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ORIGINAL ARTICLE

Prognostic factors of acute cholangitis in cases managed using the Tokyo Guidelines

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Abstract
Background/purpose In 2007, the Tokyo Guidelines (TG07) working group established diagnostic criteria for assessment of the severity of acute cholangitis. This study aimed to analyze outcomes and identify predictors of mortality in patients with acute cholangitis managed according to the TG07.
Methods In this study, 215 consecutive cases of acute cholangitis were reviewed. Risk factors associated with mortality or refractory cholangitis, which is defined on the basis of prolonged hospitalization (>28 days) or disease resulting in fatality, were examined using multivariate logistic regression analysis.
Results There were 52, 133, and 30 cases of mild, moderate, and severe cholangitis, respectively. The overall mortality rate was 4.2 % (9/215). Mortality rates in patients with mild, moderate, and severe cholangitis were 0, 2.3, and 20.0 %, respectively (moderate vs. severe, $p = 0.001$). Multivariate analysis showed that serum albumin levels ≤2.8 g/dl and PT-INR >1.5 were significant predictors of mortality. There were 57 patients (26.5 %) with refractory cholangitis. Multivariate analysis showed that serum albumin level ≤2.8 g/dl, PT-INR >1.5, etiology and inpatient status were significant predictors of refractory cholangitis.
Conclusions The TG07 severity assessment criteria for acute cholangitis were significantly predictive of mortality. Hypoalbuminemia is an important risk factor in addition to organ dysfunction.

Keywords Acute cholangitis · Endoscopic retrograde cholangiopancreatography · Severity of illness · Hypoalbuminemia

Abbreviations

EBD	Endoscopic biliary drainage
TG07	Tokyo Guidelines
PTBD	Percutaneous transhepatic biliary drainage

Introduction

Prior to the 1970s, the mortality rate for patients with acute cholangitis was reportedly >50 %; however, advances in endoscopic drainage and new antibiotics reduced the mortality rate to <7 % by the 1980s [1]. Several investigators have proposed predictors of adverse outcomes in patients with acute cholangitis using their own severity assessment systems [2–4]. No standard criteria were

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available for diagnosis and severity assessment in patients with acute cholangitis until the Tokyo Guidelines (TG07) were published in 2007 [5, 6]. The TG07 defines severe acute cholangitis as cholangitis accompanied by organ dysfunction and recommends that biliary drainage should be urgently performed for patients with severe acute cholangitis. Moderate cholangitis is defined by the TG07 as disease unresponsive to initial medical treatment, whereas mild cholangitis is defined as disease responsive to medical treatment. However, several issues arise from this severity assessment. First, acute cholangitis may worsen even after biliary drainage is performed following a failure of conservative treatment. Second, the timing of biliary drainage in patients with moderate cholangitis needs to be considered (e.g., as soon as possible, within 24 h, following conservative treatment using another antibiotic). Therefore, determination of disease severity and timing of biliary drainage in the early-stages of mild or moderate cholangitis can be difficult.

This retrospective study aimed to analyze outcomes and identify predictors of mortality and prolonged hospitalization in patients with acute cholangitis managed according to the TG07, in order to confirm the effectiveness of these guidelines in clinical practice. Early identification of more reliable risk factors in addition to organ dysfunction may help clinicians to administer timely and appropriate treatment.

Patients and methods

A total of 215 patients (138 males, 77 females; average age 66.7 years) who were admitted to Chiba University Hospital between February 2007 and July 2011 for acute cholangitis were enrolled in this study. Diagnosis and severity assessment were retrospectively made according to the TG07 [5]. All clinical data were prospectively recorded in electronic hospital medical records. Diagnostic criteria for acute cholangitis included Charcot's triad (fever and/or chills, jaundice, abdominal pain), which is the definitive diagnostic criterion for acute cholangitis (criterion 1), and in the absence of one or more components of Charcot's triad, a definite diagnosis was reached if an inflammatory response and biliary obstruction were both revealed by laboratory data and imaging findings (criterion 2). Severe cholangitis was diagnosed in cases complicated by organ/system dysfunction (cardiovascular, nervous, respiratory system, kidney, liver, or hematological system). Moderate cholangitis was diagnosed in cases in which early biliary drainage (EBD) was required after failure of initial medical treatment. Mild cholangitis was diagnosed in cases that responded to initial treatment and did not require biliary drainage. Immediate medical treatment with intravenous fluid and antibiotics was administered in all cases diagnosed with acute cholangitis. For biliary drainage, endoscopic biliary drainage (EBD) was selected as first-line therapy according to recommendations of the TG07, and it was followed by percutaneous transhepatic biliary drainage (PTBD) [6]. The study protocol was approved by the ethics committee of Chiba University Hospital.

Mortality due to cholangitis and its determining factors was the primary outcome in this study. The secondary purpose was to detect major factors that affect the duration of hospitalization in patients with acute cholangitis. For cases in which cholangitis developed during hospitalization, the duration of hospitalization was calculated from the date of onset instead of the date of admission. Organ failure was defined by the TG07 as follows: hypotension requiring dopamine $\geq$5 μl/kg per min or any dose of dobutamine, disturbance of consciousness, oxygenation index values [as measured by the ratio of the pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2)] <300, serum creatinine >2.0 mg/dl, and platelet count <100000/μl. These factors were used as potential predictors of mortality or refractory cholangitis.

All statistical analyses were performed using the Predictive Analytics Software package (PASW 18.0 for Windows, SPSS Inc., Tokyo, Japan). The *t* test was used for continuous variables with a skewed distribution, and the Chi-squared test with Yates' correction method or Fisher's exact test was used to compare categorical variables. A cut-off value was determined by receiver operating characteristic (ROC) analysis. A logistic regression test analysis was performed using the stepwise method. A p value of <0.05 was considered statistically significant. In this study, odds ratios (ORs) are reported together with their 95 % confidence intervals (CIs).

Results

Mild, moderate, and severe cholangitis were diagnosed in 52, 133, and 30 cases, respectively (Tables 1, 2). Of these 215 cases, 72 cases fulfilled criterion 1 (Charcot's triad) and 143 cases fulfilled criterion 2 (Table 2). The ratio of patients categorized under criterion 1 to those categorized under criterion 1+ criterion 2 was significantly low for patients with mild cholangitis. Fifty-two patients with mild cholangitis were successfully treated without EBD (Fig. 1). EBD was performed in 133 patients with moderate cholangitis after failure of initial medical treatment. Several cases with assumed organ failure caused by factors unrelated to cholangitis presented with moderate disease: one case with PT-INR >1.5, who was treated with warfarin, and 14 cases with thrombopenia complicated by chronic

Table 1 Clinical characteristics of the patients with acute cholangitis

	Severity of acute cholangitis		
	Severe ($n = 30$)	Moderate ($n = 133$)	Mild ($n = 52$)
Age (mean ± SD)	68.2 ± 9.1	64.5 ± 11.5**	71.5 ± 10.1**
Gender (male/female)	21/9	81/52	36/16
Body temperature >38 °C or <36° (yes/no)	17/13	65/68§	8/44§
WBC count >12000 or <4000/μl (yes/no)	13/17	39/94	11/41
CRP (mg/dl)	9.3 ± 7.8*	5.1 ± 5.7*	4.0 ± 4.5
Serum albumin (g/dl)	2.9 ± 0.7§	3.5 ± 0.7**,§	3.8 ± 0.5**
AST (IU/l)	211.3 ± 254.9	253.3 ± 256.1	228.8 ± 197.5
ALT (IU/l)	140.4 ± 138.6	201.7 ± 241.2	197.63 ± 176.6
ALP (IU/l)	1107.3 ± 914.5	1093.7 ± 741.2	880.4 ± 865.9
T. bilirubin (mg/dl)	7.6 ± 7.1	5.0 ± 5.3§	2.5 ± 1.9§
Organ dysfunction			
Hypotension requiring dopamine ≥5 μl/kg per min or any dose of dobutamine (yes/no)	19/11§	0/133§	0/52
Disturbance of consciousness (yes/no)	17/13§	0/133§	0/52
PaO_2/FiO_2 ratio <300 (yes/no)	9/21§	0/133§	0/52
Serum creatinine >2.0 mg/dl (yes/no)	4/26**	0/133**	0/52
PT-INR >1.5 (yes/no)	17/13§	1/132§	0/52
Platelet count <100000/μl (yes/no)	16/14§	14/129§	0/52

* $p = 0.007$, ** $p = 0.001$, § $p < 0.001$

Table 2 Proportion of criterion 1 (Charcot' triad) in mild, moderate and severe cholangitis

Severity	n	Criterion1 Charcot's triad		Criterion2 "inflammatory response" and "biliary obstruction"
Mild	52	4 (7.7%)	*	48
Moderate	133	53 (39.8%)		80
Severe	30	15 (50%)	*	15
Total	215	72(33.5%)		143

* $p < 0.001$

liver disease (Table 1). Severe cholangitis was diagnosed in 30 cases because of the presence of organ/system dysfunction (cardiovascular, nervous, respiratory system, kidney, liver, or hematological systems). Mean CRP level in patients with severe cholangitis is significantly higher compared to those in patients with moderate (Table 1). ROC analysis revealed that CRP level ≥5.0 mg/dl had a sensitivity of 60.0 % and a specificity of 66.9 % in differentiating severe cholangitis from moderate (Fig. 2).

Acute cholangitis developed during hospitalization in 104 patients, of whom 45 (43.2 %) had been admitted to other departments (mainly surgery). In our hospital, EBD was performed in the Department of Gastroenterology and Clinical Oncology for all cases. One hundred-eleven cases were outpatients or transfers from outlying hospitals. For these cases, the initial medical treatment period was calculated from the beginning of therapy in any hospital or hospital department. In cases unresponsive to conservative medical therapy before visiting our department, the severity of acute cholangitis was judged to be moderate at the time of admission.

The various etiologies identified for acute cholangitis examined in this study are listed in Table 3 (benign/malignant 109/106). Of the 106 cases with malignancy, 71 developed acute cholangitis due to dysfunction of a previously placed tube or metal stent. Early biliary drainage (EBD or PTBD) was performed in all 163 cases with moderate or severe acute cholangitis (Fig. 1). The overall success rate of EBD (within 48 h) was 98.1 % (160/163). EBD was performed successfully in 156/163 (95.7 %) cases. Urgent EBD (within 12 h of onset), early EBD (within 24 h of onset), and relatively early EBD (within

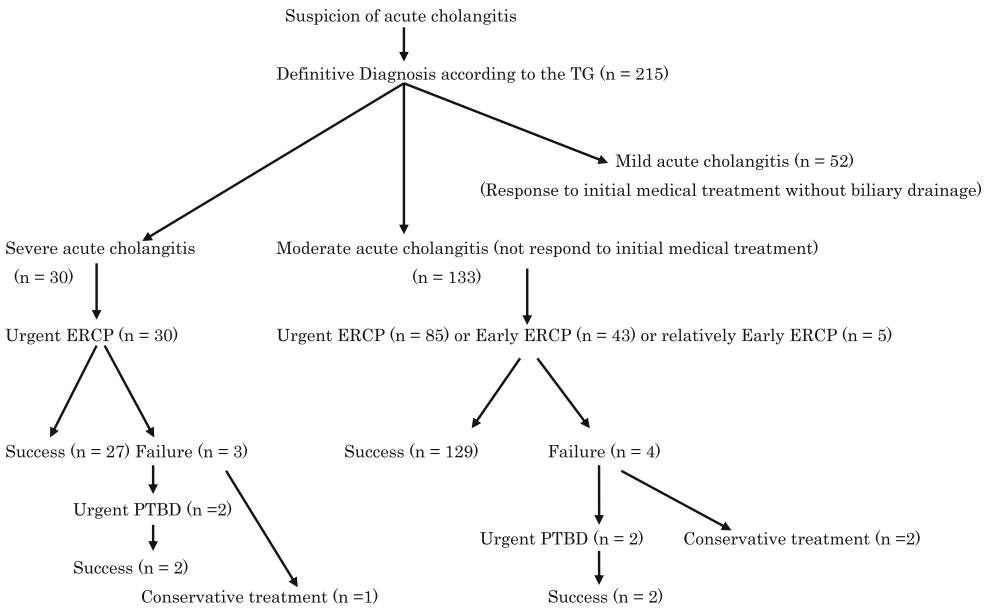

Fig. 1 Flow chart of the diagnosis and treatment of acute cholangitis in this study

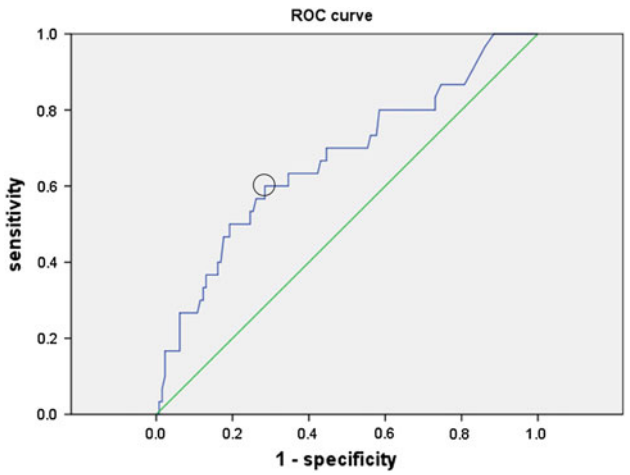

Fig. 2 Receiver operating characteristic analysis of CRP level in differentiating severe cholangitis from moderate. Area under the curve: 0.670 (95 %: 0.557–0.782); $p = 0.004$. The optimal cut-off value for predicting mortality in patients with acute cholangitis was 5.0, which yielded a sensitivity of 60.0 % and a specificity of 66.9 % (*circle*)

48 h of onset) were performed in 115, 43, and five cases, respectively. EBD failed in seven cases, of which four were successfully treated by urgent PTBD and two responded at a later stage to conservative medical treatment and elective endoscopic treatment. In the remaining patient, advanced hepatocellular cancer was complicated by uncontrolled bleeding and liver failure, and this patient died 4 days after failure of EBD. No major procedure-related complications such as post-EBD pancreatitis, bleeding, or perforation were observed.

Predictors of mortality

Risk factors for acute cholangitis were analyzed in 215 cases of acute cholangitis. The overall mortality rate was 4.2 % (9/215). Mortality rates in patients with mild, moderate, and severe cholangitis were 0 % (0/52), 2.3 % (3/133), and 20.0 % (6/30), respectively (moderate vs. severe, $p = 0.001$). Death occurred because of uncontrolled septicemia ($n = 5$) and liver failure ($n = 4$) as complications of persistent cholangitis. In all other cases except the one with advanced hepatocellular cancer complicated by uncontrolled bleeding, urgent biliary drainage within 24 h of admission proved successful. Malignant ($n = 6$) and benign ($n = 3$) biliary obstruction was also observed in the nine cases that failed to survive (Table 4). ROC analysis revealed that serum albumin level $\leq$2.8 mg/dl had a sensitivity of 83.5 % and a specificity of 88.9 % in predicting death from acute cholangitis (Fig. 3). Mean serum albumin level in patients with malignant diseases is significantly lower compared to those in patients with benign diseases (Table 5). However, a univariate analysis did not identify an association between hypoalbuminemia and host-related factors such as etiology (malignant), age ($\geq$75 years), inpatient status and stent dysfunction (Table 6). Univariate analysis of the factors associated with mortality revealed six influential factors (Table 7): serum albumin level $\leq$2.8 mg/dl, hypotension, disturbance of consciousness, PaO_2/FiO_2 ratio <300, PT-INR >1.5 and platelet count <100000/μl. According to multivariate analysis, serum albumin levels $\leq$2.8 g/dl and PT-INR >1.5 were statistically significant predictors of mortality (Table 8).

Table 3 Etiologies of cholangitis observed in this study

Etiologies	*n*	Severity of acute cholangitis		
		Severe ($n = 30$)	Moderate[a] ($n = 133$)	Mild[a] ($n = 52$)
Malignant diseases	106 (71)[b]	13 (8)	90 (63)	2
Pancreatic head cancer	49 (40)	4 (3)	44 (37)	1
Biliary tract cancer	43 (31)	9 (5)	33 (26)	1
Hepatocellular cancer	5		4	
Periampullary cancer	3		3	
Malignant lymphoma	1		1	
Others	5		5	
Benign diseases	109 (7)	17 (1)	43 (6)	50
Choledocholithiasis	90 (2)	8	32 (2)	50
Chronic pancreatitis	6 (5)	1 (1)	5 (4)	
Benign biliary stricture	4	1	3	
Primary sclerosing cholangitis	5	3	2	
Hepatolithiasis	3	2	1	
Hemobilia (liver cirrhosis)	1	1		

[a] Number of cases with malignant diseases in moderate cholangitis are significantly higher than that in mild cholangitis ($p < 0.001$)

[b] Stent in situ

Table 4 Etiologies of cases that failed to survive ($n = 9$)

Malignant diseases	
Pancreatic head cancer	3
Bile duct cancer	1
Hepatocellular cancer	2
Benign diseases	
Decompensated liver cirrhosis	1
Primary sclerosing cholangitis[a]	1
Hepatolithiasis[a]	1

[a] Complicated with secondary biliary cirrhosis in end-stage liver disease

Predictors of refractory cholangitis

Average (±SD) and median values for the duration of hospitalization were 16.3 (±23.5) days and 6 days, respectively. When refractory cholangitis was defined on the basis of prolonged hospitalization for >28 days or disease resulting in fatality, 57 cases (26.5 %) were identified as refractory (48 cases: hospital stay >28 days, nine fatal cases).

Results of the univariate analysis are listed in Table 9. Univariate analysis identified nine factors associated with refractory cholangitis: hypotension, disturbance of consciousness, oxygenation index values <300, serum albumin level ≤2.8 g/dl, PT-INR >1.5, platelet count <100000/μl, etiology (malignant), inpatient status, and stent dysfunction. In the multivariate analysis, serum albumin level ≤2.8 g/dl, PT-INR >1.5, etiology (malignant), and inpatient status were significant predictors of refractory cholangitis (Table 10).

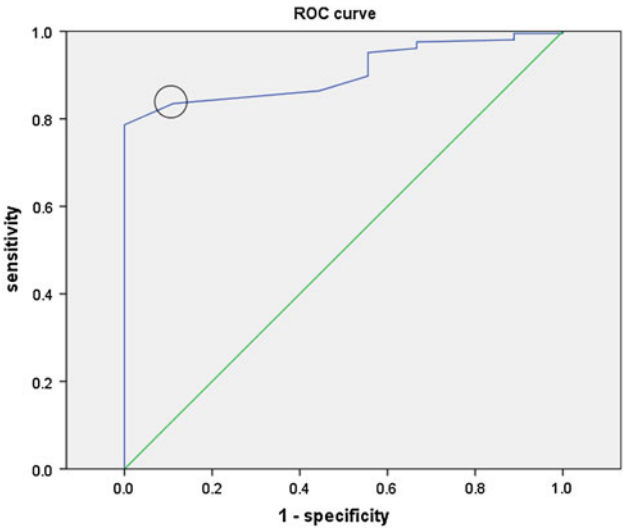

Fig. 3 Receiver operating characteristic analysis of serum albumin level as a predictor of mortality in patients with acute cholangitis. Area under the curve: 0.905 (95 %: 0.852–0.959); $p < 0.001$. The optimal cut-off value for predicting mortality in patients with acute cholangitis was 2.80, which yielded a sensitivity of 83.5 % and a specificity of 88.9 % (*circle*)

Discussion

No standard criteria were established for the diagnosis and assessment of severity of acute cholangitis until the TG07 were published in January 2007 [5, 6]. The guidelines clearly state that severe acute cholangitis is that which is complicated with organ dysfunction. The TG07 recommend urgent EBD as first-line therapy in cases with severe cholangitis [7, 8]. In the present study, assessment of the severity of acute cholangitis was significantly related to

Table 5 Comparison between the mean values of individual parameters in benign diseases and malignant diseases

	Benign ($n = 109$)	Malignant ($n = 106$)	p value
Age (mean ± SD)	69.2 ± 10.2	64.3 ± 11.8	0.001
Serum albumin (g/dl)	3.6 ± 0.7	3.4 ± 0.7	0.002
AST (IU/l)	276.9 ± 270.5	182.9 ± 199.5	0.004
ALT (IU/l)	207.4 ± 117.1	176.5 ± 248.4	0.296
T. bilirubin (mg/dl)	3.9 ± 3.7	5.7 ± 6.3	0.011
PT-INR >1.5 (yes/no)	10/99	8/98	0.807
Platelet count <100000/μl (yes/no)	19/90	13/93	0.340

Table 6 Results of univariate analysis with regard to hypoalbuminemia

	Serum albumin (g/dl)		p value	OR (95 % CI)
	≤2.8 ($n = 40$)	>2.8 ($n = 175$)		
Hypotension requiring dopamine ≥5 μl/kg per min or any dose of dobutamine (yes/no)	10/30	9/166	<0.001	6.148 (2.305–16.396)
Disturbance of consciousness (yes/no)	11/29	6/169	<0.001	10.684 (3.665–31.144)
PaO2/FiO2 ratio <300 (yes/no)	7/33	2/173	<0.001	18.348 (3.649–92.251)
Serum creatinine >2.0 mg/dl (yes/no)	2/38	2/173	0.158	4.553 (0.622–33.344)
PT-INR >1.5 (yes/no)	12/28	6/169	<0.001	12.071 (4.189–34.788)
Platelet count <100000/μl (yes/no)	16/24	16/159	<0.001	6.625 (2.932–14.969)
WBC count >12000 or <4000/μl (yes/no)	11/29	51/124	1.000	0.922 (0.428–1.985)
CRP ≥5 mg/dl (yes/no)	24/16	57/118	0.002	3.105 (1.531–6.298)
T-Bil ≥5 mg/dl (yes/no)	22/18	94/81	1.000	1.053 (0.528–2.100)
Body temperature >38 or <36 °C (yes/no)	21/19	69/106	0.156	1.698 (0.851–3.387)
Etiology (malignant/benign)	24/16	82/93	0.162	1.701 (0.846–3.422)
Age ≥75 years (yes/no)	10/30	47/128	1.000	0.908 (0.412–2.000)
Inpatient/Outpatient	25/15	79/96	0.055	2.025 (1.000–4.103)
Stent dysfunction (yes/no)	15/25	63/112	1.000	1.067 (0.524–2.171)
Death/alive	8/32	1/174	<0.001	43.500 (5.259–359.791)

Table 7 Results of univariate analysis with regard to mortality

Factor	Death ($n = 9$)	Alive ($n = 206$)	p value	OR (95 % CI)
Hypotension requiring dopamine ≥5 μl/kg per min or any dose of dobutamine (yes/no)	4/5	15/191	0.004	10.197 (2.474–41.972)
Disturbance of consciousness (yes/no)	5/4	12/194	<0.001	20.208 (4.796–85.145)
PaO_2/FiO_2 ratio <300 (yes/no)	3/6	6/200	0.004	16.667 (3.344–83.072)
Serum creatinine >2.0 mg/dl (yes/no)	0/9	4/202	1.000	0.957 (0.930–0.985)
PT-INR >1.5 (yes/no)	7/2	11/195	<0.001	62.045 (11.509–334.498)
Platelet count <100000/μl (yes/no)	4/5	28/178	0.030	5.086 (1.287–20.091)
WBC count >12000 or <4000/μl (yes/no)	4/5	58/148	0.284	2.041 (0.530–7.870)
CRP ≥5 mg/dl (yes/no)	6/3	75/131	0.084	3.494 (0.849–14.375)
Serum albumin level ≤2.8 g/dl (yes/no)	8/1	32/174	<0.001	43.500 (5.259–359.751)
T-Bil ≥5 mg/dl (yes/no)	6/3	93/113	0.307	0.412 (0.100–1.690)
Body temperature >38 °C or <36 °C (yes/no)	3/6	87/119	0.737	0.684 (0.166–2.810)
Etiology (malignant/benign)	4/5	105/101	0.746	1.300 (0.399–4.977)
Age ≥75 years (yes/no)	2/7	55/151	1.000	0.784 (0.158–3.891)
Inpatient/outpatient	5/4	99/107	0.742	1.351 (0.353–5.175)
Stent dysfunction (yes/no)	4/5	74/132	0.726	1.427 (0.372–5.497)

mortality. Therefore, severe acute cholangitis, i.e., cholangitis accompanied by organ dysfunction, should be treated immediately using EBD, as recommended by the TG07.

Before the TG07 were published, Charcot's triad (criterion 1) was recognized as the definitive criterion for diagnosing acute cholangitis. The accuracy rate of Charcot's triad as a diagnostic criterion was reported to be up to 72 % [5]. In the present study, the overall incidence of Charcot's triad was relatively low (33.4 %, 72/215). Moreover, the incidence of Charcot's triad increased according to disease severity (mild, moderate, severe; 7.7 vs. 39.8 vs. 50 %, respectively; $p < 0.001$). Therefore, the incidence of Charcot's triad may depend on the severity of acute cholangitis. Similarly, CRP value may be a useful factor in severity assessment of cholangitis as shown in that of acute pancreatitis [9], however, cut-off value (CRP ≥5.0 mg/dl) based on the ROC analysis did not show ideal sensitivity or specificity. Theoretically, mild cholangitis should account for the largest proportion of cases; however, in this study, more cases of moderate cholangitis were observed. In some cases, mild cholangitis may have resolved on its own before detection, leading to underdiagnosis. In addition, information on physical findings, laboratory results, or imaging may have been lost or not examined when acute cholangitis was not considered as part of the differential diagnosis.

Assessments of disease severity according to the TG07 have an important limitation: the definition of moderate cholangitis is vague. Moderate cholangitis is defined as disease unresponsive to initial conservative medical treatment, meaning that a conclusive severity assessment must be deferred until conservative treatment fails. From the clinical point of view, more reliable markers are required for predicting the deterioration of cholangitis. The results of this study showed that hypoalbuminemia (≤2.8 g/dl) and increased PT-INR (>1.5) were statistically significant predictors of mortality. According to the TG07, increased PT-INR occurs because of organ dysfunction. In such cases, urgent biliary drainage is recommended. However, hypoalbuminemia is listed as only one of many prognostic factors [3–5]. Hypoalbuminemia, which is a host-related risk factor, has been shown to have an adverse effect on outcome in patients with or without acute cholangitis requiring emergency surgery for intra-abdominal infection [10, 11]. In cases of acute cholangitis with hypoalbuminemia but without organ dysfunction, early endoscopic drainage should be performed without waiting for the outcome of conservative medical treatment. In the current study, host-related factors associated with hypoalbuminemia were not clarified. Future research should explore this issue.

Previous reports that analyzed cases of severe acute cholangitis documented various risk factors and advocated their own scoring systems [12–15]. The most common

Table 8 Multivariate analysis with regard to mortality

Variables	Odds ratio	(95 % CI)	*p* value
Serum albumin level ≤2.8 g/dl	15.9	(1.7–142.9)	0.017
PT-INR >1.5	22.7	(3.7–142.9)	0.001

Table 9 Results of univariate analysis with regard to refractory cholangitis

Factor	Refractory ($n = 57$)	Not refractory ($n = 158$)	*p* value	OR (95 % CI)
Hypotension requiring dopamine ≥5 μl/kg per min or any dose of dobutamine (yes/no)	11/46	8/150	0.002	4.484 (1.702–11.813)
Disturbance of consciousness (yes/no)	9/48	8/150	0.019	3.516 (1.285–9.617)
PaO_2/FiO_2 ratio <300 (yes/no)	6/51	3/155	0.012	6.078 (1.467–25.186)
Serum creatinine >2.0 mg/dl (yes/no)	1/56	3/155	1.000	0.923 (0.094–9.054)
PT-INR >1.5 (yes/no)	10/47	8/150	0.009	3.989 (1.489–10.691)
Platelet count <100000/μl (yes/no)	12/45	20/138	0.134	1.840 (0.834–4.058)
WBC count >12000 or <4000/μl (yes/no)	14/43	48/110	0.496	0.746 (0.374–1.490)
CRP ≥5 mg/dl (yes/no)	21/36	60/98	1.000	0.953 (0.509–1.783)
Serum albumin level ≤2.8 g/dl (yes/no)	20/37	20/138	0.001	3.730 (1.819–7.649)
T-Bil ≥5 mg/dl (yes/no)	38/19	78/80	0.030	2.051 (1.089–3.863)
Body temperature >38 or <36 °C (yes/no)	23/34	67/91	0.876	0.919 (0.496–1.701)
Etiology (malignant/benign)	44/13	62/96	<0.001	5.241 (2.612–10.514)
Age ≥75 years (yes/no)	14/43	43/115	0.730	0.871 (0.433–1.749)
Inpatient/outpatient	44/13	60/98	<0.001	5.528 (2.753–11.101)
Stent dysfunction (yes/no)	30/27	48/110	0.004	2.546 (1.369–4.737)

Table 10 Multivariate analysis with regard to refractory cholangitis

Variables	Odds ratio	(95 % CI)	*p* value
Serum albumin level ≤2.8 g/dl	2.4	(1.02–5.56)	0.045
PT-INR >1.5	4.8	(1.39–16.39)	0.013
Etiology (malignant)	4.3	(1.94–9.43)	<0.001
Inpatient	4.3	(1.96–9.35)	<0.001

etiology of severe acute cholangitis in those studies was choledocholithiasis. In contrast, malignant disease was the most common etiology of moderate and severe cholangitis in the present study (63.8 %, 104/163). In total, 67 % cases (71/106) with malignant biliary strictures in the present study had previously received in situ plastic or metal stent implantation. Recent developments in chemotherapy for advanced pancreatic or biliary cancer have improved survival with the help of endoscopic stent placement. Although studies have compared the patencies of various stents [16, 17], few make mention of the frequency of stent-associated acute cholangitis and its management [18]. Patients with biliary stents placed in situ are at a higher risk of septic acute cholangitis compared with those without stents [19]. Our results showed that both stent dysfunction and etiology (malignant) were not significant predictors of mortality. In the present study, all cases with stent dysfunction were included under the category of moderate or severe cholangitis following immediate biliary drainage. Early EBD may prevent further deterioration of cholangitis, even in such high-risk patients.

In this study, 48 cases required >28-day hospitalization after having received EBD. Survival in these cases may be attributed to immediate biliary drainage following intensive conservative medical treatment. Multivariate analysis in our study showed that increased PT-INR, hypoalbuminemia, etiology (malignancy), and inpatient status were significant risk factors for refractory cholangitis. All predictors except increased PT-INR were host-related factors. Therefore, when acute cholangitis develops in a hospital inpatient with hypoalbuminemia or malignancy, EBD should be performed.

The limitations of this study were that it was retrospective and conducted on a small number of cases at a single institution.

In conclusion, severe acute cholangitis, defined as cholangitis complicated with organ dysfunction, should be treated immediately using EBD, as recommended by the TG07. For cases of acute cholangitis with hypoalbuminemia but without accompanying organ dysfunction, early EBD should be performed without waiting for a response to conservative medical treatment. A multicenter prospective study should be undertaken to confirm the usefulness of hypoalbuminemia as a predictor of poor outcome.

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