

ORIGINAL ARTICLE

## 한국의 화농성 간농양 환자들의 예후 인자: 단일기관 후향 연구

손세훈, 김국현, 박재현, 김태년

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### Predictors of Mortality in Korean Patients with Pyogenic Liver Abscess: A Single Center, Retrospective Study

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**Background/Aims:** The mortality rate of pyogenic liver abscess (PLA) has decreased dramatically, but it remains a potentially life threatening disease. Most cases are cryptogenic or occur in elderly men with underlying biliary tract disease. Although several studies have addressed the characteristics and etiology of PLA, research on factors affecting PLA-associated mortality is lacking. This study intended to identify the clinical and radiological features, pathogens, complications, and predictors of mortality in Korean PLA patients.

**Methods:** The medical records of 231 PLA patients diagnosed at Yeungnam University Medical Center between January 2010 and January 2014 were analyzed. A diagnosis of PLA was made based on imaging studies and blood and abscess cultures. The clinical, radiological, and laboratory findings of patients were analyzed.

**Results:** The mean patient age was  $64.0 \pm 12.9$  years and the male to female ratio was 1.5:1. *Klebsiella pneumoniae* was the predominant organism isolated from hepatic abscesses (69.9%) and blood (74.2%). The most common complication was pleural effusion (35.8%) and most common co-infection was cholangitis (8.2%). The overall mortality rate of PLA was 6.9% (16/231), and was significantly higher in patients with a history of liver abscess (OR 5.970, 95% CI 1.207-29.529;  $p=0.028$ ), bilirubinemia ( $>2$  mg/dL) (OR 9.541, 95% CI 2.382-38.216;  $p=0.001$ ), thrombocytopenia ( $<140 \times 10^3/\mu\text{L}$ ) (OR 4.396, 95% CI 1.130-17.106;  $p=0.033$ ), or anemia ( $<12$  g/dL) (OR 13.277, 95% CI 1.476-119.423;  $p=0.021$ ).

**Conclusions:** The prognosis of PLA appears to be dependent on underlying pathologies and severity of condition. More aggressive treatment should be considered if a poor prognosis is expected. (Korean J Gastroenterol 2016;67:238-244)

**Key Words:** Pyogenic liver abscess; Risk factors; *Klebsiella pneumoniae*

### INTRODUCTION

Pyogenic liver abscess (PLA) is an uncommon disease, with an incidence ranging from 0.008% to 0.022% among hospitalized patients.<sup>1,2</sup>

However, it remains a life threatening disease and accounts for 48% of visceral and 13% of intra-abdominal

abscesses.<sup>3</sup> Early diagnosis is difficult, despite diagnostic developments such as ultrasonography (US) and CT, as presentation is often non-specific and diagnosis requires a high degree of clinical suspicion. Over the past decades, the treatment paradigm for PLA has shifted. In particular, clinical appraisal and surgical drainage have been increasingly replaced by accurate imaging and percutaneous drainage.

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Image-guided percutaneous drainage offers a low-risk approach, even in critically ill patients, and achieves effective drainage without the need for general anesthesia or surgery.<sup>4,6</sup> PLA risk factors include diabetes, an underlying hepatobiliary or pancreatic disease, and liver transplantation.<sup>7-9</sup> Biliary disease accounts for 21-31% of PLAs and extrahepatic biliary obstruction can lead to ascending cholangitis and PLA. The risk of PLA is higher in patients with diabetes or metastatic cancer,<sup>1</sup> but half of all PLA cases are idiopathic. PLA is an important clinical problem with a significant mortality rate, and in the 1990s, its reported mortality rates ranged from 8% to 31%.<sup>5,10-12</sup> However, little information is available regarding risks for PLA-associated mortality. This study was undertaken to identify clinical and radiological features, pathogens, complications, and predictors of mortality in Korean patients with PLA.

## SUBJECTS AND METHODS

### 1. Patients

Two hundred and thirty one consecutive patients with bacterial liver abscess admitted to Yeungnam University Medical Center in Korea between January 2010 and January 2014 were the subjects of this retrospective study. Patients with the following characteristics were included: (1) clinically suspicious symptoms of liver abscess, including fever, chills, and abdominal pain; (2) US or CT findings compatible with liver abscess. Patients with the following characteristics were excluded: (1) age < 18 years, (2) those without blood or pus culture data, (3) those with an amebic or eosinophilic liver abscess. Basic clinical data, underlying diseases, clinical manifestations, laboratory results, and radiologic imaging findings were obtained. The final study outcome was death. The study was approved by the Institutional Review Board of Yeungnam University Medical Center.

### 2. Culture method

Blood cultures were performed on all patients within 24 hours of admission. Two sets of blood samples were collected for culture sensitivity from different venipuncture sites and inoculated into aerobic and anaerobic culture bottles. Abscess aspiration was performed under CT or US guidance and a pus sample was sent for gram staining and culture. PLA was defined as a hepatic lesion demonstrated by US and/or

CT in a patient with compatible clinical symptoms and signs including features of sepsis, right upper quadrant pain, and abnormal liver function, plus one or more of the following: (a) a positive culture for lesion aspirate, (b) a positive blood culture, or (c) clinical response to antibiotic treatment. All cases were treated on an individual basis after identifying the predominant pathogen present by microbiological evaluation.

### 3. Statistical analysis

Statistical analysis used PASW Statistics version 18.0 for Windows (IBM Co., Armonk, NY, USA). Quantitative variables are expressed as means $\pm$ SD. Student's t-test was used to analyze continuous variables, and Fisher's exact or Pearson's chi-square tests were used to compare categorical variables. The outcome was the hospital mortality rate. Univariate analysis was performed using Pearson's chi-square or Fisher's exact test and analysis of variance. Variables significantly associated with hospital mortality on univariate analysis were subjected to logistic regression analysis to identify the independent risk factors. Null hypotheses of no difference were rejected if p-values were less than 0.05, or, equivalently, if the 95% CIs of risk point estimates excluded 1.

## RESULTS

### 1. Baseline characteristics

The baseline characteristics of the 231 study subjects are provided in Table 1. The mean patient age was 64.0 $\pm$ 12.9 years (range, 27-94 years) and the male to female ratio was 1.51:1. The mean hospital stay was 17.51 $\pm$ 12.61 days (range, 1-132 days). Clinically, 190 (82.3%) patients had fever and 35 (15.2%) patients had low blood pressure (< 90/60 mmHg) upon admission due to PLA. Of the 231 patients, 53 (22.9%) patients had diabetes, 17 (7.4%) patients had chronic hepatitis, 87 patients (37.7%) had a gallbladder or biliary tract stone, and 34 (14.7%) patients had a malignancy.

The radiologic characteristics of liver abscesses are summarized in Table 1. Abscesses were located in the right lobe in 136 (58.9%) cases, the left lobe in 72 (31.2%) cases, and in both lobes in 23 (10.0%) cases. Abscesses ranged from 1 to > 16 cm in diameter (mean 5.33 $\pm$  2.73 cm). One hundred and eighty-eight (81.4%) patients had a single abscess and 40 (17.3%) patients had multiple abscesses. Abscesses were multi-septated in 116 (50.2%) patients and gas for-

mation was observed in 20 (8.7%) patients.

## 2. Blood and abscess cultures and abscess-associated complications

*Klebsiella pneumoniae* was the predominant organism as determined by abscess aspiration (69.9%) and blood culture

(74.2%) (Table 2). Abscess-associated complications are documented in Table 3. The most common complication was pleural effusion (35.9%) and most common co-infection was cholangitis (8.2%), followed by cholecystitis (6.9%) and pneumonia (5.6%).

## 3. Risk factors related with mortality

The overall mortality rate was 6.9% (16/231) and the main causes of death were sepsis (68.8%; n=11) and empyema

**Table 1.** Patient Baseline Characteristics

Variable	Patient (n=231)
Gender (male/female)	139/92 (60.2/39.8)
Age (yr)	64.0±12.9 (27-94)
Diabetes	53 (22.9)
Chronic hepatitis B/chronic hepatitis C	14/3 (6.1/1.3)
Liver cirrhosis	13 (5.6)
Heavy alcohol use	50 (21.6)
Stone	87 (37.7)
Gallbladder/CBD/IHD	55/14/18 (23.8/6.1/7.8)
Gallbladder polyp	5 (2.2)
Malignancy	34 (14.7)
Common bile duct cancer	9 (3.9)
Gallbladder cancer	6 (2.6)
Cholangiocarcinoma	2 (0.9)
Hepatocellular carcinoma	4 (1.7)
Pancreatic cancer	1 (0.4)
Ampulla of Vater cancer	2 (0.9)
Chemotherapy or radiation history	11 (4.8)
Previous biliary surgery	46 (19.9)
Cryptogenic	95 (41.1)
Radiological characteristics	
Location	
Right/left/both	136/72/23 (58.9/31.2/10.0)
Size (cm)	5.33±2.73 (1-16)
Number	
Solitary/multiple	188/40 (81.4/17.3)
Multi-septated	116 (50.2)
Gas forming	20 (8.7)

Values are presented as n (%) or mean±SD (range).

CBD, common bile duct; IHD, intrahepatic duct.

**Table 3.** Co-infections and Complications of Pyogenic Liver Abscess

Variable	Patient (n=231)
Co-infections	
Cholangitis	19 (8.2)
Intra-abdominal abscess	17 (7.4)
Cholecystitis	16 (6.9)
Pneumonia	13 (5.6)
Urinary tract infection	6 (2.6)
Endophthalmitis	4 (1.7)
Others <sup>a</sup>	4 (1.7)
Complications	
Pleural effusion	83 (35.9)
Acute renal failure	2 (0.9)
Portal vein thrombosis	2 (0.9)
Gastrointestinal bleeding	1 (0.4)

Values are presented as n (%).

<sup>a</sup>Include 1 empyema, 1 osteomyelitis, 1 infective endocarditis, 1 pyogenic arthritis.

**Table 4.** Causes of Death in Patients with Pyogenic Liver Abscess

Variable	Patient (n=16)
Sepsis	11 (68.8)
Cancer progression	2 (12.5)
Empyema	2 (12.5)
Asphyxia	1 (6.3)

Values are presented as n (%).

**Table 2.** Micro-organisms Isolated by Site

Micro-organism	Total (n=124)	Blood (n=31)	Abscess (n=93)	Both (n=26)
<i>Klebsiella pneumoniae</i>	88 (71.0)	23 (74.2)	65 (69.9)	19 (73.1)
<i>Escherichia coli</i>	13 (10.5)	3 (9.7)	10 (10.8)	3 (11.5)
<i>Enterococcus</i> spp.	4 (3.2)	1 (3.2)	3 (3.2)	1 (3.8)
<i>Streptococci</i> spp.	4 (3.2)	2 (6.5)	2 (2.2)	2 (7.7)
<i>Pseudomonas</i> spp.	3 (2.4)	1 (3.2)	2 (2.2)	1 (3.8)
<i>Staphylococci</i> spp.	1 (0.8)	0	1 (1.1)	0
Etc. <sup>a</sup>	11 (8.9)	1 (3.2)	10 (10.8)	0

Values are presented as n (%).

<sup>a</sup>Include 2 *Acinetobacter baumannii*, 2 *Enterobacter cloacae*, 2 *Aeromonas hydrophila*, 1 *Citrobacter braakii*, 1 *Citrobacter freundii*, 1 *Actinomyces*, 1 *Salmonella typhi*, 1 *Klebsiella oxytoca*.

**Table 5.** Significant Mortality Risk Factors

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Liver cirrhosis	7.630 (2.051-28.383)	0.008		
Cancer history	5.719 (2.002-16.334)	0.002		
Biliary operation history	4.658 (1.645-13.188)	0.005		
Recurrence	3.882 (1.129-13.352)	0.045	5.970 (1.207-29.529)	0.028
Pleural effusion	6.085 (1.895-19.540)	0.001		
Hypoalbuminemia (< 3.5 g/dL)	1.778 (1.58-2)	0.001		
Bilirubinemia (> 2 mg/dL)	7.574 (2.351-24.397)	0.001	9.541 (2.382-38.216)	0.001
Thrombocytopenia (< 140×10 <sup>3</sup> /μL)	5.952 (1.855-19.23)	0.001	4.396 (1.130-17.106)	0.033
Anemia (< 12 g/dL)	25 (3.28-200)	0.001	13.277 (1.476-119.423)	0.021
Gas forming abscess	8.614 (2.733-27.151)	0.001		
Diabetes	1.166 (0.346-3.659)	0.776		

(12.5%; n=2) (Table 4). Risk factors found to be significantly associated with mortality by univariate analysis were liver cirrhosis (p=0.008, OR 7.630), underlying malignancy (p=0.002, OR 5.719), a previous biliary operation (p=0.005, OR 4.658), a gas forming abscess (p=0.001, OR 8.614), a history of abscess recurrence (p=0.045, OR 3.882), pleural effusion (p=0.001, OR 6.085), hypoalbuminemia (p=0.001, OR 1.778), bilirubinemia (p=0.0001, OR 7.574), thrombocytopenia (p=0.001, OR 5.952), and anemia (p=0.0001, OR 25) (Table 5). Diabetes was not found to be related with mortality (p=0.776, OR 1.166).

Multivariate logistic regression analysis showed that abscess recurrence (OR=5.970, 95% CI 1.207-29.529, p=0.028), bilirubinemia (> 2 mg/dL, OR 9.541, 95% CI 2.382-38.216; p=0.001), thrombocytopenia (< 140×10<sup>3</sup>/μL, OR 4.396, 95% CI 1.130-17.106; p=0.033), and anemia (< 12 g/dL, OR 13.277, 95% CI 1.476-119.423; p=0.021) were independent risk factors for mortality (Table 5).

Regarding treatment modalities, 67 patients underwent antibiotic treatment alone, 143 patients received percutaneous abscess drainage (PCD) insertion, and 21 patients received aspiration alone. Eight patients were surgically treated, including one case of enucleation due to endophthalmitis.

## DISCUSSION

Recent reports estimated the annual incidence of PLA at 2.3 cases per 100,000 of the population and found that most PLA patients are elderly (mean age, 64 years),<sup>7,13</sup> which is about 10 years older than subjects mentioned in previous reports.<sup>14,15</sup> Older research reported that *Escherichia coli*

was the most important pathogen in the etiology of PLA, but during the last two decades, *K. pneumoniae* is observed to be the major causative pathogen.<sup>16</sup> Many studies were conducted at Asian institutions, in which a large proportion of PLA cases (43% to 66%) were attributed to *Klebsiella* species, typically in association with diabetes or of cryptogenic origin.<sup>6,15,17,18</sup> On the other hand, in Western studies *E. coli* remains the most common causative organism.<sup>19,20</sup> In the present study, *K. pneumoniae* predominated (71.0%), followed by *E. coli* (10.5%), consistent with previous investigations conducted in Asia.<sup>15,21,22</sup> In addition, outcomes of *E. coli* PLA were inferior to those of *K. pneumoniae* PLA, although this may have been due to inherent demographic and clinical differences. Chan et al.<sup>7</sup> found that mortality rate of *E. coli* PLA tended to be higher than that of *K. pneumoniae* PLA (p=0.066). In the present study, patients with *E. coli* PLA were older than *K. pneumoniae* PLA patients, while gender ratios were similar. Rates of cancer, biliary operation, and ERCP were significantly higher in *E. coli* PLA patients. In addition, there were 8 (8.8%) cases of extended-spectrum beta-lactamase (ESBL)-positive *K. pneumoniae* and 4 (30.8%) cases of ESBL-positive *E. coli*, but no association was observed between these factors and mortality (Table 6).

The cause of liver abscess was cryptogenic in 41.1% patients, comparable to previous reports,<sup>10,22,23</sup> followed by biliary origin (37.7%), diabetes (22.9%), and hepatobiliary malignancy (10.4%). Cholelithiasis, benign and malignant tumors, and postoperative strictures are also associated with PLA.<sup>1,5,10,24,25</sup> In fact, any source of intra-abdominal abscess, such as acute diverticulitis, appendicitis, inflammatory bowel disease, and perforated hollow viscus, can

**Table 6.** Baseline Characteristics, Co-morbidities and Treatment Outcomes of *Klebsiella pneumoniae* and *Escherichia coli* Pyogenic Liver Abscess

	<i>K. pneumoniae</i> (n=91)	<i>E. coli</i> (n=13)	p-value
Male	52 (57.1)	7 (53.8)	0.822
Age (yr)	64.29±12.21	72.00±10.44	0.033
Co-morbidity			
Diabetes	24 (26.4)	3 (23.1)	1.000
CRF	2 (2.2)	0 (0.0)	1.000
Heavy alcohol use	19 (20.9)	1 (7.7)	0.454
GB stone	22 (24.2)	3 (23.1)	1.000
Biliary stone	12 (13.2)	4 (30.8)	0.113
Biliary operation	13 (14.3)	8 (61.5)	0.001
ERCP History	15 (16.5)	7 (53.8)	0.006
Cancer related abscess	11 (12.1)	5 (38.5)	0.028
Positive of ESBLs	8 (8.8)	4 (30.8)	0.042
Image study			
Abscess size (cm)	5.73±2.56	5.14±3.00	0.448
Gas forming abscess	10 (11.0)	2 (15.4)	0.644
Solitary abscess	74 (81.3)	8 (61.5)	0.241
Abscess location			0.137
Right	60 (65.9)	5 (38.5)	
Left	22 (24.2)	5 (38.5)	
Both or junction	9 (9.9)	3 (23.1)	
Treatment outcomes			
Median length of hospital stay (day)	19.02±15.03	14.76±10.45	0.327
PCD insertion	74 (81.3)	10 (76.9)	0.712
Operation	0 (0)	1 (7.7)	0.125
Mortality	5 (5.5)	3 (23.1)	0.060

Values are presented as n (%) or mean±SD.

CRF, chronic renal failure; GB, gallbladder; ESBLs, extended-spectrum beta-lactamases; PCD, percutaneous abscess drainage.

cause PLA via portal pyemia.<sup>1</sup> PLA by hematogenous infection via the hepatic artery is hypothesized to originate from hepatic seeding of bacteria, in cases of systemic infection, such as endocarditis or urinary sepsis. Huang et al.<sup>11</sup> reported that malignant biliary obstruction had become the leading cause of liver abscess. In PLA, a solitary lesion is more common in the right lobe,<sup>26</sup> which can be explained by the larger size of the right lobe and its receipt of most mesenteric-portal blood flow.<sup>11</sup> Diabetes is a risk factor for PLA, and the main pathogen is *K. pneumoniae* in diabetes related PLA. In the present study, liver abscesses were observed in right lobe in 60 patients (65.9%), 10 patients (8.7%) exhibited a gas forming pattern, and 45.0% were related to diabetes. Gas-forming liver abscesses are uncommon but occur in 7-24% of PLA cases and bring a high risk of mortality.<sup>27</sup> In the present study, although gas formation was found to predict mortality by univariate analysis, this relationship was not found to be significant by multivariate analysis.

Significant advances and changes have been made in the management of PLA over the past 15 years. Traditionally, pa-

tients with PLA were treated by surgical drainage and antibiotic therapy, but today percutaneous aspiration/drainage under US or CT guidance is the procedure of choice.<sup>5,6,14</sup> In the present study, 67 (29.0%) of the 231 patients were treated using antibiotics alone, 143 (61.9%) patients by PCD insertion, and eight (3.4%) patients surgically. However, these different modalities did not influence mortality significantly. We administered third generation cephalosporin (ceftriaxone) and metronidazole empirically until the identity of the organism and its sensitivity were determined, and continued antibiotic therapy until abscess cavity obliteration was observed by CT and there were no signs of infection. When clinical signs of infection resolved completely in the presence of a small abscess, as determined by CT, patients were discharged on oral antibiotics.

PLA often leads to complications such as pleural effusion, acute renal failure, multiple organ failure, abdominal abscess, and portal or hepatic vein thrombosis.<sup>28</sup> In the present study, there were 83 (35.9%) cases of pleural effusion and 4 (1.7%) cases of endophthalmitis. Septic endophthalmitis

due to *K. pneumoniae* is sometimes devastating. In the present study, the single affected patient ultimately underwent enucleation.<sup>29</sup>

Over the past few decades, mortality associated with PLA has decreased gradually. Prior to 1980, case series mortalities were consistently greater than 50%. Improvements in mortality rates in the 1980s and 1990s were attributed to highly effective broad spectrum antibiotics and the advent of cross sectional CT and US imaging. Mortality rates during and after the 1990s was between 4-10%.<sup>6,14,15,17</sup> However, an association between mortality and malignancy was recently highlighted by Mezhrir et al.,<sup>30</sup> who reported a mortality rate as high as 29%. In the present study, the overall mortality rate was 6.9%, but the mortality rate associated with malignancy was almost twice as high (12.5%).

The high mortality rate of PLA highlights the importance of prognostic factors, prompting research into risk factors. Although no consensus has been reached, marked leukocytosis, hypoalbuminemia, hyperbilirubinemia, altered renal function, septic shock, higher Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, and pleural effusion are significantly associated with mortality.<sup>10,12,22,31,32</sup> Six independent risk factors predict severe complications in *K. pneumoniae*-related PLA: thrombocytopenia ( $< 100,000/\text{mm}^3$ ), alkaline phosphatase  $> 300 \text{ U/L}$ , gas formation, an APACHE III score of  $> 40$ , the use of cefazolin (rather than extended-spectrum cephalosporin), and delayed drainage.<sup>33</sup> Co-morbid malignancy is considered a grave factor, probably because of the presence of malnutrition and immunosuppression.<sup>10,11,34</sup> In the present study, the risk factors associated with PLA mortality as determined by multiple regression were recurrent abscess, jaundice ( $> 2 \text{ mg/dL}$ ), thrombocytopenia ( $< 140 \times 10^3/\mu\text{L}$ ), and anemia ( $< 12 \text{ g/dL}$ ), which largely concurs with previous studies.<sup>10,11,34</sup> Recurrent abscess has not been commonly mentioned as a prognostic factor, but in the present study it is associated with underlying malignancy and biliary disease, underlining the need for care in the approach in PLA patients with such co-morbidities.

The main limitation of the present study is its retrospective, single center design. Furthermore, the true prevalence of PLA may have been under-estimated because we collected cases with a definitive diagnosis to reduce confounding. Nevertheless, our study has several strengths. First, it adds to factors already identified associated with

mortality in PLA, aiding treatment decision-making in high risk cases. Second, we evaluated underlying diseases and complications and explored relations between underlying diseases, complications, and disease outcomes.

Summarizing, the study shows that a history of liver abscess, bilirubinemia ( $> 2 \text{ mg/dL}$ ), thrombocytopenia ( $< 140 \times 10^3/\mu\text{L}$ ), and anemia ( $< 12 \text{ g/dL}$ ) are independently associated with mortality in patients with PLA, and suggests clinicians pay special attention to patients with these factors.

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