

# Ceftazidime/Avibactam, Polymyxin or Tigecycline as a Rescue Strategy for the Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* in Bloodstream Infection: A Retrospective Cohort Study

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**Objective:** To analyze the clinical characteristics, outcomes, and risk factors of patients treated with ceftazidime/avibactam, polymyxin, or tigecycline (CPT) compared with those receiving a conventional therapy (CT) (ie, imipenem, levofloxacin, or gentamicin).

**Methods:** A single-center retrospective cohort study included patients with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection (CRKP-BSI) treated at one Chinese tertiary hospital between March 2012 and November 2022 was performed. Clinical characteristics, outcomes, and risk factors of patients treated with CPT or CT were compared. Predictors of 30-day mortality of patients with CRKP-BSI were also analysed in our study.

**Results:** Among 184 recruited patients with CRKP-BSI, 39.7% (73/184) were treated with CPT, while 60.3% (111/184) were treated with CT. Compared to patients treated with CT, patients treated with CPT had worse conditions, as evidenced by a higher rate of underlying diseases and invasive procedures; however, they also had a better prognosis and lower rates of 14-day treatment failure ( $p = 0.024$ ). In addition, univariate analysis and multivariate analysis showed that SOFA score [odds ratio (OR) = 1.310, 95% confidence interval (CI) 1.157–1.483;  $p < 0.001$ ] and cold weather (OR = 3.658, 95% CI 1.474–9.081;  $p = 0.005$ ) were independent risk factors for 30-day mortality.

**Conclusion:** Compared to CRKP-BSI patients treated with CT, patients treated with CPT had worse conditions but better prognoses. CRKP-BSI occurred more frequently in hot weather; however, higher 30-day mortality was associated with cold weather. A randomized trial is needed to confirm these observational results.

**Keywords:** carbapenem-resistant *Klebsiella pneumoniae*, polymyxin, tigecycline, ceftazidime/avibactam, bloodstream infection, hot weather, cold weather

## Introduction

Bloodstream infections (BSIs) were strongly associated with mortality, accounting for about 11–38% of infections, due to prolonged hospital stays, invasive medical procedures, and immunosuppression.<sup>1</sup> *Klebsiella pneumoniae* (*K. pneumoniae*) was one of the major nosocomial pathogens and the second most common pathogen in Enterobacteriaceae bloodstream infections.<sup>2</sup> Some studies showed that *Klebsiella pneumoniae* bloodstream infections (KP-BSIs) account for 6.6–9.9% of all bloodstream

infections, with a mortality rate of 20–37%.<sup>2–4</sup> With the increasing use of carbapenems in hospitals, the carbapenem-resistant *Klebsiella pneumoniae* (CRKP) had become an emerging cause of healthcare-associated infections.<sup>5</sup> CRKP was widely resistant, often leading to clinical failure even with rescue antimicrobial agents (ie, fluoroquinolones, carbapenems, and aminoglycosides). In addition, although there were many studies showing that combination therapy with multiple in vitro active agents may be superior to monotherapy, the rate of clinical failure remains high.<sup>6–8</sup> Because of the few antibiotics available, CRKP was associated with a longer hospital stay and increased mortality.<sup>9,10</sup> So it is urged to identify effective treatment strategies for CRKP-BSI.

Recently, ceftazidime/avibactam, polymyxin, or tigecycline, have been proposed as salvage therapy for CRKP infections, whether alone or in combination.<sup>11–14</sup> Nevertheless, studies investigating the outcomes and prognosis of these three antibiotics compared with other antibiotics are lacking. Therefore, this study analyzed the clinical characteristics, risk factors, and outcomes of patients treated with ceftazidime/avibactam, polymyxin, or tigecycline (CPT), compared with conventional therapy (CT). In addition, we also analyzed the risk factors of 30-day mortality of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection (CRKP-BSI).

## Materials and Methods

### Study Design and Patients

This retrospective, case–control study was conducted in the clinical laboratory of the Second Affiliated Hospital of Nanchang University from March 2012 to November 2022, which is a comprehensive tertiary hospital with 4000 beds in Jiangxi Province, China. Patients' clinical information was collected through the Laboratory Information System (LIS) and Hospital Information System (HIS) database. The patient inclusion criteria were: (1) age  $\geq 18$  years old; (2) patients infected with CRKP; (3) samples were obtained from peripheral blood; only the first bacteremic episode was included; (4) complete clinical records and data.

### Data Collection

Data from LIS and HIS included demographic data (gender, age), symptoms and diagnosis, laboratory and microbiological outcomes, potential diseases and complications, as well as data regarding antimicrobial therapy, clinical outcomes (cured and improved or died), and weather. Age-adjusted Charlson Comorbidity Index (aCCI), Pitt bacteremia score, and Sepsis-related Organ Failure Assessment (SOFA) score were analyzed at the time of BSI onset.

### Definitions

Patients with at least one positive blood culture and with at least two symptoms were diagnosed with *K. pneumoniae* bloodstream infection (KP-BSI): (1) body temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ ; (2) heart rate  $>90$  beats per minute; (3) respiratory rate  $>20$  breaths per minute; (4) the peripheral blood leukocyte  $>10 \times 10^9/\text{L}$  or  $<4 \times 10^9/\text{L}$ . If the first culture-positive sample was collected more than 48 h after hospital admission or within 48 h after discharge from the hospital, it was defined as a hospital-acquired infection; otherwise, the case was considered as community-acquired. Hot weather referred to the three hottest months in local, while cold weather referred to the three coldest months in local. Clinical outcomes included cure, improvement, and failure. If all symptoms and signs of the infection disappeared and no further antibiotic treatment was needed, a clinical cure was considered successful; if the complete or partial resolution of all symptoms and signs of infection occurred but further antibiotic treatment was needed, a clinical improvement was considered; treatment failure was defined as symptoms or signs of infection that persisted or worsened or in case of death.

### Antimicrobial Susceptibilities

*K. pneumoniae* isolates were identified using the VITEK 2 Compact system (bioMérieux, France) or matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) system (bioMérieux). The antimicrobial resistance of isolates was detected by antimicrobial sensitivity tests using VITEK 2 Compact system and disc diffusion method on the Mueller-Hinton (MH) Agar plates. These antibiotics included ceftriaxone, ciprofloxacin, levofloxacin, tigecycline, amikacin, imipenem, meropenem, ceftazidime/avibactam, piperacillin/tazobactam, amoxicillin/clavulanate,

cefoperazone/sulbactam, aztreonam, gentamicin, cefepime, cotrimoxazole, and tobramycin. The antimicrobial susceptibility of tigecycline was interpreted according to Food and Drug Administration (FDA). The antimicrobial susceptibility of other antibiotics was interpreted according to Clinical and Laboratory Standards Institute (CLSI).

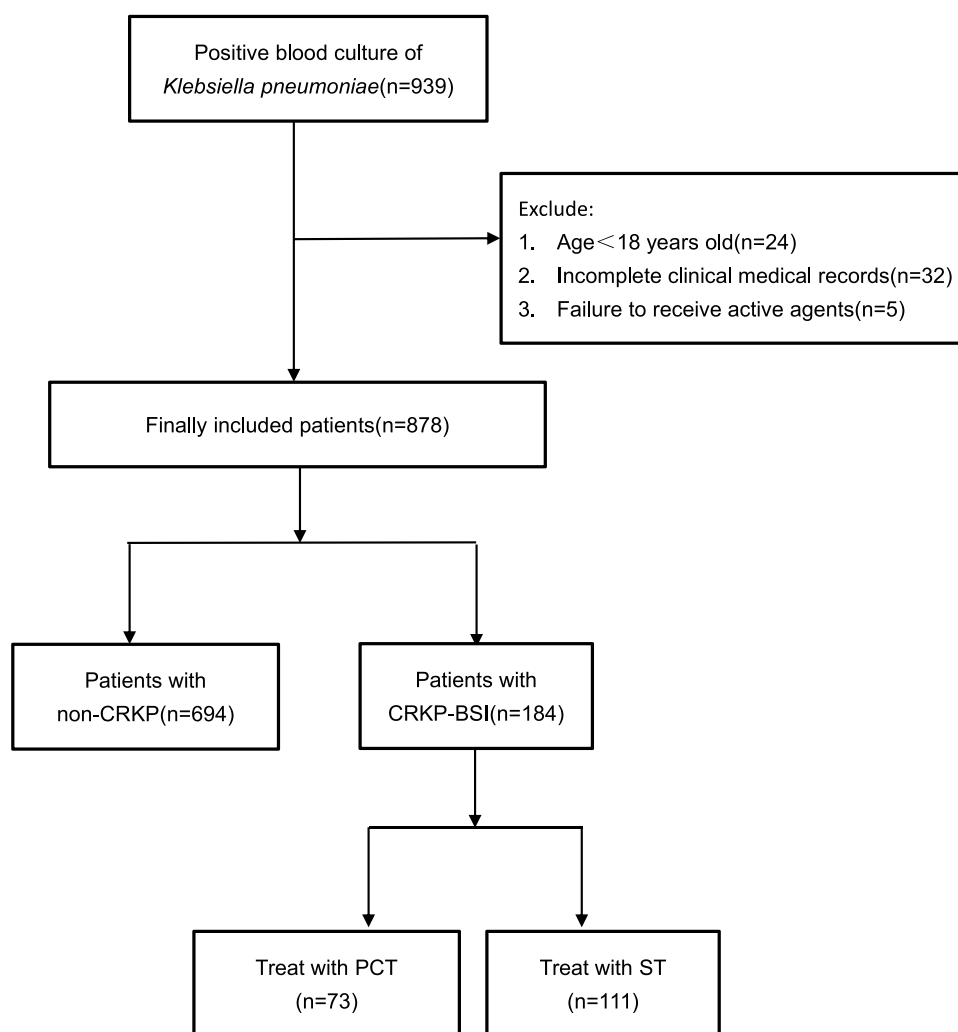
## Statistical Analysis

Data were analyzed using SPSS software, version 25.0 (IBM Inc., New York, USA). We expressed continuous variables as means  $\pm$  standard deviations and reported categorical variables as medians and percentages. Student's *t*-test and Mann–Whitney *U*-test were used to evaluate continuous variables. Categorical variables were assessed using the  $\chi^2$  test or Fisher's exact test. In order to determine independent risk factors for 30-day mortality, we included potential confounders and variables with a P-value of  $<0.05$  in the univariable analysis into the multivariable regression analysis. P values of  $<0.05$  were considered statistically significant.

## Results

### Demographic and Clinical Characteristics

A total of 939 cases of *K. pneumoniae* were isolated from blood culture. Among those, 184 patients with CRKP from blood sources were included in the final analysis. Among 184 patients, 39.7% (73/184) were treated with CPT and 60.3% (111/184) were treated with CT (Figure 1).



**Figure 1** Flow chart of patients selected.

The demographic data of enrolled patients are summarized in Table 1. Of the 184 patients, 131 (71.2%) were male and 53 (28.8%) were female ( $P = 0.045$ ), and their mean age was 62 years (SD: 15.51). Hospital-acquired infection occurred in 94.6% (174/184) of patients. The most common co-morbidities were hypoproteinaemia (42.4%), followed by kidney disease (41.3%). The proportions of hypoproteinaemia ( $P = 0.031$ ), hepatic disease ( $P = 0.013$ ), anemia ( $P = 0.001$ ), gastrointestinal disease ( $P = 0.007$ ) and surgery within 3 months ( $P = 0.012$ ) were higher in the CPT group compared to the CT group. However, there were more patients with biliary tract disease in the CT group than in the CPT group ( $P = 0.033$ ). The CPT group usually had a better clinical outcome and a lower rate of 14-day treatment failure ( $P = 0.024$ ). In addition, patients in the CPT group were cured in 90 days and had lower 30-day mortality, although there was no significant difference between the two groups ( $P > 0.05$ ).

**Table 1** Demographic and Clinical Characteristics of Patients Treated with CPT and CT

Characteristics	Total (n=184)	CPT Group (n = 73)	CT Group (n = 111)	P value
Age (years), mean $\pm$ SD	61.3 $\pm$ 15.509	59.95 $\pm$ 15.56	62.19 $\pm$ 15.482	0.338
<b>Gender, N (%)</b>				
Male	131(71.2%)	58(79.5%)	73(65.8%)	0.045
Female	53(28.8%)	15(20.5%)	38(34.2%)	
<b>Acquisition, N (%)</b>				
Hospital-acquired	174(94.6%)	71(97.3%)	103(92.8%)	0.329
Community-associated	10(5.4%)	2(2.7%)	8(7.2%)	
<b>Temperature (degrees), median (IQR)</b>				
Body temperature	38.5(37.6,39)	38.4(37.75,39)	38.6(37.1,39)	0.711
<b>Invasive procedure or device, N (%)</b>				
Surgery within 3 months	68(37.0%)	35(47.9%)	33(29.7%)	0.012
Mechanical ventilation	123(66.8%)	53(72.6%)	70(63.1%)	0.179
Urinary catheterization	132(71.7%)	55(75.3%)	77(69.4%)	0.379
Central venous catheterization	138(75.0%)	56(76.6%)	82(73.9%)	0.664
<b>Underlying diseases, N (%)</b>				
Hypoproteinaemia	78(42.4%)	38(52.1%)	40(36.0%)	0.031
Multiple organ failure	27(14.7%)	13(17.8%)	14(12.6%)	0.330
Kidney disease	76(41.3%)	32(43.8%)	44(39.6%)	0.572
Hepatic disease	61(33.2%)	32(43.8%)	29(26.1%)	0.013
Anemia	55(29.9%)	32(43.8%)	23(20.7%)	0.001
Gastrointestinal disease	27(14.7%)	17(23.3%)	10(9%)	0.007
Biliary tract disease	34(18.5%)	8(11%)	26(23.4%)	0.033
Leukemia	13(7.1%)	5(6.8%)	8(7.2%)	0.926
Diabetes	32(17.4%)	16(21.9%)	16(14.4%)	0.189
Hypertension	66(35.9%)	26(35.6%)	40(36.0%)	0.954
<b>Severity of condition, median (IQR)</b>				
aCCI score	5(3,7)	5(3,7)	5(3,7)	0.614
Pitt bacteriaemia score	3(2,5)	3(2,5)	4(2,5)	0.573
SOFA score	7(4,11)	6(4,11)	8(4,11)	0.606
<b>Clinical outcome, N (%)</b>				
14-day treatment failure	102(55.4%)	33(45.2%)	69(62.2%)	0.024
30-day mortality	67(36.4%)	23(31.5%)	44(39.6%)	0.262
Cure in 90 days	113(61.4%)	50(68.5%)	63(56.8%)	0.11
<b>Antibiotic drug use, N (%)</b>				
Cephalosporins	6(3.3%)	1(1.4%)	5(4.5%)	0.455
Amikacin	15(8.2%)	5(6.8%)	10(9.0%)	0.600
Fluoroquinolones	32(17.4%)	11(15.1%)	21(18.9%)	0.500
Carbapenems	110(59.8%)	38(52.1%)	72(64.9%)	0.083
Piperacillin/tazobactam	25(13.6%)	7(9.6%)	18(16.2%)	0.199
Cefoperazone/sulbactam	41(22.3%)	12(16.4%)	29(26.1%)	0.122

**Abbreviations:** SOFA, Sequential Organ Failure Assessment; aCCI, age-adjusted Charlson comorbidity index.

## Antibiotic Resistance and Antibiotic Treatment

The antibiotic resistance of the two groups is shown in Table 2. Among the CPT group, the highest rate of drug resistance was found for ceftriaxone, piperacillin/tazobactam, cefoperazone/sulbactam, imipenem, meropenem and amoxicillin/clavulanate, all of which were 100%, followed by aztreonam (99.1%), and the lowest rate of drug resistance was found for tigecycline (6.8%). The highest rate of drug resistance in the CT group was found for amoxicillin/clavulanate (98.5%), and the lowest drug resistance rate was found for tigecycline (19.1%). The resistance to aztreonam (97.3% vs 88.3%,  $P = 0.028$ ), gentamicin (78.0% vs 58.5%,  $P = 0.019$ ), cefepime (95.9% vs 87.3%,  $P = 0.049$ ), cotrimoxazole (81.5% vs 49.2%,  $P < 0.001$ ), and tobramycin (79.1% vs 58.3%,  $P = 0.004$ ) occurred more frequently in CPT group than in CT group.

The antibiotic treatments of the two groups are shown in Table 1. The most commonly used antibiotics were carbapenems, followed by cefoperazone/sulbactam. There was no significant difference in the use of other antibiotics between the two groups ( $P > 0.05$ ).

## Univariate and Multivariate Analysis of 30-Day Mortality

The univariate and multivariate analysis of factors associated with 30-day mortality is summarized in Table 3. The 30-day mortality was 36.4%. CRKP-BSI occurred more frequently in hot weather than in cold weather (25.5% vs 21.2%), although there was no significant difference between the two kinds of weather ( $P > 0.05$ ). The univariate analysis showed that 30-day mortality was significantly higher in the cold than in hot weather (29.9% vs 16.2%,  $P = 0.032$ ). Other factors associated with mortality identified in the univariate analysis were multiple-organ failure ( $P = 0.01$ ), central venous catheterization ( $P = 0.019$ ), mechanical ventilation ( $p < 0.001$ ), urinary catheterization ( $P = 0.036$ ), SOFA score ( $p < 0.001$ ), and Pitt bacteraemia score ( $p < 0.001$ ). At the same time, therapy with ceftazidime/avibactam was a protective factor ( $p = 0.036$ ). After adjusting for confounding factors via logistics regression analysis, risk factors of 30-Day mortality were independently associated with SOFA score (OR = 1.310, 95% CI 1.157–1.483;  $p < 0.001$ ) and cold weather (OR = 3.658, 95% CI 1.474–9.081;  $P = 0.005$ ).

## Discussion

CHINET data showed a rapid increase in the prevalence of CRKP in China, from 2.9% in 2005 to 24.2% in 2020.<sup>15,16</sup> Currently, ceftazidime/avibactam, polymyxin, and tigecycline are considered as effective treatment strategies for CRKP-BSI. So in this study, we evaluated the clinical and microbiological outcomes of patients treated with CPT compared with those treated with CT. Predictors of 30-day mortality of patients with CRKP-BSI were also analysed in this study.

**Table 2** Antimicrobial Resistance of Patients Treated with CPT and CT

Antibacterial Drugs	Total (n=184)	CPT Group (n = 73)	CT Group (n = 111)	P value
Ceftriaxone(49vs86)*	132(97.8%)	49(100%)	83(96.5%)	0.475
Ciprofloxacin(71vs102)*	163(94.2%)	69(97.2%)	94(92.2%)	0.288
Levofloxacin(72vs115)*	166(88.8%)	68(94.4%)	98(85.2%)	0.052
Tigecycline(44vs63)*	15(14.0%)	3(6.8%)	12(19.1%)	0.073
Amikacin(71vs110)*	112(61.9%)	54(76.1%)	58(52.7%)	0.145
Imipenem(70vs110)*	176(97.8%)	70(100%)	106(96.4%)	0.274
Meropenem(40vs31)*	70(98.6%)	40(100%)	30(96.8%)	0.898
Ceftazidime/avibactam(23vs13)*	3(8.3%)	2(8.7%)	1(7.69%)	1.000
Piperacillin/tazobactam(72vs111)*	176(96.2%)	72(100%)	104(93.7%)	0.075
Amoxicillin/clavulanate(30vs66)*	95(99.0%)	30(100%)	65(98.5%)	1.000
Cefoperazone/sulbactam(37vs31)*	64(94.1%)	37(100%)	27(87.1%)	0.083
Aztreonam(73vs111)*	169(91.8%)	71(97.3%)	98(88.3%)	0.028
Gentamicin(50vs94)*	94(65.3%)	39(78.0%)	55(58.5%)	0.019
Cefepime(73vs110)*	166(90.7%)	70(95.9%)	96(87.3%)	0.049
Cotrimoxazole(54vs59)*	73(64.6%)	44(81.5%)	29(49.2%)	<0.001
Tobramycin(72vs103)*	117(66.9%)	57(79.1%)	60(58.3%)	0.004

**Notes:** \*The figures in parentheses were the total numbers of *K. pneumoniae* used for antimicrobial susceptibility testing in both groups.

**Table 3** Univariate and Multivariate Analysis of Factors for Mortality in Patients with CRKP-BSI

Characteristics	Total (n=184)	Non-Survivors (n = 67)	Survivors (n = 117)	OR (95% CI)	P value
<b>Univariate analysis, n (%)</b>					
Age (years), mean $\pm$ SD	62 $\pm$ 15.51	62.88 $\pm$ 17.56	60.39 $\pm$ 14.21	1.011(0.991,1.031)	0.295
<b>Gender, N (%)</b>					
Male	131(71.2%)	52(77.6%)	79(67.5%)	1.668(0.834,3.333)	0.148
Female	53(28.8%)	15(22.4%)	38(32.5%)		
Length, median (IQR)					
Length of hospital stay	23(14,36.75)	15(10,26)	28(17,45)	0.987(0.976,0.999)	0.033
<b>Acquisition, N (%)</b>					
Hospital-acquired	174(94.6%)	65(97%)	109(93.2%)	2.385(0.491,11.576)	0.281
Community-associated	10(5.4%)	2(3%)	8(6.8%)		
<b>Weather</b>					
Cold weather	39(21.2%)	20(29.9%)	19(16.2%)	2.195(1.071,4.499)	0.032
Hot weather	47(25.5%)	16(23.9%)	31(26.5%)	0.87(0.434,1.745)	0.696
<b>Temperature (degrees), median (IQR)</b>					
Body temperature	38.5(37.6,39)	38.3(37.6,39)	38.5(37.5,39)	0.991(0.761,1.290)	0.945
<b>Severity of condition, median (IQR)</b>					
aCCI score	5(3,7)	6(3,8)	4(2,7)	1.11(0.998,1.234)	0.055
Pitt bacteraemia score	3(2,5)	5(3,6)	2(1,4)	1.477(1.271,1.717)	<0.001
SOFA score	7(4,11)	11(7,14)	5(3,8.5)	1.307(1.199,1.425)	<0.001
<b>Invasive procedure or device, N (%)</b>					
Surgery within 3 months	68(37.0%)	20(29.9%)	48(41%)	0.612(0.323,1.16)	0.132
Mechanical ventilation	123(66.8%)	58(86.6%)	65(55.6%)	5.156(2.337,11.374)	<0.001
Urinary catheterization	132(71.7%)	54(80.6%)	78(66.7%)	2.077(1.014,4.255)	0.046
Central venous catheterization	138(75.0%)	57(85.1%)	81(69.2%)	2.533(1.163,5.517)	0.019
<b>Antibiotic drug use, N (%)</b>					
Cephalosporins	6(3.3%)	1(1.5%)	5(4.3%)	0.339(0.039,2.968)	0.329
Tigecycline	42(22.8%)	14(20.9%)	28(23.9%)	0.84(0.406,1.736)	0.637
Amikacin	15(8.2%)	2(3%)	13(11.1%)	0.246(0.054,1.126)	0.071
Polymyxin	15(8.2%)	6(9%)	9(7.7%)	1.18(0.401,3.474)	0.763
Fluoroquinolones	32(17.4%)	9(13.4%)	23(19.7%)	0.634(0.275,1.465)	0.286
Ceftazidime/avibactam	31(16.8%)	6(9%)	25(21.4%)	0.362(0.14,0.934)	0.036
Piperacillin/tazobactam	25(13.6%)	8(11.9%)	17(14.5%)	0.798(0.324,1.961)	0.622
Cefoperazone/sulbactam	41(22.3%)	14(20.9%)	27(23.1%)	0.881(0.425,1.826)	0.723
Carbapenems	110(59.8%)	44(65.7%)	66(56.4%)	1.478(0.793,2.756)	0.219
<b>Underlying diseases, N (%)</b>					
Hypoproteinaemia	78(42.4%)	33(49.3%)	45(38.5%)	1.553(0.847,2.849)	0.155
Chronic obstructive pulmonary disease	8(4.3%)	3(4.5%)	5(4.3%)	1.05(0.243,4.539)	0.948
Multiple organ failure	27(14.7%)	16(23.9%)	11(9.4%)	3.023(1.309,6.983)	0.010
Kidney disease	76(41.3%)	31(46.3%)	45(38.5%)	1.378(0.75,2.53)	0.301
Anemia	55(29.9%)	17(25.4%)	38(32.5%)	0.707(0.361,1.385)	0.312
Leukemia	13(7.1%)	7(10.4%)	6(5.1%)	2.158(0.694,6.713)	0.184
Diabetes	32(17.4%)	13(19.4%)	19(16.2%)	1.242(0.569,2.708)	0.586
Hypertension	66(35.9%)	19(28.4%)	47(40.2%)	0.59(0.309,1.126)	0.110
<b>Multivariate analysis</b>					
Multiple organ failure				0.736(0.246,2.203)	0.584
Central venous catheterization				0.361(0.098,1.328)	0.125
Mechanical ventilation				2.365(0.582,9.617)	0.229
Urinary catheterization				0.701(0.229,2.143)	0.533
SOFA score				1.310(1.157,1.483)	<0.001
Pitt bacteraemia score				1.138(0.924,1.402)	0.225
Cold weather				3.658(1.474,9.081)	0.005

**Abbreviations:** SOFA, Sequential Organ Failure Assessment; aCCI, age-adjusted Charlson comorbidity.



The mortality of CRKP-BSI varies from 40% to 70%.<sup>17–19</sup> The mortality of CRKP-BSI in this study was 36.4%. The increase in mortality might be related to host factors or the delay in appropriate treatment.<sup>20</sup> Our study showed that CPT patients had worse conditions than CT patients; CPT patients often presented with diseases and underwent invasive procedures. However, patients in the CPT group had better prognosis, evidenced by a lower rate of 14-day treatment failure and 30-day mortality.

Some studies suggested that ceftazidime-avibactam was superior to other treatment options when treating CRKP.<sup>21–23</sup> Studies also indicated that CRKP infections treated with ceftazidime/avibactam were associated with lower mortality rates than previously used drug regimens.<sup>22–26</sup> In addition, polymyxin and tigecycline have also been associated with reduced mortality, improving the clinical cure and microbiological eradication rates, especially for those with critical conditions, such as severe sepsis and septic shock.<sup>27–30</sup> However, in our study, only ceftazidime/avibactam resulted as a protective factor against 30-day mortality. In addition, some studies have found that patients treated with polymyxin or tigecycline might present side effects (eg, nephrotoxicity and neurotoxicity) and increased resistance during the treatment.<sup>31–34</sup> These factors may affect treatment response and reduce survival benefit, which led to a lack of statistically significant association between polymyxin and tigecycline with mortality in the present study.

We also found that drug resistance rates were higher in the CPT group than in the CT group, which might be due to the following reasons: first, patients in the CPT group were in worse condition, and patients with underlying diseases had weak immunity and a long hospital stay, so that they were more likely to be invaded by pathogens. Second, critical patients were treated with higher doses and for a longer time, allowing more time for bacteria to develop resistance.

Patients had a higher incidence rate in hot weather than in cold weather, which was consistent with other literature.<sup>35</sup> The optimal growth temperature for *K. pneumoniae* was  $>30^{\circ}\text{C}$  ( $30^{\circ}\text{C}$ – $35^{\circ}\text{C}$ ). The rising temperature can increase bacterial growth and promote its transport and transfer.<sup>36</sup> In addition to increased morbidity, high temperatures also increased antibiotic resistance. Seasonal environmental factors, such as temperature, were the main driving forces for the persistence and proliferation of antibiotic resistance in the environment, which could lead to the exchange of resistance genes or the uptake of genetic material with other bacteria.<sup>37,38</sup> At the same time, low temperatures could inhibit microbial growth and enzyme expression.<sup>39,40</sup> Interestingly, although the incidence was high in hot weather, the mortality was higher in cold weather. Our univariate and multivariate analysis showed that cold weather was independently associated with the 30-day mortality of CRKP-BSI. Low temperature could increase the incidence rate of complications related to the autonomic nervous system, blood pressure, thermogenesis, inflammatory response, and oxidative stress reaction of patients, thus aggravating the condition of patients.<sup>41,42</sup> In addition, increased rates of respiratory infections and diseases in cold weather were also associated with mortality.<sup>43</sup> This suggests that we should pay more attention to the patient's condition and improve the treatment strategies when the weather is cold. Besides, understanding the relationship between weather and CRKP infection is helpful to develop effective control and prevention strategies.

Multiple studies have shown that SOFA can predict mortality in critically ill patients.<sup>44–47</sup> It was also found that the SOFA score could be one of the most valuable tools in evaluating the severity of healthcare-associated pneumonia.<sup>48</sup> In our study, the SOFA score resulted as one of the independent predictors of mortality in CRKP-BSI.

In summary, critical CRKP-BSI patients were more often treated with ceftazidime/avibactam, polymyxin, or tigecycline antibiotics and had higher survival chances. Ceftazidime/avibactam was the most effective antibiotic, especially for critical patients. Nevertheless, further studies are needed to confirm whether ceftazidime/avibactam, polymyxin, or tigecycline antibiotics can be effectively used to treat CRKP-BSI patients in poor conditions. In addition, we found that CRKP-BSI occurred more commonly in hot weather but was associated with higher mortality in cold weather. These results highlight the importance of studying the weather variation to better understand the epidemic trend of *K. pneumoniae* bloodstream infections and develop effective control and prevention strategies.

## Data Sharing Statement

All the data are from the database of the second affiliated Hospital of Nanchang University. The raw data supporting the conclusions of this manuscript will be made available by the corresponding authors, without undue reservation, to any qualified researcher.

## Ethics Statement

Informed consent was acquired from each participant included in the study. This study was approved by the Second Affiliated Hospital of Nanchang University Medical Research Ethics Committee (No. Review-2022-117). Our study complies with the Declaration of Helsinki.

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## Disclosure

The authors declare that they have no conflict of interest.

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