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Original Article

Tokyo Guidelines' performance in predicting acute cholangitis among emergency department patients

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ABSTRACT

INTRODUCTION. Acute cholangitis (AC) is associated with a high mortality even among treated patients. Therefore, early diagnosis and treatment are important for improving prognosis. We investigated the discriminatory ability of the Tokyo Guidelines 2018 (TG18) regarding the presence of inflammation (A criterion) and affected liver parameters (B criterion) as a guide to diagnose AC among unselected patients in the emergency department (ED).

METHODS. The study was designed as a cohort study of adult ED patient visits in the Region of Southern Denmark. The cohort included patient visits collected from seven EDs between 1 January 2016 and 20 March 2018. We examined the diagnostic accuracy of the TG18 A and B criteria. This project was approved by the Danish Patient Safety Authority (identifier 3-3013-2272/1). The Region of Southern Denmark authorised data storage (identifier 17/24904, amendment identifier 20/24502).

RESULTS. We included 202,881 ED patient visits, of which 19,816 met the TG18 A and B criteria. A total of 517 patient visits had a discharge diagnosis compatible with AC. The TG18 had a sensitivity of 85.1% (95% CI: 81.7-88.1%) and a specificity of 90.4% (95% CI: 90.3-90.6%).

CONCLUSIONS. The TG18 A and B criteria demonstrated high diagnostic accuracy for predicting AC, even among unselected adult patients in the ED, and were effective at identifying patients who required radiological imaging to confirm or rule out suspected AC.

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Acute cholangitis (AC) is an infection of the bile ducts, often triggered by gallstone obstruction or biliary strictures. Detecting AC in the emergency department (ED) is important because mortality may approach 10% despite treatment [1, 2]. Late endoscopic retrograde cholangiopancreatography (ERCP) past 24-48 hours is associated with longer hospitalisation, persistent organ failure, increased risk of death and readmission within 30 days [3, 4].

The Tokyo Guidelines 2018 (TG18) define AC and share similarities with Charcot's triad [4, 5]. The TG18 are based

on three categories: A) Systemic inflammation: presence of fever or inflammatory response. B) Cholestasis: jaundice or abnormal liver-function blood samples. C) Imaging: biliary dilatation or evidence of aetiology on imaging. The diagnosis should be considered if at least one criterion from group A is present along with an additional criterion from either group B or C [5, 6]. Therefore, early diagnostic imaging may be important for patients who meet the A and B criteria.

The TG18 has demonstrated high diagnostic accuracy for identifying AC among selected populations at high risk of AC, but its diagnostic accuracy among unselected patients in the ED remains unknown [7-9].

The aim of this study was to investigate the discriminative ability of the TG18 criteria A and B for predicting AC among unselected ED patients, with the aim of clarifying the need for radiological imaging. The research objectives were as follows: Firstly, to investigate how many ED patient visits meeting the TG18 A and B criteria result in an AC diagnosis at discharge; secondly, to examine the discriminatory ability of the TG18 A and B criteria in the subgroup of patients whose presenting symptom was abdominal pain; thirdly, to assess the discriminatory ability of the TG18 A and B criteria in the subgroup of patients whose presenting symptom was fever.

Methods

Study design and setting

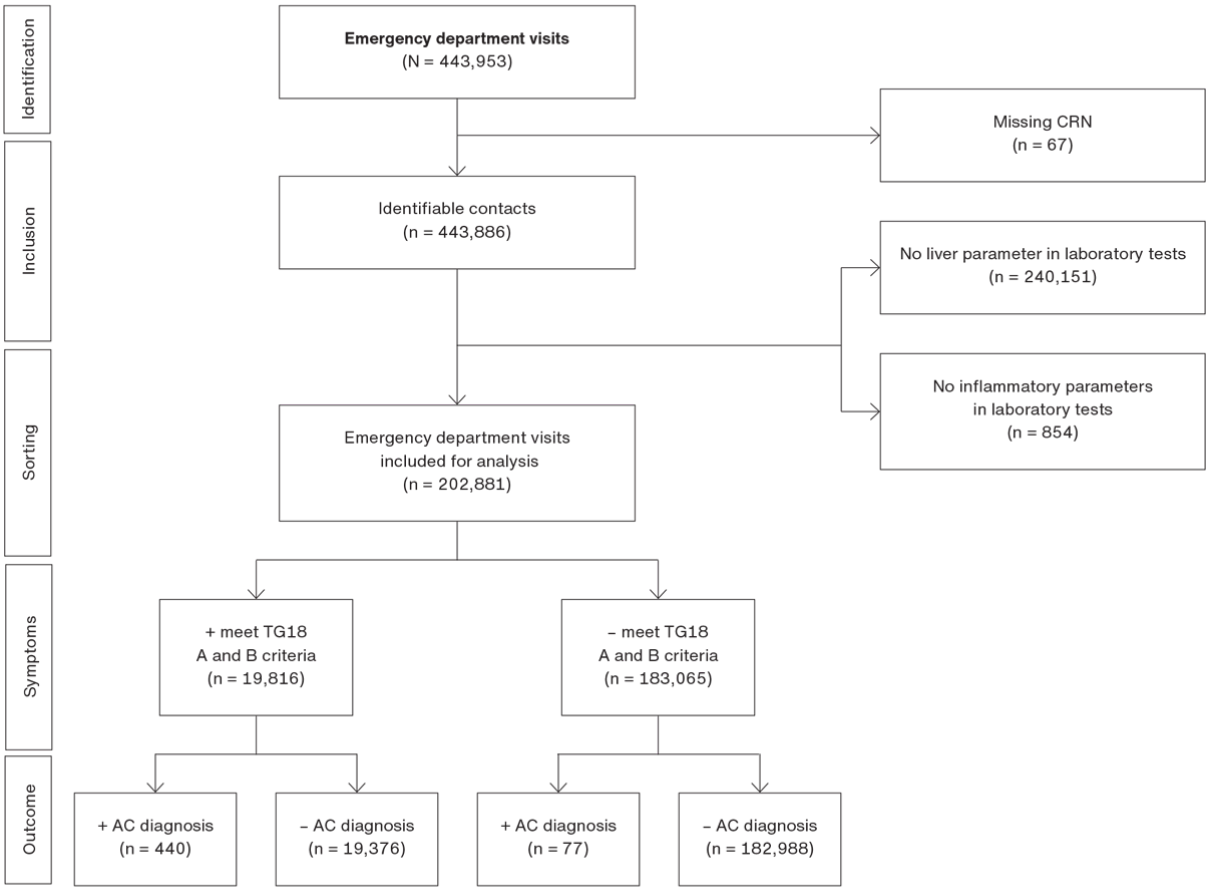
This was a register-based, multicentre, cohort study of ED patient visits in the Region of Southern Denmark (RSD), covering a population of 1.2 million citizens [10].

The study utilised a pre-existing dataset from seven EDs, encompassing patient visits between 1 January 2016 and 20 March 2018. The EDs offered 24-hour care, and patients arrived by ambulance, were referred by primary care physicians or presented as self-addressers. Patients arriving in the EDs were registered in different categories based on their primary presenting symptoms from a limited number of predefined possibilities [2]. In Denmark, patients' discharge diagnoses are recorded as International Classification of Diseases, tenth version (ICD-10) codes. Further information about the database is provided in Arving et al. [2]. Data are presented according to the Standards for Reporting of Diagnostic Accuracy Studies [11].

Participant selection

We included patients ≥ 18 years who arrived at a hospital ED in the RSD. We excluded patients without laboratory-based tests (blood samples) with at least one liver parameter (concentrations of plasma bilirubin, alkaline phosphatase (ALK phos), alanine aminotransferase (ALT), aspartate aminotransferase, γ-glutamyl transferase (GGT)) or at least one infection parameter (CRP) or white blood cell count (WBC)). Registered patient visits without a civil registration number (CRN) were excluded (**Figure 1**).

FIGURE 1 Flow diagram of the selection of patient visits arriving at an emergency department in the Region of Southern Denmark between 2016 and 2018.



AC = acute cholangitis; CRN = civil registration number; TG18 = Tokyo Guidelines 2018.

Definition of the Tokyo Guidelines 2018 criteria

In this study, the TG18 criterion A was considered positive if the body temperature was ≥ 38 °C, WBC < 4×10^9/l or > 10×10^9/l or CRP > 10 mg/l [6, 9]. Criterion B was met if the patients presented with jaundice, defined as a plasma bilirubin ≥ 2 mg/dl or abnormal liver values, which was defined as either one of the following liver parameters: ALK phos, ALT, aspartate aminotransferase (AST) or gamma-glutamyl transferase (GGT) > 1.5 × upper normal limit. We used the following cut-off values: ALT > 105 U/L, ALK phos > 105 U/l and GGT > 172 U/l [6, 8].

Variables and data sources

Patient data about presenting symptoms, vital parameters, ERCP and percutaneous transhepatic cholangiography (PTC) (Supplementary - Appendix B) and intensive care unit (ICU) stay were all retrieved from the regional electronic patient journal. Using the Danish Civil Registration System and the Danish National Patient Registry, we gathered data on length of hospital stay, 30-day mortality, discharge diagnoses including AC, and comorbidity using ICD-10 diagnoses. (Supplementary - Appendix A, C) [12, 13]. The level of comorbidity was quantified using the Charlson Comorbidity Index, which included data collected in the 10 years preceding the index date [14]. Information about laboratory-based tests was drawn from the Laboratory Automation Systems.

Statistical methods

All data were summarised as patient visits, unless otherwise stated. Proportions were presented with 95% CI.

Continuous variables were presented as medians or means. A two-sided p-value < 0.05 was considered statistically significant. Patient characteristics and outcomes were compared between patients meeting the TG18 A and B criteria (TG18+) and patients who did not meet these criteria (TG18–). We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive/negative likelihood ratios (LR+ and LR–) for the TG18 A and B criteria. The presence of an ICD-10 code for AC at hospital discharge was considered the gold standard for the AC diagnosis (Supplementary - Appendix A).

We performed two sensitivity analyses describing the discriminative ability of the TG18 A and B criteria for predicting AC in patients presenting with abdominal pain and fever, respectively. Missing data were handled using complete case analysis.

Ethics

This project was approved by the Danish Patient Safety Authority (identifier 3-3013-2272/1). The RSD authorised data storage (identifier 17/24904, amendment identifier 20/24502).

All data were stored, secured and managed in accordance with the General Data Protection Regulation and the Danish Data Protection Act [2, 15]. According to the Danish Act on Research Ethics Review of Health Research Projects, register-based studies are exempt from approval from the research ethics committee system [16].

Trial registration: not relevant.

Results

Study subject characteristics

During the inclusion period, 443,953 ED patient visits were registered. Following exclusion of patient visits without CRN (n = 67), no liver parameter in laboratory tests (n = 240,151), or no inflammatory parameters in laboratory tests (n = 854), a total of 202,881 patient visits were included for analysis (Figure 1). The median age was 65 years. A total of 517 (0.25%) patient visits had an AC diagnosis at discharge (**Table 1**).

TABLE 1 Characteristics of adult emergency department patient visits arriving at a hospital in the Region of Southern Denmark in 2016-2018. The following groups were analysed: 1) Discharge diagnosis: acute cholangitis (AC), i.e. the group of patients with the presence of an ICD-10 code for AC at hospital discharge. 2) Patients meeting the Tokyo Guidelines 2018 A and B criteria (TG18+). 3) Patients not meeting the TG18 A and B criteria (TG18–).

	Discharge diagnosis: AC	TG18			p value[a]
		TG18+	TG18–	total	
Gender, n (%)					
Total	517 (0.25)	19,816 (9.77)	183,065 (90.2)	202,881 (100)	
Male[b]	247 (48.0)	11,085 (55.9)	88,425 (48.3)	99,510 (49.1)	
Age, median (95% CI), yrs	73 (39-92)	69 (33-90)	65 (23-89)	65 (23-89)	
CCI, mean (95% CI)	1.58 (0-6)	1.89 (0-6)	1.09 (0-5)	1.17 (0-5)	< 0.0001
Comorbidity, n (%)					
Previous AMI	32 (6.20)	1,408 (7.10)	11,409 (6.20)	12,817 (6.30)	
CVD	57 (11.0)	2,796 (14.0)	25,251 (14.0)	28,047 (14.0)	
COPD	58 (11.0)	3,242 (16.0)	28,941 (16.0)	32,183 (16.0)	
Diabetes	105 (20.0)	3,700 (19.0)	22,586 (12.0)	26,286 (13.0)	
Liver	68 (13.0)	3,563 (18.0)	16,038 (8.80)	19,601 (9.70)	< 0.001
Chronic pancreatitis	36 (7.00)	629 (3.20)	1,589 (0.90)	2,218 (1.10)	< 0.001
Any malignancy	125 (24.0)	4,518 (23.0)	22,341 (12.0)	26,859 (13.0)	< 0.001
Pancreatic cancer	33 (6.40)	373 (1.90)	331 (0.20)	704 (0.40)	< 0.001
Biliary cancer	18 (3.50)	138 (0.70)	113 (0.06)	251 (0.10)	
Liver cancer	2 (0.40)	248 (1.30)	130 (0.07)	378 (0.20)	
Presenting symptom[b], n (%)					
Abdominal pain	249 (50.0)	4,173 (22.0)	30,633 (18.0)	34,806 (18.3)	< 0.001
Fever	99 (20.0)	2,382 (13.0)	13,955 (8.10)	16,337 (8.60)	< 0.001
Dyspnoea	21 (4.10)	2,380 (13.0)	19,719 (11.0)	22,099 (12.0)	< 0.001
Chest pain	11 (2.20)	511 (2.70)	13,667 (8.00)	14,178 (7.40)	< 0.001
Neurologic	2 (0.40)	370 (2.00)	10,336 (6.00)	10,706 (5.60)	< 0.001
Biochemistry, n (%)					
Abnormal liver values	464 (90.0)	19,816 (100)	5,901 (3.20)	25,717 (12.7)	
Laboratory evidence of inflammatory response or fever	485 (94.0)	19,816 (100)	106,940 (58.0)	126,756 (62.0)	
Jaundice[b]	241 (47.0)	2,547 (13.0)	522 (0.30)	3,069 (1.70)	
Vital parameters, mean (95% CI)					
Temperature[b], °C	37.7 (35.80-39.60)	37.2 (35.80-39.00)	37.0 (35.80-38.80)	37.1 (35.80-38.80)	
Respiratory rate[b], breaths/min.	19 (14-28)	19 (14-30)	18 (13-28)	19 (13-28)	
Heart rate[b], beats/min.	92 (63-122)	91 (60-125)	85 (57-120)	86 (58-120)	
Systolic blood pressure[b], mmHg	132 (99-172)	132 (94-174])	138 (102-182)	137 (101-181)	
GCS[b], score	14.80 (14-15)	14.80 (14-15)	14.80 (14-15)	14.80 (14-15)	
Performance of ERCP or PTC, n (%)	307 (59.4)	1,264 (6.38)	475 (0.26)	1,739 (0.86)	< 0.001
Hospitalisation length[c], mean (95% CI), days	8.00 (1-24)	6.10 (0-22)	2.90 (0-12)	3.20 (0-14)	< 0.0001
Discharge diagnosis[b], n (%)					
Abdominal pain	-	746 (3.90)	10,485 (5.90)	11,231 (5.70)	
Pneumonia	-	1,460 (7.60)	9,349 (5.20)	10,809 (5.50)	
Chest pain	-	-	8,304 (4.60)	8,495 (4.30)	
Sepsis	-	615 (3.20)	-	-	
AC	517 (100)	440 (2.22)	77 (0.04)	517 (0.25)	
30-day mortality, patients, n (%)	48 (9.30)	2,933 (15.0)	7,460 (4.10)	10,393 (5.10)	< 0.001

AC = acute cholangitis; AMI = acute myocardial infarction; CCI = Charlson Comorbidity Index; CVD = cardiovascular disease; ERCP = endoscopic retrograde cholangiopancreatography; GCS = Glasgow Coma Scale; PTC = percutaneous transhepatic cholangiography; TG18 = Tokyo Guidelines 2018.
a) Comparison between TG18+ and TG18–.
b) There were missing data for the following variables: gender (n = 12), hospitalization length (n = 4,514), discharge diagnosis (n = 4,514), presenting symptoms (n = 12,178), jaundice (n = 21,438), temperature (n = 82,174), respiratory rate (n = 75,370), heart rate (n = 65,255), systolic blood pressure (n = 64,946), GCS (n = 114,913).

Main results

A total of 19,816 patient visits met the TG18 A and B criteria. TG18+ had a sensitivity of 85.1% (95% CI: 81.7-88.1%), a specificity of 90.4% (95% CI: 90.3-90.6%), a PPV of 2.2% (95% CI: 2.0-2.4%) and a NPV of 99.96% (95% CI: 99.95-99.97%) for detecting AC (**Table 2**). Thirty-day mortality was 15%. A total of 440 (2.22%) visits had a diagnosis compatible with AC (Table 1).

TABLE 2 Evaluation of diagnostic criteria of acute cholangitis of the Tokyo Guidelines 2018 (TG18), TG18 with abdominal pain and TG18 with fever (N = 202,881: prevalence 0.25%).

	TG18 A and B criteria			
	total	in patients presenting with abdominal pain	in patients presenting with fever	p value
Sensitivity, median (95% CI), %	85.1 (81.7-88.1)	83.5 (78.3-87.9)	90.9 (83.4-95.8)	0.21
Specificity, median (95% CI), %	90.4 (90.3-90.6)	88.5 (88.2-88.9)	85.9 (85.3-86.4)	< 0.001
Positive predictive value, median (95% CI), %	2.2 (2.0-2.4)	5.0 (4.3-5.7)	3.8 (3.0-4.6)	
Negative predictive value, median (95% CI), %	99.96 (99.95-99.97)	99.87 (99.82-99.90)	99.94 (99.88-99.97)	
Positive likelihood ratio, median (95% CI)	8.9 (8.4-9.3)	7.3 (6.6-7.9)	6.4 (5.7-7.1)	
Negative likelihood ratio, median (95% CI)	0.16 (0.10-0.20)	0.19 (0.10-0.25)	0.11 (0.05-0.19)	

For the sub-group of TG18+ patient visits presenting mainly with abdominal pain, the sensitivity of TG18+ was 83.5% (95% CI: 78.3-87.9%) and the specificity 88.5% (95% CI: 88.2-88.9%). Among these patient visits, fulfilment of both the TG18 A and B criteria was associated with a PPV of 5.0% (95% CI: 4.3-5.7%) and a NPV of 99.87% (95% CI: 99.82-99.90%) for predicting AC (Table 2).

For the sub-group of TG18+ patient visits mainly presenting with fever, the sensitivity of TG18+ was 90.9% (95% CI: 83.4-95.8%) and the specificity was 85.9% (95% CI: 85.3-86.4%). Among these patients, meeting both the TG18 A and B criteria was associated with a PPV of 3.8% (95% CI: 3.0-4.6%) and a NPV of 99.94% (95% CI: 99.88-99.97%) (Table 2).

The study found 183,065 patient visits that did not meet the TG18 A and B criteria (TG18–). These patients had a thirty-day mortality of 4.1%. In this group, 77 (0.04%) patient visits had a diagnosis compatible with AC (Table 1).

Discussion

We investigated the discriminatory ability of the TG18 A and B criteria in predicting AC to aid in identifying patients who require radiological imaging. Our results indicate that the positive TG18 A and B criteria are effective in identifying patients with AC, both in unselected patients in the ED and in patients presenting with abdominal pain or fever. For all patient groups, the TG18 A and B criteria had high levels of sensitivity, specificity and LR+. Our findings suggest that the TG18 A and B criteria are highly valuable for identifying patients who require radiological imaging for suspected AC, but also for ruling out AC in patients presenting with abdominal pain or fever who do not meet the TG18 A and B criteria. We therefore find it relevant to use the TG18 A and B criteria as a guide to decide whether to perform radiological imaging in patients who meet the TG18 A and B criteria. Almost 10% of the included patient visits meet the TG18 A and B criteria. This does not mean that everyone should be referred for imaging diagnostics, but rather that when these criteria are met, the diagnosis should be kept in mind and clinical judgment should be used, as a positive findings make the diagnosis significantly more likely.

Because our dataset did not include radiological findings, we were unable to evaluate the discriminative ability of TG18 when including all three criteria. It is highly likely that inclusion of the C criterion would improve the accuracy as reported in previous studies [5, 7, 8, 17]. However, the A and B criteria represent the only information readily available during the initial evaluation of patients in the ED.

We did not assess the individual predictive values of TG18 criteria A or B, which were considered clinically irrelevant and likely to yield low predictive values.

Previous studies have reported a lower sensitivity for Charcot's triad and the Tokyo Guidelines 2007 (TG07) than for the TG18, supporting the use of TG18 over previous algorithms [7, 18-20].

The present study found a 30-day mortality rate of 9.3% in AC, which is comparable to previous reports [1, 2, 7]. Hou et al. and Navaneethan et al. reported that prognosis in terms of hospitalisation time, ICU admission and readmission within 30 days improved with prompt treatment with ERCP < 48 hours from admission [4, 5]. These findings underscore the importance of early diagnosis of AC to improve prognosis. The study found a 30-day mortality of 15.0% among the group that met the TG18 A and B criteria, suggesting that this group requires increased attention (Table 1).

We found a higher PPV for TG18+ in patients presenting with abdominal pain than among non-selected patients in the ED (5% versus 2.2%). Presence of abdominal pain was included in the TG07 but was excluded in the TG18 [5]. This study indicates that abdominal pain slightly increases the pre-test probability of having AC, which is why this symptom is still important to note in the patient assessment. Furthermore, this study found a significant difference between TG18+ and TG18– regarding abdominal pain and fever ($p < 0.001$).

There is likely significant overlap between the groups of patient visits with abdominal pain and with fever. This, however, is difficult to clarify because our database only records the patient's primary presenting symptom upon arrival.

The register-based study design had limitations, including that the population was selected from a database and then analysed, which increased the risk of sampling bias. Furthermore, the limited number of patient visits with missing CRN could lead to potential selection bias. Yet these account for only 67 (< 0.02%) of the excluded visits. Therefore, a missing CRN is unlikely to affect the main results of the study (Figure 1). We did not exclude patients who were readmitted during the inclusion period, which could result in problems with dependent observations.

An additional limitation of this study, compared with others, is the lack of a definitive gold standard for AC. As described by Kiriyama et al, AC, unlike other diseases, lacks a specific organ or tissue finding that permits definitive pathological diagnosis [7]. This makes it more difficult to compare different studies on AC, as they do not necessarily all use the same standard.

Although the cohort is dated, the study remains relevant as the TG18 have not changed and the treatment method remains the same. Even with the limitations listed above, the very large number of patient visits with prospective and consecutive inclusion is a strength of this study.

Conclusions

The TG18 A and B criteria perform well and are a straightforward tool for identifying unselected patients at risk of AC in the ED. We believe the TG18 A and B criteria are very useful for identifying patients requiring imaging diagnostics to confirm a diagnosis of AC. Furthermore, the very high NPV (99.8%) provides a safe rule-out strategy for AC.

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