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# Hypervirulent *Klebsiella pneumoniae* have better clinical outcomes than classical *Klebsiella pneumoniae* for lower respiratory tract infection patients

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## Abstract

**Background** The clinical outcomes and microbiological features of lower respiratory tract infections (LRTIs) caused by hypervirulent *Klebsiella pneumoniae* (hvKp) and classical *Klebsiella pneumoniae* (cKp) have not been well understood.

**Methods** This study collected 287 non-repetitive *Klebsiella pneumoniae* isolates from 287 LRTI patients. All these strains underwent annotation for resistance and virulence factors, with 141 strains undergoing mouse infection experiments to assess their virulence. The primary clinical outcomes of these patients were evaluated, including intensive care unit (ICU) admission and in-hospital mortality rates.

**Results** A total of 46 capsule serotypes were identified. Among these isolates subjected to mouse infection experiments, the proportions of strains exhibiting hypervirulent phenotypes were 92.6% (25/27), 92.1% (35/38), 80% (4/5), 25% (1/4), 10.5% (2/19), and 7.1% (1/14) for K2, K1, K20, K54, K47, and K25, respectively. Therefore, K1, K2, and K20 *K. pneumoniae* were defined as hvKp. In addition, the rates of ICU admission and in-hospital mortality for hvKp-infected patients were significantly lower than those of cKp-infected patients (51.4% vs. 65.9%, $\chi2 = 4.722$, $p = 0.03$ and 8.6% vs. 29%, $\chi2 = 12.133$, $p < 0.001$). Notably, among the cKp group, the cKp-ST11 subgroup had higher rates of ICU admission (77% vs. 58.5%, $\chi2 = 7.981$, $p = 0.005$) and in-hospital mortality (44.8% vs. 18.5%, $\chi2 = 17.585$, $p < 0.001$) than cKp-nonST11 subgroup.

**Conclusions** These findings suggest that capsule serotype is a more accurate factor for the prediction of the virulence phenotype, while hvKp have better clinical outcomes than cKp for LRTI patients. Furthermore, the cKp-ST11 subgroup has the worst prognosis than cKp-nonST11 subgroup.

**Keywords** Hypervirulent *K. pneumoniae*, Lower respiratory tract infections, Clinical outcomes, Capsule serotypes, ST11

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## Introduction

*Klebsiella pneumoniae* is notorious for its role in community- and hospital-acquired infections. Clinically, *K. pneumoniae* is classified into classical *Klebsiella pneumoniae* (cKp) and hypervirulent *Klebsiella pneumoniae* (hvKp) [1, 2]. CKp usually causes hospital-acquired infections and occurs in the elderly or immunocompromised, while hvKp is often associated with community-acquired infections in young and healthy individuals without underlying disease [3].

Currently, the definition of hvKp remains somewhat contentious. In the early stages of hvKp reports, the positive string test was commonly adopted as a diagnostic criterion for hvKp [4]. Additionally, virulence plasmid pLVPK has been frequently utilized as biomarkers to distinguish hvKp [5, 6]. Subsequent researches have used virulence genes including *rmpA/A2*, *peg344*, *iucA*, and *iroB* as crucial biomarkers for differentiating hvKp from cKp [7, 8]. Moreover, studies have indicated that hvKp predominantly occurs in capsule serotypes K1, K2, K5, K16, K20, K54, and K57 [4, 9–11]. In addition, hypervirulent phenotypes of ST11-K47 and ST11-K64 have been reported after obtaining pLVPK-like virulence plasmids [12, 13]. However, the reliability of these methods for identifying hvKp has been found to vary, with accuracy rates ranging from 0.90 to 0.98 [14]. Further investigation has demonstrated that the mouse infection model is the definitive standard for hvKp identification [15, 16].

Clinical outcomes caused by cKp and hvKp infection have been reported, but the results are inconsistent. Both Kim's [17] and Liu's [18] studies enrolled patients with *K. pneumoniae* bloodstream infections and utilized a positive string test as a criterion for identifying hvKp, their studies found no statistically significant difference in clinical outcomes between the two groups. Similarly, two studies identified hvKp based on the presence of virulence genes *rmpA* and *iucA/iutA*, and another study identified hvKp through positive string tests, also found no significant difference in 30-day mortality between cKp and hvKp [19–21]. Conversely, one study included patients with ventilator-associated pneumonia caused by *K. pneumoniae* and identified hvKp with a positive string test, the results showed higher bacteremia incidence and mortality rate in hvKp patients [22]. Furthermore, Liao's study [23], which compared the clinical outcomes of *K. pneumoniae* infections in K1/K2 capsule serotypes (KL) versus non-K1/K2, found lower in-hospital mortality rate in patients with the K1 than non-K1/K2, while no significant difference was observed between K2 and non-K1/K2. The aforementioned researches primarily identified hvKp based on the presence of virulence genes or the string test, without additional validation of their accuracy using mouse lethality experiment. In addition, ST11 *K. pneumoniae* is currently the predominant strain in China [24], but its clinical outcomes, especially in lower respiratory tract infection (LRTI) patients, is unknown.

In this study, we evaluated LRTI patients caused by cKp and hvKp at a teaching hospital in Beijing, China. Our analysis encompassed a comparison of clinical outcomes and microbiological characteristics associated with LRTIs caused by cKp and hvKp. Furthermore, we also analyzed the clinical outcomes of cKp-ST11 subgroup.

## Methods

### Patient population and bacterial strains

A total of 287 patients aged 18 years or older, who were diagnosed with LRTIs and had *K. pneumoniae* isolated from the lower respiratory tract (LRT) specimens between January 1, 2022, and June 20, 2023, were included in this study. The patients' clinical and microbiological datas were retrospectively collected from the medical record system. We collected patients' gender, age, clinical symptoms including fever, cough expectoration, chills, and chest pain, comorbid underlying diseases including diabetes mellitus, cardiovascular disease, malignancy, immunosuppression, and biliary tract disease, laboratory findings including white blood cells, C-reactive protein, and procalcitonin, and chest radiography from the electronic case system. In addition, we also collected the length of hospitalization, intensive care unit (ICU) admission, and whether there was any comorbidity with bacteremia, liver abscess, septic shock, and metastatic infections anybody sites, as well as whether there was any hospitalized death. The first *K. pneumoniae* strain isolated from the LRT specimens of the enrolled patients were further analyzed. In addition, the *K. pneumoniae* strain NUTH-K2044 was used as hvKp control, while the *K. pneumoniae* strain ATCC 700603 was used as cKp control.

### Definitions

In this study, community-acquired pneumonia (CAP) was defined as infectious inflammation of the lung parenchyma occurring outside the hospital [25]. Hospital-acquired pneumonia (HAP) was defined as new pneumonia occurring 48 h after admission to the hospital [26]. *K. pneumoniae* LRTIs included patients who had CAP or HAP, and *K. pneumoniae* was isolated from LRT specimens. HvKp was defined by KL, and the virulence was further substantiated by evaluating mortality rates within 7 days post-infection with *K. pneumoniae* in the mouse infection model. Immunosuppression was characterized by a history of bone marrow or organ transplantation, recent chemotherapy for tumors within the past three months, the use of high-dose steroids, and a marked reduction in peripheral blood neutrophils and

CD4 T cells [27]. The primary clinical outcomes included the rates of ICU admission and in-hospital mortality, while the secondary clinical outcomes included the length of hospital stay, the incidence of septic shock, and bacteremia.

#### Antimicrobial susceptibility test (AST) and string test

Antimicrobial susceptibility test was performed in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines using the Vitek 2 system (bioMérieux, France). A *K.pneumoniae* strain was considered to be hypermucoviscous if the length of the viscous string was > 5 mm, while the strain grown on the solid agar was pulled with an inoculation loop [28].

#### Whole genome sequencing (WGS) and annotation

Genomic DNA was extracted from the isolates utilizing a bacterial genomic DNA extraction kit (Tiangen, Beijing, China), followed by sequencing on the Illumina platform (NovaSeq 6000). Raw data were subsequently filtered using readfq (version 10) to procure high-quality clean data. Genome assembly was accomplished utilizing a suite of tools including SOAPdenovo (version 2.04), SPAdes (version 3.10.0), and ABySS (version 1.3.3). Comprehensive analyses for multilocus sequence typing (MLST), virulence genes, antimicrobial resistance genes (ARGs), as well as KL, were conducted using Kleborate software (version 1.0.0). The Snippy (version 4.6.0) and the FigTree (version 1.4.4) were used for the calling of single nucleotide polymorphisms (SNP) and constructing the phylogenetic tree, respectively. The sequence data for the strains have been submitted to the GenBank database (PRJNA1113824).

#### Mouse infection test

Based on the previously reported distribution of K1, K2, and K20 in hvKp, and the K47, K54, K57, and K64 are typically associated with cKp, we selected proportionally K1, K2, K20, K47, K54, K57, K64, and randomly chose one or more strains from the less common K3, K5, K10, K12, K19, K25, K30, and K38, 141 strains were chosen to evaluate their virulence using mouse infection models at last. All animal experiments in this study were performed on female BALB/c (6–8 weeks old) mice purchased from Beijing HFK Bio-Technology Co., Ltd (Beijing, China). Mice were infected intraperitoneally (i.p.) with 200 µl of a logarithmic-phase *K. pneumoniae* bacterial suspension at a final concentration of $10^6$ CFU/ml. A total of 4 mice were included in each test. Mortality was monitored for 7 days post-infection. Strains were classified as hvKp if the mortality rate was 50% or higher. For the induction of LRTIs in mice, 20 µl of a logarithmic-phase hvKp bacterial suspension (strains Kp0004 and Kp0029) at a final concentration of $10^7$ CFU/ml was delivered intranasally (i.t.). Following LRTIs, mice received a subcutaneous (s.c.) injection of 100 µl of meropenem (one time per day) at the back of the neck, with a final dosage of 22.4 mg/kg.

#### Statistical analysis

Comparison of continuous variables were conducted using the Mann–Whitney U test. Categorical variables were examined using the Chi-square test or Fisher's exact test, and when performing the chi-square test, if there were two or more expected counts ≥ 1 and < 5, the Fisher's exact test was used. All statistical evaluations were executed using SPSS (version 23.0), with a two-tailed *p*-value of less than 0.05 deemed indicative of statistical significance. The GraphPad Prism (version 9.0) was used for graphical representations.

## Results

#### Validation of virulence in the mouse infection model

Of the 141 strains that performed mouse infection experiments, 68 were identified as hvKp, including K2 ($n=25$), K1 ($n=35$), K20 ($n=4$), K54 ($n=1$), K47 ($n=2$), and K25 ($n=1$) (Fig. 1A), and the proportions of hvKp among their respective KL were 92.6% (25/27), 92.1% (35/38), 80% (4/5), 25% (1/4), 10.5% (2/19), and 7.1% (1/14), respectively (Table S1). Most of the hvKp strains typically led to mortality in mice within 72 h post-infection, while cKp strains did not lead to any fatalities within 7 days (Figs. 1B and 2A). Therefore, we defined K1, K2, and K20 of *K. pneumoniae* strains as hvKp in this study. Based on this definition, of the 287 non-repetitive *K. pneumoniae* strains, 70 belonged to hvKp and 217 belonged to cKp (Fig. 3 and Table S1).

#### Phenotypic and genotypic features

The AST results showed that cKp had significantly higher resistance rates for a variety of antibiotics than hvKp except for tigecycline (Figure S1 and Table S2). Additionally, the rate of a positive string test was markedly higher in the hvKp group compared to the cKp group (91.4% vs. 16.6%, $\chi2=130.572$, $p<0.001$) (Fig. 1C).

Among the 287 K. *pneumoniae* isolates, a total of 46 KLs were identified (Fig. 3 and Table S1). The most prevalent KL was K64 ($n=60$), accounting for 20.9% of the total strains, followed by K1 ($n=38$, 13.2%), K2 ($n=27$, 9.4%), K57 ($n=21$, 7.3%), K47 ($n=19$, 6.6%), and others (Table S1). In addition, 71 sequence types (STs) were detected, and the most prevalent ST was ST11 ($n=87$, 30.3%), followed by ST23 ($n=35$, 12.2%), ST15 ($n=13$, 4.5%), and others (Fig. 3 and Table S1).

The virulence genes for yersiniabactin (*ybt*) (81.4% vs. 65.9%, $\chi2=6.043$, $p=0.014$), aerobactin (*iuc*)

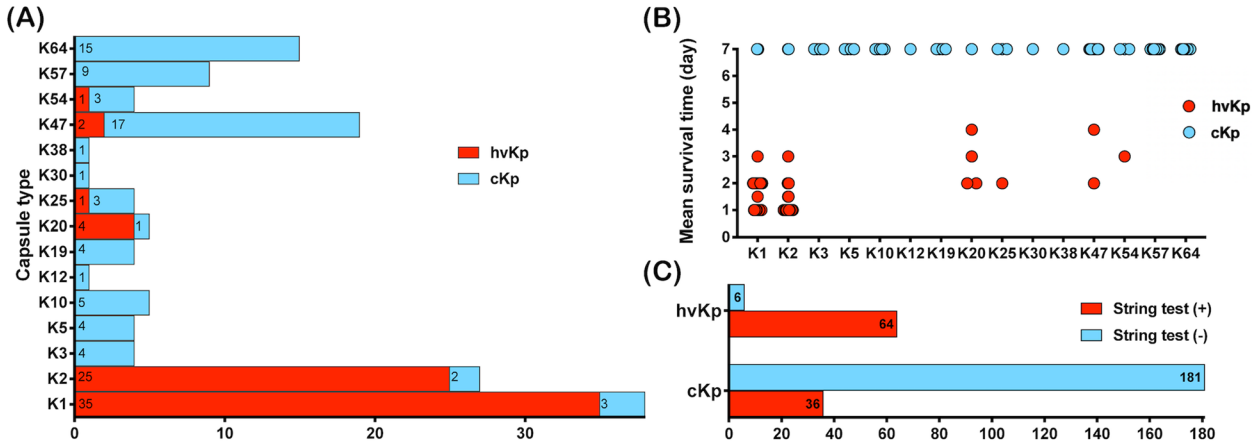


**Fig. 1** Distribution of capsule serotypes and mice survival time. **A** Distribution of capsule serotypes of hvKp and cKp among 141 strains whose virulence has been evaluated by mouse infection model. **B** Mean survival time of mice infected with hvKp and cKp. **C** the results of string test among the 287 isolates

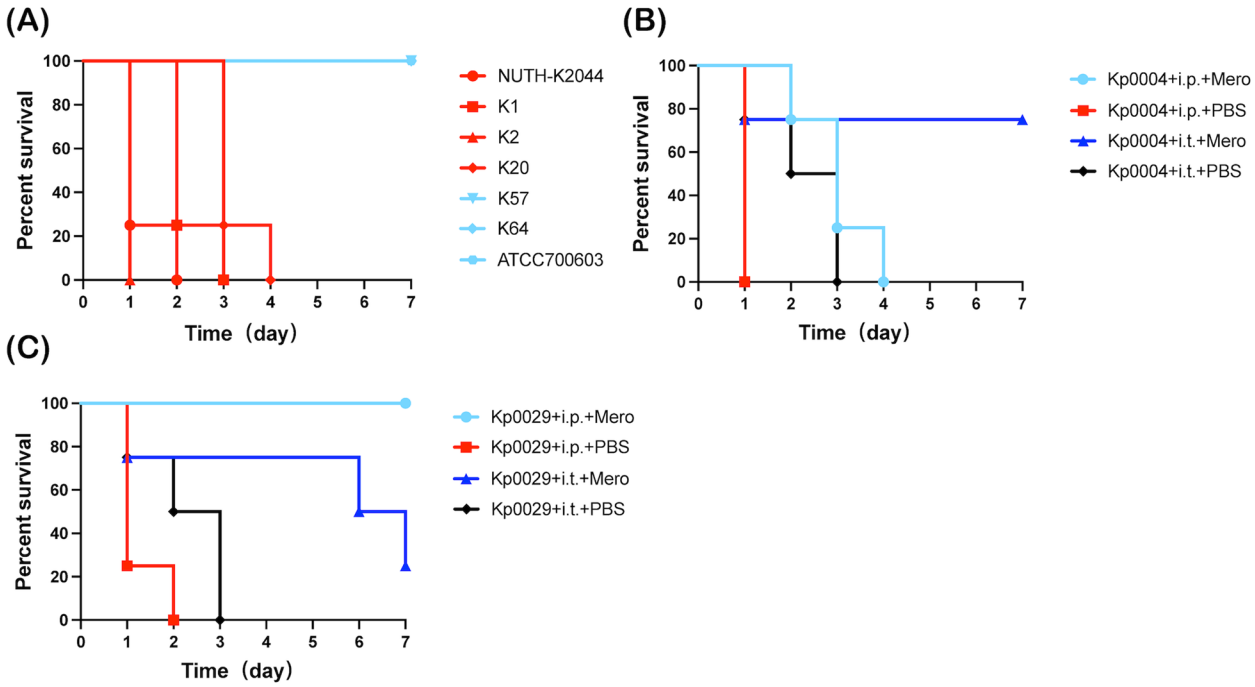


**Fig. 2** Comparison of mean survival time of mice between different groups. **A** Mean survival time of mice infected with different capsule serotypes. **B**, **C** Comparison of survival time and mortality between meropenem-treated and PBS-controlled groups in mice infected with hvKp. Mero, meropenem; PBS, phosphate-buffered saline; i.p., intraperitoneally; i.t., intranasally

(92.9% vs. 39.2%, $\chi2 = 61.145$, $p < 0.001$), salmochelin (*iro*) (85.7% vs. 14.7%, $\chi2 = 122.388$, $p < 0.001$), regulator of mucoid phenotype (*rmpA/A2*) (94.3% vs. 41.5%, $\chi2 = 59.497$, $p < 0.001$), and colibactin (*clb*) (68.6% vs. 0.5%, $\chi2 = 173.419$, $p < 0.001$) were more frequently identified in the hvKp group compared to the cKp group (Fig. 3 and Table S1). In addition, the prevalence of extended-spectrum beta-lactamase (ESBL) genes $bla_{\text{CTX-M-14}}$ (0% vs. 10.6%, $\chi2 = 8.066$, $p = 0.005$), $bla_{\text{CTX-M-15}}$ (1.4% vs. 18.9%, $\chi2 = 12.924$, $p < 0.001$), $bla_{\text{CTX-M-65}}$ (0% vs. 24.4%, $\chi2 = 20.969$, $p < 0.001$), and the carbapenemase gene $bla_{\text{KPC-2}}$ (0% vs. 40.6%, $\chi2 = 40.94$, $p < 0.001$) were significantly higher in cKp compared to hvKp (Fig. 3 and Table S1).

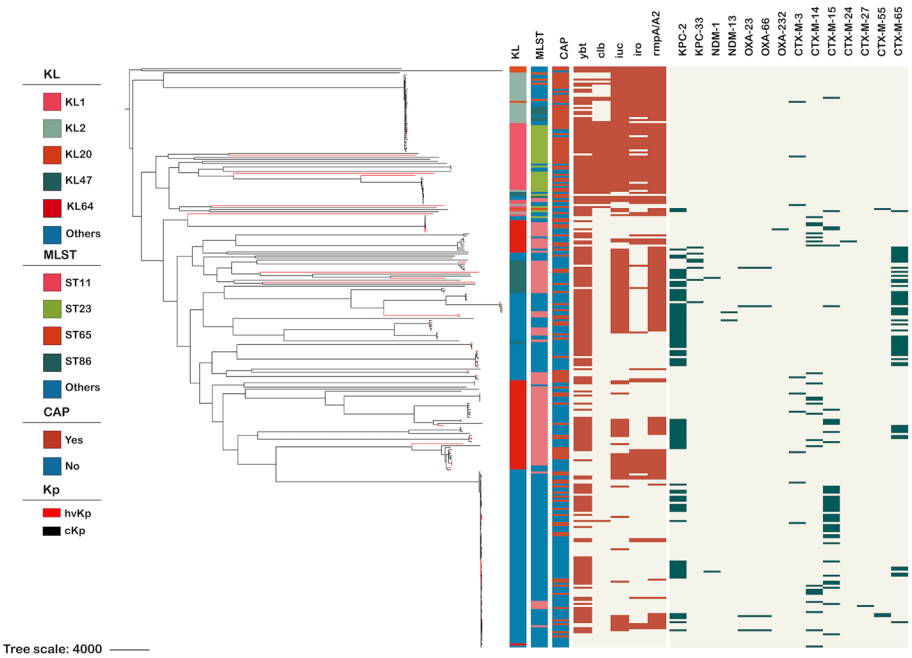


**Fig. 3** Phylogenetic tree based on SNP core genes of 287 isolates of *K. pneumoniae* and their microbiological characteristics. CAP: Community-acquired pneumonia. KL: Capsule serotypes. MLST: Multilocus sequence typing. *Ybt*: Yersiniabactin; *clb*: Colibactin; *iuc*: Aerobactin; *iro*: Salmochelin; *rmpA/A2*: Regulator of mucoid phenotype

### Demographic characteristics

Of the 287 enrolled patients, 118 cases were CAP, and the other 169 cases were HAP (Fig. 3). As shown in Table 1, the average age of hvKp infected patients was significantly lower than cKp infected patients (59 vs. 68 years, 95%confidence interval [CI] = 63.64–67.14, $p < 0.001$). Regarding underlying or concurrent conditions, there were no notable statistical differences ($p > 0.05$). Moreover, our study showed that CAP and liver abscesses were more frequently linked to hvKp (75.7% vs. 30%, $\chi2 = 45.777$, $p < 0.001$ and 8.6% vs. 0.9%, $\chi2 = 8.781$, $p = 0.003$, respectively) in comparison to cKp. Since ST11 strains are only found in the cKp group but not in the hvKp group (Table S1), we further subdivided them into cKp-ST11 and cKp-nonST11 subgroups. There were no significant differences in demographic characteristics between the two subgroups, with the exception that the cKp-nonST11 subgroup was more frequently found in patients without underlying diseases (5.4% vs. 0%, $p = 0.043$) and was more commonly associated with CAP (39.2% vs. 16.1%, $\chi2 = 13.3$, $p < 0.001$) (Table 2).

### Clinical outcomes

Crucially, patients in the hvKp group had a lower rates of ICU admission (51.4% vs. 65.9%, $\chi2 = 4.722$, $p = 0.03$), in-hospital mortality (8.6% vs 29%, $\chi2 = 12.133$, $p < 0.001$), and a shorter average hospital stay (17 vs. 21 days, 95%CI = 18.47–22.32, $p = 0.002$) than cKp group (Table 1). Notably, among the cKp group, the cKp-ST11 subgroup had worse clinical outcomes than cKp-nonST11 subgroup, including the rates of ICU admission (77% vs. 58.5%, $\chi2 = 7.981$, $p = 0.005$), in-hospital mortality (44.8% vs. 18.5%, $\chi2 = 17.585$, $p < 0.001$), septic shock (35.6% vs. 16.9%, $\chi2 = 9.883$, $p = 0.002$), and bacteremia (13.8% vs. 3.1%, $\chi2 = 8.764$, $p = 0.003$), as shown in Table 2.

### Administration of meropenem to mice infected with K. pneumoniae

Administering meropenem to mice infected with the hvKp (Kp0004) via i.p. did not reduce the mortality rates but extended survival time significantly compared to the control group. Importantly, meropenem treatment following i.t. of this strain markedly increased survival time and decreased mortality rates (Fig. 2B). Similarly, for mice infected with hvKp (Kp0029) through both i.p. and i.t., meropenem treatment resulted in a significantly extended survival time and a lower mortality rate compared to those treated with phosphate-buffered saline (Fig. 2C).

**Table 1** Comparison of clinical characteristics of patients with hvKp and cKp infections

| Clinical characteristic | hvKp (N%, *n* = 70) | cKp (N%, *n* = 217) | χ2 values | 95%CI | *p* values |
|---|---|---|---|---|---|
| Age, years | 59 (59 ± 16) | 68 (68 ± 14) | - | (63.64, 67.14) | **< 0.001** |
| Male | 52 (74.3%) | 166 (76.5%) | 0.142 | (0.477, 1.652) | 0.706 |
| **Underlying or concomitant conditions** | | | | | |
| Diabetes mellitus | 23 (32.9%) | 83 (38.2%) | 0.661 | (0.447, 1.396) | 0.416 |
| History of surgery within 1 month | 10 (14.3%) | 50 (23%) | 2.454 | (0.266, 1.167) | 0.117 |
| Cardiovascular disease | 12 (17.1%) | 60 (27.6%) | 3.109 | (0.272, 1.078) | 0.078 |
| Malignancy | 13 (18.6%) | 29 (13.4%) | 1.479 | (0.721, 3.032) | 0.284 |
| Biliary disease | 6 (8.6%) | 24 (11.1%) | 0.35 | (0.295, 1.927) | 0.554 |
| Chronic liver disease | 6 (8.6%) | 13 (6%) | 0.229 | (0.537, 4.028) | 0.632 |
| Chronic kidney disease | 7 (10%) | 41 (18.9%) | 3.006 | (0.204, 1.118) | 0.083 |
| Cerebrovascular disease | 19 (27.1%) | 83 (38.2%) | 2.85 | (0.332, 1.089) | 0.091 |
| No underlying diseases | 6 (8.6%) | 7 (3.2%) | 2.37 | (0.912, 8.67) | 0.124 |
| **Clinical Symptoms** | | | | | |
| Fever (> 37.5℃) | 43 (61.4%) | 153 (70.5%) | 2.014 | (0.379, 1.17) | 0.156 |
| Chill | 6 (8.6%) | 7 (3.2%) | 2.37 | (0.912, 8.67) | 0.124 |
| Cough expectoration | 47 (67.1%) | 124 (57.1%) | 2.198 | (0.87, 2.701) | 0.138 |
| Chest pain | 7 (10%) | 10 (4.6%) | 1.878 | (0.841, 6.291) | 0.171 |
| **Chest radiography** | | | | | |
| Unilateral infiltrates | 27 (38.6%) | 52 (24%) | 5.662 | (1.123, 3.535) | **0.017** |
| Bilateral infiltrates | 40 (57.1%) | 153 (70.5%) | 4.292 | (0.32, 0.973) | **0.038** |
| Use of hormones and/or immunosuppressants | 12 (17.1%) | 61 (28.1%) | 3.357 | (0.266, 1.053) | 0.067 |
| **Laboratory examination** | | | | | |
| White blood cell ($10^9$/L) | 9.1 (9.1 ± 4.8) | 10.5 (10.5 ± 5.4) | - | (9.56, 10.79) | **0.044** |
| C-reactive protein (mg/l) | 78.4 (78.4 ± 77.1) | 94.2 (94.2 ± 69.1) | - | (81.96, 98.67) | **0.036** |
| Procalcitonin (ng/ml) | 1.9 (1.9 ± 4.2) | 5.3 (5.3 ± 23.4) | - | (2.1, 6.95) | 0.068 |
| **Metastatic infections** | | | | | |
| Liver abscess | 6 (8.6%) | 2 (0.9%) | 8.781 | (1.986, 51.153) | **0.003** |
| Others | 3 (4.3%) | 2 (0.9%) | - | (0.788, 29.415) | 0.095 |
| **Type of infection** | | | | | |
| Community-acquired pneumonia | 53 (75.7%) | 65 (30%) | 45.777 | (3.927, 13.535) | **< 0.001** |
| **Clinical outcomes** | | | | | |
| Admission to ICU | 36 (51.4%) | 143 (65.9%) | 4.722 | (0.317, 0.946) | **0.03** |
| In-hospital mortality | 6 (8.6%) | 63 (29%) | 12.133 | (0.094, 0.556) | **< 0.001** |
| Septic shock | 10 (14.3%) | 53 (24.4%) | 3.175 | (0.247, 1.078) | 0.075 |
| Bacteremia | 3 (4.3%) | 16 (7.4%) | 0.816 | (0.159, 1.99) | 0.531 |
| Length of hospital stay, days | 17 (17 ± 17.4) | 21 (21 ± 16.2) | - | (18.47, 22.32) | **0.002** |

*χ2* Chi-square values, *CI* Confidence interval, *ICU* Intensive care unit

### Microbiological characteristics of LRTI patients with liver abscess

Among the 287 patients with LRTIs enrolled in the study, eight developed liver abscesses attributed to *K. pneumoniae* infections, and six of them were caused by hvKp (Table 1). The KLs of the hvKp isolates were K1 (*n* = 2), K2 (*n* = 3), and K20 (*n* = 1), whereas the cKp isolates were identified as K38 and K64 (Table 3). Additionally, seven of eight strains harbored the virulence genes *iuc* and *rmpA/A2*, and the string tests were positive for five of the six hvKp strains and negative for both the cKp strains. The hvKp strains lacked ARGs, whereas both cKp strains carried genes associated with $bla_{\text{CTX-M-65}}$, $bla_{\text{CTX-M-14}}$, or $bla_{\text{KPC-2}}$. Notably, no significant differences were observed in clinical characteristics and outcomes between those infected with hvKp and cKp (Table 3).

## Discussion

HvKp and cKp exhibit distinct microbiological properties, and accurately distinguishing them are essential for evaluating their clinical outcomes. To date, a definitive standard for identifying hvKp remains elusive. A previous

**Table 2** Comparison of clinical characteristics of patients with cKp-ST11 and cKp-nonST11 subgroup

| Clinical characteristics | cKp-ST11 (N%, *n* = 87) | cKp-nonST11 (N%, *n* = 130) | χ2 values | 95%CI | *p* value |
|---|---|---|---|---|---|
| Age, years | 68 (68 ± 14) | 67 (67 ± 15) | - | (65.57, 69.35) | 0.778 |
| Male | 62 (71.3%) | 104 (80%) | 2.212 | (0.329, 1.167) | 0.137 |
| **Underlying or concomitant conditions** | | | | | |
| Diabetes mellitus | 31 (35.6%) | 52 (40%) | 0.421 | (0.473, 1.456) | 0.516 |
| History of surgery within 1 month | 21 (24.1%) | 29 (22.3%) | 0.098 | (0.583, 2.105) | 0.754 |
| Cardiovascular disease | 27 (31%) | 33 (25.4%) | 0.832 | (0.725, 2.415) | 0.362 |
| Malignancy | 13 (14.9%) | 16 (12.3%) | 0.313 | (0.569, 2.753) | 0.576 |
| Biliary disease | 9 (10.3%) | 15 (11.5%) | 0.075 | (0.369, 2.122) | 0.784 |
| Chronic liver disease | 7 (8%) | 6 (4.6%) | 1.089 | (0.586, 5.576) | 0.297 |
| Chronic kidney disease | 17 (19.5%) | 24 (18.5%) | 0.04 | (0.538, 2.14) | 0.842 |
| Cerebrovascular disease | 36 (41.4%) | 47 (36.2%) | 0.603 | (0.714, 2.175) | 0.438 |
| No underlying diseases | 0 (0%) | 7 (5.4%) | - | (1.014, 1.101) | **0.043** |
| **Clinical Symptoms** | | | | | |
| Fever (> 37.5℃) | 66 (75.9%) | 87 (66.9%) | 2.003 | (0.842, 2.865) | 0.157 |
| Chill | 3 (3.4%) | 4 (3.1%) | - | (0.246, 5.155) | 1.000 |
| Cough expectoration | 43 (49.4%) | 81 (62.3%) | 3.532 | (0.341, 1.025) | 0.06 |
| Chest pain | 3 (3.4%) | 7 (5.4%) | 0.113 | (0.158, 2.496) | 0.737 |
| **Chest radiography** | | | | | |
| Unilateral infiltrates | 20 (23%) | 32 (24.6%) | 0.076 | (0.482, 1.732) | 0.783 |
| Bilateral infiltrates | 62 (71.3%) | 91 (70%) | 0.04 | (0.585, 1.931) | 0.841 |
| Use of hormones and/or immunosuppressants | 20 (23%) | 41 (31.5%) | 1.885 | (0.348, 1.206) | 0.17 |
| **Laboratory examination** | | | | | |
| White blood cell ($10^9$/L) | 11.9 (11.9 ± 6.1) | 9.6 (9.6 ± 4.7) | - | (9.81, 11.25) | **0.003** |
| C-reactive protein (mg/l) | 103.4 (103.4 ± 68.6) | 87.8 (87.8 ± 68.9) | - | (84.84, 103.5) | 0.079 |
| Procalcitonin (ng/ml) | 5.8 (5.8 ± 20) | 5 (5 ± 25.5) | - | (2.18, 8.5) | **0.002** |
| **Metastatic infections** | | | | | |
| Liver abscess | 1 (1.1%) | 1 (0.8%) | - | (0.093, 24.305) | 1.000 |
| Others | 2 (2.3%) | 0 (0%) | - | (0.946, 1.009) | 0.16 |
| **Type of infection** | | | | | |
| Community-acquired pneumonia | 14 (16.1%) | 51 (39.2%) | 13.3 | (0.152, 0.581) | **< 0.001** |
| **Clinical outcomes** | | | | | |
| Admission to ICU | 67 (77%) | 76 (58.5%) | 7.981 | (1.294, 4.377) | **0.005** |
| In-hospital mortality | 39 (44.8%) | 24 (18.5%) | 17.585 | (1.945, 6.619) | **< 0.001** |
| Septic shock | 31 (35.6%) | 22 (16.9%) | 9.883 | (1.441, 5.126) | **0.002** |
| Bacteremia | 12 (13.8%) | 4 (3.1%) | 8.764 | (1.569, 16.192) | **0.003** |
| Length of hospital stay, days | 23 (23 ± 16.5) | 20 (20 ± 16) | - | (19.18, 23.51) | 0.085 |

*χ2* Chi-square values, *CI* Confidence interval, *ICU* Intensive care unit

study indicated that the acquisition of pLVPK-like plasmids directly correlates with a hypervirulent phenotype [12]. However, our study revealed that certain strains of serotypes K54, K57, and K64, did not exhibit hypervirulence in the mice infection model, despite harboring pLVPK-like plasmids with virulence-associated genes such as *iuc* and *rmpA/A2*. Apart from this study, an increasing number of studies in recent years have also found that not all strains manifest hypervirulence upon acquiring these plasmids [29–31], and the underlying reasons remain uncertain. He [32] reported that mutations in the *wzc* and *wcaJ* genes of the ST11-K64 strains, which are involved in capsular polysaccharide synthesis, resulted in different virulence phenotypes. Other studies have posited that mutations in the *rmpA*/*A2* gene may account for the absence of hypervirulence in strains carrying the pLVPK-like plasmid [33, 34]. Similar to a recent study [10], we defined hvKp based on capsule serotype and confirmed its accuracy through mouse infection experiments.

**Table 3** Clinical and microbiological characteristics in patients with liver abscess

| | hvKp ($n=6$) | | | | | | cKp ($n=2$) | | *p* value | 95%CI |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical characteristics** | **Kp0001** | **Kp0005** | **Kp0026** | **Kp0027** | **Kp0032** | **Kp0033** | **Kp0107** | **Kp0167** | - | - |
| Age | 73 | 48 | 58 | 61 | 44 | 34 | 67 | 70 | 0.286 | (45.39, 68.36) |
| Gender | male | male | male | male | male | male | female | male | 0.25 | (0.5, 7.997) |
| Diabetes mellitus | No | No | No | Yes | Yes | Yes | Yes | No | 1.000 | (0.041, 24.547) |
| No underlying diseases | No | Yes | Yes | No | No | No | No | Yes | 1.000 | (0.019, 12.898) |
| CAP | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | - | - |
| **Clinical outcomes** | | | | | | | | | | |
| Length of hospital stay, days | 15 | 7 | 20 | 20 | 6 | 11 | 19 | 10 | 1.000 | (8.67, 18.33) |
| Admission to ICU | No | No | No | Yes | Yes | No | Yes | No | 1.000 | (0.019, 12.898) |
| In-hospital mortality | No | No | No | No | No | No | No | No | - | - |
| **Microbiological characteristics** | | | | | | | | | | |
| Capsule serotypes | K20 | K2 | K2 | K2 | K1 | K1 | K64 | K38 | - | - |
| Multilocus sequence typing | ST268 | ST25 | ST86 | ST3509 | ST23 | ST23 | ST11 | ST1738 | - | - |
| String test | - | + | + | + | + | + | - | - | 0.107 | (0.028, 0.997) |
| **Virulence genes** | | | | | | | | | | |
| Aerobactin | + | + | + | + | + | + | + | - | 0.250 | (0.5, 7.997) |
| Yersiniabactin | + | - | + | + | + | + | + | + | 1.000 | (0.583, 1.192) |
| Colibactin | + | - | - | - | + | + | - | - | 0.464 | (0.225, 1.113) |
| Salmochelin | + | + | - | + | + | + | - | - | 0.107 | (0.028, 0.997) |
| rmpA2 | + | + | + | + | + | + | + | - | 0.25 | (0.5, 7.997) |
| rmpA | + | + | - | + | + | + | + | - | 0.464 | (0.15, 166.589) |
| **Resistance genes** | | | | | | | | | | |
| ESBL genes | - | - | - | - | - | - | $bla_{\text{CTX-M-65}}$ | $bla_{\text{CTX-M-14}}$ | - | - |
| Carbapenemase gene | - | - | - | - | - | - | $bla_{\text{KPC-2}}$ | - | - | - |

*CI* Confidence interval, *CAP* Community-acquired pneumonia, *ESBL* Extended-spectrum beta-lactamase, *ICU* Intensive care unit

Using this definition, we found that hvKp have better clinical outcomes than cKp, which is different from some previous reports in which mortality was higher in the hvKp group [22], while most studies did not indicate a significant difference in mortality between the two groups [19–21, 35]. The potential reasons could be as follows. Firstly, the study population was different. Our research focused on patients with LRTIs, whereas other studies typically include patients with bloodstream infection or infections at different sites. Secondly, hvKp was defined differently. In our study, hvKp was identified based on capsule serotypes, while other research primarily used a positive string test or the presence of virulence genes. Finally, other factors may have effects on clinical outcomes, such as patients' age, underlying or concomitant conditions, and immune status.

Contrary to the clinical outcomes, in the mouse infection model, the majority of mice infected with hvKp succumbed within 72 h post-infection, whereas none of the mice infected with cKp died within a 7-day period. The discrepancy between the clinical outcomes of patients and mice infected with *K. pneumoniae* may be attributed to several factors. First, as most hvKp strains are sensitive to antibiotics, there are a wide range of effective antibiotics to choose from. Therefore, we speculate that this could help improve the prognosis of infected patients. To validate our hypothesis, mice infected with hvKp were treated with meropenem. We observed that the antibiotic treatment significantly extended the survival time and reduced mortality rates in these mice. These findings align with those of Xu [36], who demonstrated that antibiotic therapy in hvKp-infected mice decreased bacterial loads in the liver, lungs, and kidneys. In addition, the clinical outcomes observed in patients infected with *K. pneumoniae* may be influenced by various host factors, such as the presence of underlying diseases and the status of the patients' immune system. Notably, a majority of the individuals in our study cohort had one or more comorbidities.

ST11 is the predominant ST type of carbapenem-resistant *K. pneumoniae* in China [33], with ST11-K47 and ST11-K64 being the most widespread strains [37]. Recent research indicates that ST11-K64 has gradually emerged as the leading strain of ST11 *K. pneumoniae* across the country [38]. In this study, the ST11 strains

are only distributed in the cKp group, then we further grouped cKp into cKp-ST11 and cKp-nonST11 subgroups. We compared the clinical outcomes of cKp-ST11 and cKp-nonST11 subgroups, indicating that patients infected with cKp-ST11 *K. pneumoniae* had poorer clinical prognose. Therefore, it is crucial to further explore the pathogenic mechanisms of ST11 *K. pneumoniae*.

There are some limitations in our study. First, our data was retrospectively collected from only one teaching hospital, so caution is needed when translating the results. Second, we only included patients with LRTIs, and the results are not representative of infections at other body sites. Third, we did not perform a mouse infection model on all strains to verify their virulence, which may result in some hvKp categorized as cKp. Finally, the mechanisms of virulence were not further explored in this study.

In summary, LRTI patients infected with hvKp had a better prognosis than infected with cKp. Furthermore, the prognosis of patients with cKp-ST11 *K. pneumoniae* infection was worse than those with cKp-nonST11 *K. pneumoniae* infection. Therefore, the clinical outcomes of LRTIs caused by *K. pneumoniae* are closely related to the sequence type of strain. We need to be vigilant about LRTIs caused by ST11 *K. pneumoniae* strains.

**Abbreviations**

| | |
|---|---|
| LRTIs | Lower respiratory tract infections |
| hvKp | Hypervirulent *Klebsiella pneumoniae* |
| cKp | Classical *Klebsiella pneumoniae* |
| ICU | Intensive care unit |
| LRT | Lower respiratory tract |
| CAP | Community-acquired pneumonia |
| HAP | Hospital-acquired pneumonia |
| AST | Antimicrobial susceptibility testing |
| CLSI | Clinical and Laboratory Standards Institute |
| WGS | Whole genome sequencing |
| MLST | Multilocus sequence typing |
| ARGs | Antimicrobial resistance genes |
| KL | Capsule serotypes |
| SNP | Single nucleotide polymorphisms |
| i.p. | Infected intraperitoneally |
| i.t. | Intranasally |
| s.c. | Subcutaneous |
| STs | Sequence types |
| *ybt* | Yersiniabactin |
| *iuc* | Aerobactin |
| *iro* | Salmochelin |
| *rmpA/A2* | Regulator of mucoid phenotype |
| *clb* | Colibactin |
| ESBL | Extended-spectrum beta-lactamase |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12866-024-03726-2.

Supplementary Material 1: Figure S1. Comparison of the resistance rates of antibiotics for hvKp and cKp.

Supplementary Material 2.

Supplementary Material 3.

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**Clinical trial number**
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**Authors' contributions**
Research design and fund acquisition: Jiankang Zhao, Bin Cao; Data collection and experimentation: Xianxia Zhuo, Zichen Lei, Danni Pu, Yongli Wu; Writing: Xianxia Zhuo. All authors have read and approved the final work.

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**Data availability**
Sequence data that support the findings of this study have been deposited in the NCBI database with the primary accession code PRJNA1113824.

## Declarations

**Ethics approval and consent to participate**
All mouse experiments and the patient's clinical record data were approved by the Ethics Committee of China-Japan Friendship Hospital (2022-KY-232) and was conducted in compliance with the principles of the Declaration of Helsinki. As this study was retrospective and did not involve clinical intervention in patients, the ethics committee waived the requirement for informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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