Risk factors and mortality of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection in a tertiary-care hospital in China: an eight-year retrospective study

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Abstract

**Background:** The prevalence of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection (CRKP-BSI) is increasing worldwide. CRKP-BSI is associated with high rates of morbidity and mortality due to limited antibiotic choices. Here, we aim to identify the prevalence and risk factors for infection and mortality of CRKP BSI.

**Methods:** This was a retrospective study of the past data from January 1st, 2012 to December 31st, 2019 of adult patients with KP-BSI in Xiangya Hospital, China.

**Results:** Among the 706 incidences included in this study, 27.4% of them (212/753) being CR-KP strains. The occurrence of CRKP-BSI was increased from 20.69 to 37.40% from 2012 to 2019. Hematologic malignancies and ICU acquired infection were identified to be substantial risk factors of carbapenem resistance. The overall 28-day mortality rates of CRKP-BSI patients was significantly higher than that of CSKP-BSI (*P* < 0.001). Logistic regression analysis identified severe sepsis or septic shock incidents, inadequate empirical antimicrobial therapy and corticosteroids use preceding infection onset as the independent predictors of 28-day mortality of CRKP-BSI patients. However, high dose carbapenem combination therapy was identified as anticipated factors of low 28-day mortality.

**Conclusion:** The occurrence of CRKP-BSI was significantly increased during the study period. Hematologic malignancies and ICU acquired infection were associated with the development of CRKP BSI. Severe sepsis or septic shock incidents, inadequate empirical antimicrobial therapy and corticosteroids use preceding infection onset caused
significant increase of mortality rates in CRKP-BSI patients. High dose carbapenem combination therapy was associated with better outcome.

Keywords: Carbapenem resistance, *Klebsiella pneumoniae*, bloodstream infection, Risk factors, Mortality, Intensive care units

Introduction

*Klebsiella pneumoniae* (KP) is a gram-negative bacteria commonly causing nosocomial infections including pneumonia, bloodstream infections (BSIs), hepatic abscess and urinary tract infections [1–4]. Although KP is thought to be the second pathogen after *Escherichia coli* (*E. coli*), that is responsible for gram-negative BSIs in adult patients, recent studies showed the incidence of KP-BSIs had exceeded the incidence of *E. coli* BSIs in intensive care unit (ICU) patients [5, 6]. KP-BSI infections have contributed to high health-care costs and an increased mortality. The crude mortality rate of KP-BSIs patients was reported to span from 20 to 40% [6–9].

Carbapenems, a class of broad-spectrum beta-lactam antibiotic drugs for the treatment of many Gram-negative bacteria, have been recommended in first-line therapies for multidrug-resistant KP infections [7]. However, during the last decade, the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is increasing worldwide, such as Israel [4], Europe [5] and some South American countries [6, 7, 10]. In China, according to the data from CHINET (an antimicrobial resistance surveillance network in China) surveillance, the resistance rates of KP to imipenem and meropenem increased from 3.0% and 2.9% in 2005 to 26.3 and 25% in 2018 respectively [11]. Additionally, several reports have shown that resistance to carbapenem is related to the increase of KP-BSIs patients’ mortality [12–14]. Therefore, the situation is serious for CRKP-BSI patients.

Due to high morbidity and mortality and lack of appropriate medical intervention, CRKP-BSI has become a great challenge to clinical practitioners [4, 15, 16]. Recognizing the risk factors contributed to the development and mortality of CRKP-BSI may provide the basis for implementing of control measures and therapeutic strategies to prevent the CRKP BSI infection. Thus far, many clinical reports have demonstrated the various risk factors for both development and fatal outcomes of CRKP-BSI infections. For example, the source of skin and soft tissue infection, ICU-acquired infection, central venous catheter, mechanical ventilation, and previous antibiotic exposure were demonstrated to be powerful risk factors leading to the onset of CRKP-BSI [4, 12, 17], while mechanical ventilation, septic shock, inadequate empirical antibiotic therapy were reported to be independent mortality predictors of CRKP-BSI [4, 12]. However, the conclusions of these studies were inconsistent.

In this study, we not only evaluate the prevalence of CRKP-BSI in ICU, but also identify the risk factors related to infection and mortality of carbapenem resistance KP-BSI ICU.

Methods

Study design, setting and patients

A previous cohort study on patients with KP-BSIs was conducted between 1 January 2012 and 31 December 2019 in Xiangya Hospital, a tertiary healthcare hospital in Changsha, Hunan Province, China. Having approximately 3,500 beds (including 138 beds in 7 ICUs), it is known to be one of the largest comprehensive hospitals in China. This study was approved by the Xiangya Hospital Ethics Committee.

The study comprised of patients aged ≥ 18 years, who had been admitted to the hospital with KP-BSI during the period. The cases were CRKP-BSI infected patients, and the controls were patients with CSKP-BSI. In this report, only the initial positive cultures of KP in bloodstream for each patient were included. Recurrent infections were excluded. Patients with incomplete medical records or polymicrobial BSIs were also excluded. All patients were identified by searching the integrated hospital information system (IHIS), laboratory information system (LIS) and imageology achieving system (RIS) of Xiangya Hospital.

Data collection

Results of clinical and microbial characteristics were obtained from the medical records by two experienced respiratory medical doctors. The clinical data collected included: patient demographics (age, gender), comorbidities (congestive heart failure, cerebrovascular disease, chronic lung disease, hepatobiliary and pancreatic diseases, kidney diseases, hematologic malignancy, solid tumor, solid organ transplantation, diabetes mellitus, immune diseases), the ward where onset of BSI was identified, previous exposures (previous healthcare interventions, such as hospitalization, surgery, dialysis, endoscopy and mechanical ventilation; previous antibiotics exposures), therapeutic management (choice
of antibiotic), and outcomes (span of hospital stay, and mortality at 28 days). In addition, patients general state at the onset of BSI underwent adequate assessment, such as severe sepsis or septic shock. The Charlson comorbidity index (CCI) was used to determine the comorbid conditions as previously described [18]. Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to calculate the severity of illness within 24 h following the onset of BSIs. Furthermore, the adequate empirical antimicrobial therapies described by Zarkotou were also taken into consideration [19].

Definitions
KP-BSI was described to be a positive blood culture of CR-KP strain collected from a patient that showed symptoms and/or signs of the systemic inflammatory response syndrome. For patients that had several incidences of CRKP-BSI, an unusual event was defined as independent occurrence at least 30 days after the final positive blood culture [10]. The date when the blood culture was collected is defined as the onset of BSI. KP-BSIs were classified as healthcare-associated and community-acquired. Ward at the onset of BSI was defined as the first positive blood culture identified more than 2 days after the ward admission without a prior positive blood culture with the same pathogen in last 30 days. BSI sources were established based on the Centers for Disease Control and Prevention criteria [20]. BSI was considered as primary when no source was identified. Septic shock was defined as sepsis associated with organ dysfunction and persistent hypotension despite volume replacement. Combination therapy was defined as a regimen that includes two or more antibiotics, with at least one agent showing in vitro activity against the KP. An empirical antimicrobial therapy was described to be appropriate unless it included at least one drug displaying in vitro activity against the KP isolate, initiated within 48 h of the index blood culture, and given in adequate doses. High dose carbapenem combination therapy was only used for CRKP with meropenem MIC (≤16 mg/L). It was referred as combination of intravenous injection of 2 g meropenem every 8 h and infusion over 3 h.

Microbiology
The Vitek 2 system (BioMérieux, Marcy 1’Étoile, France) was used in the clinical microbiology laboratory for isolate identification and antimicrobial susceptibility testing. KP isolates were considered as carbapenem-resistant KP (CRKP) isolates when they were resistant to one or more carbapenems tested in the clinical microbiology (i.e., ertapenem, imipenem, or meropenem).

Statistical analysis
SPSS 20.0 (Chicago, IL, USA) was used for statistical analysis. Categorical variables were expressed as frequency counts and percentages with 95% confidence interval (95% CI). Continuous variables were expressed as median and interquartile ranges (IQRs). Pearson χ² or Fisher’s exact tests were used to analyze categorical variables between groups, and Student’s t-test or the Mann–Whitney U test were used to compare continuous variables as appropriate. In analysis of risk factors for CRKP infection and mortality, univariable logistic regression analysis was performed. To identify the independent risk factors, a multivariate logistic regression model was generated to control the effects of confounding variables. Variables with p-value < 0.1 in univariate testing were incorporated into the model using a backward stepwise approach. A two-tailed p value of < 0.05 was considered statistically significant.

Results
Incidence and mortality of CRKP-BSIs over the past 8 years
During the 8-year study period, 706 events of KP-BSI were consecutively collected from 1 January 2012 and 31 December 2019 in Xiangya Hospital, and 30% (212/706) of these incidences were CRKP isolates. Over the past 8 years, the drug resistance rates of KP detected in blood samples to imipenem and meropenem has been increasing (details are shown in Table 1).

The percentage of KP in blood sample from 2012 to 2019 fluctuated from 5.3 to 7% during the 8 years (5.3 in 2012, 5.7 in 2013, 5.2 in 2014, 5.9 in 2015, 6.1 in 2016, 6.3 in 2017, 6.5 in 2018 and 7 in 2019). The percentage of CRKP in KP BSI from 2012 to 2019 were 20.69, 21.88, 22.54, 27.71, 30.68, 32.29, 34.78 and 37.40% respectively, which rose fastest from 2015 to 2019, as shown in Fig. 1. Additionally, the total 28-day mortality rate of KP detected in blood samples to imipenem and meropenem has been increasing (details are shown in Table 1).

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Clinical characteristics of patients
The average age of these 706 patients was 58.9 years (range: 18–92 years), and the male patients accounted for 66.9% (472/706). The most frequent comorbidities of these patients were kidney diseases (172/706, 24.4%), chronic lung diseases (146/706, 20.7%) and diabetes mellitus (140/706, 19.8%). The number of KP-BSI patients with the Carlson comorbidity index (CCI) ≥ 3 was 348
Most of the KP-BSIs cases were acquired at ICU (300/706, 42.5%) and most of them were undergoing hospitalization (378/706, 53.5%) within 12 months preceding infection onset. The most common KP infection source was primary bloodstream infections (408/706, 57.8%).

Additionally, KP could be detected in samples from other sites (348/706, 49.3%), including pulmonary (166/706, 23.5%), pancreaticobiliary tract infection (40/706, 5.7%) and urinary tract infection (35/706, 5.0%), etc. 138 out of 706 (19.5%) KP-BSI patients were treated with corticosteroids and 150 out of 706 (21.2%) KP-BSI patients underwent chemotherapy or radiotherapy. 261 out of 706 (37.0%) KP-BSI patients did not receive adequate empirical antibiotic therapy. The number of KP-BSI patients with APACHE II score more than 15 was 240 (34.0%).

Predictors of carbapenem-resistance among patients with Klebsiella BSI

We identified the clinical characteristics affecting the development of CRKP-BSIs, by comparing patient demographics, clinical characteristics, type of infections, and prior antibiotic exposures of patients with CRKP-BSIs and CSKP-BSIs (Table 2). The factors determined to be more relevantly related with CRKP-BSIs, using the univariable logistic regression analysis, included hematologic malignancy, ICU-acquired infection, undergoing hospitalization within 12 months preceding infection onset, undergoing surgery within 30 days preceding infection onset, and undergoing hospitalization within 12 months preceding infection onset, taking corticosteroids, and undergoing chemotherapy or radiotherapy.

Table 1: Susceptibility of Klebsiella pneumoniae to antimicrobial agents from 2012 to 2019

| Antimicrobial agents | 2012 (n=58) | 2013 (n=64) | 2014 (n=71) | 2015 (n=83) | 2016 (n=88) | 2017 (n=96) | 2018 (n=115) | 2019 (n=131) |
|----------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| R (%)                | S (%)       | R (%)       | S (%)       | R (%)       | S (%)       | R (%)       | S (%)       | R (%)       |
| Ampicillin           | 89.7        | 1.72        | 98.4        | 0           | 100.0       | 0           | 100.0       | 0           |
| Ampicillin-sulbactam | 43.1        | 53.4        | 43.8        | 56.2        | 43.7        | 56.3        | 45.8        | 54.2        |
| Piperacillin-tazobactam | 22.4       | 74.1        | 28.1        | 71.8        | 25.4        | 74.5        | 30.1        | 69.9        |
| Cefoperazone-sulbactam | 20.7       | 72.4        | 24.6        | 75.4        | 20.7        | 72.4        | 24.6        | 75.4        |
| Cefazolin            | 53.4        | 46.6        | 53.4        | 46.6        | 52.1        | 47.9        | 49.4        | 50.6        |
| Cefuroxime           | 44.8        | 55.2        | 46.9        | 53.1        | 47.9        | 52.1        | 47.0        | 53.0        |
| Cefazidime           | 27.6        | 72.4        | 26.6        | 73.4        | 24.3        | 75.1        | 26.8        | 73.2        |
| Ceftriaxone          | 36.2        | 63.8        | 40.6        | 59.4        | 40.8        | 59.2        | 45.8        | 54.2        |
| Cefepime             | 27.6        | 72.4        | 29.7        | 70.3        | 31.0        | 69.0        | 30.1        | 69.9        |
| Cefotetan            | 19.0        | 77.0        | 25.0        | 75.0        | 22.5        | 77.5        | 27.7        | 72.3        |
| Aztreonam            | 32.8        | 67.2        | 37.5        | 62.5        | 36.6        | 63.4        | 38.6        | 61.4        |
| Ertapenem            | 19.0        | 81.0        | 21.9        | 78.1        | 22.5        | 77.5        | 27.7        | 72.3        |
| Imipenem             | 20.7        | 79.3        | 20.3        | 79.7        | 22.5        | 77.5        | 26.5        | 73.5        |
| Meropenem            | 20.7        | 79.3        | 21.9        | 78.1        | 22.5        | 77.5        | 27.7        | 72.3        |
| Amikacin             | 11.1        | 88.9        | 12.5        | 87.5        | 16.9        | 83.1        | 19.3        | 80.7        |
| Gentamicin           | 34.5        | 65.5        | 28.1        | 71.9        | 26.8        | 73.2        | 30.1        | 69.8        |
| Tobramycin           | 20.7        | 69.0        | 18.8        | 76.6        | 15.5        | 80.3        | 22.9        | 77.1        |
| Ciprofloxacin        | 31.0        | 68.6        | 35.9        | 64.1        | 40.8        | 56.2        | 38.6        | 61.4        |
| Levofloxacin         | 29.3        | 70.7        | 28.1        | 71.9        | 25.4        | 74.6        | 26.5        | 73.5        |
| SMZ-TMP              | 32.8        | 67.2        | 32.8        | 67.2        | 32.4        | 67.6        | 34.9        | 65.1        |
| Tigecycline          | 0           | 98.9        | 1.0         | 99.0        | 2.6         | 97.4        | 3.1         | 96.9        |

R Resistance, S susceptible, SMZ-TMP Trimethoprim-sulfamethoxazole
### Table 2  Comparison of clinical characteristics between patients with CRKP-BSI and CSKP-BSI

| Variable                                                                 | The total (N = 706) | CRKP (N = 212) | CSKP (N = 494) | P value |
|--------------------------------------------------------------------------|---------------------|----------------|----------------|---------|
| Male, n, (%)                                                             | 472 (66.9)          | 138 (65.1)     | 334 (67.6)     | 0.515   |
| Age(y), mean ± SD                                                        | 58.9 ± 16.0         | 60.8 ± 16.0    | 58.1 ± 16.2    | 0.147   |
| Comorbidities-No., %                                                     |                    |                |                |         |
| Congestive heart failure                                                 | 96 (13.6)           | 22 (10.4)      | 74 (15.0)      | 0.102   |
| Cerebrovascular disease                                                  | 122 (17.3)          | 40 (18.9)      | 82 (16.6)      | 0.465   |
| Chronic lung diseases                                                    | 146 (20.7)          | 52 (24.5)      | 94 (19.0)      | 0.098   |
| Hepatobiliary and pancreatic diseases                                    | 130 (18.4)          | 30 (14.2)      | 100 (20.2)     | 0.056   |
| Kidney diseases                                                          | 172 (24.4)          | 56 (26.4)      | 116 (23.5)     | 0.405   |
| Hematologic malignancy                                                   | 84 (11.9)           | 54 (25.5)      | 30 (6.1)       | < 0.001 |
| Solid tumor                                                              | 118 (16.7)          | 40 (18.9)      | 78 (15.8)      | 0.315   |
| Solid organ transplantation                                              | 49 (6.9)            | 19 (9.0)       | 30 (6.1)       | 0.166   |
| Diabetes mellitus                                                        | 140 (19.8)          | 36 (17.0)      | 104 (21.1)     | 0.214   |
| Immune diseases                                                          | 42 (5.9)            | 18 (8.5)       | 24 (4.9)       | 0.061   |
| Charlson comorbidity index ≥ 3                                           | 348 (49.3)          | 112 (52.8)     | 236 (47.8)     | 0.218   |
| Pre-infection healthcare interventions-No., %                           |                    |                |                |         |
| Enema                                                                    | 52 (7.4)            | 18 (8.5)       | 34 (6.9)       | 0.453   |
| Nasogastric catheter                                                     | 174 (24.6)          | 46 (21.7)      | 128 (25.9)     | 0.234   |
| Urinary catheter                                                        | 254 (36.0)          | 82 (38.7)      | 172 (34.8)     | 0.327   |
| Surgical drain                                                           | 104 (14.7)          | 38 (17.9)      | 66 (13.4)      | 0.117   |
| Central venous catheter                                                  | 190 (26.9)          | 64 (30.2)      | 126 (25.5)     | 0.198   |
| Peripheral arterial catheter                                            | 65 (9.2)            | 26 (12.3)      | 39 (7.9)       | 0.066   |
| Blood purification                                                       | 72 (10.2)           | 28 (13.2)      | 44 (8.9)       | 0.083   |
| Tracheal cannula                                                        | 288 (40.8)          | 91 (42.9)      | 197 (39.9)     | 0.450   |
| Tracheostomy                                                            | 54 (7.6)            | 20 (9.4)       | 34 (6.9)       | 0.242   |
| Mechanical ventilation                                                   | 182 (25.8)          | 64 (30.2)      | 118 (23.9)     | 0.079   |
| Gastroscopy                                                              | 15 (2.1)            | 6 (2.8)        | 9 (1.8)        | 0.394   |
| Colonoscopy                                                              | 6 (0.8)             | 2 (0.9)        | 4 (0.8)        | 0.859   |
| Bronchoscopy                                                             | 78 (11.0)           | 24 (11.3)      | 54 (10.9)      | 0.880   |
| Sputum suction                                                           | 356 (50.4)          | 115 (54.2)     | 241 (48.8)     | 0.184   |
| Thoracentesis                                                            | 56 (7.9)            | 21 (9.9)       | 35 (7.1)       | 0.204   |
| Abdominocentesis                                                        | 35 (5.0)            | 12 (5.7)       | 23 (4.7)       | 0.573   |
| Bone marrow puncture                                                     | 91 (12.9)           | 33 (15.6)      | 58 (11.7)      | 0.164   |
| Lumbar puncture                                                          | 68 (9.6)            | 25 (11.8)      | 43 (8.7)       | 0.202   |
| Previous surgery                                                         | 140 (19.8)          | 58 (27.4)      | 82 (16.6)      | 0.001   |
| Parenteral nutrition                                                     | 237 (33.6)          | 77 (36.3)      | 160 (32.4)     | 0.311   |
| Previous hospitalization                                                 | 378 (53.5)          | 134 (63.2)     | 244 (49.4)     | 0.001   |
| Previous treatments administered-No., %                                 |                    |                |                |         |
| Corticosteroids                                                          | 138 (19.5)          | 52 (24.5)      | 86 (17.4)      | 0.029   |
| Chemotherapy or radiotherapy                                             | 150 (21.2)          | 40 (18.9)      | 110 (22.3)     | 0.311   |
| Inadequate empirical antibiotic therapy                                  | 261 (37.0)          | 96 (45.3)      | 165 (33.4)     | 0.003   |
| Previous use of antibiotics                                              |                    |                |                |         |
| Carbapenems                                                              | 218 (30.9)          | 68 (32.1)      | 150 (30.4)     | 0.652   |
| Glycopeptides                                                            | 144 (20.4)          | 48 (22.6)      | 96 (19.4)      | 0.332   |
| Quinolones                                                                | 227 (32.2)          | 74 (34.9)      | 153 (31.0)     | 0.305   |
| 3rd/4th generation cephalosporins                                       | 102 (14.4)          | 38 (17.9)      | 64 (13.0)      | 0.085   |
| 1st/2nd generation cephalosporins                                       | 86 (12.2)           | 25 (11.8)      | 61 (12.3)      | 0.836   |
| Penicillins                                                              | 35 (5.0)            | 8 (3.8)        | 27 (5.5)       | 0.342   |
| β-lactamase inhibitor                                                    | 308 (43.6)          | 101 (47.6)     | 207 (41.9)     | 0.159   |
| Aminoglycosides                                                          | 27 (3.8)            | 12 (5.7)       | 15 (3.0)       | 0.096   |
infection onset, inadequate empirical antibiotic therapy, corticosteroids use preceding infection onset and probable pulmonary source of infection. Using multivariate logistic regression analysis, hematologic malignancy (Odds ratio (OR) 4.68, 95% CI 2.3–9.4) and ICU-acquired infection (OR 2.10, 95% CI 1.3–3.4) was identified to be independent predictors of carbapenem-resistance among patients with Klebsiella BSI (Table 3).

Risk factors for mortality of CRKP-BSI patients
Overall, the 28-day mortality of CRKP-BSI patients was 42.5%. In order to identify the risk factors correlated with crude 28-day mortality of CRKP-BSI patients, we compared patient demographics, clinical characteristics, type of infections, and prior antibiotic exposures of deceased and survivor patients of CRKP-BSIs (Table 4). In the univariable logistic regression analysis, congestive heart failure and ICU-acquired infection were determined to be the main risk factors. Besides, the mortality rate was also affected by various events preceding CRKP-BSI onset, such as blood purification, mechanical ventilation, corticosteroids use preceding infection onset. Additionally, inadequate empirical antibiotic therapy, high APACHE II score, severe sepsis / septic shock were associated with

### Table 2 (continued)

| Variable                                                                 | The total (N = 706) | CRKP (N = 212) | CSKP (N = 494) | P value |
|--------------------------------------------------------------------------|---------------------|----------------|----------------|---------|
| Linezolid                                                                | 41 (5.8)            | 14 (6.6)       | 27 (5.5)       | 0.553   |
| Tigecycline                                                              | 77 (10.9)           | 28 (13.2)      | 49 (9.9)       | 0.199   |
| Daptomycin                                                               | 8 (1.1)             | 2 (0.9)        | 6 (1.2)        | 0.755   |
| Nitroimidazoles                                                          | 32 (4.5)            | 13 (6.1)       | 19 (3.8)       | 0.181   |
| Source of BSI-No., %                                                     |                     |                |                |         |
| Primary                                                                  | 408 (57.8)          | 112 (52.8)     | 296 (59.9)     | 0.080   |
| KP detection in samples from other sites                                 | 348 (49.3)          | 116 (54.7)     | 232 (47.0)     | 0.059   |
| Pulmonary                                                                | 166 (23.5)          | 66 (31.7)      | 100 (20.1)     | 0.001   |
| Pleural effusion                                                         | 16 (2.3)            | 6 (2.8)        | 10 (2.0)       | 0.510   |
| Pancreatobiliary tract infection                                         | 40 (5.7)            | 14 (6.6)       | 26 (5.3)       | 0.480   |
| Live abscess                                                            | 30 (4.2)            | 12 (5.7)       | 18 (3.6)       | 0.223   |
| Urinary tract infection                                                  | 35 (5.0)            | 11 (5.2)       | 24 (4.9)       | 0.853   |
| Intestinal infection                                                     | 26 (3.7)            | 6 (2.8)        | 20 (4.0)       | 0.431   |
| Intra-abdominal infection                                                | 17 (2.4)            | 5 (2.4)        | 12 (2.4)       | 0.955   |
| Skin infection                                                          | 12 (1.7)            | 4 (1.9)        | 8 (1.6)        | 0.801   |
| Cerebrospinal fluid                                                      | 6 (0.8)             | 2 (0.9)        | 4 (0.8)        | 0.859   |
| Ward at the onset of BSI-No., %                                          |                     |                |                |         |
| Intensive care units                                                     | 300 (42.5)          | 120 (56.6)     | 180 (36.4)     | < 0.001 |
| Medical wards                                                            | 232 (32.9)          | 54 (25.5)      | 178 (36.0)     | 0.006   |
| Surgical wards                                                           | 170 (24.1)          | 38 (17.9)      | 132 (26.7)     | 0.012   |
| Severity at BSI onset-No., %                                             |                     |                |                |         |
| APACHE II score > 15                                                     | 240 (34.0)          | 86 (40.6)      | 154 (31.2)     | 0.016   |
| Severe sepsis/septic shock                                               | 244 (34.6)          | 88 (41.5)      | 156 (31.6)     | 0.011   |
| Outcome-No., %                                                           |                     |                |                |         |
| 28-day mortality                                                         | 190 (26.9)          | 90 (42.5)      | 100 (20.2)     | < 0.001 |

* During the 12 months preceding infection onset
* During the 30 days preceding infection onset
* During the 72 hours preceding infection onset

### Table 3 Multivariate analysis of factors leading to the development of CRKP-BSI

| Variable                                                                 | P value | OR   | 95% CI          |
|--------------------------------------------------------------------------|---------|------|-----------------|
| Hematologic malignancy                                                   | < 0.001 | 4.68 | 2.322–9.427     |
| Intensive care units acquired infection                                  | 0.003   | 2.101| 1.291–3.420     |
| Previous hospitalization                                                 | 0.761   | 1.097| 0.603–1.996     |
| Previous surgery                                                        | 0.247   | 1.464| 0.767–2.794     |
| Inadequate empirical antibiotic therapy                                  | 0.150   | 1.485| 0.866–2.546     |
| Corticosteroids use preceding infection onset                           | 0.083   | 1.708| 0.933–3.125     |
| Pulmonary source of BSI                                                 | 0.061   | 1.748| 0.975–3.133     |

* During the 12 months preceding infection onset
* During the 30 days preceding infection onset
Table 4  Univariate analysis of factors for 28-day mortality in patients with infections caused by CRKP-BSI

| Variable                                           | Death (N = 90) | Survivors (N = 122) | P value |
|----------------------------------------------------|----------------|---------------------|---------|
| Male, n, (%)                                       | 56 (62.2)      | 82 (67.2)           | 0.451   |
| Age(y), mean ± SD                                  | 61.1 ± 17.7    | 60.7 ± 14.8         | 0.900   |
| Comorbidities- No., %                              |                |                     |         |
| Congestive heart failure                           | 14 (15.6)      | 8 (6.6)             | 0.034   |
| Cerebrovascular disease                            | 18 (20.0)      | 22 (18.0)           | 0.717   |
| Chronic lung diseases                              | 22 (24.4)      | 30 (24.6)           | 0.981   |
| Hepatobiliary and pancreatic diseases              | 17 (18.9)      | 13 (10.7)           | 0.089   |
| Kidney diseases                                    | 24 (26.7)      | 32 (26.2)           | 0.943   |
| Hematologic malignancy                             | 26 (28.9)      | 28 (23.0)           | 0.327   |
| Solid tumor                                        | 14 (15.6)      | 26 (21.3)           | 0.290   |
| Solid organ transplantation                         | 9 (10.0)       | 10 (8.2)            | 0.650   |
| Diabetes mellitus                                  | 12 (13.3)      | 24 (19.7)           | 0.224   |
| Immune diseases                                    | 10 (11.1)      | 8 (6.6)             | 0.240   |
| Charlson comorbidity index ≥ 3                     | 46 (51.1)      | 66 (54.1)           | 0.667   |
| Pre-infection healthcare interventions-No., %      |                |                     |         |
| Enema                                               | 9 (10.0)       | 9 (7.4)             | 0.498   |
| Nasogastric catheter                               | 14 (15.6)      | 32 (26.2)           | 0.062   |
| Urinary catheter                                   | 34 (37.8)      | 48 (39.3)           | 0.817   |
| Surgical drain                                      | 16 (17.8)      | 22 (18.0)           | 0.962   |
| Central venous catheter                            | 30 (33.3)      | 34 (27.9)           | 0.392   |
| Peripheral arterial catheter                       | 15 (16.7)      | 11 (9.0)            | 0.093   |
| Blood purification                                 | 19 (21.1)      | 9 (7.4)             | 0.004   |
| Tracheal cannula                                   | 47 (48.9)      | 44 (38.5)           | 0.132   |
| Tracheostomy                                        | 11 (12.2)      | 9 (7.4)             | 0.233   |
| Mechanical ventilation                             | 36 (40.0)      | 28 (23.0)           | 0.008   |
| Gastroscopy                                         | 3 (3.3)        | 3 (2.5)             | 0.704   |
| Colonoscopy                                         | 2 (2.2)        | 1 (0.8)             | 0.393   |
| Bronchoscopy                                        | 14 (15.6)      | 10 (8.2)            | 0.095   |
| Sputum suction                                      | 52 (57.8)      | 63 (51.6)           | 0.375   |
| Thoracentesis                                       | 11 (12.2)      | 10 (8.2)            | 0.332   |
| Abdominocentesis                                    | 6 (6.7)        | 6 (5.7)             | 0.586   |
| Bone marrow puncture                               | 14 (15.6)      | 19 (15.6)           | 0.997   |
| Lumbar puncture                                     | 11 (12.2)      | 14 (11.5)           | 0.868   |
| Previous surgery                                    | 26 (28.9)      | 32 (26.2)           | 0.668   |
| Parenteral nutrition                                | 37 (41.1)      | 40 (32.8)           | 0.213   |
| Previous hospitalization                            | 60 (66.7)      | 74 (60.7)           | 0.370   |
| Previous treatments administered-No., %            |                |                     |         |
| Corticosteroids                                     | 38 (42.2)      | 14 (11.5)           | <0.001  |
| Chemotherapy or radiotherapy                        | 12 (13.3)      | 28 (23.0)           | 0.077   |
| Inadequate empirical antibiotic therapy             | 78 (86.7)      | 18 (14.8)           | <0.001  |
| Previous use of antibiotics                         |                |                     |         |
| Carbapenems                                         | 30 (33.3)      | 38 (31.1)           | 0.736   |
| Glycopeptides                                       | 22 (24.4)      | 26 (21.3)           | 0.590   |
| Quinolones                                          | 34 (37.8)      | 40 (32.8)           | 0.451   |
| 3rd/4th generation cephalosporins                   | 14 (15.6)      | 24 (19.7)           | 0.440   |
| 1st/2nd generation cephalosporins                   | 10 (11.1)      | 15 (12.3)           | 0.792   |
| Penicillin                                          | 4 (4.4)        | 4 (3.3)             | 0.660   |
| β-lactamase inhibitor                               | 49 (54.4)      | 52 (42.6)           | 0.088   |
| Aminoglycosides                                     | 5 (5.6)        | 7 (5.7)             | 0.995   |
the crude 28-day mortality in univariable logistic regression analysis, In contrast, mortality was lower in patients that underwent high doses of carbapenem combination therapy. In the final multivariable logistic regression analysis model, only corticosteroids use preceding infection onset (OR 6.45, 95% CI 1.12–37.08, \( P = 0.037 \)), inadequate empirical antibiotic therapy (OR 15.01, 95% CI 3.70–60.79, \( P < 0.001 \)), severe sepsis / septic shock (OR 8.44, 95% CI 1.84–38.39, \( P = 0.006 \)) remained adversely and independently associated with 28-days mortality, whereas a protective effect was observed for high doses of carbapenem combination therapy (OR 0.11, 95% CI 0.03–0.51, \( P = 0.004 \)) (Table 5). 

### Table 4 (continued)

| Variable                                      | Death (\( N = 90 \)) | Survivors (\( N = 122 \)) | \( P \) value |
|-----------------------------------------------|-----------------------|-----------------------------|---------------|
| Linezolid                                     | 4 (4.4)               | 10 (8.2)                    | 0.277         |
| Tigecycline                                   | 13 (14.4)             | 15 (12.3)                   | 0.648         |
| Daptomycin                                    | 1 (1.1)               | 1 (0.8)                     | 0.828         |
| Nitroimidazoles                               | 6 (6.7)               | 7 (5.7)                     | 0.781         |
| Source of BSI- No., %                         |                       |                             |               |
| Primary                                       | 44 (48.9)             | 68 (55.7)                   | 0.323         |
| KP detection in samples from other sites      | 55 (61.1)             | 61 (50.0)                   | 0.108         |
| Pulmonary                                     | 20 (22.2)             | 36 (29.5)                   | 0.234         |
| Pleural effusion                              | 2 (2.2)               | 4 (3.3)                     | 0.647         |
| Pancreaticobiliary tract infection            | 8 (8.9)               | 6 (4.9)                     | 0.250         |
| Live abscess                                  | 5 (5.6)               | 7 (5.7)                     | 0.995         |
| Urinary tract infection                       | 7 (7.8)               | 4 (3.3)                     | 0.144         |
| Intestinal infection                          | 4 (4.4)               | 2 (1.6)                     | 0.223         |
| Intra-abdominal infection                     | 3 (3.3)               | 2 (1.6)                     | 0.422         |
| Skin infection                                | 3 (3.3)               | 1 (0.8)                     | 0.184         |
| Cerebrospinal fluid                           | 2 (2.2)               | 0 (3.3)                     | 0.098         |
| Ward at the onset of BSI- No., %              |                       |                             |               |
| Intensive care units                          | 62 (68.9)             | 58 (47.5)                   | 0.002         |
| Medical wards                                 | 18 (20.0)             | 36 (29.5)                   | 0.116         |
| Surgical wards                                | 10 (11.1)             | 28 (23.0)                   | 0.026         |
| Severity at BSI onset- No., %                 |                       |                             |               |
| APACHE II score > 15                          | 45 (50.0)             | 41 (33.6)                   | 0.016         |
| Severe sepsis/septic shock                    | 60 (66.7)             | 28 (23.0)                   | <0.001        |
| Therapeutic management-No., %                 |                       |                             |               |
| Monotherapy                                   | 7 (7.8)               | 20 (16.4)                   | 0.063         |
| Combination therapy                           | 83 (93.3)             | 102 (83.6)                  | 0.063         |
| Combination with high doses of carbapenem     | 30 (33.3)             | 96 (78.7)                   | <0.001        |
| Tigecycline containing regimen                | 38 (42.2)             | 46 (37.7)                   | 0.506         |
| Aminoglycoside containing regimen             | 30 (33.3)             | 28 (23.0)                   | 0.094         |
| Polymyxin B containing regimen                | 12 (13.3)             | 16 (13.1)                   | 0.963         |
| Ceftazidime and avibactam containing regimen  | 10 (11.1)             | 8 (6.6)                     | 0.240         |

\* During the 12 months preceding infection onset  
\* During the 30 days preceding infection onset  
\* During the 72 h preceding infection onset  

### Discussion

CRKP-BSI, one of the global public health concerns, has gained much attention for its considerable mortality. In China, a rapid increase of CRKP isolates among all KP isolates has been reported since 2010, while the current national average reaches 15.6% [21]. It was also reported that the incidence of CRKP has ubiquitously increased all over the world [22, 23]. For high CRKP endemic areas such as United States, Greece, Israel, and Italy, the percentage of CRKP-BSI ranged between 18 and 68%. [24–27]. In the current study, we had an interesting observation of an increase in CRKP-BSI occurrence since 2012, which was significantly higher when comparing
average occurrences in China. The possible reason may be attributed to differences in the investigated populations and the severity of the diseases.

To enhance the empirical therapy for CRKP-BSI and to control the emergence, we investigated the predictors of carbapenem-resistance among patients with Klebsiella BSI. Our results indicate that there are several predict factors involved in CRKP infection including hematologic malignancy, ICU acquired infection, hospitalization during the 12 months preceding infection onset, surgery during the 30 days preceding infection onset, inadequate empirical antibiotic therapy, corticosteroids use preceding infection onset and pulmonary source of BSI in univariate analyses. However, only two predict factors including hematologic malignancy and ICU acquired infection were demonstrated to be independently related to CRKP infection for KP. Patients with hematologic malignancies usually have frequent long-term hospitalization, undergo more invasive procedures, are exposed with high-grade antibiotics, and have impaired immunological response, which may lead to the development of CRKP-BSI [12]. Patients with hematologic malignancies were associated with the development of CRKP-BSI [12]. Therefore, the reinforcement of hygiene protocols in healthcare facilities and rational use of antibiotics should be specially strengthened to prevent the development of CRKP-BSI for patients with hematologic malignancies.

Increasing antibiotic resistance in ICUs is a significant clinical challenge, and we revealed that 56.6% of CRKP isolates were collected from ICU patients, which was consistent with other reports [26, 29]. It indicates that prevention and control of the occurrence of CRKP-BSI should be focused on ICU. ICU has already been recognized as a factory of creating, disseminating, and amplifying antimicrobial resistance [30]. Nosocomial infection is easily obtained via the airborne and contact transmission of resistant bacteria in the confined environment of ICU [15]. Noteworthy, medical equipment and devices have been demonstrated to be common vectors of CRKP in hospitals, especially in ICUs [29]. The development and transmission of CRKP is much easier in ICU due to the heavy use of the medical equipment and devices for the invasive procedures. Moreover, most ICU patients have relatively serious complications and may be treated with broad spectrum antibiotics or with longer duration of antibiotics use, which may contribute to the induction of carbapenem resistance for KP. To reduce onset of CRKP infections, appropriate controls should be implemented after the admission in ICU, such as active surveillance culture, precautionary isolations, disinfection, initial fitting antibiotic therapy, and relevant antibiotic de-escalation [17, 31].

However, previous studies suggested other variables, including surgery within the preceding 90 days, severe chronic comorbidities, previous hospitalizations, indwelling central venous catheter, mechanical ventilation, a nasogastric tube, prior carbapenem administration, and recent exposure to antimicrobials [17, 32–36]. In our study, no antibiotic or invasive procedures were identified as risk factors for CRKP-BSI. This difference may arise from different definition of the infection of CRKP-BSI, the exposure durations to antibiotics, or different patients selected for this research.

In our report, the total mortality rate at 28th day after infection in patients with KP-BSI was 26.1%. Patients with CRKP-BSI had a significantly elevated mortality rate as compared that of CSKP-BSI (42.5 vs. 26.1, *p < 0.001*), which was consistent with some previous observation [7]. However, other studies contradicted our findings, which showed that the mortality rate between CRKP-BSI

### Table 5 Multivariate analysis of factors for 28-day mortality in patients with infections caused by CRKP-BSI

| Variable                                      | P value | OR    | 95% CI        |
|-----------------------------------------------|---------|-------|---------------|
| Congestive heart failure                       | 0.151   | 7.576 | 0.479–119.913 |
| Intensive care units acquired infection        | 0.083   | 3.774 | 0.840–16.969  |
| Blood purification<sup>b</sup>                 | 0.384   | 2.893 | 0.265–31.623  |
| Mechanical ventilation<sup>c</sup>             | 0.298   | 2.457 | 0.452–13.344  |
| Corticosteroids use preceding infection onset<sup>d</sup> | 0.037   | 6.451 | 1.122–37.081  |
| Inadequate empirical antibiotic therapy        | < 0.001 | 15.006| 3.704–60.786  |
| APACHE II score > 15                           | 0.294   | 2.189 | 0.506–9.464   |
| Severe sepsis/septic shock                     | 0.006   | 8.435 | 1.854–38.385  |
| Combination with high doses of carbapenem      | 0.004   | 0.114 | 0.026–0.508   |

<sup>b</sup> During the 30 days preceding infection onset  
<sup>c</sup> During the 72 h preceding infection onset  
<sup>d</sup> During the 30 days preceding infection onset
and CSKP-BSI was almost the same [17, 24]. The possible explanation for these conflicting results is that infection-related mortality was associated with several factors, such as host immunity, bacterial virulence, and the efficacy of antibiotics [17].

To further explore the risk factors involved in 28-day mortality, patient characteristics and the therapeutic interventions on CRKP-BSIs were extensively investigated in our study. After adjusting for numerous confounders, various parameters, such as corticosteroids use preceding infection onset, inadequate empirical antibiotic therapy, severe sepsis or septic shock and combination therapy with high doses of carbapenem were related to a higher crude 28-day mortality. In agreement with the result by Papadimitriou-Olivgeris et al., we found that the use of corticosteroids preceding infection onset might contribute to the deleterious outcomes of CRKP-BSI patients [37]. Corticosteroids may inhibit a broad range of immune responses, which may have negative effects on infection control and eventually lead to the acceleration of death.

Additionally, the well-known association between septic shock and mortality of CR-KP BSI was also observed in our study [27, 38]. However, it is worth mentioning that corticosteroids have been used as adjuncts in the treatment of septic shock according to the guidelines proposed by the Surviving Sepsis Campaign [39]. Whether corticosteroids in the treatment of septic shock due to CP-KP effective or not still needs to be observed and should be validated through randomized controlled trials.

Due to the limited treatment options, inappropriate empirical antibiotic therapy was also demonstrated to be predictive factor for death in CRKP-BSI patients, which is consistent with other studies [38, 40]. Therefore, more attention should be taken to the initial appropriate antibiotic therapy for CRKP-BSI patients. The implementation of antimicrobial stewardship program and regular surveillance of resistance should be strengthened to avoid unnecessary antibiotic exposure.

Regarding the application of protective factors, we showed that there was a significant difference of the 28-day mortality rate between patients treated or not treated with high doses of carbapenem. Although Giannella et al. reported the lack of association between combination therapy with high doses of meropenem and the 14-day mortality, it remained as a protective factor in the multivariate model when adjusted the propensity score [41]. Moreover, they stratified their model according to meropenem MIC and found the benefit of high doses of meropenem therapy for CRKP with meropenem MIC ≤ 16 mg/L. In our study, patients received high dose carbapenem combination therapy only when they infected with CRKP of meropenem MIC ≤ 16 mg/L. Maybe it was easier to reach the pharmacokinetic/pharmacodynamic of the high-dose/prolonged-infusion regimen of meropenem for patients with lower meropenem MIC CRKP strains. Further studies need to be carried out to determine the effect of carbapenem MIC on outcome in patients treated with high dose carbapenem combination therapy. Additionally, in other studies, various risk factors associated with mortality of patients with CRKP-BSI were identified, including APACHE II score, liver failure, tracheal cannula on the day of bacteremia [17], bedridden status, mechanical ventilation, hemodialysis [33], and Pitt bacteremia score [24]. This may be explained by selection bias of study population.

There are several limitations that should be mentioned in this study. Firstly, it was a retrospective analysis of patients from a single center. Clinical data was collected solely according to medical records instead of interviews and clinical examinations of patients with KP-BSI by equally trained doctors. Secondly, we only included cases of *K. pneumoniae* infection with positive blood cultures. However, cases that were suspected to have KP-BSI but did not have blood samples collected for culture were not included. Therefore, total number of reported KP-BSI incidences can be slightly lower than the actual one. Finally, the lack of more detailed microbiological data, therefore, data related to strain’s genotype was not available. According to the report by Zheng et al., the mechanisms of resistance of CRKP were related with the emergences of ESBL (extended spectrum beta-lactamase) and carbapenemase genes [42]. With respect to the ESBL genes, CTX-M type enzymes were reported as the most common type, while regarding the carbapenemase genes, KPC-2 was the most prevalent in China [42]. Further studies will be carried out on the molecular epidemiology of CRKP strains in our group.

**Conclusions**

In conclusion, our results show that in our study hematologic malignancies and ICU-acquired infection were independent risk factors associated with the occurrence of CRKP-BSI. Septic shock, inadequate empirical antimicrobial therapy and corticosteroids use preceding infection onset caused significant increase of mortality rates in CRKP-BSI patients. Combination therapy with high dose carbapenem is associated with better outcome. These findings may serve as recommendations for treatments and prevention of CRKP-BSI patients in Changsha, Hunan Province, China.

**Abbreviations**

| Term            | Definition                                                                 |
|-----------------|-----------------------------------------------------------------------------|
| APACHE II       | Acute Physiology and Chronic Health Evaluation II                           |
| BSI             | Bloodstream infections                                                     |
| CCI             | Charlson comorbidity index                                                  |
| CI               | Confidence interval                                                        |
| COPD            | Chronic obstructive pulmonary disease                                       |
| CRKP            | Carbenpenem resistant                                                       |
| K. pneumoniae   | *Klebsiella pneumoniae*                                                     |
| CRKP-BSI        | Carbapenem-resistant *Klebsiella pneumoniae*                                |
| Bloodstream     | Infection with positive blood cultures                                      |
| E. coli         | *Escherichia coli*                                                          |
| ESBL            | Extended spectrum beta-lactamase                                            |
| APACHE II score | Acute Physiology and Chronic Health Evaluation II score                     |
| IQRs            | Interquartile ranges                                                       |
| KP              | *Klebsiella pneumoniae*                                                     |
| KP-BSI          | *Klebsiella pneumoniae* bloodstream infection                              |
| OR               | Odds ratio                                                                  |

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Author contributions
JC conceived this study, collected clinical data, interpreted the results, wrote, and revised the manuscript. JC, HY, HM, XY, YC, WP, FZ, SM, MR, PZ participated in collecting data and data statistics. PP, NR, LS and HY participated in the study design and revised the manuscript. All authors read and approved the final manuscript.

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Declarations
Ethics approval and consent to participate
This study was approved by the Ethics Committee of Xiangya Hospital, Central South University (No. 202104005). Due to the nature of the retrospective study and the anonymous processing of data prior to analysis, the Ethics Committee approved the waiver of informed consent. The study we carried out strictly complies with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
None of authors declare conflicts of interest relevant to this article.

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