Outcomes and Risk Factors of Bloodstream Infections Caused by Carbapenem-Resistant and Non-Carbapenem-Resistant *Klebsiella pneumoniae* in China

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**Purpose:** To compare antimicrobial resistance, virulence, clinical characteristics, and risk factors between carbapenem-resistant *K. pneumoniae* (CRKP) and carbapenem-susceptible *K. pneumoniae* (CSKP) isolates from patients with bloodstream infections (BSIs) in China.

**Patients and Methods:** The clinical data of 103 patients with *K. pneumoniae* BSI from 10 hospitals were retrospectively analyzed. The minimum inhibitory concentrations of 15 antibiotics against the bacteria were determined. A *Galleria mellonella* infection model was used to evaluate virulence of the isolates. Kaplan–Meier curves were calculated to evaluate the 28-day and in-hospital survival rates of the isolates. The risk factors for CRKP and CSKP infection and respective mortality rate were evaluated by univariate analysis, and independent risk factors were evaluated using the multivariate logistic regression model.

**Results:** Our results indicated that CRKP isolates were more resistant to most tested antibiotics than CSKP isolates. The *G. mellonella* infection model was used to demonstrate that CRKP isolates were more virulent than CSKP isolates. We found that in-hospital deaths occurred in 39.3% (22/56) of patients with CRKP BSIs and were significantly higher than those in patients with CSKP infections (19.1%, 9/47). Patients infected with CRKP isolates had poorer outcomes than those infected with the CSKP strains. For in-hospital mortality of CRKP BSIs, the independent risk factors included carbapenem-resistant Enterobacterales bacteremia and length of hospitalization after the onset of BSI.

**Conclusion:** Our findings confirm that CRKP isolates are more drug-resistant than CSKP isolates and are associated with poorer outcomes. To prevent CRKP infection, strict infection control strategies and active surveillance should be implemented in hospitals.

**Keywords:** *Klebsiella pneumoniae*, bloodstream infections, virulence, antimicrobial resistance

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**Introduction**

*Klebsiella pneumoniae* is the most common pathogen that causes bloodstream infections (BSIs), pneumonia, peritonitis, and urinary tract infections.1 The China Antimicrobial Resistance Surveillance Network revealed that the isolation rate of *K. pneumoniae* ranked second among gram-negative bacteria in 2020. The first case of carbapenem-resistant *K. pneumoniae* (CRKP) was reported in the 1990s.2 In the following decades, CRKP was reported in the USA,3 Israel,4 Europe,5,6 and China.7–9 Notably, public health is threatened by BSIs caused by CRKP. The mortality rates...
caused by CRKP infections in Europe, South America, Asia, and North America are reportedly 50.06%, 46.71%, 44.82%, and 33.24%, respectively.\textsuperscript{5} In addition, the medical costs of CRKP-infected patients are higher than those of carbapenem-susceptible \textit{K. pneumoniae} (CSKP)-infected patients during hospitalization.\textsuperscript{10}

Previous researchers paid attention to the monitoring of long-term antibiotics of \textit{Klebsiella pneumoniae},\textsuperscript{11} the predictors of CRKP strain infection\textsuperscript{12,13} and the effect of CRKP isolates on patients’ clinical relevance,\textsuperscript{6,14–16} however, few studies have compared the differences between CRKP and CSKP strains in BSIs. Here, we conducted a retrospective case-control study in Guangdong Province, China. In this study, 103 strains were collected from 10 hospitals between 2010 and 2018. The antimicrobial resistance, virulence, clinical characteristics, and risk factors of the CRKP and CSKP isolates from patients with BSIs were clarified.

\textbf{Materials and Methods}

\textbf{Isolated Bacteria}

Between 2010 and 2018, 103 \textit{K. pneumoniae} isolates were collected from the blood of patients with BSIs in 10 tertiary hospitals in Guangdong Province, China. The isolates were cultured, and species were identified by 16S rRNA sequencing and MALDI-TOF MS (Bruker Daltonik GmbH, Bremen, Germany). Universal primer 27F (5'\textsuperscript{−} AGRTTYGATYMTGGCTCAG-3') and 1492R (5'\textsuperscript{−} RGYTACCTTGGTACGACTT-3') were used to amplify the full-length 16S rRNA gene.\textsuperscript{17}

\textbf{Patient Demographics}

Information regarding demographics, comorbidities (hypertensive, diabetes diseases, coronary heart disease, hematogenous tumor cancer, and other chronic diseases), location before admission, health-care exposures before BSI onset (previous hospitalization within 12 months, or intensive care unit [ICU] admission, surgery, immunosuppressive therapy, or antibiotic exposure within 30 days), or underlying diseases were collected as primary data; Sources of infection (central-line; pneumonia or ventilator; infections of cardiovascular or gastrointestinal systems, surgical sites, urinary tract, skin and soft tissue, reproductive tract; mechanical ventilation; central vein catheterization; septic shock; change in antibiotic treatment after positive culture results; or carbapenem-including treatment) were also collected together with microbiological data, length of hospitalization, antimicrobial therapies, and patient outcomes.

BSI onset was defined as the date of collection of an isolate that resulted in a positive blood culture. BSI can be divided into community-acquired (CA) and hospital-acquired (HA), based on the location of onset. CA-BSI patients were defined as blood culture-positive patients who had been hospitalized for <48 h and had not been hospitalized in the past 6 months. On the contrary, HA-BSI was defined as a positive blood culture from a patient 48 hours after hospitalization or a positive blood culture from a patient hospitalized for <48 h but who had been hospitalized within the past 6 months.\textsuperscript{4}

\textbf{Antimicrobial Susceptibility Testing (AST)}

The agar dilution method was used for AST, and the breakpoints of polymyxin B and tigecycline were explained based on the breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and those of other antimicrobials were based on the Clinical and Laboratory Standards Institute guidelines (CLSI).\textsuperscript{18}

The 15 antimicrobial agents tested were cefotaxime, ceftazidime, cefepime, colistin, tigecycline, imipenem, ertapenem, meropenem, ciprofloxacin, fosfomycin, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, amikacin, gentamicin, and aztreonam. Isolates with imipenem and/or meropenem minimum inhibitory concentrations (MICs) ≥4 μg/mL or ertapenem MICs ≥2 μg/mL were defined as CRKP.\textsuperscript{19}

\textbf{Construction of a Galleria Mellonella Infection Model}

Virulence of the CRKP and CSKP strains was measured using a \textit{G. mellonella} model.\textsuperscript{20,21} 11 strains were randomly selected from the CRKP and CSKP groups respectively, and the larvae were infected with the concentrations of 1×10\textsuperscript{4} CFU/mL. \textit{Escherichia coli} MG1655 was used as the non-toxic control and \textit{K. pneumoniae} strain Hvkp4 as the highly
toxic control as previously reported. The wax moth larvae were incubated in a dark room at 37 °C, and the survival rate was recorded every 12 h for 7 days.

Statistical Analysis
Statistical analyses of the data were performed using IBM SPSS. Categorical variables are presented as numbers and percentages and compared using the chi-square or Fisher’s exact test. In addition, continuous variables are indicated by the median and interquartile range (IQR; non-normally distributed data) or standard deviation (SD; normally distributed data) and mean. Continuous variables were compared according to their distributions using the nonparametric Mann–Whitney U-test or Student’s t-test. The results of the univariate analysis are indicated by P values and odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance (two-tailed) was defined as P<0.05.

Results
Patient Demographics
In this study, 103 K. pneumoniae strains were collected from patients with BSIs between 2010 and 2018 (Figure 1A and Table 1). Based on the AST results (Table 2), of the 103 strains included, 56 (54.4%) were CRKP and 47 (45.6%) were CSKP. 73 (70.87%) patients were male (37.87% and 33.01% in the CRKP and CSKP groups, respectively), and 30 (29.13%) were female (Table 1). The median age of CRKP-infected patients was 27 years (IQR 0–61) and CSKP patients was 10 years (IQR 0–61) (P = 0.48); almost half of the CRKP group was 0–17 years old (48%), followed by 41–65 years (29%) and ≥ 66 years (18%) (Figure 1B). CSKP isolates were mainly detected in 0–17 years old, 41–65 years old (58%), and ≥ 66 years old (58%, 21%, and 17%, respectively) (Figure 1C).

CRKP Strains Were More Resistant to Most Antibiotics Compared with CSKP Strains
All 103 K. pneumoniae strains were tested for susceptibility against 15 antibiotics (Figure 2, Table 2). In addition to carbapenem resistance, the CRKP group had a higher resistance rate among other antibiotics than the CSKP group, except for FOS, among which cephalosporins showed 100% non-susceptibility rates. The lowest non-sensitive rates in the CRKP group were for colistin (1.8%) and tigecycline (12.5%) (Figure 2). The value of MIC$_{50}$ and MIC$_{90}$ of the CRKP group were higher than those of the CSKP group (Table 2). The resistance rates to cefotaxime, cefepime, imipenem, ertapenem, meropenem, piperacillin-tazobactam, amikacin, aztreonam, and gentamicin in the CRKP group were higher than those in the CSKP group (P < 0.01) (Table 2).

CRKP Strains Had Higher Pathogenicity Than CSKP Strains
Using the G. mellonella infection model to predict the toxicity of strains, we randomly selected 11 strains from both the CRKP and CSKP groups. The results showed that the survival rate of the CRKP group was significantly lower than that
| Characteristic                                      | Complete Cohort | CSKP (n=47) | CRKP (n=56) | P-value |
|---------------------------------------------------|-----------------|-------------|-------------|---------|
| **Age (median, IQR)**                             |                 |             |             |         |
| 10 (0–61)                                         | 27 (0–61)       | 0.48        |
| **Sex**                                           |                 |             |             |         |
| Female                                            | 13 (27.7%)      | 0.764       |
| Male                                              | 34 (72.3%)      |             |
| **Underlying disease/comorbid conditions**        |                 |             |             |         |
| Hypertensive                                      | 0 (0%)          | 3 (5.4%)    | 0.248      |
| Diabetes diseases                                 | 8 (17.0%)       | 6 (10.7%)   | 0.352      |
| Coronary heart disease                            | 1 (2.1%)        | 4 (7.1%)    | 0.372      |
| Congestive heart failure                          | 5 (10.6%)       | 3 (5.4%)    | 0.464      |
| Connective tissue disease                         | 0 (0%)          | 2 (3.6%)    | 0.499      |
| Chronic pulmonary disease                         | 3 (6.4%)        | 1 (1.8%)    | 0.329      |
| Chronic kidney failure                            | 1 (2.1%)        | 5 (8.9%)    | 0.216      |
| End-stage liver disease                           | 1 (2.1%)        | 0           | 0.456      |
| Cancer                                            | 6 (12.8%)       | 5 (8.9%)    | 0.530      |
| Hematogenous tumor                                | 6 (12.8%)       | 2 (3.6%)    | 0.138      |
| Charlson comorbidity index > 2                    | 8 (17.0%)       | 8 (14.3%)   | 0.703      |
| **Location before admission**                     |                 |             |             |         |
| Home                                              | 27 (57.4%)      | 24 (42.9%)  | 0.14       |
| Transfer from other hospital                      | 13 (27.7%)      | 29 (51.8%)  | **0.013**  |
| Born this episode                                 | 7 (14.9%)       | 3 (5.4%)    | 0.18       |
| **Health-care exposures before BSI onset**        |                 |             |             |         |
| Antibiotic exposure (within 30 days)              | 35 (74.5%)      | 50 (89.3%)  | 0.055      |
| ICU admission (within 30 days)                    | 13 (25.5%)      | 24 (42.9%)  | 0.147      |
| Surgery (within 30 days)                          | 14 (29.8%)      | 20 (35.7%)  | 0.524      |
| Corticosteroid therapy (within 30 days)           | 6 (12.8%)       | 7 (12.5%)   | 0.968      |
| Radiation therapy or chemotherapy                 | 6 (12.8%)       | 2 (3.6%)    | 0.138      |
| Immunosuppressive therapy (within 3 months)       | 9 (19.1%)       | 11 (19.6%)  | 0.950      |
| Tracheal cannula or tracheotomy (within 30 days)  | 15 (31.9%)      | 34 (69.4%)  | **0.004**  |
| Central venous catheterization (within 30 days)   | 27 (57.4%)      | 40 (71.4%)  | 0.138      |
| Previous hospitalization (within 12 months)       | 42 (89.4%)      | 51 (91.1%)  | 1          |
| ICU at time of BSI onset                          | 13 (27.7%)      | 20 (35.7%)  | 0.383      |

(Continued)
Table 1 (Continued).

| Characteristic                                           | CSKP (n=47) | CRKP (n=56) | P-value |
|----------------------------------------------------------|-------------|-------------|---------|
| **Epidemiological classification**                       |             |             |         |
| Community acquired                                       | 11 (23.4%)  | 8 (14.3%)   | 0.235   |
| Hospital acquired                                        | 36 (76.6%)  | 48 (85.7%)  |         |
| **Source**                                               |             |             |         |
| Primary                                                  | 12 (25.5%)  | 12 (21.4%)  | 0.624   |
| Central-line associated                                  | 3 (6.4%)    | 6 (10.7%)   | 0.504   |
| Cardiovascular system infection                          | 1 (2.1%)    | 0           | 0.456   |
| Gastrointestinal system infection                        | 11 (23.4%)  | 13 (23.2%)  | 0.982   |
| Pneumonia or ventilator-associated event                 | 14 (29.8%)  | 16 (28.6%)  | 0.892   |
| Surgical site infection                                  | 1 (2.1%)    | 1 (1.8%)    | 1       |
| Skin and soft tissue infection                           | 1 (2.1%)    | 3 (5.4%)    | 0.623   |
| Urinary tract infection                                  | 4 (8.5%)    | 5 (8.9%)    |         |
| Mechanical ventilation after BSI onset                   | 16 (34%)    | 31 (55.4%)  | 0.031   |
| Hemodialysis treatment                                   | 5 (10.6%)   | 10 (17.9%)  | 0.301   |
| Temperature ≥ 39°C or < 36°C after BSI onset             | 21 (44.7%)  | 27 (48.2%)  | 0.72    |
| Severe sepsis                                             | 20 (42.6%)  | 26 (46.4%)  | 0.694   |
| Septic shock                                             | 14 (29.8%)  | 17 (30.4%)  | 0.950   |
| Active empiric antibiotic therapy                        | 44 (93.6%)  | 25 (44.6%)  | < 0.001 |
| Active directed antibiotic therapy                       | 41 (87.2%)  | 39 (69.6%)  | 0.033   |
| Combination therapy                                      | 3 (6.4%)    | 3 (5.4%)    | 1.000   |
| Carbapenem-including treatment                           | 31 (66.0%)  | 40 (71.4%)  | 0.55    |
| Polymyxin-including treatment                            | 0           | 5 (8.9%)    | 0.036   |
| Tigecycline-including treatment                          | 1 (2.1%)    | 12 (21.4%)  | 0.003   |
| Length of hospitalization before the onset of BSI        | 11 (1–19)   | 12 (3.25–28)| 0.216   |
| Length of hospitalization after the onset of BSI         | 15 (8–27)   | 14 (8.25–23.5| 0.366   |
| Total length of stay (days)                              | 28 (16–51)  | 28.5 (16–50.75)| 0.783  |
| **Outcome**                                              |             |             |         |
| 7-day mortality                                          | 7 (14.9%)   | 10 (17.9%)  | 0.687   |
| 14-day mortality                                         | 7 (14.9%)   | 16 (28.6%)  | 0.097   |
| 28-day mortality                                         | 9 (19.1%)   | 20 (35.7%)  | 0.063   |
| In-hospital mortality                                    | 9 (19.1%)   | 22 (39.3%)  | 0.026   |

**Note:** P values less than 0.05 are bolded.

**Abbreviations:** KP, *Klebsiella pneumoniae*; CRKP, carbapenem-resistant KP; CSKP, carbapenem susceptible KP; BSI, bloodstream infection.
of the CSKP group (P < 0.05; Figure 3A). The fatality rate of the CRKP group was significantly higher than that of the CSKP group from 12 to 168 h (P < 0.05; Figure 3B). The highly virulent *K. pneumoniae* strain Hvkp4 was used as a positive control. The survival curve revealed that the survival rate of the CRKP group was lower than those of *K. pneumoniae* strain Hvkp4 at different time points. The mortality rate of *G. mellonella* injected with some isolates was approximately 100% during the first 24 h (Figure 3C). In contrast, the survival rate of most strains in the CSKP group was higher than that of *K. pneumoniae* strain Hvkp4 (Figure 3D). Taken together, we have demonstrated in this study that the CRKP strain is to some extent more virulent than the CSKP strain.

### The Patients Infected by the CRKP Group Had Higher Mortality Than the CSKP Group

In-hospital deaths occurred in 22 (39.3%) of 56 CRKP BSIs and were significantly higher than those in CSKP infections (9/47 [19.1%] cases, P = 0.026, χ² test) (Table 1). The mortality rates in the CRKP group were 17.9% at 7 days, 28.6% at 14 days, and 35.7% at 28 days, compared to 14.9% at 7 days, 19.1% at 14 days, and 19.1% at 28 days in the CSKP group (P = 0.687, 0.097, and 0.063, respectively) (Table 1).

The Kaplan–Meier curve showed the survival of the CRKP and CSKP groups after bloodstream infections (Figure 4). The 28-day cumulative survival showed a significant difference between the CRKP and the CSKP groups (P = 0.0303). The in-hospital cumulative survival showed a significant difference between the CRKP and CSKP groups.

### Table 2 Antimicrobial Spectrum Evaluation Percentage of Carbapenem-Resistant *Klebsiella pneumoniae* Isolates Resistance to Various Antibiotics

| Antimicrobial Agents | CRKP Isolates (n=56) | CSKP Isolates (n=47) | P-value |
|---------------------|----------------------|----------------------|---------|
|                     | MIC50   | MIC90   | R%     | MIC50   | MIC90   | R%     |         |
| CTX                 | 256     | >256    | 100    | 48      | >128    | 74.5   | <0.01   |
| CAZ                 | >256    | >256    | 100    | 8       | 128     | 55.3   | <0.01   |
| FEP                 | 128     | >256    | 100    | 8       | 16      | 61.7   | <0.01   |
| CT                  | 0.25    | 0.5     | 1.8    | 0.5     | 0.5     | 0      | 0.362   |
| TGC                 | 1       | 4       | 12.5   | 1       | 2       | 8.5    | 0.519   |
| IMP                 | 16      | >32     | 89.3   | ≤0.25   | 0.375   | 2.1    | <0.01   |
| ETP                 | >16     | >16     | 100    | ≤0.25   | ≤0.25   | 2.1    | <0.01   |
| MEM                 | 16      | >16     | 94.6   | ≤0.25   | 0.25    | 0      | <0.01   |
| CIP                 | 2       | 128     | 57.1   | 1       | 64      | 42.6   | 0.134   |
| FOS                 | 512     | >512    | 92.9   | >512    | >512    | 97.9   | 0.24    |
| SXT                 | 2/38    | 16/304  | 48.2   | >16     | >16     | 59.6   | 0.254   |
| PTZ                 | 512     | >512    | 94.6   | 4       | 12      | 8.5    | <0.01   |
| AMK                 | 4       | >256    | 48.2   | 2       | 4       | 6.4    | <0.01   |
| GEN                 | 128     | >256    | 60.7   | ≤1      | 128     | 38.3   | 0.023   |
| ATM                 | >128    | >128    | 96.4   | 12      | 128     | 55.3   | <0.01   |

**Note:** P-values less than 0.05 are bolded.

**Abbreviations:** CTX, cefotaxime; CAZ, ceftazidime; FEP, cefepime; CT, colistin; TGC, tigecycline; IMP, imipenem; ETP, ertapenem; MEM, meropenem; CIP, ciprofloxacin; FOS, fosfomycin; SXT, trimethoprim-sulfamethoxazole; PTZ, piperacillin-tazobactam; AMK, amikacin; GEN, gentamicin; ATM, aztreonam.
These data suggest that patients infected with CRKP have poorer outcomes than those infected with the CSKP isolates.

**Risk Factors for Infections by CRKP and CSKP Strains**

The median length of hospital stay was 28.5 days for CRKP patients compared with 28 days for CSKP patients. Most BSI patients (84/103; 81.55%) were healthcare-associated, whereas the rest (19/103; 18.45%) were community-acquired. Before BSI onset, access to healthcare was more frequent among CRKP patients than among CSKP patients. More patients with CRKP BSIs were treated with ICU admission, antibiotics, surgery within 30 days before BSI onset, immunosuppressive therapy, and previous hospitalization (Table 1). Carbapenems were the most frequently used antibiotics in subsequent therapy for both CRKP BSIs (71.4%, 40/56) and CSKP BSIs (66.0%, 31/47).

Univariate analysis showed that transfer from other hospitals, tracheal cannula or tracheotomy (within 30 days), mechanical ventilation after BSI onset, active empiric antibiotic therapy, active directed antibiotic therapy, polymyxin treatment, and tigecycline treatment were associated with CRKP BSIs (Table 1). Multivariable logistic regression analysis showed that tracheal cannula or tracheotomy (within 30 days) (OR = 0.295; 95% CI = 0.102–0.852, P = 0.024), active empiric antibiotic therapy (OR = 0.008; 95% CI = 0.001–0.118, P < 0.01), and tigecycline treatment (OR = 0.061; 95% CI = 0.004–0.855, P = 0.038) were independent risk factors for CRKP BSIs (Table 3).

**Risk Factors of Mortality of CRKP, and CSKP BSIs**

Univariate analysis of risk factors for 28-day mortality (Supplementary Material Table S1) and in-hospital mortality (Supplementary Material Table S2) among the CRKP and CSKP groups was conducted. According to the results of the univariate analysis, variables with statistical differences between the death and survival groups were included in the multivariable logistic regression model. Multivariate analysis revealed that tracheal cannula or tracheotomy (within 30 days) (P = 0.018, OR = 0.014), severe sepsis (P = 0.048, OR = 0.012), and length of hospitalization after the onset of BSI.
(P = 0.004, OR = 0.699) were independent risk factors for 28-day mortality of CRKP BSIs (Table 4). Multivariate analysis showed that carbapenem-resistant Enterobacterales bacteremia (P = 0.023, OR = 0.009) and length of hospitalization after the onset of BSI (P = 0.018, OR = 0.816) were independent risk factors for in-hospital mortality of CRKP BSIs (Table 4).
Carbapenems are therapeutic antimicrobials for severe bacterial infections including those caused by *K. pneumoniae* and the last line of treatment for many other infections following antibiotic failure. We conducted a retrospective study involving 103 *K. pneumoniae* BSI cases that occurred between 2010 and 2018 in 10 hospitals. We found that the separated CRKP showed an upward trend, not only in Guangdong but also in other parts of China. Meanwhile, we found that the resistance rate to carbapenems and other antibiotics in *K. pneumoniae* is increasing. According to the data on the drug-resistant bacteria monitoring network, the drug resistance rate of *K. pneumoniae* to carbapenems was 10.9% nationwide, up 0.8% compared to 2018. Our data showed that the resistance rate of the CRKP group to cephalosporins was 100%. In addition to FOS, the antibiotic resistance of the CRKP group was higher than that of the CSKP group. There were significant differences between the two groups in antibiotics, such as CTX, CAT, FEP, IPM, ETP, MEM, PTZ, AMK, GEN, and ATM. This demonstrated that the CRKP isolates harbored more severe antimicrobial resistance profiles than the CSKP isolates.

**Table 3** Risk Factors for CRKP BSIs with Multivariate Logistic Regression Analysis

| Covariate                                 | Univariate Analysis OR (95% CI) | P value | Multivariate Analysis OR (95% CI) | P value |
|-------------------------------------------|---------------------------------|---------|----------------------------------|---------|
| Transfer from other hospital              | 2.809 (1.229–6.420)             | 0.014   | 0.374 (0.127–1.101)              | 0.074   |
| Tracheal cannula or tracheotomy (within 30 days) | 3.297 (1.460–7.446)             | 0.004   | 0.295 (0.102–0.852)              | 0.024   |
| Active empiric antibiotic therapy         | 0.055 (0.015–0.198)             | <0.01   | 0.008 (0.001–0.118)              | <0.01   |
| Active directed antibiotic therapy        | 0.336 (0.120–0.939)             | 0.038   | 0.085 (0.007–1.083)              | 0.058   |
| Tigecycline-including treatment           | 0.080 (0.010–0.639)             | 0.017   | 0.061 (0.004–0.855)              | 0.038   |

**Note:** P values less than 0.05 are bolded.

**Abbreviations:** KP, *Klebsiella pneumoniae*; CRKP, carbapenem-resistant KP; CSKP, carbapenem susceptible KP; BSI, bloodstream infection; OR, odds ratio; CI, confidence interval.

**Table 4** Risk Factors for Mortality of KP, CRKP and CSKP BSI with Multivariate Logistic Regression Analysis

| Mortality          | Items                                  | p-value | OR          | 95% CI       |
|--------------------|----------------------------------------|---------|-------------|--------------|
| 28-day mortality   | **KP** Tracheal cannula or tracheotomy (within 30 days) | 0.005   | 0.038       | 0.004–0.371  |
|                    | **KP** Septic shock                     | 0.021   | 0.066       | 0.006–0.666  |
|                    | **KP** Length of hospitalization after the onset of BSI | 0.002   | 0.838       | 0.748–0.939  |
|                    | **CRKP** Tracheal cannula or tracheotomy (within 30 days) | 0.018   | 0.014       | 0.000–0.476  |
|                    | **CRKP** Severe sepsis                  | 0.048   | 0.012       | 0.000–0.953  |
|                    | **CRKP** Length of hospitalization after the onset of BSI | 0.004   | 0.699       | 0.550–0.889  |
| In-hospital mortality | **KP** Tracheal cannula or tracheotomy (within 30 days) | 0.005   | 0.038       | 0.004–0.371  |
|                    | **KP** Septic shock                     | 0.021   | 0.066       | 0.006–0.666  |
|                    | **KP** Length of hospitalization after the onset of BSI | 0.002   | 0.838       | 0.748–0.939  |
|                    | **CRKP** Carbapenem-resistant Enterobacterales bacteremia | 0.023   | 0.009       | 0.000–0.520  |
|                    | **CRKP** Length of hospitalization after the onset of BSI | 0.018   | 0.816       | 0.689–0.965  |

**Note:** P values less than 0.05 are bolded.

**Abbreviations:** KP, *Klebsiella pneumoniae*; CRKP, carbapenem-resistant KP; CSKP, carbapenem susceptible KP; BSI, bloodstream infection; OR, odds ratio; CI, confidence interval.

**Discussion**

Carbapenems are therapeutic antimicrobials for severe bacterial infections including those caused by *K. pneumoniae* and the last line of treatment for many other infections following antibiotic failure. We conducted a retrospective study involving 103 *K. pneumoniae* BSI cases that occurred between 2010 and 2018 in 10 hospitals. We found that the separated CRKP showed an upward trend, not only in Guangdong but also in other parts of China. Meanwhile, we found that the resistance rate to carbapenems and other antibiotics in *K. pneumoniae* is increasing. According to the data on the drug-resistant bacteria monitoring network, the drug resistance rate of *K. pneumoniae* to carbapenems was 10.9% nationwide, up 0.8% compared to 2018. Our data showed that the resistance rate of the CRKP group to cephalosporins was 100%. In addition to FOS, the antibiotic resistance of the CRKP group was higher than that of the CSKP group. There were significant differences between the two groups in antibiotics, such as CTX, CAT, FEP, IPM, ETP, MEM, PTZ, AMK, GEN, and ATM. This demonstrated that the CRKP isolates harbored more severe antimicrobial resistance profiles than the CSKP isolates.
We found that the death rate was significantly higher in patients with CRKP infections than in those with CSKP infections, and some studies have shown that carbapenem resistance leads to 26–44% deaths.\textsuperscript{25} To date, the impact of carbapenem resistance on health outcomes in Chinese patients with BSI has been evaluated in only a few studies.\textsuperscript{26–28} Our study demonstrated that the in-hospital mortality of patients was significantly higher in CRKP BSIs than in CSKP BSIs. CRKP-infected patients had more frequent healthcare experiences before the onset of BSI. More patients with CRKP BSIs had been admitted to the ICU, antibiotics, surgery within 30 days before BSI onset, immunosuppressive therapy, and previous hospitalization. ICU admission within 30 days, transfer from other hospitals, tracheal cannula or tracheotomy (within 30 days), change in antibiotic treatment after positive culture, and central vein catheterization were associated with the development of CRKP BSIs. Studies have shown a 15–79% mortality rate for \textit{K. pneumoniae} BSI.\textsuperscript{29–32} In this study, the in-hospital mortality rate in the CRKP group was 39.3%. The data suggest that the survival rate of the CRKP group was lower than that of \textit{K. pneumoniae} strain HvKP4 in \textit{G. mellonella} infection model. In addition, we found that the survival rate of the CRKP group was lower than that of the CSKP group according to the Kaplan–Meier curve after the onset of BSI. Previous studies have reported an association between carbapenem resistance and BSIs.\textsuperscript{4,26} We further clarified that carbapenem resistance is a crucial factor in the clinical treatment of CRKP BSI.

\section*{Conclusion}
In conclusion, we found that the antimicrobial resistance and mortality rate of the CRKP group were higher and broader than those of the CSKP group. The survival curve showed that the outcome and prognosis of the CRKP group were worse than those of the CSKP group were. Our data provide novel information to compare antimicrobial resistance, virulence, and outcomes between CRKP and CSKP isolates.

\section*{Ethical Approval}
Ethical approval for this study was given by Zhongshan School of Medicine of Sun Yat-sen University under approval number 068.

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\section*{Disclosure}
None of the authors have any conflicts of interest related to this article.

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