Research Paper

Clinical Features and Antibiotic Resistance Patterns of hvKP and cKP Strains in Intensive Care Unit-Induced *Klebsiella pneumoniae* Pneumonia

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Reports about the increase in aggressive infections caused by highly virulent *Klebsiella pneumoniae* have risen in recent times. Nevertheless, the impact of its virulence on the progress and consequences of pneumonia patients has yet to be studied. Our research intended to evaluate and relate the clinical characteristics of highly virulent *Klebsiella pneumoniae* and classical *Klebsiella pneumoniae* strains obtained from intensive care unit patients who had pneumonia induced by *Klebsiella pneumoniae*. In this retrospective analysis, we included 173 individuals diagnosed with pneumonia induced by *Klebsiella pneumoniae*. We collected relevant demographic and clinical information from medical records. The study involved an examination of genetic markers associated with K1 and K2, antimicrobial sensitivity, and the presence of virulence genes, including regulator of mucoid phenotype A, isoform usage two-step analysis, enteroBactin, yersiniabactin, *Klebsiella* ferric iron uptake, fimbrial adhesin gene, and allantoin metabolism. Strains that showed both regulator of mucoid phenotype A and isoform usage two-step analysis were classified as hyper virulent *Klebsiella pneumoniae* (n=66), while the rest were designated as classic *Klebsiella pneumoniae* (n=107). The prevalence of patients with highly virulent *Klebsiella pneumoniae* strains was noticeably higher for bacteraemia (24.2 % *vs*. 8.4 %, p=0.004), metastatic spread (25.8 % *vs*. 8.4 %, p=0.002), liver abscess (24.2 % *vs*. 3.7 %, p<0.001), serum creatinine (63.6 % *vs*. 42.1 %, p=0.006), and 30 d mortality (25.8 % *vs*. 8.4 %, p=0.002). All 173 *Klebsiella pneumoniae* strains showed consistent sensitivity to the drug ampicillin. Multivariate regression analysis demonstrated that metastatic spread (odd ratio=3.596, 95 % confidence interval=1.193-10.838; p=0.023), liver abscess (odd ratio=7.537, 95 % confidence interval=1.850-30.715; p=0.005), acute physiology and chronic health evaluation II score (odd ratio=1.616, 95 % confidence interval=1.365-1.914; p<0.001), and serum creatinine (odd ratio=2.506, 95 % confidence interval=1.125-5.587; p=0.025) were all associated with highly virulent *Klebsiella pneumoniae* infection in patients with pneumonia induced by *Klebsiella pneumoniae*. Several clinical risk factors linked to highly virulent *Klebsiella pneumoniae* infection were identified in pneumonia patients with *Klebsiella pneumoniae*.

Key words: Hypervirulence, *Klebsiella pneumoniae*, pneumonia, risk factor, intensive care unit

Klebsiella pneumoniae (*K. pneumoniae*), a prominent etiological agent of healthcare-associated infections, is a pathogen characterized by its opportunistic nature, targeting individuals with weakened immune systems and those undergoing hospitalization[1]. The prevalence of *K. pneumoniae* as a causative agent of Community-Acquired Pneumonia (CAP) ranks 2nd in Asia, standing out as the primary Gram-negative pathogen in this context[2]. Within the spectrum of Hospital-Acquired Pneumonia (HAP), which includes cases of Ventilator-Associated Pneumonia (VAP), *K. pneumoniae* emerges as the secondary utmost prevalent Gram-negative pathogen[3].

The invasive syndromes known as hyper virulent *K. pneumoniae* (hvKP) infections have been the subject of a thorough investigation of their clinical and bacterial characteristics[4-6]. The distinguishing features of hvKP infections can be briefly outlined as follows; they are mostly documented in Taiwan and Southeast Asia, contrasting with the global prevalence of classic *K. pneumoniae* (cKP) infections; prevalent forms of hvKP infections typically encompass pyogenic liver abscesses and, on occasion, other metastatic infections; in contrast

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to cKP, which primarily causes nosocomial infections in immunocompromised patients, hvKP infections usually present as community-onset infections in both immunocompetent and immunocompromised individuals; strains derived from hvKP infections exhibit the hypermucoviscosity phenotype, indicating an augmented production of capsules, which can be readily identified through the string test and a prevalence of capsular serotypes K1 and K2[7,8].

Research has demonstrated risk factors associated with hvKP infections in individuals with *K. pneumoniae* bloodstream infections. According to Li *et al*.[9], diabetes mellitus and community-acquired Blood Stream Infections (BSIs) were recognized as autonomous risk elements for hvKP BSIs. In a study by Harada *et al*.[10], it was noted that patients affected by hvKP infection exhibited a higher prevalence of diabetes mellitus, with their infections displaying a notably increased tendency towards developing liver abscesses among Japanese individuals with *K. pneumoniae* BSIs. However, this study examined the risk factors associated with pneumonia caused by hvKP in Intensive Care Unit (ICU) patients.

MATERIALS AND METHODS

General information:

From January 2019 to May 2024, the ICU of Shanghai Pudong Hospital was the site of this retrospective case-control study. 415 patients were enrolled based on the inclusion criteria. In the course of the research, 173 patients with pneumonia due to *Klebsiella* infection were identified and included in this research, and 180 patients were excluded (fig. 1). The medical records of all patients were collected as follows; age, sex, type of pneumonia, underlying diseases, site of infection, Acute Physiology and Chronic Health Evaluation (APACHE) II, sepsis, shock, laboratory findings, antimicrobial treatment of pneumonia, and Antimicrobial Susceptibility Tests (AST) results. The principal clinical endpoint was mortality observed within a 30 d timeframe. Pneumonia was categorized into three distinct types; CAP, Healthcare-Associated Pneumonia (HCAP), and HAP. CAP was characterized as pneumonia that manifested outside of a hospital, long-term care opportunity, or nursing home environment, which did not fulfill the criteria for HCAP[11]. HCAP was characterized as pneumonia present in patients exhibiting a minimum of two of the following risk factors; hospitalization for a duration of two or more days within the preceding 90 d; living in a long-term care facility or nursing home; administration of antimicrobial treatment or chemotherapy within the last 30 d; undergoing hemodialysis and receiving home wound care[12]. HAP was defined as pneumonia that developed 48 h or more subsequent to hospital admission. hvKP was identified based on positivity for both regulator of mucoid phenotype A (rmpA) and isoform usage two-step Analysis (iutA)[13,14]. The institutional review board at Shanghai Pudong Hospital allowed the study.

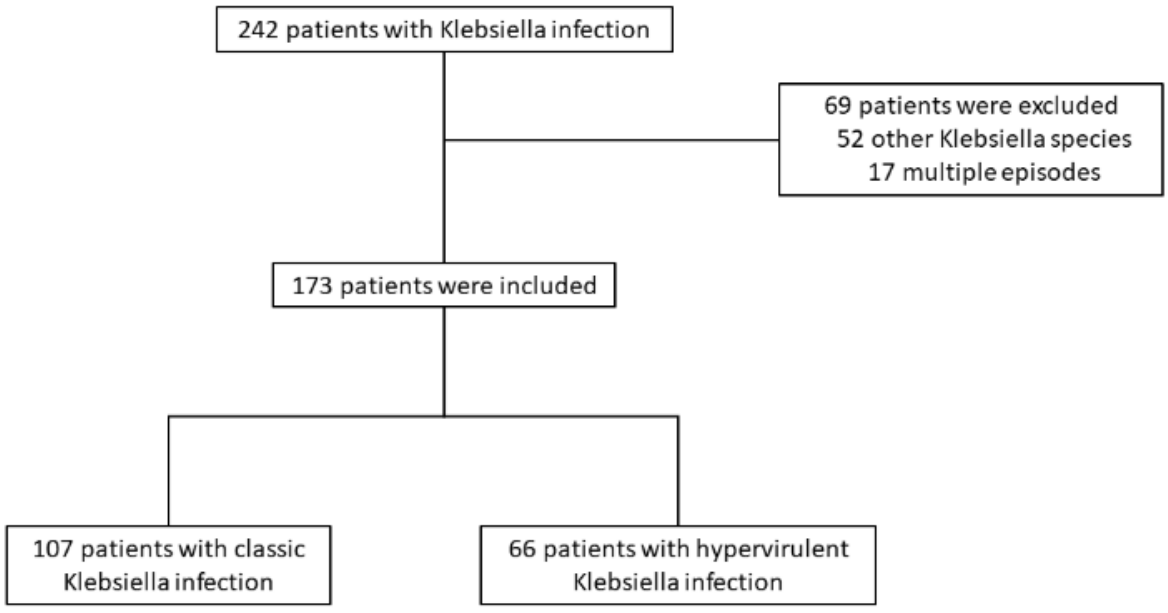

Fig. 1: Flow chart of screening of patients

Microbiology:

The microorganisms isolated from blood samples were characterized as *K. pneumoniae* by applying sophisticated conventional methodologies and the VITEK® II diagnostic system (bioMerieux, Japan). All strains were systematically gathered, with only the initial strain subsequently incorporated into the study. The isolates were preserved at -80° until they were subjected to analytical procedures. Stringent testing protocols were executed on all obtained isolates. Deoxyribonucleic Acid (DNA) was extracted from the preserved strains of *K. pneumoniae*. The sequence type was elucidated through the sequencing of Polymerase Chain Reaction (PCR) amplified products (Sangon Biotech, Shanghai, China), with comparative analysis conducted utilizing an online Comparative Genomics Environment (CGE) tool (https://cge.cbs.dtu.dk). A multiplex PCR assay was employed to identify the K1, K2, and non-K1/K2 capsular serotypes and associated virulence genes. The virulence genes assessed included rmpA, iutA, enterobactin (entb), yersiniabactin (ybtS), *Klebsiella* ferric iron uptake (Kfu), fimbrial adhesin gene (mrkD), and allantoin metabolism (allS), which have been documented in prior research. AST was carried out utilizing the VITEK® system (amikacin, ampicillin-sulbactam, aztreonam, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ertapenem, gentamicin, levofloxacin, meropenem, piperacillin-tazobactam, tigecycline), with the interpretation of results conducted by the 2017 Clinical and Laboratory Standards Institute (CLSI) guidelines.

Statistical analysis:

All statistical evaluations were performed utilizing the Statistical Package for the Social Sciences (SPSS) 20.0 statistical software package (IBM, Chicago, Illinois, USA). Categorical variables were represented through frequency analysis (expressed as percentages), while continuous variables were articulated as the mean with standard deviation. The Mann-Whitney U-test or student's t-test were utilized to analyze continuous variables, while the Chi-square (χ^2) or Fisher's exact test was done for categorical data. Logistic regression analyses, both univariate and multivariate, were used to identify the risk factors linked to hvKP infection. All statistical evaluations were executed using the SPSS 20.0 statistical software package (IBM, Chicago, Illinois, USA). A $p<0.05$ was deemed a threshold for statistical significance, and all probability values were assessed in a two-tailed manner.

RESULTS AND DISCUSSION

The patient demographics at baseline are shown in Table 1. cKP strains were identified in 107 (61.85 %) patients, while hvKP strains were found in 66 (38.15 %) patients. In all patients, CAP and serum creatinine (n=87, 50.29 %) were the most common underlying diseases, followed by HAP and diabetes mellitus (n=54, 31.21 %). Chronic lung disease, chronic kidney disease, cerebrovascular disease, other intra-abdominal infections, and chronic heart disease accounted for 29.48 % (n=51), 27.17 % (n=47), 24.28 % (n=42), 22.54 % (n=39), and 21.97 % (n=38), respectively. The frequency of patients with hvKP strains was noticeably higher for diabetes mellitus, bacteremia, metastatic spread, liver abscess, serum creatinine, shock, and 30 d mortality than those harboring cKP strains (42.4 % *vs*. 24.3 %, p=0.012; 24.2 % *vs*. 8.4 %, p=0.004; 25.8 % *vs*. 8.4 %, p=0.002; 24.2 % *vs*. 3.7 %, p<0.001; 63.6 % *vs*. 42.1 %, p=0.006; 24.2 % *vs*. 10.3 %, p=0.014 and 25.8 % *vs*. 8.4 %, p=0.002).

A comparison of the virulence factors and capsular serotype frequencies between cKP and hvKP strains was shown in Table 2. Compared to cKP strains, hvKP strains showed a significantly higher prevalence of the ST23 sequence type (36.4 % *vs*. 0 %, p<0.001). Out of all *K. pneumoniae* strains, the capsular serotypes K1 and K2 accounted for 16.76 % (29/173) and 19.08 % (33/173) of the strains, respectively. Additionally, hvKP strains showed a potentially higher prevalence of the rmpA (100 % *vs*. 22.4 %, p<0.001), iutA (100 % *vs*. 16.8 %, p<0.001), entb (87.9 % *vs*. 57.0 %, p<0.001), ybtS (77.3 % *vs*. 37.4 %, p<0.001), and allS (21.2 % *vs*. 10.3 %, p=0.047) virulence factors compared to cKP strains.

All 173 *K. pneumoniae* strains showed consistent susceptibility to ampicillin. There were no remarkable differences in antimicrobial susceptibility rates, except for susceptibility to ampicillin-sulbactam, aztreonam, and levofloxacin (p<0.05) (Table 3).

The multivariate logistic regression analyses were done to assess the clinical risk factors for hvKp infection. The study results indicated that metastatic spread (Odds Ratio (OR)=3.596, 95 % Confidence Interval (CI)=1.193-10.838; p=0.023), liver abscess (OR=7.537, 95 % CI=1.850-30.715; p=0.005), APACHE II score (OR=1.616, 95 % CI=1.365-1.914;

p<0.001), and serum creatinine (OR=2.506, 95 % CI=1.125-5.587; p=0.025) were all associated with hvKp infection in patients with pneumonia induced by *K. pneumoniae* (Table 4).

The objective of this study was to compare and assess the clinical features of hvKP and cKP strains extracted from patients who had pneumonia brought on by *K. pneumoniae* in the ICU. It also sought to investigate the effects of virulence factors and the K1 and K2 serotypes on mortality. This investigation holds significance due to its unique approach in comparing hvKP and cKP strains in various forms of pneumonia caused by *K. pneumoniae*, encompassing CAP, healthcare-associated pneumonia, and HAP. Our findings revealed that the presence of virulence factors and the K1 and K2 serotypes did not have an impact on mortality. Conversely, factors such as metastatic spread, liver abscess, APACHE II score, and serum creatinine levels emerged as independent risk factors for mortality.

TABLE 1: CLINICAL AND BACTERIAL CHARACTERISTICS OF PATIENTS INFECTED WITH *K. pneumoniae*

Characteristics	cKP (n=107)	hvKP (n=66)	p
Age	62.76±11.73	62.97±11.88	0.908
Gender (male)	57 (53.3 %)	38 (57.6 %)	0.58
Type of pneumonia			0.577
CAP	54 (50.5 %)	33 (50.0 %)	
Healthcare-associated pneumonia	22 (20.6 %)	10 (15.2 %)	
HAP	31 (29.0 %)	23 (34.8 %)	
Underlying diseases			
Diabetes mellitus	26 (24.3 %)	28 (42.4 %)	0.012
Biliary tract disease	17 (15.9 %)	9 (13.6 %)	0.687
Malignancy	20 (18.7 %)	13 (19.7 %)	0.87
Chronic lung disease	34 (31.8 %)	17 (25.8 %)	0.399
Chronic kidney disease	22 (20.6 %)	20 (30.3 %)	0.147
Chronic liver disease	13 (12.1 %)	7 (10.6 %)	0.758
Chronic heart disease	23 (21.5 %)	15 (22.7 %)	0.849
Cerebrovascular disease	28 (26.2 %)	19 (28.8 %)	0.707
Site of infection			
Bacteremia	9 (8.4 %)	16 (24.2 %)	0.004
Metastatic spread	9 (8.4 %)	17 (25.8 %)	0.002
Liver abscess	4 (3.7 %)	16 (24.2 %)	<0.001
Biliary tract infection	22 (20.6 %)	12 (18.2 %)	0.702
Other intra-abdominal infection	25 (23.4 %)	14 (21.2 %)	0.742
Urinary tract infection	22 (20.6 %)	13 (19.7 %)	0.891
Lung abscess	5 (4.7 %)	5 (7.6 %)	0.427
Other/unknown	19 (17.8 %)	9 (13.6 %)	0.475
APACHE II	13.19±2.23	16.56±3.13	<0.001
Serum creatinine (>94.69 μM)	45 (42.1 %)	42 (63.6 %)	0.006
Shock	11 (10.3 %)	16 (24.2 %)	0.014
30 d mortality	9 (8.4 %)	17 (25.8 %)	0.002

Note: Continuous variables are expressed as mean±Standard Deviation (SD), and analyzed using t-test or Wilcoxon-Mann-Whitney test. Categorical variables are expressed as frequency (%), and analyzed using the χ^2 test

TABLE 2: FREQUENCIES OF SEQUENCE TYPES, CAPSULAR SEROTYPES AND VIRULENCE FACTORS IN PATIENTS INFECTED WITH *K. pneumoniae*

Characteristics	cKP (n=107)	hvKP (n=66)	p
Sequence types			
ST23	0 (0 %)	24 (36.4 %)	<0.001
ST86	15 (14.0 %)	10 (15.2 %)	0.837
ST65	4 (3.7 %)	4 (6.1 %)	0.48
ST29	20 (18.7 %)	4 (6.1 %)	0.02
ST15	22 (20.6 %)	3 (4.5 %)	0.004
ST660	18 (16.8 %)	1 (1.5 %)	0.002
ST11	19 (17.8 %)	14 (21.2 %)	0.574
Others	9 (8.4 %)	3 (4.5 %)	0.331
Capsular serotype			
K1	0 (0 %)	29 (43.9 %)	<0.001
K2	19 (17.8 %)	14 (21.2 %)	0.574
Non K1/K2	88 (82.2 %)	23 (34.8 %)	<0.001
Virulence factor			
rmpA	24 (22.4 %)	66 (100.0 %)	<0.001
iutA	18 (16.8 %)	66 (100.0 %)	<0.001
entb	61 (57.0 %)	58 (87.9 %)	<0.001
ybtS	40 (37.4 %)	51 (77.3 %)	<0.001
kfu	15 (14.0 %)	11 (16.7 %)	0.636
mrkD	88 (82.2 %)	57 (86.4 %)	0.475
allS	11 (10.3 %)	14 (21.2 %)	0.047

Note: Categorical variables are expressed as frequency (%), and analysed using the χ^2 test

TABLE 3: FREQUENCIES OF ANTIMICROBIAL RESISTANCE IN PATIENTS INFECTED WITH *K. pneumoniae*: cKP *vs.* hvKP

Drugs	cKP (n=107)	hvKP (n=66)	p
Amikacin	14 (13.1 %)	5 (7.6 %)	0.26
Ampicillin-sulbactam	38 (35.5 %)	11 (16.7 %)	0.008
Aztreonam	49 (45.8 %)	18 (27.3 %)	0.015
Cefazolin	45 (42.1 %)	24 (36.4 %)	0.458
Cefepime	41 (38.3 %)	21 (31.8 %)	0.386
Cefotaxime	48 (44.9 %)	22 (33.3 %)	0.134
Cefoxitin	45 (42.1 %)	20 (30.3 %)	0.121
Ceftazidime	43 (40.2 %)	21 (31.8 %)	0.268
Ertapenem	17 (15.9 %)	7 (10.6 %)	0.329
Gentamicin	22 (20.6 %)	11 (16.7 %)	0.527
Levofloxacin	27 (25.2 %)	8 (12.1 %)	0.037
Meropenem	13 (12.1 %)	5 (7.6 %)	0.339
Piperacillin-tazobactam	19 (17.8 %)	6 (9.1 %)	0.115
Tigecycline	16 (15.0 %)	4 (6.1 %)	0.076

Note: Categorical variables are expressed as frequency (%), and analyzed using the χ^2 test

TABLE 4: UNIVARIATE AND MULTIVARIATE ANALYSIS OF hvKP INFECTION IN THE PATIENTS WITH PNEUMONIA CAUSED BY *K. pneumoniae*

Characteristic	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p	OR	95 % CI	p
Age	1.005	0.965-1.045	0.822			
Gender (male)	1.073	0.435-2.650	0.878			
Diabetes mellitus	2.458	0.959-6.298	0.061			
Biliary tract disease	2.803	0.631-12.452	0.176			
Malignancy	1.717	0.528-5.585	0.369			
Chronic lung disease	1.434	0.518-3.972	0.488			
Chronic kidney disease	1.822	0.614-5.407	0.28			
Chronic liver disease	1.492	0.375-5.940	0.57			
Chronic heart disease	0.946	0.302-2.960	0.924			
Cerebrovascular disease	2.141	0.793-5.780	0.133			
Bacteremia	0.884	0.223-3.502	0.861			
Metastatic spread	4.011	0.966-16.650	0.056	3.596	1.193-10.838	0.023
Liver abscess	9.958	2.028-48.909	0.005	7.537	1.850-30.715	0.005
Biliary tract infection	0.456	0.091-2.283	0.34			
Other intra-abdominal infection	1.570	0.412-5.973	0.509			
Urinary tract infection	0.723	0.189-2.762	0.635			
Lung abscess	0.551	0.065-4.705	0.586			
Other/unknown	0.829	0.208-3.306	0.791			
APACHE II	1.837	1.474-2.288	<0.001	1.616	1.365-1.914	<0.001
Serum creatinine (>94.69 μM)	3.437	1.302-9.073	0.013	2.506	1.125-5.587	0.025
Shock	0.364	0.093-1.424	0.146			

Note: Univariate and multivariate logistic regression analysis were applied to assess the clinical risk factors for hvKp infection

Several noteworthy risk factors were linked to hvKP infection compared to cKP infection. These include diabetes mellitus, bacteremia, metastatic dissemination, liver abscess, APACHE II score, serum creatinine levels, shock, and 30 d mortality, all of which were connected to a notably increased risk for hvKP infection. Nevertheless, our analysis did not reveal any significant disparity between hvKP and cKP among patients with CAP, healthcare-associated pneumonia, and HAP. Correspondingly, research conducted in China demonstrated a lack of distinction between hvKP and cKP in HAP induced by *K. pneumoniae*[15].

Studies conducted in Asia, Europe, and America have demonstrated a strong correlation between hvKP and serotypes K1 and K2[16]. Our research observed that 65.5 % of hvKP cases contained K1 and K2 serotypes, a proportion significantly more significant than that found in cKP. Recent investigations into VAP stemming from *K. pneumoniae* revealed that the prevalence rates of K1 and K2 serotypes in hvKP were 70.6 % and 64.3 %, respectively. Moreover, in cases of bacteremia CAP, the prevalence rate of K1 and K2 serotypes in hvKP stood at 53.1 %, surpassing that of cKP at 46.9 %[11,17]. The elevated prevalence of K1 and K2 in hvKP can be attributed to the heightened resistance of strains belonging to these serotypes against phagocytosis and intracellular elimination by macrophages and neutrophils compared to other serotypes[18,19]. Furthermore, a VAP study highlighted that virulence factors in hvKP were notably higher than in cKP[17].

In our study, hvKP strains demonstrated a notably higher prevalence of the ST23 sequence type (36.4 % *vs*. 0 %, p<0.001) in comparison to cKP strains. The capsular serotypes K1 and K2 accounted for 16.76 % (29/173) and 19.08 % (33/173) of all *K. pneumoniae* strains, respectively. Furthermore, hvKP strains

exhibited a significantly elevated prevalence of the rmpA (100 % *vs*. 22.4 %, p<0.001), iutA (100 % *vs*. 16.8 %, p<0.001), entb (87.9 % *vs*. 57.0 %, p<0.001), ybtS (77.3 % *vs*. 37.4 %, p<0.001), and allS (21.2 % *vs*. 10.3 %, p=0.047) virulence determinants when compared to cKP strains.

All ASTs demonstrated no significant disparity between the hvKP and cKP strains, except susceptibility to ampicillin-sulbactam, aztreonam, and levofloxacin. Previously conducted research has indicated that the resistance to third-generation cephalosporins in hvKP-related VAP ranged from 0 % to 10 %[17], 14.3 %[20], and 30 % to 40 %[21]. Within the confines of this particular investigation, the resistance level of hvKP towards cefotaxime was measured at 29.2 %. Nonetheless, the escalation in the prevalence of antibiotic-resistant hvKP underscores the necessity for continuous surveillance of antibiotic resistance in such strains, given that prompt antibiotic intervention is crucial for managing pneumonia in affected patients[22-24].

Our research faced a number of drawbacks. First, it was a small sample-size retrospective study carried out at a single center. Second, we could only analyze some potential risk factors through an observational study. Third, there is no universally recognized description of hvKP. Finally, we only examined a subset of virulence factors and did not assess any of them in an animal study. It is also significant to note that many other research groups may have variations in virulence studies.

Our investigation is pivotal for elucidating the correlation between bacterial virulence and the clinical prognosis for pneumonia. Our findings indicate that a number of clinical risk factors were significantly correlated with hvKp infection in pneumonia patients afflicted by *K. pneumoniae*. Moreover, all *K. pneumoniae* strains exhibited uniform susceptibility to the antibiotic ampicillin. Additional research is required to validate the associations between the pertinent virulence factors and the impact of other virulence determinants on the clinical outcomes of pneumonia induced by *K. pneumoniae*.

Authors' contributions:

Nian Zhu designed the project, supervised the project, and revised the manuscript. Bo Gao performed experiments and wrote the first draft of the manuscript. Huiqing Fan helped perform the experiments, collect data, analyzed the data and performed statistical analysis.

Ethical approval:

The Ethics Committee permitted (No: SPH-2019-ZA2) the research conducted at Shanghai Pudong Hospital. All procedures involving human participants strictly followed ethical principles outlined by relevant institutional and/or national research committees, the Helsinki Declaration of 1964 and its subsequent amendments, or similar ethical frameworks. Each individual participant in the investigation, or their legal representatives, provided their informed consent.

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Conflict of interests:

The authors declared no conflict of interests.

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