Disease Severity Is an Independent Risk Factor of Mortality and Outcomes in Critically Ill Patients With Carbapenem-resistant *Klebsiella Pneumoniae* Bloodstream Infections: a 5-year Retrospective Analysis

Yuzhen Qiu
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Wen Xu
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Yunqi Dai
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital https://orcid.org/0000-0002-4008-6609
Ruoming Tan
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Jialin Liu
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Feifei Gu
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Erzhen Chen
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Xiaoli Wang
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Hongping Qu (hongpingqu0412@hotmail.com)
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital https://orcid.org/0000-0002-2116-5125

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Abstract

Background: Carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections (CRKP-BSIs) are associated with high morbidity and mortality rates, especially in critically ill patients. Comprehensive mortality risk analyses and therapeutic assessment in real-world practice are beneficial to guide individual treatment.

Methods: We retrospectively analyzed 87 patients with CRKP-BSIs (between July 2016 and June 2020) to identify the independent risk factors for 28-day all-cause mortality. The therapeutic efficacies of tigecycline-and polymyxin B-based therapies were analyzed.

Results: The 28-day all-cause mortality and in-hospital mortality rates were 52.87% and 67.82%, respectively, arising predominantly from intra-abdominal (56.32%) and respiratory tract infections (21.84%). A multivariate analysis showed that 28-day all-cause mortality was independently associated with the patient's APACHE II score (p = 0.002) and presence of septic shock at BSI onset (p = 0.006). All-cause mortality was not significantly different between patients receiving tigecycline- or polymyxin B-based therapy (55.81% vs. 53.85%, p = 0.873), and between subgroups mortality rates were also similar.

Conclusions: Critical illness indicators (APACHE II scores and presence of septic shock at BSI onset) were independent risk factors for 28-day all-cause mortality. There was no significant difference between tigecycline- and polymyxin B-based therapy outcomes. Prompt and appropriate infection control should be implemented to prevent CRKP infections.

Introduction

In recent years, bacterial resistance has become a significant problem, worldwide. As one of the most threatening and critically resistant carbapenem-resistant Enterobacteriaceae (CRE) classified by the World Health Organization, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) are gradually increasing (1). According to a resistance report from the China Antimicrobial Surveillance Network, the imipenem and meropenem resistance rates for *K. pneumoniae* had increased to 25% and 26.3% in 2018, respectively (2). CRKP infections often occur in intensive care units (ICUs), leading to severe nosocomial infections, such as pneumonia, bloodstream infections (BSIs), complicated intra-abdominal infections, and urinary tract infections. These infections frequently cause multiple organ dysfunctions and septic shock, leading to an increased risk of in-hospital mortality, prolonged hospitalization, and high economic costs (3, 4). It is worth noting that the mortality rate (33–70%) associated with CRKP-BSIs is three-fold higher than that of infections occurring at other bodily locations, and has become an urgent and widely acknowledged concern in clinical practice (5). Previous studies have shown that, compared with carbapenem-susceptible *K. pneumoniae* BSIs, non-transplant patients with histories of previous gastric catheterization, carbapenem use, hypoproteinemia, and high acute physiology and chronic health evaluation (APACHE) II scores have an increased risk of acquiring CRKP-BSIs (6). Likewise, septic shock and high APACHE II, Pitt bacteremia, and Charlson comorbidity index scores are independent risk factors for CRKP-BSI mortality (6, 7). However, the prognoses of ICU patients with CRKP-BSIs are related to their underlying diseases and

demonstrates regional differences (8). Comprehensive risk assessments, based on baseline clinical features and infection severity, are of paramount importance to the early, individualized treatment of patients with CRKP-BSIs.

Although the mortality of patients with CRKP-BSIs is high, the efficacies of different antibiotic therapies vary according to the bacterial resistance mechanism(s) possessed by the infecting organisms (9). Hence, the optimal treatment remains uncertain and the clinical antibiotic therapy options are limited, despite several antibiotics having been reported as effective against CRKP infections (10). In recent years, tigecycline- and polymyxin B-based antimicrobial therapies have been recommended for and widely used against drug-resistant Gram-negative bacilli according to the Chinese consensus statement(11). In May 2019, the new β-lactamase inhibitor complex ceftazidime/avibactam was approved and available for use, in China. Nevertheless, the exact therapeutic effects of these two CRKP-BSI treatment options remains uncertain, especially in critically ill patients.

Therefore, we retrospectively reviewed the clinical data for patients with CRKP-BSIs treated, between June 2016 and June 2020, in our hospital's ICUs. Our aim was to identify the predictors of mortality associated with CRKP-BSIs and explore the therapeutic efficacies of tigecycline- and polymyxin B-based therapies in critically ill patients.

Methods

Study design and population

This retrospective study was conducted in Ruijin Hospital, affiliated to Shanghai Jiao Tong University School of Medicine, a teaching hospital with 3300 beds in Shanghai, China. The study protocol was approved by the hospital's Medical Ethics Committee (approval, 2019-1-3). Between July 2016 and June 2020, all CRKP-BSI episodes occurring in the general, emergency, respiratory, and cardiac surgical ICUs were enrolled. If one patient experienced more than one episode, only the first episode was included. Patients who were pregnant, < 18 years old, or received BSI treatment (empiric or definitive) for < 48 hours were excluded; cases with incomplete information were also excluded.

Clinical data collection

Data were retrieved from the patient medical records and independently assessed by two ICU physicians. Patient demographics (age, sex, body mass index [BMI], and background comorbidities (diabetes mellitus, chronic renal failure, chronic liver diseases, biliary tract disease, congestive heart failure, chronic obstructive pulmonary disease, malignancy, and immunosuppression) were evaluated using the Charlson comorbidity index. Data were also collected regarding previous (within 30 days) health care exposures prior to the admission of interest, including antibiotic exposure, ICU admission, surgery, immunosuppressive therapy (within 3 months), and previous hospitalization (within 12 months). The probable BSI sources, acute severity, and organ dysfunction (including biomarkers [C-reactive protein and procalcitonin], acute kidney injury [AKI], continuous renal replacement therapy [CRRT], septic shock, and

use of mechanical ventilation) at BSI onset were assessed, and further calculated by APACHE II score, pitt bacteraemia score (PBS) and sequential organ failure assessment score (SOFA score). We extracted the antimicrobial treatment administered to each patient from their medical records. Additionally, we evaluated the attributable and 28-day all-cause and in-hospital mortality rates following each patient's initial positive blood culture, along with the total lengths of hospital and ICU stays.

Microbiological methods

All blood culture isolates were processed in the hospital's clinical microbiology laboratory. Bacterial species identifications were confirmed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (bioMérieux, Marcy-l'Etoile, France) and susceptibility testing was performed (VITEK 2, bioMérieux)(12). Minimum inhibitory concentrations (MICs) were classified according to breakpoints established by the Clinical and Laboratory Standards Institute (CLSI; Annapolis Junction, MD, USA). The CRE definition was based on CLSI guidelines, with carbapenem resistance defined as in vitro resistance to at least one of the following: ertapenem (MIC ≥ 2 mg/L), imipenem (MIC ≥ 4 mg/L), or meropenem (MIC ≥ 4 mg/L, disk diffusion zone ≤ 19 mm) (13).

Definitions

Patients with CRKP-BSIs were defined as those with at least one CRKP-positive blood culture and clinical infection symptoms consistent with bacteremia (14). BSI onset was defined as the date on which the first positive blood culture was collected. The probable infection sources were classified into the following categories by the attending physicians: BSI from central lines, such as central venous or hemofiltration catheters; intra-abdominal infection (IAI); respiratory tract infection; skin and soft tissue infection (SSTI); and cardiovascular system infections such as endocarditis; or primary BSI, when a source was not identified (14). Septic shock was defined according to the definition of sepsis-3 (15). AKI was classified according to the Kidney Disease: Improving Global Outcomes clinical guidelines. Empiric antibiotic therapy was selected, according to clinical judgment, prior to receipt of the blood culture report (16). Treatment with tigecycline and/or any other antibiotics, except polymyxin B, was considered to be tigecycline-based therapy; any treatment involving polymyxin B was considered to be polymyxin B-based therapy (17, 18). Combination therapy was defined as a regimen including more than one in-vitro active antimicrobial (19, 20).

Procedures and assessments

The primary outcome of this study was the 28-day all-cause mortality rate; survivor and non-survivor subgroups were compared to identify mortality predictors. We analyzed the therapeutic efficacies of tigecycline- and polymyxin B-based therapies because the antibiotic treatment options were varied. The efficacy analyses also involved subgroup analyses based on age (≤ 65 years vs. > 65 years), men versus women, BMI (≤ 25 vs. > 25), APACHE II score (≤ 20 vs. > 20), with or without CRRT, and with or without mechanical ventilation.

Statistical analysis

Categorical variables were reported as frequencies and percentages; continuous variables were reported as means and standard deviations (SDs), if they were normally distributed, or as medians and interquartile ranges (IQRs), if they were non-normally distributed. Categorical variables were compared using chi-square or Fisher's exact tests; continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test, according to their distribution. Variables that were significant in the univariate analyses ($p < 0.1$) were added to a stepwise, multiple logistic regression model to identify the independent risk factors for 28-day mortality. The survival analysis was performed using the Kaplan–Meier method, and a p-value < 0.05 was considered statistically significant. The Cochran-Mantel-Haenszel test was used for the various subgroup analyses (age, sex, BMI, APACHE II score, CRRT, and mechanical ventilation). All statistical tests were reported as two-tailed tests, and p-values < 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS (version 23.0; IBM, Armonk, NY, USA).

Results

Characteristics of critically ill patients with CRKP-BSIs

A total of 87 patients (67 males, 77.0%) with CRKP-BSI were included in the study, the baseline characteristics and univariate analyses of the study population are shown in Table 1. The most frequent sources of the bacteremia were intra-abdominal (56.32%), respiratory tract (21.84%), central lines (9.20%), primary (5.75%), skin and soft tissue infections (3.45%), urinary tract infections (2.29%), and cardiovascular system infections (1.15%). AKI and septic shock occurred in 51.72% and 73.56% of patients, 33.33% of the patients received CRRT and 78.16% required mechanical ventilation support at the BSI onset. The mean APACHE II score at CRKP-BSI onset was 23.3 ± 7.58 and SOFA was 8 (range, 5.5–11). The 28-day all-cause and in-hospital mortality rates were 52.87% and 67.82%, respectively. The 28-day mortality and in-hospital mortality rates attributable to infection were 47.13% and 55.17%, respectively. Furthermore, the 28-day all-cause mortality rates, by major source of infection, were 53.06% (26/49) in those with IAIs, 63.16% (12/19) in those with respiratory infections, and 50.00% (4/8) in those with central line infections; there was no significant difference in the CRKP-BSI mortality rates stratified by site of infection.

Table 1
Clinical characteristics and Univariate Analysis of Factors Associated with All-Cause 28 Day Mortality of CRKP-BSIs

Variables	Total (n = 87)	Non-survivor (n = 46)	Survivor (n = 41)	P-value
Demographic variables				
Age, years,mean ± SD	58.71 ± 17.36	63.65 ± 14.65	53.17 ± 18.83	0.005
Male sex	67(77.01%)	33(71.74%)	34(82.93)	0.216
Body mass index kg/m^2	24.5 ± 4.55	24.47 ± 5.22	24.47 ± 3.77	0.997
NRS-2002	6(4–6)	6(4–6)	5(4–6)	0.165
Comorbidities				
Charlson comorbidity index	2(1–4)	3(1–5)	2(0–4)	0.072
Diabetes mellitus	27(31.03%)	13(28.26%)	14(34.15)	0.554
Chronic renal failure	8(9.20%)	3(6.52%)	5(12.20%)	0.587
Chronic liver diseases	1(1.15%)	1(2.08%)	0(0%)	1.000
Biliary tract disease	10(11.49%)	9(19.57%)	1(2.44%)	0.031
Congestive heart failure	5(5.74%)	4(8.70%)	1(2.44%)	0.429
Chronic obstructive pulmonary disease	5(5.74%)	3(6.52%)	2(4.88%)	1.000
Malignancy	15(17.24%)	8(17.39%)	7(17.07%)	0.969
Immunosuppression	8(9.20%)	3(6.52%)	5(12.20%)	0.587
Health-care exposure before hospitalization				
Antibiotic exposure (< 30 days)	57(65.52%)	28(60.90%)	29(70.73%)	0.334
ICU admission (< 30 days)	33(37.93%)	14(30.43%)	19(46.34%)	0.127
Surgery (< 30 days)	18(20.69%)	8(17.39%)	10(24.39%)	0.421
Immunosuppressive therapy (< 3 months)	9(10.34%)	3(6.52%)	6(14.63%)	0.375
Previous hospitalization (< 12 months)	51(58.62%)	28(60.87%)	23(56.10%)	0.652

Abbreviations: NRS-2002, Nutrition risk screening − 2002; BSI, bloodstream infection; PCT, procalcitonin; CRP, C-reactive protein; AKI, Acute kidney injury; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

Variables	Total (n = 87)	Non-survivor (n = 46)	Survivor (n = 41)	P-value
Length of stay before BSI	23(13–34)	23(14.75–40.25)	23(9.5–33)	0.441
Source of infection				
Central Line	8(9.20%)	4(8.70%)	4(9.76%)	1.000
Urinary tract	2(2.29%)	1(2.17%)	1(2.44%)	1.000
Intra-abdominal	49(56.32%)	26(56.52%)	23(56.10%)	0.968
Respiratory	19(21.84%)	12(26.09%)	9(21.95%)	0.310
Skin and soft tissue	3(3.45%)	2(4.35%)	1(2.44%)	1.000
Cardio-vascular system infection	1(1.15%)	1(2.17%)	0(0%)	1.000
Primary	5(5.75%)	0(0%)	5(12.20%)	0.048
Severity of illness at BSI onset				
Biomarker at BSI onset				
PCT, ng/ml	3(0.9–8.24)	3.86 (1.785–9.96)	1.33(0.49–9.10)	0.046
CRP, mg/l	123.67 ± 82.01	134.38 ± 83.24	111.81 ± 80.09	0.884
Organ dysfunction at BSI onset				
AKI	45(51.72%)	31(67.39%)	14(34.15%)	0.002
CRRT	29(33.33%)	20(43.48%)	9(21.95%)	0.033
Septic shock	64(73.56%)	43(93.48%)	21(51.22%)	< 0.001
Mechanical ventilation	68(78.16%)	40(86.96%)	28(69.29%)	0.035
APACHE II score at BSI onset	23.3 ± 7.58	26.70 ± 6.46	19.49 ± 7.05	< 0.001
SOFA score at BSI onset	8(5.5–11)	9(8–13)	6(3–8)	< 0.001
Pitt bacteremia score	4(2–5)	4(3–6)	3(1–4)	0.001
Outcomes				

Abbreviations: NRS-2002, Nutrition risk screening − 2002; BSI, bloodstream infection; PCT, procalcitonin; CRP, C-reactive protein; AKI, Acute kidney injury; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

Variables	Total (n = 87)	Non-survivor (n = 46)	Survivor (n = 41)	P-value
Length of hospital stay	48(29–86)	32.75(19.75–56.5)	78(47–109)	< 0.001
Length of stay in ICU	42(21–79)	27.75(15-47.75)	59(34–98)	< 0.001

Abbreviations: NRS-2002, Nutrition risk screening − 2002; BSI, bloodstream infection; PCT, procalcitonin; CRP, C-reactive protein; AKI, Acute kidney injury; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

Predictors of 28-day all-cause mortality in critically ill patients with CRKP-BSIs

The univariate analysis indicated that patients who died were older (63.65 ± 14.65 vs 53.17 ± 18.83 years, p = 0.005) than those who survived. Both the survivors and non-survivors had similar ratios of men, BMIs, and nutrition risk screening-2002 scores; however, non-survivors were more likely have biliary tract disease (19.57% vs. 2.44%, p = 0.031). Healthcare exposures before hospitalization and durations of hospital stay before developing BSIs were similar in both groups. There were no significant differences in the source of the infection between the survivors and non-survivors, except in patients with primary BSIs. Among those with primary BSIs, all were survivors. At BSI onset, non-survivors had higher procalcitonin levels (3.86 [range, 1.785–9.96] vs 1.33 [0.49–9.10], p = 0.046), higher frequencies of AKIs and septic shock events (67.39% vs 34.15%, p = 0.002 and 93.48% vs 51.22%, p < 0.001, respectively), required more organ function support (CRRT) (43.48% vs. 21.95%, p = 0.033), and required more mechanical ventilation (86.96% vs. 69.29%, p = 0.035). In addition, non-survivors had higher APACHE II (26.7 ± 6.46 vs. 19.49 ± 7.05, P < 0.001), SOFA (9 [8–13] vs. 6 [3–8], p < 0.001), and PBS (4 [3–6] vs. 6 [3–8], p = 0.001). Lengths of ICU and hospital stays were shorter in non-survivors (27.75 (15–47.75) vs 59 (34–98) days, p < 0.001 and 32.75 (19.75–56.5) vs 78 (47–109) days, P < 0.001) (Table 1).

In the multivariate analysis, the APACHE II score (odds ratio [OR], 1.143; 95% confidence interval [95% CI], 1.049–1.246; p = 0.002) and the occurrence of septic shock (OR, 8.529; 95% CI, 1.869–38.920; p = 0.006) were independent risk factors for 28-day all-cause mortality in patients with CRKP-BSIs (Table 2).

Table 2
Multivariate Logistic Regression Analysis of Predictors of All-Cause 28-Day Mortality Patients with CRKP-BSIs

Variables	P-value	OR (95 CI%)
APACHE II at BSI onset	0.002	1.143(1.049–1.246)
Septic shock at BSI onset	0.006	8.529(1.869–38.920)

Antibiotic prescribing patterns for critically ill patients with CRKP-BSIs

The antimicrobial therapies and outcomes for the 87 CRKP-BSI patients are shown in Table 3. Sixteen patients (18.39%) received monotherapy, including carbapenem (9.20%), tigecycline (4.60%), polymyxin B (1.15%), or ceftazidime-avibactam (1.15%); 71 (81.60%) received combination therapy. The most frequently prescribed combination regimen included carbapenem (57 cases, 65.51%), followed by tigecycline (46 cases, 52.87%), polymyxin B (25 cases, 28.74%), amikacin (7 cases, 8.05%), fosfomycin (10 cases, 11.49%), and ceftazidime-avibactam (3 cases, 3.45%). A prolonged 2 hours of infusion was used for patients receiving carbapenem treatment.

Table 3
Details of antibiotic prescribing patterns of patients with CRKP-BSIs

Antimicrobial regimens	All (87)	Death in 28-day	P-value
Tigecycline regimens	43	24(55.81%)	0.715
Polymyxin B regimens	26	14(53.85%)	
Other regimens	18	8 (44.4%)	
Tigecycline regimens	43	24(55.81%)	
Tigecycline monotherapy	4	4(100%)	
Tigecycline + Carbapenem	27	15	
Tigecycline + Amikacin	2	0	
Tigecycline + Fosfomycin	1	1	
Tigecycline + Sulfamethoxazole	2	1	
Tigecycline + Carbapenem + Amikacin	2	1	
Tigecycline + Carbapenem + Fosfomycin	3	2	
Tigecycline + Carbapenem + Sulfamethoxazole	2	0	
Polymyxin B regimens	26	14	
Polymyxin B monotherapy	1	0	
Polymyxin B + Carbapenem	13	8	
Polymyxin B + Fosfomycin	2	0	
Polymyxin B + Tigecycline	4	2	
Polymyxin B + Tigecycline + Carbapenem	3	2	
Polymyxin B + Carbapenem + Fosfomycin	1	1	
Polymyxin B + Ceftazidime-Avibactam	2	1	
Other regimens	18	8	
Carbapenem monotherapy	8	6	
Ceftazidime-Avibactam monotherapy	1	0	
Fosfomycin monotherapy	1	0	
Cefoperazone monotherapy	1	0	
Carbapenem + Fosfomycin	2	1	
Carbapenem + Amikacin	2	1	

Antimicrobial regimens	All (87)	Death in 28-day	P-value
Carbapenem + Sulfamethoxazole	1	0	
Ceftazidime-Avibactam + Amikacin	1	0	
Cefoperazone-sulbactam + Fosfomycin	1	0	

The tigecycline and colistin resistance rates for isolated *K. pneumoniae* have been ≤ 5% and have become the most important considerations for CRE treatment (2016–2020) in our hospital (2). All decisions regarding tigecycline and polymyxin B therapy were made with the aid of an infectious disease specialist. Loading doses were used, and dosages were adjusted based on creatinine clearance, if necessary. According to the actual antibiotic options for critically ill patients with CRKP-BSIs, the patients were classified into three treatment regimens: tigecycline-based (43 cases, 49.43%), polymyxin B-based (26 cases, 29.89%), and other (18 cases, 20.7%). In the tigecycline group, the most commonly prescribed regimen included tigecycline and carbapenem (27 cases, 62.79%). In the polymyxin B group, the most frequently co-prescribed drug was carbapenem (13 cases, 50%); combinations of polymyxin B plus tigecycline and polymyxin B plus ceftazidime-avibactam were used in 3 and 2 cases, respectively. There were no significant differences in 28-day all-cause mortality rates between the three groups (55.8% vs. 53.85% vs. 44.4%, respectively, p = 0.715).

Therapeutic efficacy of tigecycline- and polymyxin B-based antimicrobial regimens

To compare the efficacy of tigecycline- and polymyxin B-based therapies, we compared the demographics and clinical characteristics between the tigecycline and polymyxin B groups (Table 4). The median patient age was higher in the polymyxin B group (68.5 [55.5–73.5] years) than in the tigecycline group (58 [44–69] years, p = 0.030) and the percentage of males was lower in the polymyxin B group (61.54% vs. 88.37%, p = 0.009). There were no other significant between-group differences in clinical characteristics or illness severities at BSI onset. The 28-day all-cause mortality rates were not significantly different (55.81% vs. 53.85%, p = 0.873) for patients receiving either tigecycline- or polymyxin B-based therapies. Similarly, there were no between-group differences in all-cause mortality, attributable mortality, or attributable in-hospital mortality rates. The Kaplan–Meier curve for 28-day survival distributions is shown in Fig. 1 (log-rank, p = 0761). The lengths of hospital and ICU stays were comparable between the two groups. Moreover, we compared the tigecycline-based regimens with polymyxin B-based regimens not including ceftazidime-avibactam treatment and did not find any significant between-group difference in 28-day mortality rates (55.81% vs 54.17%, p = 0.897). Additionally, there was no significant difference in 28-day mortality rates between the tigecycline- and polymyxin B-based combination therapies (51.28% vs. 56.0%, p = 0.712).

Table 4
Comparation of the demographics and clinical characteristics between tigecycline- and polymyxin B-based regimen group

Variables	Tigecycline regimens (43)	Polymyxin B regimens (26)	P-value
Demographic variables			
Age, years,mean ± SD	58(44–69)	68.5(55.5–73.5)	0.030
Male sex	38(88.37%)	16(61.54%)	0.009
Body mass index kg/m^2	25.60±4.06	23.60±5.85	0.099
NRS-2002	5(4–6)	6(4-6.25)	0.344
Comorbidities			
Charlson comorbidity index	2(0–4)	3(1.75–4.25)	0.117
Diabetes mellitus	12(27.91%)	8(30.77%)	0.800
Chronic renal failure	4(9.30%)	3(11.54%)	1.000
Chronic liver diseases	0(0.00%)	1(3.85%)	0.377
Biliary tract disease	4(9.30%)	6(23.08%)	0.222
Congestive heart failure	0(0.00%)	2(7.69%)	0.139
Chronic obstructive pulmonary disease	3(6.98%)	1(3.85%)	0.994
Malignancy	6(13.95%)	6(23.08%)	0.521
Immunosuppression	1(2.33%)	3(11.54%)	0.291
Health-care exposure before hospitalization			
Antibiotic exposure (< 30 days)	27(62.79%)	18(69.23%)	0.586
ICU admission (< 30 days)	17(39.53%)	10(38.46%)	0.929
Surgery (< 30 days)	8(18.60%)	6(23.08%)	0.654
Immunosuppressive therapy (< 3 months)	2(4.65%)	3(11.54%)	0.555
Previous hospitalization (< 12 months)	28(65.12%)	12(46.15%)	0.122
Source of infection			

Abbreviations: NRS-2002, Nutrition risk screening − 2002; BSI, bloodstream infection; PCT, procalcitonin; CRP, C-reactive protein; AKI, Acute kidney injury; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

Variables	Tigecycline regimens (43)	Polymyxin B regimens (26)	P-value
Central Line	5(11.63%)	2(7.69%)	0.910
Urinary tract	0(0%)	1(3.85%)	0.377
Intra-abdominal	28(65.12%)	12(46.15%)	0.122
Respiratory	7(16.28%)	9(34.62%)	0.080
Skin and soft tissue	2(4.65%)	1(3.85%)	1.000
Cardio-vascular system infection	0(%)	0(%)	1.000
Primary	1(2.32%)	1(3.85%)	1.000
Severity of illness at BSI onset			
Biomarker at BSI onset			
PCT, ng/ml	2.55(0.89–7.95)	3.96(0.81–14.59)	0.635
CRP, mg/l	133.39±84.90	137.80±81.24	0.842
Organ dysfunction at BSI onset			
AKI	23(53.49%)	15(57.69%)	0.734
RRT	17(39.53%)	10(38.46%)	0.929
Septic shock	35(81.40%)	20(76.92%)	0.654
Mechanical ventilation	38(88.37%)	20(76.92%)	0.358
APACHE II	24.07±7.41	23.15±8.56	0.641
SOFA	8(6–11)	8(5.75–11.25)	0.789
Pitt bacteremia score	4(3–5)	4(2.75-6)	0.861
Outcomes			
All-cause 28-day mortality	24(55.81%)	14(53.85%)	0.873
All-cause in-hospital mortality	28(65.12%)	18(69.23%)	0.725
Attributable 28-day mortality	19(44.19%)	14(53.85%)	0.436
Attributable in-hospital mortality	22(51.16%)	17(65.38%)	0.248
Length of stay	48(28–86)	55.5(29.5–93)	0.696

Abbreviations: NRS-2002, Nutrition risk screening – 2002; BSI, bloodstream infection; PCT, procalcitonin; CRP, C-reactive protein; AKI, Acute kidney injury; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

Variables	Tigecycline regimens (43)	Polymyxin B regimens (26)	P-value
Length of stay before BSI	23(12–34)	26(14.5-68.75)	0.340
Length of stay in ICU	42(26–80)	46.5(20.75–81.75)	0.906

Abbreviations: NRS-2002, Nutrition risk screening – 2002; BSI, bloodstream infection; PCT, procalcitonin; CRP, C-reactive protein; AKI, Acute kidney injury; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

Furthermore, patients were also divided into six subgroups based on their age (≤ 65 years vs. > 65 years), sex, BMI (≤ 25 vs. > 25), APACHE II score (≤ 20 vs. > 20), CRRT use, and mechanical ventilation use, to clarify the impact of these variables and indicators of disease severity on tigecycline- and polymyxin B-based therapy outcomes. However, no significant differences in treatment efficacies were evident in the subgroup analyses (Fig. 2).

Discussion

CRKP infections are life-threatening health problems, worldwide. Critically ill patients in ICUs have a higher risk of contracting CRKP-BSIs because of their illness severity, immunosuppression, and frequent use of invasive procedures; ICU-acquired infections were previously shown to be a powerful causative factor leading to the development of CRKP-BSIs (3). Notably, patient population heterogeneity, such as infection source, underlying disease severity, and response syndrome severity at presentation, are important for determining CRKP-BSI prognoses. This is because these BSIs are inherently difficult to eradicate, eventually spreading to different sites throughout the body, and are associated with high morbidity and mortality rates. Therefore, evaluations of the pathogenic characteristics, in-hospital death risk factors, and treatment outcomes of CRKP-BSIs are important.

Here, we analyzed the risk factors for CRKP-BSI mortality rates and treatment outcomes in 87 critically ill patients. The average APACHE II and SOFA scores and the 28-day all-cause mortality rates were higher than those previously reported. The higher mortality rate may be attributed to differences in the bacteremia sources and patient disease severity heterogeneity. The infection source for CRKP-BSIs frequently affects patient prognoses, as evidenced in PANORAMA study, primary bloodstream infections were the most predominant source of BSIs (48%), followed by gastrointestinal system infections (21%) (8). In the EUROBACT study, primary bloodstream (23.7%) and catheter-related (21.4%) infections were the most common sources, followed by respiratory tract (21.1%) and intra-abdominal (11.6%) infections (21). Most patients admitted to our ICU had complicating abdominal and respiratory tract infections, and 78.16% of the CRKP-BSIs originated from these two sources, leading to 28-day mortality rates of 53.1% and 63.2%, respectively. Abdominal infections often require more than one source control interventions, and the effect of drainage is difficult to evaluate (22). Respiratory tract infections are considered to less “drainable” and such uncontrolled infection sources seem to be independently associated with poor

outcomes (23). Moreover, the patient's underlying condition and disease severity directly affect the prognosis. In our study, septic shock developed in 73.56% of patients and was 93.48% among the non-survivors; the 28-day CRKP-BSI mortality rate in patients with septic shock was 67.19%. Similarly, the risk factors for CRKP-BSI mortality identified in our analysis are consistent with those reported previously, including older age; biliary tract disease; high procalcitonin levels; high APACHE II, SOFA, and Pitt bacteremia scores; and development of AKI and septic shock upon BSI onset (in our univariate analysis). Furthermore, our multivariate analysis revealed that the APACHE II score and septic shock were independent risk factors for crude 28-day mortality (7, 24). Therefore, we should be aware that the mortality risk is based on the illness severity at BSI onset; thus, early and adequate source control and appropriate antimicrobial treatment should be implemented as soon as possible (25, 26).

The selection of antimicrobial therapies for CRKP is very limited; tigecycline and colistin/polymyxin B have been recommended by a Chinese consensus panel on the treatment of multidrug-resistant Gram-negative bacilli, and are widely used in China until now(11). The resurgence of colistin has resulted from its unique mechanism of action: disruption of the Gram-negative bacterial outer membrane and provision of rapid bactericidal activity in conjunction with other antibiotics. Polymyxin B is the preferred agent for systemic use in invasive infections because of its superior pharmacokinetics and reduced nephrotoxicity potential (27). A recent retrospective cohort study found that combination therapies, mostly polymyxin B plus amikacin, had significantly lower 30-day mortality rates than monotherapies (37.5% vs. 64.75%, $p = 0.01$) in 82 patients with CRKP-BSIs (28). However, reports still emerge of inadequate dosages, treatment failures, adverse effects, and heterogeneous resistance during polymyxin B treatment (29).

Tigecycline is a broad-spectrum glycyl cyclic peptide antibiotic that has shown in vitro activity against CRE; however, the efficacy of tigecycline against CRE infections, especially BSIs, remains debatable because of insufficient dose and low serum concentration(30). Multivariate analyses have shown that the use of tigecycline is not only an independent risk factor for CRKP-BSI development (OR, 3.915; $p = 0.005$), but its use was also associated with an increased risk of 28-day mortality (31). However, a systematic review and meta-analysis that included 21 controlled studies (1595 patients) and 5 single-arm studies (113 patients) revealed that the tigecycline groups had similar overall mortality rates as the control groups (OR, 0.96; 95% CI, 0.72–1.22; $p = 0.73$); but tigecycline combination therapies and high-dose regimens have been reported to be associated with better outcomes, without significant adverse effects in the subgroup analysis(32). These data highlight the utility of combination antimicrobial therapy for CRKP-BSIs, particularly in high-risk, severely ill patients (20, 33). Our study reflects the broad acceptance of combination therapy for the treatment of CRKP-BSIs in that 90.69% and 96.15% of cases were prescribed either tigecycline- or polymyxin B-based combination therapy, respectively. Despite this high rate of combination therapy use, the 28-day mortality rate remained > 50%, suggesting that we need to rethink and assess the efficacy of these two drugs.

Different antimicrobial treatments are associated with different prognoses, and few studies have compared the therapeutic effects of polymyxin B and tigecycline in real-world practice. Lin analyzed 64 patients with bloodstream infections caused by CRKP and carbapenem-resistant *Escherichia coli* in 16

hospitals, in Taiwan. Mortality was higher for patients receiving colistin monotherapy than for those receiving tigecycline monotherapy (57.1% vs. 19.2%, p = 0.035) (34). However, Shen et al. conducted another retrospective study that included 89 patients with CRKP-BSIs. Those who received polymyxin B therapy demonstrate a survival benefit compared with those receiving tigecycline-based therapy (hazard ratio, 0.068; 95% CI, 0.018–0.260; p < 0.001) (17). However, these conclusions may not be easily extended to patients in other circumstances because of the heterogeneity of population diseases. Our study included 43 patients treated with tigecycline-based regimens and 26 with polymyxin B-based regimens; neither demonstrated superior mortality rates. In fact, significant between-group differences were not observed in any of the outcome or subgroup analyses. Ceftazidime-avibactam and other enzyme inhibitor drugs have emerged as promising new options as rescue treatments for CRKP-BSIs; well-designed clinical studies are needed to evaluate the clinical efficacy(35, 36).

Our study had some limitations. First, this was a retrospective study with inevitable bias. Second, pathogen-associated factors, such as detailed drug susceptibility testing and resistance gene detection were not explored. Third, several details concerning the antimicrobial regimens, such drug dosages and treatment courses, were not recorded. Fourth, patient immune statuses were not included in the analyses. Fifth, this was a single-center study involving a small number of cases. Further well-designed, multicenter, prospective studies are required.

Conclusions

In conclusion, critically ill patients with CRKP-BSIs showed poor outcomes and high mortality rates. Disease severity indicators, specifically the APACHE II score and evidence of septic shock at BSI onset, were independent risk factors for 28-day all-cause mortality. Although combination therapy was commonly used, the 28-day mortality rate was high and there was no significant difference in efficacy between the tigecycline- and polymyxin B-based regimens. In this era of limited new drugs for CRKP infections, prompt and appropriate infection control should be implemented to prevent the dissemination of resistant microorganisms among high-risk patients, especially those in the ICU.

Abbreviations

CRKP: Carbapenem-resistant *Klebsiella pneumonia*; BSI: bloodstream infections; CRE: carbapenem-resistant Enterobacteriaceae; ICU: intensive care units; BMI: body mass index; AKI: acute kidney injury; CRRT: continuous renal replacement therapy; PBS: pitt bacteraemia score; SOFA: sequential organ failure assessment; MIC: Minimum inhibitory concentrations; IAI: intra-abdominal infection; SSTI: skin and soft tissue infection

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethic Committees of the Shanghai Jiao Tong University School of Medicine and Ruijin Hospital (approval, 2019-1-3).

Consent for publication

Not applicable.

Availability of data and materials

The raw data can be made available to the interested researchers by the authors of this article if requested.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yuzhen Qiu, Wen Xu, Xiaoli Wang and Hongping Qu contributed to the conception and design of the work. Yuzhen Qiu, Wen Xu and Xiaoli Wang collected and analysed the data, then wrote the manuscript. Yunqi Dai, Ruoming Tan, Jialin Liu and Feifei Gu contributed to the method and analyse. Erzhen Chen and Hongping Qu revised it critically for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Figures

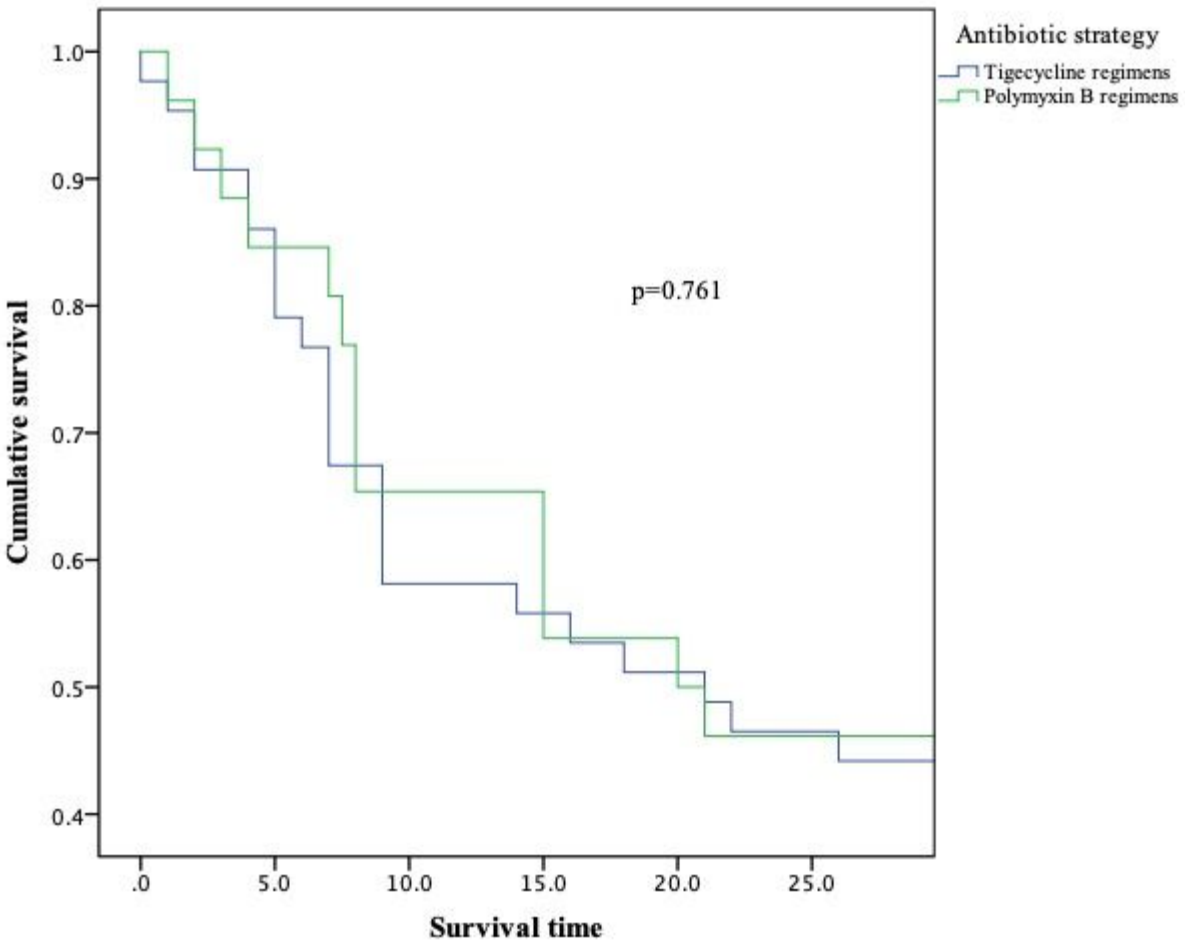

Figure 1

Kaplan–Meier analysis of 28-day survival of tigecycline- and polymyxin B-based antimicrobial regimens.

Subgroup	No. of patients	Tigecycline group	Polymyxin B group	Odds Ratio (95% CI)	p
Age					0.563
≤65	42	17/32 (53.13%)	4/10 (40.00%)	0.59(0.14-2.49)	
>65	27	7/11 (63.64%)	10/16 (62.50%)	0.95(0.19-4.68)	
Sex					0.475
men	54	20/38 (52.64%)	7/16 (43.75%)	0.58(0.04-7.66)	
women	15	4/5 (80.00%)	7/10 (70.00%)	0.70(0.22-2.27)	
BMI					0.937
≤25	36	10/19 (52.63%)	9/17 (52.94%)	1.01(0.27-3.76)	
>25	33	14/24 (58.33%)	5/9 (55.56%)	0.89(0.19-4.19)	
APACHE II					0.868
≤20	26	2/15 (13.33%)	4/11 (36.36%)	3.71(0.54-25.59)	
>20	43	22/28 (78.57%)	10/15 (66.67%)	0.54(0.13-2.22)	
RRT					0.892
Yes	27	14/17(82.35%)	5/10(50.00%)	0.21(0.04-1.24)	
No	42	10/26 (38.46%)	9/16(56.25%)	2.06(0.58-7.29)	
Mechanical ventilation					0.962
Yes	58	23/38(60.53%)	11/20(55.00%)	0.80(0.27-2.38)	
No	11	1/5 (20.00%)	3/6(50.00%)	4.00(0.27-60.33)	

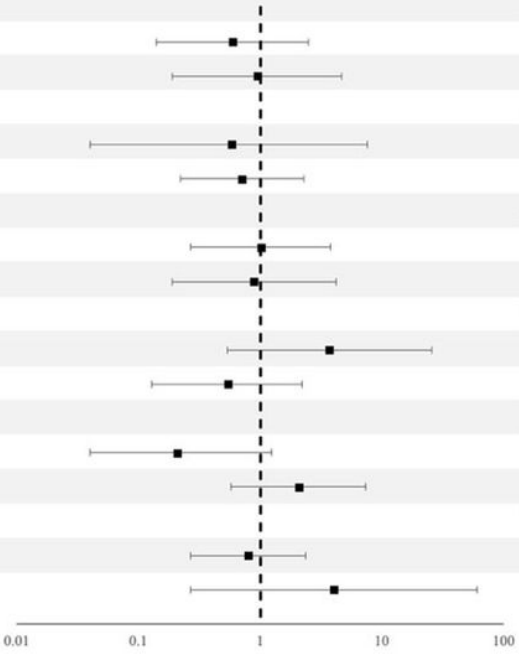

Figure 2

Therapeutic efficacy assessment of tigecycline- and polymyxin B-based antimicrobial regimens by different subgroup analysis. Abbreviations: BMI, Body Mass Index; APACHE II, Acute Physiology and Chronic Health Evaluation II