表1 急性胆管炎の重症度の定義

重症；
敗血症による全身症状をきたし，ただちに緊急胆道ドレナージを施行しな
ければ生命に危機を及ぼす胆管炎
中等症；
全身の臓器不全には陥っていないが，その危険性があり，すみやかに胆道
ドレナージをする必要のある胆管炎
軽症；
胆管炎を保存的に治療でき，待機的に成因検索とその治療（内視鏡的処置，
手術）を行える胆管炎

文献[1]より引用

表2 急性胆管炎の重症度判定基準

重症急性胆管炎；急性胆管炎の内，以下のいずれかを伴う場合
  ① ショック
  ② 菌血症
  ③ 意識障害
  ④ 急性腎不全
中等症急性胆管炎；急性胆管炎の内，以下のいずれかを伴う場合
  ① 黄疸（Bil > 2.0mg/dL）
  ② 低アルブミン血症（Alb<3.0mg/dL）
  ③ 腎機能障害（Cr > 1.5mg/dL，BUN > 20mg/dL）
  ④ 血小板数減少（<12万/mm^3）
  ⑤ 39℃以上の高熱
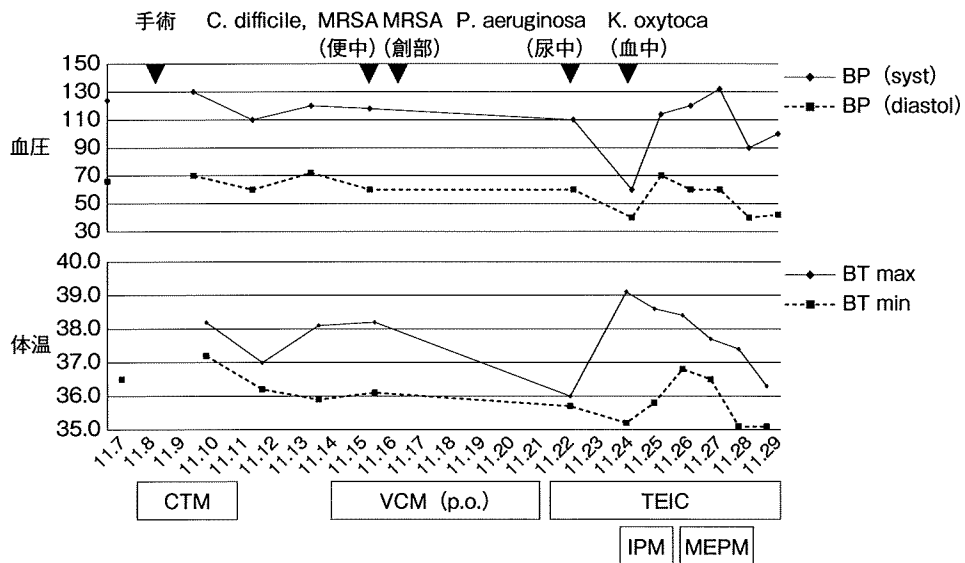軽症急性胆管炎
  急性胆管炎の内，重症・中等症の基準を満たさないもの

文献[1]より引用

図1 手術後のバイタルサイン，細菌検査結果と使用抗菌薬
    BP（syst）；収縮期血圧
    BP（diastol）；拡張期血圧
    BT；体温

浸出液貯留や，胆管拡張を認めないものの，血液生化
学検査で白血球・CRP の高値，血小板数の低下，
Alkaline Phosphatase（ALP）の上昇があり（図2），

急性胆管炎診断基準から，急性胆管炎（疑診）と診断
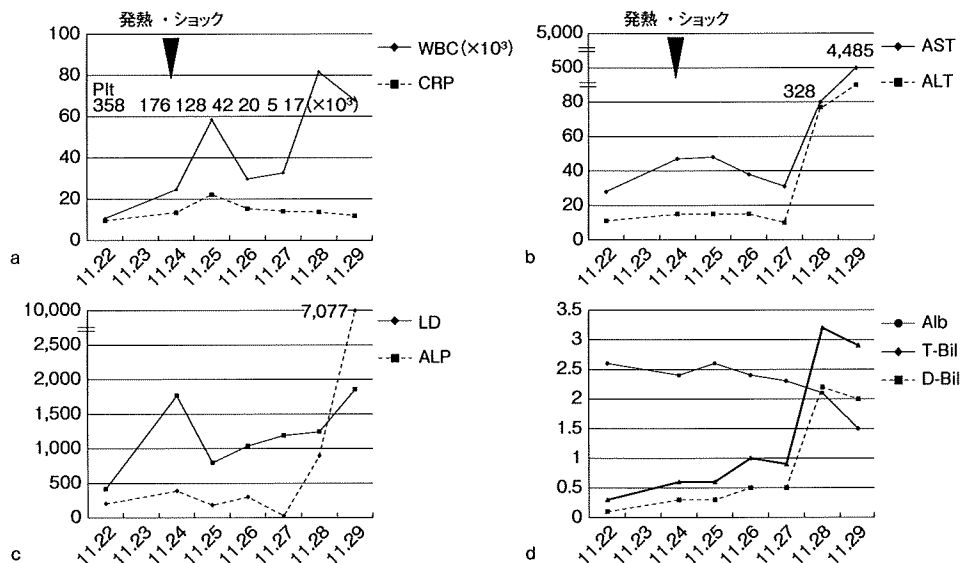した。ショックを生じ，後に判明することとなるが血
液培養にてクレブシエラが陽性であったことから，疑

図2　血液生化学検査結果の推移
　　a.　白血球（WBC），CRP と血小板
　　b.　AST と ALT
　　c.　LD と ALP
　　d.　アルブミン（Alb），総ビリルビン（T-Bil）と直接ビリルビン（D-Bil）
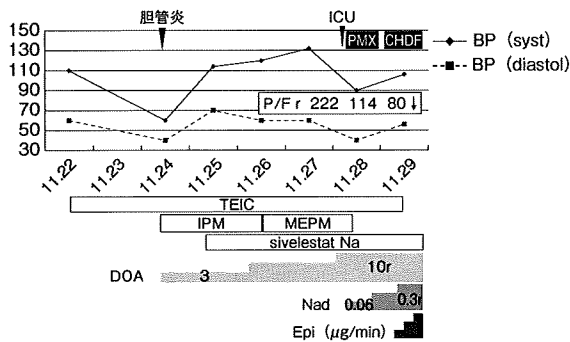

図3　胆管炎発症後の治療経過，BP（syst）：収縮期血圧，
　　BP（diastol）；拡張期血圧，DOA：ドーパミン，
　　Nad；ノルアドレナリン，Epi；エピネフリン

診例ではあったが，重症度判定基準により重症胆管炎と判断した。カルバペネム系抗菌薬を開始し，昇圧剤の投与（ドーパミン 3r）にてバイタルサインは安定化し，その後 2 日間の血液生化学検査結果も，初期治療に反応していると判断した。しかし，その後の呼吸状態の悪化とともに昇圧剤の増量を余儀なくされ，術後 19 病日（11/27）には，P/F 比 300 以下の急性肺傷害（ALI）となった（図 3）。術後 20 病日（11/28）には，血液生化学検査値の再増悪があり（図 2），原因検索のための CT 検査を行い，集中治療室（ICU）に入室し，人工呼吸管理とした。画像上，コントロール不良な感染性滲出液貯留や，胆管拡張はなく，胸部写真にて，ARDS としての両側胸部浸潤影を認めるのみであった（図 4）。胆管炎のコントロールを目的

とした胆道ドレナージは当初から勘案していたが，画像上，胆管の描出が困難なため，施行不能であった。sivelestat sodium の投与とともに，急性血液浄化療法（PMX，CHDF）を施行したが，バイタルサインは一向に改善せず，術後第 21 病日，急性胆管炎発症 5 日後に死亡した。本症例において，病態悪化の要因の一つは，ALI/ARDS であった。

Ⅲ．急性胆管炎自験例における障害臓器と重症度評価[5]

以下に，急性胆管炎自験例において，臓器障害と死亡率に関して解析した報告[5]を参照する。対象は，「何らかの臓器障害，あるいは膿性胆汁を伴っていた」急性胆管炎 35 例で，臓器障害の基準を，循環障害（ショック）は血圧 80mmHg 以下，中枢神経系障害（意識障害）は見当識障害や不穏も含めたもの，肺障害は room air で PaO_2 60mmHg 以下，肝障害は AST・LDH が正常の 2 倍以上，腎障害は血中クレアチニン値が 2mg/dL 以上のもの，とした。その結果，肝，腎，肺障害や，消化管出血を伴った際の死亡率が，それらを伴わなかった症例と比較して有意に高率であった（表 3）。とくに，ガイドラインの重症度判定基準に項目として引用のない「肺障害」は，急性胆管炎の対象症例中の 28.6％（10/35 例）の頻度で合併し，肺障害を合併した際の死亡率が 70％と極めて高率であった。また，障害臓器の総数と死亡率を検討した場合，障害臓
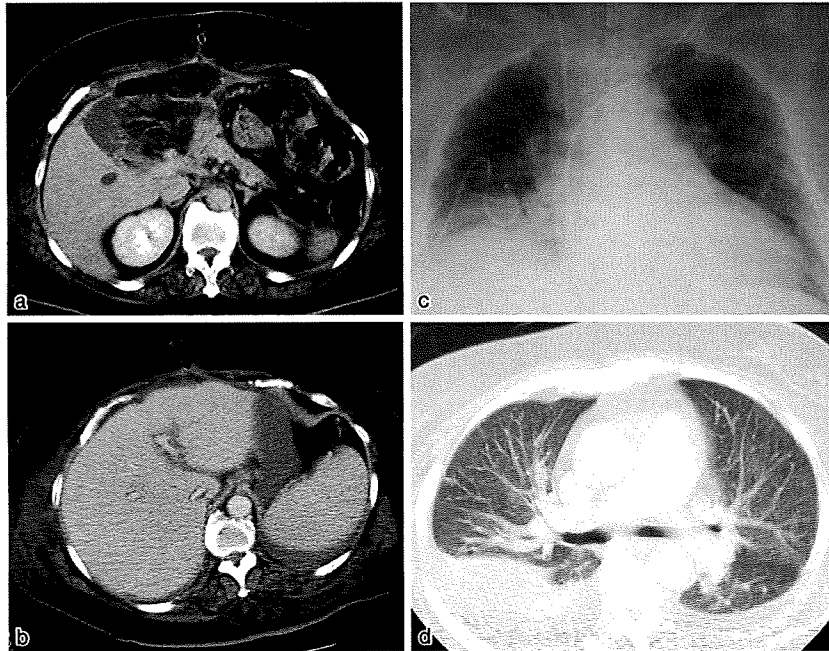
図 4　ICU 入室時の各種画像診断
a, b. 腹部造影 CT：肝内胆管拡張や縫合不全に起因した感染性滲出液貯留を認めなかった。
c. 胸部単純写真：両側胸部浸潤影
d. 胸部 CT：背側無気肺と胸水を右側に認めるが，肺実質の濃度上昇はなく，間質性肺炎には至っていなかった。

表 3　障害臓器別の死亡率

		全症例 35 例	生存 23 例	死亡 12 例	死亡率 （%）	p-value
肝障害	−	23	22	1	4	
	+	12	1	11	91	＜0.000001
腎障害	−	24	21	3	12	
	+	11	2	9	82	＜0.001
肺障害	−	25	20	5	20	
	+	10	3	7	70	＜0.01
ショック	−	19	15	4	21	
	+	16	8	8	50	0.07
意識障害	−	19	15	4	21	
	+	16	8	8	50	0.07
凝固−線溶異常	−	19	15	4	21	
	+	16	8	8	50	0.07
消化管出血	−	31	23	8	25	
	+	4	0	4	100	＜0.01
膵炎	−	31	21	10	32	
	+	4	2	2	50	0.43
肝膿瘍	−	28	18	10	36	
	+	7	5	2	29	0.54

（文献 [5] より引用）

器数の平均は，全症例（1.32 臓器），生存 23 例（0.55 臓器），死亡 12 例（2.75 臓器）で，障害臓器数と転帰が有意に相関し，さらに，全症例の障害臓器数（0-6 臓器）と死亡率には極めて有意な相関を認め（$p<$
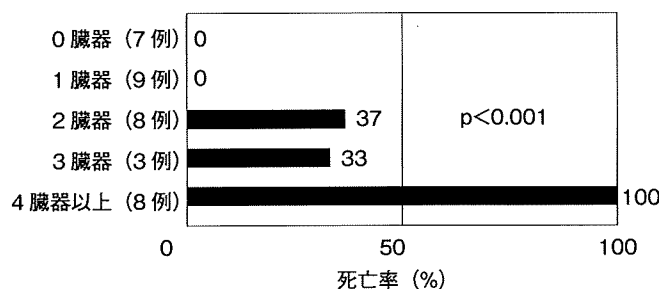
図5 障害臓器の総数と予後（文献[5]より引用）

0.0001），4臓器以上に障害を認めた場合は死亡率が100％となった（図5）。

本研究は，急性胆管炎症例が臓器障害，とくに，急性肺障害を合併した際には，致死的病態をたどる可能性が高いことを示しており，急性胆管炎の重症度判定基準において，急性肺障害に準じた項目を盛り込むことが妥当であるとする，一つの根拠になりうるものと考えられた。

IV. 考　　察

「科学的根拠に基づく急性胆管炎・胆嚢炎の診療ガイドライン（第1版)」における重症度判定基準（表2）は，今日の実地臨床に浸透・普及しつつある[6]。ガイドライン策定の大きな目的は，共通の基盤に則った「Golden standard」の確立にある。本邦を含めた世界的な基準なしに，真のエビデンスを創出することは困難なことから，本ガイドラインがそのスタートとなることが期待されている。

2006年4月，急性胆道炎の診断基準，重症度判定基準，治療方針に関する合意形成を目指した国際コンセンサス会議が東京にて開催された。これらの内容についてはその後「Tokyo Guidelines」として2007年1月に出版された[2]。コンセンサス会議では，急性胆管炎の重症度判定基準に「急性肺障害」に関する記載が盛り込まれ，急性胆管炎のうち，P/F ratio＜300をもって severe cholangitis とすることが合意された[2]。日本語版ガイドラインと国際版のそれとに齟齬を生じたが[7]，専門家によるコンセンサス形成の過程で国内外に一定の温度差をみた理由は明確に説明し得ない。

現在，急性胆管炎・胆嚢炎の診療ガイドライン，ならびに Tokyo Guidelines 策定後の前向き症例集積研究が「CLASS Tokyo study」として進行している。これらの調査研究から，急性胆管炎の重症度判定基準として，現行の項目のみならず，さらに有力な判定項目が抽出されることが想定される。

お わ り に

1）本ガイドラインにおける重症度判定基準は，臓器障害や予後を反映した因子で構成されている。2）これらの因子の中で臓器障害は，自験例の検討においても，急性胆管炎症例の予後を有意に左右していたことから，おおむね妥当である。3）急性肺障害は，日本語版ガイドラインにおいても，重症度判定基準に組み入れるよう，本邦での検討が必要と考える。

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Reconsideration of the Severity Assessment of Acute Cholangitis from the Perspective of Organ Dysfunction and the Prognosis

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In this review, we mention the process for establishing the severity assessment of acute cholangitis and also indicate the dilemma about the severity assessment. The criteria for severity assessment of acute cholangitis consist of poor prognostic factors and the factors associated with vital-organ dysfunction. Those are the bodies of evidence that have already been reported in the literature, and are also the factors as a consensus formed by experts in agreement. Acute pulmonary dysfunction is known as acute lung injury (ALI) and adult respiratory distress syndrome (ARDS), which are associated with high mortality in SIRS and severe sepsis patients. They are frequently accompanied with acute cholangitis, however, the incidence and the mortality of acute cholangitis patients who are complicated with ALI/ARDS have not been well elucidated. We previously reported that dysfunctions of the liver, kidneys, and lungs were significantly correlated with mortality, and that the number of dysfunctional organs had a strong correlation with mortality in acute cholangitis patients in a critically ill condition. From such a situation, although acute pulmonary dysfunction has not been adopted as one of the criteria for the severity assessment, we imply that it can be a factor which should be included.

総合分担研究報告

平成20〜21年度厚生労働省科学研究費補助金（地域医療基盤開発推進研究事業）

総合分担研究報告書

国内版、国際版急性胆道炎診療ガイドラインの普及と、

日本と世界の実地診療・健康アウトカム等に与える影響の検証に関する研究

分担研究　国際版急性胆道炎診療ガイドライン（Tokyo Guidelines）の検証

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【研究要旨】

Accuracy of the Tokyo Guidelines for the diagnosis of acute cholangitis and cholecystitis taking into consideration the clinical practice pattern in Japan

Abstract:

Three years have passed since the publication of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis, and we believe that the time has come to assess their validity. In this study, we validated the diagnostic accuracy of these criteria in 74 patients with an initial diagnosis of acute cholangitis and 81 patients with an initial diagnosis of acute cholecystitis. We also statistically compared the accuracy of the diagnosis made based on the Tokyo Guidelines with that based on the presence of the Charcot's triad for acute cholangitis and Murphy's sign for acute cholecystitis. The results revealed that the diagnostic sensitivity and specificity of the Tokyo Guidelines for suspected/ definitive acute cholangitis were 72.1% and 38.5%, respectively, and the corresponding values for definitive cholangitis alone were 63.9% and 69.2%, respectively. For definitive acute cholecystitits, the diagnostic sensitivity and specificity of the Tokyo Guidelines were 84.9% and 50.0%, respectively. The accuracy of diagnosis based on the Tokyo Guidelines was significantly higher than that based on the presence of Charcot's triad (acute cholangitis) or Murphy's sign (acute cholecystitis). It was therefore concluded that the Tokyo Guidelines should be used more widely for the diagnosis of acute cholangitis in the 21st century. In an effort to improve the diagnostic accuracy of the Tokyo Guidelines and to enhance their specificity, the sign of "fever" in Charcot's triad for the diagnosis of acute cholangitis and the Murphy's sign for the diagnosis of cholecystitis should be given more weight in the diagnosis of acute cholangitis and acute cholecystitis, respectively.

Introduction:

Acute cholangitis and cholecystitis are characterized by abdominal pain and are frequently encountered in daily clinical practice.

Both conditions can be life-threatening if appropriate treatment is not administered promptly. Acute cholangitis is a biliary tract infection manifesting with fever, jaundice, and abdominal pain; this triad, defined by Chracot1 more than 100 years ago, referred to as the Charcot's triad, is still used for the diagnosis of acute cholangitis in the world. While the main factors in the pathogenesis of acute cholangitis are biliary tract obstruction, bacterial invasion and proliferation in the bile, and inflammation of the bile ducts,2 it is not easy in clinical practice to demonstrate the presence of biliary infection. There is no gold standard for the diagnosis of acute cholangitis. Usually, therefore, the clinical diagnosis is made on the basis of the Charcot's triad.

On the other hand, acute cholecystitis manifests with right upper quadrant (RUQ) pain and fever, and just as Charcot's triad is used for the diagnosis of acute cholangitis, Murphy's sign3 is the characteristic physical sign for the diagnosis of acute cholecystitis. While the main factors in the pathogenesis of acute cholecystitis are impacted gallstone in the gallbladder neck or cystic duct, decreased bile secretion, and inflammation of the gallbladder,4, 5 acute cholecystitis is caused by gallstones in 90% of cases, while only 5% to 10% of the cases have acalculous cholecystitis.6 Acalculous cholecystitis can be associated with a high mortality rate.7 Since gallstones can also be asymptomatic, the presence of gallstones does not necessarily suggest a definitive diagnosis of acute cholecystitis. Strasberg8 concludes that the gold standard for the diagnosis of acute cholecystitis lies in histopathology of the gallbladder and can only be obtained after surgery. In clinical practice,

therefore, Murphy's sign is used as the surrogate gold standard for the diagnosis of acute cholecystitis.

Back Ground and Aim

Until recently, more than about 100 years after Charcot's and Murphy's great contributions, in spite of the steady advances in imaging technologies such as abdominal CT and ultrasonography, no international standardized criteria for the clinical diagnosis and assessment of severity of acute cholangitis/cholecystitis had been established. Under this circumstance, a Japanese working group (chief researcher, Tadahiro Takada) initiated a project in 2003 to prepare evidence-based guidelines for the management of acute cholangitis and cholecystitis, and the Japanese domestic version of the guidelines was completed in 2005. The following year, discussions were held on the draft guidelines by the world's leading experts in the field at an International Consensus Meeting held in Tokyo. The Tokyo Guidelines for the management of acute cholangitis and cholecystitis (Tokyo Guidelines) were finally published in 2007. Three years have passed since, and we reckoned that it is time to assess their validity.

Until today in Japan, we used both Japanese domestic guidelines and Tokyo Guidelines for the management of acute cholangitis/cholecystitis. From our clinical experience, we wanted to clarify what the most important point is on the diagnosis of acute cholangitis/cholecystitis.

In this study, we evaluated the accuracy of the Tokyo Guidelines for the diagnosis of acute cholangitis/cholecystitis based on the rate of final correct diagnosis. We also evaluated the accuracy of the diagnosis based on the presence of Charcot's triad (acute cholangitis)/ Murphy's sign (acute

cholecystitis) ,and compared it statistically with the diagnostic accuracy of the Tokyo Guidelines.

Subjects and Methods:

This study involved 74 consecutive patients with an initial diagnosis of acute cholangitis and 81 consecutive patients with an initial diagnosis of acute cholecystitis, who were admitted to the Nagoya Daini Red Cross Hospital between November 2004 and November 2005. They had visited the hospital as outpatients or emergency outpatients or had been referred from elsewhere. The initial diagnosis was made by gastrointestinal physicians. Patients who developed acute cholangitis or cholecystitis during hospitalization and those who were hospitalized for detailed examination or biliary drainage catheter replacement were excluded in this study. Since these 155 patients had been diagnosed before the Tokyo Guidelines were published, they were not influenced by the Tokyo Guidelines. Therefore, all of the 155 patients were retrospectively examined according to the Tokyo Guidelines and the diagnoses were compared with the final diagnoses. Since there is no gold standard for the diagnosis of acute cholangitis and cholecystitis, the final clinical diagnoses made by the physicians in charge of the patients were considered to be the final diagnoses. Since the final clinical diagnosis was not certain in 22 patients, it was re-examined by an Expert Panel comprising surgeons accredited by the Japan Surgical Society or the Japanese Society of Gastroenterological Surgery, gastrointestinal internists accredited by the Japanese Society of Gastroenterology, Japan Gastroenterological Endoscopy Society or the Japan Society of Hepatology, and internists accredited by the

Japanese Society of Internal Medicine. These panelists were not necessarily familiar with Tokyo Guidelines and made the final diagnoses without referring to these guidelines. Even if acute cholangitis or cholecystitis occurred associated with bile duct or gallbladder cancer, both acute cholangitis and cholecystitis were included in the final diagnosis for the evaluation of the diagnostic criteria for these two diseases. We also evaluated the diagnostic accuracy for acute cholangitis based on the presence of Charcot's triad, as well as that for acute cholecystitis based on the presence of Murphy's sign. In an effort to evaluate the validity of the Tokyo Guidelines, the diagnostic criteria of the Tokyo Guidelines for acute cholangitis and cholecystitis were compared with the accuracy of the diagnosis based on the presence of the Charcot's triad (acute cholangitis) and Murphy's sign (acute cholecystitis).

Results:

The 74 patients with the initial diagnosis of acute cholangitis included 39 male patients and 35 female patients with a mean age of 69.2 ± 15.2 years. Of these, 3 patients died (one each of pneumonia, post-ERCP pancreatitis, and bile duct cancer). A final diagnosis of acute cholangitis was made in 61 patients (82.4%). The 81 patients with the initial diagnosis of acute cholecystitis included 49 male patients and 32 female patients with a mean age of 69.0 ± 15.0 years. None of these patients died. A final diagnosis of acute cholecystitis was made in 73 patients (90.1%) (Table 1).

Based on the diagnostic criteria for acute cholangitis in the Tokyo Guidelines10 (Table 2), the diagnosis of suspected acute cholangitis was made in 9 patients, a definitive diagnosis of acute

cholangitis was made in 43 patients, and the diagnostic criteria were not met in 22 patients. Among the 52 patients with a suspected/definitive diagnosis of acute cholangitis based on the Tokyo Guidelines, a final diagnosis of acute cholangitis was made in 44 patients. The diagnostic sensitivity and specificity were 72.1% and 38.5%, respectively, the false-negative and false-positive rates were 27.9% and 61.5%, respectively, the positive and negative predictive values were 84.6% and 22.7%, respectively, and the diagnostic accuracy was 66.2%. Among the 43 patients in whom a definitive diagnosis of acute cholangitis was made based on the guidelines, a final diagnosis of acute cholangitis was made in 39 patients. The diagnostic sensitivity and specificity were 63.9% and 69.2%, respectively, the false-negative and false-positive rates were 36.1% and 30.8%, respectively, the positive and negative predictive values were 90.7% and 29.0%, respectively, and the diagnostic accuracy was 64.9% (Table 3).

On the other hand, the diagnostic criteria for acute cholecystitis in the Tokyo Guidelines (Table 4) do not allow for the diagnosis of suspected acute cholecystitis, and a definitive diagnosis was made in 66 patients, and the diagnostic criteria were not met in 15 patients. Among the 66 patients with a definitive diagnosis of acute cholecystitis based on the Tokyo Guidelines, a final diagnosis of acute cholecystitis was made in 62 patients. The diagnostic sensitivity and specificity were 84.9% and 50.0%, respectively, the false-negative and false-positive rates were 15.1% and 50.0%, respectively, the positive and negative predictive values were 93.9% and 26.7%, respectively, and the diagnostic accuracy was 81.5% (Table 5).

Of 74 patients with the initial diagnosis of acute cholangitis, 9 (12.2%) presented with all three signs of Charcot's triad, and a final diagnosis of acute cholangitis was made in 7 of the 74 patients (9.5%). The diagnostic sensitivity and specificity were 11.5% and 84.6%, respectively, the false-negative and false-positive rates were 88.5% and 15.4%, respectively, the positive and negative predictive values were 77.8% and 16.9%, respectively, and the diagnostic accuracy was 24.3%.

Of the 81 patients with the initial diagnosis of acute cholecystitis, Murphy's sign was positive in 16 patients (19.8%), and a final diagnosis of acute cholecystitis was made in 15 of the 81 patients (18.5%). The diagnostic sensitivity and specificity were 20.5% and 87.5%, respectively, the false-negative and false-positive rates were 79.5% and 12.5%, respectively, the positive and negative predictive values were 93.8% and 10.8%, respectively, and the diagnostic accuracy was 27.2% (Table 6).

A sign test was performed to statistically analyze the diagnostic criteria of the Tokyo Guidelines and the rate of diagnostic accuracy of Charcot's triad for acute cholangitis. Specifically, the true- and false-positive rates obtained using Charcot's triad were compared among the cases with a definitive diagnosis of acute cholangitis based on the Tokyo Guidelines. The results revealed that in 32 patients, a false-positive diagnosis was made using Charcot's triad and a true-positive diagnosis was made based on the Tokyo Guidelines. Conversely, a true-positive diagnosis was made using Charcot's triad and a false-positive diagnosis was made based on the Tokyo Guidelines in 2 patients. The probability was p = 6.93×10^{-8} and the diagnostic accuracy was significantly higher when the Tokyo Guidelines

was used than when theCharcot's triad was used. Then, the diagnosis of suspected/definitive acute cholangitis based on the Tokyo Guidelines was compared with true- and false-positive diagnoses when Charcot's triad was used. The results revealed that in 37 patients, false-positive diagnosis was made using Charcot's triad and true-positive diagnosis was made based on Tokyo Guidelines. Conversely, a true-positive diagnosis was made using Charcot's triad and a false-positive diagnosis was made based on the Tokyo Guidelines in 6 patients. The probability was $p = 1.63 \times 10^{-6}$ and again the diagnostic accuracy was significantly higher when the Tokyo Guidelines were used than when the Charcot's triad was used (Table 7).

Likewise, a sign test was also performed to statistically analyze the diagnostic criteria of the Tokyo Guidelines for acute cholecystitis and the rate of diagnostic accuracy of Murphy's sign. Specifically, the true- and false-positive rates obtained using Murphy's sign were compared among the cases with a definitive diagnosis of acute cholecystitis based on the Tokyo Guidelines. The results revealed that in 48 patients, a false-positive diagnosis was made using Murphy's sign and a true-positive diagnosis was made based on the Tokyo Guidelines. Conversely, a true-positive diagnosis was made using Murphy's sign and a false-positive diagnosis was made based on the Tokyo Guidelines in 4 patients. The probability was $p = 1.30 \times 10^{-10}$ and the diagnostic accuracy was significantly higher when the Tokyo Guidelines were used than when Murphy's sign was used (Table 8).

Discussion:
Clinically, Lee et al12 retrospectively evaluated the validity of the criteria for assessment of the severity in the Tokyo Guidelines in 235 patients with acute cholecystitis caused by gallstones. While numerous such studies have been conducted on the guidelines, a search of the literature in PubMed using keywords such as "Tokyo Guidelines[MeSH]" and "diagnostic accuracy[MeSH]" revealed no studies on the diagnostic accuracy of the guidelines. Our study is the world's first one on the accuracy of the Tokyo Guidelines for the diagnosis of acute cholangitis and acute cholecystitis.

The Tokyo Guidelines is a set of evidence-based international guidelines for the management of acute cholangitis and cholecystitis adopted in 2006 by the world's leading experts at the International Consensus Meeting held in Tokyo,13 and therefore, reflects current clinical practice and health care system. While Lee concluded that while having several limitations, the Tokyo Guidelines represents a notable advance towards establishing a universally accepted consensus for the definition of acute cholangitis,14 there are no studies involving specific cases. In 2010, 3 years after the publication of the Tokyo Guidelines, we evaluated the diagnostic accuracy of the guidelines. We also conducted a retrospective study to statistically compare the validity of using the Tokyo Guidelines vs. the Charcot's triad (acute cholangitis) or Murphy's sign (acute cholecystitis) in the 21st century.

The results revealed that the sensitivity and specificity of the Tokyo Guidelines for suspected/definitive diagnosis of acute cholangitis were 72.1% and 38.5%, respectively, and that the sensitivity and specificity for the definitive diagnosis of acute cholangitis/acute cholecystitis

were 63.9% and 69.2%, respectively. These values are not high enough to either allow us to make a definitive diagnosis or a rule-out diagnosis. The international criteria in the Tokyo Guidelines may not be fully applicable to Japanese patients and diagnosis by Japanese physicians. Also, since there is no international consensus on the criteria for the diagnosis of acute cholangitis, the final diagnosis still needs to be examined. Nonetheless, it is important to assess the current validity of the Tokyo Guidelines and to discuss how they should be used. Since such assessments in all races, countries and medical environments would help improve the guidelines, we believe that this pioneering study will be a cornerstone.

According to the Tokyo Guidelines, acute cholangitis cannot be diagnosed unless the patients satisfy 2 or more of the 4 criteria (Charcot's triad + a history of biliary disease). Previous studies have reported that the Charcot's triad of fever, jaundice, and abdominal pain occurs in 50% to 70% of patients presenting with acute cholangitis.15, 16, 17, 18 In our study, however, only 9 of the 74 patients (12.2%) presented with all of the three signs of Charcot's triad and the diagnostic sensitivity and specificity of the triad for acute cholangitis were 11.5% and 84.6%, respectively, indicating that the criteria can be used for a definitive diagnosis, but not for a rule-out diagnosis. Statistical analysis to compare the accuracy of using Charcot's triad and the Tokyo Guidelines for the diagnosis of suspected/definitive acute cholangitis as well as of definitive cholangitis alone revealed that the diagnostic accuracy obtained using the Tokyo Guidelines was significantly higher than that obtained based on the presence of Charcot's triad. Since the diagnostic sensitivity and specificity of

the Tokyo Guidelines were not high, there is still scope for improvement of these guidelines. In addition, the Charcot's triad is included in the Tokyo Guidelines. Charcot's contribution is significant and cannot be ignored. However, the definite difference between Charcot's triad and the Tokyo Guidelines depends on as to whether all of fever, jaundice and abdominal pain should be included in the diagnostic criteria. Patients having all the 3 signs may be diagnosed as having acute cholangitis, but not those with only fever. Among the 74 patients with acute cholangitis in our study, 53 patients (71.6%) had abdominal pain, 50 (67.6%) had jaundice, and 18 had (24.3%) fever. For the presence of abdominal pain, the diagnostic sensitivity and specificity were 67.2% and 7.7%, respectively, the false-negative and false-positive rates were 32.8% and 92.3%, respectively, and the positive and negative predictive values were 77.4% and 4.8%, respectively. For the presence of jaundice, the diagnostic sensitivity and specificity were 68.9% and 38.5%, respectively, the false-negative and false-positive rates were 31.1% and 61.5%, respectively, and the positive and negative predictive values were 84.0% and 20.8%, respectively. For fever, the diagnostic sensitivity and specificity were 26.2% and 84.6%, respectively, the false-negative and false-positive rates were 73.8% and 15.4%, respectively, and the positive and negative predictive values were 88.9% and 19.6%, respectively. For a history of biliary disease, a criterion in the Tokyo Guidelines, the diagnostic sensitivity and specificity were 44.3% and 76.9%, respectively, the false-negative and false-positive rates were 55.7% and 23.1%, respectively, and the positive and negative predictive values were 90.0% and 22.7%, respectively (Table 9). Since the diagnostic specificity of fever was relatively high,

the sign of fever should be given more weight to improve the specificity of the criteria in the Tokyo Guidelines.

On the other hand, the diagnostic criteria for acute cholecystitis in the Tokyo Guidelines allow either definitive diagnosis of acute cholecystitis or rule-out diagnosis, but not diagnosis of suspected acute cholecystitis. The diagnostic sensitivity and specificity of the guidelines were as high as 84.9% and 50.0%, respectively. Statistical analysis to compare the diagnostic accuracy of Murphy's sign and the Tokyo Guidelines revealed that the diagnostic accuracy obtained using the Tokyo Guidelines was significantly higher than that obtained based on the presence of Murphy's sign. While the Tokyo Guidelines should be used more widely than Murphy's sign for the diagnosis, it must be emphasized that they are good for a rule-out diagnosis, but not for a definitive diagnosis, because the sensitivity was relatively high and the specificity was considerably low. Since a high specificity is required to make a definitive diagnosis, the diagnostic criteria need to be re-examined. For example, Murphy's sign and RUQ mass/pain/tenderness have the same weight. In previous studies, Murphy's sign has been reported to have a sensitivity of 50% to 60% and a high specificity of 79%19 or 96%20 for the diagnosis of acute cholecystitis. In our study, the sensitivity was as low as 20.5%, while the specificity was at the same level (87.5%). Murphy's sign should be given more weight to improve the diagnostic specificity of the Tokyo Guidelines. In addition, Strasberg8 concluded that further discussions are required to use the Tokyo Guidelines as an international standard, considering, for example, that testing of the C-reactive protein level is not commonly used for the diagnosis of acute cholecystitis in the United States.

In an effort to improve and revise the Tokyo Guidelines, their diagnostic criteria need to be assessed in many countries. By performing this study, we, Japanese researchers who first prepared the guidelines, took the first initiative in this effort.

Conclusion:

We evaluated the diagnostic accuracy of the Tokyo Guidelines for acute cholangitis and cholecystitis. The sensitivity and specificity of the guidelines for the diagnosis of acute cholangitis were not high enough to either allow us to make a definitive diagnosis or a rule-out diagnosis. While the sensitivity for the diagnosis of acute cholecystis was relatively high, the specificity was low. The diagnostic accuracy of the Tokyo Guidelines was significantly higher than that based on Charcot's triad for acute cholangitis or Murphy's sign for acute cholecysitits. It was therefore concluded that the Tokyo Guidelines should be more widely used for the diagnosis of acute cholangitis and cholecystitis in the 21st century.

Table 1. Characteristic

Initial diagnosis		Acute Cholangitis (n=74)	Acute Cholecystitis (n=81)
Sex –no.(%)	Male	39(52.7%)	49(60.5%)
	Female	35(47.3%)	32(39.5%)
Age (yr)		69.2±15.2	69.0±15.0
Death –no.		3	0
Tokyo Guidelines	Fail	22	15
	Suspected	9	-
	Definite	43	66
Japanese Domestic Guidelines	Fail	14	11
	Suspected	30	14
	Definite	30	56
Final Diagnosis (Prevalence)		61 (82.4)	73 (90.1)

Table2. Tokyo Guidelines Diagnostic criteria for Acute Cholangitis

Diagnostic criteria for Acute Cholangitis		
A. Clinical context and clinical manifestations	1	History of biliary disease
	2	Fever and/or chills
	3	Jaundice
	4	Abdominal pain(RUQ or upper abdominal)
B. Laboratory data	5	Evidence of inflammatory response (Abnormal WBC count, increased of serum CRP level, and other changes indicating inflammation)
	6	Abnormal liver function tests (Increased serum ALP, γ-GTP(GGT) ,AST, and ALT levels.)
C. Imaging findings	7	Biliary dilatation, or evidence of an etiology (stricture, stone, stent, etc)
Suspected diagnosis :	Two or more items in A	
Definite diagnosis :	①	Charcot's triad(2+3+4)
	②	Two or more items in A + both items in B and item C

Table 3. Acute Cholangitis n=74 (Prevalence 82.4%)

n=74	Sensitivity (%)	Specificity (%)	False negative (%)	False positive (%)	Positive predictive value(%)	Negative predictive value(%)	Accuracy Rate (%)
Tokyo GL Sus+Def	72.1	38.5	27.9	61.5	84.6	22.7	66.2
Tokyo GL Def only	63.9	69.2	36.1	30.8	90.7	29.0	64.9

Table 4. Tokyo Guidelines Diagnostic criteria for Acute Cholecystitis

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
Definite diagnosis :	①	One item in A and one item in B are positive
	②	C confirms the diagnosis when acute cholecystitis is suspected clinically

Table 5. Acute Cholecystitis n=81 (Prevalence 90.1%)

n=81	Sensitivity (%)	Specificity (%)	False negative (%)	False positive (%)	Positive predictive value(%)	Negative predictive value(%)	Accuracy rate (%)
Tokyo GL Def only	84.9	50.0	15.1	50.0	93.9	26.7	81.5

Table 6.
Charcot's Triad on Acute Cholangitis & Murphy's sign on Acute cholecystitis

	Sensitivity (%)	Specificity (%)	False negative (%)	False positive (%)	Positive predictive value(%)	Negative predictive value(%)	Accuracy rate (%)
Charcot's Triad (n=74)	11.5	84.6	88.5	15.4	77.8	16.9	24.3
Murphy's Sign (n=81)	20.5	87.5	79.5	12.5	93.8	10.8	27.2

Table7. Results of sign tests between Tokyo Guidelines Diagnostic Criteria and Charcot's Triad

Acute Cholangitis (n=74)	Charcot's: False Tokyo GL: True	Charcot's: True Tokyo GL: False	
Tokyo GL (Def only)	32	2	$p=6.94\times10^{-8}$
Tokyo GL (Def+Susp)	37	6	$p=1.64\times10^{-6}$

Table8. Results of sign tests between Tokyo Guidelines Diagnostic Criteria and Murphy's sign

Acute Cholecystitis (n=81)	Murphy's: False Tokyo GL: True	Murphy's: True Tokyo GL: False	
Tokyo GL (Def only)	48	4	$p=1.31\times10^{-10}$

Table 9. Each symptom's diagnostic accuracy(Prevalence 82.4%)

n=74	Sensitivity (%)	Specificity (%)	False negative (%)	False positive (%)	Positive predictive value(%)	Negative predictive value(%)	Accuracy Rate (%)
Past History	44.3	76.9	55.7	23.1	90.0	22.7	50.0
Abdominal Pain	67.2	7.7	32.8	92.3	77.4	4.8	56.8
Jaundice	68.9	38.5	31.1	61.5	84.0	20.8	63.5
Fever	26.2	84.6	73.8	15.4	88.9	19.6	36.5

平成20～21年度厚生労働省科学研究費補助金（地域医療基盤開発推進研究事業）
総合分担研究報告書

国内版、国際版急性胆道炎診療ガイドラインの普及と、

日本と世界の実地診療・健康アウトカム等に与える影響の検証に関する研究

分担研究　国際版ガイドラインの検証を目的とした調査について

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【研究要旨】

2005 年に「急性胆管炎・胆嚢炎の診療ガイドライン」国内版が、2007 年に国際版が発表された。本ガイドラインの検証のため、日本外科感染症学会の協力を得た。また、日本外科感染症学会を通じ、各国の学会から国際協力を得た。2009 年に米国シカゴにおいて国際シンポジウムを開催する準備を進めたが、新型インフルエンザ流行のため実現しなかった。2010 年にドイツ国ミュンヘンにおいて、国際シンポジウムを開催し、国際版ガイドラインの検証を行った。国際版ガイドラインの改訂における問題点が検証され、ガイドライン改定のための前向き症例登録システムを世界に広めるきっかけをつくることができた。

A. 研究目的

2005 年に急性胆管炎・胆嚢炎の診療ガイドライン（以下、国内版ガイドラインと称す）が作成され、2006 年に東京で開催されたコンセンサス会議に基づき、2007 年に国際版ガイドライン Tokyo Guidelines for the management of acute cholangitis and cholecystitis （以下、国際版ガイドラインと称す）が公表された。しかし、これらのガイドラインでは、RCT のシステマティックレビューは十分でなかったため、エビデンスを重視しつつも、その他の診療に関係するあらゆる側面を加味した上で、最良の患者アウトカムが得られるような診療が提案された。国内版ガイドラインは、2007 年 1 月～2 月に研究代表者らにより、日本腹部救急医学会、日本肝胆膵外科学会、日本胆道学会の会員、厚労省研究班(高田班)班員のうち重複を除いた約 8,000 人の医師を対象にアンケート調査が実施された。一方、国際版ガイドラインの検証のためには、急性胆管炎・胆嚢炎を扱う国際的な学会の一つである、日本外科感染症学会（会員数 1607 名）や、北米外科感染症協会 Surgical Infection Society- North America（以下 SIS-NA と称す、会員数約 800 名）、欧州外科感染症 Surgical Infection Society- Europe（以下 SIS-E と称す、会員数約 300 名)の協力が必要である。国際版ガイドラインの検証を目的とした調査を実施したので報告する。

B. 研究方法

1. 研究分担者は、日本外科感染症学会理事会を通じ、評議員会（社員総会）をへて日本外科感染症学会が本ガイドラインの外部評価の学会となることについて協力を得る。

2. 研究分担者は、研究協力者を通じ、急性胆管炎・胆嚢炎を扱う国際的な学会に関する情報を収集する。

3. 研究分担者は、研究代表者、研究協力者とともに SIS-NA ならびに SIS-E 関係者と接触し、国際版ガ

イドラインの検証を目的とした調査を行う合意形成する。

4. 第3回SIS合同学会において、国際版ガイドラインのポスター展示を行い、さらに国際シンポジウムを開催する。シンポジウム参加者による総合ディスカッションにより、国際版ガイドラインを検証する。シンポジウム参加者を対象としてアンケートを実施し、検証する。第3回SIS合同学会以降も、国際版ガイドラインにかかわる国際調査を継続する。

5. 第8回World Congress on Trauma, Shock, Inflammation and Sepsis - TSIS 2010において、国際版ガイドラインの検証を目的とした国際シンポジウムを開催する。

6. 倫理面への配慮：国際版ガイドラインの検証を目的とした調査の対象者は、国際シンポジウムの参加者に限定する。研究代表者が研究協力者らと共にアンケート用紙を配布し、スライドを用いた説明によって調査の必要性を説明する。質疑応答によって調査の妥当性を検証し、記入の終了したアンケート用紙を回収する。

C. 研究結果
1. 研究分担者は、2007年11月7日、日本外科感染症学会国際渉外委員会ならびに理事会を通じ、日本外科感染症学会が本ガイドラインの外部評価の学会となることについて承認を得た。また、SIS-NAとSIS-Eに対し、2009年にSIS-NAとSIS-Eが米国シカゴで開催する合同学会において日本外科感染症学会代表を交えた合同セッションを開催することを提案することについて承認を得た。同日開催された評議員会（社員総会）において両議案の承認を得た。

2. 研究分担者は、研究協力者を通じ、2008年のSIS-NA会長がStephan Lowry氏、SIS-E会長がMetin Çakmakçı氏であるという情報を得た。また、

米国サウスカロライナにおいて開催されたSIS-NA学術集会、スペイン国バルセロナにおいて開催されたEuropean Congress on Clinical Microbiology and Infection、トルコ国アンタルヤにて開催されたSIS-E学術集会において、国際版ガイドラインに関する検証が実施されていないという情報を得た。

3. 研究分担者は、研究代表者、研究協力者とともに、2008年11月6日、ロイトン札幌ホテルにおいて直接交渉を行い、2009年のSIS合同学会において国際版ガイドラインの検証の発表を行い、参加者を対象にアンケートを実施することの合意を得た。

4. 研究分担者は、研究分担者・SIS-NA代表John Marshall氏・SIS-E代表Ulrich Schöffel氏の打ち合わせにより、国際版ガイドラインのディスカッションを行うシンポジウムの座長にブラジル人のEdmundo Ferraz氏を座長に加えた。2009年4月22日までに講演時間・ディスカッション時間の調整を終えた。しかし、23日（日本時間）、新型インフルエンザ情報がInternational Society for Infectious Diseaseで配信され(ProMED mail: Archive Number 20090422.1516)、28日、WHOがpandemic alert levelを3から4へ引き上げた。このため、日本政府が、首相を本部長とする対策本部を設置し、検疫強化など本症の国内侵入防止と在外邦人支援の対策に着手した。この影響により、第3回SIS合同学会での国際版ガイドラインの検証は実現困難となり、日本代表団派遣を断念した。

5. 研究分担者は、2009年5月26日、SIS-EがTSIS 2010と合同学会を開催する案内をTSIS 2010会長Eugen Faist氏から受けた。Faist氏は、日本外科感染症学会後援のシンポジウム開催を提案した。研究協力者を通じ研究代表者ならびに研究分担者真弓俊彦先生にこの情報を伝達した。6月8日、研究分担者は、Faist氏に提案の受諾を返答した。7月8日Faist氏から研究分担者が送った受諾の合意が確認

された。

6. 研究分担者は、日本外科感染症学会より研究協力者ならびに三鴨廣成氏をプログラム委員に推薦し、シンポジウムのテーマとして「急性胆管炎・胆嚢炎」を提案した。8日5日にFaist氏より提案と推薦の確認が返答された。7日、研究協力者はTSIS 2010の科学プログラム委員となった。13日、Faist氏より「急性胆道炎」のトピックを6名が発表するシンポジウムの企画が研究分担者に依頼された。同日以降、シンポジウムの座長・演者の内諾をすすめた。12月9日、シンポジウムが「急性胆道炎：国際版ガイドラインの検証」として開催されることが決定した。

7. 12月1日、国際版ガイドライン検証のための前向き症例登録ウェブサイトが稼働した。10日、第22回日本外科感染症学会学術集会において胆道炎ガイドライン国際ビジネスミーティングを開催し、研究代表者、研究分担者、研究協力者、SIS-NA会長Lena Napolitano氏の代理として派遣されたPhilip Barie氏、SIS-E会長Angelo Nespoli氏により、TSIS 2010における国際シンポジウムについて打ち合わせを行った。また、19日の研究班会議において、日本外科感染症学会の英語版ウェブサイトに直接アクセスできる国際症例登録のリンク作成を依頼することを決めた。研究分担者は、リンク用のバナーをうけ、リンクを稼働させた。

8. 2010年3月9-13日、ドイツ国ミュンヘンLudwig-Maximilians-Universityで日本外科感染症学会やSIS-Eを含む世界合計38学会の協力をえてTSIS 2010が開催された。国際版ガイドラインの検証シンポジウム「Management of acute biliary tract inflammation: validation of the Tokyo Guidelines」がLecture Hall Vで、現地時間3月11日15:45-18:00に開催された。6名の指名討論者によるディスカッションが開催され、検証が進められた。

第一に、研究代表者より「Why international guidelines for the management of acute cholangitis and acute cholecystitis are required to be validate?」において、国際版ガイドライン改訂の必要性が述べられ、妥当性が検証された。第二に、研究分担者真弓俊彦先生より「Difference between Tokyo Guidelines and Japanese Guidelines for management of acute cholangitis and cholecystitis」において、日本国内で問題となっている国際版ガイドラインと日本向けガイドライン（日本版ガイドライン）の差異が検証された。第三に、研究協力者横江正道先生より「The clinical evaluations of Tokyo Guidelines 2007 from actual cases.」において、2004年11月から2005年11月の155例（急性胆管炎74例・急性胆嚢炎81例）を対象に、国際版ガイドラインの診断能が検証された。Definiteと診断された症例では、日本版ガイドラインは感度72.6%、特異度62.5%であったが、国際版ガイドラインは感度84.9%、特異度50.0%で、国際版ガイドラインのほうが感度に優れていたことが述べられた。また、急性胆管炎の診断能は、日本版ガイドラインの診断率が40.5%であったものの、国際版ガイドラインの診断率は12.2%にすぎず、診断基準の問題点が述べられ。一方、急性胆嚢炎については、古典的診断徴候であるMurphy徴候が陰性の症例であっても、国際版ガイドラインで陽性であれば、急性胆嚢炎の診断率が高く（p<0.001）、国際版ガイドラインの優れた点が示された。各国の参加者により各国の診断成績がコメントされた。第四に、オランダ国Djamila Boerma先生により「Follow-up of international guidelines for the management of acute cholangitis and acute cholecystitis: a European perspective.」において、オランダ版急性胆嚢炎ガイドラインの作成と、それに伴う国際版ガイドラインとの整合性が検証された。どちらもエキスパートオピニオンが主体でエビデンスレベルは低かったことが示された。また、近年の発表から新しいエビデンスが加わることが示され、国際版ガイド