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Analysis of clinical and CT characteristics of patients with *Klebsiella pneumoniae* liver abscesses: an insight into risk factors of metastatic infection

Zhihui Chang, Jiahe Zheng, Yujia Ma, Zhaoyu Liu *

Department of Radiology, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, China

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ABSTRACT

Purpose: To compare the clinical and CT characteristics of patients with *Klebsiella pneumoniae* liver abscess (KPLA), with or without metastatic infection.
Materials and Methods: Clinical information (age, sex, clinical symptoms, underlying disease, hematological parameters, abscess-related mortality) and CT characteristics of abscesses were analyzed to investigate associations with metastatic infection. Metastatic infections were divided into septic pulmonary embolism (SPE) and extra-pulmonary metastatic infection (EMI).
Results: We identified 66 consecutive patients with KPLA. Metastatic infection occurred in 22/66 patients (33.3%); 8/66 (12.1%) patients had SPE, 6/66 (9.09%) patients had EMI; and 8/66 (12.1%) patients had both SPE and EMI. Patients with SPE were younger than patients without SPE (47.7 ± 13.7 y vs.55.6 ± 12.0 y; $p = 0.03$). Unilocular abscess was significantly more common in patients with SPE than the non-SPE group (43.75% vs 18.0%, $p = 0.036$). The mean maximal diameter of EMI was 56.5 ± 21.3 mm and was significantly smaller than that of the non-EMI which was 79.9 ± 31.4 ($p = 0.011$). SPE was significantly associated with development of EMI (50% vs17.3%, $p = 0.011$).
Conclusion: Unilocular liver abscess is associated with SPE, and SPE is strongly associated with EMI among patients with KPLA. A maximal diameter of KPLA<55 mm can be used as a predictor of EMI.

1. Introduction

Pyogenic liver abscess (PLA) is a common and severe intra-abdominal condition caused by bacterial, fungal, or parasitic infections. Until the end of the last century, *Escherichia coli* was the most common pathogen causing liver abscesses worldwide.[1] However, *Klebsiella pneumoniae* has emerged as a significant precipitant of hepatic disease in Asian countries.[2,3] Furthermore, the prevalence of *Klebsiella pneumoniae* liver abscesses (KPLA) is gradually increasing in Western countries.[4]

KPLA is often complicated by bacteremia, sepsis, and metastatic infection. The rate of metastatic infection ranges from 3.5% to 20%.[5–8] In light of the technological advances in interventional radiology and development of antimicrobial drugs, the mortality of PLA has decreased, but the mortality rate of KPLA ranges from 3% to 17.1%.[3,5,7–9]

The metastatic complications in patients with KPLA are usually severe and are associated with a poor clinical outcome and high mortality rate.[5–8] An early and timely diagnosis of metastatic infection is very important in order to expedite treatment and to improve the prognosis of patients with this infection. Some studies have demonstrated that the presence of morphological characteristics of KPLA ascertained by computed tomography (CT) and diabetes are associated with metastatic infection.[5,7,8,10] A recent study[8] shows that abscess size might be related to metastatic infection but other characteristics of KPLA such as thrombophlebitis and spontaneous rupture of the abscess, which might be associated with metastatic infection, were not reported in that study.[10,11]

This study was undertaken to analyze the clinical features, laboratory findings, and CT characteristics in patients with KPLA and to explore whether there were associations with metastatic infection.

* Corresponding author. Department of Radiology, Shengjing Hospital of China Medical University, NO.36 Sanhao Street Heping District, Shenyang, Liaoning, 110004, China. Tel.: (+86-24) 23892620; fax: (+86-24)23929902.
E-mail address: liuzy1226@126.com (Z. Liu).

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2. Materials and methods

2.1. Patient population

The Ethics Committee in Shengjing Hospital of China Medical University granted approval for this retrospective study, with a waiver of informed consent because the records were de-identified to ensure patient confidentiality. Using our institutional electronic medical database, we retrieved records of patients with a diagnosis of pyogenic liver abscess (PLA) between January 2010 and May 2014.

The inclusion criteria were: (a) presence of a focal lesion or lesions in the liver on contrast enhanced CT images; (b) frank pus aspirated from the abscess cavity through diagnostic, and/or surgical drainage procedures; (c) positive microbiological culture results from liver abscess and/or blood cultures; and (d) mono-microbial *K. pneumoniae* shown on the culture result. Patient age, sex, underlying diseases, clinical manifestations, and laboratory findings were obtained from the medical records. The major endpoint was metastatic infection. The patients had routine chest radiograph and a CT scan on the chest if their condition was clinically severe.

2.2. Liver CT characteristics

All patients underwent contrast enhanced CT of the liver before drainage of the liver abscess. In some patients, CT studies were also performed during follow-up to assess the size of the abscess cavity, monitor complications, or check the position of the drainage catheter in cases of poor or incomplete drainage. However, we only reviewed the contrast-enhanced CT images obtained before drainage of the liver abscess, for the purpose of this study.

The CT examinations were performed using one of three different scanners (Somatom Sensation 64, Siemens, Germany; Somatom Definition AS, Siemens, Germany; Aquilion ONE 640, Toshiba, Japan) available at our institution. The scanning parameters varied during the study period and with different scanners: collimation ranged from 1.25 mm to 7 mm; pitch ranged from 0.75 to 1.5; section thickness ranged from 1 mm to 5 mm. Liver examinations were conducted using 100 ml of intravenous non-ionic iodinated contrast medium (Ultravist, Schering, Berlin, Germany) and dosage was calculated based on the patients' weight and administered via a power injector at a rate of 3 mL/sec. Axial sections of 3-5 mm thickness were reconstructed, reported, and archived.

The scans were reviewed by two radiologists (Z.J.H, a radiologist with 10 years experience, and M.Y.J, a radiologist with 8 years experience) who reached agreement between them. The following features were recorded: (a) lobe involvement (unilobar [right or left] or bilobar); (b) number of abscesses (single or multiple); (c) maximal abscess diameter, with the largest abscess measured when there were multiple abscesses; (d) unilocular or multilocular (presence of ≥1-mm-thick septations), multilocular abscess is shown in Figure 1; (e) solid or cystic appearance (>50% of the abscess cavity appears hypodense or liquefied, with an attenuation value of ≤20 HU) in most of the sections showing the abscess cavity, cystic abscess is shown in Figure 2; (f) gas within the abscess cavity as shown in Figure 3; (g) thrombophlebitis (hypodense filling defects in the contrast-enhanced hepatic veins, their tributaries, and/or the inferior vena cava) as shown in Figure 1; and (h) spontaneous rupture of the abscess (based on CT and clinical symptoms)[11] as shown in Figure 1.

2.3. Statistical Analysis

Metastatic infections were categorized into septic pulmonary embolism (SPE) and extra-pulmonary metastatic infection (EMI). Case definition of SPE included the following: (1) focal or multifocal lung infiltrates compatible with septic embolism to the lung, (2) liver abscess as an embolic source, (3) exclusion of other potential causes of lung infiltrates, and (4) resolution of lung infiltrates with appropriate antimicrobial therapy. Patients were classified into metastatic infection and non- metastatic infection groups, SPE and non-SPE groups, and EMI and non-EMI groups. Variables from different groups were compared with each other. The Student's t-test was used for the analysis of continuous variables and the Chi-square test or Fisher's exact test (if the expected value of ≥1 cell was <5) for categorical variables. All statistical tests were 2 tailed, with p values ≤ 0.05 denoting statistical significance. The optimal cut-off for maximal abscess diameter to predict metastatic infection among KPLA patients was determined using the receiver-operating characteristic (ROC) curve based on the optimal sensitivity and specificity and the area under the curve. All analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical features

In total, 66 patients with liver abscess caused by *K. pneumoniae* were identified. There were 22 patients (33.3%) with metastatic

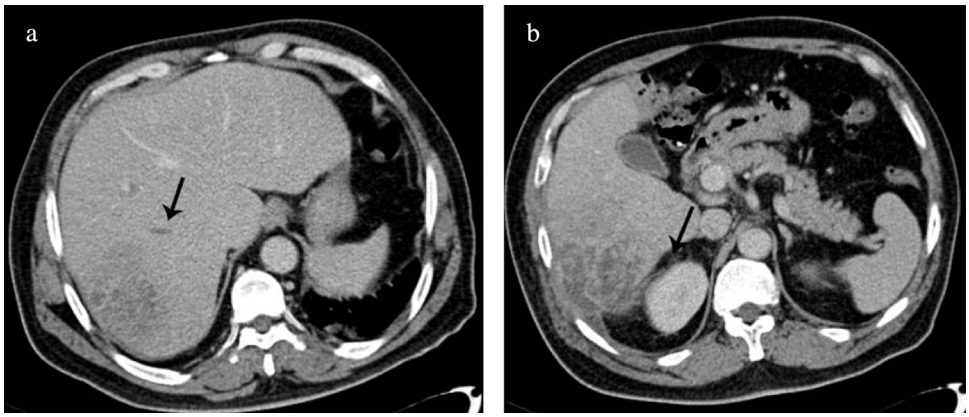

Figure 1. Images of a 61-year-old man who presented with fever and abdominal pain for 2 days. (a) Contrast-enhanced CT showed a multilocular abscess in the right lobe of the liver. Thrombophlebitis was shown by a hypodense filling defect (arrow) in the right hepatic vein. Abscess cultures were positive for *K. pneumoniae*. (b) CT showed a ruptured abscess characterized by blurred edges with a narrow strip of low density in subcapsular area, and exudation (arrow) in the fat gap between the liver and right kidney.

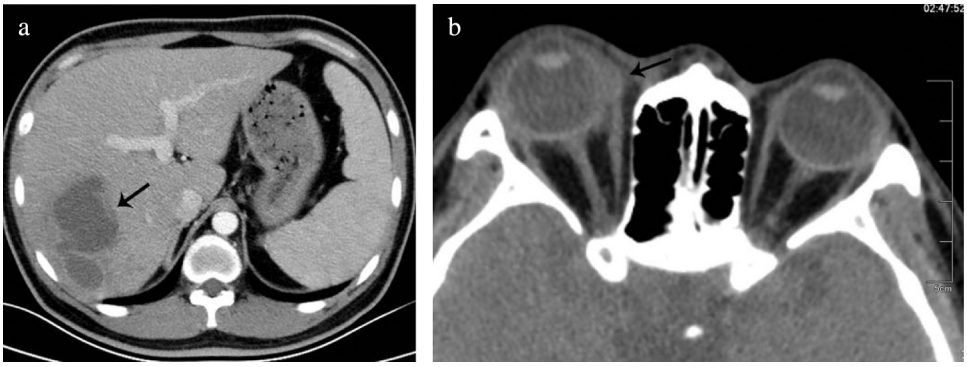

Figure 2. Images of a 34-year-old man with diabetes who presented with fever and right eye swelling for 3 days. (a) Contrast-enhanced CT showed a single abscess in the left lobe of the liver (arrow), which was predominantly cystic in appearance. Abscess and blood cultures were positive for *K. pneumoniae*. (b) CT showed the right side of the thickened peri-orbital wall (arrow).

infection; 8/66 (12.1%) patients had SPE, 6/66 (9.09%) patients had EMI; and 8/66 (12.1%) patients had both SPE and EMI. EMI including: endophthalmitis (n = 5), central nervous system abscess (n = 3), musculoskeletal abscess (n = 2), splenic abscess (n = 1), prostatic abscess (n = 1), ear abscess (n = 1), and kidney abscess (n = 1). Comparison of the demographic data and laboratory findings of the patients with KPLA in the metastatic infection and non-metastatic infection groups are shown in Table 1. A total of 54.5% (36/66) patients underwent chest CT. The patients with chest CT examination were younger than patients without CT scan (46.8 ± 14.3y vs. 56.2 ± 12. 9 y; $p = 0.04$), and had a higher APACHE II score (11.3 ± 5.7 vs. 6.7 ± 3.1; $p = 0.001$). The age difference was significant between SPE and the non-SPE group (47.7 ± 13.7y vs.55.6 ± 12.0y; $p = 0.03$).

3.2. Liver CT characteristics

The characteristics of liver abscesses are summarized in Table 2. A single abscess was found in 54 (81.8%) patients, and multiple abscesses were seen in 12 (18.2%) patients. Among the patients with multiple abscesses, the average number of lesions per patient was 2.5 ± 0.67. Unilobar involvement was seen in 54 (81.8%) patients, and multilocular abscess (Figures 1) was present in 50 (75.8%) patients. The abscesses were predominantly solid in 38 (57.6%) patients and cystic (Figure 2) in 28 (42.4%) patients. Thrombophlebitis (Figures 1) was present in 9 (13.6%) patients, and gas in the abscess cavity (Figure 3) was present in 11 patients (16.7%). There were 4 (6.1%) patients with liver abscess who experienced a spontaneous rupture of the abscess (Figure 1).

3.3. Risk factor analyses

There was no significant difference in all assessed factors when comparing the metastatic infection and non- metastatic infection groups. Unilocular abscess was significantly more common in KPLA patients with SPE than the non-SPE group (43.7% vs 18.0%, $p = 0.036$).

The mean maximal diameter of EMI was 56.5 ± 21.3 mm and was significantly smaller than that of the non-EMI which was 79.9 ± 31.4 ($p = 0.011$). In predicting EMI, maximal diameter of liver abscess = 55 mm was the optimal cutoff value as it yielded 0.70 in the area under ROC Curve with a P value of 0.034. SPE was significantly associated with development of EMI (50% vs17.3%, $p = 0.011$).

4. Discussion

KPLA with contemporaneous metastatic infection in other body sites has been referred to as a new invasive *Klebsiella pneumoniae* liver abscess syndrome.[9,12] This syndrome has recently emerged as a globally prevalent disease.[9] The lung receives systemic venous flow from other body parts, so the lung is susceptible and usually the first organ infected by blood-borne infection.[13] Pulmonary metastatic infection also known as SPE. In this study, SPE accounted for 72.7% of metastatic infection. The most important finding in this study was that 7 of the 16 patients with SPE had a unilocular abscess on CT. Unilocular abscess may be a risk factor for the formation of SPE. However the mechanism for the development of SPE in patients with unilocular KPLA is unclear. Multilocular abscess is an important feature of KPLA,[14–17] but we

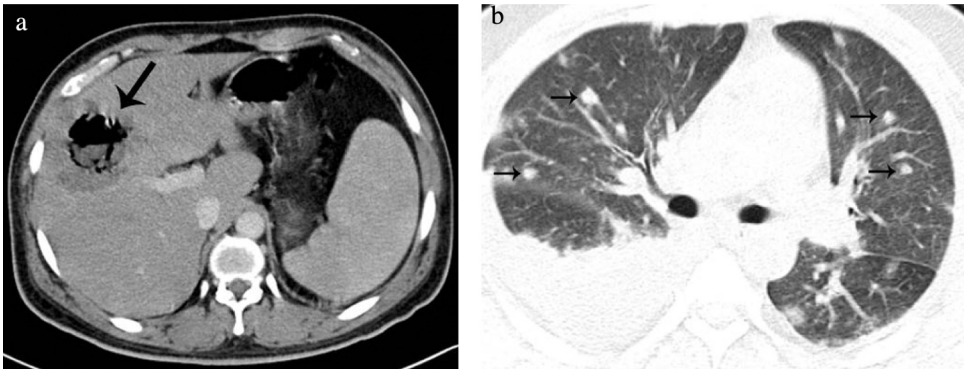

Figure 3. Images of a 59-year-old man with diabetes who presented with fever for 3 days. (a) Contrast-enhanced CT showed a single abscess with gas formation in the right lobe of the liver (arrow). Abscess cultures were positive for *K. pneumoniae*. (b) Multiple nodules (arrows) and right pleural effusion were visible on the chest CT.

Table 1
Clinical Characteristics in 66 Patients with *Klebsiella pneumoniae* liver abscess

Characteristic	MI (n = 22)	non-MI (n = 44)	p^*	SPE (n = 16)	no-SPE (n = 50)	$p^\dagger$	EMI (n = 14)	no-EMI (n = 52)	$p^\ddagger$
Age (years)	51.27 ± 13.90	55.00 ± 12.19	0.268	47.7 ± 13.7	55.6 ± 12.0	0.03	55.0 ± 12.6	53.4 ± 13.11	0.686
Male	16(72.72%)	29(65.90%)	0.575	13(81.25%)	32(64%)	0.197	10(71.42%)	35()	0.769
Underlying disease									
Diabetes mellitus	12(54.54%)	24(54.54%)	0.602	9(56.25%)	27(54%)	0.875	8(57.14%)	28(67.30%)	0.826
Biliary tract disease	3(13.63%)	5(11.36%)	0.538	2(12.5%)	6(12%)	0.957	3(21.42%)	5(9.61%)	0.229
Malignancy	2(9.09%)	4(9.09%)	0.686	2(12.5%)	4(8%)	0.627	1(7.14%)	5(9.61%)	0.775
Presenting symptoms									
Fever (>38°C)	18(81.81)	36(81.81%)	0.623	14(87.5%)	40(80%)	0.715	11(78.57%)	43(82.69%)	0.708
Abdominal pain/Discomfort	5(22.72%)	6(13.63%)	0.485	4(25%)	7(14%)	0.44	1(7.14%)	10(19.23)	0.433
Gastrointestinal symptoms (Nausea and/or vomiting)	3(13.63%)	6(13.63%)	0.657	1(6.25%)	8(16%)	0.436	4(28.57%)	5(9.61%)	0.087
APACHE II score (mean ± SD)	7.62 ± 3.14	8.32 ± 3.85	0.334	8.93 ± 4.25	7.16 ± 3.22	0.209	8.11 ± 4.09	7.47 ± 3.72	0.128
Septic shock	2(9.09%)	2(4.54%)	0.596	2(12.5%)	2(4%)	0.245	1(7.14%)	3(5.76%)	0.624
Hematologic parameters									
White blood cells ($*10^9$/L)	11.74 ± 6.36	12.71 ± 4.51	0.462	11.28 ± 5.81	12.74 ± 4.68	0.307	11.23 ± 6.95	12.69 ± 4.32	0.333
Platelets(*109/L)	178.64 ± 168.81	180.66 ± 116.56	0.955	176.81 ± 176.45	181.89 ± 120.85	1.915	162.29 ± 141.03	184.75 ± 134.21	0.584
Albumin(g/L)	27.51 ± 4.46	30.46 ± 8.4	0.129	27.21 ± 4.38	30.20 ± 8.06	0.162	27.63 ± 4.45	29.98 ± 8.00	0.297
Total bilirubin (mmol/L)	21.98 ± 17.24	19.08 ± 12.08	0.429	21.59 ± 17.64	19.55 ± 12.72	0.615	24.53 ± 17.41	18.84 ± 12.79	0.177
CRP (mg/dl)	18.21 ± 9.03	15.17 ± 9.96	0.245	15.44 ± 9.13	17.35 ± 9.54	0.425	17.64 ± 9.66	16.81 ± 10.14	0.173
SPE							7(50%)	9(17.30%)	0.011

Note. Data are presented as median (mean ± standard deviation) or *n* (%). MI: metastatic infection; SPE: septic pulmonary embolism; EMI: extra-pulmonary metastatic infection.
*MI vs. Non- MI. †SPE vs. non-SPE. ‡EMI vs. Non-EMI.

postulate that bacterial infection in multilocular KPLA may be less virulent than that seen in unilocular abscess formation. We also speculate that these could be because inflammatory response to less virulent bacteria would be weaker, and would result in more fibrosis and septa formation. In future research, we are planning to compare genetic characteristics between unilocular and multilocular KPLA. As an example, *RmpA* has been reported as a statistically significant predictor of metastatic infection[7] and we intend to elucidate the relevant mechanism through genetic research.

We hypothesized that younger patients with a stronger immune system would show more severe clinical symptoms to KPLA infection resulting in a CT scan on their chest. This was reflected in our study in which patients with chest CT examination were younger and had a higher APACHE II score. Consequently, our results showed that younger patients with KPLA had a higher rate of SPE. There might be some older patients with SPE who did not undergo CT chest examination and potentially missed a diagnosis for SPE.

Our results show that SPE is a predictor of EMI which was defined as liver abscess spread to other body parts except the lungs. We believe the main reason is that the pathogenic bacteria first pass through the pulmonary circulation, and then they spread to other parts of the body. The mean maximal diameter of a liver

Table 2
CT Findings in 66 Patients with Klebsiella pneumoniae liver abscess

Characteristic	MI (n = 22)	non-MI (n = 44)	p^*	SPE (n = 16)	no-SPE (n = 50)	$p^\dagger$	EMI (n = 14)	no-EMI (n = 52)	$p^\ddagger$
Maximal abscess diameter(mm)	65.82 ± 25.73	79.45 ± 32.52	0.091	68.62 ± 24.64	76.92 ± 32.63	0.354	56.5 ± 21.29	79.87 ± 31.37	0.011
Abscess			0.623			0.946			0.723
Single	18(81.81%)	36(81.81%)		13(81.25%)	41(82%)		11(78.57%)	43(82.69%)	
Multiple	4(18.18%)	8(18.18%)		3(18.75%)	9(18%)		3(21.42%)	9(17.30%)	
Appearance			0.332			0.647			0.762
Solid	14(63.63%)	24(54.54%)		10(62.5%)	28(56%)		9(64.28%)	29(55.76%)	
Cystic	8(36.36%)	20(45.45%)		6(37.5%)	22(40%)		5(35.71%)	23(44.23%)	
Location (lobe)			0.377			0.498			0.67
Unilobar involvement	19(86.36%)	35(79.54%)		14(87.5%)	40(80%)		12(85.71%)	42(80.76%)	
Bilobar involvement	3(13.63%)	9(20.45%)		2(12.5%)	10(20%)		2(14.28%)	10(19.23@)	
Septations within abscess			0.104			0.036			0.782
Unilocular	8(36.36%)	8(18.18%)		7(43.75%)	9(18%)		3(21.42%)	13(25%)	
Multilocular	14(63.63%)	36(81.81%)		9(56.25%)	41(82%)		11(78.57%)	39(75%)	
Gas formation	6(27.27%)	5(11.36%)	0.102	4(25%)	7(14%)	0.44	3(21.42%)	8(15.38%)	0.426
Thrombophlebitis	4(18.18%)	5(11.36%)	0.343	4(25%)	5(10%)	0.204	0()	9(17.30%)	0.099
Spontaneous rupture	3(13.63%)	1(2.27%)	0.068	2(12.5%)	2(4%)	0.245	1(7.14%)	3(5.76%)	0.624

Note. Data are presented as median (mean ± standard deviation) or *n* (%). MI: metastatic infection; SPE: septic pulmonary embolism; EMI: extra-pulmonary metastatic infection.
*MI vs. Non- MI. †SPE vs. non-SPE. ‡EMI vs. Non-EMI.

abscess in the EMI group was significantly smaller than that of the non-EMI group. Shin et al similarly reported liver abscess less than 5.8 cm can be used as an independent predictor of invasive *Klebsiella pneumoniae* liver abscess syndrome.[8] Lee et al. reported that 76.5% of metastatic infections in patients with invasive *Klebsiella pneumoniae* liver abscess syndrome occurred within the first 72 h of their initial presentation.[7] On this basis, we hypothesized that during the early period of abscess formation, when the abscess is small, EMI is more likely to occur. To further support this hypothesis, our study showed that the mean maximal diameter of KPLA being less than 55 mm can be used as a predictor of EMI.

Wang et al reported that hepatic venous thrombophlebitis is associated with 72.7% of metastatic infections. Hepatic venous thrombosis and gas are important signs of metastatic infection, but their study included only patients with diabetes. Furthermore, they also reported that poorly controlled diabetes is associated with complications in KPLA.[10] Apart from diabetes, Yoon et al reported that thrombocytopenia was independently associated with metastatic infection.[5] However in our study, these clinical and CT features are not associated with metastasis infection. The main reason for the difference could be that our study only included patients with KPLA who underwent contrast enhanced CT and drainage. Thrombophlebitis of the hepatic veins is a common complication of KPLA.[18,19] We observed that abscess was present closer to the veins, which had thrombophlebitis. We postulate that the abscess may damage small veins, and it may proceed to the hepatic vein and inferior vena cava. When we injected contrast material into the abscess cavity in a patient after percutaneous puncture drainage, we saw the contrast material went directly into the hepatic vein, and returned to the heart. This observation further supports our conjecture. Despite this, we have not found thrombophlebitis to be a predictor of metastatic infection in our study.

There were several limitations in our study. First, this retrospective study only included patients with KPLA whose pus aspirated from the abscess cavity through diagnostic, and/or surgical drainage procedures; this may lead to selection bias. Second, the study did not serotype *K. pneumoniae* isolates. Recently, capsular type K1 or K2 antigen and the presence of RmpA have been described as virulence factors in *K. pneumoniae*, and these factors contribute to the development of invasive disease.[3,9,20–22] Further investigation of the virulence factors associated with metastatic infections in patients with KPLA is required. In addition, we could not rule out the possibility of extra-hepatic infection metastasized to the liver. Currently, there is no clinical or radiologically diagnostic gold standard for metastatic infections. Increasing the sample size may validate the conclusions in the future.

On the basis of the current findings in this study, the presence of unilocular abscess is associated with SPE, and SPE strongly associated with EMI among patients with KPLA. A maximal diameter of KPLA of less than 55 mm can be used as a predictor of EMI.

Conflict of Interest/Funding: None

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