

# *Klebsiella pneumoniae* infection associated septic pulmonary embolism in an emergency department from east China

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**Background:** Septic pulmonary embolism (SPE) is attracting more attention as a special pulmonary sign in severe infection. We aimed to describe the clinical and imaging features of *Klebsiella pneumoniae* (*K. pneumonia*)-associated SPE in the emergency department.

**Methods:** Records of patients with primarily extrapulmonary infection of *K. pneumoniae* who were admitted to the emergency department between 2014 and 2019 were retrieved. The identifications of *K. pneumoniae*-associated SPE were mainly dependent on the clinical manifestations, typical imaging findings, and presence of a primary source of *K. pneumoniae* infection.

**Results:** A total of 33 cases were identified as SPE with extrapulmonary *K. pneumoniae* infection. The main clinical manifestations were a febrile/fragile state (100%), respiratory symptoms (18.2%), and digestive symptoms (33.3%). Eight patients (24.2%) developed septic shock, 2 (6.0%) experienced respiratory failure, and 2 (6.0%) complicated endophthalmitis. The major source of infection was liver abscess (n=26, 78.8%), followed by septicemia (n=8, 24.2%), intestinal infection (n=3, 9.1%), and ascites (n=1, 3.0%). The computed tomography (CT) features included the following: peripheral wedge-shaped opacity (n=12, 36.4%), a feeding vessel sign (n=3, 9.1%), multiple nodular lesions (n=5, 15.2%), multifocal lung ill-infiltrations (n=15, 45.5%), patchy ground-glass opacities (n=6, 18.2%), focal consolidations (n=9, 27.3%), lung abscesses (n=4, 12.1%), and pleural effusion (n=21, 63.6%). Re-examination of lung HRCT conducted in 7 patients demonstrated imaging improvement after treatment.

**Conclusions:** *K. pneumonia*-SPE presented special clinical and imaging characteristics, which bear similarities to the signs of pneumonia, but was potentially catastrophic. Identifying SPE in septic conditions is crucial to improving clinical outcomes.

Keywords: Septic pulmonary embolism (SPE); Klebsiella Pneumoniae; imaging findings

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# Introduction

Septic pulmonary embolism (SPE) is an uncommon and unique clinical phenomenon that occurs in a minor proportion of serious infectious diseases. SPE is a nonthrombotic, pathogen-containing thrombus causing bacterial embolism in the pulmonary vasculature derived from a primary infection site via venous circulation. During the last 2-3 decades, the epidemiology of SPE has changed due to the increasing incidence of extrapulmonary sources of infection (1,2). Klebsiella pneumoniae (K. pneumonia) is becoming the leading causative pathogen in gram-negative bacteria, and is only secondary to Staphylococcus aureus, the most common pathogenic bacterium leading to SPE (2-4). The diagnosis of SPE mainly depends on clinical evidence of infection with definite microorganism culture results and radiologic findings. The typical computed tomography (CT) scan findings that indicate SPE include peripheral nodules with or without cavities, wedge-shaped peripheral lesions near the visceral pleura or inter-lobar pleura, and pleural effusion (3).

In recent years, along with numerous populationbased studies from other Asian areas, hyper-virulent K. pneumoniae (HvK.P) has emerged in Chinese societies (4-6); K. pneumoniae-associated infection has been encountered with increasing frequency in emergency departments in Shanghai, China; and HvK.P causes rapidonset fatal infection that is prone to invade the immunecompromised subjects. As an infectious condition with presentations varying from common respiratory syndromes to severe sepsis, K. pneumoniae infection and its complications continue to garner the interest of clinical researchers. Of note, a minority of patients with primary extra-pulmonary K. pneumoniae have developed SPE as a more severe phenotype with a higher medical burden, puzzling clinicians (2-4,6). However, SPE has not been well regarded in the existing guidelines for sepsis, and a limited SPE-K. pneumonia spectrum has been described in China.

Our emergency department has accepted numerous patients with *K. pneumoniae* infection and provided them with a timely diagnosis and effective interventions. We thus conducted a retrospective study of *K. pneumoniae*infected cases with primarily extrapulmonary infection, such as hematogenous infection and liver abscess (KPLA), who were treated in our emergency department from 2014 to 2019 and focused on the phenomenon of SPE to help clinicians improve the early suspicion and recognition of this potentially life-threatening condition and strengthen the clinical experience.

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We present the following article in accordance with the STROBE Reporting Checklist (available at http://dx.doi. org/10.21037/apm-19-648).

## **Methods**

## Patients and clinical data

This retrospective study was conducted in the emergency department of Ren Ji Hospital, a tertiary referral teaching hospital affiliated with Shanghai Jiao Tong University School of Medicine. Records of patients who were consecutively admitted to the emergency ward and emergency intensive care unit (EICU) with an episode of extrapulmonary K. pneumoniae-SPE were retrieved between January 2014 and December 2019. Patient data were collected from the hospital information management system Ver. 5, a laboratory database of microorganisms and a radiological database. The medical records were reviewed and analyzed, including patients' demographic variables, clinical presentations, underlying conditions or relevant comorbidities, primary source of infected organ, laboratory data, microbiologic culture results with antimicrobial susceptibilities, radiological findings, treatment, complications, and clinical outcomes. The information and health-care identification numbers of the patients were encrypted.

# Imaging modality

The high-resolution CT (HRCT) scanning (GE Discovery, HD 750, USA) parameters were as follows: 120 kV, 100 to 320 mA, 0.8-second rotation time, 1 mm slice thickness, and 1 mm interval. The images were reviewed at a lung window setting level of 700 Hounsfield units (HU) and width of 1600 HU and a mediastinum window setting level of 40 HU and width of 400 HU. At least two radiologists independently evaluated the thoracic CT findings. Groundglass nodule (GGN) was defined as a hazy increase in attenuation without obscuration of vascular markings, and focal consolidation was defined as a localized increase in lung attenuation with obscuration of vascular markings (7).

# Definitions for critical conditions

Acute respiratory failure was defined as an arterial partial pressure of oxygen <60 mmHg or an arterial partial pressure of carbon dioxide ( $PaCO_2$ ) >45 mmHg to produce respiratory acidosis (pH <7.35) while breathing air at normal atmospheric pressure (8,9). The diagnostic criterion

for acute kidney injury (AKI) was an increase in serum creatinine by at least 0.3 mg/dL within 48 hours (10). The Berlin definition of acute respiratory distress syndrome (ARDS) was employed (11).

## Diagnostic criteria for SPE

The inclusion criteria for SPE diagnosis were adopted as follows: (I) the thoracic HRCT findings included the following patterns: peripheral pleural based wedge-shaped opacity or interlobular fissure, a feeding vessel sign, multiple nodular lesions with or without cavities, patchy groundglass opacities, multifocal lung infiltrates, air bronchograms within a nodule, focal consolidations, lung abscesses, halo signs, and pleural effusion (1,12,13); (II) the presence of a primary extrapulmonary source of *K. pneumoniae* infection as a potential hematogenous source and documented bacteremia; (III) existing septic thrombophlebitis defined as acute venous thrombosis evidenced by ultrasound and/or CT scan; and (IV) clinical improvement and radiographic resolution after appropriate antibiotic therapy.

The exclusion criteria were as follows: (I) other potential explanations of lung lesions, including patients with other diagnoses of tuberculosis, invasive pulmonary fungal infection, possible lung tumor primary or metastasis; (II) patients with insufficient medical records (1,12,13).

The protocol for the research project and human study was approved by the Ethics Committee of Ren Ji Hospital (No.[2016]080k), and the study was performed in accordance with the ethical standards outlined in the 2013 version of the Declaration of Helsinki. Because of the retrospective nature of the research, the requirement for informed consent was waived.

Categorical variables were presented as a number (%). All continuous variables were presented as the mean  $\pm$  standard deviation (SD) or as the median (IQR) for data with a normal distribution and homogeneity of variance.

# Results

# Demographic data

A total of 110 patients with extrapulmonary infection of *K. pneumoniae* were included, among which 33 patients with typical clinical features and abnormal chest HRCT scan findings met the inclusion criteria of SPE (19 males, 57.8%), with a mean age of  $61.03\pm13.95$  years. The average duration of hospitalization was  $26.88\pm17.76$  days (*Table 1*).

#### Clinical features, pathogenic microbe, comorbidities

The clinical manifestations included a febrile and generally fragile state (100%) and respiratory symptoms (n=6, 18.2%), most commonly cough/sputum, dyspnea, and hemoptysis. Symptoms of the digestive system (n=13, 39.4%) included epigastric discomfort, anorexia/vomiting, and diarrhea. There were 9 patients required intensive care, among whom 8 (24.2%) developed septic shock and 2 (6.0%) experienced acute respiratory failure. Severe complication of endophthalmitis occurred in 2 patients (6.0%) (*Table 1*). One patient was died of septic shock and multiple organ dysfunction syndrome (MODS) after accepting the resection of perirectal abscess, who had long-term medical history of uncontrolled primary Sjögren's syndrome.

All *K. pneumonia* isolates were susceptible to cephalosporines, aminoglycosides, or levofloxacin, and susceptibility to ampicillin/sulbactam, piperacillin, and carbapenems varied. No nosocomial or multi-resistant strains were identified.

The most common source of infection of the 33 cases was pyogenic liver abscess (n=26, 78.8%), followed by haematogenous infection (n=8, 24.2%), intestinal infection (n=3, 9.1%), and ascites infection (n=1, 3.0%). Thrombophlebitis or venous thrombosis occurred in 4 different individuals (12.1%), 2 cases (6.0%) with lower limb thrombophlebitis (1 was in popliteal vein), 1 case was inferior vena cava thrombosis, and thrombogenesis involved branch of the portal vein observed in other one patient. Coexistence liver abscess and bacteremia was observed in 3 patients (9.1%). Endogenous endophthalmitis was found in 2 cases (6.0%), among which 1 patient had concurrence of liver abscess, bacteremia and endophthalmitis, another patient had bacteremia, lower limb thrombophlebitis and endophthalmitis simultaneously (*Tables 1,2*).

Underlying diseases or comorbidities included diabetes mellitus (n=24, 72.7%), hypertension (n=11, 33.3%), cerebrovascular disease (n=5, 15.1%), cholelithiasis or biliary tract disease (n=4, 12.1%), hyperthyroidism (n=1, 3.0%), chronic hepatitis (n=2, 6.0%), and chronic renal insufficiency (n=3, 9.1%) (*Table 1*).

# Imaging findings

The HRCT manifestations of the SPE cases included the following: peripheral wedge-shaped opacity (n=12, 36.4%), a feeding vessel sign (n=3, 9.1%), multiple nodular lesions with or without cavities (n=5, 15.2%),

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 Table 1 Clinical characteristics of the 33 SPE cases with K.

 Pneumoniae infection

Clinical characteristics Value Age (year) 61.03±13.95 Sex (male), n (%) 19 (57.8%) Hospital duration (day) 26.88±17.76 Presented symptoms, n (%) Fever 33 (100%) General weakness 11 (33.3%) Temperature peak in hospital (°C) 39.21±0.54 Cough/sputum 3 (9.1%) Shortness of breath 5 (15.1%) Altered mental status 4 (12.1%) Hemoptysis 1 (3.0%) Right upper guadrant abdominal pain 5 (15.1%) Diarrhea 3 (9.1%) Anorexia/vomiting 5 (15.1%) Comorbidities, n (%) **Diabetes mellitus** 24 (72.7%) Hypertension 11 (33.3%) Cerebrovascular disease 5 (15.1%) Cholecystolithiasis 4 (12.1%) Hyperthyroidism 1 (3.0%) Chronic hepatitis 2 (6.0%) Chronic renal insufficiency 3 (9.1%) Complications, n (%) Septic shock 8 (24.2%) Acute respiratory failure 2 (6.0%) Acute kidney injury 7 (21.2%) Liver function impairment 10 (30.3%) Endogenous endophthalmitis 2 (6.0%) Source of infection, n (%) Liver abscess 26 (78.8%) Haematogenous infection 8 (24.2%) Intestinal infection 3 (9.1%) Ascites infection 1 (3.0%) Treatment, n (%) Antibiotics 33 (100%) Puncture drainage of hepatic abscess 21 (63.6%) Ophthalmectomy 1 (3.0%)

The data were presented as mean  $\pm$  SD. SPE, septic pulmonary embolism.

 Table 2 The imaging findings of 33 SPE patients with K.

 Pneumoniae infection

Chest imaging findings	N (%)
Peripheral wedge-shaped opacity	12 (36.4)
Feeding vessel sign	3 (9.1)
Multiple nodular lesions with or without cavities	5 (15.2)
Multifocal lung ill-infiltrations	15 (45.5)
Patchy ground-glass opacities	6 (18.2)
Focal consolidations	9 (27.3)
Lung abscess or air bronchograms within a nodule	4 (12.1)
Pleural effusion	21 (63.6)
Other imaging findings	
Thrombophlebitis/venous thrombus	4 (12.1)
Endogenous endophthalmitis	2 (6.0)
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SPE, septic pulmonary embolism.

multifocal lung ill-infiltrations (n=15, 45.5%), patchy ground-glass opacities (n=6, 18.2%), focal consolidations (n=9, 27.3%), lung abscesses (n=4, 12.1%), and pleural effusion (n=21, 63.6%) (*Table 2, Figures 1-3*). Thrombogenesis involved branch of the portal vein was observed in 1 patient with pyogenic liver abscess (*Figure 2D*). One patient had bacteremia and endophthalmitis accepted eyeball B-ultrasound detection (*Figure 3C*). All the patients underwent an echocardiogram, and no mitral or tricuspid valve infective endocarditis was found.

## Treatment, outcomes

All the 33 patients with SPE received broad-spectrum antibiotics in the initial time, followed by guidance from the results of culture and susceptibility targeted pathogen of *K. pneumonia*. There were 21 patients (63.6%) received ultrasound-guided puncture drainage, 1 patient with unilateral endophthalmitis accepted ophthalmectomy, all the patients were survived after appropriate treatment. In total, reexamination of thoracic HRCT was conducted in 7 patients after treatment, and imaging improvement after treatment was demonstrated (*Figure 1*).

#### Discussion

In the present study, we describe the spectrum of SPE in subjects with extrapulmonary infection of *K. pneumonia* 



**Figure 1** Pulmonary high-resolution computed tomography (HRCT) findings of invasive *Klebsiella pneumoniae* liver abscess (KPLA) in a 56-year-old diabetic woman who complained of repeated fever, fatigue, nausea, and cough for more than 20 days before admission to the hospital. (A,B,C) The cross-sectional HRCT scan showed bilateral lungs filled with multiple nodules, clump-shaped masses, ground-glass opacities, and pleural effusion. There were multiple peripheral sub-pleural, wedge-shaped opacities (arrowheads) and peripheral nodules with feeding vessels (arrows). (D) After treatment for two weeks, the lung window of HRCT showed significant regression of the multiple scattered pulmonary foci above, and pleural effusion decreased significantly. (E) The abdominal CT scan of this patient displayed a hypodense abscess located in the right hepatic lobe with a drainage tube in the cavity.

admitted to our emergency ward and EICU, mostly pyogenic liver abscess (KPLA) and bloodstream infection. *K. pneumonia*-SPE was identified in 33 of 110 patients (27.3%), which is some higher than the rate reported by previous studies (4.5% and 6%) (12,14), most likely because chest HRCT scans were performed on all the patients as a routine examination to avoid missed diagnosis.

The Asian area has a high prevalence of communityacquired *K. pneumonia* infection, including peripheral endogenous and exogenous site (mainly KPLA) caused by *HvK.P.* The lung is the target organ that is liable to be involved with metastatic infection (4,15-22). SPE usually presents as consolidations, multiple nodules with or without cavities and GGN in CT images (1,2,13,22); these features bear more similarities to those of pneumonia, which may confuse clinicians in the initial or progressive stage of the disease. Although a rare case study obtained pathologic findings of SPE described as many neutrophils and foamy histocytes (23), percutaneous needle aspiration biopsy is not easily available in clinical practice, and the diagnosis of SPE is thus mainly dependent on clinical and radiological judgement. Therefore, it is challenging for emergency physicians to distinguish SPE from pneumonia through imaging along with clinical features.

Extrapulmonary K. pneumoniae infection and the rapid aftermath of SPE indicated that K. pneumoniae-associated SPE can occur potentially catastrophically without early intervention. The main prevalent symptoms are fever and dyspnea. However, compared to those of thrombotic pulmonary embolism or sepsis-induced acute respiratory



**Figure 2** Pyogenic liver abscess with septic pulmonary embolism in a 66-year-old man (A) and a 77-year-old woman (B-D) with poorly controlled diabetes, both of whom were positive for *Klebsiella pneumoniae*, detected from aspirated pus and blood cultures. (A) The cross-sectional scan of HRCT at the early stage of the disease showed a peripheral pleural-based, wedge-shaped nodule with cavitation inside (white arrowhead), accompanied by a feeding vessel sign (white arrow). (B) The cross-sectional HRCT scan of the lung window showed bilateral plural effusion and pericardial effusion (black arrowheads). There was a peripheral wedge-shaped nodule close to the adjacent pleura (white arrow). (C) The enhanced abdominal CT scan identified a large hypodense and multiseptated abscess involving the right hepatic lobe; (D) the right branch of the portal vein was missing, which was suggestive of right portal vein embolism, and the accompanying phenomenon was hypo-perfusion in the corresponding blood supply area of the liver parenchyma (black arrows).

distress syndrome (ARDS), the lesions of SPE were shown to be reversible after aggressive treatment, such as broadspectrum or microbiological test-guided antibiotic therapy or early treatment of empyema by applying liver abscess drainage to deduce the occurrences of lethal conditions, in most of the patients (1,3,13,14,21). This phenomenon also existed in our study and could explain why only 1 patient developed acute respiratory failure, and persistent respiratory failure was not common due to timely control of the primary infection and advanced life support. We observed obvious regression of pulmonary infiltrates or nodules in 7 KPLA patients who underwent repeated HRCT scans after antiseptic treatment (*Figure 1*).

As another important phenotype of SPE, thrombophlebitis or venous thrombosis were observed in four different cases. Septic lower limb thrombophlebitis was identified in 2 cases; right portal vein embolism in an old female KPLA patient was detected by abdominal enhanced CT scan (*Figure 2*); inferior vena cava thrombosis in another old female patient with KPLA; Among the cases of hematogenous spread, the complex clinical manifestations of SPE, combined with lower limb thrombophlebitis and endogenous endo-ophthalmitis in a middle-aged diabetic man whose blood culture was positive for *K. pneumoniae*, revealed the rare and severe phenotypes of this type of crippling disease (*Figure 3*).

Importantly, it is well known that underlying or comorbid diseases, as well as immunocompromised conditions, contribute to the occurrence of SPE (22-25). For example, an old male patient with stage 5 chronic kidney dysfunction (CKD 5) identified as having hematogenous and ascetic *K. pneumoniae* infection showed characteristic cavitary nodules, ill-defined lung infiltration, and focal consolidation on the pulmonary HRCT scan during the disease progress. Additionally, in the 33 patients with *K. pneumoniae*-SPE, 24 (72.7%) had diabetes with a high value of glycosylated



**Figure 3** A rare and severe case of *Klebsiella pneumoniae* complicated with septic pulmonary emboli, septic thrombophlebitis, and endophthalmitis. A 45-year-old diabetic man who manifested with high fever, cough, and right lower limb swelling, along with visual deterioration, visited the emergency room. His blood culture was positive and identified as a subtype of *Klebsiella pneumoniae*. (A,B) Lung windows of cross-sectional HRCT scan showed multiple patchy ground-glass and nodular opacities in the left and right lungs, several peripheral nodules abutting the adjacent pleura (white arrowheads) and peripheral nodules with feeding vessels (arrow). (C) Eyeball B-scan ultrasonography of this patient. There were large chunks of turbidity in the right vitreous body, and retinal detachment was suspicious, indicating severe endophthalmitis in the right eye.

hemoglobin (HbA1c), indicating that poor glycemic control may have a close relationship with septic metastatic infection.

Notably, the phenomena that new SPE continued to develop regardless of aggressive antibiotic therapy and that pigtail catheter drainage of the liver abscess was also observed in our study indicated that SPE may be sequential, inevitable and reversible (12,14,21,22,26). That is, chest HRCT should be performed in all patients with the isolation of bacteria from the bloodstream and definite infectious focus (mainly in KP-PLA), especially those with SPE risk factors such as those described above. Furthermore, in a proportion of cases, follow-up CT scans showing the regression or disappearance of lung lesions reaffirmed the diagnosis of SPE (*Figure 1C,D*).

Fortunately, in this study, the pattern of antimicrobial susceptibility indicated that the *K. pneumonia* strains were community acquired and were not naturally multi-resistant

strains. It is also worth mentioning that no cardiac SPE, which was excluded by echocardiographic measurement, was found in this study. The possible reasons were as follows: (I) the most common pathogenic bacteria of cardiac SPE is *Staphylococcus aureus* rather than *K. pneumoniae*. (II) No patient had a history of intravenous drug abuse, cardiac device implants, congenital heart disease, or tricuspid valve infective endocarditis, as historically documented from other countries (25,27).

# Limitations

Two limitations were encountered when conducting this study. First, data were collected retrospectively from a single medical tertiary center, which may have resulted in selection bias. Second, histopathological confirmation was unavailable, and the current SPE diagnosis was mainly based on CT findings and clinical evidence of infection with a definitive bacteriological result.

# Conclusions

The main findings of this study are as follows. First, clinical characteristic and unique imaging signs of SPE in patients with sepsis who require critical care, especially those with vital organ involved and pyogenic liver abscess, should be provided. Second, in patients with *K. pneumonia* infection, emergency physicians should be aware of SPEs so they can distinguish SPE from common pneumonia and promptly initiate treatment. It is important to pay more attention to its different terrible appearances in the emergency department, where the patients always obtain first aid and further treatment. Misdiagnosis and treatment will lead to serious consequences. Third, early identification, appropriate antibiotic therapy, surgical intervention and respiratory support are essential for the treatment of patients with SPE who require critical care.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol for the research project and human study was approved by the Ethics Committee of Ren Ji Hospital (No.[2016]080k), and the study was performed in accordance with the ethical standards outlined in the 2013 version of the Declaration of Helsinki. Because of the retrospective nature of the research, the requirement for informed consent was waived.

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