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ORIGINAL RESEARCH

Clinical Characterization, Risk Factors, and Mortality in Patients with Carbapenem-Resistant Hypervirulent *Klebsiella pneumoniae* Intra-Abdominal Infections

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Background: The outbreak of the highly lethal Carbapenem-resistant *Klebsiella pneumoniae* (CR-hvKP) strain is increasingly prevalent. The aim of this study was to investigate the epidemiology, molecular characteristics, and mortality rate in intra-abdominal infections (IAIs) caused by CR-hvKP in a tertiary hospital, providing scientific evidence for clinical treatment to reduce mortality and improve patient prognosis.

Methods: The study included 160 patients who developed CRKP IAIs from June 2023 to December 2024. Carbapenemase and virulence genes were detected by Polymerase chain reaction assay. Antimicrobial susceptibility test was performed to determine drug resistance. Multivariate logistic regression and multivariate Cox regression were used to determine risk factors of CR-hvKP IAIs and CRKP IAIs mortality, respectively.

Results: A total of 160 patients with CRKP IAIs were enrolled: 68 with CR-hvKP IAIs and 92 with CR-non-hvKP IAIs. The mortality rate trended higher in the CR-hvKP group compared with CR-non-hvKP (17.6% vs 10.9%), but the difference was not statistically significant (P=0.218). Multivariate logistic regression identified tracheotomy as a risk factor for infection with CR-hvKP IAIs (OR 2.816, 95% CI 1.120–7.080). Multivariate Cox regression analysis identified four independent risk factors for in-hospital mortality of CRKP IAIs: age (HR 1.066, 95% CI 1.020–1.114), decreased platelet count (HR 0.995, 95% CI 0.990–0.999), septic shock (HR 9.141, 95% CI 2.082–40.133), and tracheotomy (HR 4.322, 95% CI 1.461–12.791).

Conclusion: The mortality rate was numerically higher in the CR-hvKP IAIs while the difference was not statistically significant. Our study identified tracheotomy as an independent risk factor for infection with CR-hvKP IAIs. Clinicians need to enhance their awareness and epidemiologic surveillance of this lethal bacterium.

Keywords: carbapenem-resistant hypervirulent *Klebsiella pneumoniae*, intra-abdominal infections, risk factors, mortality

Introduction

Klebsiella pneumoniae (KP) is a Gram-negative bacterium commonly found in environmental settings and constitutes part of the normal microbiota in the human intestinal tract. As an opportunistic pathogen, it can cause various severe infections, including pneumonia, bloodstream infections, intra-abdominal infections (IAIs), and even septic shock.[1–4] The high prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) strains in healthcare systems has become

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a foreseeable trend due to the extensive use of antimicrobial agents. The presence of these drug-resistant strains not only increases the complexity of clinical management but also significantly elevates the mortality risk of patients. Notably, CRKP has emerged as one of the critical pathogens responsible for IAIs and is closely associated with high mortality rates.[5] Hypervirulent *Klebsiella pneumoniae* (hvKp) represents a distinct pathogenic phenotype of *Klebsiella pneumoniae* marked by its heightened virulence.[4,6] This strain has drawn considerable attention because of its capacity to trigger serious community-acquired infections, including liver abscesses and sepsis.[6]

The string test with a length >5 mm was employed to identify hvKP in early studies. However, subsequent studies demonstrated its limitation in distinguishing hvKP strains, as some hypervirulent isolates did not exhibit this phenotype, while some classical *Klebsiella pneumoniae* (cKP) may yield positive results.[7,8] Additional factors associated with hypervirulence encompass pK2044/pLVPK-like virulence plasmids, capsular types, siderophores, lipopolysaccharide (LPS), and capsular polysaccharide (CPS). The *rmpA* and *rmpA2* genes are strongly correlated with the hypermucoviscous phenotype, whereas *iucA* is located on virulence plasmids linked to the hypervirulent phenotype.[9,10] Therefore, the hvKP strain was defined as an isolate comprising *rmpA* and/or *rmpA2* with *iucA* in our study.

In recent years, the convergence of carbapenem resistance and hypervirulence has posed a new and emerging threat: an increasing number of *Klebsiella pneumoniae* strains exhibiting both traits, referred to as carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (CR-hvKP).[11] Studies have identified three main mechanisms underlying the formation of CR-hvKP: a) the transfer of carbapenem resistance genes from CRKP to hvKP;[12] b) the acquisition of virulence plasmids encoding virulence factors by CRKP;[13] c) the acquisition of hybrid plasmids containing both carbapenemase and virulence genes by cKP.[14] The clinical manifestations of this superpathogen are diverse and complex, often presenting with both CRKP and hvKP characteristics, which result in widespread outbreaks and high mortality rates.[13]

The incidence of CR-hvKP has been on the rise globally, with China identified as a major endemic area, reporting the highest number of cases.[11,15] Although several clinical studies on CR-hvKP have been conducted, these studies vary in geographic location, and research on CR-hvKP in eastern China remains limited. Furthermore, the sample sizes of the included cases in these studies are relatively small, with inconsistent infection types, leading to a certain degree of heterogeneity in the findings.[16–18]

Our study included patients who developed CRKP IAIs during the period from June 1, 2023, to December 31, 2024. Polymerase chain reaction (PCR) assay was used to detect virulence genes and identify hypervirulent isolates, then the CRKP-infected population was divided into CR-hvKP and CR-non-hvKP groups. We compared the in-hospital mortality rate, length of hospital stay, ICU stay, microbiologic features and other clinical factors between the two groups. Additionally, multivariate logistic regression and multivariate Cox regression were used to determine risk factors of CR-hvKP IAIs and CRKP IAIs mortality, respectively. Through the retrospective analysis of patient clinical data, we hope to identify high-risk populations for this infection and provide scientific evidence for clinical treatment to reduce mortality and improve patient outcomes.

Materials and Methods

Study Design

This retrospective study was conducted in Jinling Hospital, Nanjing Medical University, a 3100-bed tertiary teaching hospital. We included patients who developed CRKP IAIs during the period from June 1, 2023, to December 31, 2024 and clinical data and outcomes of patients were collected until February 13, 2025. The inclusion criteria were: a) age ≥ 18 years; b) diagnosed with intra-abdominal infection meeting the definitions of the International Sepsis Forum Consensus Conference;[19] c) CRKP infection confirmed by microbiological culture. The exclusion criteria were: a) patients with incomplete clinical data; b) pregnant or breastfeeding women; c) patients with *Klebsiella pneumoniae* colonization. Only the first episode of each patient was included in this study. A total of 160 episodes were enrolled in this study at last. The follow-up time in this study was the period from the infection of CRKP to in-hospital death or recovery and discharge. The primary outcome of this study was the in-hospital mortality rate between the CR-hvKP and CR-non-hvKP groups. Additionally, key secondary outcomes included the length of hospital stay, ICU stay, and microbiological features.

Data Collection and Definitions

All adult patients (age ≥ 18 years) with IAIs were included in the study. This retrospective study utilized 100% complete datasets, as all variables were essential for clinical care and mandated in the hospital's digital records. The clinical data, including age, sex, underlying conditions (solid cancer, hypertension, cardiovascular disease, neurologic disorder, diabetes mellitus, gastrointestinal fistula, chronic renal disease, fatty liver, chronic liver disease, biliary tract disease, malnutrition, trauma, surgery within 30 days), antibiotics used before isolation, infection data at infection onset, invasive procedures and devices before isolation, empirical and targeted therapies, ICU stay, full hospital stay, and discharge outcome were collected from medical records. The white blood cell (WBC) count, albumin, procalcitonin (PCT), C-reactive protein (CRP), platelet count, neutrophilic granulocyte percentage (NEUT%) were collected at the onset of infection. Sequential organ failure assessment (SOFA) score and acute physiologic and chronic health evaluation II (APACHE II) score at the onset of infection were also assessed. The presence of sepsis or septic shock was assessed by Sepsis 3.0.[20]

In our study, cardiovascular disease included coronary artery disease, heart failure, arrhythmias, cardiomyopathy, and peripheral artery disease. Neurologic disorders included stroke, Parkinson's disease, epilepsy, and Alzheimer's disease. Biliary tract disease included cholecystitis, cholelithiasis, and cholangitis. Fatty liver included alcoholic fatty liver disease and non-alcoholic fatty liver disease. Chronic liver disease included viral hepatitis, autoimmune hepatitis, and liver cirrhosis. Malnutrition was defined as body mass index (BMI) < 18.5 upon admission. Empirical and targeted therapies were defined as antibiotics administered before and after obtaining the results of the antimicrobial susceptibility test. We defined appropriate empirical treatment as the use of at least one active antimicrobial agent within 72 hours of IAI onset, and the dose adhered to contemporary clinical standards.

Microbiological Methods

The Vitek2 system (Biomerieux, France) was used to identify KP isolates and antimicrobial susceptibility tests. The CRKP was defined as MIC ≥2 μg/mL of ertapenem or MIC ≥4 μg/mL of meropenem or imipenem according to Clinical and Laboratory Standards Institute guidelines (CLSI 2022). A total of 16 antimicrobial agents were tested. The interpretations for tigecycline and colistin were based on the Food and Drug Administration (FDA) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, version 13.0) breakpoints, respectively. The other antimicrobial agents MIC interpretations were based on CLSI 2022. Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 were used as quality control strains.

The polymerase chain reaction (PCR) was used to detect virulence genes (*peg-344, iucA, iroB, rmpA, rmpA2*) and carbapenem resistance genes (bla_{KPC}, bla_{NDM}, bla_{IMP}, bla_{VIM}, bla_{OXA-48}). The primers referred to previous literature.[2,21] The colloidal gold immunoassays were used to detect carbapenemase production for all isolates. The hvKP was defined as an isolate comprising *rmpA* and/or *rmpA2* with *iucA*.[16,21]

Statistical Analysis

Data are expressed as the means ± standard deviation (SD), medians with interquartile range (IQR), or n (%) as appropriate. Categorical variables were analyzed by the $\chi 2$ test or Fisher's exact test and continuous variables were compared using the student's *t* test or the Mann–Whitney *U*-test, as appropriate. Logistic regression was performed to identify the risk factors for CR-hvKP IAIs. Age, male, and variables with $P < 0.1$ in univariate logistic regression were included in the multivariate model in a forward stepwise with the use of the likelihood-ratio test. Cox regression was used to identify risk factors for in-hospital mortality of CRKP IAIs and variables with $P < 0.05$ in univariate Cox regression were included in the multivariate model. Kaplan–Meier (KM) survival curves were generated with Log rank test analysis in GraphPad Prism 9. Other statistical analyses were performed by SPSS version 25.0. A two-sided $P < 0.05$ was statistically significant.

Results

Clinical and Molecular Characteristics of Patients with CRKP IAIs

A total of 160 patients were enrolled in this study, including 68 patients with CR-hvKP IAIs and 92 patients with CR-non -hvKP IAIs. Among the 68 non-repetitive clinical CR-hvKP strains, 33.82% (23/68) were isolated from pancreatic juice, 20.59% (14/68) from abdominal drainage fluid, 16.18% (11/68) from ascites, 13.24% (9/68) from bile, 8.82% (6/68)

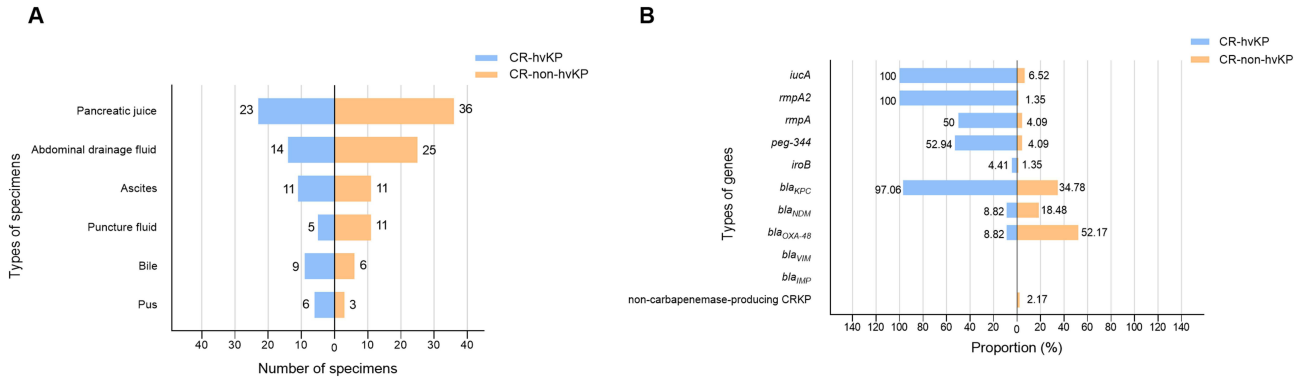

Figure 1 Specimen types (**A**) and molecular characteristics (**B**) of all clinical isolates.

from pus, and 7.35% (5/68) from puncture fluid. In the 92 CR-non-hvKp strains, 39.13% (36/92) were isolated from pancreatic juice, 27.17% (25/92) from abdominal drainage fluid, 11.96% (11/92) from ascites, 11.96% (11/92) from puncture fluid, 6.52% (6/92) from bile, and 3.26% (3/92) from pus (Figure 1A).

The virulence and carbapenem resistance genes of the CR-hvKP strains were detected as follows: all strains (68/68) carried both *iucA* and *rmpA2*, 52.94% (36/68) of isolates carried *peg-344*, 50% (34/68) of isolates carried *rmpA*, 4.41% (3/68) of isolates carried *iroB*, 97.06% (66/68) of isolates carried bla_{KPC}, 8.82% (6/68) of isolates carried bla_{NDM}, and 8.82% (6/68) of isolates carried $bla_{\text{OXA-48}}$. In the CR-non-hvKP strains, 6.52% (6/92) of isolates carried *iucA*, 4.09% (4/92) of isolates carried *peg-344*, 4.09% (4/92) of isolates carried *rmpA*, 1.35% (1/92) of isolates carried *iroB*, 1.35% (1/92) of isolates carried *rmpA2*, 52.17% (48/92) of isolates carried $bla_{\text{OXA-48}}$, 34.78% (32/92) of isolates carried bla_{KPC}, and 18.48% (17/92) of isolates carried bla_{NDM}. bla_{VIM} and bla_{IMP} were not detected in both groups (Figure 1B). In all 160 strains, there are 2 non-carbapenemase-producing CRKP isolates, which are all CR-non-hvKP.

The clinical characteristics and infection data of patients with CRKP IAIs were shown in Table 1. Compared to CR-non-hvKP infected patients, patients who suffered from CR-hvKP had higher NEUT%, and shorter hospital stay before isolation. In addition, the percentage of patients with tracheotomy was higher in CR-hvKP group. Although the difference was not statistically significant, patients with CR-hvKP IAIs had higher mortality rate than CR-non-hvKP IAIs, which is consistent with the survival curve analysis (Figure 2).

Table 1 Clinical Characteristics and Infection Data of Patients with IAIs Caused by CR-hvKP and CR-Non-hvKP

Characteristics	CR-hvKP IAIs (n=68)	CR-non-hvKP IAIs (n=92)	*P* Value
Age, years, median (IQR)	49 (39–58)	43 (37–58)	0.404
Male sex	55 (80.9%)	69 (75.0%)	0.378
Underlying conditions			
Solid cancer	6 (8.8%)	9 (9.8%)	0.837
Hypertension	16 (23.5%)	25 (27.2%)	0.602
Cardiovascular disease	5 (7.4%)	9 (9.8%)	0.591
Neurologic disorder	4 (5.9%)	7 (7.6%)	0.912
Diabetes mellitus	16 (23.5%)	23 (25.0%)	0.830
Gastrointestinal fistula	22 (32.4%)	23 (25.0%)	0.306
Chronic renal disease	2 (2.9%)	2 (2.2%)	1.000
Fatty liver	14 (20.6%)	26 (28.3%)	0.268
Chronic liver disease	2 (2.9%)	5 (5.4%)	0.710
Biliary tract disease	24 (35.3%)	45 (48.9%)	0.086
Malnutrition	7 (10.3%)	16 (17.4%)	0.206
Trauma	5 (7.4%)	11 (12.0%)	0.337
Surgery within 30 days	25 (36.8%)	30 (32.6%)	0.584

(*Continued*)

Table 1 (Continued).

Characteristics	CR-hvKP IAIs (n=68)	CR-non-hvKP IAIs (n=92)	*P* Value
Antibiotic used before KP isolation			
Drug monotherapy	26 (38.2%)	29 (31.5%)	0.377
Drug combination therapy	42 (61.8%)	63 (68.5%)	0.377
Exposure to cephalosporins	24 (35.3%)	33 (35.9%)	0.940
Exposure to carbapenems	47 (69.1%)	63 (68.5%)	0.931
Exposure to other beta-lactams	4 (5.9%)	5 (5.4%)	1.000
Exposure to quinolones	3 (4.4%)	4 (4.3%)	1.000
Exposure to aminoglycosides	2 (2.9%)	6 (6.5%)	0.509
Exposure to tigecycline	18 (26.5%)	22 (23.9%)	0.712
Exposure to polymyxin	18 (26.5%)	17 (18.5%)	0.227
Exposure to glycopeptides	13 (19.1%)	17 (18.5%)	0.918
Exposure to linezolid	4 (5.9%)	13 (14.1%)	0.094
Infection data at infection onset			
WBC count, $\times 10^9$/L, median (IQR)	9.5 (6.7–13.6)	8.5 (6.1–15.4)	0.619
Albumin, g/L, mean ± SD	31.2 ± 4.7	32.3 ± 3.6	0.094
PCT, μg/L, median (IQR)	0.3 (0.2–1)	0.6 (0.2–1.8)	0.316
CRP, mg/L, median (IQR)	93.4 (42.9–125.1)	77.7 (40.4–105.4)	0.092
Platelet count, $\times 10^9$/L, median (IQR)	259 (158–333)	234 (153–376)	0.556
NEUT%, median (IQR)	83.7 (77.1–89.2)	81.5 (71.0–85.9)	0.018*
SOFA score, median (IQR)	4 (2–9)	6 (3–10)	0.854
APACHE II score, median (IQR)	2 (0–5)	3 (1–5)	0.760
Hospital stay before isolation, median (IQR)	9 (3–15.8)	14 (5–25.5)	0.015*
Sepsis	45 (66.2%)	60 (65.2%)	0.900
Septic shock	20 (29.4%)	23 (25.0%)	0.534
Invasive procedures and devices			
PICC indwelling tube	29 (42.6%)	50 (54.3%)	0.143
CVC indwelling tube	26 (38.2%)	44 (47.8%)	0.227
Thoracic drainage tube	22 (32.4%)	29 (31.5%)	0.911
Abdominal drainage tube	49 (72.1%)	74 (80.4%)	0.214
Continuous renal replacement	17 (25.0%)	21 (22.8%)	0.749
Mechanical ventilation	38 (55.9%)	49 (53.3%)	0.742
Tracheal intubation	29 (42.6%)	36 (39.1%)	0.654
Tracheotomy	15 (22.1%)	9 (9.8%)	0.032*
Empirical therapy			
Drug monotherapy	26 (38.2%)	43 (46.7%)	0.283
Drug combination therapy	42 (61.8%)	49 (53.3%)	0.283
Fluoroquinolone-containing regimens	3 (4.4%)	2 (2.2%)	0.730
Aminoglycoside-containing regimens	0 (0.0%)	2 (2.2%)	0.614
Cephalosporin-containing regimens	9 (13.2%)	15 (16.3%)	0.591
Carbapenem-containing regimens	50 (73.5%)	59 (64.1%)	0.207
Tigecycline-containing regimens	17 (25.0%)	20 (21.7%)	0.629
Colistin-containing regimens	17 (25.0%)	18 (19.6%)	0.411
Ceftazidime-avibactam-containing regimens	9 (13.2%)	16 (17.4%)	0.474
Inappropriate empirical treatment	36 (52.9%)	49 (53.3%)	0.968
Targeted therapy			
Drug monotherapy	33 (48.5%)	35 (38.0%)	0.185
Drug combination therapy	35 (51.5%)	57 (62.0%)	0.185
Fluoroquinolone-containing regimens	2 (2.9%)	4 (4.3%)	0.966
Aminoglycoside-containing regimens	1 (1.5%)	4 (4.3%)	0.566
Cephalosporin-containing regimens	8 (11.8%)	13 (14.1%)	0.661

(*Continued*)

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Table 1 (Continued).

Characteristics	CR-hvKP IAIs (n=68)	CR-non-hvKP IAIs (n=92)	*P* Value
Carbapenem-containing regimens	39 (57.4%)	57 (62.0%)	0.557
Tigecycline-containing regimens	11 (16.2%)	22 (23.9%)	0.232
Colistin-containing regimens	16 (23.5%)	17 (18.5%)	0.435
Ceftazidime-avibactam-containing regimens	17 (25.0%)	26 (28.3%)	0.646
ICU stay, median (IQR)	32.5 (17.3–60)	44.5 (17.5–64.8)	0.427
Full hospital stay, median (IQR)	41 (24–62.5)	46.5 (32–67.5)	0.149
Outcome (dead)	12 (17.6%)	10 (10.9%)	0.218

Notes: Data are presented as No. (%) of patients unless otherwise specified. *$P < 0.05$, the comparison between CR-hvKP IAI and CR-non-hvKP IAI.

Abbreviations: KP, *Klebsiella pneumoniae*; CR-hvKP, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*; CR-non-hvKP, carbapenem-resistant non-hypervirulent *Klebsiella pneumoniae*; IAI, intra-abdominal infection; WBC, white blood cell; PCT, procalcitonin; CRP, C-reactive protein; NEUT%, neutrophilic granulocyte percentage; SOFA, sequential organ failure assessment; APACHE, acute physiologic and chronic health evaluation; PICC, peripherally inserted central catheter; CVC, central venous catheter; ICU, intensive care unit; SD, standard deviation; IQR, interquartile range.

Risk Factors Associated with CR-hvKP IAIs

The univariate analysis to identify potential risk factors for CR-hvKP infection included biliary tract disease (OR 0.570, 95% CI 0.299–1.085; P = 0.087), hospital stay before isolation (OR 0.980, 95% CI 0.958–1.003; P = 0.085), and tracheotomy (OR 2.610, 95% CI 1.066–6.390; P = 0.036). Multivariate analysis of all patients showed that tracheotomy (OR 2.816, 95% CI 1.120–7.080; P = 0.028) was the risk factor associated with CR-hvKP IAIs (Table 2).

Antimicrobial Resistance Characteristics of CR-hvKP Strains

All CR-hvKP isolates were completely resistant to piperacillin-tazobactam, ceftazidime, cefoperazone-sulbactam, cefepime, aztreonam, imipenem, meropenem, ciprofloxacin, and levofloxacin. The drug resistance rates for amikacin, tobramycin, doxycycline, minocycline, tigecycline, colistin, and trimethoprim-sulfamethoxazole were 86.76%, 92.65%, 72.06%, 72.06%, 19.12%, 26.47%, and 51.47%, respectively. As for CR-non-hvkp isolates, all were completely resistant to piperacillin-tazobactam, cefoperazone-sulbactam, cefepime, meropenem, while 98.91% were resistant to ceftazidime, 97.83% were resistant to aztreonam, 98.91% were resistant to imipenem, 34.78% were resistant to amikacin, 78.26% were resistant to tobramycin, 95.65% were resistant to ciprofloxacin and levofloxacin, 78.26% were resistant to doxycycline, 72.83% were resistant to minocycline, 26.09% were resistant to tigecycline, 9.78% were resistant to

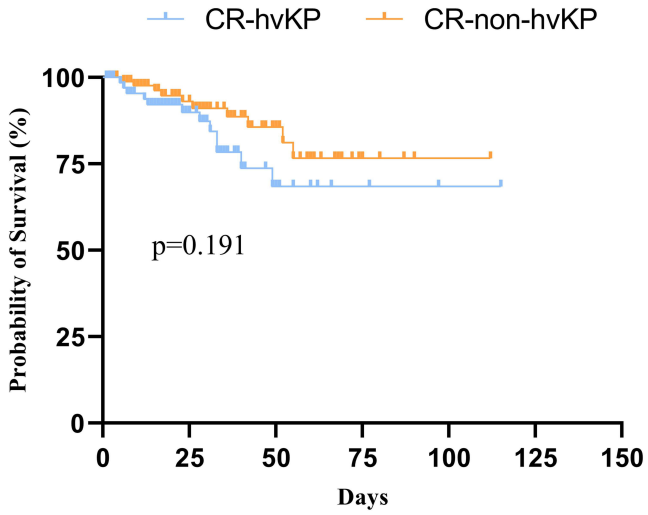

Figure 2 Kaplan–Meier survival was used to compare the in-hospital mortality among patients with CR-hvKP IAIs and CR-non-hvKP IAIs.

Table 2 Univariate and Multivariable Logistic Regression Analyses of Risk Factors Associated with CR-hvKP IAIs

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.005 (0.983–1.028)	0.662	1.010 (0.986–1.035)	0.400
Male	1.410 (0.655–3.036)	0.380	1.250 (0.542–2.878)	0.601
Biliary tract disease	0.570 (0.299–1.085)	0.087	0.577 (0.297–1.119)	0.104
Hospital stay before isolation	0.980 (0.958–1.003)	0.085	0.977 (0.953–1.002)	0.068
Tracheotomy	2.610 (1.066–6.390)	0.036*	2.816 (1.120–7.080)	0.028*

Notes: *$P < 0.05$.
Abbreviations: CR-hvKP, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*; IAI, intra-abdominal infection; OR, odds ratio; CI, confidence interval.

colistin, 77.17% were resistant to trimethoprim-sulfamethoxazole. CR-hvKP isolates had significantly higher resistance rates to amikacin and colistin than those of CR-non-hvKP isolates ($P < 0.001$ and $P = 0.005$, respectively), while the resistance rates to trimethoprim-sulfamethoxazole were significantly lower in CR-hvKP isolates compared with CR-non-hvKP isolates ($P = 0.001$) (Table 3). The detailed antimicrobial susceptibility results for all strains are provided in Supplementary Figure 1.

Clinical Characteristics Associated with in-Hospital Mortality of CRKP IAIs

The in-hospital mortality rate of CRKP IAIs was 13.75% (22/160). The mortality rates of CR-hvKP IAIs and CR-non-hvKP IAIs were 17.65% (12/68) and 10.87% (10/92), respectively. Table 4 showed that age ($P = 0.046$), cardiovascular disease ($P = 0.036$), the laboratory data PCT ($P = 0.016$), platelet count ($P = 0.001$), NEUT% ($P = 0.003$), SOFA score ($P < 0.001$), APACHE II score ($P < 0.001$), sepsis ($P < 0.001$), and septic shock ($P < 0.001$) at infection onset, invasive operations such as central venous catheter (CVC) indwelling tube ($P = 0.003$), tracheal intubation ($P = 0.005$), and tracheotomy ($P < 0.001$) had statistical significance between the survival group and the death group of CRKP IAIs (Table 4).

Table 3 Percentage of Antimicrobial Resistance of CRKP Strains

Antimicrobial Agents	CR-hvKP (n=68)	CR-non-hvKP (n=92)	*P* Value
Piperacillin-tazobactam	68 (100%)	92 (100%)	NA
Cefoperazone-sulbactam	68 (100%)	92 (100%)	NA
Ceftazidime	68 (100%)	91 (98.91%)	1.000
Cefepime	68 (100%)	92 (100%)	NA
Aztreonam	68 (100%)	90 (97.83%)	0.508
Imipenem	68 (100%)	91 (98.91%)	1.000
Meropenem	68 (100%)	92 (100%)	NA
Amikacin	59 (86.76%)	32 (34.78%)	< 0.001*
Tobramycin	64 (92.65%)	72 (78.26%)	0.005*
Ciprofloxacin	68 (100%)	88 (95.65%)	0.219
Levofloxacin	68 (100%)	88 (95.65%)	0.219
Doxycycline	49 (72.06%)	72 (78.26%)	0.366
Minocycline	49 (72.06%)	67 (72.83%)	0.914
Tigecycline	13 (19.12%)	24 (26.09%)	0.301
Colistin	18 (26.47%)	9 (9.78%)	0.005*
Trimethoprim-sulfamethoxazole	35 (51.47%)	71 (77.17%)	0.001*

Notes: Data are presented as No. (%) of patients. *$P < 0.05$, the comparison between CR-hvKPs and CR-non-hvKPs.
Abbreviations: CR-hvKP, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*; CR-non-hvKP, carbapenem-resistant non-hypervirulent *Klebsiella pneumoniae*; NA, not available.

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Table 4 Clinical Characteristics Associated with in-Hospital Mortality of CRKP IAIs

Characteristics	All CRKP IAIs			CR-hvKP IAIs			CR-non-hvKP IAIs		
	Death (n=22)	Survivors (n=138)	*P* Value	Death (n=12)	Survivors (n=56)	*P* Value	Death (n=10)	Survivors (n=82)	*P* Value
Age, years, median (IQR)	52 (41.8–65.8)	46 (37–55)	0.046*	48.5 (41.3–62.8)	48.5 (37.00–55.00)	0.338	54 (41.5–71)	43 (36.8–55)	0.075
Male sex	15 (68.2%)	109 (79.0%)	0.394	10 (83.3%)	45 (80.4%)	1.000	5 (50.0%)	64 (78.0%)	0.122
Underlying conditions									
Solid cancer	3 (13.6%)	12 (8.7%)	0.730	2 (16.7%)	4 (7.1%)	0.621	1 (10.0%)	8 (9.8%)	1.000
Hypertension	7 (31.8%)	34 (24.6%)	0.474	3 (25.0%)	13 (23.2%)	1.000	4 (40.0%)	21 (25.6%)	0.556
Cardiovascular disease	5 (22.7%)	9 (6.5%)	0.036*	2 (16.7%)	3 (5.4%)	0.211	3 (30.0%)	6 (7.3%)	0.055
Neurologic disorder	4 (18.2%)	7 (5.1%)	0.071	2 (16.7%)	2 (3.6%)	0.141	2 (20.0%)	5 (6.1%)	0.166
Diabetes mellitus	6 (27.3%)	33 (23.9%)	0.733	5 (41.7%)	11 (19.6%)	0.209	1 (10.0%)	22 (26.8%)	0.439
Gastrointestinal fistula	6 (27.3%)	39 (28.3%)	0.924	3 (25.0%)	19 (33.9%)	0.795	3 (30.0%)	20 (24.4%)	1.000
Chronic renal disease	1 (4.5%)	3 (2.2%)	0.450	1 (8.3%)	1 (1.8%)	0.324	0 (0.0%)	2 (2.4%)	1.000
Fatty liver	3 (13.6%)	37 (26.8%)	0.185	3 (25.0%)	11 (19.6%)	0.982	0 (0.0%)	26 (31.7%)	0.084
Chronic liver disease	0 (0.0%)	7 (5.1%)	0.595	0 (0.0%)	2 (3.6%)	1.000	0 (0.0%)	5 (6.1%)	1.000
Biliary tract disease	8 (36.4%)	61 (44.2%)	0.491	4 (33.3%)	20 (35.7%)	1.000	4 (40.0%)	41 (50.0%)	0.793
Malnutrition	4 (18.2%)	19 (13.8%)	0.825	1 (8.3%)	6 (10.7%)	1.000	3 (30.0%)	13 (15.9%)	0.501
Trauma	1 (4.5%)	15 (10.9%)	0.592	0 (0.0%)	5 (8.9%)	0.577	1 (10.0%)	10 (12.2%)	1.000
Surgery within 30 days	6 (27.3%)	49 (35.5%)	0.450	2 (16.7%)	23 (41.1%)	0.207	4 (40.0%)	26 (31.7%)	0.864
Antibiotic used before KP isolation									
Drug monotherapy	5 (22.7%)	50 (36.2%)	0.216	3 (25.0%)	23 (41.1%)	0.476	2 (20.0%)	27 (32.9%)	0.638
Drug combination therapy	17 (77.3%)	88 (63.8%)	0.216	9 (75.0%)	33 (58.9%)	0.476	8 (80.0%)	55 (67.1%)	0.638
Exposure to cephalosporins	7 (31.8%)	50 (36.2%)	0.688	3 (25.0%)	21 (37.5%)	0.625	4 (40.0%)	29 (35.4%)	1.000
Exposure to carbapenems	17 (77.3%)	93 (67.4%)	0.353	10 (83.3%)	37 (66.1%)	0.406	7 (70.0%)	56 (68.3%)	1.000
Exposure to other beta-lactams	0 (0.0%)	9 (6.5%)	0.462	0 (0.0%)	4 (7.1%)	1.000	0 (0.0%)	5 (6.1%)	1.000
Exposure to quinolones	2 (9.1%)	5 (3.6%)	0.546	2 (16.7%)	1 (1.8%)	0.078	0 (0.0%)	4 (4.9%)	1.000
Exposure to aminoglycosides	0 (0.0%)	8 (5.8%)	0.527	0 (0.0%)	2 (3.6%)	1.000	0 (0.0%)	6 (7.3%)	1.000
Exposure to tigecycline	8 (36.4%)	32 (23.2%)	0.185	4 (33.3%)	14 (25.0%)	0.816	4 (40.0%)	18 (22.0%)	0.384
Exposure to polymyxin	7 (31.8%)	28 (20.3%)	0.349	4 (33.3%)	14 (25.0%)	0.816	3 (30.0%)	14 (17.1%)	0.574
Exposure to glycopeptides	7 (31.8%)	23 (16.7%)	0.162	4 (33.3%)	9 (16.1%)	0.329	3 (30.0%)	14 (17.1%)	0.574
Exposure to linezolid	2 (9.1%)	15 (10.9%)	1.000	1 (8.3%)	3 (5.4%)	0.549	1 (10.0%)	12 (14.6%)	1.000
Infection data at infection onset									
WBC count, $\times 10^9$/L, median (IQR)	9.7 (5.4–15.2)	9.1 (6.6–13.4)	0.890	9.4 (5.3–15)	9.6 (7–13.3)	0.860	9.9 (6–15.8)	8.57 (6.14–13.79)	0.960
Albumin, g/L, median (IQR)	30.2 (28.6–32.4)	32 (28.7–34.2)	0.190	29.7 (29.2–31.5)	31 (28.1–34.2)	0.557	31.1 (27.9–33.9)	32.3 (29.7–34.2)	0.328
PCT, μg/L, median (IQR)	1.7 (0.4–4.7)	0.4 (0.2–1.1)	0.016*	1.7 (0.5–4.7)	0.3 (0.2–0.9)	0.017*	2.2 (0.3–6.5)	0.5 (0.2–1.3)	0.244
CRP, mg/L, median (IQR)	104.9 (60.9–168.8)	78 (38.3–112.8)	0.062	124.3 (73.20–182)	84.4 (42.4–116.9)	0.026*	78.8 (37.1–115)	76.2 (34.2–108.4)	0.759
Platelet count, $\times 10^9$/L, median (IQR)	142 (90.5–269.3)	262.5 (164.75–376)	0.001*	150.5 (82.5–246.5)	275 (161.3–367.8)	0.004*	127.5 (88.3–335.8)	243.5 (167.3–377.8)	0.079
NEUT%, median (IQR)	88.6 (82.1–93.2)	82.2 (72.8–87.1)	0.003*	90.4 (84.8–94.6)	83.2 (76.6–88.4)	0.005*	85.3 (72.5–91)	81.5 (71–85.5)	0.304
SOFA score, median (IQR)	6.5 (5–10)	2 (0–4)	<0.001*	8.0 (5.25–11.0)	2.0 (0–3.0)	<0.001*	6 (4.75–10)	2 (0–4)	<0.001*
APACHE II score, median (IQR)	10.5 (8–17)	4 (2.75–7.25)	<0.001*	12.0 (8.25–17.0)	4.0 (2.0–5.8)	<0.001*	10 (7.8–16.5)	5 (3–8)	<0.001*
Hospital stay before isolation, median (IQR)	12 (5.8–22.3)	11.5 (4–22.25)	0.747	14.5 (6.3–25.8)	6.5 (2.3–15)	0.105	10 (5–19.3)	14 (5–26.3)	0.390
Sepsis	22 (100%)	83 (60.1%)	<0.001*	12 (100.0%)	33 (58.9%)	0.017*	10 (100.0%)	50 (61.0%)	0.036*
Septic shock	17 (77.3%)	26 (18.8%)	<0.001*	9 (75.0%)	11 (19.6%)	0.001*	8 (80.0%)	15 (18.3%)	<0.001*

Invasive procedures and devices									
PICC indwelling tube	13 (59.1%)	66 (47.8%)	0.326	7 (58.3%)	22 (39.3%)	0.226	6 (60.0%)	44 (53.7%)	0.965
CVC indwelling tube	16 (72.7%)	54 (39.1%)	0.003*	8 (66.7%)	18 (32.1%)	0.057	8 (80.0%)	36 (43.9%)	0.068
Thoracic drainage tube	8 (36.4%)	43 (31.2%)	0.627	5 (41.7%)	17 (30.4%)	0.674	30 (30.0%)	26 (31.7%)	1.000
Abdominal drainage tube	18 (81.8%)	105 (76.1%)	0.554	10 (83.3%)	39 (69.6%)	0.545	8 (80.0%)	66 (80.5%)	1.000
Continuous renal replacement	8 (36.4%)	30 (21.7%)	0.134	6 (50.0%)	11 (19.6%)	0.066	2 (20.0%)	19 (23.2%)	1.000
Mechanical ventilation	16 (72.7%)	71 (51.4%)	0.063	9 (75.0%)	29 (51.8%)	0.142	7 (70.0%)	42 (51.2%)	0.431
Tracheal intubation	15 (68.2%)	50 (36.2%)	0.005*	9 (75.0%)	20 (35.7%)	0.013*	6 (60.0%)	30 (36.6%)	0.276
Tracheotomy	11 (50.0%)	13 (9.4%)	<0.001*	7 (58.3%)	8 (14.3%)	0.003*	4 (40.0%)	5 (6.1%)	0.007*
Empirical therapy									
Drug monotherapy	8 (36.4%)	61 (44.2%)	0.491	6 (50.0%)	20 (35.7%)	0.551	2 (20.0%)	41 (50.0%)	0.144
Drug combination therapy	14 (63.6%)	77 (55.8%)	0.491	6 (50.0%)	36 (64.3%)	0.551	8 (80.0%)	41 (50.0%)	0.144
Fluoroquinolone-containing regimens	2 (9.1%)	3 (2.2%)	0.139	2 (16.7%)	1 (1.8%)	0.053	0 (0.0%)	2 (2.4%)	0.495
Aminoglycoside-containing regimens	0 (0.0%)	2 (1.4%)	0.440	0	0	NA	0 (0.0%)	2 (2.4%)	0.495
Cephalosporin-containing regimens	4 (18.2%)	20 (14.5%)	0.898	2 (16.7%)	7 (12.5%)	1.000	2 (20.0%)	13 (15.9%)	1.000
Carbapenem-containing regimens	15 (68.2%)	94 (68.1%)	0.995	8 (66.7%)	42 (75.0%)	0.816	7 (70.0%)	52 (63.4%)	0.952
Tigecycline-containing regimens	4 (18.2%)	33 (23.9%)	0.554	2 (16.7%)	15 (26.8%)	0.713	2 (20.0%)	18 (22.0%)	1.000
Colistin-containing regimens	8 (36.4%)	27 (19.6%)	0.136	3 (25.0%)	14 (25.0%)	1.000	5 (50.0%)	13 (15.9%)	0.032*
Ceftazidime-avibactam-containing regimens	1 (4.5%)	24 (17.4%)	0.221	1 (8.3%)	8 (14.3%)	0.934	0 (0.0%)	16 (19.5%)	0.274
Inappropriate empirical treatment	10 (45.5%)	75 (54.3%)	0.438	7 (58.3%)	29 (51.8%)	0.680	3 (30.0%)	46 (56.1%)	0.220
Targeted therapy									
Drug monotherapy	6 (27.3%)	62 (44.9%)	0.120	4 (33.3%)	29 (51.8%)	0.246	2 (20.0%)	33 (40.2%)	0.368
Drug combination therapy	16 (72.7%)	76 (55.1%)	0.120	8 (66.7%)	27 (48.2%)	0.246	8 (80.0%)	49 (59.8%)	0.368
Fluoroquinolone-containing regimens	1 (4.5%)	5 (3.6%)	0.595	1 (8.3%)	1 (1.8%)	0.324	0 (0.0%)	4 (4.9%)	1.000
Aminoglycoside-containing regimens	0 (0.0%)	5 (3.6%)	1.000	0 (0.0%)	1 (1.8%)	1.000	0 (0.0%)	4 (4.9%)	1.000
Cephalosporin-containing regimens	3 (13.6%)	18 (13.0%)	1.000	1 (8.3%)	7 (12.5%)	1.000	2 (20.0%)	11 (13.4%)	0.933
Carbapenem-containing regimens	13 (59.1%)	83 (60.1%)	0.925	7 (58.3%)	32 (57.1%)	0.940	6 (60.0%)	51 (62.2%)	1.000
Tigecycline-containing regimens	5 (22.7%)	28 (20.3%)	1.000	2 (16.7%)	9 (16.1%)	1.000	3 (30.0%)	19 (23.2%)	0.932
Colistin-containing regimens	3 (13.6%)	30 (21.7%)	0.556	2 (16.7%)	14 (25.0%)	0.808	1 (10.0%)	16 (19.5%)	0.764
Ceftazidime-avibactam-containing regimens	8 (36.4%)	35 (25.4%)	0.280	4 (33.3%)	13 (23.2%)	0.713	4 (40.0%)	22 (26.8%)	0.616
ICU stay, median (IQR)	40.5 (18.5–61.5)	40 (17–64)	0.708	47 (28.8–70.5)	30 (14–56)	0.109	31 (15–50.3)	45 (18.5–65.3)	0.337
Full hospital stay, median (IQR)	40.5 (25.75–61.5)	45 (27–65.3)	0.554	47 (28.8–70.5)	40.5 (23.3–56.8)	0.421	37 (23.5–50.3)	47.5 (32.8–68)	0.110

Notes: Data are presented as No. (%) of patients unless otherwise specified. *$P < 0.05$ compared with survivors. All CRKP IAIs population was divided into CR-hvKP and CR-non-hvKP groups according to the isolate virulence. All CRKP IAIs refers to the total of both CR-hvKP and CR-non-hvKP.

Abbreviations: CR-hvKP, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*; CR-non-hvKP, carbapenem-resistant non-hypervirulent *Klebsiella pneumoniae*; IAI, intra-abdominal infection; WBC, white blood cell; PCT, procalcitonin; CRP, C-reactive protein; NEUT%, neutrophilic granulocyte percentage; SOFA, sequential organ failure assessment; APACHE, acute physiologic and chronic health evaluation; PICC, peripherally inserted central catheter; CVC, central venous catheter; ICU, intensive care unit; SD, standard deviation; IQR, interquartile range.

Table 5 Univariate and Multivariate COX Regression Analyses of Risk Factors for in-Hospital Mortality in Patients with CRKP IAIs

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.044 (1.013–1.075)	0.004*	1.066 (1.020–1.114)	0.005*
Cardiovascular disease	5.106 (1.181–14.339)	0.002*	1.120 (0.241–5.209)	0.885
Neurologic disorder	5.145 (1.692–15.643)	0.004*	2.773 (0.563–13.665)	0.210
Platelet count	0.994 (0.990–0.998)	0.006*	0.995 (0.990–0.999)	0.018*
SOFA score	1.221 (1.109–1.345)	<0.001*	1.213 (0.901–1.634)	0.203
APACHE II score	1.146 (1.070–1.227)	<0.001*	0.083 (0.627–1.030)	0.084
Septic shock	6.765 (2.490–18.382)	<0.001*	9.141 (2.082–40.133)	0.003*
Tracheotomy	6.377 (2.681–15.168)	<0.001*	4.322 (1.461–12.791)	0.008*

Notes: *$P < 0.05$.
Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; IAI, intra-abdominal infection; SOFA, sequential organ failure assessment; APACHE, acute physiologic and chronic health evaluation; HR, hazard ratio; CI, confidence interval.

Risk Factors Associated with CRKP IAIs Mortality

The univariate and multivariate Cox regression analyses were conducted to determine risk factors associated with in-hospital mortality in patients with CRKP IAIs (Table 5). The univariate analysis identified that age (HR 1.044, 95% CI 1.013–1.075; P = 0.004), cardiovascular disease (HR 5.106, 95% CI 1.181–14.339; P = 0.002), neurologic disorder (HR 5.145, 95% CI 1.692–15.643; P = 0.004), platelet count (HR 0.994, 95% CI 0.990–0.998; P = 0.006), SOFA score (HR 1.221, 95% CI 1.109–1.345; P < 0.001), APACHE II score (HR 1.146, 95% CI 1.070–1.227; P < 0.001), septic shock (HR 6.765, 95% CI 2.490–18.382; P < 0.001), and tracheotomy (HR 6.377, 95% CI 2.681–15.168; P < 0.001) were potential risk factors. Multivariate regression showed that age (HR 1.066, 95% CI 1.020–1.114; P = 0.005), lower platelet count (HR 0.995, 95% CI 0.990–0.999; P = 0.018), septic shock (HR 9.141, 95% CI 2.082–40.133; P = 0.003), and tracheotomy (HR 4.322, 95% CI 1.461–12.791; P = 0.008) were variables associated with in-hospital mortality of CRKP IAIs.

Discussion

CR-hvKP is characterized by its distinct virulence, which contributes to its high morbidity and mortality. The outbreak of ventilator-associated pneumonia caused by this lethal bacteria was first reported in China,[13] and subsequently, more and more hospital outbreaks were reported.[11,22–24] In addition, the effective treatment options for this pathogen remained limited.[25,26] This study conducted a retrospective analysis to investigate the clinical features, risk factors, and mortality in patients with IAIs caused by CR-hvKP, aiming to provide guidance for clinical interventions and reduce the spread of CR-hvKP.

In this retrospective study, we isolated 68 strains of CR-hvKP and 92 CR-non-hvKP. These strains were mainly isolated from pancreatic juice, abdominal drainage fluid, and ascites, which were caused by the characteristics of our center in the treatment of a large number of patients with pancreatitis and trauma. Previous studies reported that carbapenem resistance in CR-hvKP was mainly attributed to the widespread existence of $bla_{\text{KPC-2}}$ gene in China, whose detection rate was as high as 80.7%.[27] When identifying the resistance genes of these strains, we also found that bla_{KPC} was the most common resistance gene with a detection rate as high as 97.06%, while bla_{IMP} and bla_{VIM} were not detected. From a global perspective, there are significant geographic differences in carbapenemase types. In Japan, the majority of carbapenemases detected are bla_{IMP}, especially $bla_{\text{IMP-1}}$ and $bla_{\text{IMP-6}}$, which have become endemic across healthcare, community, and environmental settings.[28,29] Conversely, bla_{NDM} was first identified in India and rapidly disseminated through Indian hospitals and communities.[30] The $bla_{\text{OXA-48}}$ demonstrates pronounced prevalence in Turkey, North Africa, and the Middle East. The bla_{VIM} is prevalent in southern Europe and coexists with $bla_{\text{OXA-48}}$ in some areas.[31] The bla_{KPC} profile observed in Nanjing aligns with mainland China's broader epidemiological landscape but vigilance is still required for other carbapenemase types. Our cohort also included 2 non-carbapenemase-producing CRKP isolates, which are all CR-non-hvKP isolates. Non-carbapenemase-producing CRKP is of clinical significance and were associated with a high 14-day mortality.[32] Study demonstrated that carbapenem resistance in non-carbapenemase-

producing CRKP strains arises through synergistic mechanisms involving non-carbapenemase β-lactamase production coupled with chromosomal mutations, such as missense variants or functional loss of the OmpK porin and frameshift mutations in efflux regulatory components.[33] The non-carbapenemase-producing CRKP may indicate an increased risk of multidrug-resistant infections, complicating treatment options and potentially leading to poorer patient outcomes. We acknowledge this heterogeneity in our study, however, its limited number has little impact on outcomes.

The definition of virulence in CR-hvKP was intricate and differed between various studies. Here we defined hvKP as isolates comprising *rmpA* and/or *rmpA2* with *iucA*. Among all CR-hvKP strains, we observed a low prevalence of the *iroB* gene. A study demonstrated that the absence of *iroBCDN* increased the viability of CR-hvKP without reducing its virulence, which may explain the phenomenon we observed.[34]

We calculated that the overall mortality rate of all patients was 13.75%, which was slightly higher than the 9.43% observed in the subgroup of IAIs in a study.[2] The mortality rate numerically trended higher in the CR-hvKP group (17.6%) compared with CR-non-hvKP group (10.9%), but this difference did not reveal statistical significance (P=0.218). This contrasted with reports of numerically higher positive outcome for CR-hvKP infections in a previous study. The discrepancy could be due to differences of the infection types included in our study, which solely focused on intra-abdominal infections, while the other study included various types such as pulmonary, urinary tract, bloodstream, and intracranial infections. Additionally, the total number of CR-hvKP cases in the latter study was only 27, which might explain the heterogeneity of results due to the difference in infection types and sample size,[16] as a recently published large-sample clinical retrospective study indicated that hvKP led to a higher early mortality rate.[9] It is noteworthy that a small number of isolates in our CR-non-hvKP group carried a single virulence gene. This genetic heterogeneity could partially attenuate the differences between groups, as strains harboring one virulence gene may exhibit mildly enhanced pathogenic potential. To assess its impact, we performed a sensitivity analysis excluding these single-gene–positive isolates; the primary endpoints remained consistent with the original analysis. On the whole, the difference in mortality rates between the two groups underscored the need for increased clinical attention to this hybrid strain. Tigecycline in combination with other drugs is one of the treatment options for CRKP infections,[35] but some studies have shown that the empirical use of tigecycline is an independent risk factor for death in CRKP infections.[36] The clinical use of tigecycline may also contribute to the colonization and widespread dissemination of CR-hvKP strains according to a study.[37] In our study, we found that the use of tigecycline prior to infection was indeed higher in the death group and the CR-hvKP group compared to the control group, although this difference was not statistically significant. The results required verification with a larger sample size. Moreover, the CR-hvKP group exhibited a higher NEUT% and a shorter hospitalization prior to infection, indicating the highly progressive nature of this strain and its association with more pronounced inflammatory responses.

Previous studies have identified several risk factors for CR-hvKP infection, including cardiovascular disease,[38] tracheal intubation,[16] and bed change.[17] A case report highlighted that comorbidities such as diabetes and chronic diseases are major risk factors for CR-hvKP infections.[39] Additional, a number of outbreaks of CR-hvKP with liver abscess,[40] pneumonia,[41] and bloodstream infection have been reported.[42] In this study, we found no significant differences in the underlying health conditions between the two groups. However, tracheostomy was significantly higher in CR-hvKP group and was identified as a risk factor for CR-hvKP infection. Invasive procedures may significantly increase the risk of CR-hvKP infections. This is supported by studies reporting ventilator-associated pneumonia caused by CR-hvKP.[13,43] Notably, a recent investigation found that all patients infected with CR-hvKP had undergone invasive procedures, with tracheal intubation being the most common intervention.[44] During the course of abdominal sepsis, patients may develop systemic inflammatory response syndrome and immune dysfunction, leading to compromised host immunity.[45] The lung, which is one of the most vulnerable organs in sepsis, often require invasive interventions such as tracheal intubation or tracheostomy. However, tracheostomy creates a portal of entry for exogenous bacterial colonization and iatrogenic infections.[46,47] For patients who need to perform repeated clinical operations such as sputum suction, airway irrigation and mechanical ventilation, if the hand hygiene of medical staff is not strict, the instrument is not thoroughly disinfected, or the pipeline is exposed to the environment, it may become the link of cross contamination of pathogens, thereby promoting the horizontal transmission of bacteria in the ward.[48–50] Therefore, in order to minimize

the risk of horizontal transmission in hospital, it is necessary to strengthen the aseptic technique, standardize the implementation of hand hygiene and strengthen the preventive disinfection of equipment while treating patients.

The antimicrobial susceptibility test showed that CR-hvKP isolates were completely resistant to piperacillin-tazobactam, ceftazidime, cefoperazone-sulbactam, cefepime, aztreonam, imipenem, meropenem, ciprofloxacin, and levofloxacin, which limits the treatment options. However, the CR-hvKP isolates showed lower resistance to trimethoprim-sulfamethoxazole, compared to CR-non-hvKP isolates (P = 0.001). A study showed CR-hvKP were completely sensitive to ceftazidime-avibactam, which may provide an option for this multidrug-resistant (MDR) bacteria.[17]

The study also identified age, lower platelet count, septic shock, and tracheotomy as predictors of CRKP death. Older patients tend to have more comorbidities and poorer immune status, which increases the risk of death. Studies have shown that old age is an independent risk factor for hospital death for many diseases, such as pneumonia and cardiovascular disease.[51,52] A lower platelet count is a marker of severe infection and septic shock.[53] A single-center retrospective study also confirmed that lower platelet counts on the day of CRKP infection onset were associated with a higher 28-day mortality.[54] Crucially, our study identified tracheotomy as an independent risk factor for CR-hvKP IAIs and for subsequent in-hospital mortality among all CRKP IAI patients. These findings highlight the critical need for heightened vigilance and strict infection control measures, particularly in patients undergoing tracheotomy. Clinicians must maintain a high awareness for CR-hvKP, particularly in patients with IAIs who have undergone tracheotomy or are critically ill with the identified mortality risk factors. Stringent infection prevention and control practices, including meticulous hand hygiene, environmental cleaning, and contact precautions are paramount. Also, we have strictly implemented a comprehensive control bundle to ensure sustained reduction in horizontal transmission in clinical work after the study.

Finally, our study has several limitations. First, it is a single-center retrospective study, so larger, multi-center studies are required to minimize data bias. Second, our study focused only on patients with IAIs, so the conclusions may not be applicable to other types of infections. Third, 30-day mortality is a common outcome measure but was not assessed in this study due to the limitations of retrospective data, so we selected in-hospital mortality as the primary outcome measure, which needs to be improved in our future research. Lastly, to better understand the evolutionary transmission characteristics of CR-hvKP, whole-genome sequencing of the strains is needed to obtain more molecular biological information.

Conclusion

In conclusion, our study included 68 CR-hvKP IAIs and 92 CR-non-hvKP IAIs. We analyzed the clinical, molecular biological characteristics and drug resistance of the isolates. Our data suggest that patients with CR-hvKP IAIs had a numerically higher mortality rate with no statistical significance and that tracheotomy was a risk factor for infection. In addition, we identified four independent risk factors for in-hospital mortality of CRKP IAIs: age, decreased platelet count, septic shock, and tracheotomy. Given the increasing mortality and prevalence of CR-hvKP globally, we should pay more attention to prevention and control in clinical settings. High-risk populations should be closely monitored, and infected patients must be strictly isolated. In addition, medical staff and wards should undergo thorough disinfection procedures to prevent the spread of the bacteria in the hospital.

Ethical Approval

The Institutional Review Board Ethics Committee of Jinling Hospital, Nanjing, China provided the ethical approval for this research (2024DZKY-001-01). We have complied with the Declaration of Helsinki. The informed consent was waived as the biological characteristics and data in this study have been de-identified, all information collected during the investigation will be kept confidential to the highest degree, ensuring maximum privacy protection. The microbiological testing was undertaken under Biosafety Level 3 conditions.

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Disclosure

The authors report no conflicts of interest in this work.

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