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ORIGINAL ARTICLE

Clinical and Imaging Characteristics of Primary Severe Community-Acquired Pneumonia Caused by Hypervirulent *Klebsiella Pneumoniae*

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SUMMARY

Background: **To investigate the CT imaging features and microbial phenotypes of primary severe community-acquired pneumonia caused by hypervirulent *Klebsiella pneumoniae* (hvKp).**
Methods: **Patients diagnosed with primary hvKp pneumonia were included, and their clinical data were analyzed, including the baseline characteristics and CT imaging results. After hypermucoviscosity phenotyping, the strains, serological types, and virulence genes of hvKp were identified using multiplex PCR.**
Results: **Twelve patients with primary hvKp pneumonia were included (11 males, 1 female). All patients were infected via respiratory tract inhalation. Ten patients were long-term drinkers. Four patients (33.3%), who were long-term alcohol abusers, died within 30 days after diagnosis. No extrapulmonary metastatic infection was found in any patient. The imaging of lung lesions at the early disease stage exhibited an extensive consolidation in the lungs. As the disease progressed, the most common imaging features were pleural effusion (9/12), cavitation and necrosis (8/12), and pneumothorax (3/12). The serological typing of the capsular polysaccharides on hvKp strains were K1 (6/12) and K2 (6/12). Furthermore, the virulence genotyping showed *rmpA* (11/12), *magA* (11/12), *ureA* (12/12), *mrkD* (12/12), *fim-1* (12/12), *wabG* (12/12), *ybtS* (12/12), and *iucB* (11/12).**
Conclusions: **Primary severe community-acquired hvKp-associated pneumonia is more common in men, especially those with a long-term history of alcohol consumption. CT scanning at the early disease stage mostly showed extensive pulmonary consolidation, which was prone to be combined with cavitation, necrosis, and pleural effusion. K1 and K2 serotypes were identified among the hvKp strains, which were not prone to form extrapulmonary metastasis via the bloodstream.**
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KEY WORDS

community-acquired pneumonia; hypervirulent *Klebsiella pneumoniae;* clinical characterization; genetic detection

LIST OF ABBREVIATIONS

CT: Computed tomography
hvKp: Hypervirulent *Klebsiellapneumoniae*
cKp: Classical *Klebsillapneumoniae*

PCR: Polymerase chain reaction
NCCLS: National Committee for Clinical Laboratory Standardization
OR: Odds ratio
ENT outpatient: Ear, nose & throat outpatient
RR: Relative risk
CI: Confidence interval
rmpA [gene name] regulator of mucoid phenotype A
magA [gene name] Mucoviscosity-associated protein
ureA [gene name] urease subunit alpha
mrkD [gene name] type 3 fimbria adhesin subunit MrkD
fim-1 [gene name] type 1 fimbrial gene
wabG [gene name] Glucuronic acid transferase
ybtS [gene name] yersiniabactin biosynthesis salicylate synthase
iucB [gene name] N(6)-hydroxylysine O-acetyltransferase

INTRODUCTION

Classical *Klebsiella pneumoniae* (cKp) is a major opportunistic pathogen that can colonize in patients with multiple comorbidities and cause nosocomial infections. In contrast to cKp, hvKp in younger healthy hosts can lead to serious community-acquired infectious syndromes, with the potential to disseminate and establish multiple sites of infection simultaneously. Although most hosts targeted by hvKP lacked any obvious underlying diseases, the mortality rate of bloodstream infection of hvKP reached 37.1% [1]. Another study [2] disclosed that a mortality rate greater than 50% was observed among patients with hvKp-associated pneumonia and bloodstream coinfection. A retrospective analysis in China [3] studied the isolation of community-acquired *Klebsiella pneumoniae* strains from 2010 to 2012 and found an increasing frequency of hvKp isolates in patients (25.5%, 26.7%, 54.5%) with an annually-increasing antimicrobial resistance.

Nonetheless, current clinical research on hvKp is relatively insufficient. Certain variations and inconsistencies still exist among the research achievements on the epidemiological characteristics, virulence mechanism, antimicrobial resistance, and clinical features of hvKp. hvKp-associated pneumonia is mainly categorized into primary and secondary pneumonia. Primary pneumonia is predominantly a result of infection initiated via the respiratory tract, while secondary pneumonia is caused by bloodstream infection. Due to its strong ability to infiltrate the bloodstream, hvKp infection usually manifests as a primary liver abscess initially. A previous report disclosed that hvKp-associated hepatic abscesses accounted for 51.9% of patients with bacteremia [4]. Other studies on hvKp-associated pneumonia have mostly focused on secondary pneumonia caused by bloodstream-transmitted extrapulmonary infectious sites. Moreover, another study [5] showed a significantly higher risk of septic infection in patients who had primary liver abscesses caused by *Klebsiella pneumoniae* than those who had liver abscesses caused by non-*Klebsiella pneumoniae*. Empirically, primary and secondary hvKp-associated pneumonia exhibit different clinical symptoms, lung imaging features, systemic complications, treatment regimens, and prognosis outcomes. However, such differences have not been distinguished in most studies.

Therefore, we retrospectively analyzed the clinical data of patients diagnosed with primary community-acquired hvKp-associated pneumonia and identified both serotypes, virulence genes and drug resistance of the detected hvKp strains. This research aimed to further elucidate the clinical characteristics and obtain evidence for strengthening the prevention and treatment of hvKp-associated pneumonia.

MATERIALS AND METHODS

Patients

Twelve patients with hvKp-associated pneumonia (October 2016 - November 2018) were included and analyzed. The inclusion criteria were: 1) disease initiated with respiratory symptoms; 2) presence of pulmonary exudates from lung imaging at the early stage; 3) clinical diagnosis made according to the *Guideline for the diagnosis and treatment of adult community-acquired pneumonia in China (2016 Edition)* [6]; and 4) *Klebsiella pneumoniae* confirmed by the microbial culture (≥ 1 time) of the specimens from the lower respiratory tract and/or the peripheral blood. All strains were identified by multiplex PCR, along with the serological typing of capsular polysaccharides and the virulence genes in hvKp. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University. All procedures involving human participants followed the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Computed tomography (CT) scan

Patients in this study underwent CT scanning of their chests via a CT scanner (SOMATOM Definition AS 64-slices, Siemens Medical Solutions USA, Inc.) without contrast enhancement. The following aspects were inspected carefully: lesion features (consolidating, nodular or diffuse lesions), lesion location (right, left or both lungs) and other abnormal signs (ground-glass opacification, bronchial wall thickening, pulmonary nodules, cavitation and necrosis changes, pleural effusion, and hilar/mediastinal lymphadenopathy).

Specimen collection

The specimens were collected from the lower respiratory tract using bronchoalveolar lavage and aspirate from bronchoscopic aspiration or tracheal intubation. Moreover, the specimens were collected simultaneously

from superficial veins of both upper limbs for the blood culture. BacT/ALERT® SA bottles and BacT/ALERT® SN bottles (Mérieux NutriSciences France) were used for the blood culture of aerobic and anaerobic microorganisms, respectively. To isolate bacteria, the sample was first inoculated in Columbia agar with blood and Chocolate agar, then placed into an incubator under 35.5% CO_2 for 18 to 24 hours. When bacterial colonies became visible, the VITEK® MS (BioMérieux) system was employed for rapid identification of bacteria.

Detection of bacteria

The cultivation and identification of *Klebsiella pneumoniae* were strictly conducted following the "National Clinical Laboratory Procedures." A Kirby-Bauer test (disc-diffusion antibiotic susceptibility test) was performed to determine drug susceptibility. The conduction and result determination of this test followed the National Committee for Clinical Laboratory Standardization (NCCLS).

Hypermucoviscosity (HM) phenotyping

The string test was utilized to determine the hypermucoviscosity phenotypes [7]. Specifically, an inoculating loop was used to gently touch the fresh colonies that were established on a blood agar plate overnight, then it was pulled outwards. This step was repeated twice. If viscous strings of ≥ 5 mm in length formed twice, it was denoted as a positive HM phenotype, which indicates a hypermucoviscous strain.

DNA extraction and multiplex PCR

DNA from hypermucoviscous strains was extracted via thermal lysis procedures. According to the *Diagnosis and Illustration of Clinical Microbiology*, primers were designed for genes involved in drug-resistance (KPC, IMP, VIM, NDM-1), hypervirulent serotypes (K1, K2, K5, K20, K57), and virulence (mrkD, fimH-1, ureA, wabG, uge, ybtS, rmpA, and iucB) of the HvKp strains (Table 1). The primers were synthesized by Shanghai Biological Engineering Co., Ltd. Afterwards, multiplex PCR was conducted to screen these genes. The total reaction system (25 μL) was set as follows: 12 μL PCR-Mix (SanTaq), 1 μL forward primer, 1 μL reverse primer, 1 μL DNA template, and 10 μL ddH_2O. The reaction was performed as follows: 5 minutes of pre-denaturation at 94°C, 30 seconds of denaturation at 94°C, 30 seconds of annealing at 58°C, and 30 seconds of elongation at 72°C sequentially for a total of 35 cycles. After PCR, the DNA fragments were processed for visualization using gel electrophoresis, which was conducted with 8 μL of the amplified DNA samples and an equal volume of DNA ladder. The images were then recorded and analyzed. The hypermucoviscous strain with positive presence of *rmpA* gene was identified as hypervirulent *Klebsiella pneumoniae* (hvKp) [8]

Statistical analysis

The SPSS 18.0 software was employed to statistically analyze the obtained data. The measurement results were denoted as mean ± standard deviation, while the count data were denoted as the number of cases.

RESULTS

General clinical features

Twelve patients with hvKp-associated pneumonia were included (11 male and 1 female, Table 2). The average age of patients was 59.7 ± 12.6 years, all of whom were infected via respiratory tract inhalation. Among the 12 patients, there were 3 chronic smokers and 10 long-term drinkers, including 7 alcohol abusers. Four patients (33.3% as the mortality rate) died within 30 days after diagnosis, all of whom were long-term alcohol abusers. Among these 12 patients, a list of their underlying diseases was exhibited as follows: chronic obstructive pulmonary disease (2/12), alcoholic liver cirrhosis (3/12), hypertension (2/12), diabetes mellitus (2/12), old pulmonary tuberculosis (1/12), and prostate cancer (1/12). All patients experienced certain respiratory symptoms, including pyrexia (12/12), cough (12/12), cough with phlegm (12/12), and dyspnea (12/12). The less common symptoms were hemoptysis (7/12) and chest pain (4/12). A series of comorbidities occurred among these patients, including septic shock (9/12), pleural effusion (9/12), ascites (1/12), pneumothorax (2/12), cardiac insufficiency (7/12), renal insufficiency (6/12), hepatic insufficiency (5/12), gastrointestinal bleeding (2/12), thrombocytopenia (4/12), and sudden cardiac arrest (1/12). Among them, 9 patients (75.0%) experienced multiple organ failure. No extrapulmonary metastatic infection was found in these cases.

CT imaging characteristics

In the early disease stage, an extensive consolidation was found in lung imaging (Figure 1). Consolidation of both lungs was observed in 9 patients. The less frequent changes in lungs were ground-glass opacification (4/12), bronchial wall thickening (3/12), pulmonary nodules (2/12), cavitation and necrosis changes (1/12), pleural effusion (1/12), and hilar/mediastinal lymphadenopathy (1/12). Two or more imaging lesions were observed in 7 patients. With disease progression, imaging lesions changed rapidly (Figure 2), which included pleural effusion (9/12), cavitation and necrosis (8/12), and pneumothorax (2/12). In Figure 3, we can observe the inflammation absorption when patients experienced disease amelioration.

Antimicrobial susceptibility of hvKp strains

All isolated hvKp strains exhibited sensitivity towards piperacillin/tazobactam, levofloxacin, imipenem, cefepime, ceftazidime, ceftriaxone, aztreonam, amikacin, and gentamicin, indicating an antimicrobial resistance

Table 1. Primer sequences.

Gene	Sequence of primers (5'→3')	Length of primers (bp)
KPC	Forward: ATGTCACTGTATCGCCGTCTA Reverse: TTACTGCCCGTTGACGCCCAA	1050
IMP	Forward: CGGCCKCAGGAGMGKCTTT Reverse: CGGCCKCAGGAGMGKCTTT	740
VIM	Forward: CTTTACCAGATTGCYGATGG Reverse: GGYAGRCCGTGCCCSGGAAT	865
NDM-1	Forward: TAAAATACCTTGAGCGGGC Reverse: AAATGGAAACTGGCGACC	439
mrkD	Forward: CCACCAACTATTCCCTCGAA Reverse: ATGGAACCCACATCGACATT	240
fimH	Forward: ATGAACGCCTGGTCCTTTGC Reverse: GCTGAACGCCTATCCCCTGC	688
ureA	Forward: GCTGACTTAAGAGAACGTTATG Reverse: GATCATGGCGCTACCTA	337
wabG	Forward: CGGACTGGCAGATCCATATC Reverse: ACCATCGGCCATTTGATAGA	683
uge	Forward: GATCATCCGGTCTCCCTGTA Reverse: TCTTCACGCCTTCCTTCACT	534
ybtS	Forward: AGTGGTGCGTTCTGCGTC Reverse: ATTTCTACATCTGGCGTTA	477
rmpA	Forward: ACTGGGCTACCTCTGCTTCA Reverse: CTTGCATGAGCCATCTTTCA	535
iucB	Forward: ATGTCTAAGGCAAACATCGT Reverse: TTACAGACCGACCTCCGTGA	948
K1	Forward: GGTCTCTTTACATCATTGC Reverse: GCAATGGCCATTTGCGTTAA	1283
K2	Forward: GACCCGATATTCATACTTGACAGAC Reverse: CCTGAAGTAAAATCGTAAATAGATGGG	641
K5	Forward: TGGTAGTGATGCTCGCGA Reverse: CCTGAACCCACCCCAATC	280
K20	Forward: CGGTGCTACAGTGCATCATT Reverse: GTTATACGATGCTCAGTCGC	774
K54	Forward: CATTAGCTCAGTGGTTGGCT Reverse: GCTTGACAAACACCATAGCAG	881
K57	Forward: CTCAGGGCTAGAAGTGTCAT Reverse: CACTAACCCAGAAAGTGGAC	1036

rate of 0%. However, they were all resistant to ampicillin.

Genotype detection

Microbial culture tests showed that hvKp strains were detected in specimens from the lower respiratory tract of all included patients. Specifically, 9 cases tested positive more than once for hvKp strains, while the other 3 cases were positive only once. Results from the blood culture showed that only 3 cases tested positive. Furthermore, specimen from the pleural effusions of 2 patients tested positive for hvKp strains. Comparable drug susceptibility was found between patients with positive blood cultures and other patients (data not shown). Therefore, hvKp isolates were obtained from the specimens collected from the lower respiratory tract, then were processed to the following genotyping.

The serological typing of the capsular polysaccharides on the hvKp strains were K1 (6/12) and K2 (6/12) serotypes. Furthermore, the genotyping of the virulence genes included *rmpA* (11/12), *magA* (11/12), *ureA* (12/12), *mrkD* (12/12), *fim-1* (12/12), *wabG* (12/12), *ybtS* (12/12), and *iucB* (11/12). After further analysis of the association between hvKp serotypes and disease prognosis, we found that among the 3 fatal cases, one of their isolates was K1 serotype and the other two were K2 serotype. Among the cured patients, 5 isolates were K1 serotype and the other 4 were K2 serotype. This result implies that there is no clear association between the hvKp serotypes and disease outcome.

Table 2. Clinical characteristics of patients with hyKp pneumonia.

	Number of cases (n = 12)
Male	**11**
Female	**1**
Underlying diseases	
Chronic obstructive pulmonary disease	**2**
Alcoholic liver cirrhosis	**3**
Hypertension	**2**
Diabetes mellitus	**2**
Old pulmonary tuberculosis	**1**
Prostate cancer	**1**
Clinical symptoms	
Pyrexia	**12**
Cough	**12**
Cough with phlegm	**12**
Dyspnea	**12**
Hemoptysis	**7**
Chest pain	**4**
Infection via respiratory tract inhalation	**12**
Chronic smoking	**3**
Long-term drinking	**10**
Alcohol abuse	**7**
Comorbidities	
Septic shock	**9**
Pleural effusion	**9**
Ascites	**1**
Pneumothorax	**2**
Cardiac insufficiency	**7**
Hepatic insufficiency	**5**
Renal insufficiency	**6**
Gastrointestinal bleeding	**2**
Thrombocytopenia	**4**
Sudden cardiac arrest	**1**
Extrapulmonary metastatic infection	**0**
Multiple organ failure	**9**

Treatment and disease prognosis

All patients were treated empirically with antibiotics on the day of admission. Seven patients initially received combined treatment of piperacillin and tazobactam. Among these 7 patients, 3 remained in remission afterwards, while the other 4 who experienced disease progression were given carbapenem treatment. Among the latter 4 patients, 1 experienced disease amelioration, while the other 3 patients died (on the 10th, 12th, and 35th day after admission). On the other hand, among the 5 patients initially given carbapenem, 4 experienced disease amelioration, while 1 patient died on the 4th day after admission.

DISCUSSION

In recent years, hvKp has been regarded as a leading cause of community-acquired pneumonia, liver abscesses, and disseminated infection. The high mortality

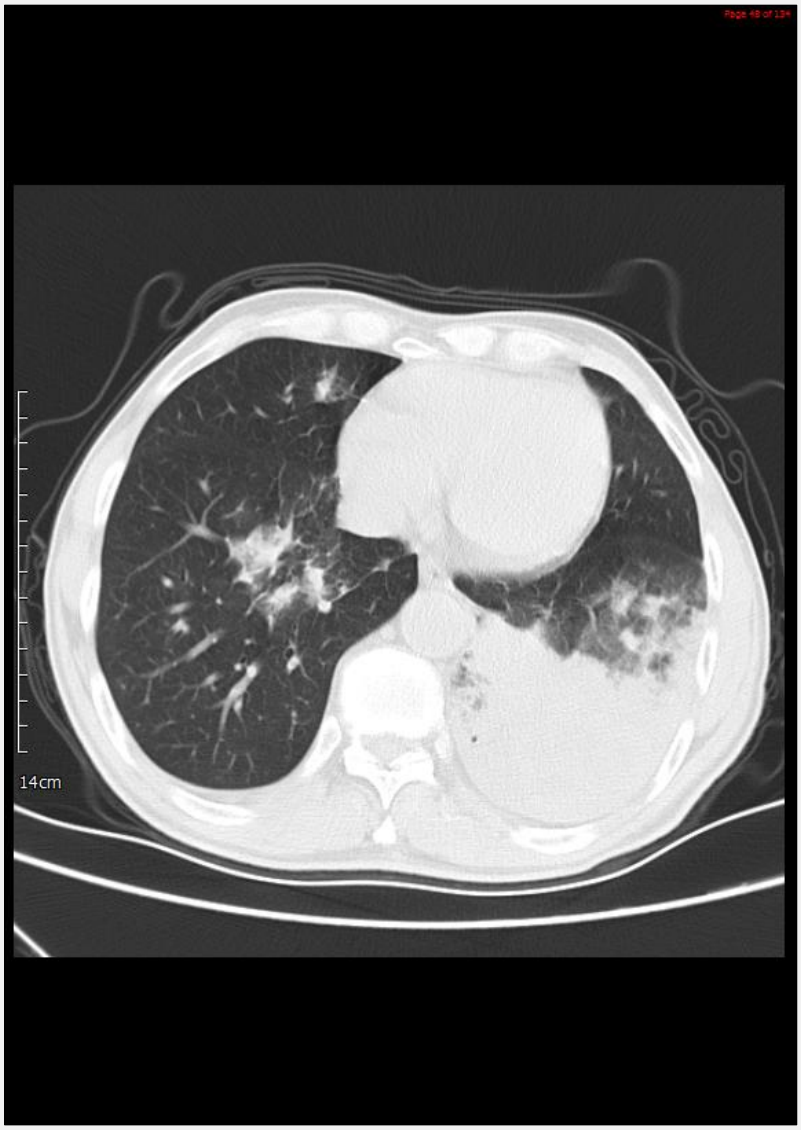

Figure 1: An example of the extensive consolidation changes in the left lung of patient at the early stage of disease onset.

rate and increasing incidence of hvKp year-by-year potentially result in serious sequelae. Several studies in China [3,8] disclosed that 37.8% of *Klebsiella pneumoniae*-associated infections were caused by hvKp strains. Due to difficulties in distinguishing hvKp from cKp in practice, clinical research on hvKp is lacking. With the advancement of methods to isolate hvKp, more hvKp colonies have been detected in seriously-ill patients of all ages. A clinical multivariate analysis [1] revealed that community-acquired infection acts as an independent risk factor for hvKp infection (OR = 4.898). To date, we are still in the exploratory stage of hvKp strains globally.

In our current study, we found that all the included patients experienced pyrexia, cough, cough with phlegm, and dyspnea with a surprisingly high incidence of hemoptysis. While the occurrence of hemoptysis in pulmonary infectious diseases is relatively rare, it can happen more frequently in patients with hvKp-associated pneumonia, which was possibly the result of pulmonary necrosis caused by highly aggressive hvKp. Besides hemoptysis, other symptoms, including blood in sputum and brick red sputum, were observed. In this study, the incidence of hemoptysis in hvKp-associated patients reached 58.3%, indicating that hemoptysis can be used as a warning flag for hvKp infection.

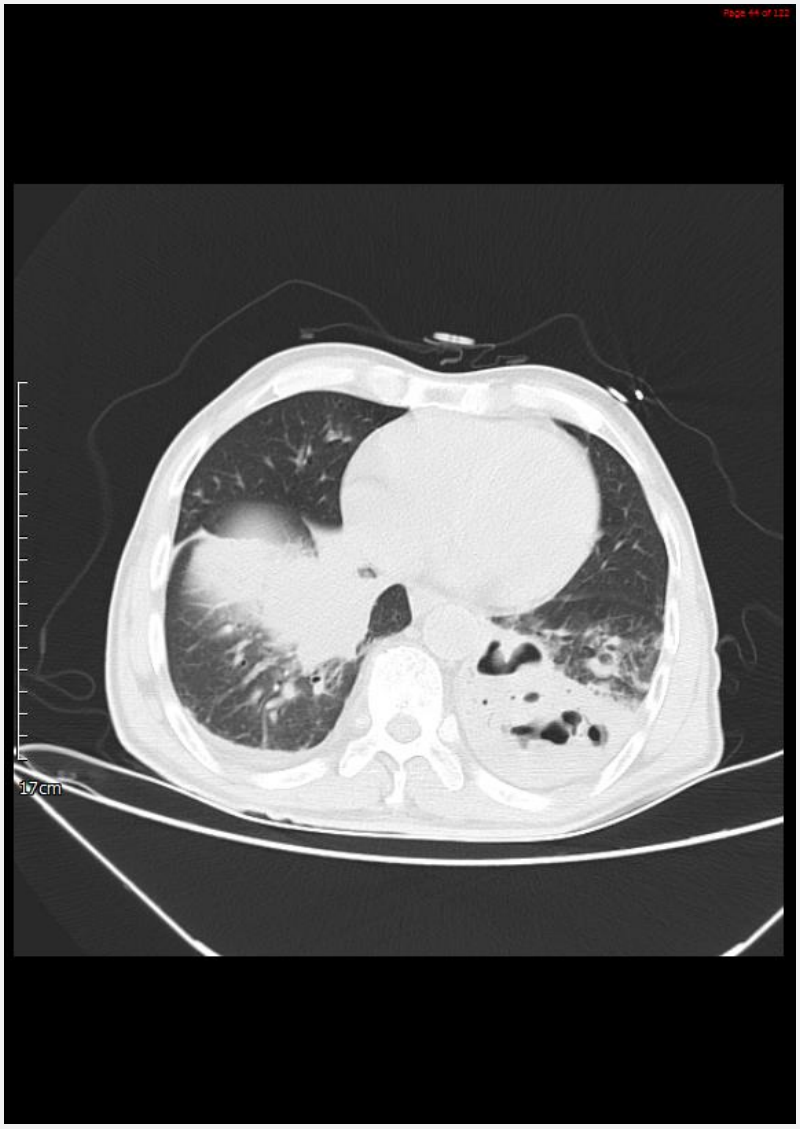

Figure 2: An example of the cavitation and necrosis changes within the consolidated area with disease progression.

Respiratory inhalation is the infection mode of primary hvKp-associated pneumonia, but its colonization in the gastrointestinal system may be one of the prerequisites for a successful hvKp infection. A study in China [9] revealed that K1/K2 *Klebsiella pneumonia* isolates were found in the stool of about 9.8% of the tested population. K1 and K2 serotypes have been reported as the most common serotypes and the major virulent factors for hvKp-associated infectious diseases [10,11]. In this study, the number of K1 and K2 serotypes was half and half, exhibiting consistency with their epidemiological characteristics. Nasopharyngeal tract transfer may be another entry for hvKp. One study [12] reported that the serotype distribution and genetics of *Klebsiella pneumoniae* isolates from nasopharyngeal specimens obtained from the ENT outpatient shared similarities with those hvKp-associated pneumonia patients, suggesting its association with hvKp nasopharyngeal colonization. All patients in this study were infected via respiratory tract inhalation without extrapulmonary metastatic infection sites.

An epidemiological analysis from China [3] revealed that hvKp-associated infection occurs more frequently in males (77.5%), which is consistent with our work (90.0%). In this study, 10 patients were long-term drinkers (83.3%), including 7 alcohol abusers (58.3%),

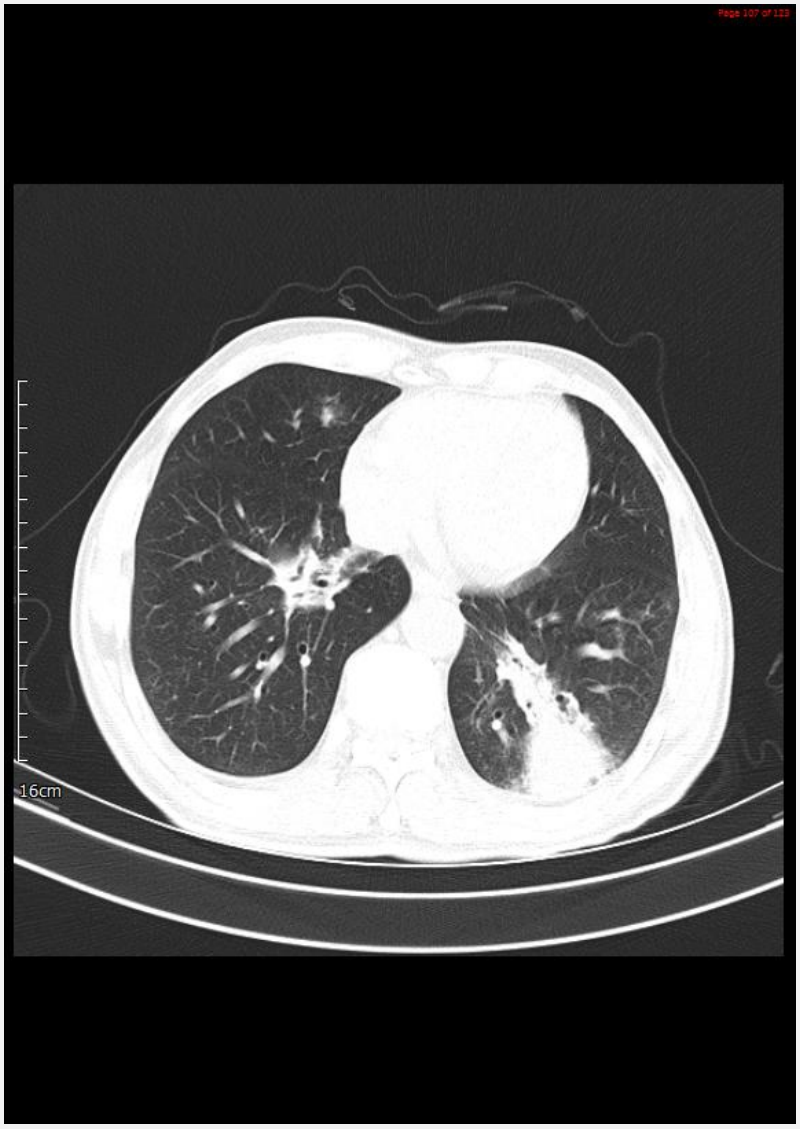

Figure 3: An example of inflammation absorption in the left lung of a patient at the recovery stage.

suggesting that long-term alcohol consumption may be associated with a poorer prognosis of hvKp-associated pneumonia. Moreover, one study [13] disclosed that alcoholic hepatitis was another potential risk factor for hvKp infection. Those patients who died in this study were all long-term alcohol abusers, implying the impact of alcohol abuse on the disease prognosis.

It has been reported that 65.3% of patients with hvKp-associated pneumonia usually exhibit lesions in both lungs based on chest X-rays [14]. A study conducted in Taiwan [15] suggests that *Klebsiella pneumoniae* is the most common cause of community-acquired pneumonia and primary hepatic abscess, where hvKp isolates were found in a large proportion of *Klebsiella pneumoniae* infection cases. Our current study discloses that primary hvKp pneumonia is prone to affect both lungs, with a consolidation change that occurs in the early stage of the disease. With the extensively involved lesion area, the disease progressed rapidly. Additionally, large-scale consolidation was prone to combine with necrotic changes, pleural effusion, and even pneumothorax.

Due to its strong virulence, hvKp strains can trigger an intensive local and systemic inflammatory response, which affects multiple systems [16,17]. In this study, 75% of the patients experienced multiple organ failures, indicating that hvKp-associated pneumonia is prone to

result in multiple organ failure. A controlled study by Rafat C et al. [18] also revealed that hvKp infection is more possible to induce multiple organ failure compared to non-hvKp-associated infection (83.3% vs. 35.7%). Our study showed that patients with hvKp-associated pneumonia had a higher mortality rate within 30 days (33.3%), suggesting the strong invasiveness and lethality of hvKp.

Moreover, hvKp infection is prone to disseminate to multiple distant tissues and organs through the bloodstream. Sohei et al. [19] found that hvKp patients were likely to have disseminated infections (RR = 6.58; 95% CI, 1.16 to 37.4), hepatic abscess (RR = 5.85; 95% CI, 1.39 to 24.6), and pneumonia (RR = 5.85; 95% CI, 1.39 to 24.6). However, no extrapulmonary metastatic infection was found in this study, even in patients with positive blood cultures [20]. The possible reason for the inconsistency with previous studies may be the different hvKp infection modes and routes. The dissemination potential of hvKp strains was also distinct. Some clinical features of primary hvKp-associated pneumonia differed from a previously-studied hvKp infection model, which was not intended to cause extrapulmonary infection sites through the bloodstream. Additionally, all patients were treated empirically with either carbapenem or a combination of piperacillin and tazobactam following admission. Antimicrobial treatment was shown to quickly eliminate pathogenic bacteria in the blood, which helps to control the dissemination of infection. Nevertheless, more than half of the patients who received the "piperacillin and tazobactam" combined treatment exhibited disease progression, which could be controlled after changing to carbapenems. Thus, it can be suggested that the efficacy of carbapenems on hvKp may be more beneficial than the combined treatment with piperacillin and tazobactam.

Despite the challenges of highly pathogenic and lethal hvKp, fortunately most hvKp strains found in clinics are sensitive to antibiotics, excluding ampicillin [21]. The resistance of hvKp is significantly lower than that of cKp, which enables a higher efficacy of antimicrobial treatment on hvKp. This is consistent with the antimicrobial susceptibility test in this study. Moreover, the number of reports on multi-drug resistant hvKp strains is increasing [22,23]. For instance, the extended-spectrum β-lactamase-producing hvKp strains increased from 1.6% in 2001 to 14.3% in 2011. If more and more hvKp strains build stronger multi-drug resistance, the clinical management of hvKp will become more challenging.

In conclusion, primary community-acquired hvKp pneumonia possesses the following characteristics. 1) The infection mostly manifests as severe pneumonia with clinical symptoms, including pyrexia, dyspnea, hemoptysis, blood in sputum, and red currant jelly sputum; and it is prone to cause multiple organ failure. 2) Long-term alcohol consumption, especially alcohol abuse, might be associated with a higher mortality rate. 3) The infection usually exhibits an extensive consolidation in the lungs during the early stage, then progresses rapidly. On the basis of consolidation, it is likely to co-occur with cavitation, necrosis, and pleural effusion. 4) The infection is less frequently caused by extrapulmonary invasion through the bloodstream. 5) carbapenem may serve as a better initial empirical treatment. Nevertheless, this study still faced several limitations. For instance, the retrospective analysis of 12 previous confirmed cases may limit the generalized pattern of the current conclusions. While the obtained results of our study are consistent with previous works in some aspects, we found limited bloodstream-based dissemination of hvKp strains in patients with primary community-acquired hvKp pneumonia, suggesting that we should focus more on local treatment and reduce systemic medication to minimize side effects. In order to elucidate the epidemiological characteristics, virulence mechanism, clinical features, and antimicrobial resistance of hvKp, basic scientific research and comprehensive prospective clinical studies are required. The outcome of such continued research can help guide the prophylaxis and clinical treatment to reduce the prevalence and lethality of hvKp infection.

Ethics Approval and Consent to Participate:

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Consent for Publication:

Consent to publish has been obtained.

Availability of Data and Materials:

The datasets generated and analyzed during the present study are available from the corresponding author per reasonable request.

Declaration of Interest:

The authors declare that they have no conflict of interest.

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