

# 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, respiratory 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).<sup>1,2</sup> With more and more KP isolates producing extended-spectrum  $\beta$ -lactamase, and therefore exhibiting

resistance to many penicillin and cephalosporin antibiotics, carbapenems are the most widely used first-line antibiotics for such infections.<sup>3</sup> However, the widespread use of these antibiotics has caused the emergence of carbapenem-resistant strains, mostly because of the propagation of carbapenem-hydrolyzing  $\beta$ -lactamases like the KP carbapenemase (KPC). KPC-producing KP was first reported in 1996,<sup>4</sup> and in the People's Republic of China, the first KPC-positive KP isolates were found in intensive care unit (ICU) from a 75-year-old patient in 2004;<sup>5</sup> it has subsequently emerged as a global health care threat and is now endemic in many countries.<sup>6-8</sup>

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.<sup>7,8</sup> Prior studies show that BSIs caused by carbapenem-nonsusceptible *Klebsiella pneumoniae* (CnSKP) are associated with disappointing outcomes; the hospital death rates associating with these infections range from 40% to 72% compared with 20% to 30% in patients with carbapenem-susceptible *Klebsiella pneumoniae* (CSKP) infections.<sup>9-12</sup> Furthermore, being older, hospital-acquired infections, ICU stay, illness severity, and inappropriate regimens have been identified as risk factors contributing to increased mortality rates in patients with CnSKP-BSI.<sup>13,14</sup>

In previous retrospective studies, tigecycline combined with colistin, carbapenems, or aminoglycosides was found to be the most common regimen used for the management of carbapenem-resistant Enterobacteriaceae infection,<sup>15,16</sup> although the most beneficial of the regimens has not yet been identified.<sup>12,17,18</sup> Therefore, studies recognizing risk factors for the development of CnSKP-BSI and exploring the most effective therapeutic approaches are required. In this study, a retrospective group of patients with KP-BSIs were analyzed to identify the risk factors accompanied by CnSKP, explore prognosis, and evaluate treatments.

## Methods

### Study design

This retrospective study was conducted at the First Affiliated Hospital, College of Medicine, Zhejiang University, a 2500-bed teaching hospital in Eastern China, after receiving approval from the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. This study did not directly interfere with the patients or show the patients' name, medical record number, or other personal information. Moreover, there was no adverse effect on the rights of patients; therefore, consent to review their medical records was not required by the Institutional Review Board. The study

population comprised patients treated for BSI caused by KP (KP-BSI) between January 1, 2013, and December 31, 2015. Patients whose age was <16 years were excluded. If there were more than two episodes of KP-BSI in one patient, only the first episode was included. For the mortality analysis, patients who did not accept >48 hours of antimicrobial treatment for any reason were excluded. Patient demographics; clinical and microbiological data; laboratory analyses; data on 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.<sup>19</sup> Charlson comorbidity index was used to determine comorbid conditions.<sup>20</sup>

### 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.<sup>21</sup> When an absolute neutrophil count was <1500/ $\mu$ L on BSI onset, it was defined as neutropenia. Steroid therapy was defined as >20 mg/day prednisone or its equivalent administered for  $\geq$ 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.<sup>22</sup> Overall mortality included all

causes of death during hospitalization. During the study period, tigecycline was used to treat CnSKP-BSI, and its dosing was classified into conventional (100 mg loading dose, followed by 50 mg every 12 hours) or high dose (100 mg every 12 hours).<sup>23</sup>

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-nonsusceptibility is defined as an MIC of  $\geq 1$  mg/L for ertapenem or  $\geq 2$  mg/L for imipenem or meropenem.<sup>24</sup> The US Food and Drug Administration (FDA) break points were used to judge tigecycline susceptibilities.<sup>25</sup>

## 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  $\chi^2$  test or two-tailed Fisher's exact test appropriately. For continuous variables, results are expressed as median (interquartile range) or mean  $\pm$  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  $\leq 0.05$  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  $\leq 0.05$  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 ( $\chi^2=63.180$ , *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

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

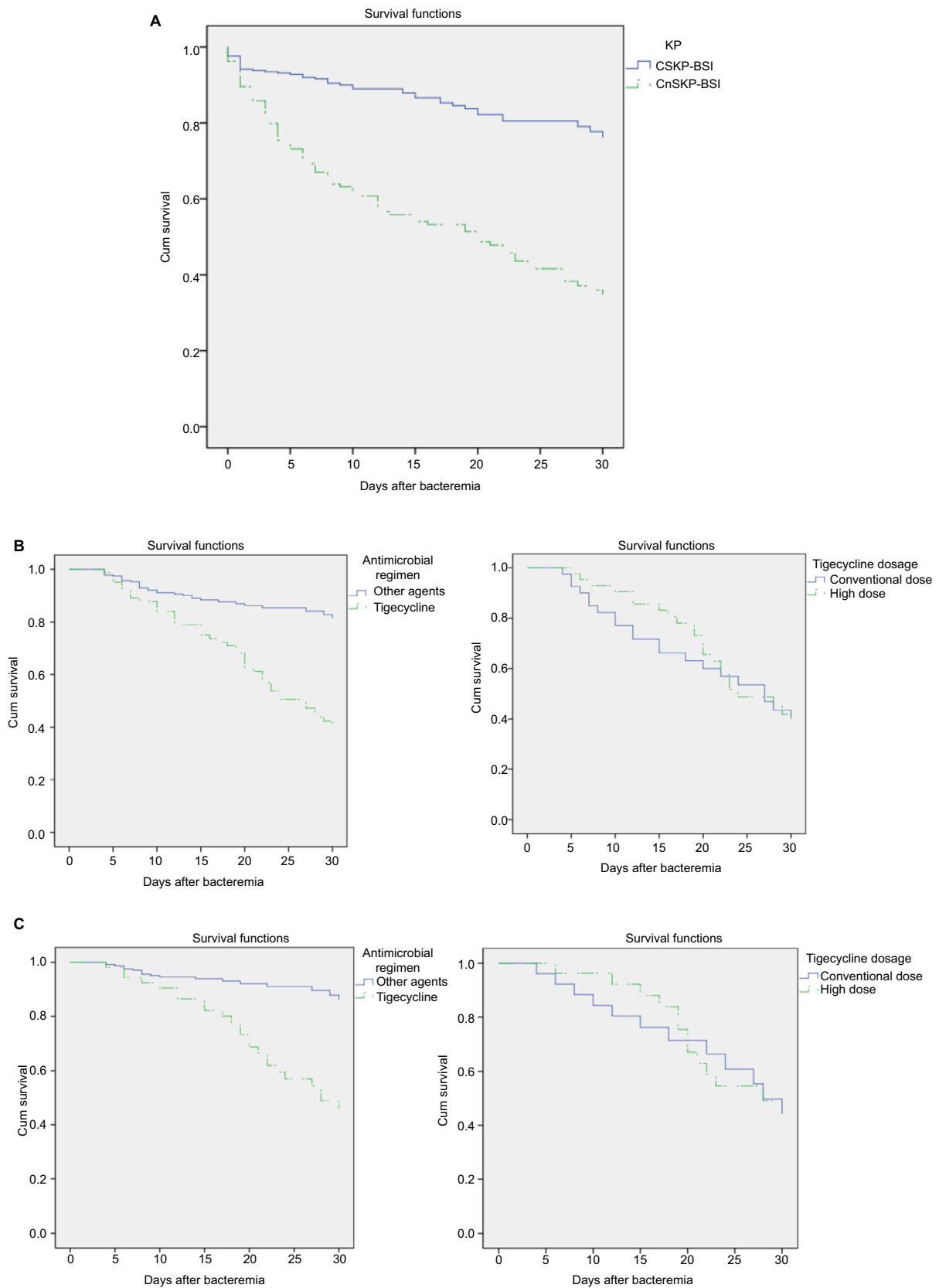
	Univariate analysis			Multivariable analysis			
	CSKP (n=293)	CnSKP (n=135)	P-values	Sig.	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
<b>Demographic</b>							
Gender, male, n (%)	198 (67.6)	101 (74.8)	0.129				
Age, years, mean ± SD	58.7±16.4	59.1±15.4	0.799				
Duration before bacteremia, days (IQR)	4 (1–16)	16 (6–37)	<0.001				
<b>Preexisting medical conditions</b>							
Pulmonary disease	33 (11.3)	51 (37.8)	<0.001	0.008	2.599	1.280	5.280
Hepatic disease	90 (30.8)	30 (22.2)	0.066				
Hepatopostema	45 (15.4)	6 (4.4)	0.001				
Solid tumor	60 (10.5)	13 (9.6)	0.006				
CCI score (≥3), n (%)	105 (35.8)	60 (44.8)	0.078				
<b>Likely source of bacteremia</b>							
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	69 (23.5)	6 (4.4)	<0.001				
Hospital-acquired infection	253 (86.3)	135 (100)	<0.001				
Prior hospitalization <sup>a</sup>	127 (43.3)	92 (68.1)	<0.001	0.004	2.395	1.326	4.328
Prior ICU stay <sup>b</sup>	52 (17.7)	87 (64.4)	<0.001				
Prior surgery <sup>b</sup>	95 (32.4)	65 (48.1)	0.002				
Previous transplantations <sup>b</sup>	5 (1.7)	21 (15.6)	<0.001				
Invasive procedure or devices <sup>b</sup>	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	<0.001	5.277	2.748	10.134
Percutaneous tube	61 (20.8)	58 (43)	<0.001				
Prior hemodialysis <sup>b</sup>	19 (6.5)	36 (26.7)	<0.001				
Prior chemotherapy or radiotherapy <sup>b</sup>	38 (13)	6 (4.4)	0.007				
Prior corticosteroid use <sup>b</sup>	39 (13.3)	42 (31.1)	<0.001				
Prior immunosuppressant use <sup>b</sup>	21 (7.2)	28 (20.7)	<0.001	0.001	4.093	1.734	9.661
Use of antibiotics within 14 days prior to BSI <sup>c</sup>	128 (43.7)	120 (88.9)	<0.001	0.007	2.739	1.311	5.721
Number of antibiotics	0 (0–1)	2 (1–3)	<0.001				
Cephalosporin	12 (4.1)	17 (12.6)	0.001				
β-lactam and/or β-lactamase inhibitor	84 (28.7)	66 (48.9)	<0.001				
Tigecycline	10 (3.4)	26 (19.4)	<0.001				
Carbapenem	36 (12.3)	73 (54.1)	<0.001	<0.001	4.591	2.331	9.044
Fluoroquinolone	22 (7.5)	25 (18.5)	0.001				
<b>Laboratory examination</b>							
Serum total protein, g/L	61.8 (54.7–66.8)	57.9 (53.0–65.4)	0.023				
Serum albumin <30 g/L	93 (31.7)	52 (38.5)	0.169				
Mean APACHE II score ± SD	8.9±4.4	12.6±5.6	<0.001	0.001	1.100	1.042	1.162

**Notes:** Data are expressed as numbers (%) unless otherwise stated; <sup>a</sup>During the 3 months preceding the BSI onset; <sup>b</sup>during the 30 days preceding BSI onset. <sup>c</sup>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 *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

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).



**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

	Univariate analysis			Multivariable analysis			
	Survivors (292)	Nonsurvivors (78)	P-values	Sig.	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
Demographic							
Gender, male, n (%)	202 (69.2)	57 (73.1)	0.504				
Age, years, mean ± SD	58.5±16.6	58.6±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)	<0.001				
Hepatic disease	87 (29.8)	16 (20.8)	0.117				
Hepatopostema	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)	<0.001	0.014	5.266	1.396	19.866
Multiple organ failure	12 (4.1)	30 (38.5)	<0.001	0.008	4.104	1.438	11.709
Hospital-acquired infection							
Prior hospitalization <sup>a</sup>	135 (46.2)	49 (62.8)	0.009				
Prior ICU stay <sup>b</sup>	75 (25.7)	44 (56.4)	<0.001				
Prior surgery <sup>b</sup>	106 (36.3)	36 (46.2)	0.112				
Previous transplantation <sup>b</sup>	10 (3.4)	13 (16.7)	<0.001				
Invasive procedure or devices <sup>b</sup>							
Mechanical ventilation <sup>b</sup>	82 (28.1)	54 (69.2)	<0.001				
Central venous catheterization <sup>b</sup>	86 (29.5)	52 (66.7)	<0.001				
Urinary catheterization <sup>b</sup>	100 (34.2)	56 (71.8)	<0.001				
Percutaneous tube <sup>b</sup>	75 (25.7)	34 (43.6)	0.002				
Invasive procedure or devices after BSI <sup>c</sup>							
Mechanical ventilation <sup>c</sup>	54 (18.5)	53 (67.9)	<0.001				
Central venous catheterization <sup>c</sup>	73 (25.0)	57 (73.1)	<0.001				
Urinary catheterization <sup>c</sup>	103 (35.3)	62 (79.5)	<0.001				
Prior hemodialysis <sup>b</sup>	25 (8.6)	18 (23.1)	<0.001				
Prior corticosteroid use <sup>b</sup>	39 (13.4)	25 (32.1)	<0.001				
Prior immunosuppressant use <sup>b</sup>	24 (8.2)	16 (20.5)	0.002				
Hemodialysis after BSI	19 (6.5)	18 (23.1)	<0.001				
Corticosteroid use after BSI	46 (15.8)	27 (34.6)	<0.001				
Immunosuppressant use after BSI	18 (6.2)	11 (14.1)	0.020				
Prior receipt of antibiotics within 14 days prior to BSI <sup>c</sup>							
Number of antibiotics	0 (0–2)	2 (1–3)	<0.001				
Cephalosporin	20 (6.8)	8 (10.3)	0.312				
β-lactam and/or β-lactamase inhibitor	88 (30.1)	40 (51.3)	<0.001				
Tigecycline	17 (5.8)	14 (17.9)	0.001				
Carbapenem	52 (17.8)	36 (46.2)	<0.001				
Fluoroquinolone	29 (9.9)	7 (9.0)	0.800				
Carbapenem nonsusceptible	55 (18.8)	52 (66.7)	<0.001	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	<0.001	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)	<0.001	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 (3.9)					
b. Combination therapy	34 (11.6)	40 (51.9)					

(Continued)

**Table 2** (Continued)

	Univariate analysis			Multivariable analysis		
	Survivors (292)	Nonsurvivors (78)	P-values	Sig.	Exp(B)	95% CI for Exp(B)
						Lower Upper
Carbapenem	198 (67.8)	56 (71.8)	0.500			
Fluoroquinolone	45 (15.5)	14 (17.9)	0.595			
Appropriate empirical treatment	237 (81.2)	33 (42.3)	<0.001			
1) Monotherapy	232 (79.5)	33 (42.3)	<0.001			
2) Combination therapy	60 (20.5)	45 (57.7)				
Appropriate definitive treatment	246 (84.2)	50 (64.1)	<0.001			

**Notes:** Data are expressed as numbers (%) unless otherwise stated; <sup>a</sup>During the 3 months preceding BSI onset; <sup>b</sup> during the 30 days preceding BSI onset; <sup>c</sup> 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; SD, standard deviation.

## 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.

The assessment of empirical treatment in the CnSKP-BSI group showed that 69 (64.5%) patients received at least two drugs within 48 hours of the onset of bacteremia, while 38 (35.5%) patients received monotherapy; no significant differences in the 30-day mortality were found among these two subgroups (36.8% vs 55.1%,  $P=0.071$ ) or between those who received appropriate empirical treatment versus inappropriate empirical treatment ( $P=0.896$ ). For definitive treatment, 61 (55.2%) patients received therapy with no active drug due to multiresistance, 37 patients (34.6%) received one active drug, and 9 patients (8.4%) received at least two active drugs; no significant differences were found in mortality between appropriate definitive treatment and inappropriate definitive treatment (54.3% vs 44.3%,  $P=0.220$ ).

## Discussion

KP is one of the most important pathogens of nosocomial infection, and while carbapenem antibiotics are an effective treatment approach,<sup>3</sup> surveillance data showed that the rate of CnSKP has increased year on year in the People's Republic of China, and has increased worldwide over the past 10 years.<sup>6–8</sup> 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.<sup>13,14</sup> 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.<sup>11</sup> 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,<sup>3,11</sup> although some studies showed no association between CnSKP infection and prior antibiotic therapy.<sup>14</sup> Our results also demonstrated that the use of cephalosporin,  $\beta$ -lactam and/or  $\beta$ -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-

ated with CnSKP-BSI was 58.5%, significantly higher than that associated with CSKP (15.4%); these data are similar to figures found in previous reports.<sup>9,10</sup> In addition, resistance to carbapenem was associated with an increased risk of mortality, which is in contrast to some previous studies.<sup>13</sup> As previously reported,<sup>9,22</sup> multiple organ dysfunction, respiratory failure, or high APACHE II scores were found as independent predictors of death; our analysis also found that KP-BSI patients with neutropenia were likely to have a poor outcome.

Tigecycline has a broad spectrum of action and excellent *in vitro* antimicrobial activity. It has been commonly used in infections caused by mixed pathogens or multidrug-resistant pathogens and is approved primarily for use in respiratory tract infections, complicated skin and skin structure infections, and complicated intra-abdominal infections caused by Enterobacteriaceae. Because of the lack of appropriate antibiotics for the treatment of multidrug-resistant bacteria such as CnSKP, tigecycline has become more widely used, although its efficacy in the treatment of KP-BSI remains controversial.<sup>15,16,26–28</sup> The present study demonstrated significantly higher mortality rates in the tigecycline group than in controls (51.2% and 12.2%,  $P < 0.001$ ); for patients with APACHE II scores  $< 15$ , the 30-day mortality rate of patients receiving tigecycline was 45.3%, versus 7.7% in patients receiving other antibiotics. These data are consistent with the FDA warning and a previous meta-analysis,<sup>26,28</sup> which showed that the proportion of patients with septic shock was significantly higher in those treated by tigecycline than in the controls (relative risk = 7.01). For patients whose infection is not resolved by conventional doses of tigecycline, an increased dose is often used, which is an approach that has also been recommended in a recent consensus statement.<sup>15</sup> However, a study of mortality among patients receiving conventional versus higher-dose regimens suggested that differences were dependent on the underlying infection severity, and there is limited clinical evidence to support high-dose tigecycline regimens.<sup>23</sup> Indeed, there were similarities in mortality between KP-BSI patients with APACHE II scores  $< 15$  treated with conventional dosing of tigecycline and higher dosing regimens in our analysis. Based on these observations, tigecycline does not appear to be superior to standard antimicrobial agents to treat KP-BSI, and physicians should exercise caution when selecting tigecycline for the therapy of multidrug-resistant infections.

In this study, deaths among patients with CnSKP-BSI were directly and independently related to the severity of infection, multiple organ dysfunction, and high APACHE II score. At present, a best practice treatment program for patients with CnSKP-BSI has not been established. In this

study, most patients received carbapenem, with monotherapy accounting for 23.9% of regimens and combination treatments accounting for 76.1%; no significant difference in CnSKP 30-day mortality was found among the two treatment regimens. The previous examination of the outcome of KPC-KP bacteremia in 125 patients treated at three large Italian teaching hospitals showed the overall 30-day mortality rate to be 42%, while mortality in patients receiving colistin, tigecycline, and meropenem combination regimens was significantly lower (34%, vs 54% with monotherapy;  $P = 0.02$ ).<sup>22</sup> By contrast, a review of 141 patients with CRKP-BSIs found that there were similarities in the 30-day mortality of patients who were treated with monotherapy and those with combination regimens (38% vs 26%,  $P = 0.1$ ).<sup>12</sup> 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  $< 4$  mg/L.<sup>29,30</sup> In patients treated with carbapenem combination therapy, we found successful treatment in 75% of patients with meropenem MIC  $\leq 4$   $\mu$ g/mL, compared with 47.9% with meropenem MIC  $\geq 8$   $\mu$ g/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  $\leq 4$   $\mu$ g/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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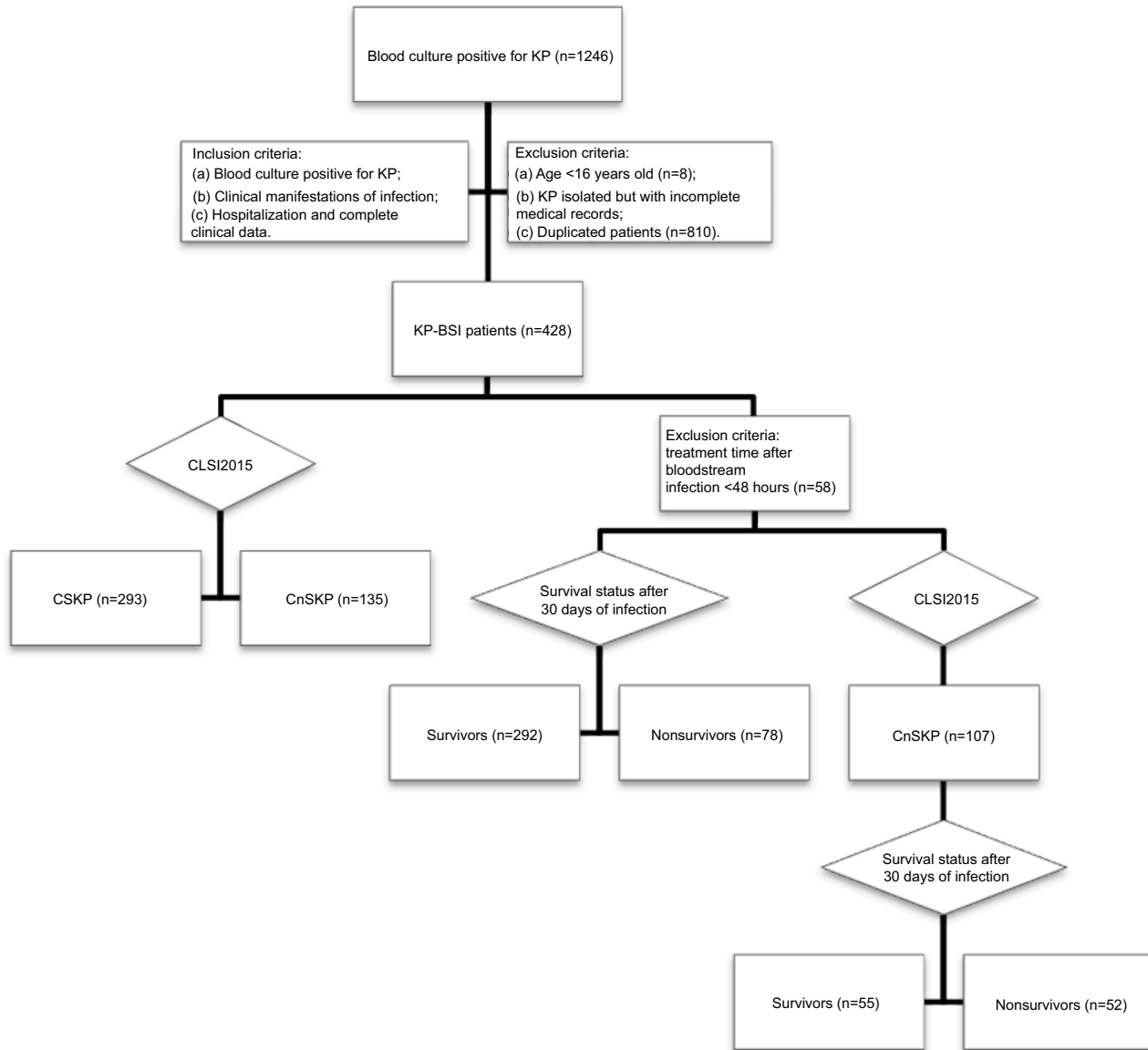
## Disclosure

The authors report no conflicts of interest in this work.

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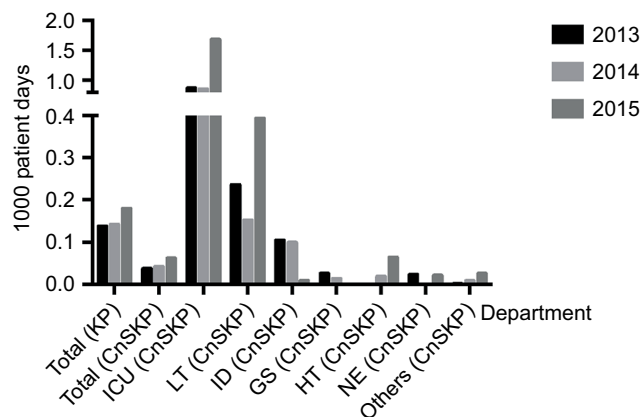
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### Supplementary materials



**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

	Univariate analysis			Multivariable analysis			
	Survivors (55)	Nonsurvivors (52)	P-values	Sig.	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
<b>Demographic</b>							
Gender, male, n (%) <sup>a</sup>	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				
<b>Comorbid conditions</b>							
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 <sup>a</sup>	35 (63.6)	37 (71.2)	0.407				
<b>Invasive procedure or devices<sup>a</sup></b>							
Mechanical ventilation	38 (69.1)	45 (86.5)	0.031				
Central venous catheterization	36 (65.5)	45 (86.5)	0.011	0.013	3.704	1.325	10.356
Urinary catheterization	42 (76.4)	47 (90.4)	0.053				
<b>Invasive procedure or devices after BSI</b>							
Mechanical ventilation	25 (45.5)	42 (80.8)	<0.001				
Central venous catheterization	29 (52.7)	44 (84.6)	<0.001				
Urinary catheterization	36 (65.5)	47 (90.4)	0.002				
<b>Prior receipt of antibiotics within 14 days before BSI<sup>b</sup></b>							
Number of antibiotics	2 (1–3)	2 (2–3)	0.157				
<b>Severity of illness at the time of BSI</b>							
Mean APACHE II score ± SD	11.55±5.266	15.62±5.15	<0.001	0.002	1.154	1.054	1.263
<b>Total antimicrobial regimen after BSI</b>							
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)					
<b>Antimicrobial regimen</b>							
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; <sup>a</sup>During the 30 days preceding BSI onset; <sup>b</sup>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.

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