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Original Article

Risk factors and outcomes for carbapenem-resistant *Klebsiella pneumoniae* bacteremia in onco-hematological patients

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Abstract

Introduction: Carbapenem-resistant *Klebsiella pneumoniae* (KP) serves as a major threat to onco-hematological patients, resulting in great morbidity and mortality. The purpose of our study was to identify the risk factors for KP bloodstream infections (BSIs) and mortality in onco-hematological patients.

Methodology: A retrospective observation study was conducted on KP BSIs in the onco-hematology departments at Xiangya hospital from January 2014 to September 2018. Multivariate analysis was employed to identify the independent risk factors for carbapenem-resistant (CR) KP BSIs and related mortality.

Results: A total of 89 strains of KP were analyzed in our study, in which 20 strains were CRKP. The only risk factor for CRKP BSI was carbapenem exposure within 30 days before the onset of BSIs (HR 25.122). The 30-day mortality was 24.7%. CRKP caused more mortality than carbapenem-susceptible KP (55.0% vs 15.9%, P = 0.001). In the multivariate analysis, unresolved neutropenia (HR 16.900), diarrhea (HR 3.647) and RDW > 14% (HR 6.292) were independent risk factors for mortality, and appropriate empirical therapy (HR 0.164) was protective against mortality.

Conclusions: Our findings showed that carbapenem resistance was spreading in our setting, and a precise combination of antibiotics covering the common pathogen is crucial to improving patient survival.

Key words: *Klebsiella pneumoniae* bacteremia; carbapenem-resistant; mortality; risk factors.

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Introduction

In recent years, the overall survival rate for onco-hematological patients improved dramatically with the development of chemotherapy and stem cell transplantation. However, bloodstream infections (BSIs) are closely associated with mortality in onco-hematological patients due to long hospitalizations, invasive medical procedures and immunosuppression, accounting for approximately 11-38% of infections, with a mortality rate of up to 40% [1]. Furthermore, multidrug resistant (MDR) bacteremia has been reported worldwide, causing global concerns for control for the spread of MDR strains and medicine decisions for MDR infection treatment. More importantly, *Klebsiella pneumoniae* resistant to carbapenem (CRKP) has been reported worldwide, including in China. A rapid increase in CRKP incidence has been noted in China, with prevalence rates of 2.9% in 2005 and 20.9% in 2017 [2]. Because of the few antibiotics available, CRKP has become a major threat to patients with onco-hematological disorders, resulting in high mortality [3,4]. It is urgent to describe the risk factors for CRKP infection, which would improve the control of CRKP spread. However, limited information has been reported regarding the epidemiology, outcomes and risk factors for *K. pneumoniae* bacteremia among patients with onco-hematological disorders.

Therefore, we conducted a retrospective study of onco-hematological patients who had *K. pneumoniae* bacteremia, regarding the clinical characteristics, laboratory results, outcomes and antimicrobial sensitivity, to assess the risk factors for mortality among patients with *K. pneumoniae* bacteremia.

Methodology

A retrospective observational study was conducted at Xiangya Hospital, Central South University, Changsha, China, a university-affiliated tertiary teaching hospital with three separate departments for onco-hematological disorders and a department for hematopoietic stem cell transplantation. From January 2014 to September 2018, patients who were admitted to the onco-hematology departments were enrolled if they had one episode of *K. pneumoniae* bacteremia. Only the first episode for each patient was included, and recurrent BSI was excluded. Clinical data, including patient characteristics, underlying diseases, antimicrobial susceptibility profiles, and laboratory results were reviewed from medical records and laboratory databases, and no additional medical procedures were performed. The main clinical outcome was death within 30 days after the infection episode; however, if the patient died because of *K. pneumoniae* infection, the episode was also enrolled in our study.

The study was approved by the Ethics Committee of Xiangya Hospital, Central South University. No informed consent was taken because this study did not cause additional medical procedures.

Microbiological tests

Blood samples were routinely taken in the case of fever (> 38 °C) or systemic symptoms indicating bacteremia and were cultured with an automated system (BACTECTM FX 200, Becton Dickinson). The bacterial identification and antibiotic susceptibility tests were performed with a microflex™ LT/SH mass spectrometer (Bruker Daltonik, Bremen, Germany) and a VITEK® system (bioMérieux, Hazelwood, MO, USA) according to the manufacturers' instructions. Cefazolin, cefoperazone-sulbactam and tigecycline were determined by the Kirby-Bauer disk diffusion method.

Definitions

Neutropenia was defined as an absolute neutrophil count (ANC) < 0.5 $\times 10^9$/L or an expected ANC < 0.5 $\times 10^9$/L within two or three days of the day on which fever developed; neutropenia was considered unresolved if it lasted for 14 days after the onset of BSIs, or until death before day 14.

Fever was defined as axillary membrane temperatures above 37.5 °C. Shock was defined as a systolic blood pressure < 90 mmHg or received inotropic agents to maintain blood pressure.

K. pneumoniae bacteremia was diagnosed when at least one of the blood sample cultures was positive for *K. pneumoniae*. Polymicrobial infection was defined as the isolation of bacteria other than *K. pneumoniae* on the same day as the *K. pneumoniae* was identified. Previous antimicrobial therapy was defined as exposure to any systemic antibiotics for more than 48 hours within 30 days.

Hospital-associated infection for *K. pneumoniae* BSIs was defined as the blood samples were collected > 48 hours after the patients were admitted; otherwise, the BSIs were considered community-acquired.

Empirical antibiotic therapy was considered appropriate if at least one drug was active against the strain of *K. pneumoniae* (as determined by *in vitro* susceptibility tests).

Previous infection was defined as any culture positive of sterile body fluids within one year before the *K. pneumoniae* BSIs, except for coagulase-negative staphylococci unless the strain was proven not to be contamination.

Antibiotic susceptibility was determined according to the Clinical and Laboratory Standards Institute 2015 recommendations [5]. For tigecycline, the US Food and Drug Administration interpretive criteria were used [6]. Intermediate and resistant were recognized as nonsusceptible. MDR was defined as nonsusceptible to at least one agent in ≥ 3 antimicrobial categories, according to Magiorakos *et al.* [7].

Statistical analysis

Numbers and percentages were reported for categorical variables. The means and standard deviations with variations or medians with interquartile ranges (IQRs) were reported for continuous variables, depending on their distribution patterns. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, when appropriate. Continuous variables were compared with the Mann-Whitney U test. P values < 0.05 were considered statistically significant. All variables that were associated with CRKP infections in the univariate analysis (P < 0.10) were entered into a multivariate logistic regression analysis. A Cox regression model was conducted to reveal the independent variables for 30-day mortality. SPSS (version 22, IBM Corporation, Armonk, NY, USA) was used for all analyses.

Results

Patient characteristics

Between January 2014 and September 2018, 89 onco-hematological patients with *K. pneumoniae* bacteremia were included in our study. Table 1 shows the baseline characteristics of the 89 patients. The

median age of the patients was 24 years (range 1-71), with an equal distribution of gender (51.6% were female). Acute lymphoblastic leukemia (36, 40.5%) was the most common disorder, followed by acute myeloid leukemia (30, 33.7%), lymphoma (7, 7.9%), severe aplastic anemia (6, 6.7%), myelodysplastic syndromes (3, 3.4%), solid tumor (4, 4.5%) and one each for plasmocytic leukemia, multiple myeloma and hemophagocytic syndrome. Concerning the stage of the underlying disorders, 14/89 (15.7%) were newly diagnosed with hematological disorders, 52/89 (58.4) were in complete remission and 19/89 (21.3%) were after relapse/refractory. Eleven patients were prepared for hematopoietic stem cell transplantation (5 autologous and 6 allogeneic). Regarding the comorbidities, 7.9% patients had liver disease, and 5.6% had diabetes. In total, 81/89 (91.0%) of all patients were neutropenic at the onset of BSIs, with a mean duration of 16.5 days (16.5 ± 9.5), and in 28/89 (31.5%) patients, neutropenia was considered unresolved. A total of 68.5% were exposed to antibiotics within 30 days before BSIs occurred, while 36.0% received antibiotics including carbapenems. A total of 41.6% of the patients had a peripherally inserted central catheter (PICC).

Immediately after the blood samples were collected for microbiology tests, patients reveived empirical antibiotics. Carbapenems remained the first choice (72,

Table 1. Baseline characteristics of 89 episodes of *K. pneumoniae* bacteremia according to Carbapenem-resistance of isolate.

Characteristics	All patients (n = 89)	CRKP (n = 20)	CSKP (n = 69)	*P* values
Age at BSI, median (range)	24 (1-71)	23 (7-71)	23 (1-64)	0.992
Sex, number of females, n (%)	46 (51.6)	10 (50.0)	41 (59.4)	0.613
Underlying disorders, n (%)				
Acute myeloid leukemia	30 (33.7)	6 (30.0)	24 (34.8)	0.792
Acute lymphoblastic leukemia	36 (40.5)	7 (35.0)	29 (42.0)	0.615
Severe aplastic anemia	6 (6.7)	3 (15.0)	3 (4.3)	0.124
Lymphoma	7 (7.9)	3 (15.0)	4 (5.8)	0.186
Others	10 (11.2)	1 (5.0)	9 (13.0)	0.446
Comorbidities, n (%)				
Liver disease	7 (7.9)	4 (20.0)	3 (4.3)	**0.043**
Diabetes mellitus	5 (5.6)	2 (10.0)	3 (4.3)	0.313
Stage of hematological disorders, n (%)				**0.208**
Newly diagnosed	14 (15.7)	5 (25.0)	9 (13.8)	
Complete remission	52 (58.4)	9 (45.0)	43 (66.2)	
After relapse/refractory	19 (21.3)	6 (30.0)	13 (20.0)	
Hematopoietic stem cell transplantation, n (%)	**11 (12.4)**			
Autologous	5 (5.6)	1 (5.0)	4 (5.8)	1.000
Allogeneic	6 (6.7)	3 (15.0)	3 (4.3)	0.124
Appropriateness of empirical therapy	71 (79.8)	4 (20.0)	67 (97.1)	**< 0.001**
Empirical therapy				**0.022**
Carbapenem	72 (80.9)	12 (60.0)	60 (80.9)	
Fluoroquinolone	5 (5.6)	2 (10.0)	3 (4.3)	
β-lactam/β-lactamase inhibitor	4 (4.5)	2 (10.0)	2 (2.9)	
Glycopeptide	2 (2.2)	1 (5.0)	1 (1.4)	
Aminoglycosides	4 (4.5)	3 (15.0)	1 (1.4)	
Cephalosporins	2 (2.2)	0 (0.0)	2 (2.9)	
Neutropenic				
Neutropenic, n (%)	81 (91.0)	18 (90.0)	63 (91.3)	1.000
Length of days for neutropenia, mean ± SD	16.5 ± 9.5	18.2 ± 12.4	16.0 ± 8.4	0.764
Unresolved neutropenic, n (%)	28 (31.5)	11 (55.0)	17 (24.6)	**0.014**
Central venous catheter, n (%)				
PICC	37 (41.6)	9 (45.0)	28 (40.6)	0.799
Gastric tube	5 (5.6)	1 (5.0)	4 (5.8)	1.000
Previous infections, n (%)	23 (25.8)	11 (55.0)	12 (17.4)	**0.001**
Previous antimicrobial therapy, within 30 days, n (%)	61 (68.5)	19 (95.0)	42 (60.9)	**0.005**
Carbapenem exposure, within 30 days	32 (36.0)	18 (90.0)	14 (20.3)	**< 0.001**
30-day mortality, n (%)	22 (24.7)	11 (55.0)	11 (15.9)	**0.001**

BSI, blood stream infection; PICC, peripherally inserted central catheter.

80.9%), followed by fluroquinolone (5, 5.6%), β-lactam/β-lactamase inhibitor (4, 4.5%), aminoglycosides (4, 4.5%), cephalosporins (2, 2.2%) and glycopeptide (1, 2.2%) (Table 1). Less patients in CRKP group received carbapenem treatment than that of patients in carbapenem-susceptible *K. pneumoniae* (CSKP) group (60.0% vs 80.9%).

Infection-related characteristics were summarized in Table 2. In total, most of the episodes (92.1%) were hospital-associated. Considering the originates, 74.1% of all episodes were primary BSIs, followed by gastrointestinal tract (16.9%), respiratory tract (7.9%) and urinary tract (1.1%). Polymicrobial infections were noticed in three patients: one with *Pseudomonas aeruginosa*, one with *Enterococcus faecium*, and one with *Escherichia coli* and *Candida*. Shock was noticed in 31.5% of all patients. The median values for white blood cell (WBC), ANC and red blood cell distribution width (RDW) were 0.2×10^9, 0.0×10^9 and 14.6%, respectively, in which 57/89 (64.0%) had a RDW value above 14%. For the 89 isolates of *K. pneumoniae* in our study, 50/89 (56.2%) were classified as MDR strains, in which 20 isolates were CRKP. In general, tigecycline, amikacin and imipenem remained the most effective antibiotics against all strains, with resistance rates of 5.6%, 12.4% and 22.5%, respectively. Of note, the CRKP strains were highly resistant to the tested antibiotics, except for tigecycline. Interestingly, trimethoprim-sulfamethoxazole showed similar antimicrobial resistance rates towards CRKP and CSKP (50.0% vs 58.0%, P = 0.612), as shown in Table 2.

Risk factors for CRKP BSIs

In the study period, 20 strains of CRKP and 69 strains of CSKP were collected. The clinical characteristics compared between the CRKP and CSKP infection groups are listed in Table 1. No significant differences were noticed in the comorbidities and underlying diseases between the two groups, except for liver disease, in which a higher rate was identified in the CRKP group (20.0% vs 4.3%, P = 0.043). In addition, the CRKP group was significantly more likely to experience unresolved neutropenia (55.0% vs 24.6, P = 0.014), increased exposure to antibiotics and carbapenem within 30 days (95.0% vs 60.9%, P = 0.005; 90.0% vs 60.9%, P < 0.001, respectively) and had more previous infections (55.0% vs 17.4%, P = 0.001). The CRKP group showed a lower rate for receiving appropriate empirical therapy (20.0% vs 97.1%, P < 0.001). No significant differences were discovered in the complications and laboratory results of the two groups.

Table 2. Clinical characteristics of 89 episodes of *K. pneumoniae* bacteremia according to Carbapenem-resistance of isolate.

Characteristics	All patients (n = 89)	CRKP (n = 20)	CSKP (n = 69)	*P* values
Infection on admission, n (%)				**0.342**
Community acquired	7 (7.9)	0 (0.0)	7 (10.1)	
hospital associated	82 (92.1)	20 (100.0)	62 (89.9)	
Infection site, n (%)				
Respiratory tract	7 (7.9)	2 (10.0)	5 (7.2)	1.000
Gastrointestinal tract	15 (16.9)	5 (25.0)	10 (14.5)	0.313
Urinary tract	1 (1.1)	1 (5.0)	0 (0.0)	0.225
Primary	66 (74.1)	12 (60.0)	54 (78.3)	0.145
Polymicrobial infection, n (%)	3 (3.4)	1 (5.0)	2 (2.9)	0.539
Complications, n (%)				
Diarrhea	19 (21.3)	4 (20.0)	15 (21.7)	1.000
Mucositis	17 (19.1)	4 (20.0)	13 (18.8)	1.000
Shock	28 (31.5)	8 (40.0)	20 (29.0)	0.415
Laboratory results				
WBC count ($\times10^9$/L)	0.2 (0.1-16.3)	0.2 (0.1-1.2)	0.2 (0.1-16.3)	0.444
ANC count ($\times10^9$/L)	0.0 (0.0-14.9)	0.0 (0.0-1.1)	0.0 (0.0-14.9)	0.171
RDW (%)	14.6 (9.4-24.3)	14.7 (11.3-18.2)	14.6 (9.4-24.3)	0.470
Antimicrobial susceptibility				
Piperacillin-tazobactam	34 (38.2)	20 (100.0)	14 (20.2)	**< 0.001**
Tigecycline	5 (5.6)	5 (25.0)	0 (0.0)	**< 0.001**
Amikacin	11 (12.4)	10 (50.0)	1 (1.4)	**< 0.001**
Gentamycin	33 (37.1)	13 (65.0)	20 (29.0)	**0.007**
Imipinem	20 (22.5)	20 (100.0)	0 (0.0)	/
Trimethoprim-sulfamethoxazole	50 (56.2)	10 (50.0)	40 (58.0)	0.612
Cefoperazone-sulbactam	30 (33.7)	19 (95.0)	11(15.9)	**< 0.001**

WBC, white blood cell; ANC, absolute neutrophil count; RDW, red blood cell distribution width; HB, hemoglobin.

Outcomes

A univariate analysis of factors associated with 30-day mortality is summarized in Table 3. In the study period, the 30-day mortality rates were 55.0% in the CRKP group and 15.9% in the CSKP group (P = 0.001). The median time between BSIs and death was 4 days (range: 2-31). Considering the baseline characteristics, the stage of hematological disorders between the surviving and nonsurvivial groups was significantly different: the nonsurvival patients were more likely to be newly diagnosed or under relapse/refractory, while the survivors underwent more in complete remission (P = 0.020). Other factors associated with mortality identified in the univariate analysis were unresolved neutropenia, previous antimicrobial therapy within 30 days, diarrhea, shock, MDR infection and elevated RDW values (> 14%), while the appropriate empirical therapy was a protective factor.

Risk factors for CRKP BSIs and 30-day mortality

In the multivariate analysis, only carbapenem exposure within 30 days (HR 25.122, 95% CI 2.734-230.874, P = 0.004) was revealed to be associated with CRKP BSI infection (Table 4). A Cox regression model revealed the following factors predicting mortality: unresolved neutropenia (HR 16.900, 95% CI 4.126-69.232, P < 0.001), diarrhea (HR 3.647, 95% CI 1.123-11.846, P = 0.031) and elevated RDW values (> 14%, HR 6.292, 95% CI 1.202-32.938, P = 0.029). The appropriateness of empirical therapy (HR 0.164, 95% CI 0.038-0.109, P = 0.016) was significantly associated with survival. However, MDR infection was not identified as a risk factor for mortality in the multivariate analysis (HR 1.390, 95% CI 0.367-5.262, P = 0.627) (Table 4).

Table 3. Univariate and multivariate analysis of factors for mortality in patients with *K. pneumoniae* BSIs in onco-hematology department.

Characteristics	Non-survivors n = 22	survivors n = 67	OR (95% CI)	*P* values
Univariate analysis, n (%)				
Age at BSI, median (range)	23 (2-64)	23 (1-71)		0.966
Sex, number of females	11 (50.0)	35 (52.2)	0.91 (0.35-2.40)	1.000
Acute myeloid leukemia	4 (18.2)	26 (38.8)	0.35 (0.11-1.15)	0.118
Acute lymphoblastic leukemia	8 (36.4)	28 (41.8)	0.79 (0.29-2.15)	0.803
Severe aplastic anemia	3 (13.6)	3 (4.5)	3.37 (0.628-18.08)	0.138
Lymphoma	3 (13.6)	4 (6.0)	2.48 (0.51-12.10)	0.358
Others	4 (18.2)	6 (9.0)	2.26 (0.57-8.89)	0.255
Stage of hematological disorders			/	**0.020**
Liver disease	2 (9.1)	5 (7.5)	1.24 (0.22-6.89)	1.000
Diabetes mellitus	2 (9.1)	3 (4.5)	2.13 (0.33-13.68)	0.594
Hospital associated	20 (90.9)	62 (92.5	1.24 (0.22-6.89)	1.000
Respiratory tract	3 (13.6)	4 (6.0)	2.48 (0.51-12.10)	0.358
Gastrointestinal tract	3 (13.6)	12 (17.9)	0.72 (0.18-2.84)	0.754
Urinary tract	1 (4.5)	0 (0.0)	/	0.247
Primary	15 (68.2)	51 (76.1)	0.67 (0.23-1.93)	0.575
Polymicrobial infection	2 (9.1)	1 (1.5)	6.60 (0.57-76.64)	0.150
Neutropenic	21 (95.5)	60 (89.6)	2.45 (0.28-21.11)	0.674
Unresolved neutropenic	18 (81.8)	10 (14.9)	25.56 (7.17-91.78)	**< 0.001**
Previous antimicrobial therapy, within 30 days	20 (90.9)	41 (61.2)	6.34 (1.37-29.41)	**0.016**
Appropriate empirical therapy	11 (50.0)	60 (89.6)	0.12 (0.037-0.367)	**< 0.001**
Diarrhea	9 (40.9)	10 (14.9)	3.95 (1.335-11.67)	**0.016**
Mucositis	7 (33.3)	10 (14.9)	2.85 (0.922-8.81)	0.109
Shock	13 (59.1)	15 (22.4)	5.01 (1.80-13.97)	**0.002**
MDR infection	17 (77.3)	33 (49.3)	3.50 (1.16-10.59)	**0.027**
WBC count < 0.3 $\times 10^9$/L	13 (59.1)	35 (52.2)	1.32 (0.50-3.50)	0.629
RDW >14%	20 (90.9)	37 (55.2)	8.11 (1.75-37.49)	**0.022**
Multivariate analysis				
Unresolved neutropenic			16.90 (4.12-69.23)	**< 0.001**
Appropriate empirical therapy			0.164 (0.038-0.109)	**0.016**
Diarrhea			3.66 (1.12-11.85)	**0.031**
RDW >14%			6.29 (1.20-32.94)	**0.029**

BSI, blood stream infection; PICC, peripherally inserted central catheter; MDR, multi-drug resistant; WBC, white blood cell; ANC, absolute neutrophil count; RDW, red blood cell distribution width; HB, hemoglobin.

Table 4. Multivariate analysis of risk factor for Carbapenem-resistance *K. pneumoniae* BSIs.

Variables	HR	95% CI	*P* value
Carbapenem exposure, within 30 days	25.122	2.734-230.874	0.004

Discussion

Here, in this study, we present the clinical characteristics, microbial susceptibilities and outcomes of 89 episodes of *K. pneumoniae* BSIs in onco-hematology departments to identify the risk factors associated with CRKP infections and mortality.

Klebsiella pneumonia resistant to carbapenem has been reported worldwide, including in China. Different prevalence rates for CRKP were significant according to geography, from up to 60% in India, and approximately 10% in China [8]. In our setting, from January 2014 to September 2018, 20 strains (22.4%) were classified as CRKP, which is lower than other studies based on hematological patients [3,4]. For the 89 strains of *K. pneumonia*, tigecycline, amikacin and imipenem exhibited excellent in vitro effects, with resistance rates of 5.6%, 12.5% and 22.5%, consistent with other study in China [9]. Tigecycline, a glycylcycline antimicrobial agent, is widely used in complicated bacterial infection treatment and has been proven to improve the survival rate significantly in cancer patients [10]. In our study, only five strains of CRKP were resistant to tigecycline, which is much higher than the resistance rate of 4.3% reported in Greece [11]. However, it is much lower than the resistance rate of 59.8% reported by the China CRE Network in 2015 [12].

Several risk factors for the occurrence of carbapenem-resistant (CR) bacteremia have been reported in different studies [13,14]. Wang Q et al. pointed out that previous use of third- or fourth-generation cephalosporins and carbapenems was an independent risk factor for carbapenem resistant *Enterobacteriaceae* infection in 94 episodes of nosocomial infections [15]. The relationship between exposure of carbapenems and carbapenem resistant *Enterobacteriaceae* infection was further validated by research conducted in children [16]. Other broad-spectrum antibiotics, including β-lactam/β-lactamase inhibitor, and trimethoprim-sulfamethoxazole, have also been proven to predict CRKP infections [3]. In the current study, the exposure to carbapenem was the only risk factor for CRKP BSIs. A possible reason is that broad-spectrum antibiotics alter the microflora in the intestine and act as a selection for CR bacteria. However, due to the vulnerable nature to infections, onco-hematological patients are unlikely to avoid antibiotics exposure, especially carbapenem; therefore, it is essential that a screening for CR bacterial colonization in the gastrointestinal tract is of importance for onco-hematological patients. Asymptomatic CR bacteria has been proven to elevate the incidence of the rate of subsequent CR bacteremia in intensive care unit patients [17]. An identification of CR bacterial colonization could serve as a guidance for medical treatment.

The overall 30-day mortality rate was 24.7%, however, the mortality of the CRKP group reached 55.0%, in line with previous works [3,4]. Not surprisingly, the appropriate empirical antibiotic therapy was discovered as a protective factor for BSI patients, a factor that has been proven by some previous studies on BSIs caused by *Enterobacteriaceae* in both common populations and hematological patients [4,15,18]. Interestingly, although the mortality in the CRKP group was higher than that in the CSKP group (55.0% vs 15.9%, P = 0.001), CRKP infection was not a risk factor for mortality. Different studies based on carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter baumannii* have also drawn the same conclusion, probably because of the high prevalence of CR bacteremia, resulting in a higher rate of inappropriateness of empirical therapy [19,20]. In this regard, the precise use of combination antibiotics to cover the most prevalent resistant strains should be considered, and new laboratory methods to detect resistant strains should be equipped to improve the outcome.

The other variables associated with mortality included unresolved neutropenia and diarrhea. Unresolved neutropenia was identified as a risk factor reported by Tofas P et al., who conducted a study based on 50 cases of CRKP BSIs in neutropenic patients with hematological disorders [21]. Diarrhea was also common in neutropenic patients, indicating that clinical complications significantly influence the outcomes [22].

Another risk factor identified in our study was an elevated RDW value (> 14%) at the onset of BSIs. RDW is a parameter commonly tested in the complete blood count, reflecting anisocytosis. In recent studies, the RDW value has been proven to predict mortality in coronary artery disease, kidney dysfunction, liver diseases, stroke and even among normal populations

[23,24]. Although the underlying connection between RDW and mortality has not been fully discovered, some theories have been proposed. RDW is affected by systemic inflammation, oxidative stress and malnutrition [24]. Systemic inflammation and oxidative stress are common in hematological patients and influence bone marrow function, iron metabolism and the integrality of erythrocytes, resulting in an increase in the RDW value. Malnutrition is also common in onco-hematological patients because of the use of chemotherapeutics. This finding was also in line with a recent study conducted by Kim et al., which showed that RDW values and RDW changes could predict mortality in severe sepsis patients [25]. Taken together, although further analysis is needed, it is convincing that the RDW value could reflect the underlying condition for a patient with onco-hematologic disorders.

However, our study had several limitations that should be mentioned. First, it was a retrospective, single-center study with a relatively small-sized CRKP group; thus, the power of the risk factors was limited, and the results may not be generalizable to other settings and should be tested in prospective studies. Second, our susceptibility tests were performed using the VITEK auto system. Third, our study did not include VitB12, iron and erythropoietin and a screening for CR bacteria by rectal swabs due to a lack of clinical information.

Conclusion

In conclusion, our study expounded that carbapenem exposure within 30 days before onset of BSIs was the only risk factor for CRKP BSIs in onco-hematological patients at Xiangya hospital. Unresolved neutropenia, diarrhea and RDW > 14% were independent risk factors for 30-day mortality, while the appropriate empirical therapy was a protective factor. Thus, the precise use of antibiotics to cover the most prevalent resistant strains could improve the outcomes and restrain the spread of CRKP.

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