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The Clinical Comparison Between Tokyo Guidelines and A Novel Auxiliary Scoring System in Guiding the Urgent Drainage of Acute Cholangitis

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1. Abstract

Background. To assess the predictive power of Tokyo Guidelines (TG)18/13 and TG07 for the urgent drainage of Acute Cholangitis (AC) and establish a novel auxiliary scoring system that could be a supplement to the guidelines described above. Methods. A total of 197 patients diagnosed with AC were retrospectively studied and the time interval from admission to urgent drainage was considered as the dependent variable, while a series of factors were considered as the independent variables. Results. Five factors including platelet count<170.0*109/L, serum albumin<25.1 g/dL, total bilirubin>3.13 mg/dL, direct bilirubin>0.81 mg/dL and Charcot's triad were identified as significant predictive factors for urgent drainage. According to the above results, a new scoring system was established and evaluated. The results indicated that combination of the new scoring system with TG18/13 showed feasible performance for urgent drainage. Survival analysis indicated that patients with a positive indication in the combination of the new scoring system and TG18/13 would expect to have a greater benefit than those with a positive indication in TG18/13 alone. Conclusions. Our study provided a new scoring system for early evaluation of AC, which could be a significant supplement to TG18/13.

2. Introduction

Acute Cholangitis (AC) is a clinical syndrome first reported by Charcot in 1877[1]. With the development of medical technology, AC is no longer a severe fatal disease. However, it can still be a burden for clinical therapy due to its characteristics of hidden onset and rapid deterioration. According to recent studies, the mortality rates range from 8% to 10% [2,3]. Therefore, a convenient and accurate evaluation system is required in clinical practice.

The diagnosis of AC is mainly based on Charcot's triad (right upper abdominal pain, fever and jaundice) or Reynold's pentad (Charcot's triad combined with mental confusion and shock) [4], which were thought to be inadequate and controversial. There were no widely recognized diagnostic criteria or evaluating systems for AC until the publication of Tokyo Guidelines 2007 (TG07) [5]. TG07 was the first clinical practice guideline primarily for AC worldwide,

which provided a standard for the diagnosis (Table 1), classification (Table 2) and treatment of AC. However, clinical application revealed that TG07 was a diagnostic criteria deficient in sensitivity and specificity with difficulties in the severity classification process for AC [6,7]. Thus, an improved version of TG07 was published in Tokyo in 2013, which was known as Tokyo Guideline 2013 (TG13) [8]. On this basis, combined with a large amount of medical evidence and numerous expert opinions worldwide, TG13 was revised and improved into a new version, known as Tokyo guideline 2018 (TG18) [9]. TG18 was divided into 10 parts, mainly related to background formation, diagnosis of AC (Table 1), severity grading (Table 2), application of antibiotics, selection of biliary drainage techniques, medical treatment process, etc. TG18 still used the diagnostic criteria and severity grading of TG13 for AC. For the first time, this guideline introduced the Charlson Comorbidity Index (CCI) and the American Society of Anesthesiologists Physical Status (ASA-PS) into the diagnosis and treatment flow chart for AC. Additionally, a series of special techniques used in endoscopic bile duct drainage were first mentioned in TG18. However, there were still shortcomings in TG18/13, especially in guiding the choice of urgent drainage.

Therefore, our study focused on the choice and indications of urgent drainage within the first 24h after admission based on an evaluation and comparison of the predictive value of TG18/13 and TG07, and our aim is to provide a more optimized solution to the TG18 system as a useful complement to it.

Table 1: Diagnostic criteria of TG07 and TG18/13 for acute cholangitis

Diagnostic criteria	TG18/13	TG07
A	A1. Fever[1] and/or shaking chills	A1. History of biliary disease
	A2.Laboratory data: evidence of inflammatory response[3]	A2. Fever[1] and/or chills
		A3. Jaundice[2]
		A4. Abdominal pain
B	B1. Jaundice[2]	B1. Inflammatory response[4]
	B2. Laboratory data: abnormal liver function tests[6]	B2. Abnormal liver function tests[5]
C	C1. Biliary dilatation	C1. Biliary dilation or evidence of an aetiology (stricture, stone, stent, etc.)
	C2. Evidence of the etiology on imaging (stricture, stone, stent etc.)	
Suspected diagnosis	one item in A + one item in either B or C	one item in A + one item in either B or C
Definite diagnosis	one item in A, one item in B and one item in C	Charcot's triad(A2+A3+A4)
		Two or more items in A+ both items in B and item C

[1]Body temperature >38^{0}C; [2]T-Bil ≥2mg/dL ; [3]WBC(10^9/L) <4 or >10 or C-reactive protein (CPR) >1mg/dL; [4]WBC(10^9/L) >10 or elevated CPR;[5]Elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) or gamma-glutamyl transferase (γ-GT);[6]AST >1.5 upper limit of normal value (STD), ALT >1.5 STD, ALP >1.5 STD or γ-GT >1.5 STD, STD: lower limit of normal value.

Table 2: Severity assessment criteria of TG07 and TG18/13 for acute cholangitis

Severity criteria	TG18/13	TG07
Severe	At least in any one of the following organs/systems:	In the following two points:
	1.Cardiovascular dysfunction: hypotension requiring dopamine ≥5 μg/kg per min, or any dose of norepinephrine	1.organ or system dysfunction: yes
		2.initial treatment: noneffective
	2.Neurological dysfunction: disturbance of consciousness	
	3.Respiratory dysfunction: PaO2/FiO2 ratio <300	
	4.Renal dysfunction: oliguria, serum creatinine >2.0 mg/dL	
	5. Hepatic dysfunction: PT-INR >1.5	
	6. Hematological dysfunction: platelet count <100,000/mm3	
Moderate	Any two of the following conditions:	In the following two points:
	1.Abnormal WBC count >12,000/mm3, <4,000/mm3	1.organ or system dysfunction: no
	2. High fever (≥39°C)	2.initial treatment: noneffective
	3. Age ≥75 years old	
	4.Hyperbilirubinemia (total bilirubin ≥5 mg/dl)	
	5. Hypoalbuminemia <STD1×0.7	
Mild	Without criteria for severe or moderate acute cholangitis	In the following two points:
		1.organ or system dysfunction: no
		2.initial treatment: effective

PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PT-INR, prothrombin time-international normalised ratio;[1]STD, lower limit of normal value.

3. Methods

This study is a single-center observational cohort study. A total of 197 patients diagnosed with AC were retrospectively examined. 8 patients died during hospitalization, and the remaining 189 patients were observed in this study, including 91 patients in the Derivation Group (DG) hospitalized from May 30, 2015 to December 31, 2017 and 98 patients in the Validation Group (VG) hospitalized from January 1, 2018 to June 15, 2019 at Shandong Provincial Qianfoshan Hospital Affiliated to Shandong University. The specific grouping method is shown in Figure 1. All patients observed in this study had to meet the following conditions: (1) evidence of purulent bile, useful biliary tract drainage, or clinical remission after antibiotic treatment and no other site infection (which was also the diagnostic criteria of AC); (2) the development and selection of all treatment plans were based on the clinical judgment of competent doctors who were excluded from this study and the agreement of the patients or their guardians.

Urgent drainage in this study was performed in the first 24h of hospitalization by experienced senior doctors from Shandong Provincial Qianfoshan Hospital Affiliated to Shandong University. 62 patients underwent Endoscopic Retrograde Cholangiopancreatography (ERCP), but Post-ERCP Pancreatitis (PEP) occurred in 4 patients and bleeding occurred in 1 patient. Because of the adverse events, we also adopted Percutaneous Transhepatic Biliary Drainage (PTBD) and laparoscopic or traditional surgery for drainage. The factors were observed and analyzed in this study during patient hospitalization, including baseline information, clinical symptoms, laboratory tests, drainage timing and Length of Hospital Stay (LOS) (Table 3). All patients involved were divided into an Urgent Drainage Group (UDG) and a Nonurgent Drainage Group (NUDG) according to the application of urgent drainage.

Table 3: Baseline characteristics of patients with acute cholangitis on admission

	Derivation group			Validation group		
	Urgent drainage (n=15)	Nonurgent drainage (n=76)	*P** value	Urgent drainage (n=22)	Nonurgent drainage (n=76)	*P** value
Age (years, mean ± SD)	69.93±11.06	67.67±11.25	0.477	67.36±12.35	62.61±14.85	0.174
Gender (male/female)	8-Jul	39/37	0.742	14/8	34/42	0.118
Body temperature(0C)	38.59±1.05	38.08±1.15	0.11	38.58±1.15	37.23±1.19	＜0.001‡
Heart rate	93.53±15.88	85.92±17.18	0.116	85.05±14.06	82.00±10.63	0.276
Breathing rate	21.73±3.69	20.22±3.26	0.112	21.82±3.70	19.95±2.33	0.033†
WBC count (10^9/L)	13.07±6.07	9.43±5.77	0.029†	14.35±6.33	7.37±4.97	＜0.00¹‡
NEUT count (10^9/L)	11.81±6.14	7.95±6.12	0.028†	12.70±5.90	5.24±4.31	＜0.001‡
NEUT%	87.99±10.23	73.40±19.03	＜0.00¹‡	87.20±8.04	66.54±15.13	＜0.001‡
Platelet count (10^9/L)	153.47±76.75	212.39±94.72	0.026†	223.68±130.38	245.28±101.06	0.412
Serum albumin (g/dL)	33.09±8.88	37.33±5.85	0.094	36.46±5.57	39.72±5.51	0.017†
ALP (U/L)	181.67±86.02	235.32±240.30	0.397	213.52±103.52	212.67±174.99	0.983
γGT (U/L)	390.75±259.02	439.81±485.05	0.705	468.68±336.58	424.19±499.89	0.696
ALT (U/L)	200.07±151.35	140.40±151.20	0.166	195.93±199.49	127.07±156.66	0.092
AST (U/L)	208.93±183.39	123.13±193.18	0.117	198.29±262.08	85.69±99.49	0.061
Total bilirubin (mg/dL)	6.56±5.85	3.59±4.08	0.019†	5.24±5.56	3.50±4.64	0.141
Direct bilirubin (mg/dL)	4.38±4.93	2.40±3.06	0.043†	4.08±4.81	2.70±4.20	0.194

BUN (mmol/L)	7.81±5.87	6.34±5.16	0.328	7.44±4.17	4.40±1.78	0.003†
Cr (umol/L)	81.49±52.65	72.93±50.04	0.55	90.04±58.01	64.01±20.91	0.051
PT (s)	12.82±1.49	12.71±2.30	0.855	12.72±1.60	11.61±1.21	0.005†
INR	1.12±0.12	1.09±0.20	0.533	1.09±0.12	1.01±0.11	0.003†
Charcot's triad	9	17	0.008†	13	5	＜0.001‡
Reynold's pentad	1	3	0.52	0	1	0.224
Abdominal pain	12	46	0.152	21	39	＜0.001‡
SIRS	9	38	0.479	15	24	0.002†
TG07						
classification standard						
I	1	32		7	61	
II	10	33		12	11	
III	4	11		3	4	
TG18/13						
classification standard						
I	2	53		4	62	
II	9	12		15	10	
III	4	11		3	4	

*The *P* value is calculated by t-test (for continuous variables) and Chi-square test (for categorical variables)

WBC count, white blood cell count; NEUT, neutrophil; NEUT%, neutrophil percentage; ALP, alkaline phosphatase; γ-GT, gamma- glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatine; PT, prothrombin time; INR, international normalised ratio; SIRS, systemic inflammatory response syndrome; TG, Tokyo guidelines.

"† " is used to indicate a significant difference.

"‡ " is used to indicate a highly significant difference.

4. Statistical Analysis

Descriptive statistical methods were used, with continuous variables using mean ± Standard Deviation (SD) and categorical variables using percentage (%). The t-test was used for continuous variables with skewed distributions, and the chi-square test was used to compare categorical variables. Univariate and multivariate logistic regression analyses were used to select the significant factors. A Receiver Operator Characteristic (ROC) curve and a z-test were used to estimate the specificity of different evaluation systems. The cut-off values were determined by a ROC curve. A survival analysis was used to further validate the clinical value of the combination of the new scoring system with TG18/13. All statistical analyses described above were conducted by SPSS 22.0 (IBM, Chicago, IL, USA), and the results were considered statistically significant with a P-value of less than 0.05. Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) were applied.

5. Results

In the present study, 189 patients diagnosed with AC were observed, including 91 patients in the DG and 98 patients in the VG. The baseline characteristics of the patients enrolled are summarized in Table 3. In addition, every patient enrolled was graded according to TG18/13 and TG07, and the specific classification is also shown in Table 3. We used LOS as the endpoint for logistic regression analysis. The median LOS in each group was analyzed. The therapeutic schedule (including opportunity for biliary drainage) of patients with an LOS less than the median LOS was considered effective and appropriate.

5.1. Results of the Logistic Regression Analysis

Through univariate analysis, the following five factors were found to be statistically significant: total bilirubin (HR 1.212, 95% CI 1.022-1.438, p=0.027), direct bilirubin (HR 1.265, 95% CI 1.010-1.584, p=0.041), platelet count (HR 0.989, 95% CI 0.978-0.999, p=0.038), serum albumin (HR 0.862, 95% CI 0.762-0.976, p =0.019), Charcot's triad (HR 19.800 95% CI 3.094-126.714, p=0.002).

Incorporated the above five factors into multivariate analysis and found one factor associated with acute drainage: Charcot's triad (HR 19.800 95% CI 3.094-126.714, p=0.002).

5.2. The Establishment of the New Scoring System

The ROC curve was used to calculate the cut-off values for continuous variables, and the results are shown in Table 4 as follows: platelet count<170.0*109/L, serum albumin<25.1 g/dL, total bilirubin>3.13 mg/dL, direct bilirubin>0.81 mg/dL. According to the results above, a new scoring system was established with a maximum score of 6 points, which was expected to be significant for guiding the choices of urgent drainage. Four factors were assigned 1 point according to the identification of univariate analysis, including platelet count<170.0*109/L, serum albumin<25.1 g/dL, total bilirubin>3.13 mg/dL, and direct bilirubin>0.81 mg/dL. Additionally, Charcot's triad would be assigned 2 points for statistical

significance in multivariate analysis. Thus, a new scoring system was established and is shown in Table 4. According to the results of the ROC curve, point 2.5 served as a cut-off value, and urgent drainage was considered beneficial among patients who received points greater than or equal to 3.0.

5.3. Evaluation of TG07, TG18/13 and the New Scoring System in Guiding Urgent Drainage

A total of 98 patients hospitalized from January 1, 2018 to June 15, 2019 were enrolled in the VG, and their data were used to evaluate the clinical value of TG07, TG18/13 and the new scoring system in guiding urgent drainage. Among patients with an effective therapeutic schedule (whose LOS was less than the median LOS in the VG), the results of the ROC curve (Figure 2) indicated that combination of TG18/13 and the new scoring system had a higher sensitivity and approximate specificity than both TG07 and TG18/13 in assessing the necessity of urgent drainage (Table 5). The Area Under The Curve (AUC) of the new scoring system in the ROC curve was 0.765 (95% CI 0.584-0.946), the AUC of TG07 was 0.697 (95% CI 0.508-0.887) and the AUC of TG18/13 was 0.781 (95% CI 0.610-0.952), which were all significantly less than the AUC of the combination of the new scoring system with TG18/13 (P<0.001 vs. TG07 and P=0.038 vs. TG18/13) (Table 5).

To further validate the clinical value of the combination of new scoring system and TG18/13, survival analysis was conducted among all VG patients. As shown in Figure 3, patients with a positive indication in either TG18/13 (grade II/III) or the combination of the new scoring system with TG18/13 (new scoring system points>2.5 or TG18/13 grade II/III) would benefit from urgent drainage, expressed as a shorter LOS. In addition, patients with a positive indication in the combination of the new scoring system with TG18/13 would expect to have a greater benefit than that of patients with a positive indication in TG18/13 alone (P=0.003, x^2=8.907 vs. P=0.008, x^2=6.969).

Table 4: The new scoring system in predicting urgent drainage

Factor	*P* value	HR	95%CI		Cut off value	Point
			Down	Up		
Platelet count	0.038	0.99	0.98	0.999	170.0*10_9/L	1
Serum albumin	0.019	0.86	0.76	0.976	25.1g/dL	1
Total bilirubin	0.027	1.21	1.02	1.438	3.13mg/dL	1
Direct bilirubin	0.041	1.27	1.01	1.584	0.81mg/dL	1
Charcot's triad	0.002	19.8	3.09	126.71		2*

*The *P* value, HR and 95%CI of Charcot's triad were calculated by multivariate analyses.

Table 5: Comparison of AUC,95%CI, sensitivity, and specificity between the TG07, TG18/13, the new scoring system, and the combination of the new scoring system with TG18/13

	AUC	95%CI		*P* value		Sensitivity	Specificity
		Down	Up	Vs.TG18/13	Vs.TG07		
Combination of new scoring system with TG18/13	0.89	0.78	1	0.038	＜0.001	0.917	0.868
New scoring system	0.77	0.58	0.95	0.789	0.279	0.583	0.947
TG18/13	0.78	0.61	0.95		0.169	0.667	0.895
TG07	0.7	0.51	0.89	0.169		0.5	0.895

TG, Tokyo guidelines.

6. Discussion

As a life-threatening systemic condition, AC is normally characterized by sterile bile infection and biliary obstruction [1]. Until now, biliary drainage is still a basic treatment for AC. Related research has reported that the timing of biliary decompression was advantageous in AC and that a delay in biliary drainage could lead to an increase in mortality [10-13]. According to TG18/13, patients classified as grade III needed urgent drainage, but there was no clear definition of urgent drainage. Thus, different opinions on the timing of urgent drainage were presented in various studies, and the first 12 h to 48 h after admission were proposed to be suitable for implementing urgent drainage [14-19]. This study focused on the exploration of the indications for urgent drainage within 24 h after admission. Patients who accepted drainage within 24 h after admission were enrolled in the UDG, and other patients were enrolled in the NUDG.

TG18/13 had a shortcoming that might underestimate the severity of some patients classified as grade I/II who required urgent drainage by Takayoshi Nishino et al [20]. Therefore, urgent drainage is also needed for grade I/II patients in clinical work, which would lead to a decrease in both LOS and cost. Therefore, this study attempted to devise a new scoring system to predict the requirement

for urgent drainage, which was expected to be a supplement to TG18/13 in guiding the choice of urgent drainage, especially in patients classified as grade I/II. We also verified the clinical applicability of TG07, TG18/13 and the new scoring system. Moreover, we discussed the improvement and deficiency of each system.

A number of studies have indicated that TG18/13 was more suitable for clinical work than TG07, which was much more helpful in judging the condition of AC patients and making timely treatments [21,22]. Studies have also found deficiencies in TG18/13 and have attempted to identify new predictors to improve TG18/13 in guiding urgent drainage [20,23-25]. According to the present study, heart rate, serum albumin, serum bilirubin, and prothrombin time were risk factors for urgent drainage [23]. However, another study suggested that the serum alanine aminotransferase level and the leukocyte count were predictive of the need for urgent drainage [24]. Hence, the current studies still have some differences in the risk factors for urgent drainage. In this study, five factors were confirmed to be associated with urgent drainage, including platelet count<170.0*109/L, serum albumin<25.1 g/dL, total bilirubin>3.13 mg/dL, direct bilirubin>0.81 mg/dL and Charcot's triad. According to the results of logistic analysis, Charcot's triad was assigned 2 points due to its statistical significance in multivariate analysis, and the other four factors, including total bilirubin, direct bilirubin, platelet count and serum albumin, were assigned 1 point due to the statistical significance in univariate analysis. Based on these findings, we devised a new scoring system to predict the choice of urgent biliary drainage as a supplement to TG18/13.

To verify the clinical value of the new scoring system, ROC curves were applied in the VG, and the results indicated that compared to TG18/13, the new scoring system had an approximate significance in guiding urgent drainage with an AUC of 0.765 versus 0.781 (P=0.789). In development, we discussed the clinical significance of combining the new scoring system with TG18/13. As the ROC curve showed, the combination of the two systems could provide a much more significant reference for the choice of urgent drainage, with a sensitivity of 91.7% and a specificity of 86.8% and a larger AUC (0.893) compared to that for TG18/13 (AUC=0.781, P=0.038) and TG07 (AUC=0.697, P<0.001). Additionally, the survival analysis indicated that the patients with a positive indication in the combination of the new scoring system with TG18/13 were expected to receive a greater benefit from urgent drainage than those with a positive indication in TG18/13. Based on the results described above, we suggested that the condition of an AC patient should be evaluated not only by TG18/13 but also by the new scoring system as a supplement. Analyses of the data obtained from these two assessment systems could be helpful for clinicians to design applicative plans of biliary drainage for AC patients.

However, this study also has some limitations. This study was based on a retrospective analysis conducted at a single center. To analyze the predictive value of clinical elements for urgent drainage and determine the prognosis of AC more accurately and objectively, randomized controlled trials enrolling many more patients and centers are required.

In conclusion, considering the rapid progress and the serious consequences of AC, urgent drainage at the right time is of great significance to its therapeutic effects. Through this study, we identified the predictive value of TG18/13 for urgent drainage compared to that for TG07 and established a new scoring system as a supplement to TG18/13. We hope that the results of this study will provide a reference for the clinical therapy of AC.

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