A retrospective, comparative analysis of risk factors and outcomes in carbapenem-susceptible and carbapenem-nonsusceptible *Klebsiella pneumoniae* bloodstream infections: tigecycline significantly increases the mortality

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**Background:** Carbapenem-nonsusceptible *Klebsiella pneumoniae* (CnSKP) is rapidly emerging as a life-threatening nosocomial infection. The efficacy of tigecycline in the treatment of bloodstream infections (BSIs) remains controversial.

**Methods:** Data from a total of 428 patients with carbapenem-susceptible *Klebsiella pneumoniae* (CSKP) and CnSKP BSIs were collected at a single center between January 2013 and December 2015. A three-part analysis was conducted to identify the risk factors associated with CnSKP, explore prognosis, and evaluate treatments.

**Results:** Data from 428 patients with *Klebsiella pneumoniae* (KP) BSIs were included, 31.5% (n=135) of them with CnSKP. Multivariate analysis showed that prior hospitalization, urinary catheterization, the use of immunosuppressive agents, prior use of antibiotics, pulmonary disease, and high Acute Physiology and Chronic Health Evaluation (APACHE) II scores were independent risk factors for CnSKP-BSIs. The 30-day mortality was higher in patients with CnSKP than in those with CSKP (58.5% vs 15.4%; *P*<0.001). In patients with KP-BSIs, neutropenia, multiple organ dysfunction, respiraory failure, CnSKP infection, high APACHE II score, and tigecycline therapy were independently associated with higher mortality risk. Among patients whose APACHE II score was <15, higher mortality rates were observed in patients treated with tigecycline than in those treated with other antibiotics (45.3% vs 7.7%; *P*<0.001). Central venous catheterization, multiple organ dysfunction, and high APACHE II scores were independent risk factors for death from CnSKP.

**Conclusion:** A significant increase in the incidence of CnSKP-BSIs was observed during the study period, with a higher mortality rate found in these patients. Exposure to carbapenems and severe illness were independent risk factors for the development of CnSKP-BSIs, and tigecycline therapy resulted in a significant increase in mortality.

**Keywords:** *Klebsiella pneumoniae*, bloodstream infection, carbapenem nonsusceptible, risk factors, tigecycline

**Introduction**

*Klebsiella pneumoniae* (KP) is a pathogen that is mainly associated with community and nosocomial infections; after *Escherichia coli*, it is the second most common pathogen that leads to gram-negative bloodstream infections (BSIs). With more and more KP isolates producing extended-spectrum β-lactamase, and therefore exhibiting
resistance to many penicillin and cephalosporin antibiotics, carbapenems are the most widely used first-line antibiotics for such infections. However, the widespread use of these antibiotics has caused the emergence of carbapenem-resistant strains, mostly because of the propagation of carbapenem-hydrolyzing β-lactamases like the KP carbapenemase (KPC). KPC-producing KP was first reported in 1996, and in the hydrolyzing strains, mostly because of the propagation of carbapenem-antibiotics has caused the emergence of carbapenem-resistant identified. Therefore, studies recognizing risk factors although the most beneficial of the regimens has not yet been identified. As well as being a serious public health issue and infection control challenge, carbapenem-resistant Klebsiella pneumoniae (CRKP) is related to higher treatment failure rates, mortality, and cost. Prior studies show that BSIs caused by carbapenem-nonsusceptible Klebsiella pneumoniae (CnSKP) are associated with disappointing outcomes; the hospital death rates associated with these infections range from 40% to 72% compared with 20% to 30% in patients with carbapenem-susceptible Klebsiella pneumoniae (CSKP) infections. Furthermore, being older, hospital-acquired infections, ICU stay, illness severity, and inappropriate antimicrobial therapy, underlying diseases, and comorbidities; and other relevant information were retrieved from the hospital information system. Illness severity was assessed by using the Acute Physiology and Chronic Health Evaluation (APACHE) II scores calculated when BSIs attack. Charlson comorbidity index was used to determine comorbid conditions.

Data analysis
In order to assess treatment outcomes, 30-day mortality was investigated. As illustrated in Figure S1, a three-part analysis was conducted: 1) to evaluate the risk factors associated with CnSKP-BSI, 428 patients were divided into CSKP and CnSKP patient groups; 2) to explore the prognosis of KP-BSI and antibiotic treatment programs, the patients were categorized as survivors if they were alive after 30 days of infection or nonsurvivors if they were not (patients whose treatment time was <48 hours were excluded); and 3) to assess the risk factors associated with the 30-day mortality and treatment among patients with CnSKP-BSI, a case-controlled study was conducted.

Microbiological assessment and definition of terms
KP-BSI onset was defined as the collection date of the first positive blood culture. The probable infectious source was determined by using Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance definitions; primary BSI was recorded if no source was identified. When an absolute neutrophil count was <1500/µL on BSI onset, it was defined as neutropenia. Steroid therapy was defined as >20 mg/day prednisone or its equivalent administered for ≥7 days. Antimicrobial drug exposure referred to the use of antibiotics for >72 hours at any point 2 weeks prior to BSI diagnosis. Empirical therapy indicated all antimicrobial drugs administered to treat a suspected BSI. Definitive therapy referred to antimicrobial therapy administered after the susceptibility testing results were available and was classified as “appropriate” if an adequate dose of at least one drug was administered to which the pathogen was susceptible (as indicated by in vitro susceptibility testing) or “inappropriate” if these criteria were not met. Overall mortality included all
Categorical variables were analyzed by using the χ² test (for variables that are not normally distributed) was used.

The identification and antimicrobial susceptibility of KP were determined by using the Vitek2 system (bioMérieux, Marcy-l’Etoile, France). The minimum inhibitory concentration (MIC) of tigecycline was determined by using standard broth microdilution tests with fresh (<12 hours) Mueller–Hinton II Broth (cation-adjusted; Solarbio Science and Technology Ltd., Beijing, People’s Republic of China). According to the guidelines of the Clinical and Laboratory Standards Institute standards (2015), carbapenem-non-susceptibility is defined as an MIC of ≥1 mg/L for ertapenem or ≥2 mg/L for imipenem or meropenem. The US Food and Drug Administration (FDA) break points were used to judge tigecycline susceptibilities.

Statistical analysis
In order to evaluate continuous variables, the Student’s t-test (for normally distributed variables) or Mann–Whitney U test (for variables that are not normally distributed) was used. Categorical variables were analyzed by using the χ² test or two-tailed Fisher’s exact test appropriately. For continuous variables, results are expressed as median (interquartile range) or mean ± standard deviation, and categorical variables are expressed using the percentages of the group. The strength of all associations that emerged was determined using odds ratios (ORs) and 95% confidence intervals (CIs). Two-tailed tests were used to determine statistical significance. For multivariate analysis to identify independent predictors, variables with a P-value ≤0.05 in the univariate analysis were used in binary logistic regression. Kaplan–Meier product limit method was used to estimate the survival distribution function; nonparametric (log rank and Wilcoxon) tests were used to compare survival functions in different groups. In all analyses, P-values ≤0.05 were considered significant. All statistical analyses were carried out by using the SPSS Version 23.0 (IBM Corporation, Armonk, NY, USA).

Results
During the 3-year study period, 436 patients with at least one positive blood culture for Klebsiella were evaluated; 8 patients aged <16 years were excluded. Of the 428 patients included, 31.5% (n=135) had CnSKP. The overall incidence of KP-BSI was 0.154/1000 patient-days during the 3-year period (Figure S2). The overall incidence of CnSKP-BSI increased from 0.037/1000 patient-days in 2013 to 0.062/1000 patient-days in 2015, with the highest incidence occurring in the ICU (1.030/1000 patient-days). The results of antimicrobial susceptibility testing showed that the resistance rate of KP isolates to most antimicrobial agents was 35.0%–60%.

Table 1 shows the patient demographics and clinical characteristics. Regarding the probable infectious source of KP-BSI, intra-abdominal infection was most common (38.3%), followed by respiratory tract infection (31.8%) and primary bacteremia (17.5%). The overall all-cause 30-day mortality rate of KP-BSI patients was 29% (124 of 428); this was found to be significantly higher in patients with CnSKP-BSI (58.5%) than in those with CSKP (15.4%). Survival curve analysis confirmed the higher risks of mortality related to CnSKP-BSI (χ²=63.180, P<0.001; Figure 1A).

Risk factors associated with the development of CnSKP-BSIs
The univariate analysis showed that, compared with patients with CSKP-BSIs, those with CnSKP-BSIs were more likely to have nosocomial infection, respiratory tract origination, prior hospitalization, prior ICU hospitalization, or previous transplantations or to have undergone a nonsurgical invasive procedure, hemodialysis, chemotherapy, or radiotherapy. They also had lower total protein and high APACHE II scores and were more likely to have received corticosteroid therapy, immunosuppression, or prior exposure to drugs in the previous 14 days. In the multivariate analysis, logistic regression analysis (Table 1) showed the following factors to be independent risk factors for CnSKP-BSIs: hospitalization within 90 days before infection (OR =2.395, P<0.004), prior Foley catheterization (OR =5.277, P<0.001), immunosuppressive exposure (OR =4.093, P=0.001), prior use of antibiotics within 14 days prior to BSI (OR =2.739, P<0.001), previous carbapenem exposure (OR =4.591, P<0.001), pulmonary disease comorbidity (OR =2.599, P=0.008), and high APACHE II score (OR =1.100, P=0.001).

Risk factors for 30-day mortality in patients with KP-BSI
Of the 428 patients, 292 were classified as survivors and 78 as nonsurvivors; 58 patients were excluded as their treatment time was <48 hours. In the multivariate analysis (Table 2), factors independently associated with a higher risk of mortality were as follows: neutropenia, multiple organ dysfunction, respiratory failure, CnSKP infection, high APACHE II score, and tigecycline therapy after BSI. As shown in Table 2, carbapenem (n=254, 68.6%) was the most commonly used...
agent, followed by β-lactam and/or β-lactamase inhibitor (n=180, 48.6%) and tigecycline (n=84, 22.7%). Among KP-BSI patients treated with tigecycline, 48.8% received conventional dosing and 51.2% were treated with the high-dose regimen; no significant differences were seen in terms of 30-day mortality between the groups (Figure 1B). For patients with APACHE II scores <15 at the onset of bacteremia, the 30-day mortality rate of patients receiving tigecycline was higher than that of patients receiving other antibiotics (45.3% vs 7.7%; Figure 1C).

### Table 1 Clinical and demographic characteristics of patients with BSI caused by *Klebsiella pneumoniae*

|                        | CSKP (n=293) | CnSKP (n=135) | P-values | Multivariable analysis |
|------------------------|--------------|---------------|----------|------------------------|
| **Demographic**        |              |               |          |                        |
| Gender, male, n (%)    | 198 (67.6)   | 101 (74.8)    | 0.129    |                        |
| Age, years, mean ± SD  | 58.7±16.4    | 59.1±15.4     | 0.799    |                        |
| Duration before bacteremia, days (IQR) | 4 (1–16) | 16 (6–37) | <0.001 |                        |
| **Preexisting medical conditions** |          |               |          |                        |
| Pulmonary disease       | 33 (11.3)    | 51 (37.8)     | <0.001   | 0.008                  |
| Hepatic disease         | 90 (30.8)    | 30 (22.2)     | 0.066    |                       |
| Hematopoietic cancer    | 45 (15.4)    | 6 (4.4)       | 0.001    | 0.006                  |
| Solid tumor             | 60 (10.5)    | 13 (9.6)      | 0.006    |                        |
| **CCI score (≥3), n (%)** | 105 (35.8) | 60 (44.8)     | 0.078    |                        |
| **Likely source of bacteremia** |          |               |          |                        |
| Catheter-related        | 7 (2.4)      | 9 (6.7)       | 0.030    |                        |
| Pneumonia               | 69 (23.5)    | 67 (49.7)     | <0.001   |                        |
| Intra-abdominal         | 123 (42)     | 41 (30.4)     | 0.022    |                        |
| Urinary tract           | 6 (2.0)      | 1 (0.7)       | 0.441    |                        |
| Intracranial infection  | 3 (1.0)      | 4 (3.0)       | 0.214    |                        |
| Mixed infection         | 13 (4.4)     | 14 (10.4)     | 0.019    |                        |
| **Primary bloodstream infection** |      |               |          |                        |
| Hospital-acquired infection | 253 (86.3) | 135 (100)     | <0.001   |                        |
| Prior hospitalizationa  | 127 (43.3)   | 92 (68.1)     | <0.001   | 0.004                  |
| Prior ICU staya         | 52 (17.7)    | 87 (64.4)     | <0.001   |                        |
| Prior surgeryb          | 95 (32.4)    | 65 (48.1)     | 0.002    |                        |
| Previous transplantionsb| 5 (1.7)      | 21 (15.6)     | <0.001   |                        |
| Invasive procedure or devicesb | 96 (32.8) | 74 (54.8)     | <0.001   |                        |
| Mechanical ventilation  | 58 (19.8)    | 100 (74.1)    | <0.001   |                        |
| Central venous catheterization | 64 (21.8) | 101 (74.8)    | <0.001   |                        |
| Urinary catheterization | 77 (26.3)    | 110 (81.5)    | <0.001   | 5.277                  |
| Percutaneous tube       | 61 (20.8)    | 58 (43)       | <0.001   | 2.748                  |
| Prior hemodialysisa     | 19 (6.5)     | 36 (26.7)     | <0.001   |                        |
| Prior chemotherapy or radiotherapyb | 38 (13) | 6 (4.4)  | 0.007    |                        |
| Prior corticosteroid useb | 39 (13.3) | 42 (31.1)     | <0.001   |                        |
| Prior immunosuppressant useb | 21 (7.2) | 28 (20.7)     | <0.001   | 0.004                  |
| Prior surgeryb          | 95 (32.4)    | 65 (48.1)     | 0.002    |                        |
| Prior surgeryb          | 95 (32.4)    | 65 (48.1)     | 0.002    |                        |

**Notes:** Data are expressed as numbers (%) unless otherwise stated; aDuring the 3 months preceding the BSI onset; bDuring the 30 days preceding BSI onset; cDuring the 14 days preceding BSI onset.

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CCI, Charlson comorbidity index; CI, confidence interval; CnSKP, carbapenem-susceptible *Klebsiella pneumoniae*; CSKP, carbapenem-nonsusceptible *Klebsiella pneumoniae*; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.
Figure 1 Kaplan-Meier survival estimates: (A) patients with BSI caused by CSKP and CnSKP ($P<0.001$); (B) KP-BSI patients treated with tigecycline (or other agents) and its dose effect; (C) KP-BSI patients (APACHE II score <15) treated with tigecycline (or other agents) and its dose effect.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CnSKP, carbapenem-nonsusceptible KP; CSKP, carbapenem-susceptible KP; KP, Klebsiella pneumoniae.
Table 2  Analysis of risk factors for 30-day mortality in 370 patients with KP-BSI

| Demographic                                      | Survivors (292) | Nonsurvivors (78) | P-values | Multivariable analysis | Exp(B) | 95% CI for Exp(B) |
|--------------------------------------------------|-----------------|-------------------|----------|------------------------|--------|-------------------|
| Gender, male, n (%)                              | 202 (69.2)      | 57 (73.1)         | 0.504    |                        |        |                   |
| Age, years, mean ± SD                            | 58±16.6         | 58±15.8           | 0.951    |                        |        |                   |
| Hospital stay before bacteremia, days (IQR)      | 5 (1–19)        | 13.5 (3–30.25)    | 0.001    |                        |        |                   |
| Preexisting medical conditions                   |                 |                   |          |                        |        |                   |
| Pulmonary disease                                | 43 (14.7)       | 25 (32.1)         | <.001    |                        |        |                   |
| Hepatic disease                                  | 87 (29.8)       | 16 (20.8)         | 0.117    |                        |        |                   |
| Hepatapostema                                    | 46 (15.8)       | 2 (2.6)           | 0.002    |                        |        |                   |
| Comorbid conditions                              |                 |                   |          |                        |        |                   |
| CCI score (≥3) n (%)                             | 96 (32.9)       | 38 (48.7)         | 0.010    |                        |        |                   |
| Respiratory failure                              | 6 (2.1)         | 13 (16.7)         | <.001    | 0.014                  | 5.266  | 1.396 19.866      |
| Multiple organ failure                           | 12 (4.1)        | 30 (38.5)         | <.001    | 0.008                  | 4.104  | 1.438 11.709      |
| Hospital-acquired infection                      | 254 (87)        | 78 (100)          | 0.001    |                        |        |                   |
| Prior hospitalization a                         | 135 (46.2)      | 49 (62.8)         | 0.009    |                        |        |                   |
| Prior ICU stay b                                 | 75 (25.7)       | 44 (56.4)         | <.001    |                        |        |                   |
| Prior surgery b                                  | 106 (36.3)      | 36 (46.2)         | 0.112    |                        |        |                   |
| Previous transplantation b                       | 10 (3.4)        | 13 (16.7)         | <.001    |                        |        |                   |
| Invasive procedure or devices b                  | 105 (36.0)      | 43 (55.1)         | 0.002    |                        |        |                   |
| Mechanical ventilation b                         | 82 (28.1)       | 54 (69.2)         | <.001    |                        |        |                   |
| Central venous catheterization b                 | 86 (29.5)       | 52 (66.7)         | <.001    | 0.008                  | 4.104  | 1.438 11.709      |
| Urinary catheterization b                        | 100 (34.2)      | 56 (71.8)         | <.001    |                        |        |                   |
| Percutaneous tube b                              | 75 (25.7)       | 34 (43.6)         | 0.002    |                        |        |                   |
| Invasive procedure or devices after BSI b        | 79 (27.1)       | 16 (20.5)         | 0.240    |                        |        |                   |
| Mechanical ventilation i                         | 54 (18.5)       | 53 (67.9)         | <.001    |                        |        |                   |
| Central venous catheterization i                 | 73 (25.0)       | 57 (73.1)         | <.001    | 0.008                  | 4.104  | 1.438 11.709      |
| Urinary catheterization i                        | 103 (35.3)      | 62 (79.5)         | <.001    |                        |        |                   |
| Prior hemodialysis b                             | 25 (8.6)        | 18 (23.1)         | <.001    |                        |        |                   |
| Prior corticosteroid use b                       | 39 (13.4)       | 25 (32.1)         | <.001    |                        |        |                   |
| Prior immunosuppressant use b                    | 24 (8.2)        | 16 (20.5)         | 0.002    |                        |        |                   |
| Hemodialysis after BSI                          | 19 (6.5)        | 18 (23.1)         | <.001    |                        |        |                   |
| Corticosteroid use after BSI                     | 46 (15.8)       | 27 (34.6)         | <.001    |                        |        |                   |
| Immunosuppressant use after BSI                  | 18 (6.2)        | 11 (14.1)         | 0.020    |                        |        |                   |
| Prior receipt of antibiotics within 14 days prior to BSI |             |                   |          |                        |        |                   |
| Number of antibiotics                            | 0 (0–2)         | 2 (1–3)           | <.001    |                        |        |                   |
| Cephalosporin                                    | 20 (6.8)        | 8 (10.3)          | 0.312    |                        |        |                   |
| β-lactam and/or β-lactamase inhibitor            | 88 (30.1)       | 40 (51.3)         | <.001    |                        |        |                   |
| Tigecycline                                      | 17 (5.8)        | 14 (17.9)         | 0.001    |                        |        |                   |
| Carbenapem                                       | 52 (17.8)       | 36 (46.2)         | <.001    |                        |        |                   |
| Fluoroquinolone                                  | 29 (9.9)        | 7 (9.0)           | 0.800    |                        |        |                   |
| Carbenapen nonsusceptible                        | 55 (18.8)       | 52 (66.7)         | <.001    | 0.009                  | 2.847  | 1.302 6.227       |
| Laboratory examination                           |                 |                   |          |                        |        |                   |
| Neutropenia                                      | 21 (7.2)        | 12 (15.4)         | 0.024    | 0.008                  | 4.104  | 1.438 11.709      |
| Serum fibrinogen d                               | 3.9 (2.7–5.1)   | 3.5 (1.7–4.7)     | 0.015    |                        |        |                   |
| Serum albumin <30 g/L                            | 91 (31.2)       | 34 (43.6)         | 0.039    |                        |        |                   |
| Severity of illness at time of BSI              |                 |                   |          |                        |        |                   |
| Mean APACHE II score ± SD                        | 9.2±4.4         | 14.2±5.8          | <.001    | 0.018                  | 1.990  | 0.988 4.007       |
| Total antimicrobial regimen after BSI            |                 |                   |          |                        |        |                   |
| β-lactam and/or β-lactamase inhibitor            | 144 (49.3)      | 36 (46.2)         | 0.620    |                        |        |                   |
| Tigecycline                                      | 41 (14.0)       | 43 (55.1)         | <.001    | 0.034                  | 2.300  | 1.065 4.969       |
| <0.2 g/day                                       | 20 (6.8)        | 21 (26.9)         |          |                        |        |                   |
| ≥0.2 g/day                                       | 21 (7.2)        | 22 (28.2)         |          |                        |        |                   |
| a. Monotherapy                                   | 7 (2.4)         | 13 (9)            |          |                        |        |                   |
| b. Combination therapy                           | 34 (11.6)       | 40 (51.9)         |          |                        |        |                   |

(Continued)
Risk factors for 30-day mortality in patients with CnSKP-BSI

A total of 107 patients (excluding 28 patients with CnSKP-BSI who died within 48 hours of diagnosis) were included in this analysis; 65.4% of patients stayed in the ICU after infection, and the 30-day mortality rate was 48.6%. Table S1 shows the main characteristics of the CnSKP-BSI survivor and nonsurvivor subgroups. The logistic regression analysis indicated that prior indwelling central venous catheter (OR =3.704, 95% CI =1.325–10.356, P =0.013), multiple organ dysfunction (OR =5.498, 95% CI =1.727–17.504, P =0.004), and a high APACHE II score (OR =1.154, 95% CI =1.054–1.263, P =0.002) were independent risk factors for 30-day death from CnSKP infection.

In the present study, we also observed an increase in CnSKP-BSI during the study period, rising from 26.9% in 2013 to 33.3% in 2015. With the emergence of antibiotic-resistant strains, effective clinical treatment and control of infection are likely to present an increasing challenge.

This study represents the largest 3-year evaluation of KP-BSIs in Mainland China up to present. Data from 428 KP-BSI patients were evaluated, demonstrating prior hospitalization, urinary catheterization, and high APACHE II scores to be independent risk factors for the development of CnSKP-BSI, which reflects risk factors reported in previous studies.\(^3\)\(^,\)\(^11\) The highest incidence of CnSKP infections was observed in the ICU, with 65.4% of CnSKP-BSI patients admitted to the ICU before infection. It is well known that KP often colonizes in the respiratory tract or intestinal tract and can invade the body when immunity is compromised. In the present study, recent solid organ or stem cell transplantation was associated with invasive CnSKP infection independently, and prior studies showed KP infection to be a greater cause of BSIs in liver transplant recipients.\(^11\) In our hospital, we found the second highest incidence of CnSKP-BSI in the department of liver transplantation, which may be due to having frequent hospitalization of the patients and long-term exposure to immunosuppressive agents.

Antimicrobial use prior to BSI is known as an important factor in drug-resistant infections,\(^4\)\(^,\)\(^11\) although some studies showed no association between CnSKP infection and prior antibiotic therapy.\(^14\) Our results also demonstrated that the use of cephalosporin, β-lactam and/or β-lactamase inhibitors, fluoroquinolones, tigecycline, or carbapenem in the 14 days prior to BSI differed between the CSKP and CnSKP groups, with multivariate analysis showing that antibiotic exposure, particularly carbapenem use, in this period was an independent risk factor for CnSKP.

In order to explore the high mortality rate associated with KP-BSI further, we evaluated patient characteristics and treatments. In this study, the 30-day death rate associ-
tigecycline has become more widely used, although its efficacy in the treatment of multidrug-resistant bacteria such as CnSKP, KPC-KP, is emerging as a serious health care issue associated with high mortality rates and limited treatment options. Several clinical studies suggest that CRKP-BSI patients who were treated by carbapenem-containing combination regimens have significantly lower mortality rates than those treated by non-carbapenem-containing regimens, especially in cases where the MIC of KP was <4 μg/mL. In patients treated with carbapenem combination therapy, we found successful treatment in 75% of patients with meropenem MIC ≤4 μg/mL, compared with 47.9% with meropenem MIC ≥8 μg/mL, while 54.7% of patients who received non-carbapenem-containing regimens were successfully treated, although the difference was not statistically significant. In future studies, it would be valuable to expand the sample size to explore the efficacy of carbapenem in a larger group of patients with an MIC ≤4 μg/mL. Because of the retrospective nature and selection bias of our study and lack of appropriate antibiotics, we cannot comment on the effectiveness of appropriate empirical and definitive therapy among patients with CnSKP infection.

We acknowledge a number of limitations to this study. First, our analysis was a retrospective study, and it is possible that there may have been some degree of misclassification of the source of infection. Second, it was a single center study with a high incidence of CnSKP. Clone spread of KPC-2 and KPC-3 may make the hospital dissemination of CnSKP and influence therapy or prognosis; therefore, certain observations may not be applicable to other settings.

**Conclusion**

CnSKP is emerging as a serious health care issue associated with high mortality rates and limited treatment options. This study demonstrated that prior hospitalization, urinary catheterization, receipt of immunosuppression agents, pulmonary disease, high APACHE II score, and exposure to carbapenems represent significant risk factors for the
development of CnSKP-BSI. Neutropenia, low serum albumin, multiple organ dysfunction, respiratory failure, carbapenem-non-susceptibility, tigecycline therapy, and high APACHE II score are independent risk factors for mortality in patients with KP-BSI. With a higher observed mortality rate, we suggest that tigecycline may not be as effective as other antibiotics and that tigecycline should be used with caution for the treatment of multidrug-resistant KP.

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Disclosure
The authors report no conflicts of interest in this work.

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Supplementary materials

**Figure S1** Flowchart of the case selection process.

**Abbreviations:** BSI, bloodstream infection; CLSI, Clinical and Laboratory Standards Institute, CnSKP, carbapenem-nonsusceptible KP; CSKP, carbapenem-susceptible KP; KP, Klebsiella pneumoniae.

**Figure S2** Annual incidence of Klebsiella pneumoniae bloodstream infections (KP and CnSKP) in hospital departments.

**Abbreviations:** CnSKP, carbapenem-nonsusceptible KP; CSKP, carbapenem-susceptible KP; GS, Department of General Surgery; HT, Department of Hematology; ICU, intensive care unit; ID, Department of Infectious Diseases; KP, Klebsiella pneumoniae; LT, Department of Liver Transplantation; NE, Department of Nephrology.
Table S1 Analysis of risk factors for mortality in patients with BSI caused by CnSKP

| Demographic                          | Survivors (n) | Nonsurvivors (n) | P-values | Multivariable analysis |
|--------------------------------------|---------------|------------------|----------|------------------------|
|                                     |               |                  |          | Sig | Exp(B) | 95% CI for Exp(B) |
|                                      | Survivors     | Nonsurvivors     |           |    |        |                  |
|                                      | (SS)          | (SS)             |          |    |        |                  |
| Gender, male, n (%)                  | 42 (76.4)     | 39 (75)          | 0.869    |    |        |                  |
| Age, years, mean ± SD                | 57.8±16.5     | 59.1±15.2        | 0.679    |    |        |                  |
| Duration before bacteremia, days (IQR) | 19 (6–32)   | 18 (7–49.5)      | 0.781    |    |        |                  |
| Comorbid conditions                  |               |                  |          |    |        |                  |
| CCI score (≥3), n (%)                | 25 (45.5)     | 24 (46.2)        | 0.942    |    |        |                  |
| Respiratory failure                  | 1 (1.8)       | 8 (15.4)         | 0.014    |    |        |                  |
| Heart failure                        | 1 (1.8)       | 5 (9.6)          | 0.106    |    |        |                  |
| Kidney failure                       | 3 (5.5)       | 4 (7.7)          | 0.711    |    |        |                  |
| Multiple organ failure               | 5 (9.1)       | 20 (38.5)        | <0.001   | 0.004 | 5.498 | 1.727–17.504     |
| Prior ICU stay                       | 35 (63.6)     | 37 (71.2)        | 0.407    |    |        |                  |
| Prior receipt of antibiotics within 14 days before BSI | 2 (1–3) | 2 (2–3) | 0.157 |
| Mean APACHE II score ± SD           | 11.55±5.266   | 15.62±5.15       | <0.001   | 0.002 | 1.154 | 1.054–1.263      |
| Total antimicrobial regimen after BSI|               |                  |          |    |        |                  |
| Tigecycline                          | 30 (54.5)     | 34 (65.4)        | 0.253    |    |        |                  |
| ≤0.2 g/day                           | 14 (25.5)     | 17 (32.7)        | 0.790    |    |        |                  |
| ≥0.2 g/day                           | 16 (29.1)     | 17 (32.7)        |          |    |        |                  |
| Carbapenem                           | 37 (67.3)     | 34 (65.4)        | 0.836    |    |        |                  |
| MIC <4 μg/mL                         | 6 (16.2)      | 1 (2.9)          | 0.109    |    |        |                  |
| MIC ≥8 μg/mL                         | 31 (83.8)     | 31 (91.2)        | 0.482    |    |        |                  |
| Aminoglycoside                       | 11 (20)       | 13 (25)          | 0.535    |    |        |                  |
| Fluoroquinolone                      | 9 (16.4)      | 10 (19.2)        | 0.698    |    |        |                  |
| Appropriate empirical treatment      | 9 (16.4)      | 9 (17.3)         | 0.896    |    |        |                  |
| 1) Monotherapy                       | 24 (43.6)     | 14 (26.9)        | 0.071    |    |        |                  |
| 2) Combination therapy               | 31 (56.4)     | 38 (73.1)        |          |    |        |                  |
| Appropriate definitive treatment     | 20 (36.4)     | 25 (48.1)        | 0.220    |    |        |                  |
| 1) No active drug                    | 34 (61.8)     | 27 (51.9)        | 0.236    |    |        |                  |
| 2) At least two active drugs         | 3 (5.5)       | 6 (11.5)         |          |    |        |                  |
| 3) One active drug                   | 18 (32.7)     | 19 (36.5)        |          |    |        |                  |
| Antimicrobial regimen                |               |                  |          |    |        |                  |
| 1) Tigecycline monotherapy           | 6 (10.9)      | 2 (3.8)          | 0.272    |    |        |                  |
| 2) Tigecycline combination therapy   | 24 (43.6)     | 32 (61.5)        | 0.064    |    |        |                  |
| APACHE II ≤15                        | 16 (66.7)     | 16 (50)          | 0.212    |    |        |                  |
| APACHE II ≥15                        | 8 (33.3)      | 16 (50)          |          |    |        |                  |
| 3) Carbapenem monotherapy            | 11 (20)       | 6 (11.5)         | 0.231    |    |        |                  |
| 4) Carbapenem-containing regimen     | 26 (47.3)     | 28 (53.8)        | 0.497    |    |        |                  |
| MIC ≤4 μg/mL                         | 3 (11.5)      | 1 (3.6)          | 0.342    |    |        |                  |
| MIC ≥8 μg/mL                         | 23 (88.5)     | 25 (89.3)        | 1.000    |    |        |                  |

Notes: Data are expressed as number (%) unless otherwise stated; *During the 30 days preceding BSI onset; †During the 14 days preceding BSI onset.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CCI, Charlson comorbidity index; CI, confidence interval; CnSKP, carbapenem-nonsusceptible KP; CSKP, carbapenem-susceptible KP; ICU, intensive care unit; KP, Klebsiella pneumoniae; IQR, interquartile range; MIC, minimum inhibitory concentration; SD, standard deviation.
