Infection and Drug Resistance

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ORIGINAL RESEARCH

Clinical and Molecular Characteristics of Patients with Bloodstream Infections Caused by KPC and NDM Co-Producing Carbapenem-Resistant *Klebsiella pneumoniae*

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Purpose: *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo-β-lactamase (NDM) co-producing carbapenem-resistant *Klebsiella pneumoniae* (KPC-NDM-CRKP) isolates have been increasingly reported worldwide but have not yet been systematically studied. Thus, we have conducted a study to compare the risk factors, molecular characteristics, and mortality involved in clinical bloodstream infections (BSIs) caused by KPC-NDM-CRKP and KPC-CRKP strains.

Methods: A retrospective study was conducted on 231 patients with BSIs caused by CRKP at Jinling Hospital in China from January 2020 to December 2022. Antimicrobial susceptibility testing, carbapenemase genes detection and whole-genome sequencing were performed subsequently.

Results: Overall, 231 patients were included in this study: 25 patients with KPC-NDM-CRKP BSIs and 206 patients with KPC-CRKP BSIs. Multivariate analysis implicated ICU-acquired BSI, surgery within 30 days, and longer stay of hospitalization prior to CRKP isolation as independent risk factors for KPC-NDM-CRKP BSIs. The 30-day mortality rate of the KPC-NDM-CRKP BSIs group was 56% (14/25) compared with 32.5% (67/206) in the KPC-CRKP BSIs control group ($P = 0.02$). The ICU-acquired BSIs, APACHE II score at BSI onset, and BSIs caused by KPC-NDM-CRKP were independent predictors for 30-day mortality in patients with CRKP bacteremia. The most prevalent ST in KPC-NDM-CRKP isolates was ST11 (23/25, 92%), followed by ST15 (2/25, 8%).

Conclusion: In patients with CRKP BSIs, KPC-NDM-CRKP was associated with an excess of mortality. The likelihood that KPC-NDM-CRKP will become the next "superbug" highlights the significance of epidemiologic surveillance and clinical awareness of this pathogen.

Keywords: KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*, Bloodstream infections, risk factors, molecular characteristics, mortality

Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represents a catastrophic threat to global public health and clinical settings due to the presence of mobile carbapenemases. *Klebsiella pneumoniae* carbapenemase (KPC, class A) and New Delhi metallo-β-lactamase (NDM, class B) are two of the more prevalently encountered carbapenemases worldwide.[1,2] Recently, KPC and NDM co-producing *K. pneumoniae* (KPC-NDM-CRKP) isolates have been increasingly reported in China and many regions of the world.[3,4]

Received: 15 December 2023
Accepted: 22 April 2024
Published: 2 May 2024

KPC and NDM belong to different carbapenemase classes. The infection caused by KPC-producing organisms has been partially solved by the introduction of newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam. This solution is limited because these newer β-lactamase inhibitors could not cover NDM. In addition, NDM is able to hydrolyze all β-lactams except monobactams, while KPC can also deactivate monobactams.[5–7] Thus, the emergence of KPC-NDM-CRKPs results in higher level of antimicrobial resistance and extremely limited treatment options, which may further lead to increased mortality rates.[3,8]

However, several studies have been conducted on risk factors and clinical outcomes for CRKP bloodstream infections (BSIs).[9] The results of risk factors are highly heterogeneous, and deaths attributable to CRKP BSIs vary from 20% to 45%.[10,11] To the best of our knowledge, no studies have focused on BSIs caused by KPC-NDM-CRKPs. The identification of risk factors and mortality of infections caused by KPC-NDM-CRKPs is important to highlight the significance of epidemiologic surveillance and clinical awareness of this pathogen. Thus, we have conducted a study to compare the risk factors, molecular characteristics, and mortality involved in clinical BSIs caused by KPC-NDM-CRKP and KPC-CRKP strains.

Materials and Methods

Study Design

The study was conducted at Jinling Hospital, a teaching hospital in Nanjing, mainland China, with a 2500-bed capacity. Clinically isolated CRKPs of BSIs were continuously collected over three years, from January 1, 2020, to December 31, 2022. Only the first bacteremia episode for each patient was included in this retrospective study.

Study Population and Data Collection

All hospitalized patients (aged ≥ 16 years) with BSIs caused by CRKP were included in this study. Data were collected from the medical records, including gender and age, underlying diseases (solid cancer, hypertension, cardiovascular disease, gastrointestinal fistula, diabetes mellitus, chronic liver disease, fatty liver, biliary tract disease, chronic renal failure, neurologic disorder, trauma, and malnutrition), surgery performed in the past 30 days prior to CRKP isolation, probable source of BSI, empirical antibiotic treatment, days of hospitalization prior to CRKP isolation, total length of hospital stay, and ICU stay. BSI episodes were classified as community- or ICU-acquired, as previously described.[11] Appropriate empirical treatment was defined as the use of at least one active antimicrobial agent within 72 hours of BSI onset, and the dose was up to current medical standards.

Laboratory data including white blood cell (WBC) count, neutrophilic granulocyte percentage (NEUT%), C-reactive protein (CRP), procalcitonin (PCT), platelet count, and albumin were also obtained at the time of the first positive BSI episode. In addition, the severity of illness at the onset of BSI was estimated by the Pitt bacteremia score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The presence of sepsis or septic shock was also assessed by Sepsis 3.0 when bacteremia occurred.[12] The outcome was measured as 30-day mortality, which was defined as the death occurring within 30 days after the onset of CRKP BSI.

Microbiological Methods

CRKP was defined as *K. pneumoniae* harboring the carbapenemase genes or having a minimum inhibitory concentration (MIC) of ≥ 2 mg/L for ertapenem, ≥ 4 mg/L for imipenem or meropenem, according to Clinical and Laboratory Standards Institute guidelines (CLSI-M100, 2020). Confirmation of the *K. pneumoniae* isolates and antimicrobial susceptibility testing were performed using the Vitek 2 system (bioMe´rieux, Marcy l'Etoile, France). Polymerase chain reaction (PCR) and NG-test Carba 5 (NG Biotech, Guipry, France) were used to determine the presence of carbapenemase genes, including bla_{KPC}, bla_{NDM}, bla_{IMP}, bla_{VIM}, and $bla_{OXA\text{-}48\text{-}like}$.[13,14] The PCR primers were based on previous references.[9]

The following antimicrobial agents were tested: piperacillin-tazobactam, cefoperazone-sulbactam, ceftazidime, cefepime, aztreonam, ertapenem, imipenem, meropenem, amikacin, tobramycin, ciprofloxacin, levofloxacin, doxycycline, minocycline, tigecycline, colistin, and trimethoprim-sulfamethoxazole. The interpretive criteria 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 MICs were interpreted according to CLSI breakpoints (M100, 2020). *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 were used as quality controls.

Genomic DNA extraction of 242 CRKP isolates was performed with the TIANamp Bacteria DNA Kit (Tiangen Biotech) and subjected to whole-genome sequencing (WGS) on the Illumina NovaSeq PE150 platform. Assemblies were performed using SPAdes (version 3.13.0). Kleborate (version 2.3.0),[15] ResFinder,[16] and CARD[17] were used to determine multilocus sequence typing (MLST), resistance and virulence determinants. All sequence data have been submitted to the National Center for Biotechnology Information (NCBI) database under BioProject PRJNA1092646.

Statistical Analysis

Data were expressed as the medians with interquartile range (IQR), the means ± standard deviation (SD), or n (%) as appropriate. Categorical variables were analyzed by the χ^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 used to identify risk factors for KPC-NDM-CRKP BSIs and independent predictors of 30-day mortality. All variables with $P < 0.1$, age, and sex were included in the multivariate model in a forward stepwise with the use of the likelihood-ratio test. All statistical analyses were performed by SPSS software (Version 25.0). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Clinical Characteristics of Patients with CRKP BSIs

A total of 242 consecutive cases of CRKP BSIs were collected over three years, between January 1, 2020, and December 31, 2022. Overall, 231 patients were included in this study: 25 patients with KPC-NDM-CRKP BSIs and 206 patients with KPC-CRKP BSIs. One isolate coharboring $bla_{\text{KPC-2}}$ and $bla_{\text{OXA-232}}$, as well as three isolates carrying $bla_{\text{NDM-1}}$, one isolate carrying $bla_{\text{NDM-5}}$, and six isolates carrying $bla_{\text{OXA-232}}$ were excluded due to the small sample size (Supplementary Figure 1).

The number of CRKP isolates included in this study was 84 in 2020, 68 in 2021, and 79 in 2022. The proportion of KPC-NDM-CRKP isolates was 11.9% (10/84) in 2020, 13.2% (9/68) in 2021, and 7.6% (6/79) in 2022 (Supplementary Figure 2). The mean age was 52.3 ± 15.3 years old, with a male predominance (n = 177, 76.6%), and 140 cases (60.6%) were ICU-acquired BSIs. The most common underlying diseases were gastrointestinal fistula (n = 91, 39.4%), biliary tract disease (n = 79, 34.2%), hypertension (n = 76, 32.9%), and diabetes mellitus (n = 51, 22.1%). Ninety-two (39.8%) patients underwent surgery in the past 30 days prior to CRKP isolation.

The main sources of CRKP BSIs were abdomen (n = 177, 76.6%) and respiratory tract (n = 40, 17.3%). A total of 121 patients (52.4%) developed sepsis or septic shock at BSI onset. The three major antimicrobial agents of empirical treatment were carbapenem-containing regimens (n = 177, 76.6%), tigecycline-containing regimens (n = 75, 32.5%), and colistin-containing regimens (n = 56, 24.2%). The length of hospital stay was 41 (25–67) days and the duration of ICU stay was 30 (13–51) days.

Risk Factors Associated with KPC-NDM-CRKP BSIs

The clinical characteristics of KPC-NDM-CRKP and KPC-CRKP bacteremia are shown in Table 1. The mean age was comparable between patients with KPC-NDM-CRKP and KPC-CRKP BSIs. A male preponderance was observed in both groups. Neither sex nor age were associated with KPC-NDM-CRKP BSIs. ICU-acquired BSIs were identified in more KPC-NDM-CRKP patients (21/25, 84%) than in KPC-CRKP patients (119/206, 57.8%) ($P = 0.011$). Comparing KPC-NDM-CRKP BSIs to KPC-CRKP BSIs, the percentage of patients with hypertension or surgery within 30 days or longer hospitalization before CRKP isolation was higher, although the difference was not statistically significant ($0.05 < P < 0.1$).

When entering the multivariate regression analysis, ICU-acquired BSIs (95% CI 1.216–11.631; $P = 0.021$), surgery within 30 days (95% CI 1.055–6.203; $P = 0.038$), and longer stay of hospitalization prior to CRKP isolation (95% CI 1.003–1.047; $P = 0.023$) were more likely to get KPC-NDM-CRKP BSIs (Table 2).

Table 1 Clinical Characteristics and Infection Data of Patients with BSIs Caused by KPC-NDM-CRKP and KPC-CRKP

Characteristics	KPC-NDM-CRKP BSI (n=25)	KPC-CRKP BSI (n=206)	*P* value
Age, years, mean ± SD	54.2 ± 12.3	52.1 ± 15.7	0.546
Male sex	21 (84%)	156 (75.7%)	0.356
Acquisition			
Community-acquired	0	6 (2.9%)	1.000
ICU-acquired	21 (84%)	119 (57.8%)	0.011*
Underlying conditions			
Solid cancer	3 (12%)	27 (13.1%)	1.000
Hypertension	12 (48%)	64 (31.1%)	0.089
Cardiovascular disease	4 (16%)	30 (14.6%)	1.000
Neurologic disorder	1 (4%)	38 (18.4%)	0.124
Diabetes mellitus	3 (12%)	48 (23.3%)	0.198
Gastrointestinal fistula	12 (48%)	79 (38.3%)	0.351
Chronic renal failure	1 (4%)	14 (6.8%)	0.916
Fatty liver	2 (8%)	24 (11.7%)	0.833
Chronic liver disease	3 (12%)	19 (9.2%)	0.932
Biliary tract disease	8 (32%)	71 (34.5%)	0.806
Malnutrition	2 (8%)	27 (13.1%)	0.683
Trauma	6 (24%)	28 (13.6%)	0.277
Surgery within 30 days	14 (56%)	78 (37.9%)	0.080
Source of BSI			
Respiratory tract	1 (4%)	39 (18.9%)	0.113
Abdomen	22 (88%)	155 (75.2%)	0.155
Urinary tract	1 (4%)	9 (4.4%)	1.000
Skin and soft tissue	1 (4%)	3 (1.5%)	0.370
Infection data			
WBC count, $\times 10^9$/L, median (IQR)	9.2 (4.8–18.5)	10.1 (6.5–15.1)	0.796
Albumin, g/L, mean ± SD	31.1 ± 4.7	31.4 ± 5.0	0.794
PCT, μg/L, median (IQR)	11.8 (1.8–28.5)	3.6 (1–13.5)	0.117
CRP, mg/L, median (IQR)	147.6 (74.9–204.6)	143.2 (90.2–204)	0.872
Platelet count, $\times 10^9$/L, median (IQR)	133 (47–238.5)	171 (90.2–251.2)	0.619
NEUT%, median (IQR)	90.4 (77.6–93.6)	88.8 (83.5–93)	0.877
Hospital stay prior to CRKP isolation, median (IQR)	20 (8–32.5)	15 (5–25)	0.099
ICU stay, median (IQR)	32 (18.5–67.5)	29 (11–51)	0.162
Full hospital stay, median (IQR)	42 (19.5–89)	40.5 (25–66)	0.761
APACHE II score at infection onset, median (IQR)	17 (8.5–21)	11 (7–18)	0.192
Pitt bacteremia score at infection onset, median (IQR)	4 (2–5)	2 (0–4)	0.023*
Sepsis/septic shock at infection onset	16 (64%)	105 (51%)	0.218
Empirical therapy			
Monotherapy	5 (20%)	69 (33.5%)	0.172
Combination therapy	20 (80%)	137 (66.5%)	0.172
Fluoroquinolone-containing regimens	4 (16%)	27 (13.1%)	0.928
Aminoglycoside-containing regimens	3 (12%)	12 (5.8%)	0.451
Cephalosporin-containing regimens	0	11 (5.3%)	0.492
Carbapenem-containing regimens	16 (64%)	161 (78.2%)	0.114
Tigecycline-containing regimens	9 (36%)	66 (32%)	0.690
Colistin-containing regimens	6 (24%)	50 (24.3%)	0.976
Ceftazidime-avibactam-containing regimens	6 (24%)	20 (9.7%)	0.072
Inappropriate empirical treatment	14 (56%)	120 (58.3%)	0.829
30-day mortality	14 (56%)	67 (32.5%)	0.020*

Notes: Data are presented as No. (%) of patients unless otherwise specified. *$P < 0.05$, the comparison between KPC-NDM-CRKP BSI and KPC-CRKP BSI.

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; KPC-NDM-CRKP, KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*; KPC-CRKP, KPC-producing carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; ICU, intensive care unit; 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.

Table 2 Multivariable Logistic Regression of Risk Factors Independently Associated with KPC-NDM-CRKP BSIs

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.009 (0.982–1.037)	0.501		
Male	1.683 (0.551–5.135)	0.361		
ICU-acquired	3.838 (1.272–11.582)	0.017*	3.761 (1.216–11.631)	0.021*
Hypertension	2.048 (0.886–4.736)	0.094		
Surgery within 30 days	2.089 (0.903–4.830)	0.085	2.558 (1.055–6.203)	0.038*
Hospital stay prior to CRKP isolation	1.023 (1.003–1.043)	0.023*	1.025 (1.003–1.047)	0.023*

Notes: *$P < 0.05$.
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; KPC-NDM-CRKP, KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Percentage of Antimicrobial Resistance of KPC-NDM-CRKP and KPC-CRKP Strains

Overall, both KPC-NDM-CRKP and KPC-CRKP strains exhibited high antimicrobial-resistant rates for piperacillin-tazobactam (231/231, 100%), cefoperazone-sulbactam (229/231, 99.1%), ceftazidime (230/231, 99.6%), cefepime (229/231, 99.1%), aztreonam (231/231, 100%), ertapenem (231/231, 100%), imipenem (231/231, 100%), meropenem (231/231, 100%), tobramycin (191/231, 82.7%), ciprofloxacin (230/231, 99.6%), and levofloxacin (229/231, 99.1%). For KPC-NDM-CRKPs, 32% (8/25) were resistant to tigecycline, and 12% (3/25) were resistant to colistin. For KPC-CRKPs, 35.4% (73/206) were resistant to tigecycline, and 9.7% (20/206) were resistant to colistin. It is noteworthy that KPC-NDM-CRKP isolates had significantly higher resistance rates to amikacin and trimethoprim-sulfamethoxazole than those of KPC-CRKP isolates ($P = 0.004$ and < 0.001, respectively). Nevertheless, the antimicrobial resistance rate to doxycycline of KPC-CRKP isolates was significantly higher than that of KPC-NDM-CRKP isolates (168/206, 81.6% vs 11/25, 44%, $P < 0.001$) (Table 3).

Table 3 Percentage of Antimicrobial Resistance of CRKP Strains

Antimicrobial agents	KPC-NDM-CRKP (n=25)	KPC-CRKP (n=206)	*P* value
Piperacillin-tazobactam	25 (100%)	206 (100%)	NA
Cefoperazone-sulbactam	25 (100%)	204 (99%)	1.000
Ceftazidime	25 (100%)	205 (99.5%)	1.000
Cefepime	25 (100%)	204 (99%)	1.000
Aztreonam	25 (100%)	206 (100%)	NA
Ertapenem	25 (100%)	206 (100%)	NA
Imipenem	25 (100%)	206 (100%)	NA
Meropenem	25 (100%)	206 (100%)	NA
Amikacin	24 (96%)	140 (68%)	0.004*
Tobramycin	24 (96%)	167 (81.1%)	0.113
Ciprofloxacin	25 (100%)	205 (99.5%)	1.000
Levofloxacin	25 (100%)	204 (99%)	1.000
Doxycycline	11 (44%)	168 (81.6%)	< 0.001*
Minocycline	16 (64%)	165 (80.1%)	0.065
Tigecycline	8 (32%)	73 (35.4%)	0.734
Colistin	3 (12%)	20 (9.7%)	0.994
Trimethoprim-sulfamethoxazole	25 (100%)	110 (53.4%)	< 0.001*

Notes: Data are presented as No. (%) of patients. *$P < 0.05$, the comparison between KPC-NDM-CRKPs and KPC-CRKPs.
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; KPC-NDM-CRKP, KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*; KPC-CRKP, KPC-producing carbapenem-resistant *Klebsiella pneumoniae*; NA, not available.

Molecular Characteristics of KPC-NDM-CRKP and KPC-CRKP Isolates

Among the 231 CRKP isolates, nine STs were represented. The most prevalent ST in KPC-NDM-CRKP isolates was ST11 (23/25, 92%), followed by ST15 (2/25, 8%). In KPC-CRKP isolates, ST11 was the most dominant, with a prevalence of 82.5% (n = 170), followed by ST15 (13.6%, 28/206), ST2237 (n = 2), ST17 (n = 1), ST111 (n = 1), ST551 (n = 1), ST1027 (n = 1), ST2286 (n = 1), and ST5422 (n = 1). The majority of KPC-NDM-CRKP isolates were KPC-2-NDM-5-CRKP (n = 22, 88%), with KPC-2-NDM-1-CRKP (n = 3, 12%) being the next most common. The $bla_{\text{KPC-2}}$ gene was detected in 205 (99.5%) out of 206 KPC-CRKP isolates and only one isolate carried the $bla_{\text{KPC-12}}$ gene (Supplementary Figure 2).

Outcome Study

The overall 30-day mortality rate was 35.1% (81/231). KPC-NDM-CRKP and KPC-CRKP BSIs had 30-day mortality rates of 56% (14/25) and 32.5% (67/206), respectively ($P = 0.02$). Identification of clinical characteristics and microbiological features associated with 30-day mortality was also performed in both the KPC-NDM-CRKP BSIs group and the KPC-CRKP BSIs group. As presented in Table 4, age ($P = 0.001$), ICU-acquired BSIs ($P < 0.001$), underlying disease with hypertension ($P < 0.001$) or biliary tract disease ($P = 0.034$), laboratory data including PCT ($P < 0.001$), CRP ($P < 0.001$), platelet count ($P < 0.001$), and NEUT% ($P < 0.001$) at BSI onset, the length of full hospital stay ($P < 0.001$) and ICU stay ($P = 0.006$), the APACHE II score ($P < 0.001$) and the Pitt bacteremia score ($P < 0.001$) at BSI onset, the presence of sepsis or septic shock at BSI onset ($P < 0.001$), BSIs caused by KPC-NDM-CRKP ($P = 0.02$), empirical combination antimicrobial therapy ($P = 0.003$), colistin-containing empirical treatment ($P = 0.007$), and inappropriate empirical treatment ($P = 0.005$) were associated with 30-day mortality in the cases of CRKP BSIs.

Univariate analysis demonstrated that older age (95% CI 1.012–1.051; $P = 0.001$), hypertension (95% CI 1.600–5.027; $P < 0.001$), biliary tract disease (95% CI 1.044–3.218; $P = 0.035$), higher levels of inflammation markers at BSI onset including PCT (95% CI 1.009–1.037; $P = 0.001$), CRP (95% CI 1.005–1.012; $P < 0.001$), NEUT% (95% CI 1.040–1.143; $P < 0.001$), and platelet count (95% CI 0.990–0.996; $P < 0.001$), ICU-acquired BSIs (95% CI 2.156–7.656; $P < 0.001$), BSIs caused by KPC-NDM-CRKPs (95% CI 1.138–6.127; $P = 0.024$), higher APACHE II score at infection onset (95% CI 1.256–1.458; $P < 0.001$), higher Pitt bacteremia score at infection onset (95% CI 1.383–1.810; $P < 0.001$), the presence of sepsis or septic shock at infection onset (95% CI 4.844–18.920; $P < 0.001$), empirical combination antimicrobial therapy (95% CI 1.353–4.848; $P = 0.004$), colistin-containing empirical treatment (95% CI 1.244–4.258; $P = 0.008$), and inappropriate empirical treatment (95% CI 0.265–0.797; $P = 0.006$) were associated with 30-day mortality (Table 5).

Multivariate analysis further demonstrated that ICU-acquired BSIs (95% CI 2.707–38.559; $P = 0.001$), APACHE II score at BSI onset (95% CI 1.288–1.599; $P < 0.001$), and BSIs caused by KPC-NDM-CRKP (95% CI 1.103–63.270; $P = 0.04$) were independent predictors for 30-day mortality in patients with CRKP bacteremia. Patients with longer length of full hospital stay (95% CI 0.937–0.999; $P = 0.043$) and ICU stay (95% CI 0.921–0.996; $P = 0.03$) had a significantly lower risk of nonsurvival (Table 5).

Discussion

To our knowledge, this is the first systematic study on KPC-NDM-CRKP, which provides the most comprehensive understanding of KPC-NDM-CRKP BSIs, including risk factors, molecular characteristics, and clinical outcomes. In this study, the 30-day mortality ranged from 32.5% in patients with KPC-CRKP BSIs to 56% in those with KPC-NDM-CRKP BSIs. These findings have remarkable importance and novelty.

CRKP represents a devastating threat to global public health and clinical settings.[18–20] The prevalence of meropenem-resistant *K. pneumoniae* has increased rapidly in China, from 2.9% in 2005 to 24.2% in 2022, according to the China Antimicrobial Surveillance Network (CHINET, http://www.chinets.com/). According to an antimicrobial resistance surveillance study from the Swiss ICU, carbapenem-resistant Enterobacterales (CRE) have been steadily increasing from 1% to 5% between 2008 and 2019.[21] The most common mechanism underlying carbapenem resistance in CRKP is the production of carbapenemases, including class A carbapenemases (mainly KPC), class B metallo-β-lactamases (MBLs, mainly NDM), and some class D OXA-48-like carbapenemases (mainly OXA-181 and OXA-232).[22,23]

Table 4 Clinical and Microbiological Characteristics Associated with 30-Day Mortality of CRKP BSIs

Characteristics	All CRKP BSIs			KPC-NDM-CRKP BSIs			KPC-CRKP BSIs		
	Death (n=81)	Survivors (n=150)	*P* value	Death (n=14)	Survivors (n=11)	*P* value	Death (n=67)	Survivors (n=139)	*P* value
Age, years, mean ± SD	56.8 ± 13.4	49.9 ± 15.8	0.001*	56.6 ± 10.7	51.2 ± 14.1	0.280	56.8 ± 14	49.8 ± 15.9	0.002*
Male sex	65 (80.2%)	112 (74.7%)	0.339	11 (78.6%)	10 (90.9%)	0.775	54 (80.6%)	102 (73.4%)	0.258
Acquisition									
Community-acquired	1 (1.2%)	5 (3.3%)	0.601	0	0	NA	1 (1.5%)	5 (3.6%)	0.690
ICU-acquired	65 (80.2%)	75 (50.0%)	< 0.001*	13 (92.9%)	8 (72.7%)	0.416	52 (77.6%)	67 (48.2%)	< 0.001*
Underlying conditions									
Solid cancer	10 (12.3%)	20 (13.3%)	0.831	1 (7.1%)	2 (18.2%)	0.823	9 (13.4%)	18 (12.9%)	0.923
Hypertension	39 (48.1%)	37 (24.7%)	< 0.001*	9 (64.3%)	3 (27.3%)	0.066	30 (44.8%)	34 (24.5%)	0.003*
Cardiovascular disease	16 (19.8%)	18 (12.0%)	0.112	2 (14.3%)	2 (18.2%)	1.000	14 (20.9%)	16 (11.5%)	0.074
Neurologic disorder	16 (19.8%)	23 (15.3%)	0.392	0	1 (9.1%)	0.440	16 (23.9%)	22 (15.8%)	0.163
Diabetes mellitus	15 (18.5%)	36 (24.0%)	0.338	2 (14.3%)	1 (9.1%)	1.000	13 (19.4%)	35 (25.2%)	0.358
Gastrointestinal fistula	34 (42.0%)	57 (38.0%)	0.555	6 (42.9%)	6 (54.5%)	0.561	28 (41.8%)	51 (36.7%)	0.481
Chronic renal failure	8 (9.9%)	7 (4.7%)	0.125	1 (7.1%)	0	1.000	7 (10.4%)	7 (5.0%)	0.250
Fatty liver	5 (6.2%)	21 (14.0%)	0.072	1 (7.1%)	1 (9.1%)	1.000	4 (6%)	20 (14.4%)	0.078
Chronic liver disease	8 (9.9%)	14 (9.3%)	0.893	2 (14.3%)	1 (9.1%)	1.000	6 (9%)	13 (9.4%)	0.926
Biliary tract disease	35 (43.2%)	44 (29.3%)	0.034*	6 (42.9%)	2 (18.2%)	0.378	29 (43.3%)	42 (30.2%)	0.064
Malnutrition	12 (14.8%)	17 (11.3%)	0.446	0	2 (18.2%)	0.183	12 (17.9%)	15 (10.8%)	0.156
Trauma	11 (13.6%)	23 (15.3%)	0.720	2 (14.3%)	4 (36.4%)	0.417	9 (13.4%)	19 (13.7%)	0.963
Surgery within 30 days	33 (40.7%)	59 (39.3%)	0.835	7 (50%)	7 (63.6%)	0.783	26 (38.8%)	52 (37.4%)	0.847
Source of BSI									
Respiratory tract	19 (23.5%)	21 (14.0%)	0.070	1 (7.1%)	0	1.000	18 (26.9%)	21 (15.1%)	0.044*
Abdomen	61 (75.3%)	116 (77.3%)	0.729	13 (92.9%)	9 (81.8%)	0.823	48 (71.6%)	107 (77.0%)	0.406
Urinary tract	1 (1.2%)	9 (6.0%)	0.174	0	1 (9.1%)	0.440	1 (1.5%)	8 (5.8%)	0.299
Skin and soft tissue	0	4 (2.7%)	0.340	0	1 (9.1%)	0.440	0	3 (2.2%)	0.552
Infection and microbiological data									
WBC count, $\times 10^9$/L, median (IQR)	10.8 (7.4–17.2)	9.2 (6.3–14.4)	0.222	9.7 (4.5–19.9)	9.2 (5.1–17.5)	0.979	10.8 (7.5–16)	9.3 (6.3–14.3)	0.163
Albumin, g/L, mean ± SD	31.6 ± 5.5	31.2 ± 4.6	0.563	31.4 ± 5.5	30.7 ± 3.5	0.695	31.6 ± 5.6	31.2 ± 4.7	0.602
PCT, μg/L, median (IQR)	9.2 (2.7–25.1)	2.1 (0.7–13.5)	< 0.001*	13.4 (6.5–36.9)	5.7 (0.7–13.5)	0.120	7.7 (2.6–24.8)	1.9 (0.7–13.5)	< 0.001*
CRP, mg/L, median (IQR)	182.4 (128–250.7)	129.6 (66.9–182.4)	< 0.001*	184.6 (136.3–250.6)	67.7 (39.8–154.1)	0.014*	180 (127.4–252.6)	130.7 (70.7–184.2)	< 0.001*
Platelet count, $\times 10^9$/L, median (IQR)	94 (44–169.5)	206 (108.5–277.8)	< 0.001*	81 (37.8–179.8)	231 (76–401)	0.051	94 (49–170)	205 (110–277)	< 0.001*
NEUT%, median (IQR)	91.2 (86.5–94.2)	87.1 (81.4–92.2)	< 0.001*	91.7 (85.6–94.5)	82.6 (74.5–93)	0.166	91.1 (86.6–93.9)	87.3 (82.2–92.1)	< 0.001*
Hospital stay prior to CRKP isolation, median (IQR)	16 (9–25.5)	15 (4–26.2)	0.416	18 (10.2–32)	25 (7–33)	0.767	15 (8–25)	15 (4–25)	0.483
Full hospital stay, median (IQR)	28 (18–37.5)	54.5 (34.8–82.2)	< 0.001*	24.5 (17.2–41.8)	83 (43–140)	0.004*	29 (18–38)	54 (34–76)	< 0.001*
ICU stay, median (IQR)	24 (13–35)	37 (13–63.5)	0.006*	24.5 (17.2–39)	50 (19–121)	0.120	24 (11–35)	33 (12–62)	0.011*
APACHE II score at infection onset, median (IQR)	19 (16.5–23)	9 (6–12)	< 0.001*	19 (16.8–23)	6 (4–13)	< 0.001*	18 (16–23)	9 (6–12)	< 0.001*
Pitt bacteremia score at infection onset, median (IQR)	5 (3–7)	1.5 (0–3)	< 0.001*	5 (4–8)	2 (0–3)	< 0.001*	4 (3–6)	1 (0–3)	< 0.001*
Sepsis/septic shock at infection onset	68 (84.0%)	53 (35.3%)	< 0.001*	12 (85.7%)	4 (36.4%)	0.033*	56 (83.6%)	49 (35.3%)	< 0.001*
KPC-NDM-CRKP	14 (17.3%)	11 (7.3%)	0.020*	—	—	—	—	—	—

(*Continued*)

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Table 4 (Continued).

Characteristics	All CRKP BSIs			KPC-NDM-CRKP BSIs			KPC-CRKP BSIs		
	Death (n=81)	Survivors (n=150)	*P* value	Death (n=14)	Survivors (n=11)	*P* value	Death (n=67)	Survivors (n=139)	*P* value
Empirical therapy									
Combination therapy	65 (80.2%)	92 (61.3%)	0.003*	13 (92.9%)	7 (63.6%)	0.190	52 (77.6%)	85 (61.2%)	0.019*
Carbapenem-containing regimens	66 (81.5%)	111 (74.0%)	0.200	9 (64.3%)	7 (63.6%)	1.000	57 (85.1%)	104 (74.8%)	0.095
Tigecycline-containing regimens	32 (39.5%)	43 (28.7%)	0.093	4 (28.6%)	5 (45.5%)	0.650	28 (41.8%)	38 (27.3%)	0.037*
Colistin-containing regimens	28 (34.6%)	28 (18.7%)	0.007*	6 (42.9%)	0	0.043*	22 (32.8%)	28 (20.1%)	0.047*
Ceftazidime-avibactam-containing regimens	13 (16.0%)	13 (8.7%)	0.090	4 (28.6%)	2 (18.2%)	0.895	9 (13.4%)	11 (7.9%)	0.210
Inappropriate empirical treatment	37 (45.7%)	97 (64.7%)	0.005*	6 (42.9%)	8 (72.7%)	0.277	31 (46.3%)	89 (64%)	0.015*

Notes: Data are presented as No. (%) of patients unless otherwise specified. *$P < 0.05$ compared with survivors.

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; KPC-NDM-CRKP, KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*; KPC-CRKP, KPC-producing carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; ICU, intensive care unit; 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; NA, not available.

Table 5 Multivariate Analysis for Predictors of 30-Day Mortality in Patients with CRKP BSIs

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.031 (1.012–1.051)	0.001*		
ICU-acquired	4.062 (2.156–7.656)	< 0.001*	10.216 (2.707–38.559)	0.001*
Hypertension	2.836 (1.600–5.027)	< 0.001*	2.705 (0.974–7.511)	0.056
Fatty liver	0.404 (0.146–1.116)	0.080		
Biliary tract disease	1.833 (1.044–3.218)	0.035*		
Respiratory tract	1.882 (0.944–3.755)	0.073		
PCT	1.023 (1.009–1.037)	0.001*		
CRP	1.008 (1.005–1.012)	< 0.001*		
Platelet count	0.993 (0.990–0.996)	< 0.001*		
NEUT%	1.090 (1.040–1.143)	< 0.001*		
Full hospital stay	0.958 (0.944–0.972)	< 0.001*	0.967 (0.937–0.999)	0.043*
ICU stay	0.981 (0.971–0.992)	0.001*	0.958 (0.921–0.996)	0.030*
APACHE II score at infection onset	1.353 (1.256–1.458)	< 0.001*	1.435 (1.288–1.599)	< 0.001*
Pitt bacteremia score at infection onset	1.582 (1.383–1.810)	< 0.001*		
Sepsis/septic shock at infection onset	9.573 (4.844–18.920)	< 0.001*		
KPC-NDM-CRKP	2.640 (1.138–6.127)	0.024*	8.355 (1.103–63.270)	0.040*
Combination therapy	2.561 (1.353–4.848)	0.004*		
Tigecycline-containing regimens	1.625 (0.920–2.870)	0.094		
Colistin-containing regimens	2.302 (1.244–4.258)	0.008*		
Ceftazidime-avibactam-containing regimens	2.015 (0.886–4.583)	0.095		
Inappropriate empirical treatment	0.459 (0.265–0.797)	0.006*		

Notes: *$P < 0.05$.

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; KPC-NDM-CRKP, KPC and NDM co-producing carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; ICU, intensive care unit; PCT, procalcitonin; CRP, C-reactive protein; NEUT%, neutrophilic granulocyte percentage; APACHE, acute physiologic and chronic health evaluation; OR, odds ratio; CI, confidence interval.

Several recent studies have reported CRKPs carrying multiple carbapenemase genes.[24] KPC and NDM belong to different carbapenemase classes. KPCs hydrolyze penicillins, cephalosporins, carbapenems, and monobactams. Newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam, have activity against most KPC-CRKP isolates. On the contrary, NDMs hydrolyze penicillins, cephalosporins, and carbapenems, but not monobactams. Neither ceftazidime-avibactam, meropenem-vaborbactam, nor imipenem-cilastatin-relebactam has activity against NDM-CRKP isolates.[6,25] Thus, the synergistic effect of KPC and NDM results in higher level of antimicrobial resistance and extremely limited treatment options, which may further lead to increased mortality rates.

Until 2020, the prevalence of KPC-NDM-CRKP strains was significantly lower than that of KPC-CRKP or NDM-CRKP. The Chinese Carbapenem-resistant Enterobacteriaceae (CRE) Network detected a total of seven strains of KPC-2-NDM-1-CRKP (0.34%) within a collection of 2057 CRKP isolated from 2012 to 2017 in China.[3] Only three KPC-NDM-CRKPs (0.06%) were identified out of 4635 *K. pneumoniae* species complex bloodstream isolates that were collected between 2014 and 2019, according to the Blood Bacterial Resistant Investigation Collaborative System (BRICS) in China.[26] In the United States, the Centers for Disease Control and Prevention (CDC) and the Antibiotic Resistance Laboratory Network (AR Lab Network) reported 12 cases of KPC-NDM-CRKP infections between 2012 and 2019.[24] An epidemiological study in the United States reported the trends of carbapenemases among CRE. A total of 27,834 Enterobacterales isolates were collected from 74 US medical centers consecutively between 2019 and 2021. Three *K. pneumoniae* isolates had two carbapenemases: one carrying $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-181}}$, and two isolates carrying $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$, with none of KPC-NDM-CRKP detected.[27] In a surveillance study conducted in Europe, a total of 310 carbapenem-resistant or intermediate *K. pneumoniae* isolates were collected in 15 Greek hospitals from 2013 to 2022. The presence of $bla_{\text{KPC-2}}$ in different combinations with $bla_{\text{NDM-1}}$, $bla_{\text{OXA-48}}$, and/or $bla_{\text{VIM-1}}$ was observed in 24 specimens.[28]

Unfortunately, sporadic cases of KPC-NDM-CRKP strains have been increasingly reported worldwide in recent years. In 2021, Huang et al reported that a KPC-2-producing *K. pneumoniae* strain acquired a $bla_{\text{NDM-5}}$-harbouring plasmid during ceftazidime/avibactam treatment.[29] The emergence of CRKP coharboring $bla_{\text{KPC-3}}$ and $bla_{\text{NDM-1}}$,[30] CRKP coharboring $bla_{\text{KPC-2}}$ and $bla_{\text{NDM-6}}$,[31] hypervirulent CRKP coharboring $bla_{\text{KPC-2}}$ and $bla_{\text{NDM-1}}$,[32] tigecycline-resistant hypervirulent *K. pneumoniae* cocarrying $bla_{\text{KPC-2}}$ and $bla_{\text{NDM-5}}$,[33] polymyxin B-resistant hypervirulent *K. pneumoniae* coharboring $bla_{\text{KPC-2}}$ and $bla_{\text{NDM-1}}$,[34] and CRKP coharboring $bla_{\text{KPC-2}}$, $bla_{\text{NDM-1}}$, and *tmexCD1-toprJ1* have been successively reported.[35]

The proportion of KPC-NDM-CRKP isolates was 10.8%, which was 30 times higher than that reported in the previous study. Additionally, 20 isolates of ST11 KPC-2-NDM-5-CRKP, three isolates of ST11 KPC-2-NDM-1-CRKP, and two isolates of ST15 KPC-2-NDM-5-CRKP were identified in the present study. Combined, these data suggested that the nosocomial infection transmission might contribute to the extraordinary high prevalence and mortality of KPC-NDM-CRKPs. Therefore, infection prevention and control measures should be taken to prevent pathogen transmission and reduce the risk of death. The basic operations include the isolation management of infected patients, ensuring hand hygiene, periodic environmental cleansing, and equipment disinfection.

KPC-NDM-CRKP has been increasingly reported but has not yet been systematically studied. Several studies have been conducted on risk factors for CRKP BSIs but have combined heterogeneous data with different carbapenemase types (including KPC, NDM, and OXA-48-like).[36] Previous studies have shown that both ICU-acquired, length of hospital stay and operation history increased the risk of CRKP infection compared with carbapenem-susceptible *K. pneumoniae* (CSKP),[9,37] while our study found that these also increased the risk of KPC-NDM-CRKP infection compared with KPC-CRKP. Multicenter prospective studies with larger samples should be performed to identify more risk factors for KPC-NDM-CRKP infection.

In addition, there was little information on infection data for BSIs caused by KPC-NDM-CRKPs. The levels of inflammation markers, including WBC count, NEUT%, PCT, CRP, albumin, and platelet count, exhibited no significant differences between the two groups. The patients who suffered KPC-NDM-CRKP BSIs appeared significantly higher in the Pitt bacteremia score at infection onset ($P = 0.023$). However, no statistically significant differences were observed in the APACHE II score ($P = 0.192$) or the occurrence of sepsis or septic shock at the onset of BSIs ($P = 0.218$) in both groups.

Several studies have also described an increased mortality of CRKP BSIs compared with CSKP BSIs. According to a meta-analysis of 37 papers published between 2009 and 2017, the overall mortality rate associated with KPC-CRKP infection was 41.0%, with oncology patients having the highest mortality rate at 56.0%.[38] A prospective cohort study in 19 Italian hospitals estimated the mortality attributable to different types of carbapenem-resistant gram-negative bacilli (GNB). The 30-day mortality rates were 26.6% and 36.4% in patients with BSIs caused by KPC-producing CRE and MBL-producing CRE, respectively.[10] However, currently, no research has been conducted to explicitly investigate the clinical outcomes of BSIs induced by KPC-NDM-CRKP. In the present study, BSIs caused by KPC-NDM-CRKP showed significantly higher 30-day mortality compared to KPC-CRKP BSIs (56%, 14/25 vs 32.5%, 67/206, $P = 0.02$). This observation is particularly significant given the changing epidemiology of CRKP on a global scale. At the outset of the study design, both KPC-CRKP and NDM-CRKP BSIs were assigned as control groups to investigate the synergistic effect of KPC and NDM in CRKPs. However, only four isolates carrying bla_{NDM} were detected using PCR and WGS during the three years, and one of four (25%) patients did not survive. Due to the limited sample size, the four patients with NDM-CRKP BSIs were excluded from this study.

Appropriate empirical therapy was associated with decreased risk of mortality in patients with CRKP BSIs.[39] However, receiving appropriate empirical antibiotics did not show a protective effect on the prognosis of patients who had CRKP BSIs in our study. During the study period, tigecycline-containing regimens (n = 75, 32.5%) and colistin-containing regimens (n = 56, 24.2%) were the major antibiotics administered for empirical treatment. Among 231 CRKP isolates, 35.1% (81/231) were resistant to tigecycline, and 10% (23/231) were resistant to colistin. Colistin and tigecycline had a lower resistance rate to CRKP isolates in our investigation.

Based on previous studies, the effectiveness of using tigecycline was comparable to other antimicrobial drugs in treating BSIs caused by CRKP with a MIC of 0.5 mg/L or below.[40] Nevertheless, only four isolates (1.7%) showed MICs of tigecycline $\leq$ 0.5 mg/L in our study. Moreover, tigecycline is not suggested for the treatment of CRE BSIs.[5] Although

colistin is the main available and in vitro susceptible antibiotic, several observational studies and randomized controlled trials have demonstrated that treatment with colistin in CRKP BSI patients is associated with higher mortality and increased nephrotoxicity relative to comparator agents.[41,42] Colistin is not recommended for treating infections caused by CRE.[5] All six patients in our study who had KPC-NDM-CRKP BSIs and were treated with colistin as initial therapy unfortunately did not survive. Not surprisingly, colistin-containing empirical treatment was a risk factor for 30-day mortality of CRKP BSI in univariate analysis (95% CI 1.244–4.258; $P = 0.008$). Additionally, a total of six patients (24%, 6/25) with KPC-NDM-CRKP BSIs received ceftazidime/avibactam as empirical therapy and four of these patients died. Therefore, the ability to detect and differentiate carbapenemases rapidly might be considered crucial for initial antibiotic therapy.[43]

Regarding the treatment of patients with KPC-NDM-CRKP, the preferable options can refer to the Infectious Diseases Society of America (IDSA) guidelines on MBL-producing CRE, which recommend a combination regimen of ceftazidime-avibactam and aztreonam or monotherapy of cefiderocol.[5] A recent meta-analysis including four articles with a moderate or serious risk of bias found that the combination of ceftazidime-avibactam and aztreonam was associated with lower 30-day mortality when compared to polymyxins in patients with MBL-producing CRE BSI.[44] Cefiderocol has a strong stability of carbapenemases. Two clinical trials including patients with MBL-producing infections showed that the clinical cure of cefiderocol was higher than that of alternate therapy (70.8% vs 40%).[45]

The main limitation of our study derives from its retrospective design and a relatively small study population. Given that it was a retrospective study, exposure history to antimicrobial agents, previous history of CRKP infection within 90 days prior to BSI, and CRKP colonization could not be obtained due to a lack of sufficient data. The relevant analysis for KPC-NDM-CRKP and KPC-CRKP subgroups was not implemented because of the limited sample size. Future studies could further investigate the risk factors and attributable mortality of patients with BSIs caused by KPC-NDM-CRKP after taking these factors into account.

Conclusion

In conclusion, our study included 231 patients, not a large number, but to date, it is the first and largest cohort to investigate the risk factors and outcomes of KPC-NDM-CRKP BSIs compared with KPC-CRKP BSIs, to our knowledge. Our data indicated that KPC-NDM-CRKP strains were strongly associated with clinical mortality in cases of BSIs. This finding highlights the need for increased attention, as the prevalence of KPC-NDM-CRKPs is growing globally.

Ethics Approval and Informed Consent

This retrospective study was conducted in accordance with the ethical standards of the Institutional Review Board Ethics Committee of Jinling Hospital (2022DZSKT-007) and the Declaration of Helsinki and national and institutional standards. The requirement to obtain informed written consent was waived because the biometric information and data in this study have been de-identified, and any information obtained during the investigation will be treated with the utmost confidentiality.

Funding

This work was supported by the National Natural Science Foundation of China (grant number 82272237), Jiangsu Provincial Medical Innovation Center (grant number CXZX202217), and Key Research and Development Program of Jiangsu Province (grant number BE2022823).

Disclosure

The authors report no conflicts of interest in this work.

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