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Risk Factors Affecting Clinical Outcome in Patients with Carbapenem-Resistant *K. pneumoniae*: A Retrospective Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The increased prevalence of carbapenem-resistant *K. pneumoniae* (CRKP) poses a great threat worldwide. Early identification of CRKP in patients is paramount. Moreover, fully understanding the risk factors affecting clinical outcome and actively providing targeted treatment can improve the cure rate of patients with CRKP. Therefore, our study aimed to describe the clinical characteristics and identify the risk factors affecting clinical outcomes in patients with CRKP.

Material/Methods: From January 2016 to September 2017, CRKP strains and clinical data from 97 hospitalized patients were collected. We first performed an antibiotic susceptibility test on CRKP strains using the Kirby-Bauer disc agar diffusion method. Logistic regression analysis was then performed to analyze risk factors.

Results: According to clinical outcome, among the 97 CRKP patients, 67 were in the effective group and 30 patients were in the noneffective group. Risk factors found to correlate with poor clinical outcome in patients with CRKP included ICU admission, arteriovenous catheterization, indwelling gastric tube, indwelling urethral catheter, tracheal intubation, mechanical ventilation, hypoproteinemia, and exposure to carbapenems. Multivariate analysis showed that hypoproteinemia (OR: 2.83, p=0.042), presence of an indwelling gastric tube (OR: 4.54, p=0.005), and exposure to carbapenems (OR: 2.77, p=0.045) negatively affected clinical outcome in patients with CRKP.

Conclusions: Adverse risk factors correlated with poor clinical outcomes in patients with CRKP were determined. This could be of help in identifying high-risk patients with whom clinicians should take extra precautions and adjust therapeutic strategy to supplement conventional basic treatment with additional measures.

MeSH Keywords: Fatal Outcome • *Klebsiella pneumonia* • Risk Factors

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Background

K. pneumoniae is one of the most common gram-negative bacterial pathogens seen in hospital-acquired infections, including bloodstream infection, lower biliary tract infection, urinary tract infection, and pneumonia [1–3]. Carbapenemase-producing *K. pneumoniae* can hydrolyze carbapenems, which is a serious threat to clinical and public health. For the past few years, the global rate of resistance to carbapenem antibiotics among the *Enterobacteriaceae*, especially *Klebsiella pneumoniae*, has increased rapidly. In 2013, the Centers for Disease Control and Prevention (CDC) ranked carbapenem-resistant *Enterobacteriaceae* as the highest level of 'urgent threat' in the USA [4]. The first antimicrobial resistance surveillance report released by the World Health Organization (WHO), a survey of 114 countries, showed that carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has appeared all over the world, and that over half of the patients with CRKP infection have received ineffective treatment in some countries [5]. In China, the prevalence of CRKP has increased rapidly, from 2.9% in 2005 to 13.4% in 2014 [6].

The rapid spread of CRKP has remained an urgent global threat, despite the efforts of researchers to control its spread [7,8]. Unfortunately, CRKP is becoming prevalent in China, bringing new challenges to clinical anti-infective treatment [9,10]. Of note, several studies have concluded that CRKP could increase the mortality rate from *K. pneumoniae* to approximately 40–50% [11,12]. High mortality rates and lack of effective treatment puts patients in a perilous situation [13]. A number of recent studies have reported that identifying the risk factors for CRKP infections could improve empiric therapy by facilitating early identification and timely intervention [14–17]. Early identification of risk factors affecting clinical outcome in patients with CRKP is essential and can help clinicians adjust treatment strategies. However, there has been little research on the clinical outcomes of patients with CRKP. Our study therefore evaluated risk factors for poor clinical outcome in patients with CRKP to provide targeted clinical strategies for patients with CRKP.

Material and Methods

Ethics approval

This study was approved by the Institutional Ethics Committee of the First Hospital of Changsha and was conducted in accordance with the Declaration of Helsinki. All enrolled participants provided written informed consent.

Study design and patients

This study was conducted at the First Hospital of Changsha, a tertiary-care teaching hospital with 1700 beds. Data on *K. pneumoniae* strains and clinical data for patients with CRKP were collected from January 2016 to September 2017. Inclusion criteria were: 1) patients diagnosed with CRKP, in compliance with the standards of the "Diagnostic Standards for Nosocomial Infections (Trial)" formulated by the Chinese Medical Association; and 2) patients who tested positive for CRKP in multiple pathogenic cultures. Exclusion criteria were: 1) patients with a positive result for *K. pneumoniae* by culture but who had received anti-infective drug treatment for less than 24 h; and 2) patients with a positive pathogenic culture result but showing no clinical symptoms of CRKP (e.g., asymptomatic bacteriuria).

Data collection and definitions

All data were collected by reviewing and recording medical histories, including: the clinical department(s) where CRKP strains were isolated; the patient's age, sex, and length of hospital stay; comorbidities such as liver insufficiency, cardiac insufficiency, renal insufficiency, diabetes mellitus, hypertension, malignancy, and hypoproteinemia (plasma albumin <30 g/l); hospitalization (ICU, hospital history, and APCHE II score), mechanical ventilation, and invasive procedures (e.g., arteriovenous catheterization, indwelling gastric tube, indwelling urethral catheter, tracheal intubation, peripherally inserted central venous catheters, or indwelling jejunal tube); and history of antimicrobials taken in the past 90 days, including the use of carbapenems, tigecycline, and compound sulfamethoxazole.

Based on other studies [18,19], our clinical outcomes included the clinical manifestations and auxiliary examination results of patients, such as body temperature, laboratory test results for blood, liver and kidney function, coagulation function, and infection-related biomarkers (procalcitonin and C-reactive protein), as well as microbial culture results, drug susceptibility tests, and imaging results. For any patient with 2 or more positive test results, only the clinical data related to the first positive result were collected. Each patient was assigned to the effective or noneffective group after drug administration for 28 days or death.

The inclusion criteria for the effective group were as follows. 1) Full cure: all clinical signs and symptoms of the patients with CRKP had disappeared. 2) Improvement: clinical signs and symptoms of the patients with CRKP had partially disappeared, or patients were transferred from the intensive care unit (ICU) to the general ward to continue treatment, or the laboratory test results had improved. The inclusion criteria

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for the noneffective group were either a worsening of clinical signs and symptoms or death.

Antibiotic susceptibility test

The susceptibility of CRKP strains to 18 antibiotics (ampicillin, ampicillin/sulbactam, piperacillin/sulbactam, cefazolin, ceftazidime pentahydrate, ceftriaxone sodium, cefepime, cefotetan, aztreonam, imipenem, ertapenem, amikacin, gentamicin, tobramycin, levofloxacin, ciprofloxacin, furadantin, and compound sulfamethoxazole) was determined by the Kirby-Bauer disc agar diffusion method. Tigecycline drug sensitivity was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. The rest of the antibacterial results were determined according to the standards recommended by the Clinical and Laboratory Standards Institute (CLSI) in 2017.

The extent of drug resistance was defined as follows. Multidrug resistance (MDR): resistant to 3 or more antibacterial drugs in the antibacterial spectrum. Extensive drug resistance (XDR): resistant to almost all antibacterials except 1–2 antibacterials. Pan-drug resistance (PDR): resistant to all types of antibacterial drugs [20].

Statistical analysis

Numbers and percentages were used to represent categorical variables. Continuous variables are expressed as mean±standard deviation (SD) (normally distributed). Chi-square test and *t* test or Mann-Whitney U test were employed to analyze categorical variables and continuous variables, respectively. Two-sided P<0.05 was considered statistically significant. All statistical analyses were performed with SPSS 17.0 software.

Results

Characteristics of patients

We identified a total of 97 unique cases of patients with CRKP during the study period. Isolates were obtained from different clinical samples such as: sputum (n=62, 63.92%), bronchoalveolar lavage (n=15, 15.46%), urine (n=11, 11.34%), blood (n=2, 2.06%), bile (n=1, 1.03%), pus (n=1, 1.03%), fluid (n=2, 2.06%), ascites (n=2, 2.06%), and throat swab (n=1, 1.03%). As shown in Figure 1, most of the study patients were from the Departments of Neurology, Respiratory Medicine, Critical Care Medicine, and Neurosurgery. Furthermore, we distributed patients with CRKP into effective and noneffective groups based on the clinical outcome of the patient, with 67 cases (69%) identified as effective and 30 cases (31%) identified as noneffective.

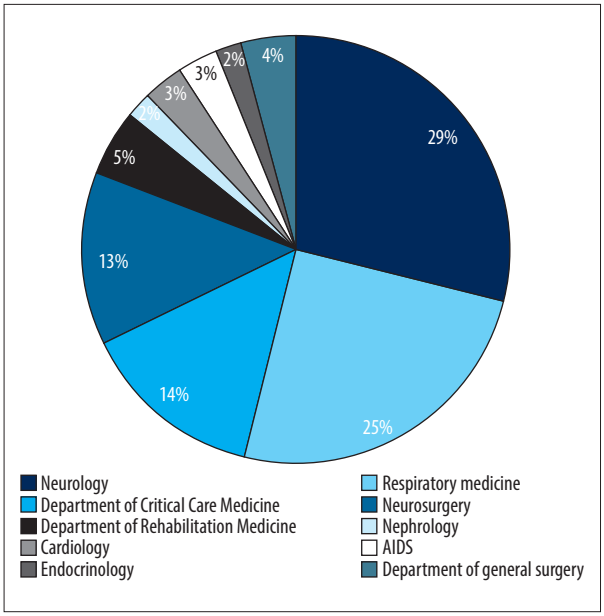

Figure 1. Frequency distribution of hospital departments in which carbapenem-resistant *K. pneumoniae* was detected in the study patients.

The basic clinical features of each dataset are listed in Table 1. The mean age of the patients was 71.2±16.37 and 71.57±18.26 years in the effective and noneffective groups, respectively, and male patients accounted for 57% of the total study population. Compared with the effective group, a significantly larger percentage of patients in the noneffective group were admitted to the ICU (73.33% *vs.* 45.78%, P=0.009) and received mechanical ventilation (80% *vs.* 53.73%, P=0.014), as well as higher APCHE2 scores (14.73±5.90 *vs.* 11.48±5.31 5, P=0.008). A larger fraction of patients in the noneffective group received invasive procedures compared with the effective group, including arteriovenous catheterization (70% *vs.* 43.28%, P=0.015), indwelling gastric tube (50% *vs.* 23.88%, P=0.011), and indwelling urethral catheter (86.67% *vs.* 62.28%, P=0.017). Moreover, we observed that patients in the noneffective group were more likely to be prescribed carbapenems than those in the effective group (70% *vs.* 41.79%, P=0.01).

Antibiotic susceptibility test

The drug resistance rates for aminoglycosides, β-lactams, carbapenems, quinolones, and sulfa drugs among the 97 CRKP isolates are summarized in Table 2. The drug sensitivity results demonstrated that compound sulfamethoxazole had the lowest resistance rate (21.65%), followed by amikacin (48.45%), gentamicin (59.79%), tobramycin (63.92%), levofloxacin (94.85%), and ciprofloxacin (94.85%). The remaining antibiotics had resistance rates of 100%. The percentages of MDR, XDR, and PDR were 94%, 3%, and 3%, respectively (Table 3). The most frequently isolated MDR strains, from the Neurology Department, are shown in Table 3.

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Table 1. Characteristics of 97 patients with CRKP in the effective and noneffective groups.

Variable	Total (n=97)	Effective (n=67)	Noneffective (n=30)	p-Value
Age	71.32±16.79	71.2±16.37	71.57±18.26	0.924
Male	55 (57.00)	36 (53.73)	19 (63.33)	0.383
APCHE2 score	12.28±5.68	11.48±5.31	14.73±5.90	0.008
Length of hospitalization (days)	64.91±103.48	62.56±99.67	70.17±114.76	0.741
ICU	52 (53.61)	30 (45.78)	22 (73.33)	0.09
Surgical	40 (41.23)	24 (35.82)	16 (53.33)	0.105
History of antimicrobials in the past 90 days	58 (59.79)	39 (58.21)	19 (63.33)	0.63
Hospital history in the past 90 days	46 (47.42)	29 (43.28)	17 (56.66)	0.222
Multisite infection	47 (48.45)	34 (50.74)	13 (43.33)	0.5
Mixed infection	66 (68.04)	45 (67.16)	21 (70.00)	0.782
Hypertension	61 (62.88)	45 (67.16)	16 (53.33)	0.193
Diabetes mellitus	20 (20.62)	14 (20.89)	6 (20.00)	0.92
Hypohepatia	31 (31.96)	19 (28.35)	12 (40.00)	0.256
Cardiac insufficiency	52 (53.61)	37 (55.22)	15 (50.00)	0.633
Renal insufficiency	20 (20.62)	11 (16.41)	9 (30.00)	0.126
Malignancy	3 (3.09)	1 (1.49)	2 (6.67)	0.174
Hypoproteinemia	50 (51.55)	30 (44.77)	20 (66.67)	0.046
Mechanical ventilation	60 (61.85)	36 (53.73)	24 (80.00)	0.014
Arteriovenous catheterization	50 (51.55)	29 (43.28)	21 (70.00)	0.015
Indwelling gastric tube	31 (31.96)	16 (23.88)	15 (50.00)	0.011
Indwelling urethral catheter	68 (70.10)	42 (62.68)	26 (86.67)	0.017
Tracheal intubation	44 (45.36)	25 (37.31)	19 (63.33)	0.017
Peripherally inserted central venous catheters	27 (27.83)	17 (25.37)	10 (33.33)	0.419
Indwelling jejunal tube	9 (9.28)	4 (5.97)	5 (16.6)	0.093
Exposure to carbapenems	49 (50.52)	28 (41.79)	21 (70.00)	0.01
Exposure to tigecycline	8 (8.25)	4 (5.97)	4 (13.33)	0.223
Exposure to compound sulfamethoxazole	4 (4.12)	3 (4.47)	1 (3.33)	0.793

Risk factor analysis

To identify risk factors for poor clinical outcomes in patients with CRKP, we conducted a retrospective study. Clinical variables are listed in Table 4. Firstly, we performed a univariate analysis of these clinical variables. In this univariate analysis, the following factors were negatively correlated with good clinical outcomes: ICU admission (OR: 3.39, p=0.011), exposure to arteriovenous catheterization (OR: 3.06, p=0.017), indwelling gastric tube (OR: 3.19, p=0.013), indwelling urethral catheter (OR: 3.87, p=0.023), tracheal intubation (OR: 2.90, p=0.019), mechanical ventilation (OR: 3.44, p=0.017), hypoproteinemia (OR: 2.47, p=0.049), and exposure to carbapenems (OR: 3.25, p=0.012).

The multivariate analyses of the effective and noneffective groups were carried out with the adjustment of the logistic regression model for 8 variables, wherein the risk factors dramatically differed from the univariate analyses. As shown in Table 5, hypoproteinemia (OR: 2.83, p=0.042), presence of an indwelling gastric tube (OR: 4.54, p=0.005), and exposure to carbapenems (OR: 2.77, p=0.045) were found to be independent risk factors for poor clinical outcomes in patients with CRKP.

Discussion

Currently, carbapenem-resistant *Enterobacteriaceae*, especially CRKP, are an urgent public health challenge worldwide [21–24].

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Table 2. Drug sensitivity of CRKP strains.

Antimicrobial agent	Number of resistant strains	Drug resistance rate (%)
Ampicillin	97	100.00
Ampicillin/sulbactam	97	100.00
Piperacillin/sulbactam	97	100.00
Cefazolin	97	100.00
Ceftazidime pentahydrate	97	100.00
Ceftriaxone sodium	97	100.00
Cefepime	97	100.00
Cefotetan	97	100.00
Aztreonam	97	100.00
Imipenem	97	100.00
Ertapenem	97	100.00
Amikacin	47	48.45
Gentamicin	58	59.79
Tobramycin	62	63.92
Levofloxacin tablets	92	94.85
Ciprofloxacin	92	94.85
Furadantin	97	100.00
Compound sulfamethoxazole	21	21.65

Table 3. Departments from which CRKP strains with MDR, XDR, and PDR were isolated.

Clinical department	MDR	XDR	PDR
Neurology	27	1	
Respiratory Medicine	23	1	
Department of Critical Care Medicine	13		
Neurosurgery	11	1	1
Department of Rehabilitation Medicine	5		
Nephrology	2		
Cardiology	1		2
AIDS	3		
Endocrinology	2		
Department of General Surgery	4		
Total	91 (94%)	3 (3%)	3 (3%)

MDR – multidrug resistance; XDR – extensive drug resistance; PDR – pan-drug resistance.

Antibiotics, particularly carbapenem and tigecycline antibiotics, have been recommended for the treatment of CRKP, and have had a degree of therapeutic effect. However, the treatment process for CRKP is still a challenge. On the one hand, CRKP has a certain resistance to existing antibacterial drugs, which leads to a high mortality rate in patients with CRKP. On the other hand, CRKP strains are either MDR, XDR, or PDR, resulting in limited treatment options available for patients with CRKP [25]. Identification of the risk factors for poor clinical outcome in patients can provide guidance for the treatment of CRKP. In this study, our findings demonstrated that exposure to carbapenems, hypoproteinemia, and presence of an indwelling gastric tube were negatively correlated with good clinical outcome in patients with CRKP.

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Table 4. Univariate analysis of risk factors for poor clinical outcome in patients with CRKP.

Variable	Effective (n=67)	Noneffective (n=30)	Univariate analysis	
			OR (95% CI)	P
Age	75 (61–84)	78 (60–83)		0.710
Male	36	19		0.379
APCHE2 score	11 (8–14)	15 (10–20)		0.094
Length of hospitalization (days)	29 (15–66)	32 (18–57)		0.329
ICU	30 (45.78)	22 (73.33)	3.39 (1.323–8.697)	0.011
Surgical	24 (35.82)	16 (53.33)		0.108
History of antimicrobials in the past 90 days	39 (58.21)	19 (63.33)		0.635
Hospital history in the past 90 days	29 (43.28)	17 (56.66)		0.224
Multisite infection	34 (50.74)	13 (43.33)		0.5
Mixed infection	45 (67.16)	21 (70.00)		0.782
Hypertension	45 (67.16)	16 (53.33)		0.195
Diabetes mellitus	14 (20.89)	6 (20.00)		0.920
Hypohepatia	19 (28.35)	12 (40.00)		0.258
Cardiac insufficiency	37 (55.22)	15 (50.00)		0.634
Renal insufficiency	11 (16.41)	9 (30.00)		0.131
Malignancy	1 (1.49)	2 (6.67)		0.213
Hypoproteinemia	30 (44.77)	20 (66.67)	2.47 (1.004–6.061)	0.049
Mechanical ventilation	36 (53.73)	24 (80.00)	3.44 (1.248–9.508)	0.017
Arteriovenous catheterization	29 (43.28)	21 (70.00)	3.06 (1.221–7.659)	0.017
Indwelling gastric tube	16 (23.88)	15 (50.00)	3.19 (1.283–7.917)	0.013
Indwelling urethral catheter	42 (62.68)	26 (86.67)	3.87 (1.209–12.383)	0.023
Tracheal intubation	25 (37.31)	19 (63.33)	2.90 (1.189–7.084)	0.019
Peripherally inserted central venous catheters	17 (25.37)	10 (33.33)		0.42
Indwelling jejunal tube	4 (5.97)	5 (16.6)		0.107
Exposure to carbapenems	28 (41.79)	21 (70.00)	3.25 (1.296–8.151)	0.012
Exposure to tigecycline	4 (5.97)	4 (13.33)		0.235
Exposure to compound sulfamethoxazole	3 (4.47)	1 (3.33)		0.794

CRKP – carbapenem-resistant *Klebsiella pneumoniae*; OR – odds ratio; CI – confidence interval.

In the present study, we found that clinical outcome was associated with various factors, including ICU stay, exposure to arteriovenous catheterization, indwelling gastric tube, indwelling urethral catheter, tracheal intubation, mechanical ventilation, hypoproteinemia, and exposure to carbapenems. Among these, presence of an indwelling gastric tube, hypoproteinemia and exposure to carbapenems were independent risk factors for poor clinical outcome in patients with CRKP in multivariate analyses. These findings indicated that clinicians should attach great importance to appropriate antibiotic use and aseptic invasive procedures.

In our study, we found that CRKP had a low resistance rate to compound sulfamethoxazole (21.65%), which was similar to the findings in a previous report [26]. *In vitro*, Su et al. [27] found that compound sulfamethoxazole combined with polymyxin

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Table 5. Multivariate analysis of risk factors for poor clinical outcome in patients with CRKP.

Risk factor	OR value	95% CI	p-Value
Age	2.56	0.901–7.246	0.078
Male	1.38	0.462–4.096	0.567
ICU	1.14	0.331–3.887	0.840
Hypoproteinemia	2.83	1.040–7.704	0.042
Mechanical ventilation	1.96	0.622–6.165	0.25
Arteriovenous catheterization	2.12	0.726–6.196	0.169
Indwelling gastric tube	4.54	1.567–13.12	0.005
Indwelling urethral catheter	1.67	0.42–6.652	0.465
Tracheal intubation	0.88	0.230–3.368	0.851
Exposure to carbapenems	2.77	1.022–7.495	0.045

CRKP – carbapenem-resistant *Klebsiella pneumoniae*; OR – odds ratio; CI – confidence interval.

could quickly kill CRKP isolates within 2 to 24 h. However, there was a lack of evidence-based medicine for clinical treatment of CRKP using compound sulfamethoxazole, and this finding needed to be confirmed by further clinical studies [27]. In our study, the respiratory tract was the most common site of infection in the patients (n=62, 63.92%), followed by bronchoalveolar lavage (n=15, 15.46%) and the urinary tract (n=11, 11.34%), while other studies showed bacteremia and the urinary tract as the main sites of infection [28–30], perhaps because most elderly patients from the Neurology Department were more likely to contract CRKP because of their poor ability to discharge sputum spontaneously. Univariate analyses indicated 8 variables that differed significantly between the effective and the noneffective groups. Consistent results have also been identified in other studies [17,31–33]. This could be because people who have been exposed to these risk factors might not respond well to treatment, with their own condition exacerbated. ICU stays, mechanical ventilation, and various invasive manipulations increase the risk of other bacterial infections [16], resulting in unsatisfactory clinical outcomes in patients with CRKP. Patients with hypoalbuminemia had low disease resistance, which also negatively affected the clinical outcome of patients with CRKP. Regarding antibiotic exposure during hospitalization, the frequent usage of carbapenems was correlated with the poor clinical outcome of patients with CRKP. These results support the use of antibiotics based on the results of susceptibility tests, instead of using broad-spectrum antibiotics.

The multivariate analyses showed that exposure to carbapenems, hypoproteinemia, and an indwelling gastric tube were independent risk factors for poor clinical outcome in patients with CRKP. Emerging evidence has indicated that carbapenem administration is an independent risk factor for CRKP infection, as well as for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infection/colonization [16,34–36]. Our study demonstrated that patients with CRKP who used carbapenems had worse clinical outcomes. This phenomenon was probably caused by the very high MIC of carbapenems (>16 μg/ml) against CRKP. This result supports the importance of choosing the right antibacterials in light of drug sensitivity results and promptly implementing antibiotic de-escalation to avoid similar incidents [37]. Moreover, medical invasive devices, such as an indwelling gastric tube, greatly increase the chance of bacterial infection [38], which to some extent increases the difficulty of treatment and negatively affects the clinical outcome of patients with CRKP. Of note, our results showed that the presence of an indwelling gastric tube increased the risk for poor clinical outcome by 4.53-fold; therefore, hospitals should strictly implement disinfection and isolation measures and strengthen monitoring of the hospital environment. In addition, hypoproteinemia was also an adverse independent risk factor for clinical outcome in patients with CRKP. Serum albumin level and plasma colloid osmotic pressure were decreased in patients with hypoproteinemia, affecting the function of various organs and tissues in the body [39]. This would serve to significantly reduce the body's resistance and increase the incidence of poor clinical outcomes in patients with CRKP. For such patients, among the most beneficial measures is improvement of nutritional status to increase albumin levels. Overall, nosocomial transmission and the selection of appropriate antimicrobial therapy, as well as patient nutrition, can play critical roles in the clinical outcome of CRKP-infected patients.

Conclusions

We found that the presence of an indwelling gastric tube, hypoproteinemia, and exposure to carbapenems were risk factors for poor clinical outcome in patients with CRKP. These findings

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may provide a theoretical foundation for the adjustment of clinical therapeutic strategies. Clinicians should pay close attention to the condition of CRKP-infected patients and ensure rational use of carbapenems. In addition, strengthened monitoring of the hospital environment could improve the prognoses of patients with CRKP.

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