What Are the Risk Factors for Acute Suppurative Cholangitis Caused by Common Bile Duct Stones?

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Background/Aims: Acute suppurative cholangitis (ASC), a severe form of acute cholangitis, is a life-threatening condition that must be treated with appropriate and timely management. The purpose of this study was to identify the factors that predispose patients to ASC. **Methods:** We retrospectively investigated 181 patients (100 men, 81 women; age, 70.66 ± 7.38 years, mean $\pm$ SD) who were admitted to Wonkwang University Hospital between January 2005 and June 2007 for acute cholangitis with common bile duct (CBD) stones. All patients underwent endoscopic retrograde cholangiopancreatogram to remove the stones. Variables and factors that could be assessed upon admission were analyzed to identify the risk factors for the development of ASC. **Results:** Of the 181 patients, 44 (24.3%) presented with ASC. On multivariate analysis, the followings were found to be independent risk factors for the development of ASC: impacted common bile duct stone ($p=0.010$), current smoker status ($p=0.008$), advanced age (>70 years; $p=0.002$), and gallstone ($p=0.016$). The most commonly isolated organisms in bile culture were *Enterococcus* species, *Escherichia coli*, and *Klebsiella* species. **Conclusions:** Impacted bile-duct stones, current smoking, advanced age, and gallstones were identified as independent risk factors for the development of ASC in patients with CBD stones. These results suggest that emergency biliary drainage is beneficial in patients with these risk factors. (*Gut Liver* 2010;4:363-367)

Key Words: Cholangitis; Bile duct stone; Risk factor

INTRODUCTION

Acute cholangitis ranges from mild forms that respond to medical therapy to severe forms that lead to septicemia, a potentially lethal condition requiring urgent drainage of the biliary system.^{1,2} Acute suppurative cholangitis (ASC) refers to the presence of pus in the bile ducts. The accumulation of pus in a bile duct may cause increased intrabiliary pressure, which can lead to biliary sepsis. Urgent medical or surgical decompression of the bile duct should be performed in patients with ASC.³ Formerly, the management of this life-threatening condition was urgent surgical biliary decompression; however, this treatment was associated with high morbidity and mortality.^{1,2} Endoscopic drainage has recently become an accepted method for treating acute cholangitis that is combined with common bile duct (CBD) stones, and this treatment has reduced the morbidity, mortality, and length of hospitalization.⁴ Therefore, the differentiation between suppurative and nonsuppurative cholangitis is important for early and effective treatment.

While analysis of the conditions related to the development ASC is warranted, most studies have focused primarily on the treatment and outcomes of ASC; thus, the predisposing factors for developing ASC are not fully understood, and studies that report on the risk factors for ASC in patients with bile duct stones are rare.⁵ Therefore, it is important to identify the factors that predispose patients to ASC and to determine the proper timing for performing biliary drainage.

The purpose of this retrospective study was to identify the risk factors for developing ASC and to determine the factors that identify early-stage ASC in patients with CBD

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stones.

MATERIALS AND METHODS

1. Patients

We retrospectively investigated 181 patients who were admitted to Wonkwang University Hospital between January 2005 and June 2007 for acute cholangitis with CBD stones. The diagnosis of acute cholangitis combined with CBD stones was based on the clinical features of acute cholangitis (fever, abdominal pain, and abnormal liver chemistry suggestive of biliary obstruction) and abdominal ultrasonography and/or computed tomography. All the patients underwent endoscopic retrograde cholangiopancreatogram (ERCP) to remove the CBD stones. The diagnosis of ASC was based on the clinical features of acute cholangitis, accompanying septic shock (systolic blood pressure [SBP] <90 mm Hg), impaired consciousness, and evidence of purulent bile.

Blood tests, including complete blood count, prothrombin time, C-reactive protein (CRP) levels, renal and liver function tests, blood cultures, and glucose and amylase levels, were performed on admission and repeated whenever necessary. Abdominal ultrasonography and/or computed tomography were performed on all patients within 12 hours of admission. Administration of intravenous broad-spectrum antibiotics began once the clinical diagnosis of acute cholangitis was made. Patients received intravenous fluid based on their hydration status, and a central venous line was inserted in patients admitted with septic shock.

2. Endoscopic management of acute cholangitis

Written informed consent was obtained from all patients or their families before the endoscopic procedures were performed. This study was conducted in accordance with the Helsinki Declaration.

All ERCP procedures were performed by experienced endoscopists. CBD stones was performed by endoscopic sphincterotomy (EST) with a pull-type sphincterotome or endoscopic papillary balloon dilation (EPBD) with a controlled radial expansion balloon (Boston Scientific Co., Natick, MA, USA) after limited sphincterotomy. Stones or sludge were then removed using a Dormia basket and/or a balloon extraction catheter. A 7-Fr pigtail-tipped (Wilson-Cook Medical Inc., Winston-Salem, NC, USA) was inserted over a guidewire, if deemed necessary, by the endoscopist. Bile samples were obtained by means of a nasobiliary catheter and the samples were then cultured. After ERCP and biliary drainage, all the patients were closely observed for evidence of ERCP-related

complications.

3. Data collection and statistical analysis

To identify the risk factors for ASC, we compared the characteristics of patients with (n=44) and without (n=137) ASC. The following factors were analyzed: age, gender, body temperature, smoking status, history of alcohol consumption, coexisting disease, gallstones, presence of periampullary diverticulum, CBD diameter, presence of dilatation, size and number of CBD stones, prior cholecystectomy, impaired consciousness, presence of impacted bile duct stone, systolic BP, and blood test results. Smoking status was divided into 2 groups: current smoker and non-smoker.

All statistical analyses were performed using the SPSS version 11.5 for Windows, (SPSS Inc., Chicago, IL, USA). The chi-square test or Fisher exact test was used to analyze the categorical variables. Continuous variables were analyzed by the unpaired t-test. Predictive factors with a p value less than 0.05 on univariate analysis were included in the multivariate analysis using a backward stepwise logistic regression model. Multivariate logistic regression analyses were performed to define the risk factors associated with ASC. Statistical significance was defined as a p value less than 0.05.

RESULTS

A total of 181 patients (100 men and 81 women) were enrolled in this study. Their mean age was 70.66 ± 7.38 years (range, 38-98 years). Of the 181 patients, 44 (24.3%) presented with ASC. Among the patients with ASC, 31 (70.5%) were elderly (>70 years), 21 patients (47.7%) were current smokers, and 19 (43.2%) had an underlying disease such as diabetes, hypertension, a neurologic disorder, previous *Clonochiasis sinensis* infection, liver cirrhosis, or malignancy. ENBD catheter insertion was performed in 35 patients (79.5%), and biliary plastic stent insertion was performed in 5 patients (11.4%). ASC improved rapidly after biliary decompression with successful ERCP in all patients. One patient (2.3%) died from uncontrolled septicemia despite successful decompression of the biliary obstruction; this patient had underlying hematologic disease. Post-ERCP pancreatitis, mostly mild grade, developed in 4 patients (9.1%) with ASC and 14 patients (10.2%) without ASC.

On univariate analysis, the significant risk factors for ASC among the categorical predictive variables were as follows: current smoker, gallstone, impacted bile duct stone, and presence of periampullary diverticulum (Table 1). Significant factors for ASC among the continuous pre-

Table 1. Univariate Analysis of Risk Factors for ASC

Characteristics	Total	ASC	No ASC	p-value
Patient (M/F)	181 (100/81)	44 (25/19)	137 (75/62)	0.863
Age >70 yr	104 (57.5)	31 (70.5)	73 (53.3)	0.054*
Body temperature >37.7°C	33 (18.3)	12 (27.3)	21 (15.4)	0.115
Smoking	57 (32.8)	21 (47.7)	36 (27.5)	0.014*
Alcohol	63 (36)	14 (32.6)	49 (37.1)	0.715
Diabetes	14 (9.1)	4 (10.8)	10 (8.5)	0.744
Hypertension	64 (39)	11 (29.7)	53 (41.7)	0.251
Neurologic disorder	15 (9.4)	3 (8.3)	12 (9.8)	1.000
<i>C. sinensis</i> infection	13 (10.5)	2 (8.7)	11 (10.9)	1.000
Liver cirrhosis	5 (3.4)	2 (5.9)	3 (2.7)	0.331
Hepatobiliary cancer	21 (13.1)	2 (5.7)	19 (15.2)	0.169
Gastrointestinal cancer	6 (3.9)	0	6 (5.1)	
Gallstone	52 (35.6)	19 (57.6)	33 (29.2)	0.004*
Periampullary diverticulum	151 (88.8)	39 (97.5)	112 (86.2)	0.048*
CBD dilatation	167 (92.8)	42 (95.5)	125 (91.9)	0.738
No. of CBD stones >4	28 (15.6)	5 (11.6)	23 (16.9)	0.479
Cholecystectomy	39 (25.8)	6 (17.1)	33 (28.4)	0.270
Mortality	1 (0.5)	1 (2)	0	
Impaired consciousness	7 (3.9)	7 (15.9)	0	
Impacted stone	12 (8.2)	8 (18.6)	4 (3.8)	0.006*

Values are presented as number or number (%).

ASC, acute suppurative cholangitis; CBD, common bile duct.

*p<0.05.

Table 2. Predictive Accuracy of Continuous Variables on ASC with CBD Stones

Variable	No ASC	ASC	p-value
SBP [†]	120 (90-180)	110 (50-160)	0.0001*
Hemoglobin, g/dL	12.67±0.145	12.53±0.215	0.6220
WBC, /μL	9,192±383	12,350±865.8	0.0002*
Platelet, ×10 ³ /mL	200.2±7.304	161.7±10.06	0.0069*
Total bilirubin	3.574±0.2481	5.544±0.7229	0.0012*
AST, IU/L	166.6±12.74	297.2±44.60	0.0002*
ALT, IU/L	186.3±17.93	265.7±35.82	0.0362*
ALP, IU/L	508.1±36.9	520.5±40.86	0.8574
GTP, IU/L	449.1±37.18	471.5±55.94	0.7593
CRP, IU/L	61.3±6.257	129.3±11.01	0.0001*
CBD diameter, mm	14.35±0.4923	15.14±0.7023	0.4121

CBD, common bile duct; ASC, acute suppurative cholangitis; SBP, systolic blood pressure; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GTP, glutamyl transferase; CRP, C-reactive protein.

*p<0.05; [†]SBP value expressed as median (interquartile range).

Table 3. Multivariate Analysis of Risk Factors for ASC

Risk factors	OR	95% CI	p-value
Impacted stone	34.126	2.363-492.788	0.010
Current smoker	9.863	1.822-53.394	0.008
Advanced age (>70 yr)	8.909	2.242-35.406	0.002
Gallstone	4.742	1.334-16.864	0.016

OR, odds ratio; CI, confidence interval.

Table 4. Results of Bile Cultures in the No ASC (n=67) and ASC (n=35) Study Group

Pathogens	No ASC (59/67, 88%)	ASC (30/35, 86%)
<i>Enterococcus</i> species	25 (42.3)	10 (33.3)
<i>Escherichia. coli</i>	18 (30.1)	16 (53.3)
<i>Pseudomonas</i>	8 (13.5)	3 (1.0)
<i>Klebsiella</i>	4 (6.8)	4 (13.3)
Others	8 (13.6)	6 (2.0)

Values are presented as number (%).

ASC, acute suppurative cholangitis.

dictive variables were systolic BP, white blood cell (WBC) count, platelet count, and total bilirubin, AST, ALT and CRP levels (Table 2). Impacted bile duct stone, current smoker, advanced age (>70 years), and gall stone were independent risk factors for ASC on multivariate analysis (Table 3).

Bacteriologic examination was performed on bile from 35 patients (80%) with ASC and on bile from 67 patients (49%) without ASC. Of the 35 bile cultures from patients with ASC, 30 (86%) yielded aerobic and anaerobic bacteria: *Escherichia coli* and *Enterococci* were the predominant bacterial flora in the bile of these patients. *Escherichia coli* and *Enterococcus* were the most common pathogens in patients with and without ASC, respectively (Table 4).

DISCUSSION

ASC is a fatal disorder unless adequate biliary drainage is performed in a timely manner. The major cause of ASC is bile duct stones, but the clinical factors that predispose patients with bile duct stones to ASC are not completely understood.^{1,2} The decision to perform biliary drainage in patients with acute cholangitis is based on clinical findings of progressive disease or the failure to respond to medical treatment.^{1,6} Since urgent biliary drainage in all patients with acute cholangitis is not always necessary or feasible, the early prediction of patients who are likely to require urgent biliary decompression is very important.⁴ Consequently, determining the predisposing factors for developing ASC would allow clinicians to identify patients in the poor prognostic group and closely monitor them in an intensive care setting. It would also allow the earlier identification of patients who are unlikely to respond to medical treatment alone, so that more aggressive treatment to relieve the underlying obstruction could be performed at an earlier time.^{4,7}

Multivariate analysis identified impacted bile duct stone, chronic smoking, advanced age (>70 years), and gallstone as independent risk factors for the development of ASC. Tsujino *et al.*⁵ previously identified advanced age (>70 years), comorbid neurologic disease, and the presence of periampullary diverticulum as independent risk factors for the development of ASC based on multivariate analysis. In the present study, the presence of a peripapillary diverticulum and comorbid neurological disease were not identified as risk factors, whereas gallstone and current smoker status were. A possible explanation for the difference in results may be the retrospective nature of the data and the small number of patients in each study.

The current study reveals that advanced age is an independent risk factor for ASC, a finding also reported in other studies.^{7,8} Elderly patients often present without the typical symptoms of acute cholangitis, which include Charcot's triad. This can lead to misdiagnosis or a delayed diagnosis. In addition, elderly patients with acute cholangitis have a high incidence of severe cholangitis, concomitant medical illnesses, hypotension, altered sensorium, and renal failure, and they have higher mortality even after undergoing successful biliary drainage.⁹ Pang *et al.*¹⁰ recommended that earlier biliary drainage be considered in patients older than 75 years and/or who are chronic smokers because such patients are less likely to respond to conservative treatment.

Acute cholangitis due to impacted bile duct stone is sometimes fatal and thus requires prompt bile duct decompression. A previous study showed that bacterial

cholangitis caused by impacted bile duct stones is a serious condition in elderly patients.¹¹ Csendes *et al.*¹² reported that common bile duct pressure was significantly greater than 30 cm H₂O in patients with an impacted stone at the distal end of the CBD. Intrabiliary pressure is a key factor in the development of cholangitis because of the breakdown of barrier mechanisms, which adversely influences system defenses, including tight junctions, Kupffer cell functions, bile flow, and secretory IgA production, resulting in a higher incidence of septicemia and endotoxemia in patients with impacted bile duct stones.¹³ In the present study, impacted bile duct stone was independently identified as a risk factor for developing ASC.

Smoking was a newly identified risk factor for ASC in patients with CBD stones in this study. The effect of smoking has been assessed in several hepatobiliary diseases, although smoking has been the main focus of only a few of these studies. Several studies examined the relationship between smoking and the clinically increased risk of gallstone disease, with most reporting that smoking is associated with an increased risk of gallstone disease.¹⁴ Smoking also appears to be a major risk factor for systemic infections. The pathogenesis of the effects of smoking on the immune system is not well understood, but cigarette smoking is associated with a variety of altered functions of the cellular and humoral immune systems. In particular, smoking, via the effects of nicotine, can stimulate the release of catecholamines, and corticosteroids, mediators that are thought to increase the number of CD8+ lymphocytes in the cell mediated immune system, thereby suppressing host defenses against infections.¹⁵ Based on these reports, current smoker may be a risk factor for developing ASC.

We identified SBP and serum concentrations of total bilirubin, AST, ALT, WBC, platelet, and CRP as predictive factors of severe cholangitis in the univariate analysis. The early predictors for emergency biliary decompression in patients with acute cholangitis have been previously identified.^{4,10} A recent study⁴ suggested that tachycardia greater than 100 beats per minute, albumin levels less than 30 g/L, bilirubin levels greater than 50 mmol/L, and a prothrombin time greater than 14 seconds are 4 factors that predict the failure of conservative treatment for patients with acute cholangitis. Using a scoring system based on these 4 factors, it was found that patients with a score of 1 or higher required emergency ERCP with significantly more frequency than patients with none of the 4 risk factors. For that study, investigators used the biochemical profiles obtained on admission without consideration of clinical profiles, and a logistic regression equation was applied.

Age is known to affect the outcome and survival in patients with acute cholangitis. One study¹⁰ further demonstrated that age, chronic smoking, prothrombin time, blood glucose levels and CBD size correlate with the need for urgent biliary decompression. The clinical importance of these predictive factors for urgent biliary drainage needs to be interpreted with caution. First, there is no worldwide indication for urgent biliary drainage. Second, many factors can affect actual biochemical profile values, including preexisting medical conditions, hydration status, the status of any underlying liver disease, and the presence of renal disease.

Bacteriologic studies have shown that, in patients with cholangitis, bile cultures usually reveal several kinds of bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Streptococcus* species.^{16,17} The microbiologic profile has changed because of the frequent use of antibiotics in hospitals and increased instrumentation of the bile ducts. In a study of the bacteriologic examination of bile from 356 patients with cholangitis in Korea,¹⁸ the most commonly isolated organisms were *Enterococcus*, *Escherichia coli*, and *Klebsiella*. Attention has been focused on *Enterococcus* due to its increasing incidence as a nosocomial infection and its resistance to antibacterial agents.¹⁸ In the present study, bacterial examination was performed on the choledochal bile of patients with and without ASC. Commonly isolated pathogens in patients with cholangitis were *Escherichia coli*, *Enterococcus*, *Klebsiella*, and *Pseudomonas*. The most common pathogens in patients with ASC and those without ASC were *Escherichia coli* and *Enterococcus*, respectively.

In conclusion, impacted bile duct stone, current smoker status, advanced age (>70 years), and gallstone are risk factors independently associated with ASC in patients with CBD stones. Emergency biliary drainage is essential for patients with these risk factors to decrease morbidity and mortality and is strongly recommended.

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