Title: Impact of inadequate initial antimicrobial therapy on mortality in patients with bacteraemic cholangitis: A retrospective cohort study

Authors: Yasuaki Tagashira [1,2], Naoya Sakamoto [3], Toshiaki Isogai [4], Mayu Hikone [3], Atsushi Kosaka [3], Ran Chino [1], Masanori Higuchi [1], Yuki Uehara [2], Hitoshi Honda [1]

Affiliation:

1. Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

2. Department of Infection Control Science, Juntendo University Graduate School of Medicine, Tokyo, Japan

3. Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, Tokyo Japan

4. Department of Cardiology, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan.

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18 Corresponding author:

19 Dr. Hitoshi Honda,

20 Division of Infectious Diseases, Tokyo Metropolitan Tama Medical Center,

21 Tokyo, Japan

22 2-8-29, Musashidai, Fuchu, Tokyo, 183-8524, Japan.

23 Email: hondah@hotmail.com

24 Tel: 81-42-323-5111

25 Fax: 81-42-323-9209

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Abstract

Objectives: Acute cholangitis is a common cause of bacteraemia resulting in severe sepsis or septic shock. The impact of the appropriate initial antimicrobial therapy on short-term mortality in bacteraemic cholangitis has not been well investigated.

Methods: We conducted a retrospective cohort study of patients with bacteraemic cholangitis at two large tertiary care centres in Tokyo, Japan between 2009 and 2015. We determined the factors associated with 30-day all-cause mortality from the date of drawing the first positive blood culture, using a multivariate logistic regression analysis.

Results: We identified 573 patients with bacteraemic cholangitis (median age, 77 years; male, 58.3%). The 30-day all cause mortality rate was 6.6% (38/573). Inadequate initial antimicrobial therapy occurred in 133 (23.2%) patients. Factors associated with 30-day all cause mortality included the Charlson comorbidity index score >3 (adjusted odds ratio ([aOR], 4.12; 95% confidence interval [CI], 1.18-14.38), jaundice (total bilirubin > 2.5mg/dl) (aOR, 3.39; 95% CI, 1.46-7.89), septic shock within 48 hours of the first positive blood culture (aOR, 3.34; 95% CI, 1.42-7.89), biliary obstruction due to hepatobiliary malignancy (aOR, 8.00; 95% CI, 2.92-21.97), and inadequate initial antimicrobial therapy (aOR, 2.78; 95% CI, 1.27-6.11).

Conclusions: Inadequate initial antimicrobial therapy was an important, modifiable determinant of survival.

Introduction

Acute cholangitis in the context of an obstructed biliary tree results from a wide spectrum of bacterial pathogens, and commonly results in bacteraemia. The proportion of cholangitis cases leading to bacteraemia reportedly ranges from 20 to 71 % [1-4]. Acute cholangitis requires a combination of medical and surgical therapy, including adequate antimicrobial therapy and biliary decompression according to disease severity [5]. Within the past two decades, mortality among patients with acute cholangitis has fallen to the range of 2.7 ~ 10 %, presumably due to advances in broad-spectrum antimicrobial therapy and improved access to emergency biliary decompression [6].

Bloodstream infection in cholangitis is a major cause of mortality [1, 7, 8]. The proper choice of antimicrobial agents has been shown to lead to a favourable outcome including a decrease in mortality in critically ill patients with bacteraemia or other serious infections [9]. Conversely, inadequate initial antimicrobial therapy was associated with an increased risk of overall mortality due to severe sepsis and septic shock [10-13]. The pathogens in cholangitis are frequently polymicrobial and include enterobacteriaceae (i.e., *Escherichia coli*, *Klebsiella* species [spp.], *Enterobacter* species), anaerobes, *Enterococcus spp.*, and less commonly, *Streptococcus spp.* and *Pseudomonas spp.* [14]. Furthermore, an increase in the incidence of cholangitis due to highly drug-resistant organisms (e.g., drug-resistant Enterobacteriaceae) has become a great concern worldwide

[15]. Given the lack of adequate studies describing the impact of proper empirical antimicrobial therapy on outcomes in bacteraemic cholangitis, we aimed to investigate the association between treatment strategies and clinical outcomes at two large tertiary care centres in the Tokyo metropolitan area in Japan.

Materials and Methods

Study setting

The present report comprises a retrospective observational cohort study of adult patients with bacteraemic cholangitis conducted at two tertiary care hospitals (Tokyo Metropolitan Tama Medical Center and Tokyo Metropolitan Bokutoh General Hospital) from January 2009 to December 2015. Tokyo Metropolitan Tama Medical Center is a 790-bed tertiary care centre with 29 subspecialties, and Tokyo Metropolitan Bokutoh General Hospital is a 765-bed tertiary care centre with 39 subspecialties. Both medical centres each have a division of GI (Gastroenterology) and ID (Infectious Diseases), respectively. Obtaining blood cultures prior to initiating parenteral antimicrobials was a standard practice at the participating hospitals. ERCP was performed at the discretion of the attending gastroenterologist if biliary decompression was indicated. The institutional review board at Tokyo Metropolitan Tama Medical Center and Tokyo Metropolitan Bokutoh General Hospital approved this project and the patient's consent was waived because this study would not have influenced current management of participating patients (being a retrospective cohort study).

Patient selection

We included all patients with bacteraemic cholangitis defined in accordance with the criteria for cholangitis in the Tokyo Guidelines and based on a positive blood culture at the time of diagnosis of acute cholangitis [16]. We enrolled patients starting in January 2009 because the electronic medical record was retrievable starting in that year. We initially identified eligible patients as those whose condition fit the ICD-10 code for “cholangitis” and who had a positive blood culture. We then screened patients by reviewing their electronic medical records and identified cholangitis patients who met the diagnostic criteria of the Tokyo Guidelines for definite or suspected acute cholangitis [16]. If an uncommon pathogen was suspected of causing the cholangitis, we reviewed electronic medical records to determine if the patient had bacteraemic cholangitis. For patients with multiple episodes of bacteraemic cholangitis, only the first episode was included in the study.

We excluded the following conditions: 1) patients aged <18 years old; 2) the presence of bacteraemic cholangitis following ERCP or percutaneous transhepatic cholangiodrainage, 3) the presence of bacteraemic cholangitis due to *Candida spp*, 4) death within 24 hours of blood culture obtained, 5) absence of follow-up data on 30-day mortality, and 6) the presence of bacteraemia likely due to other infections (e.g., urinary tract infection).

Variables of interest and data collection

Thirty-day all-cause mortality, tracked from the day when a positive blood culture was drawn, was used to assess the impact of inadequate initial antimicrobial therapy on the mortality of patients with bacteraemic cholangitis. Electronic medical charts were reviewed for this purpose, and if mortality data were unavailable from the electronic medical records, the (family of) patients who had no readmission data after Day 30 following the obtainment of a positive blood culture, were contacted by telephone to determine whether the patient was alive at Day 30. The demographic characteristics and the clinical and microbiological data of patients who met the inclusion criteria were obtained from the electronic medical records. Severity according to the Tokyo Guidelines, the Charlson comorbidity index, and the Pitt bacteremia score were computed for each patient [16, 17, 18].

Definition

True bacteraemia was identified based on the presence of a causative organism (Gram-negative bacilli, anaerobes, or Gram-positive cocci) in at least 1 set of blood cultures. For normal skin flora and other potential pathogens (i.e., coagulase-negative staphylococci or *Corynebacterium*, *Propionibacterium*, or *Bacillus species*), two sets of positive blood cultures obtained at separate sites were required for diagnosis of true bacteraemia [19]. Polymicrobial bacteraemia was defined as the presence of two or more species of microorganisms in the same blood culture or the growth of

different species in two or more separate blood cultures grown from the same sampling. Bacteraemia was also categorized based on onset, as previously described [20]. Septic shock was defined as bacteraemia evoking systemic inflammatory response syndrome with concomitant evidence of organ hypoperfusion and arterial systolic blood pressure <90 mmHg refractory to fluid resuscitation or the need for vasopressors to maintain blood pressure [21]. The severity of illness and the comorbidity index were measured using the Pitt bacteremia score, the severity assessment criteria of the Tokyo Guidelines, and the Charlson comorbidity index. The Charlson comorbidity index score was categorized as 0-1, 2-3, or >3 [17].

Inadequate antimicrobial therapy was defined as either 1) the administration of empiric antimicrobials which were inactive against subsequently isolated organisms or 2) no administration of antimicrobial agents between drawing a blood culture and obtaining a positive culture result [22]. In this study, we considered cephamycins (e.g., cefmetazole and cefmandole) to be inadequate antimicrobial choices for the treatment of bacteraemic cholangitis due to the presence of extended-spectrum β-lactamase (ESBLs)-producing enterobacteriaceae; although the antimicrobial susceptibility results showed that these pathogens were susceptible to cephamycin, treatment failure resulting from cephamycin use has frequently been reported [23, 24].

Statistical analysis

Categorical variables were compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. All significant variables with $P < 0.10$ in univariate analysis were considered to be candidates for entry into a forward stepwise multivariate logistic regression model. The multivariate logistic regression model for assessing the factors associated with inadequate antimicrobial therapy followed the rule of thumb of 1 covariate per 10 events; however, the ratio of events to independent variable in the final model assessing factors associated with mortality was 1:5, given the lower number of outcome events. Variables were retained in the final model if $P<0.05$. A 2-sided $P<0.05$ was considered statistically significant. The Spearman's rho test was used to examine collinearity of independent variables. The Hosmer-Lemeshow test was used for goodness of fit for the logistic regression model. All statistical analyses were performed using SPSS version 23 (IBM, Armonk, NY, USA).

Results

In total, 1019 episodes were initially screened. Among these, 365 (35.8%) failed to fulfil the definition of bacteraemic cholangitis, and 81 (7.5%) were excluded because they had recurrent episodes of bacteraemic cholangitis during the study period, leaving 573 (56.2%) episodes in the study period for analysis. (Figure 1.) The patient characteristics are summarized in Table 1.

Of the 573 patients, 133 (23.2%) had inadequate initial antimicrobial therapy in the interval between drawing the blood culture and the notification of positive blood culture result. Among 133 patients with inadequate antimicrobial therapy, the majority (132/133: 99.2%) had received ineffective initial antimicrobial therapy against the isolated pathogens, and one patient (1/133:0.8%) had received no antimicrobial therapy at the time of diagnosis. Empirical antimicrobial therapy was found to be inadequate in patients with bacteraemic cholangitis due to Gram-negative bacilli (70/133; 52.6%), *Enterococcus spp.* (40/133; 30.1%), or anaerobes (11/133; 8.3%). No vancomycin-resistant enterococci were identified. In patients with inadequate initial antimicrobial therapy, 83/133 (62.4%) were switched to other antimicrobials or given other additional antimicrobials to provide adequate coverage following identification of the inadequate therapy. In our cohort, the patients with bacteraemic cholangitis due to enterococcal, nosocomial, and polymicrobial infections were

significantly more likely to have received inadequate antimicrobial therapy. Factors independently associated with inadequate empirical antimicrobial therapy are shown in Table 2.

The prevalence of 30-day all-cause mortality among patients with bacteraeamic cholangitis was 6.6% (38/573). In these 38 patients, the median time between the date of the positive blood culture and the date of death was 18 days (range 2-30 days). Predictors of mortality in patients with bacteraemic cholangitis are shown in Table 3. In the multivariate model, factors associated with mortality included the Charlson comorbidity index score >3 (adjusted odds ratio ([aOR], 4.12; 95% confidence interval [CI], 1.18-14.38), jaundice (total bilirubin > 2.5mg/dl) (aOR, 3.39; 95% CI, 1.46-7.89), septic shock within 48 hours of the first positive blood culture (aOR, 3.34; 95% CI, 1.42-7.89), biliary obstruction due to hepatobiliary malignancy (aOR, 8.00; 95% CI, 2.92-21.97), and inadequate initial antimicrobial therapy (aOR, 2.78; 95% CI, 1.27-6.11).

Discussion

This study evaluated the impact of the adequacy of empirical antimicrobial therapy on mortality in bacteraemic cholangitis at two Japanese tertiary care centres, and demonstrated that inadequate empirical antimicrobial therapy was independently associated with 30-day mortality in patients with bacteraemic cholangitis even after adjusting for preexisting co-morbidities and the severity of illness. The findings were consistent with those of previous studies demonstrating that inappropriate initial antimicrobial therapy increased the odds of mortality in patients with bacteraemic biliary tract infection approximately two-fold [25, 26]. However, these previous studies considered various types of biliary infection including cholecystitis. Moreover, the impact of inadequate antimicrobial therapy on the outcome was assessed without adjusting for the effect of biliary decompression, or based on the relatively lower performance rate of biliary decompression in the respective studies. In contrast, the present study focused exclusively on bacteraemic cholangitis and assessed the impact of inadequate initial antimicrobial therapy on mortality under circumstances in which ERCP was promptly available.

In the current study, inadequate initial antimicrobial therapy was a single modifiable factor independently associated with increasing mortality among patients with bacteraemic cholangitis.

This finding demonstrates the importance of initial antimicrobial choice in the management of bacteraemic cholangitis.

As seen in the Table 1, a considerable proportion of patients received cephalosporins as an initial antimicrobial therapy in the study population. Where enterococcal bacteraemic cholangitis was concerned, inadequate antimicrobial therapy was specifically due to cephalosporin administration. Additionally, because cefmetazole, 3rd generation cephalosporins, and ampicillin/sulbactam, which were not active against drug-resistant Gram-negative bacilli, were commonly used as the initial antimicrobial therapy even in nosocomial settings, this might have resulted in inadequate antimicrobial therapy in the nosocomial bacteraemic cholangitis as well. It is noteworthy that in our study, patients with nosocomial bacteraemic cholangitis tended to have a higher Charlson comorbidity index (Appendix 1), and that a trend towards inadequate antimicrobial therapy in patients with a higher Charlson comorbidity index was evident although this variable was not retained in the final model (Table 2). Although frequent use of broad spectrum antimicrobial agents may be able to minimize the occurrence of inadequate antimicrobial therapy, their unnecessary use may counteract the effects of antimicrobial stewardship. Assessing the involvement of organisms potentially contributing to inadequate antimicrobial therapy after risk stratification is imperative for choosing the most appropriate empirical antimicrobial therapy. More importantly, treating physicians

214 should have a high level of suspicion for pathogens that are not routinely covered by empirical
215 treatment choices.

216 We also found that some non-modifiable patient–related factors including septic shock within 48 hours
217 of the first positive blood culture and biliary obstruction due to hepatobiliary malignancy were
218 independent predictors of mortality. Our findings were consistent with those of other reports showing
219 that significant underlying comorbidities and severity of illness at the time of presentation were also
220 independent predictors of mortality in cases of bacteraemic cholangitis [25, 26].

221 In this study, although a large number of patients underwent ERCP within 1 calendar day of
222 obtaining a positive blood culture, ERCP did not confer any benefit in terms of reduced mortality
223 rate in the final model despite being a statistically significant variable in univariate analysis. Previous
224 studies revealed variable associations between ERCP and mortality. Whereas ERCP contributed to a
225 reduction in mortality in patients with cholangitis, and delayed ERCP was associated with in-hospital
226 mortality and organ failure in patients with acute cholangitis [3, 27, 28], up to 50.0 % of patients
227 with cholangitis responded to antimicrobial therapy alone in another study [26]. In the present study,
228 the benefits of ERCP in cholangitis may have been underestimated because of the smaller numbers
229 of events (i.e., deaths), differences in disease severity, and the impact of other, unmeasured factors
230 associated with decreased mortality, such as advances in medical practice other than biliary

decompression. ERCP is considered to be one of the most important treatment strategies from various perspectives including biliary decompression, stone removal, and achieving biliary tract patency via drainage or stents.

Our study has several important limitations. As with any other observational study, even after adjusting for known predisposing factors, other unmeasured factors may have contributed to patient mortality. Although this study included a large population, the subjects were all derived from just two urban tertiary care centres in Japan such that the results may not be generalizable to other hospitals. Although the majority of patients underwent ERCP within one calendar day of obtaining a positive blood culture, the impact of the interval from presentation to the initiation of ERCP on the outcome was not assessed.

Conclusion

The current study demonstrated that inadequate initial antimicrobial therapy negatively impacted mortality in bacteraemic cholangitis patients. Inadequate antimicrobial therapy frequently occurred in bacteraemic cholangitis cases due to *Enterococcus spp.*, and polymicrobial organisms as well as nosocomial cases. Given the circumstances associated with the spectrum of causative pathogens and

the prevalence of drug-resistant organisms, an appropriate, initial antimicrobial choice against bacteraemic cholangitis, complemented by rigorous antimicrobial stewardship is extremely important to improve clinical outcomes while avoiding the overuse of antimicrobial agents.

Transparency declaration

All authors declare no conflicts of interest.

Authors' contributions

YT, and HH designed the study protocol. YT, NS, AK, RC, and MH collected the patient data. YT, TI, and HH performed the data analysis. YT drafted the first version of the manuscript. YU performed the critical review. HH and YU revised the manuscript, and all the authors contributed to the final version of manuscript.

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359 **Table and Figure legends**

Table 1. Baseline characteristics of patients with bacteraemic cholangitis

Table 2. Comparison of patients with bacteraemic cholangitis receiving adequate or inadequate initial antimicrobial therapy

Table 3. Comparison of clinical characteristics, and outcomes between 30-day survivors and nonsurvivors

Figure 1. Description of the study population

Table1. Baseline characteristics of patients with bacteraemic cholangitis

Characteristic	Total (n=573)
Demographics	
Age, year, median (range)	77 (26-97)
Male gender	334 (58.3)
Asian	573 (100)
Co-morbidities/past medical history	
History of smoking	208 (36.3)
History of alcohol use	188 (32.8)
History of malignancies	231 (40.3)
Diabetes mellitus	135 (23.6)
Congestive heart failure	49 (8.6)
Peripheral vascular disease	17 (3.0)
Cerebrovascular disease	63 (11.0)
Chronic pulmonary disease	34 (5.9)
Peptic ulcer disease	47 (8.2)
Chronic liver disease	91 (15.9)
Chronic kidney disease	18 (3.1)
Connective tissue disease	20 (3.5)
Systemic steroid use (≥ 5 mg) in the last 28 days	17 (3.0)
Chemotherapeutic agent use in the last 28 days	60 (10.5)
Charlson comorbidity index, median (IQR)	2 (1-4)
Score 0-1	218 (38.0)
Score 2-3	186 (32.5)
Score >3	169 (29.5)

Characteristics at presentation	
Jaundice (total bilirubin > 2.5mg/dl)	296 (51.7)
Septic shock within 48 hours after the first positive blood culture	111 (19.4)
Classification of bacteraemia [a]	
Community-acquired	214 (37.3)
Healthcare-associated	269 (46.9)
Nosocomial	90 (15.7)
Severity of cholangitis (Tokyo Guidelines)	
Grade Ⅰ	178 (31.1)
Grade Ⅱ	150 (26.2)
Grade Ⅲ	245 (42.8)
Causes of biliary obstruction	
Choledocholithiasis	326 (56.9)
Biliary obstruction due to hepatobiliary malignancy	148 (25.8)
Benign biliary stricture	99 (17.3)
ERCP for biliary decompression at bacteraemic cholangitis diagnosis	444 (77.5)
Time to ERCP, median, days (range)	0 (0-10)
Causative pathogen	
Monomicrobial bacteraemia	457 (79.8)
Enterobacteriaceae	378 (66.0)
Other Gram-negative bacilli	15 (2.6)
Enterococcus spp.	18 (3.1)
Anaerobes	24 (4.2)
Other pathogens	22 (3.8)

Polymicrobial bacteraemia [b]	116 (20.2)
Two organisms	91 (15.9)
More than three organisms	25 (4.4)
Resistant pathogens	
3rd generation cephalosporin-resistant enterobacteriaceae	34 (5.9)
Extended-spectrum β-lactamase-producing enterobacteriaceae	15 (2.6)
Carbapenem-resistant enterobacteriaceae	0 (0)
Vancomycin-resistant enterococci	0 (0)
Initial antimicrobial choice	
Cephalosporin / beta-lactamase inhibitor	210 (36.6)
Penicillins / beta-lactamase inhibitor	176 (30.7)
Cephalosporin	124 (21.6)
Carbapenem	31 (5.4)
Any single agent other than cephalosporin or carbapenem	7 (1.2)
Cephalosporin with metronidazole	3 (0.5)
Any combination therapy other than cephalosporin with metronidazole [c]	22 (3.8)
Treatment outcome	
Pitt bacteraemia score, median (IQR)	1 (0-2)
Inadequate initial empirical antimicrobial therapy [d]	133 (23.2)
Due to Gram-negative bacilli	70 (52.6)
Due to *Enterococcus spp.*	40 (30.1)
Due to anaerobes	11 (8.3)
Duration of antimicrobial therapy, median, day (range)	12 (1-108)
Length of hospital stay from the onset of cholangitis, median, day (range)	15 (2-154)

Died within 30 days	38 (6.6)

Data are presented as number (%) unless otherwise specified.

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; T-bil, total serum bilirubin level

[a, b, d] See methods for definition

[c] Includes carbapenem and other antimicrobials (n=5), cephalosporin and beta-lactam / beta-lactamase inhibitors (n=4), two different penicillins / beta-lactamase inhibitors (n=3), and two different cephalosporins (n=3).

Table2. Comparison of patients with bacteraemic cholangitis receiving adequate or inadequate initial antimicrobial therapy

Characteristic	Adequate initial antimicrobial therapy (n=440)	Inadequate Initial antimicrobial therapy (n=133)	*P*	Adjusted OR (95% CI)	*P*
Demographics					
Age, years					
≤ 50	8 (1.8)	6 (4.5)	Ref.	Ref	
51-65	51 (11.6)	27 (20.3)	0.56		
66-80	227 (51.6)	62 (46.6)	0.07		
≥ 81	154 (35.0)	38 (28.6)	0.05	0.29 (0.09-0.97)	0.05
Male gender	257 (58.4)	77 (57.9)	0.92		
Co-morbidities/past medical history					
History of smoking	153 (34.8)	55 (41.4)	0.18		
History of alcohol use	142 (32.3)	46 (34.6)	0.67		
History of malignancies*	167 (38.0)	64 (48.1)	0.04		
Diabetes mellitus	107 (24.3)	28 (21.1)	0.49		
Congestive heart failure	35 (8.0)	14 (10.5)	0.38		

Peripheral vascular disease	12 (2.7)	5 (3.8)	0.56
Cerebrovascular disease	43 (9.8)	20 (15.0)	0.11
Chronic pulmonary disease	27 (6.1)	7 (5.3)	0.84
Peptic ulcer disease	38 (8.6)	9 (6.8)	0.59
Chronic liver disease	67 (15.2)	24 (18.0)	0.42
Chronic kidney disease	12 (2.7)	6 (4.5)	0.39
Connective tissue disease	14 (3.2)	6 (4.5)	0.43
Systemic steroid use (≥ 5 mg) in the last 28 days	12 (2.7)	5 (3.8)	0.56
Chemotherapeutic agent use in the last 28 days	48 (10.9)	12 (9.0)	0.63
Charlson comorbidity index			
Score 0-1	180 (40.9)	38 (28.6)	Ref.
Score 2-3	141 (32.1)	45 (33.8)	0.10
Score >3	119 (27.0)	50 (37.6)	0.005
Characteristics at presentation			
Jaundice (T-bil > 2.5 mg/dl)	234 (53.2)	62 (46.6)	0.20
Septic shock within 48 hours after the first positive blood culture	85 (19.3)	26 (19.5)	1.00

Classification of bacteraemia [a]					
Community-acquired	177 (40.2)	37 (27.8)	Ref.		
Healthcare-associated	210 (47.7)	59 (44.4)	0.21		
Nosocomial	53 (12.0)	37 (27.8)	<0.001	3.57 (1.93-6.61)	<0.001
Severity of cholangitis (Tokyo Guidelines)					
Grade Ⅰ	134 (30.5)	44 (33.1)	Ref.		
Grade Ⅱ	119 (27.0)	31 (23.3)	0.38		
Grade Ⅲ	187 (42.5)	58 (43.6)	0.80		
Causes of biliary obstruction					
Choledocholithiasis	267 (60.7)	59 (44.4)	Ref.		
Biliary obstruction due to hepatobiliary malignancy	101 (23.0)	47 (35.3)	0.001		
Benign biliary stricture	72 (16.4)	27 (20.3)	0.05		
Bacteraemia					
Polymicrobial bacteraemia [b]	63 (14.3)	53 (39.8)	<0.001	1.94 (1.10-3.43)	0.02
Pathogens					
Enterobacteriaceae	348 (79.1)	54 (40.6)	Ref.		

Enterococcus spp.[c]	24 (5.5)	40 (30.1)	<0.001	8.19(4.08-16.45)	<0.001
Others	68 (15.5)	39 (29.3)	<0.001	3.15(1.84-5.41)	<0.001

Data are presented as number (%) unless otherwise specified.

Abbreviations: ERCP, Endoscopic retrograde cholangiopancreatography; T-bil, total serum bilirubin level; N/A, not applicable

[a,b] See methods for definition

[c.] Includes both monomicrobial and polymicrobial bacteraemic cholangitis (18 episodes were of monomicrobial enterococcal bacteraemic cholangitis and 46 episodes were of polymicrobial enterococcal bacteraemic cholangitis).

* The variable, 'history of malignancies' was not included in the final model despite its statistical significance in univariate analysis because this variable showed strong collinearity with the Charlson comorbidity index (rs = 0.62 [P<.001])

Variables considered but not retained in the final model were the Charlson comorbidity index and causes of biliary obstruction.

The Hosmer-Lemeshow goodness of fit χ^2 test was 3.74 (P= 0.81)

Table 3. Comparison of clinical characteristics, and outcomes between 30-day survivors and nonsurvivors

Characteristics	Survived > 30 days (n=534)	Died ≤ 30 days (n=38)	*P*	Adjusted OR (95% CI)	*P*
Demographics					
Age					
≤ 50	13 (2.4)	1 (2.6)	Ref.		
51-65	75 (14.0)	3 (7.9)	0.58		
66-80	267 (49.9)	22 (57.9)	0.95		
≥ 81	180 (33.6)	12 (31.6)	0.90		
Male gender	312 (58.3)	22 (57.9)	0.96		
Co-morbidities/past medical history					
History of smoking	196 (36.6)	12 (31.6)	0.60		
History of alcohol use	177 (33.1)	11 (28.9)	0.72		
History of malignancies*	202 (37.8)	29 (76.3)	<0.001		
Diabetes mellitus	128 (23.9)	7 (18.4)	0.55		
Congestive heart failure	43 (8.0)	6 (15.8)	0.12		
Peripheral vascular disease	17 (3.2)	0			

Cerebrovascular disease	61 (11.4)	2 (5.3)	0.42		
Chronic pulmonary disease	34 (6.4)	0			
Peptic ulcer disease	44 (8.2)	3 (7.9)	1.00		
Chronic liver disease	82 (15.3)	9 (23.7)	0.17		
Chronic kidney disease	16 (3.0)	2 (5.3)	0.34		
Connective tissue disease	19 (3.6)	1 (2.6)	1.00		
Systemic steroid use (≥ 5 mg) in the last 28 days	17 (3.2)	0	NA		
Chemotherapeutic agent use in the last 28 days	51 (9.5)	9 (23.7)	0.01		
Charlson comorbidity index					
Score 0-1	214 (40.0)	4 (10.5)	Ref.		
Score 2-3	179 (33.5)	7 (18.4)	0.25		
Score >3	142 (26.5)	27 (71.1)	<0.001	4.12(1.18-14.38)	0.03
Characteristics at presentation					
Jaundice (T-bil > 2.5 mg/dl)	269 (50.3)	27 (71.1)	0.02	3.39 (1.46-7.89)	0.005
Septic shock within 48 hours after the first positive blood culture	95 (17.8)	16 (42.1)	0.001	3.34 (1.42-7.89)	0.006
Classification of bacteraemia [a]					

Community-acquired	210 (39.3)	4 (10.5)	Ref.		
Healthcare-associated	249 (46.5)	20 (52.6)	0.01		
Nosocomial	76 (14.2)	14 (36.8)	<0.001		
Severity of cholangitis (Tokyo Guidelines)					
Grade Ⅰ	171 (32.0)	7 (18.4)	Ref.		
Grade Ⅱ	145 (27.1)	5 (13.2)	0.77		
Grade Ⅲ	219 (40.9)	26 (68.4)	0.02		
Causes of biliary obstruction					
Choledocholithiasis	318 (59.94)	8 (21.1)	Ref.	Ref.	
Biliary obstruction due to hepatobiliary malignancy	121 (22.6)	27 (71.1)	<0.001	8.00 (2.92-21.97)	<0.001
Benign biliary stricture	96 (17.9)	3 (7.9)	0.75		
ERCP for biliary decompression at bacteraemic cholangitis diagnosis	423 (79.1)	21 (55.3)	0.002		
Time to ERCP, days (range)	0 (0-10)	0 (0-4)	0.62		
Bacteraemia					
Enterococcus bacteraemia [b]	57 (10.7)	7 (18.4)	0.18		
Polymicrobial bacteraemia [c]	106 (19.9)	10 (26.3)	0.40		

Treatment outcome					
Pitt bacteraemia score, median (IQR)	1 (0-2)	1 (0.75-3)	0.11		
Inadequate initial antimicrobial therapy [d]	116 (21.7)	17 (44.7)	0.002	2.78 (1.27-6.11)	0.01
Duration of antimicrobial use, days (range)	12 (1-108)	12.5 (2-30)	0.71		

Data are presented as number (%) unless otherwise specified.

Abbreviations: OR, odds ratio; ERCP, Endoscopic retrograde cholangiopancreatography; T-bil, total serum bilirubin level; N/A, not applicable

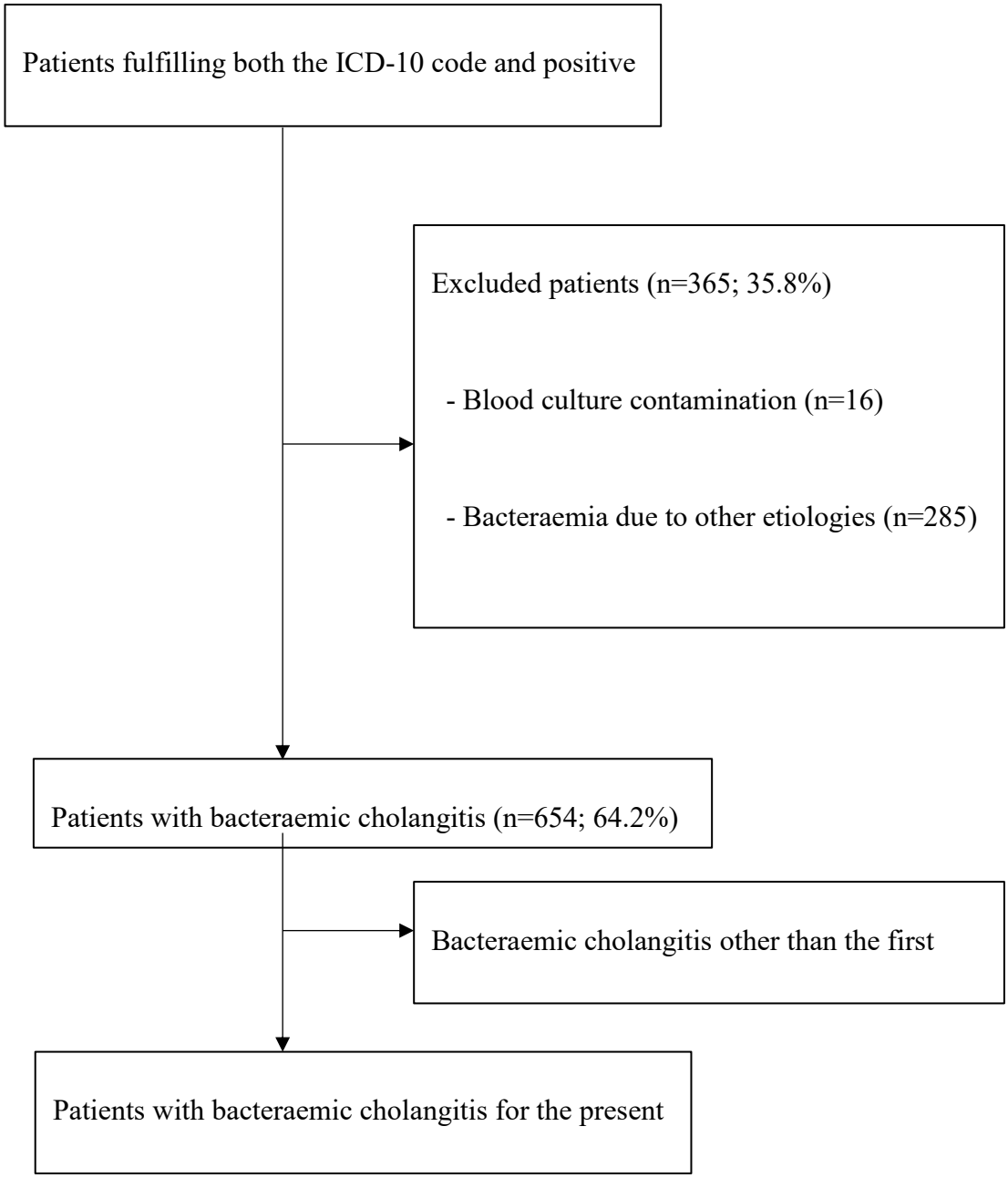
[a-d] See methods for definition.

* The variable, 'history of malignancies' was not included in the final model despite its statistical significance in univariate analysis because this variable had a strong collinearity with the Charlson comorbidity index (rs = 0.62 [P<.001])

Variables considered but not retained in the final model were chemotherapeutic agent use in the last 28 days, classification of bacteraemia, severity of cholangitis (Tokyo Guidelines) and ERCP for biliary decompression at bacteraemic cholangitis diagnosis.

The Hosmer-Lemeshow goodness of fit χ^2 test was 3.60 (P= 0.89)

Figure 1. Description of the study population



Appendix

Title: Impact of inadequate initial antimicrobial therapy on mortality in patients with bacteraemic cholangitis: A retrospective cohort study

Authors: Yasuaki Tagashira [1,2], Naoya Sakamoto [3], Toshiaki Isogai [4], Mayu Hikone [3], Atsushi Kosaka [3], Ran Chino [1], Masanori Higuchi [1], Yuki Uehara [2], Hitoshi Honda [1]

Appendix 1.

Supplementary tables for 1) proportion of Charlson comorbidity index in classification of bacteraemia and 2) proportion of Charlson comorbidity index in adequate/inadequate initial antimicrobial therapy

		Classification of bacteraemia		
		Community	Healthcare-associated	Nosocomial
Charlson comorbidity index	0-1	121 (56.5)	82 (30.5)	15 (16.7)
	2-3	64 (29.9)	96 (35.7)	26 (28.9)
	>3	29 (13.6)	91 (33.8)	49 (54.4)

	Adequate initial antimicrobial therapy (n=53)	Inadequate initial antimicrobial therapy (n=37)

Charlson comorbidity index	0-1	10 (18.9)	5 (13.5)
	2-3	14 (26.4)	12 (32.4)
	>3	29 (54.7)	20 (54.1)