.18 and 0.09, respectively. The diagnostic accuracy was 94.0 %. On the other hand, of the 219 patients with a suspected or definite diagnosis of acute cholecystitis based on the proposed new diagnostic criteria, a final diagnosis of acute cholecystitis was made in 208 patients. We constructed  $2 \times 2$  contingency tables between patients with acute cholecystitis by pathology and the cases with suspected or definite diagnosis using the proposed new diagnostic criteria, with 208 true-positive cases, 11 false-positive cases, 19 false-negative cases, and 213 true-negative cases (Table 8). The diagnostic sensitivity and specificity of suspected or definite diagnosis were 91.6 % (208/227) and 95.1 % (213/224), respectively. The false-negative and false-positive rates were 8.4 % (19/227) and 4.9 % (11/224), respectively. The positive and negative predictive values were 95.0 and 91.8 %, respectively. The positive and negative likelihood ratios were 18.66 and 0.09, respectively. The diagnostic accuracy was 93.3 %.

From those results the diagnostic validities were compared between the definite diagnosis of TG07 and that of the proposed new diagnostic criteria (Table 9).

This comparison of the two diagnostic criteria in terms of diagnostic precision shows that the proposed new diagnostic criteria achieved better performance than TG07. These diagnostic criteria have therefore been chosen as the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines (TG13).

On the other hand, the TG07 severity assessment criteria for acute cholecystitis did not have significant problems that required major revision of the definitions or structures. The TG07 severity assessment criteria have been adopted

**Table 5** Prognostic factors in acute cholecystitis

Prognostic factor	Positive value	References
Leukocytosis	$\geq 15,000/\text{mm}^3$	[13–19]
	$>14,900/\text{mm}^3$	[20]
	$>13,000/\text{mm}^3$	[21]
	$>13,000/\text{mm}^3$	[22]
	$15,885/\text{mm}^3$ vs. $9,948/\text{mm}^3$	[23]
ALP		[17, 24, 25]
Age	$>26$ years old	[19]
	$>45$ years old	[22]
	$>60$ years old	[23]
Diabetes mellitus		[17, 20, 21]
Male		[20, 21]
Heart rate	$>90$ bpm	[22]
Gallbladder wall thickness $>4.5$ mm		[22]
Pericholecystic fluids		[17]
CBD dilatation		[25]
Admission delay		[18]

ALP alkaline phosphatase, CBD common bile duct

**Table 6** TG13 severity assessment criteria for acute cholecystitis

“Grade III” (severe) acute cholecystitis is associated with dysfunction of any one of the following organs/systems

1. Cardiovascular dysfunction Hypotension requiring treatment with dopamine  $\geq 5 \mu\text{g}/\text{kg}$  per min, or any dose of norepinephrine
2. Neurological dysfunction Decreased level of consciousness
3. Respiratory dysfunction  $\text{PaO}_2/\text{FiO}_2$  ratio  $<300$
4. Renal dysfunction Oliguria, creatinine  $>2.0$  mg/dl
5. Hepatic dysfunction PT-INR  $>1.5$
6. Hematological dysfunction Platelet count  $<100,000/\text{mm}^3$

“Grade II” (moderate) acute cholecystitis is associated with any one of the following conditions

1. Elevated WBC count ( $>18,000/\text{mm}^3$ )
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

WBC white blood cell

in the updated Tokyo Guidelines (TG13) with minor changes in descriptions as above (Table 6).

**Discussion**

The most important role of diagnostic criteria and severity assessment is to allow early diagnosis and to provide the most appropriate treatment for the disease depending on its severity. TG07 of acute cholecystitis aimed at this by systematic literature search and integration of expert opinions through a consensus conference held in Tokyo in

2006 [27]. The guidelines should reflect the current clinical practice but they need periodic assessment and revision. However, in the case of TG07 this was particularly so because of shortcomings that became evident through application in clinical practice and as a result of new information in the literature.

For the diagnosis of acute cholecystitis, clinicians all over the world have provided treatment for acute cholecystitis based on Murphy’s sign. However, Murphy’s sign has been reported in previous studies to have a sensitivity of 50–60 % and a high specificity of 79 % [28] or 96 % [2] for the diagnosis of acute cholecystitis. The sensitivity of

**Table 7** 2 × 2 contingency tables of multi-center analysis for definite diagnosis of TG13 criteria

		Acute cholecystitis by pathology		Total
		Yes	No	
TG13 definite diagnosis	Yes	207	7	214
	No	20	217	237
Total		227	224	451

**Table 8** 2 × 2 contingency tables of multi-center analysis for a suspected or definite diagnosis of TG13 criteria

		Acute cholecystitis by pathology		Total
		Yes	No	
TG13 suspected or definite diagnosis	Yes	208	11	219
	No	19	213	232
Total		227	224	451

**Table 9** Comparison of TG07 and TG13 criteria for acute cholecystitis ( $n = 451$ , prevalence 50.3 %)

	TG07 (definite)	TG13 (definite)
Sensitivity (%)	92.1	91.2
Specificity (%)	93.3	96.9
False-negative (%)	7.9	8.8
False-positive (%)	6.7	3.1
Positive predictive value (%)	93.3	96.7
Negative predictive value (%)	92.1	91.6
Positive likelihood ratio	13.75	29.18
Negative likelihood ratio	0.08	0.09
Accuracy rate (%)	92.7	94.0

Murphy's sign was once reported to be as low as 20.5 %, while the specificity was 87.5 % [6]. In the same study, the sensitivity and specificity of TG07 were as high as 84.9 and 50.0 %, respectively [6]. In this study, a sign test, which detects the difference in accuracy, was also performed to analyze statistically the diagnostic criteria of TG07 for acute cholecystitis and the rate of diagnostic accuracy of Murphy's sign. The diagnostic accuracy was significantly higher when the TG07 were used than when Murphy's sign was used [6]. TG07 can be used with more confidence among clinicians. However, the shortcomings of TG07 were recognized by the Tokyo Guidelines Revision Committee in that the definite diagnosis of TG07 had two categories. These two categories were ambiguous and the schema was difficult to use for many clinicians.

**Table 10** Distribution of severity grading of acute cholecystitis with TG07 and TG13

Severity assessment	Asai et al. [30] (TG07)	Lee et al. [14] (TG07)	Present study (TG13)
Severe (Grade III)	2 (1.2 %)	14 (6.0 %)	12 (5.3 %)
Moderate (Grade II)	97 (59.5 %)	60 (25.5 %)	104 (45.8 %)
Mild (Grade I)	64 (39.3 %)	161 (68.5 %)	111 (48.9 %)
Total	163	235	227

In addition to clinical and laboratory assessments, radiological and nuclear imaging techniques are widely used to identify individuals with complications of gallbladder disease [21]. Ultrasonographic diagnosis of acute cholecystitis was made when thickening and/or edema of gallbladder wall, distension of the gallbladder by gallstones, and pericholecystic fluid collection were seen [29].

Based on the above understanding, tentative new diagnostic criteria of acute cholecystitis were developed and their validity was analyzed among the patients from multiple institutions in Japan. Better diagnostic accuracy was obtained with the new criteria, with high sensitivity and high specificity on definite diagnosis. The new criteria validated by a retrospective analysis have been adopted as the revised diagnostic criteria of TG13 for acute cholecystitis.

The severity assessment criteria were reconsidered by the Tokyo Guidelines Revision Committee with new information, evidence, and evaluations of TG07. Lee et al. [14] revealed that there was a significantly shorter mean length of hospital stay in the patient group for whom the Tokyo guidelines (TG07) were utilized compared with those without compliance with TG07. Asai et al. [30] suggested that more precise severity grades may need to be established, including age and C-reactive protein as additional parameters.

The distribution of severity grading varies as follows: 39.3–68.5 % of the cases were classified as Grade I, 25.5–59.5 % as Grade II, and 1.2–6 % as Grade III [14, 30]. The present study shows that 48.9 % of the cases were classified as Grade I, 45.8 % as Grade II, and 5.3 % as Grade III. The proportions in the present study were not different from the proportions in other TG07 studies (Table 10).

In summary, TG13 presents new diagnostic and severity assessment criteria based on a large patient base and a reasonable “gold standard”. These criteria allow early diagnosis and severity assessment of the disease and should be clinically very useful in the management of acute cholecystitis.



## Conclusion

The updated Tokyo Guidelines (TG13) introduce a new standard for the diagnosis and severity assessment of acute cholecystitis. In the TG13 diagnostic criteria, a “suspected” diagnosis is achieved when one item from section A and one item from section B are present. A “definite” diagnosis is achieved when imaging findings characteristic of acute cholecystitis (Item C) are also present. Compared with TG07, the validity of the diagnostic criteria has been improved and the severity assessment criteria of TG07 have been adopted with minor changes from TG07.

**Open Access** This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

## References

1. Strasberg SM. Acute calculous cholecystitis. *N Engl J Med* 2008; 358: 2804–11.
2. Eskelinen M, Ikonen J, Lipponen P. Diagnostic approaches in acute cholecystitis; a prospective study of 1333 patients with acute abdominal pain. *Theor Surg*. 1993;8:15–20.
3. Halasz NA. Counterfeit cholecystitis, a common diagnostic dilemma. *Am J Surg*. 1975;130:189–93.
4. Johnson H Jr, Cooper B. The value of HIDA scans in the initial evaluation of patients for cholecystitis. *J Natl Med Assoc*. 1995;87:27–32.
5. Hirota M, Takada T, Kawarada Y, Nimura Y, Miura F, Hirata K, Mayumi T, Yoshida M, Strasberg S, Pitt H, Gadacz TR, de Santibanes E, Gouma DJ, Solomkin JS, Belghiti J, Neuhaus H, Büchler MW, Fan ST, Ker CG, Padbury RT, Liao KH, Hilvano SC, Belli G, Windsor JA, Dervenis C. Diagnostic criteria and severity assessment of acute cholecystitis: TokyoGuidelines. *J Hepatobiliary Pancreat Surg*. 2007;14(1):78–82 (Epub 2007 Jan 30).
6. Yokoe M, Takada T, Mayumi T, Yoshida M, Hasegawa H, Norimizu S, Hayashi K, Umemura S, Orito E. Accuracy of the Tokyo Guidelines for the diagnosis of acute cholangitis and cholecystitis taking into consideration the clinical practice pattern in Japan. *J Hepatobiliary Pancreat Sci*. 2011;18:250–7.
7. Ralls PW, Colletti PM, Lapin SA, Chandrasoma P, Boswell WD Jr, Ngo C, Radin DR, Halls JM. Real-time sonography in suspected acute cholecystitis. Prospective evaluation of primary and secondary signs. *Radiology*. 1985; 155(3):767–71.
8. Hunt DR, Chu FC. Gangrenous cholecystitis in the laparoscopic era. *Aust NZ J Surg*. 2000;70:428–30.
9. Alobaidi M, Gupta R, Jafri SZ, Fink-Bennet DM. Current trends in imaging evaluation of acute cholecystitis. *Emerg Radiol*. 2004;10:256–8.
10. Rosen CI, Brown DF, Chang Y, Moore C, Averill NJ, Arkoff LJ, McCabe CJ, Wolfe RE. Ultrasonography by emergency physicians in patients with suspected cholecystitis. *Am J Emerg Med* 2001; 19: 32–36.
11. Kendall JL, Shimp RJ. Performance and interpretation of focused right upper quadrant ultrasound by emergency. *J Emerg Med*. 2001;21:7–13.
12. Fidler J, Paulson EK, Layfield L. CT evaluation of acute cholecystitis: findings and usefulness in diagnosis. *AJR*. 1996;166:1085–8.
13. Gruber PJ, Silverman RA, Gottesfeld S, Flaster E. Presence of fever and leukocytosis in acute cholecystitis. *Ann Emerg Med*. 1996;28:273–7.
14. Lee SW, Yang SS, Chang CS, Yeh HJ. Impact of the Tokyo guidelines on the management of patients with acute calculous cholecystitis. *J Gastroenterol Hepatol*. 2009; 24(12):1857–61 (Epub).
15. Lee SW, Chang CS, Lee TY, Tung CF, Peng YC. The role of the Tokyo guidelines in the diagnosis of acute calculous cholecystitis. *J Hepatobiliary Pancreat Sci*. 2010; 17(6): 879–84 (Epub 2010 Apr 24).
16. Juvonen T, Kiviniemi H, Niemela O, Kairaluoma MI. Diagnostic accuracy of ultrasonography and C reactive protein concentration in acute cholecystitis: a prospective clinical study. *Eur J Surg*. 1992;158:365–9.
17. Nguyen L, Fagan SP, Lee TC, Aoki N, Itani KM, Berger DH, Awad SS. Use of a predictive equation for diagnosis of acute gangrenous cholecystitis. *Am J Surg*. 2004;188(5):463–6.
18. Contini S, Corradi D, Busi N, Alessandri L, Pezzarossa A, Scarpignato C. Can gangrenous cholecystitis be prevented?: a plea against a “wait and see” attitude. *J Clin Gastroenterol*. 2004;38(8):710–6.
19. Girgin S, Gedik E, Taçyıldız IH, Akgün Y, Baç B, Uysal E. Factors affecting morbidity and mortality in gangrenous cholecystitis. *Acta Chir Belg*. 2006; 106(5):545–9.
20. Fagan SP, Awad SS, Rahwan K, Hira K, Aoki N, Itani KM, Berger DH. Prognostic factors for the development of gangrenous cholecystitis. *Am J Surg*. 2003;186(5):481–5.
21. Aydin C, Altaca G, Berber I, Tekin K, Kara M, Titiz I. Prognostic parameters for the prediction of acute gangrenous cholecystitis. *J Hepatobiliary Pancreat Surg*. 2006;13(2):155–9.
22. Yacoub WN, Petrosyan M, Sehgal I, Ma Y, Chandrasoma P, Mason RJ. Prediction of patients with acute cholecystitis requiring emergent cholecystectomy: a simple score. *Gastroenterol Res Pract*. 2010; 2010:901739 (Epub 2010 Jun 8).
23. Wang AJ, Wang TE, Lin CC, Lin SC, Shih SC. Clinical predictors of severe gallbladder complications in acute acalculous cholecystitis. *World J Gastroenterol*. 2003;9(12):2821–3.
24. McChesney JA, Northup PG, Bickston SJ. Acute acalculous cholecystitis associated with systemic sepsis and visceral arterial hypoperfusion: a case series and review of pathophysiology. *Dig Dis Sci*. 2003;48(10):1960–7.
25. Young AL, Cockbain AJ, White AW, Hood A, Menon KV, Toogood GJ. Index admission laparoscopic cholecystectomy for patients with acute biliary symptoms: results from a specialist centre. *HPB (Oxford)*. 2010;12(4):270–6.
26. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–10.
27. Mayumi T, Takada T, Kawarada Y, Nimura Y, Yoshida M, Sekimoto M, et al. Results of the Tokyo Consensus Meeting Tokyo Guidelines. *J Hepatobiliary Pancreat Surg*. 2007;14:114–21.
28. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? *JAMA*. 2003;289:80–6.
29. Weiss CA III, Schwartz RW. Current diagnosis and treatment of cholecystitis. *Curr Surg*. 2002;59:51–4.
30. Asai K, Watanabe M, Kusachi S, Tanaka H, Matsukiyo H, Osawa A, Saito T, Kodama H, Enomoto T, Nakamura Y, Okamoto Y, Saida Y, Nagao J. Bacteriological analysis of bile in acute cholecystitis according to the Tokyo guidelines. *J Hepatobiliary Pancreat Sci*. 2011 (Epub ahead of print).