Evaluation of Charcot Triad, Reynolds Pentad, and Tokyo Guidelines for Diagnosis of Cholangitis Secondary to Choledocholithiasis Across Patient Age Groups

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Abstract

Objective: To determine the prevalence of Charcot triad, Reynolds pentad, and Tokyo Guidelines criteria and clinical outcomes among patients with cholangitis across different age groups.

Patients and Methods: We conducted a retrospective analysis of 257 consecutive hospitalized adult patients with acute cholangitis due to endoscopic retrograde cholangiopancreatography−confirmed choledocholithiasis between January 1, 2015, and December 31, 2019. Patients were divided into 3 age groups: less than 65 years, 65 to 79 years, and 80 years or older. Symptoms, vital signs, and laboratory data on admission were collected. Outcomes included length of hospitalization, intensive care unit stay, and 3-month mortality. Nominal variables were tested with the Pearson χ^2 test, and continuous variables were tested with the Wilcoxon rank sum test.

Results: Charcot triad decreased with older ages. In the group that was age 80 years or older, malaise was the most common symptom; 33.6% (37 of 110) presented with altered sensorium, 9.1% (10 of 110) had no pain, fever, or jaundice, and positive blood culture results were more frequent. Tokyo cholestasis criterion was present in 96.0% (247 of 257), while inflammation (considered essential for diagnosis) was present in 75.9% (195 of 257). Patients 80 years or older had significantly higher mean length of hospital stay ($P<.001$) and mean length of intensive care unit stay ($P=.021$).

Conclusion: Compared with patients in younger age groups, patients with cholangitis who are 80 years or older are less likely to have Charcot triad, are more likely to have features of Reynolds pentad, or present with unexplained malaise. Within the Tokyo Guidelines, cholestasis should replace inflammation as an essential diagnostic criterion.

T he vast majority of cases of cholangitis are secondary to stones impacted in the common bile duct with resulting biliary stasis. Transpapillary microbial contamination persists in the setting of duct stones, and consequent to the biliary obstruction, the resulting high biliary pressure favors rapid translocation of bacteria into the bloodstream, giving rise to septicemia. Cholangitis can be life-threatening if the diagnosis is delayed and prompt biliary drainage not carried out. Because the diagnosis of cholangitis can be challenging,

various diagnostic criteria have been proposed, including Charcot triad (fever with chills, right upper abdominal pain, jaundice),[1] Reynolds pentad (hypotension and altered mental status in addition to Charcot triad),[2] and Tokyo Guidelines, which groups signs and symptoms into 3 criteria: a diagnosis of acute cholangitis is suspected if 2 of 3 criteria are met.[3] The 3 diagnostic criteria include systemic inflammation (fever [temperature >38 °C], elevated white blood cell [WBC] count or C-reactive protein [CRP] level), cholestasis (total bilirubin, ≥2 mg/dL

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[to convert to µmol/L, multiply by 17.104] and alkaline phosphatase [AP], alanine aminotransferase [ALT], and aspartate aminotransferase [AST] levels >1.5 times the upper limit of normal), and imaging (biliary dilatation or evidence of etiology on imaging), of which systemic inflammation is considered essential. All 3 criteria must be met for a definite diagnosis of cholangitis. The Tokyo Guidelines were updated in 2013[3] and in 2018.[4]

Charcot triad and Reynolds pentad have high specificity but low sensitivity for diagnosing cholangitis.[5] The sensitivity of Charcot triad may be as low as 7%[6] and that of Reynolds pentad less than 5%.[7] The Tokyo Guidelines have not been validated in elderly patients or in a US population. We therefore sought to determine in a US cohort which of these criteria would best suggest the diagnosis of cholangitis secondary to choledocholithiasis. The aims of this study were to compare (1) the sensitivity of Charcot triad, Reynolds pentad, and the Tokyo Guidelines as diagnostic criteria for cholangitis and (2) the presentation of cholangitis in older patients vs younger patients. In order to include a homogeneous group of patients, we focused only on patients with the most common cause of cholangitis, which is choledocholithiasis.

PATIENTS AND METHODS

Patient Selection

We performed a retrospective study of 633 consecutive patients 18 years or older who were admitted to Mayo Clinic hospitals in Rochester, Minnesota, from January 1, 2015, to December 31, 2019, and were diagnosed as having cholangitis (Figure 1). For the purposes of this study, documentation of common bile duct (CBD) stones or CBD stone equivalent such as sludge or pus on endoscopic retrograde cholangiopancreatography (ERCP) in the absence of other biliary abnormalities was the criterion standard for diagnosis of cholangitis secondary to choledocholithiasis.[5] We could not include a control group of patients with suspected infection and normal ERCP findings because ERCP, which poses risk of severe complications, is performed only as a therapeutic procedure when there is a strong suspicion of biliary obstruction. Patients with cholangitis due to biliary stent occlusion, strictures

(including primary sclerosing cholangitis), or malignancy were excluded (n=288) because these patients may have symptoms unrelated to cholangitis. The cohort with a medical record diagnosis of cholangitis secondary to CBD stones or CBD stone equivalent such as sludge or pus seen on ERCP therefore included 345 patients. Among these patients, 88 were excluded because of an indwelling biliary stent (n=1), missing computed tomography (CT)/ultrasonography (US) reports (n=46), prior ERCP (n=36), and current ERCP not documenting CBD stones or ERCP not carried out (n=5). The final cohort for the study included 257 patients. Patients were divided into 3 age groups: less than 65 years, 65 to 79 years, and 80 years or older.

Variables Collected

Patient demographic characteristics and the presence of relevant comorbidities including hypertension, type 2 diabetes mellitus, coronary artery disease, cirrhosis, and chronic kidney disease were documented. Presenting symptoms evaluated included the presence of (1) abdominal pain suggestive of biliary colic, (2) fevers, (3) general malaise, (4) jaundice, and (5) altered mental status. Symptoms were assessed by review of initial emergency department documentation, patient history and physical examination findings obtained by the admitting physician and the gastroenterology fellow and supervising gastroenterology/hepatology consultant's notes. Vital signs during the first 24 hours after admission were also collected in order to document the presence of tachypnea (>20 breaths/min), hypotension (systolic blood pressure <100 mm Hg), or fevers (temperatures >38 °C). Home medications were also reviewed to determine if patients were using medications that could potentially mask clinical and laboratory manifestations of cholangitis, including nonsteroidal anti-inflammatory drugs, opioids, or immunosuppressant therapy (including prednisone or other corticosteroids).

Laboratory data collected included WBC count, liver biochemistry studies (ALT, AST, AP, total bilirubin, direct bilirubin levels), and the presence of positive blood culture results at any point during the hospitalization. Ultrasonography and CT reports were reviewed for features documenting biliary dilation or stones

in the CBD and/or gallbladder. Notes from ERCP procedures were reviewed to assess for features of suppurative cholangitis, biliary obstruction, and the presence of bile duct stones or sludge.

The criteria for Charcot triad and Reynolds pentad, as described previously, were recorded. The 3 criteria for the Tokyo Guidelines included (1) systemic inflammation as defined by either fever (temperature $\geq$38 °C) with shaking chills or laboratory evidence of an inflammatory response as determined by a WBC count of less than 4000 cells/mm^3 (4 $\times$ 10^9 cells/L) or more than 12,000 cells/mm^3 (12 $\times$ 10^9 cells/L), (2) cholestasis defined by jaundice (total bilirubin, $\geq$2 mg/dL) or abnormal liver biochemistry tests (>1.5 times the upper limit of normal for ALT, AST, or AP), and (3) imaging documenting biliary dilation of 7 mm or greater or evidence of CBD stones.

Statistical Analyses

Clinical outcomes studied were length of hospital stay (days), length of stay in the intensive care unit, in-hospital death, and 3-month mortality. We used χ^2 and Fisher exact tests to assess the strength of association between presentation and outcome in the 3 study populations. Nominal variables were tested with the Pearson χ^2 test, and continuous variables were tested with the Wilcoxon rank sum test. This study was approved by the Mayo Clinic Institutional Review Board.

RESULTS

Baseline Patient Characteristics

Among the 257 patients included, 62 (24.1%) were younger than 65 years with a median age of 57.5 years, while the 65 to 79 years and 80 years or older age groups included 85 (33.1%) and 110 (42.8%) patients with median ages of 74 years and 87 years, respectively (Table 1). Notably, the prevalence of comorbidities such as hypertension (50.0% [31 of 62] vs 76.5% [65 of 85] vs 80.0% [88 of 110]; P<.001), coronary artery disease (12.9% [8 of 62] vs 32.9% [28 of 85] vs 49.1% [54 of 110]; P<.001), and chronic kidney disease (12.9% [8 of 62] vs 18.8% [16 of 85] vs 31.8% [35 of 110]; P=.01) was higher with increasing age. However, there were no significant age-related differences in the proportions
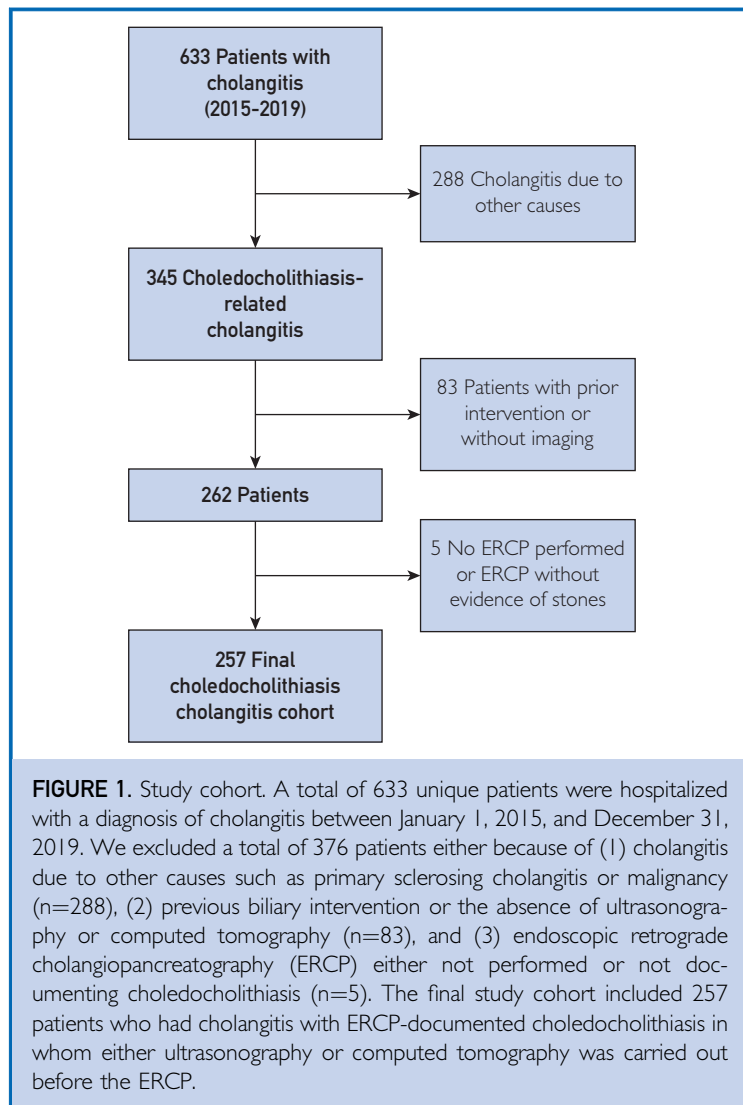

FIGURE 1. Study cohort. A total of 633 unique patients were hospitalized with a diagnosis of cholangitis between January 1, 2015, and December 31, 2019. We excluded a total of 376 patients either because of (1) cholangitis due to other causes such as primary sclerosing cholangitis or malignancy (n=288), (2) previous biliary intervention or the absence of ultrasonography or computed tomography (n=83), and (3) endoscopic retrograde cholangiopancreatography (ERCP) either not performed or not documenting choledocholithiasis (n=5). The final study cohort included 257 patients who had cholangitis with ERCP-documented choledocholithiasis in whom either ultrasonography or computed tomography was carried out before the ERCP.

of patients with diabetes mellitus (33.9% [21 of 62] vs 38.8% [33 of 85] vs 27.3% [30 of 110]; P=.228), cirrhosis (1.6% [1 of 62] vs 2.4% [2 of 85] vs 0.9% [1 of 110]; P=.721), nonsteroidal anti-inflammatory drug use (12.9% [8 of 62] vs 5.9% [5 of 85] vs 4.5% [5 of 110]; P=.106), opioid use (11.3% [7 of 62] vs 7.1% [6 of 85] vs 10.0% [11 of 110]; P=.651), or patients in an immunosuppressed state (4.8% [3 of 62] vs 9.4% [8 of 85] vs 2.7% [3 of 110]; P=.121).

Clinical, Laboratory, and Radiologic Features

Table 2 summarizes the clinical, laboratory, and radiologic features of the patients. There were statistically significant differences among the 3 age groups in the prevalence of RUQ/

TABLE 1. Baseline Characteristics of the 257 Study Patients[a,b]

Variable	Age <65 y (N=62)	Age 65-79 y (N=85)	Age ≥80 y (N=110)	P value
Age (y)				NA
Median (Q1, Q3)	57.5 (45.2, 61.0)	74.0 (71.0, 77.0)	87.0 (82.0, 89.8)	
Mean ± SD	50.9±13.0	73.6±4.2	86.8±5.5	
Range	20-64.0	65.0-79.0	80.0-105.0	
Sex				.738
Male	36 (58.1)	51 (60.0)	60 (54.5)	
Female	26 (41.9)	34 (40.0)	50 (45.5)	
Body mass index (kg/m^2)				<.001
Median (Q1, Q3)	34.1 (28.2, 39.7)	31.5 (26.5, 37.0)	27.1 (23.3, 30.9)	
Mean ± SD	34.8±9.6	32.3±7.8	27.8±5.9	
Range	18.5-77.3	16.4-57.0	18.5-50.5	
Hypertension	31 (50.0)	65 (76.5)	88 (80.0)	<.001
Diabetes mellitus	21 (33.9)	33 (38.8)	30 (27.3)	.228
Coronary artery disease	8 (12.9)	28 (32.9)	54 (49.1)	<.001
Cirrhosis	1 (1.6)	2 (2.4)	1 (0.9)	.721
Chronic kidney disease	8 (12.9)	16 (18.8)	35 (31.8)	.010
NSAIDs	8 (12.9)	5 (5.9)	5 (4.5)	.106
Opioids	7 (11.3)	6 (7.1)	11 (10.0)	.651
Immunosuppression	3 (4.8)	8 (9.4)	3 (2.7)	.121

[a]NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; Q1, first quartile; Q3, third quartile.
[b]Data are presented as No. (percentage) of patients unless indicated otherwise.

abdominal pain, the feeling of being unwell/fatigued, and altered mental status. Specifically, RUQ/abdominal pain was less prominent with increasing age (90.3% [56 of 62] vs 89.4% [76 of 85] vs 64.5% [71 of 110]; P<.001), while lower body mass index (calculated as weight in kilograms divided by height in meters squared; median, 34.1 vs 31.5 vs 27.1 kg/m^2; P<.001), feeling unwell/fatigued (37.1% [23 of 62] vs 68.2% [58 of 85] vs 73.6% [81 of 110]; P<.001), and the presence of altered mental status (4.8% [3 of 62] vs 16.5% [14 of 85] vs 33.6% [37 of 110]; P<.001) were more prevalent in the older age groups. Jaundice (50.0% [31 of 62] vs 44.7% [38 of 85] vs 36.4% [40 of 110]; P=.193) and fever (50.0% [31 of 62] vs 49.4% [42 of 85] vs 41.8% [46 of 110]; P=.458) were not statistically distinct across the 3 groups. In contrast, hypotension (21.0% [13 of 62] vs 31.8% [27 of 85] vs 39.1% [43 of 110]; P=.045) was more prevalent in the older age groups. Four patients (1 in the age 65 to 79 years group, 3 in the age ≥80 years group) presented with both altered consciousness and hypotension, and 5 patients (all aged ≥80 years) presented with only hypotension or altered consciousness in the absence of other symptoms. Blood culture results were also significantly more likely to be positive with increasing age (30.6% [19 of 62] vs 48.2% [41 of 85] vs 52.7% [58 of 110]; P=.018). Because CRP was available only in a minority of patients, these results were excluded from analysis. In summary, patients 80 years of age or older were less likely to have biliary colic as a presenting symptom and more likely to present with altered mental status, general malaise, and leukocytosis and have positive blood culture results than the age less than 65 and age 65 to 79 groups.

Charcot Triad, Reynolds Pentad, and Tokyo Guidelines

Only 3 patients (1 in the age 65 to 79 group, 2 in the age ≥80 group) had all 5 Reynolds criteria (Figure 2). Neither the Tokyo or Reynolds criteria showed statistical differences among the age groups (P=.225 and P=.484, respectively); however, the presence of all 3 Charcot criteria ("Charcot triad") was less likely in the older age groups (29.0% [18 of

TABLE 2. Symptoms/Signs, Laboratory Values, and Imaging/ERCP Findings in the 257 Study Patients[a,b]			
Variable	Age <65 y (N=62)	Age 65-79 y (N=85)	Age ≥80 y (N=110)	P value
Symptoms/signs[c]				
RUQ/epigastric pain	56 (90.3)	76 (89.4)	71 (64.5)	<.001
Jaundice	31 (50.0)	38 (44.7)	40 (36.4)	.193
Fever	31 (50.0)	42 (49.4)	46 (41.8)	.458
Unwell or fatigued	23 (37.1)	58 (68.2)	81 (73.6)	<.001
Tmax, °C				
<38	31 (50.0)	46 (54.1)	69 (62.7)	.240
38-39	21 (33.9)	22 (25.9)	30 (27.3)	.504
39-40	9 (14.5)	15 (17.6)	7 (6.4)	.062
>40	1 (1.6)	2 (2.4)	4 (3.6)	.342
Altered mental status	3 (4.8)	14 (16.5)	37 (33.6)	<.001
SBP <100 mm Hg	13 (21.0)	27 (31.8)	43 (39.4)	.045
Respiratory rate >20/min	29 (46.8)	42 (49.4)	62 (56.9)	.378
Heart rate >90 bpm	40 (64.5)	43 (50.6)	58 (52.7)	.206
Laboratory findings[c]				
White blood cell count (×10⁹/L)				.036
Median (Q1, Q3)	12.1 (9.1, 15.0)	12.5 (8.9, 15.2)	13.2 (9.1, 18.6)	
Mean ± SD	12.3±5.0	12.9±6.1	14.7±7.4	
Range	3.1-31.4	2.4-39.2	1.0-38.0	
AST (IU/L)				.359
Median (Q1, Q3)	219 (127, 365)	169 (100, 288)	172.5 (98, 344.5)	
Mean ± SD	309.1±325.7	244.6±239.4	291.6±303.6	
Range	18-2169	19-1276	17-1388	
ALT (IU/L)				.040
Median (Q1, Q3)	278 (166.5, 390)	162 (108, 318)	218 (102, 404.5)	
Mean ± SD	321.2±265.2	220.4±164.4	299.2±296.6	
Range	22-1354	19-682	10-1903	
Alkaline phosphatase (IU/L)				.296
Median (Q1, Q3)	210.5 (144, 365)	225 (144, 369)	221 (146.5, 340)	
Mean ± SD	269.0±162.9	315.2±277.5	270.8±187.5	
Range	80-759	50-1671	40-1196	
Total bilirubin (mg/dL)				.329
Median (Q1, Q3)	3.7 (2.1, 5.9)	3.0 (1.8, 4.7)	3.7 (2.0, 4.7)	
Mean ± SD	4.2±2.8	3.5±2.2	3.9±3.0	
Range	0.4-15.5	0.5-13.0	0.2-25.7	
Direct bilirubin (mg/dL)				.384
Median (Q1, Q3)	3.2 (1.4, 4.7)	3.0 (1.3, 4.2)	2.5 (1.2, 3.6)	
Mean ± SD	3.4±2.2	3.1±2.1	3.0±3.0	
Range	0.2-9.3	0.2-11.4	0.1-25.1	
Positive blood cultures	19 (30.6)	41 (48.2)	58 (52.7)	.018
Imaging/ERCP findings[d]				
Biliary dilatation	43 (69.4)	59 (69.4)	86 (78.2)	
Only CT	10	25	42	.290
Only US	23	22	26	
US + CT	10	12	18	
Common bile duct stone	15 (24.2)	33 (38.8)	63 (57.3)	<.001
Only CT	10	21	39	
Only US	5	7	19	
US + CT	0	5	5	

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TABLE 2. Continued				
Variable	Age <65 y (N=62)	Age 65-79 y (N=85)	Age ≥80 y (N=110)	P value
ERCP findings				
Sludge	1 (1.6)	4 (4.7)	2 (1.8)	.504
CBD stone/recent passing	40 (64.5)	62 (72.9)	75 (68.2)	.143
Pus	1 (1.6)	0 (0.0)	2 (1.8)	.386
CBD stone/sludge and pus	20 (32.3)	19 (22.4)	31 (28.2)	.108

[a]ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; CBD, common bile duct; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; Q1, first quartile; Q3, third quartile; RUQ, right upper quadrant; SBP, systolic blood pressure; Tmax, maximum temperature; US, ultrasonography.
[b]Data are presented as No. (percentage) of patients unless indicated otherwise.
[c]First 24 hours during admission.
[d]During admission.

62] vs 18.8% [16 of 85] vs 9.1% [10 of 110]; $P<.001$) (Figure 2). Within the Tokyo Guidelines, systemic inflammation, considered an essential criterion for cholangitis, was absent in 24.1% of the entire cohort (62 of the 257 patients); cholestasis was absent in only 4.0% (10 of 252), and imaging criteria were absent in 22.6% (58 of 257) (Figure 3). A trend toward a higher prevalence of imaging criteria (biliary dilatation or CBD stones) (71.0% [44 of 62] vs 72.9% [62 of 85] vs 84.5% [93 of 110]; $P=.059$) was noted with increasing age (Figure 3). Documentation of CBD stones on CT or US was, however, significantly more likely in older patients (24.2% [15 of 62] vs 38.8% [33 of 85] vs 57.3% [63 of 110]; $P<.001$). Requiring the presence of both inflammation and cholestasis criteria without imaging to indicate cholangitis would have excluded the diagnosis in 44 of the 257 patients (17%) with cholangitis. Using cholestasis and imaging without inflammation criteria would have excluded cholangitis in 48 patients (19%). Using inflammation and imaging but not cholestasis criteria would have excluded cholangitis in only 8 patients (3%). That is, if cholestasis was included as the only essential criteria to indicate cholangitis, the diagnosis of cholangitis would not have been considered in only 4% of patients (11 of 257) (false-negative rate). Requiring all 3 criteria for a definite diagnosis of cholangitis would have missed 55.3% of patients (142 of 257) with documented cholangitis. There was no association between blood culture positivity and Tokyo criteria ($P=.98$). In those with positive blood culture results, 56.8% (67 of 118) had 3 criteria and 37.2% (44 of 118) had 2 criteria. In those with negative blood culture results, 53.2% (74 of 139) had 3 criteria and 42.4% (59/139) had 2 criteria present.

Clinical Outcomes

In terms of clinical outcomes, only the length of hospitalization was significantly different among the age groups, with longer mean hospital length of stay (5.0 days vs 6.2 days vs 8.3 days; $P<.001$) and intensive care unit (ICU) length of stay (0.8 days vs 1.1 days vs 2.0 days; $P=.021$) for the older age groups (Table 3). In-hospital mortality (3.2% [2 of 62] vs 1.2% [1 of 85] vs 5.5% [6 of 110]; $P=.270$) and 3-month mortality (3.2% [2 of 62] vs 7.1% [6 of 85] vs 11.8% [13 of 110]; $P=.12$) revealed a trend toward worse outcomes with increasing age but did not reach statistical significance (Table 3).

DISCUSSION

The key findings of this study in patients with cholangitis secondary to ERCP-documented choledocholithiasis in a Western cohort are the following. (1) Patients 80 years age or older comprised the largest subgroup. (2) In patients 80 years or older, cholangitis can present without associated abdominal pain, fever, or jaundice. In this age group, malaise occurs more frequently than fever or abdominal pain, blood culture results are more frequently positive than in other age groups, and the only manifestation of cholangitis seen in 9 patients was unexplained hypotension or alteration of consciousness with elevated levels on liver function tests. (3) Cholestasis is the only criterion that is almost invariably present irrespective of
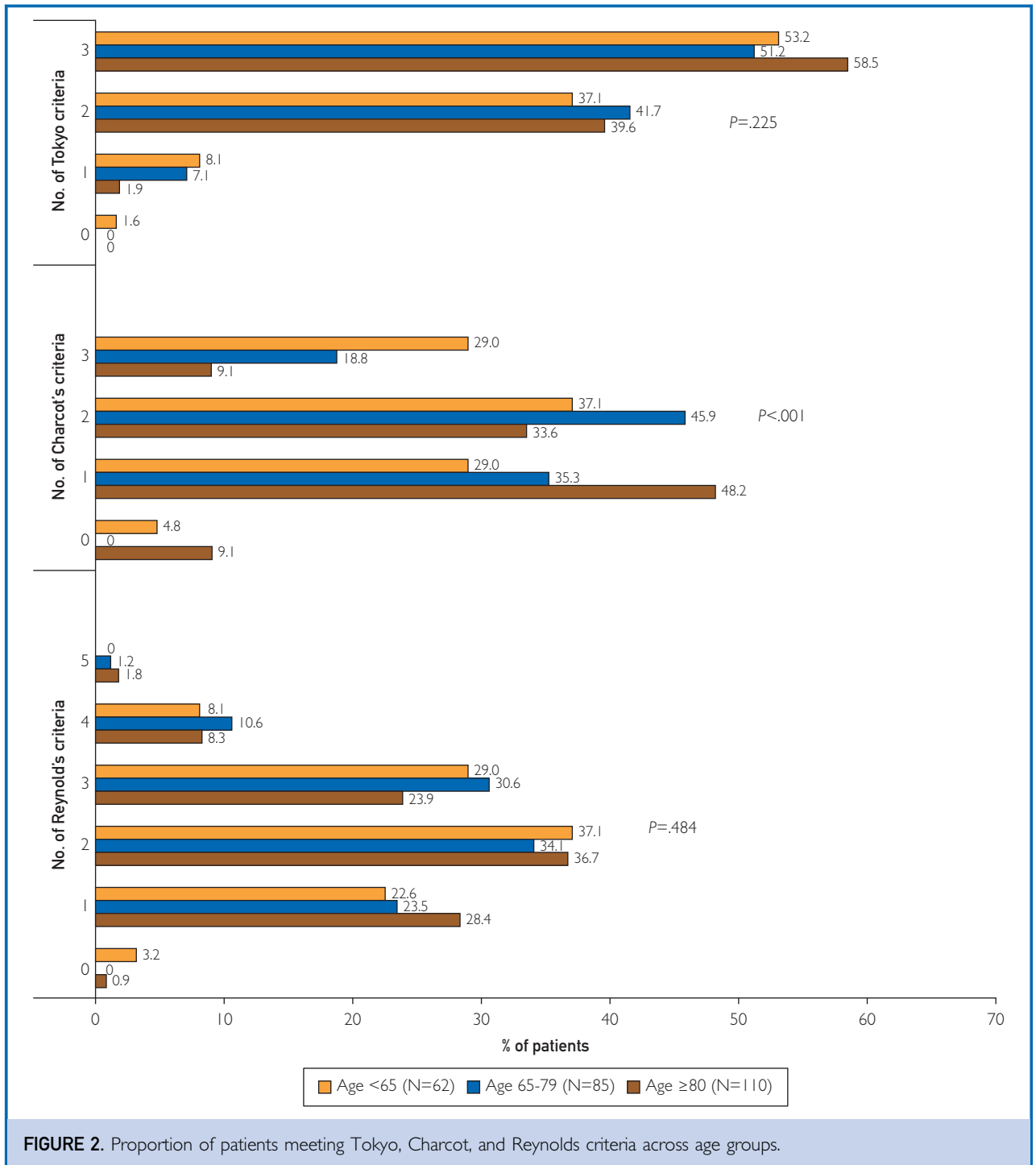
FIGURE 2. Proportion of patients meeting Tokyo, Charcot, and Reynolds criteria across age groups.

the age of the patient. Because cholestasis is defined by abnormalities on liver function tests (total bilirubin ≥2 mg/dL; AP, γ-glutamyltransferase, ALT, and AST >1.5 times the upper limit of normal), normal liver biochemical test results essentially rule out choledocholithiasis-related cholangitis. (4) Tokyo Guidelines perform better than Charcot or Reynolds criteria, but systemic inflammation criteria, an essential requirement for the diagnosis of cholangitis according to the latest Tokyo Guidelines, are absent in approximately 25% of patients
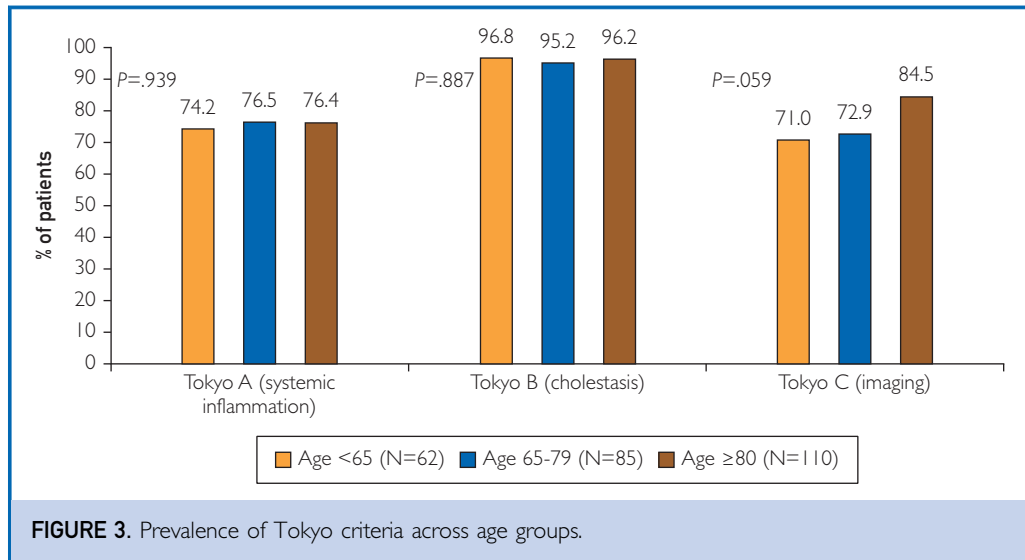
FIGURE 3. Prevalence of Tokyo criteria across age groups.

(Figure 3). (5) Requiring all 3 Tokyo Guidelines criteria to make a diagnosis of definite cholangitis potentially misses the diagnosis in over half the patients and (6) none of the criteria for either Charcot triad or Reynolds pentad are particularly helpful in either ruling in or ruling out cholangitis. The findings from this study documenting the limited utility of Charcot triad and Reynolds pentad confirm previous observations.[5,7] The atypical presentation of cholangitis in patients 80 years or older was highlighted. The current investigation, arguably the first in the Western hemisphere, systematically evaluated Charcot triad, Reynolds pentad, and the Tokyo Guidelines criteria in a large, homogeneous group of patients with cholangitis due to ERCP-documented CBD stones, 110 of whom were 80 years of age or older.

Whereas Charcot triad and Reynolds pentad have come to define the classic presentation of acute cholangitis, the literature varies widely regarding the prevalence of these typical symptoms/signs on initial presentation. In a study of 21 patients with suppurative cholangitis ranging from 49 to 81 years of age (mean age, 64.7 years), Charcot triad was observed in 85% of patients.[8] Elderly patients (defined as >70 years of age) were significantly more likely to present with disturbances of consciousness and Reynolds pentad than younger patients (defined as <70 years of age). In a smaller study of 17 patients with cholangitis only, 4 patients (23.5%) presented with Charcot triad while only 1 patient presented with the complete pentad.[9] A similarly low prevalence was noted in a study that also included patients with biliary strictures

TABLE 3. Clinical Outcomes				
Variable	Age <65 y (N=62)	Age 65-79 y (N=85)	Age ≥80 y (N=110)	P value
Length of hospital stay (d)				<.001
Median (Q1, Q3)	4.0 (3.0, 5.8)	5.0 (4.0, 7.0)	6.5 (4.0, 9.8)	
Mean ± SD	5.0±3.8	6.2±3.7	8.3±7.4	
Range	2.0-30.0	3.0-20.0	2.0-43.0	
Length of ICU stay (d)				.021
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.3)	
Mean ± SD	0.4±1.2	1.0±2.2	2.0±4.9	
Range	0.0-6.0	0.0-12.0	0.0-40.0	
Hospital death, No. (%)	2 (3.2)	1 (1.2)	6 (5.5)	.270
3-Month mortality, No. (%)	2 (3.2)	6 (7.1)	13 (11.8)	.123
ICU, intensive care unit; Q1, first quartile; Q3, third quartile.				

and primary sclerosing cholangitis with only 15.6% of younger patients and 18.8% of elderly patients presenting with the complete triad.[10] Another small study in 6 patients older than 80 years found that such patients were less likely to manifest typical symptoms of acute cholangitis such as jaundice and biliary colic, leading to delays in appropriate care.[11] In a retrospective study, 122 patients with cholangitis due to stones, strictures, or malignancy who underwent ERCP were divided into 2 groups: younger than 75 years and 75 years or older. No significant difference was found between the 2 age groups in prevalence of abdominal pain or jaundice.[10] The presentation with symptoms of falls, incontinence, and confusion in the older group led to a significant delay in diagnosis and subsequent ERCP, without a difference in overall mortality and incidence of septic shock between the 2 groups. More recently, a study from Taiwan in 443 patients with pancreaticobiliary disease that divided the cohort into various age groups (young, 18 to 64 years; young-old, 65 to 74 years; old-old, 75 to 84 years; and very old, ≥85 years) concluded that older patients with choledocholithiasis were less likely to present with biliary colic, jaundice, or elevated liver test results.[12]

Our study has specific relevance to patients 80 years or older, who comprised the major subgroup (42.8%). In this group, the most common symptom of cholangitis was lethargy or feeling unwell (73.6%). Neither biliary colic nor jaundice was universal, and temperature was usually less than 38 °C. Presentations included altered consciousness and/or hypotension without pain, fever, or jaundice. Indeed, 39.6% of patients 80 years or older presented with hypotension. Lower body mass index, which may reflect frailty, was also more prevalent in this age group. The presentation of patients 80 years or older with only nonspecific symptoms such as altered mental status, general malaise, and tachypnea could lower the suspicion for a diagnosis of cholangitis. In contrast, greater than 80% of patients younger than 80 years age presented with biliary colic, likely raising suspicion for biliary pathology early during presentation. The reasons why older patients present less frequently with biliary colic cannot be determined from this study. Given the elderly population's higher likelihood for presentation without classic

symptoms, we hypothesized that potential delays in diagnosis and subsequent delays in treatment could lead to worse outcomes in this population. However, despite their atypical symptomatology, elderly patients did not fare more poorly than their younger counterparts, with similar lengths of hospital stay, rates of ICU admission, hospital mortality, and 3-month mortality.

It is possible that the setting in which patients were hospitalized substantially improved clinical outcomes. Although at large centers it is common for most patients to undergo comprehensive laboratory testing, including liver biochemistries, on presentation to the emergency department regardless of symptomology, this is likely not the case at smaller facilities or stand-alone emergency departments. In these settings, more in-depth laboratory studies are most likely only drawn when initial data and clinical assessment are unrevealing. Therefore, this could potentially delay the diagnosis of cholangitis in elderly patients who present without fever or biliary colic. When biliary pathology is suspected, timely access to hepatobiliary imaging and ERCP services may be unavailable outside large tertiary care centers. Therefore, we suspect that data collected across various levels of care would potentially demonstrate worse clinical outcomes in elderly patients with cholangitis.

The Tokyo Guidelines are the most helpful in suggesting a diagnosis of cholangitis due to CBD stones, but Charcot criteria may be useful as an initial screen. A strength of the Tokyo Guidelines is that age did not seem to make a difference in the diagnostic accuracy. Liver test results were abnormal in 96% of patients in our series. Thus, in a patient with undiagnosed sepsis, in which liver test abnormalities are common, normal liver biochemistries should point to a source of infection other than the biliary tree. Inflammation and biliary imaging criteria were less sensitive in suspecting cholangitis. A "definite" diagnosis of cholangitis requiring all 3 Tokyo Guidelines criteria would have been possible in less than 50% of patients. We suggest that instead of requiring systemic inflammation, cholestasis defined by jaundice, or abnormal liver biochemical test results, greater than 1.5 times the upper limit of normal for ALT, AST, or AP should be essential criteria for the diagnosis of cholangitis since this is very sensitive

for a diagnosis of cholangitis, but with likely low specificity. We suggest obtaining liver biochemical tests in patients with unexplained malaise, hypotension, or altered consciousness. Imaging with US or CT for detection of biliary dilatation should be performed in patients with either abdominal pain or elevated liver test results and undiagnosed sepsis, with a low threshold for considering early ERCP in patients with fever as well. No biliary imaging is required if patients have fever with normal liver test results.

The strengths of our study include that it was carried out at a tertiary care referral center with ERCP confirmation of choledocholithiasis. Other causes of cholangitis including strictures, tumors, and indwelling biliary stents were excluded. The numbers of patients, especially those older than 80 years is much larger than in previous studies.[10,11] Follow-up was complete through 90 days. The fact that the study reflects care at a tertiary referral center could also be perceived as a weakness in that our results might not be generalizable to all environments of care. A delayed diagnosis and time to ERCP may be associated with worse outcomes in a center with more limited expertise. Only white blood cell criteria for inflammation were used in the study; CRP data were unavailable in the majority of patients. It is possible that the addition of CRP may have increased the sensitivity of inflammation criteria. The absence of a hospitalized control group with suspected infection but with normal cholangiography is also a weakness of the study. Whereas a control group would be helpful to determine specificity of the criteria, such a study is not possible given that ERCP is only employed for presumptive therapy and not for diagnostic purposes because of the risks of the procedure. It is important to emphasize that diagnostic sensitivity, which was obtained in our study, is more important than specificity for diseases that can be life-threatening if not diagnosed rapidly and treated appropriately.

CONCLUSION

Patients 80 years of age or older who have cholangitis secondary to choledocholithiasis are less likely to meet Charcot triad criteria but more likely to have features of Reynolds pentad than younger age groups. Elderly patients with cholangitis may present with only

malaise, hypotension, or altered consciousness without abdominal pain or fever, lowering the suspicion for cholangitis. Within the Tokyo Guidelines, cholestasis as defined by a serum bilirubin level greater than 2 mg/dL or AST, ALT, and AP levels greater than 1.5 times the upper limit of normal should replace inflammation as the essential diagnostic criterion for cholangitis. Increasing age is associated with longer length of hospital and ICU stay among patients with cholangitis. We recommend early liver biochemistry testing in elderly patients with unexplained altered consciousness, hypotension, or malaise. Normal results on liver biochemistry studies essentially rule out cholangitis.

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