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Risk factors and clinical outcomes of hypervirulent *Klebsiella pneumoniae* induced bloodstream infections

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Abstract

The prevalence of hypervirulent *Klebsiella pneumoniae* (hvKP) is high in China, but clinical characteristics and outcomes of hvKP induced bloodstream infections (BSIs) are not clear. The purpose of the present study was to determine the risk factors and clinical outcomes of hvKP-BSIs in populations admitted in a teaching hospital of Nanjing, China. The genetic characteristics and antibiotic resistance patterns of the hvKP strains were further analyzed. A retrospective study was conducted in 143 patients with *K. pneumoniae* BSIs at Jinling Hospital in China from September 2015 to December 2016. A positive polymerase chain reaction (PCR) amplification of the plasmid-borne *rmpA* (*p-rmpA*) and aerobactin (*iucA*) was identified as hvKP. Overall, 24.5% (35/143) of *K. pneumoniae* isolates were hvKP. Multivariate analysis implicated diabetes mellitus (OR = 3.356) and community-acquired BSIs (OR = 4.898) as independent risk factors for hvKP-BSIs. The 30-day mortality rate of the hvKP-BSIs group was 37.1% (13/35) compared with 40.7% (44/108) in the cKP-BSIs control group (P = 0.706). The KPC-producing isolates (OR = 2.851), underlying disease with gastrointestinal fistula (OR = 3.054), APACHE II score ≥ 15 (OR = 6.694) and Pitt bacteremia score ≥ 2 (OR = 6.232) at infection onset were independent predictors for 30-day mortality of *K. pneumoniae* bacteremia patients. A high percentage (57.1%, 20/35) of KPC-producing isolates was observed among hvKP strains and ST11 was dominant in hvKP strains (17/35, 48.6%). KPC-producing hvKP is emerging, indicating the importance of epidemiologic surveillance and clinical awareness of this pathogen.

Keywords Hypervirulent *Klebsiella pneumoniae* · Bloodstream infections · *Klebsiella pneumoniae* Carbapenemase · Risk factors · Molecular characteristics · Mortality

Introduction

Klebsiella pneumoniae is one of the most important pathogens responsible for serious infections such as bacteremia, pneumonia, intra-abdominal infections and urinary tract infections [1, 2]. The *K. pneumoniae* strains extensively studied by most

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clinicians and microbiologists are designated as "classic" *K. pneumoniae* (cKP) which have been notorious for their capacity to cause hospital outbreaks with high disability and mortality rates [3, 4]. During the past two decades, a new variant termed hypervirulent *K. pneumoniae* (hvKP) has been reported in Asia, and this strain is emerging globally [5]. The hvKP strains are characterized by causing invasive liver abscess syndrome with or without metastatic complications such as endophthalmitis, or necrotising fasciitis, especially meningitis [6].

Since these new strains were described for the first time in Taiwan [7], hypermucoviscous *K. pneumoniae* (hmKP) strains have been considered as hypervirulent [8]. That is to say, hvKP was only determined by string test in most of the previous studies [9–11]. Although the populations of hypermucoviscous strains and hypervirulent strains are largely overlapping, apparently, hmKP and hvKP are two different phenotypes [12]. In our study, hvKP strains were defined on the basis of two

genetic indicators: detection of plasmid-borne *rmpA* (*p-rmpA*) and aerobactin synthase gene (*iucA*) together, which were commonly used to differentiate hvKP from cKP based on previous studies [8].

Recently, there have been several case reports and researches on hvKP infections regarding pyogenic liver abscess, community-acquired infections, ventilator-associated pneumonia and primary osteomyelitis [13–17]. Although the prevalence of hvKP is high in China [18], few studies have focused on bloodstream infections (BSIs) caused by hvKP strains. The aim of this study was to systematically analyze the risk factors, molecular characteristics and patient mortality of hvKP induced BSIs.

Materials and methods

Study setting and design

A total of 143 consecutive cases of *K. pneumoniae* BSIs between September 2015 and December 2016 were collected from patients hospitalized at Jinling Hospital, a teaching hospital in Nanjing, mainland China, with a 2000-bed capacity. Only the first bacteremia episode for each patient was included in this retrospective study.

Variables and definitions

The following data were collected: gender and age, BSI acquisition, underlying diseases (solid malignancy, hypertension, cardiovascular disease, neurologic disorder, diabetes mellitus, gastrointestinal fistula, chronic liver disease, fatty liver, biliary tract disease, chronic renal failure, immunosuppression, and malnutrition), probable source of BSI, surgery performed in the past 30 days prior to *K. pneumoniae* cultured, days of hospitalization prior to *K. pneumoniae* isolated, poly-microbial BSI, empirical antibiotics received, total length of hospital stay and ICU stay, and 30-day mortality rates of patients. Additionally, the severity of illness on the onset of BSI was estimated by Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Pitt bacteremia score, and the presence of sepsis or septic shock was further assessed when bacteremia occurred. Laboratory data including white blood cell (WBC) count, neutrophilic granulocyte percentage (NEUT %), platelet, albumin, C-reactive protein (CRP) and procalcitonin (PCT) were also obtained at the time of the first positive episode collected from blood.

An empirical antimicrobial therapy was considered adequate when the *K. pneumoniae* isolate was susceptible to at least one drug prescribed, within 24 h from the BSI onset and the dose was up to current medical standards. The major endpoint was 30-day mortality rate, which was defined as death occurring within 30 days after the onset of *K. pneumoniae* BSI.

Microbiological studies

The Vitek 2 system (bioMe'rieux, Marcy l'Etoile, France) was used in the clinical microbiology laboratory for isolate identification and antimicrobial susceptibility testing. Vitek MICs of antimicrobial agents were interpreted according to the breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI, M100-S27). A positive PCR amplification of *p-rmpA* and *iucA* was identified as hvKP. The serotype-specific genes for the K1, K2, K5, K20, K54, K57 capsular serotypes and another nine virulence-associated factor genes including *entB*, *mrkD*, *fimH*, *ureA*, *wabG*, *ybtS*, *kfu*, *allS*, *iutA* were detected in hvKP isolates by polymerase chain reaction (PCR). The capsular serotype not belonging to K1, K2, K5, K20, K54 or K57 was designated as K-nontypable isolate. Confirmation of carbapenemase genes bla_{KPC} of every strain was done by PCR. The PCR primers used were based on previous reference [19–22]. Multilocus sequence typing (MLST) of seven housekeeping genes was performed as described on the *K. pneumoniae* MLST website, including amplifying and DNA sequencing. Alleles and STs were determined by using the MLST database.

Statistical analysis

SPSS software (version 23.0) was used for data analysis. Categorical variables were analyzed by using χ^2 test or Fisher's exact test and continuous variables were compared using Student's *t* test or the Mann–Whitney *U* test, as appropriate. $P < 0.05$ was considered statistically significant. Logistic regression was used to identify risk factors for hvKP-BSIs and independent predictors of 30-day mortality. All variables with $P < 0.1$ were included in the multivariate model in a forward stepwise approach with use of the likelihood-ratio test.

Results

Patient characteristics and risk factors for HvKP-BSIs

One hundred forty-three patients were identified as *K. pneumoniae* BSIs during the study period. Thirty-five out of 143 (24.5%) isolates were positive for *p-rmpA* and *iucA*, which were identified as hvKP strains.

The patient characteristics with hvKP and cKP bacteremia are shown in Table 1. Overall, 67.8% (97/143) were males and 32.2% (46/143) were females; the mean age was 54.1 ± 17.1 years. Neither sex nor age was associated with hvKP-BSIs. Community-acquired BSIs were identified in more hvKP patients (8/35, 22.9%) than in cKP patients (4/108,

Table 1 Clinical characteristics and infection data of hvKP-BSI

Characteristics	hvKP-BSI (n = 35)	cKP-BSI (n = 108)	P value
Age, years, mean ± SD	54.9 ± 17.1	53.9 ± 17.2	0.746
Male sex	26 (74.3%)	71 (65.7%)	0.347
Acquisition			
Community-acquired	8 (22.9%)	4 (3.7%)	0.001*
ICU-acquired	13 (37.1%)	46 (42.6%)	0.569
Underlying conditions			
Solid malignancy	6 (17.1%)	36 (33.3%)	0.068
Hypertension	16 (45.7%)	32 (29.6%)	0.080
Cardiovascular disease	12 (34.3%)	26 (24.1%)	0.235
Neurologic disorder	9 (25.7%)	20 (18.5%)	0.358
Diabetes mellitus	10 (28.6%)	9 (8.3%)	0.005*
Gastrointestinal fistula	9 (25.7%)	26 (24.1%)	0.844
Chronic renal failure	4 (11.4%)	11 (10.2%)	1.000
Fatty liver	4 (11.4%)	5 (4.6%)	0.299
Chronic liver disease	2 (5.7%)	11 (10.2%)	0.645
Biliary tract disease	13 (37.1%)	29 (26.9%)	0.245
Immunosuppression	2 (5.7%)	26 (24.1%)	0.017*
Malnutrition	4 (11.4%)	16 (14.8%)	0.825
Surgery within 30 days	12 (34.3%)	48 (44.4%)	0.290
Origin of bacteremia			
Unknown	4 (11.4%)	28 (25.9%)	0.074
Respiratory tract	6 (17.1%)	12 (11.1%)	0.521
Intra-abdomen	18 (51.4%)	42 (38.9%)	0.191
Liver abscess	5 (14.3%)	2 (1.9%)	0.012*
Vascular catheter	2 (5.7%)	16 (14.8%)	0.264
Other(s)	0	8 (7.4%)	0.217
Infection data			
WBC count, mean ± SD	15.1 ± 8.3	11.2 ± 6.7	0.007*
Albumin, mean ± SD	29.7 ± 4.3	31 ± 5.6	0.179
PCT, mean ± SD	24.2 ± 29.2	13.6 ± 25.3	0.078
CRP, mean ± SD	173.1 ± 98	138.4 ± 84.6	0.058
Platelet, mean ± SD	150.6 ± 97.9	154.6 ± 107.7	0.850
NEUT %, mean ± SD	90 ± 5.2	88.1 ± 9.1	0.153
Poly-microbial bacteremia	5 (14.3%)	21 (19.4%)	0.492
Hospital stay prior to KP isolated, median (IQR)	11 (1–20)	10 (4–29)	0.278
ICU stay, median (IQR)	14 (3–27)	8.5 (0–19)	0.266
Full hospital stay, median (IQR)	26 (15–41)	28.5 (16–52)	0.487
APACHE II score at infection onset, mean ± SD	13 ± 7.3	12.5 ± 6.1	0.731
Pitt bacteremia score at infection onset, mean ± SD	2.8 ± 2.5	2.8 ± 2.6	0.947
Sepsis/Septic Shock at infection onset	18 (51.4%)	39 (36.1%)	0.108
Empirical therapy			
Monotherapy	29 (82.9%)	79 (73.1%)	0.246
Combination therapy	6 (17.1%)	28 (25.9%)	0.289
Cephalosporin	1 (2.9%)	6 (5.6%)	0.848
Carbapenem	23 (65.7%)	64 (59.3%)	0.497
β-Lactam/β-lactamase inhibitor combination	12 (34.3%)	32 (29.6%)	0.604
Tetracycline	2 (5.7%)	21 (19.4%)	0.055
Fluoroquinolone	2 (5.7%)	14 (13%)	0.382
Empirical treatment appropriate	15 (42.9%)	51 (47.2%)	0.653

Table 1 (continued)

Characteristics	hvKP-BSI (n = 35)	cKP-BSI (n = 108)	*P* value
Empirical treatment inappropriate	20 (57.1%)	56 (51.9%)	0.586
30-day mortality	13 (37.1%)	44 (40.7%)	0.706

Data are presented as number(%) of patients unless otherwise specified

ICU intensive care unit, *KP Klebsiella pneumoniae*, *WBC* white blood cell, *PCT* procalcitonin, *CRP* C-reactive protein, *NEUT %* neutrophilic granulocyte percentage, *APACHE* acute physiologic and chronic health evaluation, *SD* standard deviation, *IQR* interquartile range

*P < 0.05 compared with cKP-BSI

3.7%) (P = 0.001). In contrast to patients with cKP-BSIs, patients with BSIs due to hvKP were more likely to have diabetes mellitus (28.6% vs 8.3%, P = 0.005) and were less likely to present the state of immunosuppression (5.7 vs 24.1%, P = 0.017). The sources of these BSIs were compared between cKP and hvKP. Pyogenic liver abscess was more frequently to be the source of hvKP-BSIs (5/35, 14.3%) than cKP-BSIs (2/108, 1.9%) (P = 0.012). There was no difference in empirical antibiotic treatment between these two groups. Using multivariate regression analysis, community-acquired BSIs (OR = 4.898) and diabetes mellitus (OR = 3.356) appeared to be independent risk factors associated with hvKP-BSIs, while immunosuppression (OR = 0.164) was an independent protective factor for hvKP-BSIs (Table 2) (Hosmer-Lemeshow test, P = 0.527; C-statistic (95% CI), 0.708(0.608–0.808)).

The infection data and laboratory findings of patients with BSIs caused by hvKP and cKP were also compared (Table 1). No difference among these two groups in poly-microbial bacteremia, hospital stay prior to *K. pneumoniae* isolated, ICU stay or full hospital stay was detected. We found that patients with hvKP-BSIs had a higher WBC count than cKP infected patients (P = 0.007) when bacteremia occurred. The presentation with sepsis or septic shock, APACHE II score and Pitt bacteremia score upon onset of BSI were not significantly different between the groups.

Antimicrobial resistance among HvKP and CKP

Both cKP and hvKP strains exhibited high antimicrobial-resistant rates for almost all tested antimicrobials (Table 3). HvKP strains showed a high resistance rate which was similar to cKP strains among clinical often used antimicrobials such as 3rd or 4th generation cephalosporins (ceftazidime and cefepime), piperacillin-tazobactam, imipenem and meropenem. KPC production was identified in 84 isolates (84/143, 58.7%). Astonishingly, there was no statistically significant difference in the number of KPC-producing isolates between hvKP and cKP (20/35, 57.1% vs 64/108, 59.3%, P = 0.825).

Molecular characteristics of HvKP and CKP isolates

A total of 18 (18/35, 51.4%) isolates were positive for K1, K2, K20 and K57 serotypes, while K5 and K54 serotypes were not

detected in hvKP isolates. Capsular genotypes K1, K2, K20 and K57 comprised 14.3% (5/35), 20% (7/35), 2.9% (1/35) and 14.3% (5/35) of all hvKP strains, respectively. Besides *p-rmpA* and *iucA*, nine virulence-associated factor genes were tested among hvKP. All hvKP strains harbored *entB*, *mrkD*, *fimH*, *ureA* and *wabG*. The positive rates of *iutA*, *ybtS*, *allS* and *kfu* among hvKP isolates were 97.1% (34/35), 74.3% (26/35), 17.1% (6/35) and 14.3% (5/35), respectively. Interestingly, all K1 strains were positive for *allS* and *kfu* genes, but conversely all K57 and all K-nontypable strains were negative for these two genes.

MLST analysis revealed ten STs among 35 hvKP strains. Among these identified STs, the most prevalent ST in hvKP isolates was ST11 (17/35, 48.6%), followed by ST23 (5/35, 14.3%). The STs accounting for three isolates (3/35, 8.6%) were ST218. The remaining STs were ST65, ST86 and ST375 (n = 2 each) and ST25, ST412, ST592 and ST893 (n = 1 each). ST11 was identified exclusively among K-nontypable isolates and ST11 accounted for all K-nontypable isolates. Further investigation found that these ST11-K-nontypable isolates were strongly correlated with KPC-producing (16/17, 94.1%) and most of them (9/17, 52.9%) were acquired from ICU. Similarly, we also found a strong association between ST23 and K1 serotype. ST11-K-nontypable (n = 16), ST218-K57 (n = 3) and ST23-K1 (n = 1) were identified among hvKP strains with KPC production.

Capsular serotyping and MLST were also performed in 108 cKP strains. Among these cKP strains, only two K2 isolates, one K1 and one K57 isolate were detected. A total of 34 STs were identified in the MLST database and ST11 was the most prevalent ST (50%, 54/108), followed by ST15 (6.5%, 7/108). ST37 (n = 3) and ST23, ST35, ST340 and ST685 (n = 2 each) were also found among cKP isolates. There were nine genotypes that did not belong to any known ST.

Outcome study

The overall 30-day mortality rate was 39.9% (57/143) during the study period. As presented in Table 4, underlying disease with gastrointestinal fistula (P = 0.016), ICU-acquired BSIs (P = 0.003), longer ICU length of stay (P = 0.027), inadequate empirical antimicrobial treatment (P = 0.008), the presence of sepsis or septic shock when bacteremia (P < 0.001), APACHE

Table 2 Multivariate analysis of variables associated with hvKP-BSI

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	P Value
Community-acquired	7.704 (2.158–27.506)	0.002	4.898 (1.143–20.997)	0.032
Diabetes mellitus	4.4 (1.616–11.981)	0.004	3.356 (1.072–10.509)	0.038
Liver abscess BSI source	8.833 (1.631–47.833)	0.011	5.786 (0.917–36.502)	0.062
Immunosuppression	0.191 (0.043–0.851)	0.03	0.164 (0.032–0.84)	0.03
Malignancy	0.414 (0.158–1.087)	0.073		
Hypertension	2 (0.914–4.375)	0.083		
Unknown BSI source	0.369 (0.119–1.138)	0.083		

OR odds ratio, *CI* confidence interval, *BSI* bloodstream infection

II score ≥ 15 ($P < 0.001$) and Pitt bacteremia score ≥ 2 ($P < 0.001$) upon onset of BSI were associated positively with 30-day mortality in the cases of *K. pneumoniae* induced BSIs. In addition, as to the microbiological characteristics, infection by KPC-producing *K. pneumoniae* was associated with mortality ($P < 0.001$), whereas, no such association was detected in hypervirulent strains. In the 30-day mortality analysis, 37.1% (13/35) and 40.7% (44/108) died in the hvKP group and cKP group, respectively. Identification of clinical and microbiological characteristics associated with 30-day mortality was also performed in both the hvKP-BSIs group and cKP-BSIs group. Multivariate analysis further demonstrated that KPC-producing *K. pneumoniae* infected (OR = 2.851), underlying disease with gastrointestinal fistula (OR = 3.054), APACHE II score ≥ 15 (OR = 6.694)

and Pitt bacteremia score ≥ 2 (OR = 6.232) at infection onset were independent predictors for 30-day mortality in patients with *K. pneumoniae* bacteremia (Table 5) (Hosmer-Lemeshow test, P = 0.841; C-statistic (95% CI), 0.877(0.818–0.936)).

Discussion

This retrospective study was conducted in 143 *K. pneumoniae* BSIs patients hospitalized in Jinling hospital during a 16-month period from September 2015 to December 2016. A positive PCR amplification of *p-rmpA* and *iucA* was identified as hvKP. We tried to reveal the risk factors and clinical outcomes of hvKP-BSIs in Chinese patients and analysis of

Table 3 Percentage of antimicrobial resistance and KPC production of *Klebsiella pneumoniae* strains

Antimicrobial agents	hvKP (n = 35)	cKP (n = 108)	P value
Ampicillin	35 (100%)	108 (100%)	NA
Ampicillin-sulbactam	22 (62.9%)	88 (81.5%)	0.023*
Piperacillin-tazobactam	20 (57.1%)	67 (62%)	0.606
Cefazolin	22 (62.9%)	87 (80.6%)	0.033*
Cefotan	20 (57.1%)	67 (62%)	0.606
Ceftriaxone	22 (62.9%)	87 (80.6%)	0.033*
Ceftazidime	21 (60%)	80 (74.1%)	0.112
Cefepime	22 (62.9%)	74 (68.5%)	0.535
Aztreonam	22 (62.9%)	80 (74.1%)	0.202
Imipenem	19 (54.3%)	64 (59.3%)	0.604
Meropenem	20 (57.1%)	65 (60.2%)	0.750
Tobramycin	14 (40%)	60 (55.6%)	0.109
Gentamicin	14 (40%)	74 (68.5%)	0.003*
Amikacin	14 (40%)	46 (42.6%)	0.787
Levofloxacin	18 (51.4%)	73 (67.6%)	0.084
Ciprofloxacin	20 (57.1%)	81 (75%)	0.044*
Trimethoprim-sulfamethoxazole	3 (8.6%)	42 (38.9%)	0.001*
KPC-producing	20 (57.1%)	64 (59.3%)	0.825

Data are presented as number (%) of patients

*P < 0.05 compared with cKP

Table 4 Clinical and microbiological characteristics associated with 30-day mortality of *Klebsiella pneumoniae* bacteremia patients

Characteristics	All *K. pneumoniae* BSIs			HvKP-BSIs			CKP-BSIs		
	Death (n = 57)	Survivors (n = 86)	P value	Death (n = 13)	Survivors (n = 22)	P value	Death (n = 44)	Survivors (n = 64)	P value
Age, years, mean ± SD	52.8 ± 14.9	55 ± 18.5	0.443	56.2 ± 15.3	54.2 ± 18.4	0.738	51.8 ± 14.8	55.3 ± 18.6	0.292
Male sex	37 (64.9%)	60 (69.8%)	0.543	10 (76.9%)	16 (72.7%)	1.000	27 (61.4%)	44 (68.8%)	0.427
Acquisition									
Community-acquired	2 (3.5%)	10 (11.6%)	0.160	1 (7.7%)	7 (31.8%)	0.210	1 (2.3%)	3 (4.7%)	0.893
ICU-acquired	32 (56.1%)	27 (31.4%)	0.003*	9 (69.2%)	4 (18.2%)	0.004*	23 (52.3%)	23 (35.9%)	0.092
Underlying conditions									
Solid malignancy	13 (22.8%)	29 (33.7%)	0.161	1 (7.7%)	5 (22.7%)	0.377	12 (27.3%)	24 (37.5%)	0.268
Hypertension	21 (36.8%)	27 (31.4%)	0.499	8 (61.5%)	8 (36.4%)	0.179	13 (29.5%)	19 (29.7%)	0.987
Cardiovascular disease	12 (21.1%)	26 (30.2%)	0.224	6 (46.2%)	6 (27.3%)	0.292	6 (13.6%)	20 (31.3%)	0.061
Neurologic disorder	12 (21.1%)	17 (19.8%)	0.852	3 (23.1%)	6 (27.3%)	1.000	9 (20.5%)	11 (17.2%)	0.668
Diabetes mellitus	5 (8.8%)	14 (16.3%)	0.195	1 (7.7%)	9 (40.9%)	0.055	4 (9.1%)	5 (7.8%)	1.000
Gastrointestinal fistula	20 (35.1%)	15 (17.4%)	0.016*	5 (38.5%)	4 (18.2%)	0.243	15 (34.1%)	11 (17.2%)	0.044*
Chronic renal failure	6 (10.5%)	9 (10.5%)	0.991	2 (15.4%)	2 (9.1%)	0.618	4 (9.1%)	7 (10.9%)	1.000
Fatty liver	6 (10.5%)	3 (3.5%)	0.179	3 (23.1%)	1 (4.5%)	0.134	3 (6.8%)	2 (3.1%)	0.666
Chronic liver disease	7 (12.3%)	6 (7%)	0.280	1 (7.7%)	1 (4.5%)	1.000	6 (13.6%)	5 (7.8%)	0.510
Biliary tract disease	15 (26.3%)	27 (31.4%)	0.514	7 (53.8%)	6 (27.3%)	0.157	8 (18.2%)	21 (32.8%)	0.092
Immunosuppression	12 (21.1%)	16 (18.6%)	0.718	0	2 (9.1%)	0.519	12 (27.3%)	14 (21.9%)	0.519
Malnutrition	9 (15.8%)	11 (12.8%)	0.613	2 (15.4%)	2 (9.1%)	0.618	7 (15.9%)	9 (14.1%)	0.791
Surgery within 30 days	24 (42.1%)	36 (41.9%)	0.977	4 (30.8%)	8 (36.4%)	1.000	20 (45.5%)	28 (43.8%)	0.861
Origin of bacteremia									
Unknown	10 (17.5%)	22 (25.6%)	0.259	1 (7.7%)	3 (13.6%)	1.000	9 (20.5%)	19 (29.7%)	0.282
Respiratory tract	6 (10.5%)	12 (14%)	0.545	1 (7.7%)	5 (22.7%)	0.377	5 (11.4%)	7 (10.9%)	1.000
Intra-abdomen	29 (50.9%)	31 (36%)	0.078	8 (61.5%)	10 (45.5%)	0.489	21 (47.7%)	21 (32.8%)	0.118
Liver abscess	2 (3.5%)	5 (5.8%)	0.818	2 (15.4%)	3 (13.6%)	1.000	0	2 (3.1%)	0.513
Vascular catheter	8 (14%)	10 (11.6%)	0.671	1 (7.7%)	1 (4.5%)	1.000	7 (15.9%)	9 (14.1%)	0.791
Other(s)	2 (3.5%)	6 (7%)	0.609	0	0	NA	2 (4.5%)	6 (9.4%)	0.570
Infection and microbiological data									
Poly-microbial BSI	13 (22.8%)	13 (15.1%)	0.243	1 (7.7%)	4 (18.2%)	0.630	12 (27.3%)	9 (14.1%)	0.088
ICU stay, median (IQR)	14 (3.5–23)	6 (0–19.5)	0.027*	17 (7.5-32.5)	7 (0–25)	0.091	12 (2–19)	5.5 (0–18.75)	0.099
APACHE II score ≥ 15 at infection onset	38 (66.7%)	13 (15.1%)	<0.001*	8 (61.5%)	5 (22.7%)	0.033*	30 (68.2%)	8 (12.5%)	<0.001*
Pitt bacteremia score ≥ 2 at infection onset	50 (87.7%)	29 (33.7%)	<0.001*	11 (84.6%)	8 (36.4%)	0.006*	39 (88.6%)	21 (32.8%)	<0.001*
Sepsis/Septic shock at infection onset	38 (66.7%)	19 (22.1%)	<0.001*	12 (92.3%)	6 (27.3%)	<0.001*	26 (59.1%)	13 (20.3%)	<0.001*
KPC-producing strains	45 (78.9%)	39 (45.3%)	<0.001*	11 (84.6%)	9 (40.9%)	0.016*	34 (77.3%)	30 (46.9%)	0.002*

Table 4 (continued)

Characteristics	All K. pneumoniae BSIs			HvKP-BSIs			CKP-BSIs		
	Death (n = 57)	Survivors (n = 86)	P value	Death (n = 13)	Survivors (n = 22)	P value	Death (n = 44)	Survivors (n = 64)	P value
Empirical therapy									
Combination therapy	15 (26.3%)	19 (22.1%)	0.561	2(15.4%)	4(18.2%)	1.000	13(29.5%)	15(23.4%)	0.477
Treatment inappropriate	38 (66.7%)	38 (44.2%)	0.008*	11(84.6%)	9(40.9%)	0.016*	27(61.4%)	29(45.3%)	0.101

Data are presented as number (%) of patients unless otherwise specified

ICU intensive care unit, *APACHE* acute physiologic and chronic health evaluation, *KPC Klebsiella pneumoniae* carbapenemase, *SD* standard deviation, *IQR* interquartile range, *NA* not applicable

*P < 0.05 compared with survivors

antibiotic resistance patterns and molecular characteristics were also performed in this study, using cKP-BSIs as reference.

Since hvKP strains were described for the first time in Taiwan [7], the strains of hmKP and hvKP have often been used synonymously. HvKP was defined by "string test" in the previous studies [9–11]. In 2014 in China, Zhang et al. suggested that hvKP should be defined by genotype rather than hypermucoviscosity and defining hvKP only by string test may lead to a biased result especially in studies with small sample sizes [23]. In 2016, Yan et al. studied 49 ventilator-associated pneumonia cases caused by *K. pneumoniae* and 19 isolates were classified as hvKP strains which were determined by a positive PCR amplification of *p-rmpA* and aerobactin (*iucA*) and *iroB* [16]. Another study in China analyzed 230 *K. pneumoniae* isolates from ten major cities, defining hvKP strains by aerobactin detection [18]. A recent study conducted retrospectively in Taiwan, the author used three virulence determinants as follows: hypermucoviscosity phenotype, K1/K2 capsule serotypes, a positive PCR amplification of *p-rmpA* gene, or *rmpA2* gene. The *K. pneumoniae* strains including any of these virulence determinants were designated as hvKP [24]. Although there is no consensus definition of hvKP, the factor associated with hypermucoviscous in combination with iron-acquisition systems were unequivocal markers for hvKP identification [8, 25]. Therefore, *rmpA* (present on the virulence plasmid) and the iron siderophore aerobactin synthase gene (*iucA*) were served to groups hvKP and cKP in our study.

A retrospective study conducted by a single medical center in Beijing reported that 22 (31.4%) of 70 *K. pneumoniae* strains isolated from blood were hvKP [11]. Another study also from Beijing showed that the prevalence of hvKP bacteremia was 36.8% (28/76) [26]. Our study indicated that the prevalence of bacteremia caused by hvKP was 24.5% (35/143), which is lower than those aforementioned Chinese reports, but higher than 6% (53/878) reported by a teaching hospital in Spain from 2007 to 2013 [27] and 17.1% (22/129) recently reported in east China [28].

In previous risk factor studies, community-acquired infections and underlying disease with diabetes mellitus, solid malignancy and hypertension have been considered as significant risk factors for hvKP infections [10, 18, 28]. However, in the present study, among all variables listed, only diabetes mellitus and community-acquired infections were identified as independent risk factors for hvKP-BSIs. The proportion of patients with solid malignancy or hypertension among hvKP-BSIs was higher than that among cKP-BSIs, but only showed a statistical trend in univariate analysis. Interestingly, we found immunosuppression was negatively correlated with hvKP-BSIs. Patients who were undergoing chemotherapy, radiotherapy and/or using immunosuppressive drugs during the bacteremia were regarded as immunosuppression. HvKP

Table 5 Multivariate analysis for predictors of 30-day mortality in patients with *Klebsiella pneumoniae* bacteremia

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
APACHE II score ≥ 15 at infection onset	11.043 (4.881–24.982)	<0.001	6.694 (2.523–17.761)	<0.001
Pitt bacteremia score ≥ 2 at infection onset	14.039 (5.659–34.828)	<0.001	6.232 (2.183–17.792)	0.001
KPC-producing isolates	4.519 (2.102–9.715)	<0.001	2.851 (1.081–7.519)	0.034
Gastrointestinal fistula	2.559 (1.175–5.573)	0.018	3.054 (1.038–8.984)	0.043
ICU-acquired	2.797 (1.398–5.597)	0.004		
Intra-abdomen BSI source	1.838 (0.93–3.63)	0.08		
ICU stay	1.014 (0.997–1.031)	0.1		
Sepsis/Septic shock at infection onset	7.053 (3.331–14.933)	<0.001		
Empirical treatment inappropriate	2.474 (1.232–4.967)	0.011		

OR odds ratio, *CI* confidence interval, *APACHE* acute physiologic and chronic health evaluation, *KPC Klebsiella pneumoniae* carbapenemase, *ICU* intensive care unit, *BSI* bloodstream infection

strains have been proven to be more resistant to complement and neutrophil-mediated bactericidal activity than cKP strains, which suggested that hvKP strains were prone to infect non-immunocompromised and healthy individuals [29]. It is worth noting that pyogenic liver abscess infection source was more frequently seen in patients with hvKP-BSIs, which suggests that an early and appropriate source control procedure such as drainage of pus collection or definitive surgery is vital to prevent the development of hvKP bacteremia.

There was little information on laboratory data of bacteremia caused by hvKP. The patients who suffered hvKP-BSIs appeared significantly higher in WBC count at infection onset [(15.1 ± 8.3) vs (11.2 ± 6.7) × 10^9/L, P = 0.007], but no difference was found in WBC count when admitted to hospital [(12 ± 6.5) vs (10.8 ± 7.7) × 10^9/L, P = 0.447]. Moreover, inflammation markers such as CRP and PCT in the hvKP group were higher than that in the cKP group, even though the differences were not statistically significant. These laboratory features indicated that hvKP strains may have a higher potency to generate inflammatory reaction at onset of *K. pneumoniae* bacteremia, which is needed to be further demonstrated by in vivo animal experiments or some basic researches. Sepsis or septic shock is an inflammatory reaction to bacterial infection involving the whole body. In 2014 in Japan, Togawa et al. reported that the hypermucoviscous *K. pneumoniae* of blood isolates was significantly associated with septic shock when bacteremia occurred but they could not explain it [30]. Even though this phenomenon was not found in our study, a better understanding of the potential relationship between hypervirulence determinants and septic shock needs to be deeply studied.

Previous reports have consistently confirmed that the overwhelming majority of hvKP strains exhibited more susceptible to most currently available antibiotics relative to cKP strains and hypervirulent and multidrug-resistant were

commonly nonoverlapping. However, unlike the previous reports, the results of our study showed that hvKP strains exhibited significantly less resistant than cKP only to six of 17 drugs tested. The rate of KPC production among hvKP strains is significantly higher than other studies [18, 28], which is a worrisome finding of our investigation. Since limited available antibiotics are effective in treating infections caused by hvKP phenotypes combining enhanced virulence with extreme or pan-drug resistance, these strains may result in a deleterious outcome [31]. Epidemiologic surveillance and implementation of stricter infection control measures such as hand hygiene enhancement, periodic environmental and equipment disinfection, patient screening of antibiotic resistant strains and antimicrobial stewardship are needed to prevent community and hospital outbreaks.

As previous studies reported, all K1 isolates were positive for *kfu* and *allS* while all K2 isolates were negative [32]. However, in our investigation, all K57 and all K-nontypable isolates were negative for these two genes and *allS* was detected in one K2 isolate with ST25. Contrary to the previous studies with ST23 being the most prevalent ST among hvKP strains, our study revealed that ST11 was the most common ST and ST11 hvKP isolates were strongly associated with K-nontypable capsular serotype. These microbiology features differ to some extent from previous studies. We characterized ST11-K-nontypable, ST218-K57 and ST23-K1 hvKP isolates with KPC production and this is the first report of KPC-producing hvKP belonging to ST218 with K57 serotype, to our knowledge.

Siu et al. have confirmed that the KPC plasmid can be successfully transferred into a K2-ST65 hvKP strain without losing its virulence [33], which indicated that hypervirulent clonal populations including ST25 and ST65 of *K. pneumoniae* have evolved to be extreme or pan-drug resistant. Although ST11 is the dominant clone of KPC-producing

K. pneumoniae in China [34], several previous studies reported that ST11 *K. pneumoniae* with KPC production has evolved to become hypervirulent [31, 35]. Taken together, it can be speculated that hypervirulent strains can acquire antibiotic-resistant plasmids without loss of virulence and some drug resistance genes can be long-term retained when they become hypervirulent. These new emerging bidirectional evolution strains which are simultaneously multidrug resistant, hypervirulent and transmissible should be considered as the real "superbug" to public health.

Based on previous studies, severity scores, sepsis or septic shock at infection onset, comorbidity with chronic renal failure, the carriage of carbapenemase genes and inappropriate antimicrobial treatment on empirical phase are predictive factors for death in patients with *K. pneumoniae* bacteremia [36, 37]. Our study expounded KPC-producing isolates, underlying disease with gastrointestinal fistula, APACHE II score ≥ 15 and Pitt bacteremia score ≥ 2 were strong prognostic factors of 30-day mortality. The development of sepsis/septic shock and inadequate initial antimicrobial therapy were only determined by univariate analysis. Most gastrointestinal fistula occur after surgical procedures, trauma and inflammatory bowel diseases in our investigation and these patients are usually complicated with severe intra-abdominal infection. Urgent and effective source control procedures are important strategies for surgeons to manage intra-abdominal infection and prevent the bacteremia developed from intra-abdomen, which may improve patient outcomes.

The overall 30-day mortality rate was shown to be 39.9%, which is higher than the rates reported by other studies [38, 39]. Some researchers suggested that the patients with hvKP-BSIs had lower mortality rate than the cKP-BSIs group (4.5 vs 16.7%) [11]. In 2016 in Taiwan, Yu et al. performed a retrospective study to assess the clinical outcomes between hvKP and cKP among 48 patients with bacteremia caused by ESBL (extended-spectrum β-lactamase)-producing *K. pneumoniae* and no difference was found in mortality between these two groups (52.6 vs 58.6%, P = 0.77) [24]. In our study, we also observed that hypervirulent strains did not have a significant effect on 30-day mortality (37.1 vs 40.7%, P = 0.706). Moreover, 84 patients were infected by KPC-producing isolates in our study and the 30-day mortality was further assessed in this subgroup. The 30-day mortality rate was higher than 50% in the KPC-producing subgroup and there was no statistical difference in 30-day mortality between KPC-hvKP and KPC-cKP (11/20, 55% vs 34/64, 53.1%, P = 0.883). Therefore, it is difficult to conclude that the hypervirulent strains have an impact on 30-day mortality in our relative small sample sizes. Further research about the patient mortality of hvKP-BSIs in large sample sizes, focusing on different antibiotic-resistant pattern subgroups, may be warranted.

The study has certain limitations, including its retrospective nature and a relatively small study population. Our study included 143 patients, not a large number, but to date this study is the largest cohort to investigate the risk factors and outcomes of hvKP-BSIs, to our knowledge. The strains with carbapenemase production are particularly difficult to treat and control. Consequently, a further study that includes more patients, especially for carbapenem-resistant hvKP strains, is needed.

In conclusion, using a retrospective single-center study of patients with *K. pneumoniae* bacteremia, we clearly demonstrated that diabetes mellitus and community-acquired infections were independent risk factors associated with hvKP-BSIs. The KPC-producing strains, underlying disease with gastrointestinal fistula, APACHE II score ≥ 15 and Pitt bacteremia score ≥ 2 appeared to be independent predictors for 30-day mortality of *K. pneumoniae* bacteremia patients. HvKP strains had a significant impact on clinical characteristics, but not on 30-day mortality. Furthermore, we found a high proportion of KPC-producing isolates among hvKP cultures in a teaching hospital in China, which underscores the added importance of epidemiologic surveillance and clinical awareness of this pathogen.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board Ethics Committee of Jinling Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

This article does not contain any studies with animals performed by any of the authors.

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