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A Scoring System to Predict Positive Follow-up Blood Culture in Acute Cholangitis

Masashi TSUNEMATSU, Koichiro HARUKI, Yoshihiro SHIRAI, Jungo YASUDA, Kenei FURUKAWA, Shinji ONDA, Taro SAKAMOTO, Takeshi GOCHO, and Toru IKEGAMI

Department of Surgery, The Jikei University School of Medicine

ABSTRACT

Background : Optimal treatments, including antibiotics and biliary drainage, can improve patient outcomes for acute cholangitis regardless of blood stream infection. The utility of follow-up blood culture (FUBC) for bacteremic acute cholangitis has not been well investigated.

Methods : The study included 95 cases of bacteremic acute cholangitis from April 2013 through March 2018. We retrospectively investigated the relation between results of FUBCs and clinical characteristics and then developed a scoring system to predict positive FUBC.

Results : At least 1 FUBC was had by 53 patients, and FUBCs were positive in 8 patients (15%). A positive FUBC was more likely ($p<0.01$) in patients who had fever on the day of FUBC, an initial blood culture with Gram-positive cocci, or a high serum alkaline phosphatase level on the 3rd day after starting treatment. With these 3 factors a clinical scoring system was developed. Within a total possible score of 0 to 3, the area under the curve of the scoring system was 0.900 on the basis of the receiver operating characteristic curve analysis of the prediction score.

Conclusions : Our clinical scoring system can be used to predict a positive FUBC for patients with bacteremic acute cholangitis and can enable us to know reasonable case for FUBC.

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Key words : acute cholangitis, follow-up blood culture, scoring system, Tokyo Guidelines 2018

INTRODUCTION

A common cause of bacteremia is biliary tract infection, and for cases of acute cholangitis the standard of care has been biliary drainage and antimicrobial therapy[1]. To choose the most appropriate antibiotics, blood cultures are helpful. So that both treatment decisions and clinical outcomes can be improved, causative organisms can be better understood through antibiotic susceptibility profiles ; for this purpose, repeated blood culture, referred to as follow-up blood culture (FUBC), has been recommended[2]. The most organism most often causing cholangitis ascending from the gastrointestinal tract is the Enterobacteriaceae, and its isolates from patients with cholangitis often show antimicrobial resistance[1,3]. However, clinical symptoms dramatically improve within a few days if patients receive optimal treatments, including antibiotics and biliary drainage[4-6]. Therefore, the utility of FUBC in the management of bacteremic acute cholangitis remains unclear.

In the present study we analyzed 95 cases of bacteremic acute cholangitis. We examined the difference between patients with positive or negative FUBC results to investigate which patients have sustained bacteremia and need to be followed up.

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恒松　雅，春木孝一郎，白井　祥睦，安田　淳吾，古川　賢英，恩田　真二，坂本　太郎，後町　武志，池上　徹

Mailing address : Koichiro HARUKI, Department of Surgery, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan.

E-mail : haruki@jikei.ac.jp

PATIENTS AND METHODS

Patient selection

A retrospective cohort study was conducted at the Department of Surgery, The Jikei University Hospital, Tokyo, from April 2013 through March 2018. This study was approved by the Ethics Committee of The Jikei University School of Medicine for Biomedical Research 27-177(8062) and conformed with the provisions of the Declaration of Helsinki.

The participants of this study were patients who had been hospitalized because of bacteremic acute cholangitis or had bacteremic acute cholangitis that had developed during hospitalization. The diagnostic criteria of Tokyo Guidelines 2018[7] were used to confirm the diagnosis of acute cholangitis. Excluded from the study were 4 patients with hepatic abscesses.

Data collection and analysis

Medical records for clinical and microbiological data were collected and reviewed. Hematologic and chemical profiles were routinely measured when acute cholangitis was diagnosed and 1 day and 3 days after the first blood test. To measure the serum alkaline phosphatase (ALP) level, the Japan Society of Clinical Chemistry method was used. Two sets of blood cultures were obtained before the start of antibiotic therapy. The antibiotic used to treat patients with acute cholangitis were chosen on the basis of Tokyo Guidelines 2013 or Tokyo Guidelines 2018[7,8]. Endoscopic retrograde cholangiography (ERC) was performed if necessary. Percutaneous transhepatic biliary drainage or percutaneous transhepatic gallbladder drainage was performed if ERC was too difficult to perform. Gram stain results of the initial blood culture were revealed on the 3rd day after the diagnosis of cholangitis. When blood cultures were positive, blood samples were drawn and cultured at approximately 4-day intervals until the FUBC became negative. An infection control physician examined all patients who had a positive blood culture. To assess FUBCs, the patients were classified into 2 groups : those with a positive FUBC and those with a negative FUBC.

We investigated the relations between clinicopathologic variables and positive FUBCs by univariate analysis. The following variables were examined : the patient's sex and age, the patient's medical history (the presence of diabetes mellitus, common bile duct stones, concomitant hepatobiliary-pancreatic cancer, or a biliary stent ; a history of surgery with reconstruction of the bile duct, and treatment with chemotherapy), and details of the present case of acute cholangitis (community- or hospital-acquired, of new onset or recurrence, grade of severity on the basis of Tokyo Guidelines 2018, use of antibiotics on the day of FUBC, biliary drainage, the presence of Gram-positive cocci in the initial blood culture, antibiotic susceptibility, presence of fever on the day of FUBC, the duration of the antibiotic therapy, the need for intensive care, whether the patient died while hospitalized, and laboratory data on day 3). Patients were considered to have a fever, according to previous studies[9], if the recorded temperature was $\geq 38^{o}$C.

Microbiologic studies

Samples of blood from all patients suspected of having acute cholangitis were cultured in 2 types of medium (Bactec Plus Aerobic and Anaerobic ; BD Biosciences, Frankland Lakes, NJ, USA) and processed with the BD BACTEC-FX blood culture system (BD Biosciences). Identification and testing for susceptibility to antimicrobial agents were performed for the types of bacteria as follows : Gram-negative bacilli, *Staphylococcus* sp., and *Enterococcus* sp. were both identified and susceptibility tested with commercially available panels (Microscan WalkAway automated system, Beckman Coulter, Brea, CA, USA) ; *Streptococcus* sp. were identified with standard biochemical testing and susceptibility tested with commercially available panels (Beckman Coulter) ; anaerobes were identified with standard biochemical testing and susceptibility tested with the disc diffusion method, judged on the basis of the category of Enterobacteriaceae in document M100-S23, *Performance Standards for Antimicrobial Susceptibility Testing, Twenty-third Information Supplement*, of the Clinical and Laboratory Standards Institute (REFERENCE). For all bacteria cultured, Clinical and Laboratory Standards Institute recommendations and criteria were used to define susceptibility to antimicrobial agents.

Statistical analysis

All statistical analyses were conducted with the software program Stata/SE version 14.0 (StataCorp LLC, College Station, TX, USA). Univariate analysis was performed with the Mann-Whitney U-test, Chi-square test, or Fisher's ex-

act test, as appropriate. The cut-off value of the predictive score was calculated with a receiver operating characteristic (ROC) curve. We used the two-sided α level of 0.05.

Results

The participants were 95 patients in whom bacteremic acute cholangitis had been diagnosed during the study period. Of these patients, 53 (56%) had at least 1 FUBC after the initial blood culture (Supplementary Table 1). The clinical characteristics of the patients with bacteremic acute cholangitis are shown in Supplementary Table 1.

Microbiologic analyses showed that the microorganism categories of the causative pathogens were Gram-negative bacilli (n=37, 70%), Gram-positive cocci (n=7, 13%), and polymicrobial (n=9, 17%) (Supplementary Table 2). The most common pathogen was *Escherichia coli* (n=16, 30%), which was followed by *Klebsiella pneumoniae* (n=15, 28%), *Klebsiella oxytoca* (n=6, 11%), *Enterococcus faecium* (n=5, 9%), *Enterobacter cloacae* (n=4, 8%), *Enterobacter aerogenes* (n=4, 8%), *Enterococcus faecalis* (n=3, 6%), and *Enterococcus raffinosus* (n=3, 6%).

Of the 53 FUBCs, 8 (15%) had positive results (Table 1). Factors associated with positive results were Gram-positive cocci in the initial blood culture (p=0.003), fever on the day of FUBC (p=0.001), antibiotic therapy for a longer time (p=0.036), a higher rate of dying in the hospital (p=0.003), and higher serum levels on day 3 of ALP γ-glutamyl transpeptidase level (Fig. 1). For a positive FUBC, the optimal cutoff serum ALP level on day 3 was set, on the basis of ROC analysis, at 1,106 U/l, with the area under the curve of 0.8169 (95% confidence interval, 0.635-0.999) (Supplementary Fig. 1).

A clinical scoring system for predicting positive FUBC was developed with 3 factors—the presence of Gram-positive cocci in the initial blood culture, febrile temperature (a sustained fever or a new fever), and serum ALP level on day 3≥1,106 U/l— and a total score of 0 to 3 points (Fig. 2a). An increased score was correlated with an increased rate of a positive FUBC. The area under the curve of the scoring system, based on the ROC curve analysis of the prediction score, was 0.900 (95% confidence interval, 0.811-0.989) (Fig. 2b).

Table 1. Difference between patients whose follow-up blood cultures were positive or negative (n=53)

Variables	Positive (n=8)	Negative (n=46)	P value
Male	7 (88%)	29 (63%)	0.198
Age, years*	75 (64-79)	70 (61-77)	0.419
Diabetes mellitus	1 (13%)	3 (7%)	0.565
Common bile duct stone	0 (0%)	5 (11%)	0.322
Concomitant hepatobiliary-pancreatic cancer	7 (66%)	32 (70%)	0.658
History of surgery with reconstruction of bile duct	5 (63%)	17 (37%)	0.191
Biliary stent	3 (38%)	22 (48%)	0.515
During chemotherapy	2 (25%)	18 (39%)	0.42
Community acquired	3 (38%)	28 (61%)	0.191
Recurrent cholangitis	7 (88%)	26 (57%)	0.11
Tokyo Guidelines 2018 grade (I : II : III)	3 (38%) : 5 (63%) : 0 (0%)	9 (20%) : 17 (37%) : 19 (41%)	0.071
Biliary drainage	5 (63%)	25 (54%)	0.715
Antibiotics on the day of FUBC	7 (88%)	41 (89%)	0.747
Gram-positive cocci in initial blood culture	5 (63%)	7 (16%)	0.003
Microorganism sensitive to those antibiotics	5 (63%)	33 (72%)	0.585
Fever on the day of FUBC	5 (63%)	5 (11%)	0.001
Duration of antibiotic therapy, days*	23 (18-30)	14 (12-17)	0.036
Need for intensive care unit	3 (38%)	5 (11%)	0.055
In-hospital death	3 (38%)	2 (4%)	0.003

*Median (interquartile range)
FUBC, follow-up blood culture

Table 2. Scoring system for prediction of positive follow-up blood culture

Prognostic factors	Points
Gram-positive cocci in initial blood culture	
No	0
Yes	1
Febrile (sustained fever or new fever)	
None	1
Yes	0
Serum alkaline phosphatase level on day 3	
<1,106 U/l	0
≥ 1,106 U/l	1
Total	0-3

DISCUSSION

In the present study, the positivity rate for FUBCs was 15%. Patients with positive FUBCs received antibiotic therapy for a longer time and had a higher in-hospital death rate than did patients with negative FUBCs. Furthermore, patients with positive FUBCs were more likely to have these 3 factors : fever on the day of FUBC, initial blood culture showing Gram-positive cocci, and a high serum ALP level 3 days after the start of treatment. With these 3 factors, we established a clinical scoring system for the prediction of a positive FUBC that could enable us to know reasonable cases for FUBC.

A previous study has suggested that FUBC has little utility in management of bloodstream infections with Gram-negative bacilli[10]. In that study, which focused on cases of persistent bacteremia, Gram-negative bacilli bacteremia was usually transient and was not shown to require FUBC. However, cases of intra-abdominal infections in which cholangitis was classified were few in number. Furthermore, a study of bacteremic urinary tract infection did not recommend routine FUBC for cases that were mild to moderately severe or exhibiting rapid clinical improvements[11]. However, in the management of Gram-negative bacilli bacteremia in children, FUBC was recommended, especially for patients with medical devices and patients with resistance to empirical antibiotics[12]. These studies warn that routine FUBC for cases of bacteremic cholangitis might result in false-positive results, longer hospital stays, and higher healthcare costs.

The present study suggests that FUBC is reasonable to perform for patients who have a new or continuing fever or have shown a poor improvement in laboratory data. If optimal treatments with antibiotics or successful biliary drainage or both are achieved, the clinical manifestations improve rapidly[4-6]. Previous prospective studies have demonstrated that, even in patients with bacteremia, the duration of antibiotic therapy for acute cholangitis can be shortened without any complications if the fever has resolved[13,14]. Clinically, a decreasing fever is often used to determine whether therapy has been effective. The serum ALP level is related

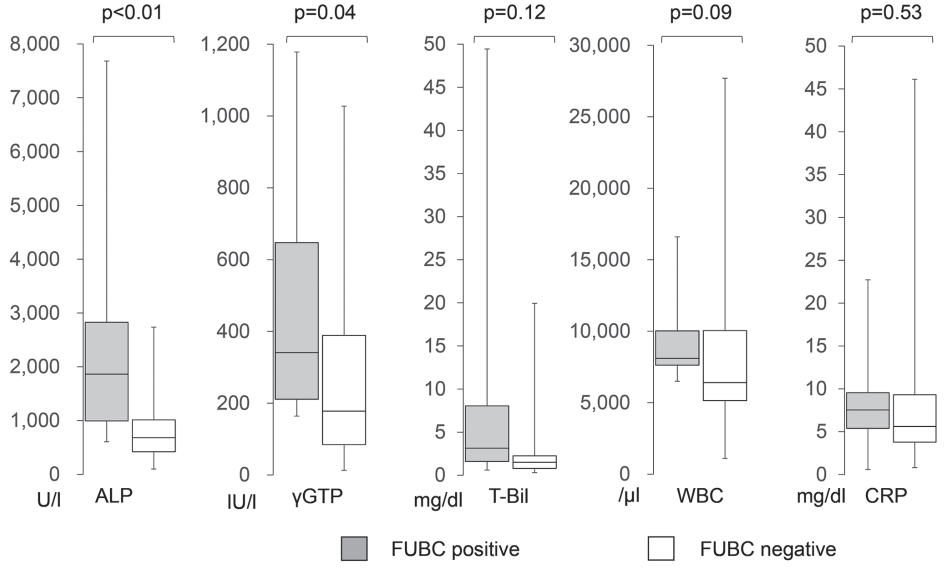

Fig. 1. Difference of laboratory data on day 3 between on patients whose follow-up blood cultures were positive or negative.

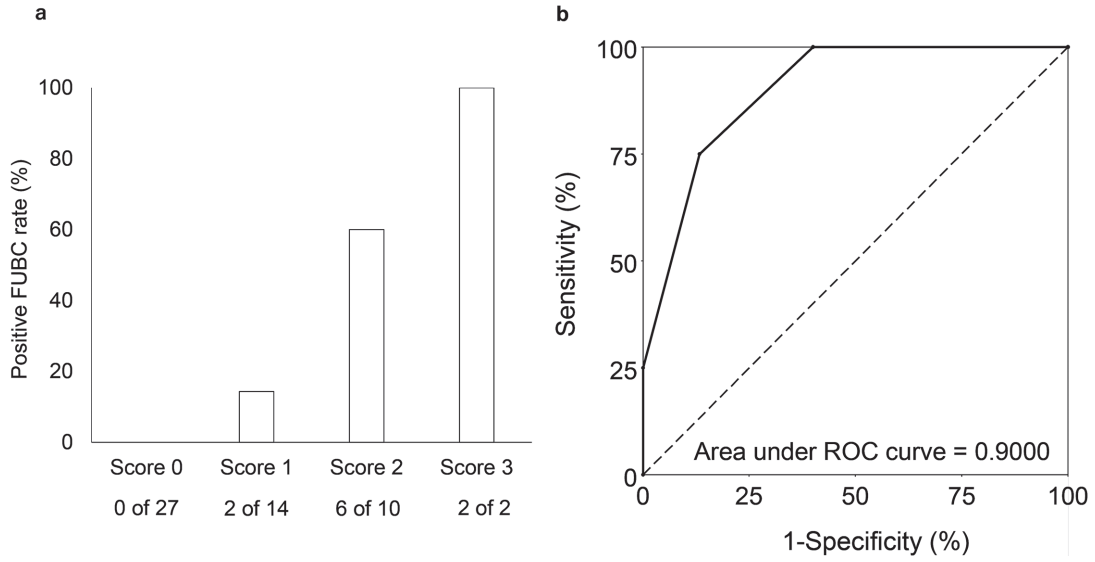

Fig. 2. (a) Relationship between positive follow-up blood culture and our scoring system. (b) receiver operating characteristic curve of scoring system for the positive follow-up blood culture.

to the degree of bile duct obstruction and increased pressure within the biliary tract associated with obstruction is the primary factor responsible for the pathogenesis of bacteremia in acute cholangitis[15,16]. A high serum ALP level included in the Tokyo Guidelines 2018 diagnostic criteria is considered an appropriate surrogate marker of therapeutic effect[7,17,18].

Even if clinical symptoms improve, FUBC is currently recommended, owing to the possibility of bacteremia remaining or recurring. However, this recommendation was based on a study for the management of *Staphylococcus aureus* bacteremia[19]. If Gram-positive cocci are present, antimicrobial therapy should be continued for at least 2 weeks because bacteremia persists more frequently with Gram-positive cocci infection than with Gram-negative bacilli infection and because Gram-positive cocci are likely to cause infective endocarditis[1]. In the present study, the positive FUBC rate for Gram-positive cocci bacteremia was 41.6% (5 of 12 FUBCs)[5,6]. In acute cholangitis, performing FUBC also seems reasonable owing to persistent Gram-positive cocci infection in the bloodstream. Incidentally, in recent studies of acute cholangitis, *Staphylococcus aureus* was isolated from both the blood and bile of less than 1% of patients[20] and the incidence of infective endocarditis was 0.3%[11].

The present study had several limitations. First, this was a retrospective single-center study with an inherent selection bias. The acute cholangitis had been caused in a lot of our patients by a hepatobiliary pancreatic tumor ; therefore, whether our findings can be extended to patients who have acute cholangitis due to other cases, such as bile duct stones, is uncertain. However, the distribution of causative microorganisms in our study was similar to that of previous studies[1,3]. A second limitation was that we routinely perform blood cultures for patients with symptoms of infection, even if they are terminally ill owing to cancer. The almost of such patients eventually die due to infection[21]. It might increase the mortality of our study and persistent bacteremia.

In conclusion, we have developed a clinical scoring system consisting of febrile temperature on the day of FUBC, Gram-positive cocci in initial blood culture, and a high serum ALP level on the 3rd day after the start of treatment. This simple scoring system can provide a more accurate prediction of positive FUBC that can enable us to know reasonable cases for FUBC.

Authors have no conflict of interest.

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Supplementary Table 1. Characteristics of patients with follow-up blood cultures (n = 53)

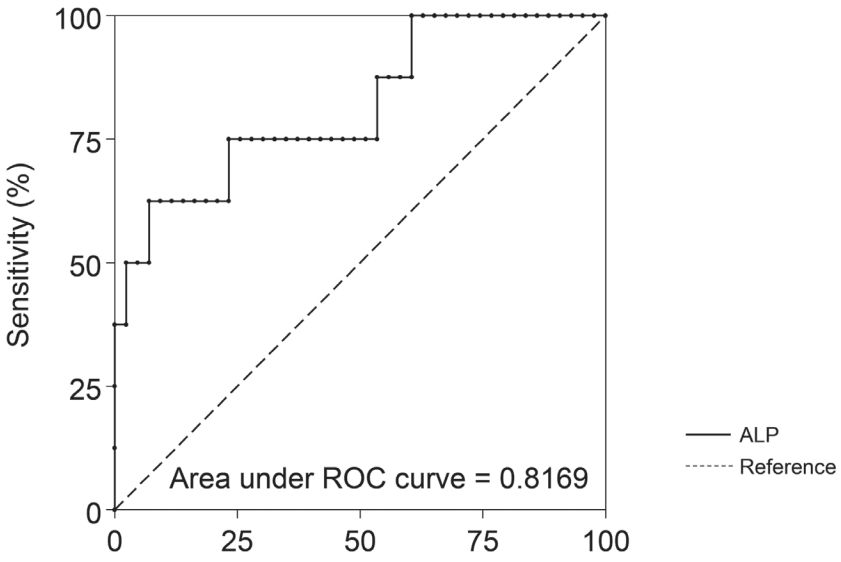
Variables	Median (interquartile range) or number
Male : female sex	36 (68%) : 17 (32%)
Age, years	70 (62–78)
Diabetes mellitus	8 (15%)
Common bile duct stone	5 (9%)
Concomitant hepatobiliary-pancreatic cancer	39 (74%)
History of surgery with reconstruction of bile duct (pancreaticoduodenectomy : liver transplantation : other : none)	10 (19%) : 5 (9%) : 7 (13%) : 31 (58%)
Biliary stent	25 (47%)
During chemotherapy	23 (43%)
Community acquired	31 (58%)
Recurrent cholangitis	30 (57%)
Tokyo Guideline 2018 grade (I : II : III)	12 (23%) : 22 (42%) : 19 (36%)
Biliary drainage (endoscopic retrograde biliary or nasobiliary drainage : percutaneous transhepatic cholangial drainage : none)	25 (47%) : 4 (8%) : 24 (45%)
Antibiotics on the day of FUBC	48 (91%)
Microorganism sensitive to those antibiotics	38 (72%)
Fever on the day of FUBC	10 (19%)
Duration of antibiotic therapy	14 (12.3–18)
Need for intensive care unit	8 (15%)
In-hospital death	5 (9%)

FUBC, follow-up blood culture

Supplementary Table 2. Isolated microorganisms from initial blood culture

Microorganisms	No.	Microorganisms	No.
Gram-negative bacilli	70	Gram-positive bacilli	1
Escherichia coli	16 (ESBL 1)	*Corynebacterium* spp.	1
Klebsiella pneumoniae	15	Gram-positive cocci	7
Klebsiella oxytoca	6	*Enterococcus faecium*	5
Enterobacter cloacae	4	*Enterococcus faecalis*	3
Enterobacter aerogenes	4	*Enterococcus raffinosus*	3
Aeromonas hydrophila	1	*α-Streptococcus*	1
Achromobacter xylosoxidans	1		
Haemophilus influenzae	1		
Morganella morganii	1		
Pseudomonas aeruginosa	1		

ESBL, extended-spectrum β-lactamase



Supplementary Fig. 1. Receiver operating characteristic curve of serum alkaline phosphatase levels on day 3 for the positive follow-up blood culture