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Original paper

Validation of TG07 and TG13/TG18 criteria for acute cholangitis and predictors of in-hospital mortality in patients over 80 years old

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Abstract

Aim of the study: This study aims to validate Tokyo guidelines (TG) TG07/TG13/TG18 criteria and identify predictors of in-hospital mortality in acute cholangitis (AC) patients over 80 years old.

Material and methods: This is a retrospective audit of AC patients from January 2009 to December 2016. Demographic, clinical, investigation, management, and mortality data were studied. Multinomial logistic regression analysis with stepwise variable selection identified predictors for in-hospital mortality.

Results: Three hundred and eighty-eight patients were treated for AC. One hundred and sixty-two (41.8%) patients were male. 230 (59.3%) patients had a history of biliary disease, 161 (41.5%) patients had type 2 diabetes mellitus (T2DM), and 98 (25.3%) patients had ischaemic heart disease (IHD). Abdominal pain (n = 226, 58.2%), pyrexia (n = 247, 63.7%), and vomiting (n = 159, 41.0%) were the common presenting symptoms. 191 (49.2%) patients had abdominal tenderness. Positive blood cultures were recorded in patients 158 (40.7%) patients. *Escherichia coli* was the most commonly identified organism (n = 117, 30.2%). 77 (19.8%), 188 (48.5%) and 123 (31.7%) patients were graded with mild, moderate, and severe AC, respectively. 30-day, 90-day, and in-hospital mortality were 9 (2.3%), 19 (4.9%) and 38 (9.8%), respectively. On multivariate analysis, systolic blood pressure $\leqslant$ 100 mmHg (OR = 3.817, 95% CI: 1.365-10.761, p = 0.011), hypoalbuminaemia < 28 gm/l (OR = 6.052, 95% CI: 2.635-13.904, p < 0.001), serum creatinine $\geqslant$ 176.8 (OR = 2.787, 95% CI: 1.146-6.778, p = 0.024) and international normalized ratio (INR) > 1.5 (OR = 3.247, 95% CI: 1.234-8.544, p = 0.017) were independent predictors of in-hospital mortality.

Conclusions: Hypotension, hypoalbuminaemia, elevated creatinine, and elevated INR predict in-hospital mortality in AC patients over 80 years old.

Key words: sepsis, cholangitis, biliary.

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Introduction

Gallstone disease is a common population health issue. An estimated 15% of adults develop gallstones, and about 15% of these patients manifest stones in the common bile duct (CBD) [1]. This presence of CBD stones leads to an increase in intrabiliary pressure, and the resulting cholangiovenous reflux introduces infected bile into the systemic circulation [2]. Gram-negative sepsis resulting from biliary infection, acute cholangitis (AC), is a critical care urgency due to associated endotoxemia and high mortality risk. With improved understanding of the pathophysiology of sepsis, refinements in critical care practice, advances in technol-

ogy for biliary instrumentation, and improved access to healthcare, mortality outcomes are improving [3]. However, AC is still associated with high mortality if timely diagnosis, proactive resuscitation, and prompt biliary decompression is not performed, especially in the elderly. Co-morbidity, malnutrition, frailty, diminished physiologic reserves, and immunosenescence contributes to higher mortality risk in the elderly population [4]. In a study including 132 patients with severe sepsis or septic shock and admitted to an intensive care unit (ICU), Nasa *et al*. reported that age independently predicted ICU mortality (p = 0.002, odds ratio (OR) = 1.038, 95% CI: 1.014-1.062), with 1.49 relative risk of death in patients age 80 and above [5]. However, only 16.7% of included patients had abdominal sepsis. In a retrospective study including 85 ICU patients with severe AC, Novy *et al*. reported 18% mortality [6]. There is inconsistency in the definition of the elderly population. The Tokyo guidelines (TG) define the elderly as age ≥ 75 years [7-9]. The initial Tokyo Guidelines 2007 (TG07) reported better diagnostic accuracy than Charcot's triad [7, 10]. Kiriyama and colleagues reported that Tokyo Guidelines 2013 (TG13) improved the diagnostic accuracy of AC [8, 11]. There is a paucity of studies validating the Tokyo Guidelines 2018 (TG18), especially in the elderly. Thus, it remains to be shown that improved diagnostic accuracy and risk stratification by TG18 contribute to good outcomes. There is emerging evidence that mortality does not differ between the elderly (≥ 80 years old) and non-elderly patients (< 80 years old) with AC [12]. This study aims to identify the mortality predictors in patients over 80 years of age.

Material and methods

This is a retrospective cohort study of all AC patients aged over 80 years, treated at a university-affiliated academic hospital between January 2009 and December 2016. All the patients were identified electronically using the following ICD10 (International Statistical Classification of Disease) codes for primary or secondary AC diagnosis: K83.0, K80.30, K80.31, K80.32, K 80.33, K80.34, K80.35, K80.36, K80.37, and K74.3) [13]. Patients who were terminally ill or were moribund were excluded as the goal of care was palliation and comfort. The local institutional review board (National Healthcare Group Domain Specific Review Board, No. 2017/00200) approved this study.

All AC patients were admitted to general medical or general surgical units in our institution, depending on the doctor's decision in the emergency department. Patients with single organ failure were admitted to the high dependency unit. Patients with multi-organ failure or requiring intubation or renal replacement therapy were admitted to the ICU. Patients with mild AC were admitted to the general ward. All patients had blood cultures done before the initiation of intravenous (IV) empirical antibiotics. Based on institution guidelines, we started patients on a combination of amoxicillin with clavulanic acid along with a stat dose of gentamicin or a third-generation cephalosporin, such as ceftriaxone along with metronidazole [14]. The blood cultures were sent for gram stain, aerobic and anaerobic cultures, and antibiotic susceptibility analysis. Based on the culture data, IV antibiotics were modified. The duration of IV antibiotics, switching to oral formulation, and total duration of antibiotics were determined by clinical response and individual specialist. Patients with negative culture results were treated empirically based on a local antibiogram [15].

Diagnostic imaging modalities included ultrasound (US) scan, computed tomography (CT) scan, or magnetic resonance cholangiopancreatography (MRCP) scan. The choice of imaging modality was determined by the timing of admission, index of suspicion for CBD stone, and need to rule out possible differential diagnosis. The timing of urgent biliary drainage was at the endoscopists' discretion. Endoscopic retrograde cholangiopancreatography (ERCP) was the first-line modality for biliary decompression, except in patients with altered biliary anatomy. Percutaneous transhepatic biliary drainage (PTBD) was reserved for patients when the endoscopic attempt failed or when ERCP was not feasible. Index admission cholecystectomy was done in patients with biliary stones and mild AC. Multidisciplinary teams were available for treatment planning of patients with concomitant malignant aetiologies.

TG13/18 guidelines were used to determine the definite diagnosis of AC: systemic inflammation (fever, chills, or laboratory data), cholestasis (jaundice or laboratory data), and biliary tree imaging (dilatation, stricture, stone, or stent) [8, 9]. We retrospectively assigned TG07, TG13/18 diagnostic, and severity grading criteria. The three diagnosis groups were: 'Does not meet criteria'; 'Suspected diagnosis'; 'Definite diagnosis' while the three severity groups were: 'Grade I/Mild'; 'Grade II/Moderate'; 'Grade III/Severe'. As age ≥ 75 years is used to define disease severity for AC, and we only included patients over 80 years of age, in this study, we did not assign severity based on age. All cut-off values were derived from the TG and supplemented from institutional laboratory reference ranges and quick sequential organ failure assessment (qSOFA) values. The cut-off for hypotension was used as systolic blood pressure

≤ 100 mmHg. Hypoalbuminaemia was defined as serum albumin < 28 gm/l. The cut-off for serum creatinine and international normalized ratio (INR) were set as ≥ 176.8 and > 1.5 units, respectively. Mortality was defined as death from any cause during hospitalization. Moribund patients were defined as patients who were bed bound and dependent for activities of daily living due to significant co-morbidity. In addition, such patients with a declared wish not to receive invasive procedures or interventions for severe sepsis, or where the medical team adjudged the risk for a procedure as prohibitive/futile, no intervention was done.

Categorical data are presented as total number (n) and percentage (%), and continuous data are presented as either mean and standard deviation (SD) or median and interquartile range (IQR), as necessary. One-way ANOVA test for continuous variables and the χ^2 test for categorical variables (continuity corrected) were used as hypothesis test functions. Fisher's exact t-test for categorical variables and the Kruskal-Wallis rank sum test for continuous variables were used for variables without normal distribution. We performed multinomial logistic regression analysis with stepwise variable selection to identify variables that were independent severity predictors based on TG13/18 severity grading with in-hospital mortality as the outcome. Variables with a p-value < 0.1 in univariate analysis were included in the multivariate analysis. P-value < 0.05 was used to indicate statistical significance in the multivariate analysis. Statistical analysis was done by R Studio 1.2.5019 using the 'tableone' package for analysis. IBM SPSS Version 26 was used for univariate and multivariate regression analysis.

Results

Three hundred and eighty-eight patients were treated for AC during the eight years. One hundred and sixty-two (41.8%) patients were male. 161 (41.5%) patients had type 2 diabetes mellitus (T2DM), and 98 (25.3%) patients had ischaemic heart disease (IHD). Nineteen (4.9%) patients had chronic obstructive pulmonary disease (COPD) or asthma, 68 (17.5%) patients had chronic renal impairment, and 230 (59.3%) patients had a history of biliary disease. Abdominal pain (n = 226, 58.2%), pyrexia (n = 247, 63.7%), and vomiting (n = 159, 41.0%) were the common presenting symptoms. On physical examination, 159 (41.0%) patients had jaundice, and 191 (49.2%) patients had abdominal tenderness. Positive blood cultures were recorded in 158 patients (40.7%) patients. *Escherichia coli* was the most commonly identified organism (n = 117, 30.2%). A US scan was done in 139 (35.8%) patients, a CT scan was done in 146 (37.6%) patients, and an MRCP scan was done in 164 (42.3%) patients. ERCP was done in 237 (61.1%) patients. 77 (19.8%), 188 (48.5%) and 123 (31.7%) patients were graded as having mild, moderate, and severe AC, respectively. 30-day, 90-day, and in-hospital mortality were 9 (2.3%), 19 (4.9%) and 38 (9.8%), respectively.

TG07 diagnostic criteria

Of the 388 patients, 126 (32.5%) patients had a definite AC, and 154 (39.7%) patients had suspected AC diagnoses. Higher median age (p < 0.001), pyrexia (p < 0.001), abdominal pain (p < 0.001), and history of biliary disease (p < 0.001) predicted suspected or definite AC diagnosis. Jaundice (p = 0.011) and abdominal tenderness (p = 0.005) predicted suspected or definite AC diagnosis (Table 1).

TG13/TG18 diagnostic criteria

Of the 388 patients, 257 (66.2%) patients had a definite AC, and 53 (13.7%) had suspected AC diagnosis. Pyrexia (p < 0.001) on admission predicted the definite or suspected AC cohorts. Patients with a definite AC diagnosis were more likely to be offered ERCP (p < 0.001) (Table 2).

TG13/TG18 severity grading

History of biliary disease (p = 0.028), abdominal pain (p = 0.001), and abdominal tenderness (p = 0.028) predicted mild AC. Chronic renal impairment (p = 0.025), jaundice (p = 0.045), pyrexia (p < 0.001), tachycardia (p < 0.001), lower systolic blood pressure (p = 0.001), and vasopressor requirements (p < 0.001) predicted severe AC. Patients with severe AC are more likely to have higher total white blood cell counts (p < 0.001), lower platelet counts (p < 0.001), higher total bilirubin (p < 0.001), and higher serum creatinine (p < 0.001). Among patients with positive blood culture results, polymicrobial growth (p = 0.031) was more common in patients with severe AC. A significantly higher proportion of mild to moderate AC patients was treated with ERCP (p < 0.001). In-hospital mortality was high in severe AC patients (p < 0.001) (Table 3).

On multivariate analysis, systolic blood pressure ≤ 100 mmHg (OR = 3.817, 95% CI: 1.365-10.761, p = 0.011), hypoalbuminaemia < 28 gm/l (OR = 6.052, 95% CI: 2.635-13.904, p < 0.001), serum creatinine ≥ 176.8 (OR = 2.787, 95% CI: 1.146-6.778, p = 0.024) and INR > 1.5 (OR = 3.247, 95% CI: 1.234-8.544, p = 0.017)

Table 1. Tokyo Guidelines 2007 (TG07) diagnostic criteria

N = 388	Does not meet criteria, *n* = 108 (%)	Suspected diagnosis, *n* = 154 (%)	Definite diagnosis, *n* = 126 (%)	*p*-value
Age, median [IQR]	83.77 [81.86, 85.61]	85.01 [82.36, 87.53]	82.47 [81.28, 84.20]	< 0.001
Gender (male), *n* (%)	51 (47.2)	66 (42.9)	45 (35.7)	0.193
Diabetes mellitus, *n* (%)	41 (38.0)	61 (39.6)	59 (46.8)	0.324
Ischaemic heart disease, *n* (%)	25 (23.1)	41 (26.6)	32 (25.4)	0.815
COPD/asthma, *n* (%)	5 (4.6)	9 (5.8)	5 (4.0)	0.761
Chronic renal impairment, *n* (%)	18 (16.7)	30 (19.5)	20 (15.9)	0.705
History of biliary disease, *n* (%)	16 (14.8)	119 (77.3)	95 (75.4)	< 0.001
Abdominal pain, *n* (%)	40 (37.0)	100 (64.9)	86 (68.3)	< 0.001
Pyrexia, *n* (%)	30 (27.8)	117 (76.0)	100 (79.4)	< 0.001
Vomiting, *n* (%)	41 (38.0)	58 (37.7)	60 (47.6)	0.182
Jaundice, *n* (%)	9 (8.3)	27 (17.5)	29 (23.0)	0.011
Abdominal tenderness, *n* (%)	39 (36.1)	82 (53.2)	70 (55.6)	0.005
Arrythmia, *n* (%)	6 (5.6)	9 (5.8)	3 (2.4)	0.339
Inotrope use, *n* (%)	2 (1.9)	2 (1.3)	6 (4.8)	0.163
Blood cultures (total *n* of positive cultures)	(*n* = 42)	(*n* = 61)	(*n* = 55)	0.410
Monomicrobial	34 (81.0)	50 (82.0)	38 (69.1)	
Polymicrobial	8 (19.0)	11 (18.0)	17 (30.9)	
Cholelithiasis, *n* (%)	83 (76.9)	112 (72.7)	87 (69.0)	0.410
Malignancy, *n* (%)	16 (14.8)	25 (16.2)	26 (20.6)	0.456
Ultrasound done, *n* (%)	46 (42.6)	47 (30.5)	46 (36.5)	0.131
CT scan, *n* (%)	46 (42.6)	51 (33.1)	49 (38.9)	0.279
MRCP scan, *n* (%)	55 (50.9)	63 (40.9)	46 (36.5)	0.076
ERCP, *n* (%)	65 (60.2)	91 (59.1)	81 (64.3)	0.658

COPD – chronic obstructive pulmonary disease, CT – computed tomography, MRCP – magnetic resonance cholangiopancreatography, ERCP – endoscopic retrograde cholangiopancreatography

were independent predictors of in-hospital mortality (Table 4).

Discussion

This single-centre retrospective study includes a large dataset of AC patients over 80 years of age and shows that TG13/18 diagnostic criteria are superior to TG07 diagnostic criteria. In patients over 80 years of age, in-hospital mortality was 9.8%. Hypotension, hypoalbuminaemia, elevated creatinine, and elevated INR predict in-hospital mortality.

With the increase in life expectancy, it is predicted that by 2050, an estimated 10% of the global population will be over 80 years of age [16]. Many authors have witnessed an increase in elderly patients in routine clinical practice [17, 18]. Older patients are more prone not only to infections but also to worse outcomes from sepsis [4, 19]. Inferior clinical outcomes in the elderly could be attributed to increased medical co-morbidity, malnutrition, frailty, diminished physiologic reserves, immunosenescence, altered pharmacokinetics and pharmacodynamics, polypharmacy, and institutionalization [20-22]. Though the World Health Organization has defined young elderly (aged 65-85 years) and old elderly (over 85 years), many authors continue to use the age cut-offs of 70 years, 75 years, and 80 years to study the impact of age [6, 12, 23]. The TG has made efforts to standardize diagnostic and severity stratification criteria, and the system is regularly reviewed and updated. The original TG07 classification did consider an age cut-off of 75 years as determinant of an inferior clinical outcome, and considered this group of patients as "compromised patients who should be monitored closely" [7].

TG07 criteria refer to two key publications to propose an age cut-off of 75 years in prognostication

Table 2. Tokyo Guidelines 2013 (TG13) and Tokyo Guidelines 2018 (TG18) diagnostic criteria

N = 388	Does not meet criteria, *n* = 78 (%)	Suspected diagnosis, *n* = 53 (%)	Definite diagnosis, *n* = 257 (%)	*p*-value
Age, median [IQR]	83.61 [81.48, 85.76]	83.64 [82.08, 85.48]	83.68 [81.49, 85.98]	0.884
Gender (male), *n* (%)	37 (47.4)	25 (47.2)	100 (38.9)	0.282
Diabetes mellitus, *n* (%)	30 (38.5)	27 (50.9)	104 (40.5)	0.308
Ischaemic heart disease, *n* (%)	26 (33.3)	12 (22.6)	60 (23.3)	0.184
COPD/asthma, *n* (%)	3 (3.8)	4 (7.5)	12 (4.7)	0.603
Chronic renal impairment, *n* (%)	16 (20.5)	10 (18.9)	42 (16.3)	0.671
History of biliary disease, *n* (%)	44 (56.4)	31 (58.5)	155 (60.3)	0.822
Abdominal pain, *n* (%)	50 (64.1)	26 (49.1)	150 (58.4)	0.230
Pyrexia, *n* (%)	32 (41.0)	39 (73.6)	176 (68.5)	< 0.001
Vomiting, *n* (%)	23 (29.5)	22 (41.5)	114 (44.4)	0.065
Jaundice, *n* (%)	16 (20.5)	6 (11.3)	43 (16.7)	0.384
Abdominal tenderness, *n* (%)	44 (56.4)	23 (43.4)	124 (48.2)	0.297
Arrhythmia, *n* (%)	5 (6.4)	0 (0.0)	13 (5.1)	0.199
Inotrope use, *n* (%)	1 (1.3)	1 (1.9)	8 (3.1)	0.633
Blood cultures (total *n* of positive cultures)	(*n* = 23)	(*n* = 21)	(*n* = 114)	0.069
Monomicrobial	19 (82.6)	19 (90.5)	84 (73.7)	
Polymicrobial	4 (17.4)	2 (9.5)	30 (26.3)	
Cholelithiasis, *n* (%)	56 (71.8)	41 (77.4)	185 (72.0)	0.713
Malignancy, *n* (%)	16 (20.5)	4 (7.5)	47 (18.3)	0.118
Ultrasound done, *n* (%)	31 (39.7)	14 (26.4)	94 (36.6)	0.269
CT scan, *n* (%)	32 (41.0)	15 (28.3)	99 (38.5)	0.296
MRCP scan, *n* (%)	28 (35.9)	21 (39.6)	115 (44.7)	0.351
ERCP, *n* (%)	45 (57.7)	16 (30.2)	176 (68.5)	< 0.001

COPD – chronic obstructive pulmonary disease, CT – computed tomography, MRCP – magnetic resonance cholangiopancreatography, ERCP – endoscopic retrograde cholangiopancreatography

[24, 25]. In a retrospective study of AC patients at Paul Brousse Hospital from 1963 to 1983, Gigot *et al.* performed multivariate analysis and proposed a scoring system [24]. The authors reported seven factors with independent significance in predicting mortality: acute renal failure, cholangitis associated with liver abscesses or liver cirrhosis, cholangitis secondary to high malignant biliary strictures or after percutaneous transhepatic cholangiography, female gender, and age ≥ 50 years. The second study alluded to in the TG07 guidelines was a prospective study of AC patients at the University of Chile from 1980 to 1988 [25]. Csendes *et al.* reported age > 60 years as a predictor for mortality [25]. Thus, it remains uncertain regarding the age cut-off of 75 years in the original TG07 system. The subsequent revisions in the TG13/18 guidelines included an age cut-off of 75 years to determine severity stratification without much added clinical evidence [8, 9]. The TG13 criteria refer to the TG07 criteria and a retrospective study from Chiba University Hospital, Tsuyuguchi *et al.* [7, 26]. In a retrospective study of 215 patients with a mean age of 66.7 years, Tsuyuguchi *et al.* validated the TG07 criteria [26]. To our knowledge, this is the first report using the 75 years age cut-off for severity stratification, and age ≥ 75 years did not predict refractory cholangitis (p = 0.730, OR = 0.871, 95% CI: 0.433-1.749) or mortality (p = 1.0, OR = 0.784, 95% CI: 0.158-3.89) on univariate analysis. Despite this, an age cut-off of 75 years has been retained in the TG18 classification system [9]. Thus, there is no scientific basis for selecting 75 years of age as the cut-off for severity stratification. We propose that the next revision of TG guidelines and classification critically appraise the available evidence and consider a review of age cut-off.

Though the TG classification system has improved the specificity and sensitivity for AC diagnosis compared to the previously used Charcot's triad, its validation is poor [27]. In particular, there is a paucity in

Table 3. Clinical characteristics compared by Tokyo Guidelines 2013 (TG13) severity grading

Parameter	*N* = 388	Grade I: mild, *n* = 77 (19.8%)	Grade II: moderate, *n* = 188 (48.5%)	Grade III: severe, *n* = 123 (31.7%)	*p*-value
Age, median [IQR]	83.65 [81.63, 85.86]	83.69 [80.94, 87.54]	83.45 [81.61, 85.66]	83.81 [81.81, 85.44]	0.614
Gender (male), *n* (%)	162 (41.8)	29 (37.7)	76 (40.4)	57 (46.3)	0.421
Diabetes mellitus, *n* (%)	161 (41.5)	31 (40.3)	71 (37.8)	59 (48.0)	0.197
Ischaemic heart disease, *n* (%)	98 (25.3)	24 (31.2)	37 (19.7)	37 (30.1)	0.049
COPD/asthma, *n* (%)	19 (4.9)	2 (2.6)	11 (5.9)	6 (4.9)	0.537
Chronic renal impairment, *n* (%)	68 (17.5)	10 (13.0)	27 (14.4)	31 (25.2)	0.025
History of biliary disease, *n* (%)	230 (59.3)	54 (70.1)	113 (60.1)	63 (51.2)	0.028
Abdominal pain, *n* (%)	226 (58.2)	52 (67.5)	119 (63.3)	55 (44.7)	0.001
Pyrexia, *n* (%)	247 (63.7)	41 (53.2)	126 (67.0)	80 (65.0)	0.099
Vomiting, *n* (%)	159 (41.0)	30 (39.0)	76 (40.4)	53 (43.1)	0.827
Jaundice, *n* (%)	65 (16.8)	6 (7.8)	33 (17.6)	26 (21.1)	0.045
Abdominal tenderness, *n* (%)	191 (49.2)	38 (49.4)	104 (55.3)	49 (39.8)	0.028
Inotrope use, *n* (%)	10 (2.6)	0 (0.0)	0 (0.0)	10 (8.1)	< 0.001
Temperature (°C)	37.79 (1.08)	37.36 (0.79)	37.89 (1.11)	37.90 (1.13)	< 0.001
Heart rate (bpm)	89.91 (19.73)	83.44 (18.94)	89.54 (17.38)	94.54 (22.37)	< 0.001
Systolic blood pressure (mmHg)	128.12 (27.84)	133.61 (27.64)	130.69 (25.79)	120.76 (29.65)	0.001
Respiratory rate (rpm)	17.36 (1.25)	17.17 (1.43)	17.38 (1.22)	17.46 (1.19)	0.291
White blood cell count (10^9/l)	13.07 (6.56)	8.82 (2.34)	14.28 (5.53)	13.89 (8.49)	< 0.001
Platelet count (10^9/l)	210.89 (92.87)	208.81 (77.05)	228.65 (86.95)	185.03 (104.46)	< 0.001
Bilirubin (µmol/l)	75.13 (68.03)	46.19 (25.11)	84.55 (75.65)	78.85 (69.57)	< 0.001
Creatinine (µmol/l)	125.66 (81.53)	101.08 (33.67)	99.97 (32.37)	180.33 (119.83)	< 0.001
Blood cultures (total *n* of positive cultures)	(*n* = 158)	(*n* = 26)	(*n* = 68)	(*n* = 64)	0.031
Monomicrobial, *n* (%)	122 (77.2)	21 (80.8)	54 (79.4)	47 (73.4)	
Polymicrobial, *n* (%)	36 (22.8)	5 (19.2)	14 (20.6)	17 (26.6)	
Escherichia coli, *n* (%)	117(30.2)	21 (80.8)	49 (72.1)	47 (73.4)	0.138
Cholelithiasis, *n* (%)	282 (72.7)	64 (83.1)	132 (70.2)	86 (69.9)	0.072
Malignancy, *n* (%)	67 (17.3)	10 (13.0)	35 (18.6)	22 (17.9)	0.533
Ultrasound done, *n* (%)	139 (35.8)	31 (40.3)	61 (32.4)	47 (38.2)	0.387
CT scan, *n* (%)	146 (37.6)	30 (39.0)	75 (39.9)	41 (33.3)	0.488
MRCP scan, *n* (%)	164 (42.3)	33 (42.9)	83 (44.1)	48 (39.0)	0.666
ERCP, *n* (%)	237 (61.1)	55 (71.4)	125 (66.5)	57 (46.3)	< 0.001
30-day mortality, *n* (%)	9 (2.3)	0 (0.0)	5 (2.7)	4 (3.3)	0.302
90-day mortality, *n* (%)	19 (4.9)	2 (2.6)	11 (5.9)	6 (4.9)	0.537
In hospital mortality, *n* (%)	38 (9.8)	1 (1.3)	11 (5.9)	26 (21.1)	< 0.001

COPD – chronic obstructive pulmonary disease, AST – aspartate aminotransferase, ALT – alanine transaminase, ALP – alkaline phosphatase, GGT – γ-glutamyl transferase, CT – computed tomography, MRCP – magnetic resonance cholangiopancreatography, ERCP – endoscopic retrograde cholangiopancreatography

validating these guidelines outside Japan [28, 29]. Our study adds to the validation of the latest guidelines focusing on a particularly vulnerable cohort, patients over 80 years of age. Compared to younger patients, the elderly have poorer clinical outcomes in the context of sepsis and biliary surgical interventions. Brunt *et al*. reported four-fold increased conversion rates and longer mean postoperative stays in octogenarian patients undergoing laparoscopic cholecystectomy [30]. In a prospective registry at a community hospital including 1080 patients, Vardi *et al*. reported that complications (61.9% vs. 51.1%, $p = 0.032$) and mortality

Table 4. Univariate and multivariate analysis of patient variables vs. in-hospital mortality (*n* = 38)

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Ischaemic heart disease, *n* (%)	1.417 (0.686-2.928)	0.347	–	–
Chronic renal impairment, *n* (%)	1.070 (0.450-2.542)	0.879	–	–
History of biliary disease, *n* (%)	0.521 (0.265-1.022)	0.058	0.882 (0.398-1.955)	0.757
Abdominal pain, *n* (%)	0.546 (0.278-1.072)	0.079	0.776 (0.352-1.713)	0.531
Jaundice, *n* (%)	2.233 (1.046-4.769)	0.038	1.051 (0.408-2.710)	0.918
Abdominal tenderness, *n* (%)	0.727 (0.369-1.432)	0.357	–	–
Heart rate (> 90 bpm)	1.366 (0.698-2.671)	0.362	–	–
Systolic blood pressure (⩽ 100 mmHg)	4.995 (2.336-10.682)	< 0.001	3.817 (1.365-10.761)	0.011
High fever (⩾ 39°C)	0.362 (0.108-1.213)	0.099	0.261 (0.063-1.092)	0.066
White blood cell count (> 12,000/m^3 or < 4,000/m^3)	1.880 (0.931-3.793)	0.078	1.510 (0.673-3.391)	0.318
Hyperbilirubinaemia (⩾ 85.5 µmol/l)	2.040 (1.027-4.052)	0.042	0.892 (0.375-2.120)	0.796
Hypoalbuminaemia (< 28 gm/l)	7.297 (3.559-14.963)	< 0.001	6.052 (2.635-13.904)	< 0.001
Cardiovascular: Inotropes used	4.200 (1.039-16.972)	0.044	0.502 (0.076-3.301)	0.473
Neurologic: Glasgow Coma Scale <15	2.795 (0.975-8.013)	0.056	2.033 (0.544-7.598)	0.292
Renal: Creatinine ⩾ 176.8	5.333 (2.596-10.959)	< 0.001	2.787 (1.146-6.778)	0.024
Hepatic: INR > 1.5	4.049 (1.838-8.918)	0.001	3.247 (1.234-8.544)	0.017
Haematologic: Platelets < 100	2.259 (0.803-6.359)	0.123	–	–

OR – odds ratio, CI – confidence interval, INR – international normalized ratio, AST – aspartate aminotransferase, ALT – alanine transaminase, ALP – alkaline phosphatase, GGT – γ-glutamyl transferase, COPD – chronic obstructive pulmonary disease

rates (37.3% vs. 20.1%, $p < 0.001$) were higher in nonagenarian patients with sepsis [19]. In a retrospective study including 85 AC patients ≥ 75 years old and admitted to an ICU, Novy *et al.* reported 18% ICU and 48% 6-month mortality [6]. Multivariate analysis revealed that malnutrition and a decrease in SOFA score at 48 hours predicted 6-month mortality. Though the outcomes in elderly patients are reported to be inferior by some authors, others report that age is not a determinant of outcomes, but underlying associations of co-morbidity, malnutrition, and frailty are the root cause of mortality [2, 31-33]. With appropriate patient selection and operator experience, common bile duct exploration and laparoscopic cholecystectomy procedures can be safe and feasible in the elderly [34, 35]. In a single-centre retrospective study reporting on the efficacy and safety of ERCP in elderly patients with AC, Tohda *et al.* reported that patients ≥ 80 years old had equal technical success rates (95.1% vs. 95.2%) and ERCP-related complications (6.9% vs. 6.7%) as compared to patients < 80 years age [36]. In a propensity-score matched study including 224 patients AC patients (112 patients ≥ 80 years, 112 patients < 80 years age), Chan *et al.* reported no statistically significant differences in overall in-hospital mortality, 30-day mortality, and 90-day mortality between the elderly and non-elderly in both the unmatched and matched cohorts [12]. Thus, it is likely that mortality risk is not solely determined by age. In a local study including 272 patients with AC, we reported that T2DM ($p = 0.026$, OR = 12.5, 95% CI: 0.354-116.015), systolic blood pressure < 100 mmHg ($p = 0.041$, OR = 10.1, 95% CI: 1.094-93.395), Glasgow Coma Scale score < 15 ($p = 0.019$, OR = 38.2, 95% CI: 1.804-807.191), and malignant disease ($p = 0.049$, OR = 14.1, 95% CI: 1.017-196.394) predicted in-hospital mortality [37]. However, due to the small sample and low mortality in the study population, the confidence intervals are wide, and the results need to be validated. The current study adds evidence as we report mortality predictors in patients over 80 years of age.

In this study, the Charcot triad and history of biliary disease were predictive of AC based on TG07. However, only pyrexia remained significant in predicting definite AC in the TG13/TG18 guidelines. It is well known that the signs and symptoms of AC are

closely mimicked by acute cholecystitis. Patients with acute cholecystitis have a higher probability of having abdominal tenderness. This was taken into consideration in the TG13/TG18 guidelines and explains the increased sensitivity of the TG18 guidelines. From the comparison based on severity assessment, it was interesting to note that ERCP was performed to a greater extent in patients with mild to moderate disease. This could be due to increased hesitance to employ ERCP as a treatment modality for patients with organ dysfunction or haemodynamic instability, despite the evidence for safety [36, 38]. This is especially true in cases where pre-ERCP optimization with resuscitation is essential. It is acceptable to delay ERCP to restore any electrolyte or haemodynamic derangements and correct coagulopathies and consult the anaesthesia team for moderate sedation or anaesthesia for the endoscopic procedure. Treatment of gram-negative sepsis and resulting endotoxemia in the AC setting presents a "chicken-and-egg" type dilemma, i.e., resuscitation first or decompression first. One should not wait for the patient to have normal haemodynamic and laboratory parameters before biliary decompression. We propose that resuscitation and endoscopic decompression plans should take place in parallel and not sequentially.

Multivariate analysis revealed that lower systolic blood pressure was independently predictive of in-hospital mortality. Lowered systolic blood pressure is part of the Reynolds pentad and has been previously documented to predict worse outcomes [39]. To increase awareness about sepsis and to reduce the burden of sepsis management, the Japanese Association for Acute Medicine established the Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST) study to comprehensively describe the epidemiology and outcomes associated with severe sepsis and to understand how clinicians use guidelines in routine clinical practice in Japan. In the FORECAST study, hypotension was defined as systolic blood pressure < 90 mmHg, and septic shock correlated with mortality (OR = 1.01, 95% CI: 0.63-1.62) [40]. We used the cut-off systolic blood pressure of 100 mmHg based on the recent sepsis-3 criteria and qSOFA score [41]. We did not study the role of vasopressors in this study. It remains unknown whether the increased mortality risk in patients with hypotension is attributed to a delay in vasopressor therapy. Elevated creatinine predicts severity of AC and mortality [42]. Serum creatinine levels correlate with oxidative stress, endothelial dysfunction, and atherosclerosis [43]. These may reduce cardiac output and renal blood flow and cause diastolic left ventricular dysfunction, contributing to cardiac events. We did not study the cause of death and hence are unable to comment on the exact mechanism by which elevated creatinine contributes to mortality risk. We hypothesize that interaction of T2DM, chronic renal parenchymal disease, metabolic syndrome, and atherosclerosis is multifactorial and associated with elevated creatinine levels. Hypotension, severe chronic kidney disease, and age > 80 years are part of the Physiological Parameters for Prognosis in Abdominal Sepsis (PIPAS) score [44]. The PIPAS score is a bedside early warning score including eight variables and is prospectively derived from 3137 peritonitis patients from 153 surgical departments across 56 countries. The overall mortality was 2.9% for patients who had scores of 0-1, 22.7% for those who had scores of 2-3, 46.8% for those who had scores of 4-5, and 86.7% for those who had scores of 7-8. In the PIPAS score, a low platelet count is used for mortality prediction. In this study, elevated INR was predictive of mortality. Coagulation abnormalities are nearly universal in septic patients and likely play a key role in multisystem organ dysfunction due to microvascular fibrin deposition [45]. INR is a marker of hepatic dysfunction, and impaired coagulation is associated with mortality risk in sepsis [46]. Elevated INR is used as an inclusion criterion in randomized studies to investigate the effect of intervention in patients with sepsis-associated coagulopathy [47]. A large prospective randomized, double-blind, multinational, placebo-controlled (PROWESS) study including 840 patients from 164 medical centres reported that both baseline abnormalities and first-day changes in coagulation biomarkers (including an increase in prothrombin time by 2 seconds) correlated with 28-day mortality [48]. In this study, we found that hypoalbuminaemia predicted mortality. This is similar to the report of Sun *et al*. [10]. Sun *et al*. validated the TG07 criteria and reported that hypoalbuminaemia (≤ 25.0 g/l; OR = 17.3, 95% CI: 3.5-313.6) was an independent predictor of 30-day mortality [10]. Similar findings were reported in a TG18/13 validation study by Gravito *et al*. [49]. These findings are not entirely unexpected. Hypoalbuminaemia is a known predictor of morbidity and mortality risk in acute illness, critical illness, and elective major abdominal surgery. In a comprehensive assessment of 204,819 patients undergoing 16 major surgical procedures, Meyer *et al*. reported hypoalbuminaemia as an independent predictor of complications in 12/16 procedures and 30-day mortality in 11/16 procedures [50]. Even modest low albumin levels in patients undergoing colorectal oncologic procedures have increased postoperative complications or mortality [50, 51]. Though the association is clear, the pathophysiology as to the link between hypo-

albuminaemia and poor prognosis is unclear. Albumin is a marker of nutritional status and a negative acute-phase protein. Therefore low serum albumin indicates an inflammatory state [52].

The strength of our study is a relatively large sample population allowing a multivariable analysis to reduce confounding variables. Single-centre, retrospective design, heterogeneity in clinical care, changes in clinical practice over the study duration, and lack of mortality causes are limitations of our study. Further, we did not report the choice of antibiotics, duration of antibiotics, timing for ERCP, data related to vasopressor support, or serum lactate levels. However, our study is essential as it adds to the limited body of evidence that validates TG13/TG18 from an institution outside of Japan. It is also a critical study as it identifies predictors and validity of the guidelines in a vulnerable cohort in which such guidelines are imperative, the elderly. Until further evidence emerges from prospective multicentre studies, TG may review the age cut-off to determine AC severity.

Disclosure

The authors declare no conflict of interest.

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