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Cryptogenic and non-cryptogenic liver abscess: A retrospective analysis of 178 cases revealed distinct characteristics

Jing Chen*, Minwei Zhang*, Jinlong Chen, Yaogui Ning, Xiaoyang Cai, Li Zhang, Hao Xu and Jing Guo

Abstract

Objective: To enhance theoretical support of pyogenic liver abscess (PLA) treatment by comparing characteristics of patients with either PLA with an identified infectious origin (non-cryptogenic) or PLA with no obvious underlying cause (cryptogenic).

Methods: This retrospective study included all first episodes of PLA in adults admitted to a tertiary hospital between 2009 and 2016. Relevant clinical data were collected for patients with cryptogenic or non-cryptogenic PLA and compared across a number of characteristics.

Results: In all, 178 patients were included: 111 cases (62.4%) of cryptogenic PLA, and 67 cases (37.6%) of non-cryptogenic PLA. Diabetes mellitus was significantly more prevalent in patients with cryptogenic PLA than those with non-cryptogenic PLA. The proportion of multidrug resistance/poly-microbial infection was significantly lower and *Klebsiella pneumoniae* infection was significantly higher in the cryptogenic versus non-cryptogenic PLA group. Metastatic infection occurred in four patients with cryptogenic PLA only, and all had diabetes and *K. pneumoniae* infection. Multivariate logistic regression analysis revealed that male sex, diabetes and *K. pneumoniae* were independent predictors for cryptogenic PLA.

Conclusions: Cryptogenic and non-cryptogenic PLA have distinctly different characteristics, suggesting a potential need for different treatment approaches.

Department of Critical Care Medicine, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

*These authors contributed equally to this work.

Corresponding author:
Minwei Zhang, Department of Critical Care Medicine, The First Affiliated Hospital of Xiamen University, 55 Zhenhai Road, Xiamen 361003, Fujian, China.
Email: zmwicu@126.com

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Introduction

Pyogenic liver abscess (PLA) is an uncommon but serious life-threatening infection with pathophysiological characteristics that have changed over time. The incidence of PLA ranges from 1.1 to 17.6 per 10 000 throughout the world, with a mortality rate of approximately 6–19%, even when patients are treated.[1–4] A large population-based retrospective study in Northeast China reported an incidence rate in China of 5.7 per 10 000.[5] PLA-associated heterogeneities and complications remain a major diagnostic and therapeutic challenge worldwide. PLA usually develops following biliary infections or infections of organs drained by the portal vein, such as appendicitis or inflammatory bowel disease, with causes and microbiological agents associated with PLA largely differing between the East and West. In the East, liver abscesses are predominately cryptogenic, whereas in the West, biliary abnormalities or malignancy are the main causes.[6,7]

In their 1938 paper, Ochsner et al.[1] reported that PLA occurred primarily in young males affected by intra-abdominal infections (usually caused by phlebitis secondary to acute appendicitis) and had a mortality rate of over 50%. By the 1980s, the infectious origin of PLA had changed dramatically, and was most frequently associated with biliary tract disease,[2,3] with *Escherichia coli* thought to be the most common causative pathogen. Since the 1990s, PLA has most commonly been reported to be of cryptogenic origin, where a significant underlying cause cannot be determined. More recently, cryptogenic PLA has increased in prevalence worldwide, particularly in some Asian regions, such as Taiwan,[8,9] Korea[6] and Hong Kong,[10] where cryptogenic PLA has a predominance of 48–65%, and *Klebsiella pneumoniae* has replaced *E. coli* as the major pathogenic bacteria.[11] The features of *K. pneumonia* PLA have been widely described.[11,12] The mortality rate of PLA has declined substantially over time, while the average age of patients with PLA has increased.[6,10,13,14]

Pyogenic liver abscess may be classified as non-cryptogenic or cryptogenic according to aetiology. Although a great deal of research has focused on the epidemiology and clinical outcome of PLA, the characteristics of cryptogenic PLA are not well described.[15–17] Due to a current lack of research focus on the difference between cryptogenic and non-cryptogenic PLA, it remains unclear if there is an apparent discrepancy in epidemiologic, microbiologic or treatment characteristics between the two. Studies that focused on PLA of biliary origin found that such cases often involved multidrug resistant bacteria and mixed infections caused mainly by *E. coli* and other isolates, quite different from cryptogenic PLA.[6,14] Since the prevalence of cryptogenic PLA has increased worldwide, particularly in some Asia regions, gaining knowledge of any characteristic differences between cryptogenic and non-cryptogenic PLA has become more urgent.

The purpose of the present study was to compare epidemiologic, microbial or treatment characteristics between cryptogenic and non-cryptogenic PLA, by reviewing clinical data collected over a 7-year period

from patients in a tertiary teaching hospital, in order to provide theoretical support for PLA treatment.

Patients and methods

Study population

This retrospective study included clinical data from consecutively enrolled adult patients with PLA who were admitted to the First Affiliated Hospital of Xiamen University, a 2 500-bed tertiary-level hospital in Xiamen, China, between January 2009 and December 2016. All included PLA diagnoses met more than one of the following criteria:[7] (1) $\geq$1 liver abscess in an image-guided puncture, (2) $\geq$1 liver abscess discovered during surgery, (3) $\geq$1 sign of liver inflammatory lesions (multiple low density spots in the liver observed by computed tomography [CT] or abdominal ultrasonography) with no completely liquefied necrosis, or an abscess found on imaging associated with the patient's symptoms/signs of infection, (4) positive bacterial cultures from abscess samples, and (5) cryptogenic abscess in which no source of infection could be identified. Each lesion was correlated with microorganisms in blood cultures or acute inflammation in liver biopsies, and all were treated with antimicrobial agents. The antibiotic strategy was adjusted based on the clinical presentation and the initial bacterial culture results. All microbiology samples, including blood and pus, were processed for bacterial culture in the Division of Clinical Microbiology, the First Affiliated Hospital of Xiamen University. Patients were excluded if PLA was caused by fungi, tubercle bacillus, amoebas or primary hepatic carcinoma. Patients <18 years of age were also excluded. The experimental protocol was approved by the Ethics Committee of Xiamen University and every participant provided written informed consent.

Study design

The following data were retrospectively collected: (1) patient demographics, including age, sex, and duration of symptoms; (2) co-existing conditions (including alcoholism, diabetes mellitus [diabetes], hepatitis B virus or hepatitis C virus, malignancy, chronic kidney disease, hypertension and cardiovascular disease); (3) symptoms/signs and laboratory findings on admission, and imaging and microorganism findings; (4) initial treatment modality and outcomes. Percutaneous or surgical intervention-acquired abscess samples and at least two blood cultures were assessed using Gram stain and bacterial cultures. Clinical severity was evaluated as Charlson scores[18] and acute physiology and chronic health evaluation (APACHE)-II scores.[19] The infectious origins of PLA were determined by imaging (ultrasound and CT) or based on medical history and surgical information. In each case, the infectious origin of PLA was classified as one of the following six categories: by (1) biliary tract, (2) portal vein, (3) direct extension, (4) trauma, (5) hepatic artery (all grouped as non-cryptogenic PLA), or (6) cryptogenic, meaning without obvious source of extrahepatic infection following full investigation.[7] Metastatic infection was diagnosed based on imaging findings or when the pathogen found to cause PLA was also found in a distant infection site. Patients were divided into non-cryptogenic or cryptogenic PLA groups, depending on PLA being with or without an obvious infectious origin, respectively.

Pathogens and treatment outcome

Microorganisms from blood and PLA samples were isolated at the Division of Clinical Microbiology, the First Affiliated Hospital of Xiamen University, where they were identified using standard aerobic and anaerobic diagnostic techniques and tested for

antimicrobial susceptibility using the disk diffusion method. Strains were designated as multidrug resistant if they showed non-susceptibility to $\geq$ one agent in $\geq$ three classes of antimicrobial drugs.[20] Complex infection was defined as multidrug resistant isolates or polymicrobial infection. Initial treatment modalities were divided into the following three types: antibiotics alone, percutaneous drain plus antibiotics, or surgery plus antibiotics. Outcomes were evaluated including the time to defervescence following admission, complications (septic shock or metastatic infection), intensive care unit (ICU) admission, duration of treatment with antibiotics, duration of hospital stay and overall 28-day mortality in the hospital.

Statistical analyses

Data are presented as mean $\pm$ SD or median (interquartile range [IQR]) for continuous variables, or *n* (% prevalence) for categorical variables, and were statistically analysed using SPSS software, version 22 (IBM, Armonk, NY, USA). As this was a retrospective study with a relatively small sample size, odds ratios (ORs) and 95% confidence intervals (CIs) of associations between dependent and independent variables were estimated using exact methods instead of conventional logistic regression procedures.[21] For all OR estimates, sex, age and the duration of symptoms prior to admission were considered as possible confounders. All continuous data were analysed by independent samples one- or two-tailed *t*-test, and χ^2-test or Fisher's exact test was used to analyse categorical data. Risk factors related to cryptogenic and non-cryptogenic PLA were investigated by multivariate analyses of demographics, comorbidities, symptoms/signs, laboratory findings, imaging features, microorganisms, and complications using a forward stepwise method of logistic regression. All factors analysed in the single factor study were included as input variables. A P value <0.05 was defined as statistically significant.

Results

Demographic and baseline characteristics

During the 7-year study period, 178 patients with PLA (mean $\pm$ SD age of 54.9 ± 15.7 years; 114/178 [64.0%] male) were treated at the First Affiliated Hospital of Xiamen University. Overall, 67/178 patients (37.6%) were classified into the non-cryptogenic PLA group, and most cases (111/178 [62.4%]) were cryptogenic. The infectious origins of PLA are shown in Figure 1. Biliary tract disease (cholecystitis/cholecystolithiasis, 55 cases; and hepato-biliary and pancreatic tumours, eight cases) was the most commonly identified infectious origin (63/178 [35.4%]). Patients were younger in the cryptogenic PLA group than in the non-cryptogenic PLA group (mean age, 51.9 ± 15.2 versus 59.7 ± 15.4 years, $P = 0.001$), and there was a higher proportion of male patients in the cryptogenic PLA group (79/111 [71.2%] versus 35/67 [52.2%], $P = 0.011$) (Table 1). The median duration of symptoms prior to hospital admission was 5.0 days (IQR, 3.0–8.0 days) in the cryptogenic PLA group and 6.0 days (IQR, 1.0–10.0 days) in the non-cryptogenic PLA group.

Clinical presentation and investigations

Analyses of clinical characteristics in the cryptogenic and non-cryptogenic PLA groups (Table 1), showed that diabetes was more common in patients with cryptogenic PLA (47/111 [42.3%]) versus those with non-cryptogenic PLA (15/67 [22.4%]; adjusted OR 3.906, 95% CI 1.797, 8.490; $P = 0.001$), while malignancies occurred at lower frequencies in patients with cryptogenic PLA than in those with non-cryptogenic PLA (2/111 [1.8%] versus 12/67 [17.9%],

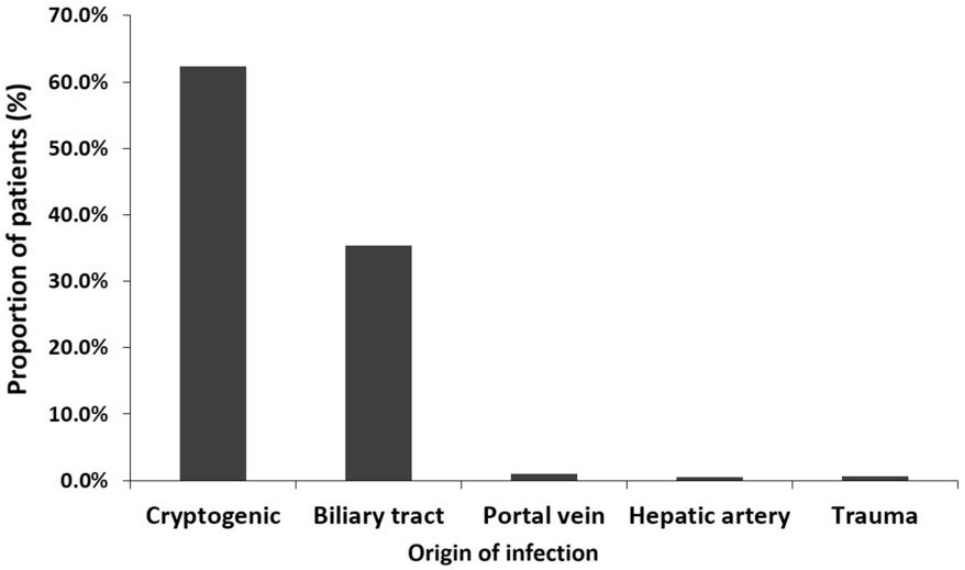

Figure 1. The distribution of infectious origin in 178 adult patients with pyogenic liver abscess, showing mainly cryptogenic (62.4%) or biliary tract (35.4%) origins, with a small proportion of infections originating from the portal vein (1.0%), hepatic artery (0.6%) or trauma (0.6%).

respectively; adjusted OR 0.087, 95% CI 0.018, 0.419; $P = 0.002$). There were no statistically significant between-group differences in presenting symptoms/signs, except for lower proportions of upper abdominal pain in patients with cryptogenic PLA (58/111 [52.3%]) versus those with non-cryptogenic PLA (47/67 [70.1%]; adjusted OR 0.444, 95% CI 0.222, 0.886; $P = 0.021$), and lower proportions of diarrhoea (2/111 [1.8%] versus 5/67 [7.5%], cryptogenic versus non-cryptogenic PLA, respectively; adjusted OR 0.172, 95% CI 0.031, 0.957; $P = 0.044$).

Imaging findings on admission

Every patient underwent a chest and abdomen CT scan on admission, and abdominal ultrasound examinations were performed in all patients. There were no statistically significant between-group differences in findings from images obtained on admission (Table 1), except proportionally more abscesses between >5 cm and ≤ 10 cm diameter in the non-cryptogenic versus cryptogenic PLA group. Pleural effusion was seen in 27/111 (24.3%) patients in the cryptogenic PLA group and 23/67 (34.3%) patients in non-cryptogenic PLA group. One-third of the abscesses (37/111 [33.3%]) in the cryptogenic PLA group and 17/67 (25.4%) of the abscesses in the non-cryptogenic PLA group were ≤ 5 cm in diameter. Multiple abscesses were found in 34/111 (30.6%) patients in the cryptogenic PLA group and 22/67 (32.8%) patients in the non-cryptogenic PLA group.

Laboratory findings on admission

Laboratory findings recorded on admission are shown in Table 2. The most frequently observed abnormal parameter in both PLA groups was C reactive protein. After adjustment for confounders, there were no statistically significant between-group differences in rates of abnormal laboratory findings for any of the parameters tested.

Table 1. Demographic and clinical characteristics and severity in adult patients with cryptogenic or non-cryptogenic pyogenic liver abscess, admitted to the First Affiliated Hospital of Xiamen University, Xiamen, China between 2009 to 2016

Variable	Cryptogenic PLA $n=111$	Non-cryptogenic PLA $n=67$	Statistical significance	Adjusted OR (95% CI)[a]
Age, years	51.9 ± 15.2	59.7 ± 15.4	$P=0.001$	
Male	79 (71.2)	35 (52.2)	$P=0.011$	1.636 (1.126, 2.378)
APACHE II score (≥8)	40 (36.0)	35 (52.2)	NS	0.640 (0.333, 1.244)
Charlson score (≥3)	6 (5.4)	9 (13.4)	NS	0.464 (0.142, 1.512)
Comorbidities				
Alcoholism	12 (10.8)	8 (11.9)	NS	0.603 (0.216, 1.683)
Diabetes mellitus	47 (42.3)	15 (22.4)	$P=0.001$	3.906 (1.797, 8.490)
Hepatitis[b]	9 (8.1)	5 (7.5)	NS	1.349 (0.387, 4.699)
Malignancies	2 (1.8)	12 (17.9)	$P=0.002$	0.087 (0.018, 0.419)
Chronic Kidney disease	2 (1.8)	1 (1.5)	NS	0.927 (0.078, 11.058)
Hypertension	14 (12.6)	13 (19.4)	NS	0.770 (0.317, 1.870)
Heart failure	9 (8.1)	6 (9.0)	NS	1.480 (0.460, 4.765)
Symptoms				
Fever/Chills	96 (86.5)	57 (85.1)	NS	0.786 (0.306, 2.018)
Upper abdominal pain	58 (52.3)	47 (70.1)	$P=0.021$	0.444 (0.222, 0.886)
Weight loss	17 (15.3)	8 (11.9)	NS	1.200 (0.460, 3.131)
Diarrhoea	2 (1.8)	5 (7.5)	$P=0.044$	0.172 (0.031, 0.957)
Nausea/vomiting	19 (17.1)	16 (23.9)	NS	0.661 (0.297, 1.469)
Cough	23 (20.7)	9 (13.4)	NS	1.520 (0.628, 3.680)
Imaging findings				
Pleural effusion	27 (24.3)	23 (34.3)	NS	0.660 (0.322, 1.351)
Abscess site				
Right lobe	82 (73.9)	53 (79.1)		1
Left lobe	21 (18.9)	11 (16.4)	NS	0.526 (0.125, 2.213)
Both lobes	8 (7.2)	3 (4.5)	NS	0.677 (0.141, 3.254)
Abscess size				
Diameter ≤5 cm	37 (33.3)	17 (25.4)		1
Diameter >5cm, and ≤10 cm	64 (57.7)	40 (59.7)	$P=0.047$	3.209 (1.017, 10.124)
Diameter >10 cm	10 (9.0)	10 (14.9)	NS	2.052 (0.735, 5.728)
Abscesses number				
Single	77 (69.4)	45 (67.2)		1
Multiple	34 (30.6)	22 (32.8)	NS	1.058 (0.529, 2.114)

Data presented as mean ± SD or *n* (%) prevalence.

[a]The logistic regression model included adjustments for age, sex, and duration of symptoms before admission.

[b]Hepatitis includes hepatitis B virus and hepatitis C virus.

PLA, pyogenic liver abscess; OR, odds ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation.

NS, no statistically significant between-group difference ($P>0.05$, χ^2-test or Fisher's exact test).

Microbiology characteristics

Microbiological analyses of blood or abscess cultures revealed that 103 patients were positive for microbial infection: 60/111 (54.1%) patients with cryptogenic PLA and 43/67 (64.2%) patients with non-cryptogenic PLA (Table 3). In terms of specific pathogens, complex infections (multidrug resistant isolates or polymicrobial infection) were less frequent in the cryptogenic PLA group than

Table 2. Laboratory findings in adult patients with cryptogenic or non-cryptogenic pyogenic liver abscess, admitted to the First Affiliated Hospital of Xiamen University, Xiamen, China between 2009 to 2016

Variable	Cryptogenic PLA $n = 111$	Non-cryptogenic PLA $n = 67$	Adjusted OR (95% CI)[a]
Abnormal WBC, $>10 \times 10^9$/l or $<4 \times 10^9$/l	93 (83.8)	55 (82.1)	0.885 (0.374, 2.094)
Abnormal Hb, male <12 g/l or female <11 g/l	89 (80.2)	58 (86.6)	0.436 (0.172, 1.107)
Abnormal PLT, $<10 \times 10^9$/l	23 (20.7)	15 (22.4)	0.803 (0.364, 1.774)
Abnormal ALB, <35 g/l	77 (69.4)	48 (71.6)	1.071 (0.515, 2.227)
Abnormal ALT, >40 U/l	77 (69.4)	39 (58.2)	1.249 (0.635, 2.455)
Abnormal TBIL, >13 mg/l	22 (19.8)	18 (26.9)	0.606 (0.281, 1.306)
Abnormal CRP, >8 mg/l	95/105 (90.5)	58/61 (95.1)	0.495 (0.123, 1.990)
Abnormal CRE, >13 mg/l	18 (16.2)	10 (14.9)	0.907 (0.65, 2.252)

Data presented as *n* (%) prevalence.

[a]The logistic regression model included adjustments for age, sex, and the duration of symptoms before admission.

PLA, pyogenic liver abscess; OR, odds ratio; CI, confidence interval; WBC, white blood cells; Hb, haemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; TBIL, total bilirubin; CRP, C reactive protein; CRE, creatinine.

Table 3. Microbiological characteristics of adult patients with cryptogenic or non-cryptogenic pyogenic liver abscess, admitted to the First Affiliated Hospital of Xiamen University, Xiamen, China between 2009 to 2016

Pathogen	Cryptogenic PLA $n = 60$	Non-cryptogenic PLA $n = 43$	Statistical significance	Adjusted OR (95% CI)[a]
Complex infection	3 (5.0)	11 (25.6)	$P = 0.044$	0.228 (0.054, 0.959)
Multidrug resistant isolates	3 (5.0)	8 (18.6)		
Polymicrobial infection	0 (0.0)	5 (11.6)		
Gram positive organisms				
Staphylococcus aureus	0	3 (7.0)	NS	–
CoNS	0	3 (7.0)	NS	–
Enterococcus spp.	0	1 (2.3)	NS	–
Streptococcus spp.	4 (6.7)	1 (2.3)	NS	2.335 (0.209, 26.125)
Gram negative organisms				
Klebsiella pneumoniae	51 (85.0)	17 (39.5)	$P < 0.001$	11.592 (3.658, 36.732)
Escherichia coli	3 (5.0)	15 (34.9)	$P = 0.003$	0.124 (0.031, 0.496)
Pseudomonas aeruginosa	0 (0.0)	4 (9.3)	NS	–
Enterobacter spp	1 (1.7)	3 (7.0)	NS	0.308 (0.025, 3.781)
Citrobacter freundii	0	1 (2.3)	NS	–
Acinetobacter	1 (1.7)	0 (0.0)	NS	–

Data presented as *n* (%) patient prevalence.

[a]The logistic regression model included adjustments for age, sex, and the duration of symptoms before admission.

PLA, pyogenic liver abscess; OR, odds ratio; CI, confidence interval; CoNS, coagulase-negative staphylococci.

NS, no statistically significant between-group difference ($P > 0.05$; χ^2-test or Fisher's exact test).

non-cryptogenic PLA group (3/60 [5.0%] versus 11/43 [25.6%], respectively; adjusted OR 0.228, 95% CI 0.054, 0.959; $P = 0.044$). *K. pneumoniae* was more frequent in the cryptogenic PLA group than non-cryptogenic PLA group (51/60 [85.0%] versus 17/43 [39.5%], respectively; adjusted OR 11.592, 95% CI 3.658, 36.732; $P < 0.001$). Two extended-spectrum β-lactamase (ESBL)-producing strains of *K. pneumoniae* were found in both the cryptogenic PLA group and the non-cryptogenic PLA group. *E. coli* were more frequently found in the non-cryptogenic PLA group than in cryptogenic PLA group (15/43 [34.9%] versus 3/60 [5.0%], respectively; adjusted OR 0.124, 95% CI 0.031, 0.496; $P = 0.003$). Thus, the infection origins of the cryptogenic and non-cryptogenic PLA groups were shown to be significantly different.

Treatment outcomes and complications

Recorded treatments and outcomes for the patients with PLA are presented in Table 4. All 178 patients with PLA were treated with antibiotics, and half of them were percutaneously treated. Between-group comparison of treatment modalities revealed that the rate of surgical treatment was significantly lower in patients with cryptogenic PLA than in patients with non-cryptogenic PLA (5/111 [4.5%] versus 12/67 [17.9%], respectively; adjusted OR 4.200, 95% CI 1.285, 13.731; $P = 0.031$), and a significantly higher proportion of patients in the cryptogenic PLA group were treated percutaneously (50.5% versus 44.8%, respectively; adjusted OR 3.800, 95% CI 1.134, 12.730). Regarding complications, four cases of metastatic infection were found, and all were in patients with cryptogenic PLA (Table 4). Representative photographic and imaging findings for one patient in the cryptogenic PLA group, who had three sites of metastatic infection, are shown in Figure 2. Overall, the most common sites of metastatic infection were eye (2/4 cases), brain (2/4 cases) and lung (3/4 cases). All four patients with metastatic infection had diabetes and were infected with *K. pneumoniae*.

Table 4. Treatments and outcomes in adult patients with cryptogenic or non-cryptogenic pyogenic liver abscess, admitted to the First Affiliated Hospital of Xiamen University, Xiamen, China between 2009 to 2016

Variable	Cryptogenic PLA $n = 111$	Non-cryptogenic PLA $n = 67$	Statistical significance	Adjusted OR (95% CI)[a]
Initial treatment				
Antibiotics alone	50 (45.0)	25 (37.3)	NS	1
Percutaneous antibiotic treatment	56 (50.5)	30 (44.8)		3.800 (1.134, 12.730)
Surgery plus antibiotics	5 (4.5)	12 (17.9)		4.200 (1.285, 13.731)
Duration of antibiotics >4 weeks	53 (47.7)	28 (41.8)	NS	1.537 (0.796, 2.969)
Duration of antibiotics, days	28 (23, 35)	27 (22, 38)		
Complication	11 (9.9)	8 (11.9)	NS	0.868 (0.316, 2.386)
Septic Shock	9 (8.1)	8 (11.9)		
Metastatic infection	4 (3.6)	0		
ICU admission	22 (19.8)	12 (17.9)	NS	0.870 (0.379, 1.996)
28-day mortality	3 (2.7)	5 (7.5)	NS	2.184 (0.484, 9.856)

Data presented as *n* (%) prevalence or median (interquartile range).

[a]The logistic regression model included adjustments for age, sex, and the duration of symptoms before admission.

PLA, pyogenic liver abscess; OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

NS, no statistically significant between-group difference ($P > 0.05$; χ^2-test or Fisher's exact test).

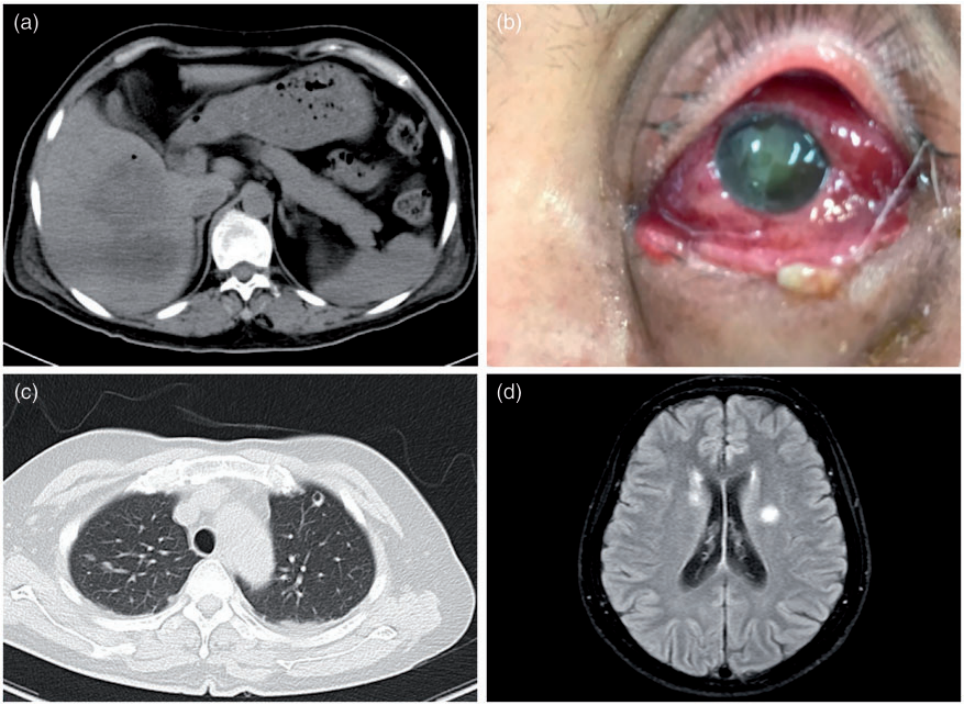

Figure 2. Representative images from an adult patient with cryptogenic pyogenic liver abscess with metastatic infection: (a) image from abdominal computed tomography (CT) scan in which two large polylobar right lobe hypodense lesions can be clearly identified; (b) photograph of the eye showing a turbid lens and swollen conjunctiva with purulent exudation; (c) image from chest CT showing a hole filled with liquid in the upper left lung, suggesting an interstitial pulmonary and bilateral pleural effusion; and (d) image from magnetic resonance imaging scan of the head performed one week following presentation revealing multiple 5-mm ring-enhancing lesions.

There was no significant difference in the frequency of complications between the cryptogenic and non-cryptogenic PLA groups. Overall 28-day mortality rates in the cryptogenic and non-cryptogenic PLA groups were 3/111 (2.7%) and 5/67 (7.5%), respectively, with no statistically significant difference between them (adjusted OR 2.184, 95% CI 0.484, 9.856).

Predictors for cryptogenic and non-cryptogenic PLA

In multivariate logistic regression analyses, patients' demographics, comorbidities, symptoms/signs, laboratory findings, imaging features, microorganisms, and complications were processed using a forward stepwise method. Results showed that male sex ($P = 0.023$; OR 4.070, 95% CI 1.218, 13.601), diabetes ($P = 0.003$; OR 8.387, 95% CI 2.107, 33.379) and *K. pneumoniae* ($P = 0.036$; OR 5.018, 95% CI 1.109, 22.704) were independent predictors for cryptogenic PLA, while age ($P = 0.015$; OR 1.057, 95% CI 1.011, 1.015) was an independent predictor for non-cryptogenic PLA.

Discussion

In the present study, significant differences in demographics, comorbidities and microbiological features were found between

patients with cryptogenic PLA and non-cryptogenic PLA. Over the last century, remarkable changes have occurred in the epidemiology, infectious origins, microbiology, treatment, and mortality rate of PLA.[1,22,23] In the present study, most cases of PLA were considered to be cryptogenic, while biliary disease was the most common identifiable cause of PLA in non-cryptogenic cases. The findings related to infectious origin were in accordance with those reported in two recent large case reports in China,[5,13,24] and changes to the infectious origin of PLA are likely to be the result of improvements in antibiotics and treatment modalities.

The proportion of patients with diabetes was nearly 2-fold higher in the present cryptogenic versus non-cryptogenic PLA population and was similar to recent reports in patients with PLA, in which prevalence rates ranged from 35.4% to approximately 44.3%.[5,13,15] The present results are also generally consistent with those presented in a study by Chen et al.,[25] in which 48% of the cryptogenic group also had diabetes. In another study, diabetes was the most common comorbidity and reported to be one of the recognized risk factors for PLA.[26] A large population-based epidemiological study[27] reported that patients with diabetes had a 3.6-fold higher risk of experiencing PLA than those without diabetes. One potential reason for this finding is that hyperglycaemia is known to alter neutrophil metabolism and impair chemotaxis and phagocytosis, thus interfering with the immune response.[28]

Key findings in the present study were that microbiological characteristics were very different between the cryptogenic and non-cryptogenic PLA groups, and that *K. pneumoniae* had replaced *E. coli* as the predominant pathogen in both PLA groups. The frequency at which *K. pneumoniae* was isolated was found to be significantly higher in patients with cryptogenic PLA than in those with non-cryptogenic PLA, while *E. coli* was more prevalent in patients with non-cryptogenic PLA. These findings agree with results from other recent studies that reported the frequency of *K. pneumoniae* isolates in cryptogenic PLA, ranging from 41% to 88%.[6,14,25] Furthermore, the distribution of bacteria associated with non-cryptogenic PLA in the present study was consistent with the pathogenic distribution reported in biliary tract infections.[29]

Incidence of complex infection (multi-drug resistant/polymicrobial infection) was significantly higher in the present non-cryptogenic PLA group than in the cryptogenic PLA group. Other studies[14,30] have suggested that polymicrobial PLA is usually secondary to biliary tract stones, malignancies, or intra-abdominal infections. Two patients with cryptogenic PLA and two with non-cryptogenic PLA were found to have ESBL-producing *K. pneumoniae* isolates in the present study population, but none of these *K. pneumoniae*-infected patients had carbapenem-resistant strains. ESBL-producing strains of this bacterium present a challenge for clinicians because they can be resistant to third-generation cephalosporin, and carbapenems are therefore used as the first choice in affected individuals.[31]

In the present study, four cases in the cryptogenic PLA group were identified to have *K. pneumoniae* invasive syndrome with metastatic infections at various sites, including a lung abscess, brain abscess and endophthalmitis, and all four of these patients had diabetes. This finding contrasts with those reported in recent larger case studies of PLA in China,[5,14,17,24] in which no cases with metastatic infections were observed. Invasive syndrome was first reported in Taiwan in the 1980s,[32] and subsequent cases have been described in other Asian countries, such as Hong Kong,[33] Korea[6] and Singapore.[34] One

study reported that among patients with a *K. pneumoniae* liver abscess,[35] the incidence of metastatic infection was 15.5%, while the rate of meningitis was 64.7% and that of endophthalmitis was 23.5%. Thus, all patients with PLA, and particularly those with *K. pneumoniae* associated cryptogenic PLA, should be screened for metastatic infection at sites including the lungs, eyes and brain. Furthermore, diabetes may be a risk factor for metastatic infection. For example, diabetes has been found to increase the frequency of metastasis 20-fold.[9] Prior studies[36,37] have demonstrated that the K1 and K2 serotypes of *K. pneumoniae* were associated with invasive syndrome. Although the origin of infection in cryptogenic PLA is unclear, several studies have indicated that *K. pneumoniae* strains infect the liver via the gastrointestinal tract.[38,39] One study noted that *K. pneumoniae* strains isolated from patients with PLA and healthy carriers of *K. pneumoniae* expressed the same virulence-related genes on pulsed-field gel electrophoresis profiles.[39] The findings of an animal-model study[40] suggested that *K. pneumoniae* strains can cross the intestinal barrier to cause liver abscesses. Further studies in animal models are therefore needed to explore the relationship between *K. pneumoniae* and diabetes in the development of cryptogenic PLA.

In the present study, the main therapeutic methods used to treat PLA included antimicrobials and adequate drainage of the abscess. An age of $\geq$55 years, an abscess $\geq$5 cm in size, and involvement of both lobes of the liver have been reported as factors that predict the need for aspiration in a liver abscess.[41] Initial surgery may also be indicated in patients with larger abscesses measuring >10 cm in diameter. In the present study population, the rate of surgery was higher in patients with non-cryptogenic PLA than in those with cryptogenic PLA. The reasons for surgery were typically a large abscess, difficulty accessing the abscess, multiple comorbidities, and other complicating factors.

In the present case series, the overall 28-day mortality in patients with PLA was 4.5%, which is slightly lower than previously reported rates of 5–12.5%.[13,14,29,31] This may be partly because the patients in the present study were relatively young compared with those in previous reports. Additionally, the relatively high rate of ICU admission (19.1%) in the present study likely contributed to the decreased mortality.

Some study limitations should be noted. First, this was a retrospectively study, and all data were reviewed through medical records. Secondly, the incidence of cryptogenic PLA may be overestimated; as none of the patients underwent colonoscopy or endoscopic retrograde cholangiopancreatography, the incidence of colonic or biliary tract disease may have been underestimated. Thirdly, the number of patients was relatively small. Nevertheless, the First Affiliated Hospital of Xiamen University is one of the largest hospitals in South-eastern China, and the present study is therefore likely to present a true reflection of the actual features of this region.

In conclusion, *K. pneumoniae* was found to be the most common infectious origin in cases of cryptogenic PLA, which was a distinct category of PLA. These data reveal a potential need for the classification of PLA into cryptogenic and non-cryptogenic types at onset, to guide empiric antimicrobial therapies, treatment modality, and screening for complications including metastatic infection.

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Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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