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Original Article

Mortality associated with carbapenem resistance in *Klebsiella pneumoniae* bloodstream infection: A propensity score–matched study

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Abstract

Objective: *Klebsiella pneumoniae* are common pathogens causing bloodstream infection (BSI) that increasingly express carbapenem resistance worldwide. To date, no study has precisely investigated the impact of carbapenem resistance in *K. pneumoniae* (CRKP) BSI on mortality.

Methods: This retrospective study included 87 patients with CRKP BSI and 321 patients with carbapenem-susceptible *K. pneumoniae* (CSKP) BSI from 2015 to 2020. Propensity score analyses with stabilized inverse probability of treatment weighting (IPTW-S) was applied to balance covariates. The hazard ratio for 30-day mortality associated with carbapenem resistance was estimated using Cox regression and Kaplan-Meier curves.

Results: The 30-day crude mortality rates were 43.7% in patients with CRKP BSI and 17.8% in patients with CSKP BSI ($P < .001$). Age ≥55 years, underlying hematological malignancies and hemodialysis were independently associated with mortality in CRKP BSI. A skin or soft-tissue infection source, urinary catheter, and underlying chronic obstructive pulmonary disease were predictors of mortality in CSKP BSI. The group characteristics were well balanced after IPTW-S. The adjusted hazard ratio for 30-day mortality for CRKP BSI was 1.607 (interquartile range, 0.814–3.171).

Conclusions: Carbapenem resistance was not associated with a significant increase in 30-day mortality in KP BSI; patient and disease factors were primary determinants of outcomes.

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Klebsiella pneumoniae (*K. pneumoniae,* KP) is an important opportunistic pathogen that can cause bloodstream infection (BSI) with high mortality,[1] ranging from 20% to 60% in different studies.[2–5] The dissemination of antibiotic-resistant strains, especially carbapenem-resistant KP (CRKP),[6] further complicates management of these infections.

Infection control measures and active surveillance are in place to prevent nosocomial spread and potential outbreaks of CRKP worldwide. Quantifying the benefits of such a strategy by analyzing the attributable mortality that reflect the additional disease burden of CRKP infection is essential. In gram-negative bacteremia, the third-generation cephalosporin-resistant (3GC-R) mortality attribution has been well explored and is associated with increased mortality.[7] The burden of carbapenem resistance in KP BSI on mortality has not been quantified.

However, measuring the impact of antimicrobial resistance is challenging because antibiotic-resistant infections are more likely to develop in severely ill patients, and the severity of the condition may be independently associated with poor outcomes. These potential cofounders and/or the methods used for statistical analysis are largely responsible for the difference of carbapenem resistance-associated mortality in KP BSI between studies.[2,8–10] However, randomization to the exposure before infection to ensure the same baseline characteristics is not feasible. Propensity score analyses with stabilized inverse probability of treatment weighting (IPTW-S) is a robust statistical method appropriate for adjusting the selection bias of control and exposure groups in observational studies. This method is now increasingly used to study infections and to attributable mortality.[11–13] However, such matching has rarely been used to study the impacts of antimicrobial resistance on clinical outcomes.

Here, we conducted an observational study to identify the key factors associated with the development and outcomes of CRKP BSI, focused particularly on the impact of carbapenem resistance on mortality in KP BSI using propensity score–based IPTW-S.

Methods

Setting and patients

This retrospective observational study was conducted at a 2,500-bed tertiary-care teaching hospital in Guangzhou, Guangdong Province, in southern China. The number of

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admissions to this hospital is nearly 90,000 per year. The study protocol was approved by the Institutional Review Board of Zhujiang Hospital. Informed consent was not obtained due to the retrospective nature of the study.

A team of infectious diseases physicians and microbiologists identified all patients aged ≥18 years between January 1, 2015, and December 31, 2020, who had KP BSI. Only the first KP isolate from blood for each patient was included. Data were extracted from medical records, including age, sex, comorbidities, and past medical and treatment histories. All patients were followed until 30 days after diagnosis or death.

Microbiological studies

Species confirmation and antibiotic susceptibility testing were performed in the microbiology laboratory of the hospital using the Vitek 2 automated system (bio-Mérieux, Marcy-l'Étoile, France) using the broth microdilution and disk diffusion methods. Antimicrobial susceptibilities were interpreted following Clinical and Laboratory Standards Institute (CLSI) guidelines. *K. pneumoniae* that displayed resistance to 1 or more carbapenem agents, such as ertapenem (MICs ≥ 2 mg/L), meropenem (MICs ≥ 4 mg/L), or imipenem (MICs ≥ 4 mg/L), were defined as CRKP. Otherwise, they were defined as carbapenem-susceptible KP (CSKP).[14]

Definitions

BSI was defined as the isolation of KP from the blood culture with or without infection symptoms (fever or hypothermia). The onset of BSI was considered the date of collection of the first positive blood-culture sample. The probable sources of BSI (eg, pneumonia, genitourinary infection, intra-abdominal infection, intravascular catheter–related, skin and soft-tissue infection, intracranial infection) were assessed according to the National Healthcare Safety Network definitions. Primary BSI was defined as BSI without an identified site of infection.[15] The definitions of hospital-acquired, healthcare-associated, and community-acquired KP BSI were based on previously described criteria.[16] For each BSI patient, we calculated a Charlson comorbidity index score (CCI).[17]

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 software (IBM, Armonk, NY) and R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables with a normal distribution are expressed as the mean ± standard deviation (SD) and were analyzed using the Student t test. Continuous variables with a nonnormal distribution are expressed as the median and interquartile range (IQR) and were analyzed using the Mann–Whitney U test. Categorical variables are reported as frequencies and were compared using the χ^2 or Fisher exact test. Multivariate logistic regression was used to investigate the independent risk factors for infection and mortality. The Box–Tidwell test was used to assess the assumption of linearity in the logit for the continuous variable. Multicollinearity was examined by checking the variance inflation factor on a multiple regression model with the same dependent and independent variables. Odds ratios (ORs) with associated 95% confidence intervals (CIs) and corresponding P values are presented using forest plots. $P < .05$ was considered statistically significant.

A propensity score analysis with IPTW-S was performed to balance the distribution of potential confounders between the CRKP BSI and CSKP BSI groups. Compared with classical propensity-score matching, the stabilization feature of IPTW-S methods has the advantage of preserving the size of the study population, not only avoiding the need for adjustment of standard errors in an inflated sample but also preventing study participants from dropping and statistical power from being lost.[18,19] All potential confounders associated with CRKP BSI or death with P values ≤ .20 in the univariate analysis were included for IPTW-S calculation in R software. Any covariates with a standardized mean difference (SMD) < 0.20 were considered balanced. The Kaplan–Meier method was used to plot survival curves, and the differences were compared via the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression to estimate the strength of the impact of carbapenem resistance on 30-day mortality.

Results

Study subjects

Between 2015 and 2020, some 782 nonrepetitive KP strains were isolated from blood samples. In total, 408 adult patients with KP BSI were included in the study according to the enrolment criteria: 87 (21.3%) with CRKP BSI and 321 (78.7%) with CSKP BSI. All CRKP isolates were resistant to imipenem and/or meropenem.

The characteristics of patients are described in Table 1. Overall, the median age of these 408 patients was 57.0 (IQR, 46.0–67.8) years, and 66.4% (271 of 408) of them were male. The most frequent source was primary bloodstream infection (31.4%), followed by pneumonia (30.4%), intra-abdominal infection (17.2%), genitourinary infection (8.3%), liver abscesses (5.4%), and intravascular catheter (3.4%) infections.

Factors associated with CRKP BSI

The following factors were associated with carbapenem-resistance in KP isolates from patients with KP BSI: male sex, pneumonia infection, longer hospitalization stay or intensive care unit (ICU) stay, history of ICU stay, long-term corticoid therapy, previous exposure to antimicrobial therapy, exposure to invasive procedures such as surgical procedure, intravascular catheter, urinary catheter, mechanical ventilation, drainage tube, nasogastric or nasobiliary tube, and receipt of hemodialysis treatment in the past 30 days ($P < .05$) (Table 1). Community-acquired infection, primary BSI and underlying diabetes mellitus were more common in the CSKP group ($P < .05$) (Table 1).

In the multivariate logistic analysis, patients with a longer hospitalization time (OR, 1.019; 95% CI, 1.002–1.036, $P = .024$), history of ICU stay (OR, 4.982; 95% CI, 2.694–9.215; $P < 0.001$), receipt of hemodialysis treatment (OR, 4.676; 95% CI, 1.831–11.942; $P = .001$) and previous exposure to antibiotics (OR, 2.700; 95% CI, 1.412–5.164; $P = .003$) were more likely to have CRKP BSI. Primary BSI (OR, 0.402; 95% CI, 0.203–0.795; $P = .003$) and diabetes mellitus (OR, 0.423; 95% CI, 0.187–0.961; $P = .040$) were associated with reduced odds of CRKP BSI compared to CSKP BSI (Fig. 1A).

Outcomes and risk factors for mortality in CRKP BSI and CSKP BSI

During the 30 days following KP BSI onset, 95 (23.3%) of these 408 patients died. The crude 30-day mortality was higher in patients

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Table 1. Observed and Weighted Baseline Characteristics of Study Patients

Variable	Total (n=408), No. (%)	Unweighted				IPTW-S			
		CRKP (n=87), No. (%)	CSKP (n=321), No. (%)	*P* Value	SMD	CRKP (n = 91.77), No. (%)	CSKP (n = 314.44), No. (%)	*P* Value	SMD
Age, median y (IQR)	57 (46–67.8)	54.0 (44–68)	58.0 (47.5–67.5)	.307	0.065	52. 9 (34.5–69.3)	55.9 (47.5–71.4)	.328	0.187
Sex, male	271 (66.4)	66 (75.9)	205 (63.9)	.036	0.264	58.0 (63.2)	205.4 (65.3)	.838	0.045
Origin of infection									
Hospital-acquired	175 (42.9)	41 (47.1)	134 (41.7)	.368	0.079	52.4 (57.1)	134.8 (42.9)	.168	0.198
Healthcare associated	87 (21.3)	23 (26.4)	64 (19.9)	.189	0.154	18.3 (19.9)	67.0 (21.3)	.841	0.035
Community-acquired	145 (35.5)	23 (26.4)	122 (38.0)	.046	0.223	21.1 (23.0)	112.6 (35.8)	.195	0.187
Probable source of infection									
Pneumonia	125 (30.6)	40 (46.0)	85 (26.5)	<.001	0.414	30.4 (33.2)	99.4 (31.6)	.863	0.033
Genitourinary infection	34 (8.3)	8 (9.2)	26 (8.1)	.743	0.039	6.3 (6.9)	26.5 (8.4)	.682	0.058
Intra-abdominal infection[a]	70 (17.2)	58 (18.1)	12 (13.8)	.437	0.117	16.6 (18.1)	51.7 (16.4)	.860	0.044
Liver abscesses	22 (5.4)	1 (1.1)	21 (6.5)	.088	0.283	2.3 (2.5)	17.3 (5.5)	.420	0.154
Intravascular catheter	14 (3.4)	4 (4.6)	10 (3.1)	.509	0.077	3.0 (3.3)	11.3 (3.6)	.892	0.017
Skin and soft-tissue infection	8 (2.0)	4 (4.6)	4 (1.2)	.067	0.177	1.2 (1.3)	5.0 (1.6)	.733	0.029
Intracranial infection	6 (1.5)	1 (1.1)	5 (1.6)	1.000	0.035	0.4 (0.4)	4.4 (1.4)	.268	0.101
Primary	128 (31.4)	17 (19.5)	111 (34.6)	.007	0.343	31.5 (34.4)	98.8 (31.4)	.764	0.063
Comorbidities									
Coronary heart disease	43 (10.5)	11 (12.6)	32 (10.0)	.471	0.085	5.6 (6.1)	31.3 (10.0)	.237	.144
Chronic liver diseases	22 (5.4)	2 (2.3)	20 (6.2)	.187	0.196	4.2 (4.5)	19.3 (6.1)	.706	.072
COPD	14 (3.4)	2 (2.3)	12 (3.7)	.743	0.840	1.0 (1.1)	11.5 (3.7)	.104	.169
Chronic renal disease	38 (9.3)	12 (13.8)	26 (8.1)	.105	0.183	13.2 (14.4)	28.1 (8.9)	.382	.171
Solid malignancy	85 (20.8)	12 (13.8)	73 (22.7)	.068	0.233	13.0 (14.1)	66.4 (21.1)	.268	.184
Hematological malignancies	56 (13.7)	12 (13.8)	44 (13.7)	.984	0.002	12.8 (13.9)	43.8 (13.9)	.999	<.001
Diabetes mellitus	92 (22.5)	10 (11.5)	82 (25.5)	.005	0.368	23.6 (25.7)	72.6 (23.1)	.806	.061
CCI (IQR)	3 (2–4)	2 (1–4)	3 (2–5)	.06	0.224	2.9 (0.7–5.0)	3.3 (1.1–5.5)	.298	.189
Length of hospital stay (IQR)	10 (2–21.8)	11 (11–30)	7 (1–18)	<.001	0.681	14.5 (1.9–27.1)	13.9 (0–32.5)	.798	.039
Previous ICU stay	88 (21.6)	48 (55.2)	40 (12.5)	<.001	1.012	16.9 (18.4)	61.7 (19.6)	.812	.032
Length of ICU stay (IQR)	0 (0–0)	4 (0–15)	0 (0–0)	<.001	0.733	2.89 (0–11.0)	3.03 (0–13.7)	.911	.014
Surgical procedure	103 (25.2)	31 (35.6)	72 (22.4)	.012	0.294	22.3 (24.3)	75.9 (24.1)	.984	.004
Long-term corticoid therapy	115 (28.2)	32 (36.8)	83 (25.9)	.045	0.237	23.0 (25.0)	88.0 (28.0)	.705	.067
Long-term use of immunosuppressor	31 (7.6)	4 (4.6)	27 (8.4)	.234	0.155	6.5 (7.1)	25.6 (8.2)	.824	.041
Intravascular catheter	146 (35.8)	56 (64.4)	90 (28.0)	<.001	0.783	30.1 (32.8)	108.2 (34.4)	.845	.034
Urinary catheter	151 (37.0)	59 (67.8)	92 (28.7)	<.001	0.852	30.8 (33.5)	111.8 (35.6)	.810	.043
Mechanical ventilation	94 (23.0)	40 (46.0)	54 (16.8)	<.001	0.662	17.2 (18.8)	67.9 (21.6)	.639	.070
Nasogastric or nasobiliary tube	103 (25.2)	43 (49.4)	60 (18.7)	<.001	0.686	22.7 (24.8)	74.6 (23.7)	.882	.025
Drainage tube	136 (33.3)	48 (55.2)	88 (27.4)	<.001	0.588	28.8 (31.4)	98.4 (31.3)	.995	.001
Hemodialysis treatment	30 (7.4)	19 (21.8)	11 (3.4)	<.001	0.577	5.8 (6.4)	18.7 (5.9)	.879	.017
Chemotherapy/Radiotherapy	64 (7.4)	11 (15.7)	53 (16.5)	.379	0.110	12.2 (13.3)	49.4 (15.7)	.672	0.069
Previous use of antibiotics	202 (49.5)	69 (79.3)	133 (41.4)	<.001	0.840	55.8 (60.8)	153.3 (48.8)	.245	0.186

Note. CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; IPTW-S, stabilized inverse probability of treatment weighting; SMD, standardized mean differences; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index score; ICU, intensive care unit.
[a]Excluding liver abscesses.

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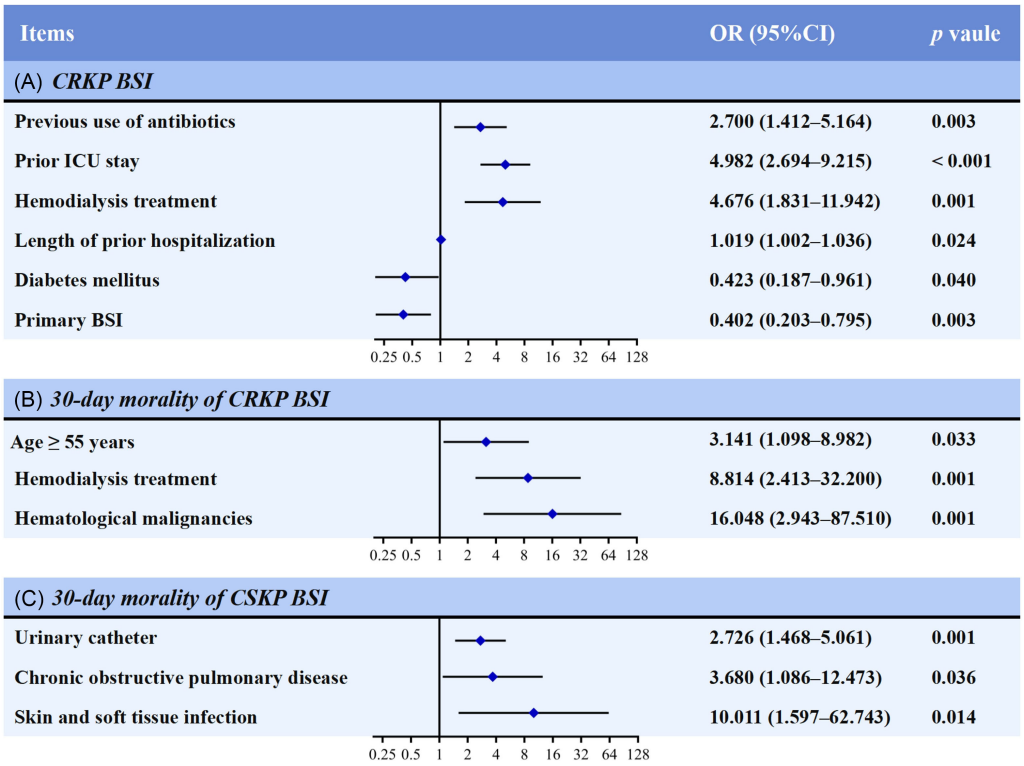

Fig. 1. Multivariate logistic regression analysis of (A) risk factors for CRKP BSI and 30-day crude morality of (B) CRKP BSI and (C) CSKP BSI. Note. CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; BSI, bloodstream infection; ICU, intensive care unit; OR, odds ratio; 95% CI, 95% confidence interval.

with CRKP BSI (43.7%, 38 of 87) than in those with CSKP BSI (17.8%, 57 of 321; $P < .001$).

Factors associated with crude mortality among CRKP BSI patients included age (≥55 years), chronic obstructive pulmonary disease (COPD), chronic renal diseases, hematological malignancies, higher CCI, longer hospital stay and receipt of hemodialysis treatment in the past 30 days before CRKP BSI onset ($P < .05$) (Table 2). Multivariable logistic regression showed that age ≥ 55 years (OR, 3.141; 95% CI, 1.098–8.982; $P = .033$), accompanying hematological malignancies (OR, 16.048; 95% CI, 2.943–87.510; $P = .001$), and receipt of hemodialysis treatment (OR, 8.814; 95% CI, 2.413–32.200; $P = .001$) were independent risk factors for crude 30-day mortality in CRKP BSI (Fig. 1B).

For CSKP BSI patients, the following factors were associated with crude 30-day mortality: BSI source from pneumonia, genitourinary, skin and soft-tissue or intracranial infection, accompanying COPD, and exposure to a urinary catheter in the past 30 days before CSKP BSI onset ($P < .05$) (Table 2). On multivariate logistic analysis, the following factors were independently associated with crude 30-day mortality in CSKP BSI: skin and soft tissue infection source (OR, 10.011; 95% CI, 1.597–62.743; $P = .014$), exposure to urinary catheters (OR, 2.726; 95% CI, 1.468–5.061; $P = .001$), and COPD (OR, 3.680; 95% CI, 1.086–12.473; $P = .036$) (Fig. 1C).

Propensity score-based IPTW-S and the impact of carbapenem resistance on mortality for KP BSI

Before weighting, 21 of 34 characteristics had an SMD >0.2. The survival analysis showed that the 30-day survival probability of patients with CRKP BSI was significantly worse than that of those with CSKP BSI (HR, 2.897; 95% CI, 1.920–4.370; $P < .001$) (Fig. 2A). After adjusting for IPTW-S, the CRKP BSI (n = 91.77) and CSKP (n = 314.44) groups had similar characteristics, with SMD < 0.2 for each (Table 1). The survival analysis of weighted groups showed that the 30-day survival probability of patients with CRKP BSI was worse than that of those with CSKP BSI, but the difference was not significant (HR, 1.607; 95% CI, 0.814–3.171; $P = .298$) (Fig. 2B).

Discussion

Carbapenem-resistant *K. pneumoniae* is typically resistant to many first- and second-line antibiotics and is an emergent threat to public health. The rapid recognition of patients with CRKP infection is critical for early appropriate empirical regimen selection and source control of nosocomial dissemination. At present, several published works have focused on the potential risk factors for CRKP BSI infection, but the results vary,[2,4,8,10] possibly due to different sample sizes, selection bias, and differences among bacterial strains causing infection. The current analysis showed that a longer hospital stay, history of ICU stay, exposure to antibiotics, and receipt of hemodialysis prior to bacteremia were independently associated with BSI due to CRKP rather than CSKP. Hospitalization increases the risk of acquisition and colonization of antibiotic-resistant bacteria, as ~75% of healthcare-associated infections are caused by organisms that are resistant to first-line antimicrobial therapy.[20] In particular, the ICU has been increasingly reported as a severe source of creating, spreading and amplifying antimicrobial resistance due to a diversity of complex infections in critically ill patients, the frequent performance of invasive procedures, and the high consumption of first-line antimicrobials.[21] Selective pressures exerted by using various classes of antibiotics for treatment in the ICU could result in the

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Table 2. Univariate Analysis of Risk Factors Associated With 30-Day Mortality of CRKP and CSKP BSI

	CRKP BSI			CSKP BSI		
Variables	Death (n = 38), No. (%)	Survival (n = 49), No. (%)	*P* Value	Death (n = 57), No. (%)	Survival (n = 264), No. (%)	*P* Value
Age (IQR)	63 (45.5-73)	51 (42.5-57.5)	.039	58 (50-68)	58 (47-67)	.302
≥55	24 (63.2)	17 (34.7)	.008	38 (66.7)	149 (56.4)	.156
Sex, male	28 (73.7)	38 (77.6)	.676	40 (70.2)	165 (62.5)	.274
Origin of infection						
Nosocomial infection	20 (52.6)	21 (42.9)	.365	19 (33.3)	115 (43.6)	.156
Healthcare associated	10 (26.3)	13 (26.5)	.982	15 (26.3)	49 (18.6)	.184
Community-acquired	8 (21.1)	15 (30.6)	.316	23 (40.4)	99 (37.5)	.688
Probable source of infection						
Pneumonia	1 (2.6)	1 (2.0)	1.000	22 (38.6)	63 (23.9)	.022
Genitourinary infection	1 (2.6)	7 (14.3)	.131	0 (0)	26 (9.8)	.007
Intra-abdominal infection[a]	4 (10.5)	8 (16.3)	.436	8 (14.0)	50 (18.9)	.383
Liver abscesses	0 (0)	1 (2.0)	1.000	2 (3.5)	19 (7.2)	.391
Intravascular catheter	0 (0)	4 (8.2)	.128	1 (1.8)	9 (3.4)	1.000
Skin and soft tissue infection	1 (2.6)	3 (6.1)	.629	3 (5.3)	2 (0.8)	.041
Intracranial infection	1 (2.6)	0 (0)	.437	3 (5.3)	2 (0.8)	.041
Primary	7 (18.4)	9 (18.4)	.995	14 (24.6)	72 (27.7)	.675
Comorbidities						
Coronary heart disease	6 (15.8)	5 (10.2)	.523	7 (12.3)	25 (9.5)	.521
Chronic liver diseases	1 (2.6)	1 (2.0)	1.000	2 (3.5)	18 (6.8)	.546
COPD	24 (63.2)	16 (32.7)	.005	5 (8.8)	7 (2.7)	.043
Chronic Renal diseases	2 (5.3)	10 (20.4)	.042	6 (10.5)	20 (7.6)	.429
Solid malignancy	7 (18.4)	5 (10.2)	.270	10 (17.5)	63 (23.9)	.384
Hematological malignancies	10 (26.3)	2 (4.1)	.003	8 (14.0)	36 (13.6)	.937
Diabetes mellitus	3 (7.9)	7 (14.3)	.503	18 (31.6)	64 (24.2)	.249
CCI (IQR)	3 (2–5)	2 (1–4)	.023	3 (2–5)	3 (2–4)	.320
Length of hospital stay (IQR)	26 (16–20)	17 (7.5–30)	.039	4 (0–18.5)	8 (1–18)	.143
ICU stay	24 (63.2)	24 (49.0)	.187	11 (19.3)	29 (11.0)	.085
Length of ICU stay (IQR)	8.5 (0–18.5)	0 (0-12.5)	.180	0 (0-0)	0 (0-0)	.144
Surgical procedure	11 (28.9)	20 (40.8)	.252	12 (21.1)	60 (22.7)	.783
Long-term corticoid therapy	16 (42.1)	16 (32.7)	.364	16 (28.1)	67 (25.4)	.674
Long-term use of immunosuppressor	2 (5.3)	2 (4.1)	1.000	6 (10.5)	21 (8.0)	.597
Intravascular catheter	27 (71.1)	29 (59.2)	.252	21 (36.8)	69 (26.1)	.103
Urinary catheter	26 (68.4)	33 (67.3)	.915	25 (43.9)	67 (25.4)	.005
Mechanical ventilation	19 (50.0)	21 (42.9)	.507	14 (24.6)	40 (15.2)	.085
Nasogastric or nasobiliary tube	18 (47.4)	25 (51.0)	.735	15 (26.3)	45 (17.0)	.103
Drainage tube	24 (63.2)	24 (49.0)	.187	17 (29.8)	71 (26.9)	.653
Hemodialysis treatment	15 (39.5)	4 (8.2)	<.001	2 (3.5)	9 (3.4)	1.000
Chemotherapy/Radiotherapy	8 (21.1)	3 (6.1)	.052	8 (14.0)	45 (17.0)	.579
Previous use of any antibiotics	33 (86.8)	36 (73.5)	.127	26 (45.6)	107 (40.5)	.480
Coinfection with any bacteria	2 (5.3)	8 (16.3)	.175	6 (10.5)	45 (17.0)	.222
Inappropriate empirical therapy	10 (26.3)	14 (28.6)	.815	1 (1.8)	5 (1.9)	.815

Note. CRKP, carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infection; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index score; ICU, intensive care unit.
[a]Excluding liver abscesses.

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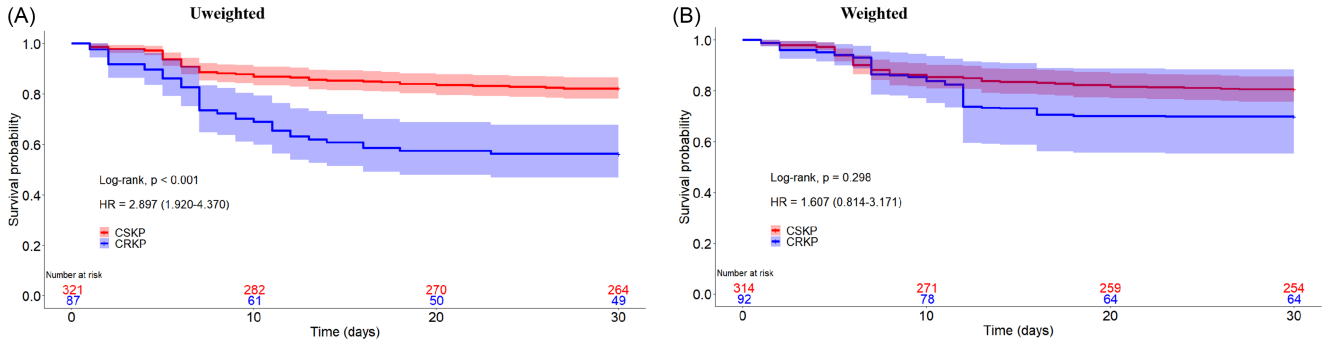

Fig. 2. Crude mortality (A) and weighted mortality (B) of CRKP BSI and CSKP BSI. Note. CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; HR, hazard ratio.

selection of strains that are resistant to these antibiotics. Hemodialysis treatment was also associated with CRKP infection, possibly due to greater exposure to invasive procedures and the hospital environment. All of these risk findings strongly suggest that infection control policies involving the environment, healthcare personnel, and antimicrobial prescribing are needed to prevent nosocomial and nosocomial-community dissemination of antibiotic-resistant strains.

Interestingly, among patients with KP BSI, those with diabetes mellitus were more likely to be infected with carbapenem-susceptible strains. This result is similar to the findings of previous studies that have described diabetes mellitus as a risk factor for various infections, including those due to hypervirulent KP (hvKP),[4,22] which is typically susceptible to most firstline antibiotics except for a natural resistance to ampicillin. The gut is currently considered an important source of primary BSI caused by KP.[23,24] Approximately half of nosocomial KP BSIs are primary infections and are associated with intestinal colonization.[5] The characteristics that differentiate hvKP from non-hvCRKP that might have contributed to the higher proportion of primary BSI observed among patients with CSKP BSI, as compared to CRKP BSI, include excessive capsule production and high production of multiple siderophores and are considered critical factors for initial invasion at the colonization site of gut and subsequent bloodstream survival and dissemination.[25]

In this study, we identified several risk factors for 30-day crude mortality among cases of CRKP BSI and CSKP BSI: older age (≥55 years), accompanying hematological malignancies, and history of hemodialysis treatment for CRKP BSI, and the skin and soft-tissue infection source, exposure to urinary catheters, and COPD for CSKP BSI. Consistent with previous studies,[26] older age has been noted as a risk factor associated with death from CRKP infection as well as other pathogens. The further stratified analysis of age showed that patients aged ≥55 years had a 3.1-fold increased risk for mortality compared with those <55 years. Hematological malignancies, such as leukemia and lymphoma, can affect the immune system directly, resulting in an increased risk for infection. Most patients who received hemodialysis treatment had renal failure and shock in our study; they were vulnerable to CRKP infection and died due to treatment failure. Fewer studies have reported the factors related to mortality in CSKP BSI. In our study, 4 of the 5 patient who died had underlying COPD, and all 3 patients who died who had an infection source from skin and soft-tissue died due to septic shock. This finding shows that preventing the development of respiratory failure in COPD patients in the early stage of septic shock and protecting the integrity of skin and mucosal barriers from persistent infection is vital.

The crude 30-day mortality among CRKP BSI patients in our study was 43.7%, similar to other areas of China,[2,8,27] which was much higher than the 17.8% of CSKP BSI patients. As our results and those of other studies indicate,[9] these 2 groups of patients had significantly different baseline characteristics, which partly contributed to the risk of infection and outcomes. This fact obscures how and to what extent carbapenem resistance impacts the mortality of KP BSI. To address this problem, we applied propensity scores with IPTW-s to adjust for potential confounders. The 30-day mortality was higher in the CRKP BSI group than in the CSKP BSI group after weighting, but the confidence intervals indicated nonstatistical significance, suggesting that patient and disease factors, such as those identified in our study, are the primary determinants of outcome. These findings contrast with those of several prior studies that reported markedly increased mortality attributed to ESBL-producing or 3GC-R in *Enterobacterales* infections.[28–30] Our findings are more consistent with other recent studies on 3GC-R *Enterobacteriaceae* bloodstream infections in South Africa[31] and 3GC-R gram-negative infections in the Netherlands,[7] which also reported that antibiotic resistance did not increase 30-day mortality. Accurate evaluations of the impact of carbapenem-resistance on outcomes of KP BSI have rarely been conducted. Similar to our findings, a recent meta-analysis showed increased mortality from CRKP infection when associated with comorbidities.[32]

The absence of a statistically significant impact of carbapenem resistance on mortality in KP BSI could be due to a higher portion of hvKP among CSKP than CRKP,[22] with the attributed mortality of carbapenem resistance being offset by higher virulence. Assessment for hvKP among BSI isolates was not performed in this study. Liver abscess is a common complication of hvKP infections and should raise suspicion of hvKP strains,[22] but liver abscess was not more common among CRKP BSIs than CSKP BSIs and was not associated with mortality in this study, suggesting that hvKP is not the primary driver of our findings. Nevertheless, infection with hvKP should be considered as a potential contributor to the mortality observed in patients with CSKP BSI, and this should be specifically evaluated in future studies. Notably, this balance might be tipped along with the global emergence of CR-hvKP that has evolved from the confluence of carbapenem resistance determinants of CRKP and the virulence genes of hvKP on the same or coexisting plasmids.

Outcomes of CRKP infection may vary based on the mechanism of carbapenem resistance (eg, carbapenemase production versus

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other mechanisms of resistance such as AmpC beta-lactamase in combination with a porin mutation).[33] The retrospective design of this study did not allow for the determination of the mechanism of carbapenem resistance among included isolates. However, all CRKP strains in this study were resistant to imipenem or meropenem. Based on the knowledge that non–carbapenemase-producing organisms are often resistant to ertapenem but susceptible to other carbapenems, we suspected that all CRKP strains in this study were carbapenemase producing and that the balanced distribution of KPC would not contribute to the difference in outcomes. Indeed, most of the KP isolates in China may have been KPC producers.[34]

In addition to the patient and isolate factors, the local practices of treating hospitalized patients should be considered, such as empirical antibiotic therapy. Our findings are in line with other studies that have reported no impact of inappropriate initial therapy on outcome.[7,35] Given the potential limitations including the single-center retrospective nature of the study and the modest sample size, a larger, multicenter study is needed for a more precise assessment of the impact of carbapenem resistance on mortality.

Even though there was no obvious impact on mortality, antibiotic-resistant pathogens increase the burden of disease by replacing their antibiotic-susceptible counterparts and increasing the total number of infections. Antibiotic-resistant infections may increase mortality among critically ill patients with comorbidities and may increase costs due to frequent healthcare exposure and usage of expensive antimicrobials that may further select for antimicrobial-resistant pathogens. Thus, early recognition and effective control measures are needed to minimize the potential impact and mortality risk of CRKP BSI.

In conclusion, our study used propensity-score–based IPTW-S to produce an unbiased estimate of the impact of carbapenem resistance on outcomes of KP BSI. Carbapenem resistance was not an independent predictor of 30-day mortality, and outcomes appear to be determined primarily by patient and disease factors.

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Conflicts of interest. All authors declare no conflict of interest related to this research.

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