

The Risk Factors of Carbapenem-Resistant *Klebsiella pneumoniae* Infection: A Single-Center Chinese Retrospective Study

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Objective: The present study aims to explore potential infection and death risk factors in patients infected with carbapenem-resistant *Klebsiella pneumoniae* (CRKP).

Methods: A retrospective case-control study was performed at Beijing Shijitan Hospital, China. The clinical and microbiological data of patients infected with *K. pneumoniae* (K.pn) were collected; the clinical characteristics of patients infected with carbapenem-susceptible K.pn and CRKP were analyzed using logistic regression analysis.

Results: CRKP infection was significantly associated with prior carbapenem use (odds ratio [OR] and 95% credibility interval [CI]: 5.161 [1.840–32.233], $P < 0.001$), the use of more than three types of antibiotics for seven or more days (OR and 95% CI: 9.681 [2.662–18.122], $P < 0.001$), tracheotomy (OR and 95% CI: 5.015 [2.343–11.724], $P < 0.001$), and intensive care unit (ICU) stay (OR and 95% CI: 6.322 [2.02–12.231], $P < 0.001$). The risk of death in patients with CRKP infection was significantly associated with older age (OR and 95% CI of 70–80 years: 8.894 [1.972–67.346], $P < 0.001$; ≥ 80 years: 15.234 [2.072–93.452], $P < 0.001$), renal dysfunction (OR and 95% CI: 1.672 [1.104–7.451], $P = 0.016$), tracheotomy (OR and 95% CI: 2.051 [1.217–11.235], $P = 0.002$), and ICU stay (OR and 95% CI: 3.043 [2.174–18.453], $P < 0.001$).

Conclusion: Prior to carbapenem use, older age, renal dysfunction, tracheotomy, and ICU stay were independent risk factors for death in patients infected with CRKP.

Keywords: *Klebsiella pneumoniae*, carbapenems, drug resistance, risk factors, antibiotics, Beijing

Introduction

Klebsiella pneumoniae (K.pn) is a Gram-negative bacteria and a major pathogen type that causes nosocomial infection, such as pyogenic liver abscess, urinary tract infection, bacteremia, and pneumonia.¹ After *Escherichia coli* (*E. coli*),² K.pn is the second most common pneumoniae cause (with occurrence rates of 29.9% and 19.8%, respectively) in Gram-negative organisms.

The incidence of K.pn in China is growing.² *Klebsiella pneumoniae* isolates may be induced to express resistance phenotypes through carbapenemase (KPC) and/or cephalosporinase production, or outer membrane protein loss.^{3–5} The KPC gene is primarily plasmid-encoded; thus, it is disseminated among different K.pn clones and even among different bacterial species or genera.⁶ In clinical practice, an infection caused by enterobacterales (ENT) with extended-spectrum β -lactamases (ESBLs) was generally treated using carbapenem;⁷ however, the bacteria developed resistance to carbapenem.⁸

Carbapenem-resistant K.pn (CRKP) has been on the rise in most geographical areas since the 1990s, leading to increases in mortality, morbidity, hospitalization time, and medical costs.^{3,9} In China, the isolation rate of CRKP reached 3.5–5.9% in 2011–2012,¹⁰ 6.4% in 2014,¹¹ and 7.6% in 2015.²

Carbapenems belong to atypical β -lactam antibiotics with strong antimicrobial activity. As they are stable to β -lactamases and have low toxicity, carbapenems serve as a major antibacterial agent in severe bacterial infection

and have been considered the last line of treatment for infection caused by multi-drug resistant (MDR) Gram-negative pathogens. However, the dissemination of CR bacteria has become a global health problem.¹² The emergence of CRKP has challenged carbapenem use.

Although several risk factors have been noted in existing studies, their conclusions have been inconsistent.^{13–15} To control nosocomial infection and improve empirical therapy efficacy, the present study attempted to identify the possible risk factors of CRKP-induced infection and death in hospitalized adults.

Methods

Study Design

A retrospective case-control study was performed to identify infection and death risk factors in patients infected with CRKP at Beijing Shijitan Hospital. Patients diagnosed with nosocomial K.pn infection between January 1, 2015, and June 30, 2018, were included in the present study. In cases of multiple K.pn infection episodes in one patient, only the first occurrence was included in the data analysis.

Inclusion criteria: (1) patients who were not infected with K.pn before admission; (2) patients with a hospital stay duration of ≥ 48 h; (3) patients aged ≥ 18 years. The patients were divided into two groups, ie, the case and control groups. Patients infected with CRKP were assigned to the case group, while patients infected with carbapenem-susceptible (CS) KP were assigned to the control group. The results of the two groups were subsequently compared.

Klebsiella pneumoniae infection: patients with fever, increased white blood cell count and/or neutrophil ratio, and whose specimen culture only isolated K.pn; K.pn was cultured in the specimen, but the patient had no inflammation and showed a K.pn value, which was excluded from this study.

Case-control data were matched according to the K.pn infection types, eg, respiratory tract infection, urinary system infection, thoracic and abdominal infection, bloodstream infection, and wound infection. The control and case groups were matched according to a 2–3:1 ratio. The patients received appropriate antibiotic treatment. In patients with CRKP infection, the death and survival groups were matched not only according to the type of infection but also based on the course of antibiotic treatment using a matching ratio of 1:2–3. This study complies with the Declaration of Helsinki. The ethics committee of Beijing Shijitan Hospital, Capital Medical University approved this study (No. Sjtjy11-1x-2022(22)).

Data Collection

Data derived from medical records and microbiology were collected. Variables that were analyzed as potential risk factors included gender, age, medical unit, treatment, exposure to antibiotics, the length of hospital stay, comorbidities, and invasive procedures performed prior to infection. Exposure to antibiotics was defined as the use of antibiotics >48 h before K.pn infection.

Microbiological Examination

The antibiotics that were used in drug sensitivity tests were levofloxacin, ciprofloxacin, meropenem, imipenem, ceftazidime, ceftriaxone/sulbactam, cefepime, piperacillin/tazobactam, chloramphenicol, co-sulfamethoxazole, aztreonam, minocycline, ampicillin, and amikacin. *Klebsiella pneumoniae* isolate identification and drug susceptibility testing (AST) were carried out using the Vitek-2 Compact system. The AST results were interpreted in accordance with the Clinical and Laboratory Standards Institute criteria.¹⁶ In the case of CRKP, Hodge tests and combined disk tests using carbapenems with either ethylenediaminetetraacetic or boronic acid were performed.^{17,18} These experiments were phenotypic verification experiments of carbapenem drug resistance, as well as further verification of drug sensitivity results for meropenem, imipenem, and other carbapenem drugs using the minimal inhibitory concentration method. Quality control was conducted by testing Kpn ATCC 700603 and *E. coli* ATCC 25922. Quality control strains were used to monitor the accuracy and reliability of bacterial identification and drug sensitivity tests.

Statistical Analysis

Data were presented as n (%) or mean \pm standard deviation (SD; range) and analyzed using the Statistical Package for Social Sciences 19.0 software. In the analysis of the risk factors for CRKP infection/colonization and mortality, a univariate logistic regression analysis was performed. To identify the independent risk factors, variables with $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression model and analyzed using backward stepwise regression. Odds ratio (OR) and a 95% confidence interval (CI) were also calculated. For all statistical analyses, $P < 0.05$ indicated a statistical significance.

Results

A total of 333 patients with Kpn infection were included in this study, including 95 cases of CRKP infection (case group), and 238 cases of CSKP infection (control group). There were 207 male patients and 126 female patients in an age range of 39–97 years old (average age, 66.3 ± 11.3 years). Specimens were collected from 103 cases of respiratory tract infection, 78 cases of urinary tract infection, 64 cases of thoracic and abdominal infection, 54 cases of bloodstream infection, and 34 cases of wound infection.

In this study, primary diseases did not include single diseases and most conditions coexisted with multiple illnesses. Table 1 indicates the concomitant diseases in this regard, which include 147 cases of lung disease, 91 cases of cardiac dysfunction, 107 cases of renal dysfunction, 37 cases of neurological disease, 77 cases of liver disease, 87 cases of diabetes mellitus, 169 cases of hypoalbuminemia, and 46 tumor cases.

In this study, the risk factors of carbapenem drug resistance to Kpn were primarily studied. Data concerning drug resistance of other antimicrobials were not collected. In addition, Kpn in this study was not included in the study because it was infected with other pathogens. The infection site was a matching factor and was not included in the risk factors. Mechanical ventilation and sepsis were added to the risk factor analysis, as shown in Tables 1 and 2.

Carbapenem-Resistant *Klebsiella pneumoniae* Infection Risk Factors

In the univariate analysis, CRKP infection was significantly associated with a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score, prior exposure to fluoroquinolones, cefoperazone plus sulbactam and glycopeptides, the use of more than three types of antibiotics for seven or more days, deep venous catheterization, tracheotomy, indwelling urethral catheter, ICU stay, third-generation cephalosporins, and carbapenems ($P < 0.05$) (Table 1). The multivariable logistic regression analysis revealed significant associations between CRKP infection and prior carbapenem use (OR and 95% CI: 5.161 [1.840–32.233], $P < 0.001$), the use of more than three types of antibiotics for seven or more days (OR and 95% CI: 9.681 [2.662–18.122], $P < 0.001$), tracheotomy (OR and 95% CI: 5.015 [2.343–11.724], $P < 0.001$), and ICU stay (OR and 95% CI: 6.322 [2.02–12.231], $P < 0.001$) (Table 1).

Death Risk Factors in Patients Infected with Carbapenem-Resistant *Klebsiella pneumoniae*

The results of the univariate analysis showed that in patients infected with CRKP, death was significantly associated with older age, a higher APACHE II score, lung disease, renal dysfunction, prior carbapenem exposure, the use of more than three types of antibiotics for seven or more days, deep venous catheterization, tracheotomy, and ICU stay ($P < 0.05$) (Table 2).

The multivariable logistic regression analysis revealed significant associations between death and older age (OR and 95% CI of 70–80 years: 8.894 [1.972–67.346], $P < 0.001$; ≥ 80 years: 15.234 [2.072–93.452], $P < 0.001$), renal dysfunction (OR and 95% CI: 1.672 [1.104–7.451], $P = 0.016$), tracheotomy (OR and 95% CI: 2.051 [1.217–11.235], $P = 0.002$), and ICU stay (OR and 95% CI: 3.043 [2.174–18.453], $P < 0.001$) (Table 2).

Discussion

Following the findings of existing reports,^{14,19} completing a stay in the ICU before Kpn infection was a risk factor for CRKP infection. Patients in the ICU are typically in a serious condition with relatively severe complications;

Table I Risk Factors for CRKP Infection

Risk Factors [n (%)]		CRKP (n=95)	CSKP (n=238)	Univariable Analysis		Multivariate Analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Age (Year)							
<60		12	43	1.000			
60–70		23	61	1.351 (0.607–3.006)	0.460		
70–80		32	77	1.489 (0.696–3.188)	0.304		
≥80		28	57	1.760 (0.804–3.854)	0.155		
Sex							
Male		55	152	1.000			
Female		40	86	1.285 (0.791–2.089)	0.310		
APACHE II score							
< 18		13	60	1.000		1.000	
18–20		17	50	1.569 (0.695–3.541)	0.276	1.028 (0.262–3.014)	0.453
20–22		20	41	2.251 (1.008–5.027)	0.045	1.941 (0.730–4.228)	0.327
22–24		22	46	2.207 (1.006–4.844)	0.046	2.102 (0.804–4.822)	0.121
>24		23	41	2.589 (1.178–5.691)	0.016	2.662 (0.903–5.164)	0.088
Concomitant diseases							
Lung disease	No	49	137	1.000			
	Yes	46	101	1.273 (0.790–2.053)	0.321		
Cardiac dysfunction	No	66	176	1.000			
	Yes	29	62	1.247 (0.739–2.106)	0.408		
Renal dysfunction	No	55	171	1.000		1.000	
	Yes	40	67	1.856 (1.131–3.047)	0.014	1.642 (0.875–4.823)	0.104
Neurological disease	No	81	215	1.000			
	Yes	14	23	1.616 (0.793–3.292)	0.183		
Liver disease	No	76	180	1.000			
	Yes	19	58	0.776 (0.433–1.390)	0.393		
Diabetes mellitus	No	60	186	1.000		1.000	
	Yes	35	52	2.087 (1.243–3.503)	0.005	1.805 (0.742–5.721)	0.103
Hypoalbuminemia	No	42	122	1.000			
	Yes	53	116	1.327 (0.823–2.141)	0.245		
Tumor	No	83	204	1.000			
	Yes	12	34	0.867 (0.428–1.757)	0.693		
Septicemia	No	38	120	1.000			
	Yes	57	118	1.525 (0.941–2.472)	0.086		
Antibiotics application before K.pn infection							
Fluoroquinolones	No	40	141	1.000		1.000	
	Yes	55	97	1.999 (1.234–3.238)	0.005	2.107 (0.871–5.105)	0.092
2nd generation cephalosporins	No	55	125	1.000			
	Yes	40	113	0.805 (0.498–1.300)	0.374		
3rd generation cephalosporins	No	66	193	1.000		1.000	
	Yes	29	45	1.885 (1.094–3.247)	0.021	1.846 (0.825–6.292)	0.156
Amikacin	No	78	209	1.000			
	Yes	17	29	1.571 (0.818–3.017)	0.173		
Carbapenems	No	42	165	1.000		1.000	
	Yes	53	73	2.852 (1.748–4.655)	<0.001	4.244 (1.637–12.623)	<0.001
Cefoperazone plus sulbactam	No	58	190	1.000		1.000	
	Yes	37	48	2.525 (1.501–4.247)	<0.001	2.868 (0.903–6.128)	0.068

(Continued)

Table 1 (Continued).

Risk Factors [n (%)]		CRKP (n=95)	CSKP (n=238)	Univariable Analysis		Multivariate Analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Glycopeptides	No	49	170	1.000		1.000	
	Yes	46	68	2.347 (1.436–3.834)	0.001	3.528 (0.811–7.391)	0.101
Using more than 3 antibiotics	< 7 days	44	177	1.000		1.000	
	≥ 7 days	51	61	3.363 (2.045–5.530)	<0.001	5.412 (2.124–10.101)	<0.001
Surgery							
No		68	190	1.000			
Yes		27	48	1.572 (0.910–2.716)	0.104		
Invasive procedures							
Deep venous catheterization	No	35	144	1.000		1.000	
	Yes	60	94	2.626 (1.607–4.292)	<0.001	2.242 (0.905–6.821)	0.093
Tracheotomy	No	34	150	1.000		1.000	
	Yes	61	88	3.058 (1.864–5.018)	<0.001	3.527 (2.131–7.511)	<0.001
Mechanical ventilation	No	28	142	1.000		1.000	
	Yes	67	96	3.539 (2.122–5.903)	<0.001	2.983 (0.842–6.431)	0.089
Indwelling urethral catheter	No	27	112	1.000		1.000	
	Yes	68	126	2.239 (1.340–3.741)	0.002	2.488 (0.724–5.418)	0.105
Indwelling gastric tube	No	55	142	1.000			
	Yes	40	96	1.076 (0.664–1.743)	0.767		
Hospital stay							
< 14 days		49	145	1.000			
≥ 14 days		46	93	1.464 (0.906–2.364)	0.118		
ICU stay							
< 3 days		31	145	1.000		1.000	
≥ 3 days		64	93	3.219 (1.949–5.316)	<0.001	5.211 (1.882–10.663)	<0.001

Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; K.pn, *Klebsiella pneumoniae*; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

accordingly, they may be treated with a combination of different antibiotics with a longer usage duration. They may also undergo more invasive procedures compared with patients in other wards. These factors may be beneficial for reducing CRKP dissemination and screening.

Carbapenems are highly effective antibacterial agents in the treatment of infections caused by MDR-ENT bacteria that produce ESBLs and/or the ampicillinase C enzyme.²⁰ Thus, a relationship between CRKP infections and carbapenem use can be anticipated. In the present study, prior carbapenem use was an independent risk factor of CRKP-induced infections. This result was consistent with the results of existing studies.^{14,21,22} In a different study, carbapenem use was not an independent risk factor in the multivariate analysis.²³

CRKP infection was associated with the use of more than three types of antibiotics for seven or more days. Although the long-term combined application of several antibacterial agents could significantly inhibit bacterial growth, it may also cause bacterial mutation and drug resistance due to the selective antibiotic pressure imposed on the microorganism environment. If more than one antibiotic type is present in microbial communities, the pressure caused by these antibiotics may lead to bacteria employing multiple drug resistance mechanisms. Thus, the bacteria will select one optimized drug resistance mechanism or increase mutational events to survive in bacterial stress situations.^{22,24,25}

The results of the present study showed a significant association between CRKP infection and tracheotomy; frequent invasive operations may result in respiratory tract mucosal injury, increasing bacterial infection susceptibility.

Table 2 Risk Factors for Death in Patients with CRKP Infection

Risk Factors [n (%)]		Death (n=28)	Survival (n=60)	Univariable Analysis		Multivariate Analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Age (Year)							
< 60		2	28	1.000		1.000	
60–70		4	16	3.500 (0.576–21.282)	0.155	2.777 (0.582–17.782)	0.109
70–80		10	9	15.556 (2.859–84.623)	<0.001	8.692 (1.822–67.641)	<0.001
≥80		12	7	24.000 (4.337–132.801)	<0.001	15.721 (2.521–94.630)	<0.001
Sex							
Male		14	38	1.000			
Female		14	22	1.727 (0.697–4.283)	0.236		
APACHE II score							
< 18		1	20	1.000		1.000	
18–20		3	17	3.529 (0.335–37.146)	0.269	2.132 (0.631–29.247)	0.154
20–22		4	9	8.889 (0.866–91.199)	0.059	9.132 (0.898–78.238)	0.081
22–24		9	8	22.500 (2.437–207.732)	0.001	16.751 (0.856–178.821)	0.061
>24		11	6	36.667 (3.899–344.837)	<0.001	19.739 (0.888–215.561)	0.068
Concomitant diseases							
Lung disease	No	10	36	1.000		1.000	
	Yes	18	24	2.700 (1.066–6.841)	0.034	1.536 (0.775–5.834)	0.087
Cardiac dysfunction	No	16	45	1.000			
	Yes	12	15	2.250 (0.871–5.815)	0.091		
Renal dysfunction	No	10	43	1.000		1.000	
	Yes	18	17	4.553 (1.751–11.837)	0.001	1.785 (1.224–8.327)	0.015
Neurological disease	No	25	53	1.000			
	Yes	3	7	0.909 (0.217–3.811)	0.896		
Liver disease	No	23	48	1.000			
	Yes	5	12	0.870 (0.274–2.762)	0.813		
Diabetes mellitus	No	14	44	1.000		1.000	
	Yes	14	16	2.750 (1.078–7.012)	0.031	2.662 (0.879–7.152)	0.088
Hypoalbuminemia	No	16	24	1.000			
	Yes	12	36	0.500 (0.201–1.241)	0.133		
Tumor	No	23	54	1.000			
	Yes	5	6	1.957 (0.542–7.060)	0.299		
Septicemia	No	14	39	1.000			
	Yes	14	21	1.857 (0.747–4.619)	0.181		
Antibiotics use after K.pn infection							
Fluoroquinolones	No	8	28	1.000			
	Yes	20	32	2.188 (0.834–5.737)	0.108		
2nd generation cephalosporins	No	19	32	1.000			
	Yes	9	28	0.541 (0.211–1.388)	0.199		
3rd generation cephalosporins	No	16	47	1.000		1.000	
	Yes	12	13	2.712 (1.030–7.140)	0.040	2.886 (0.711–8.175)	0.101
Amikacin	No	24	50	1.000			
	Yes	4	10	0.833 (0.237–2.931)	0.776		
Carbapenems	No	7	32	1.000		1.000	
	Yes	21	28	3.429 (1.268–9.268)	0.013	2.326 (0.886–13.974)	0.079
Cefoperazone plus sulbactam	No	13	40	1.000			
	Yes	15	20	2.308 (0.923–5.770)	0.071		

(Continued)

Table 2 (Continued).

Risk Factors [n (%)]		Death (n=28)	Survival (n=60)	Univariable Analysis		Multivariate Analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Glycopeptides	No	18	29	1.000			
	Yes	10	31	0.520 (0.206–1.309)	0.162		
Using more than 3 antibiotics	< 7 days	5	32	1.000		1.000	
	≥ 7 days	23	28	5.257 (1.764–15.668)	0.002	5.042 (0.940–15.125)	0.070
Surgery before admission							
No		19	45				
Yes		9	15	1.421 (0.531–3.806)	0.483		
Invasive procedures							
Deep venous catheterization	No	5	28	1.000		1.000	
	Yes	23	32	4.025 (1.351–11.996)	0.009	2.524 (0.798–10.321)	0.096
Tracheotomy	No	5	25	1.000		1.000	
	Yes	23	35	3.286 (1.099–9.820)	0.028	2.149 (1.103–10.262)	0.005
Mechanical ventilation	No	10	37	1.000		1.000	
	Yes	18	23	2.896 (1.140–7.353)	0.023	1.782 (0.852–4.931)	0.094
Indwelling urethral catheter	No	9	15	1.000			
	Yes	19	45	0.704 (0.263–1.885)	0.483		
Indwelling gastric tube	No	17	33	1.000			
	Yes	11	27	0.791 (0.317–1.971)	0.614		
ICU stay							
< 3 days		9	49	1.000		1.000	
≥ 3 days		19	11	9.404 (3.364–26.287)	<0.001	3.646 (2.101–19.126)	<0.001

Abbreviations: CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; K.pn, *Klebsiella pneumoniae*; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

In addition, older age, renal dysfunction, tracheotomy, and ICU stay were independent death risk factors in patients infected with CRKP. Older age and severe concomitant diseases lead to a decline in immunity, thereby increasing the risk of CRKP infection and even death.¹⁵

Although several independent risk factors of CRKP-induced infection and death were identified, the present study has limitations. (1) The number of included patients was relatively small; (2) risk factor omissions may be present; (3) as the present report was a single-center case-control study, selection bias was inevitable and the presented data were limited. Thus, a multicenter, large-scale study should be conducted in the future; (4) only prior infection by Kpn was tested, whereas prior colonization by such Kpn was not screened for. This study analyzed the risk factors of CSKP or CRKP infection for the first time; it did not, however, analyze the risk factors of CRKP isolated after the initial CSKP isolation. We aim to address this aspect in follow-up research. Nonetheless, according to the risk factors of CRKP infection, the long-term use of more than three antibiotics, the long-term use of carbapenems, long-term endotracheal intubation, and long-term ICU stay (for the same patient) may promote the transformation of CSKP to CRKP. Therefore, the rational use of antibiotics should be based on drug sensitivity results in clinical treatment. In addition, its use time should be shortened as much as possible, and do a good job in maintaining sterile conditions to avoid secondary CRKP infection.

Conclusion

The present study provided evidence that prior carbapenem use, the use of more than three types of antibiotics for seven or more days, tracheotomy, and ICU stay increased the risk of CRKP infection, while older age, renal dysfunction, tracheotomy, and ICU stay increased the risk of death in patients infected with CRKP. In this respect, the present findings are significant for clinicians controlling CRKP infections.

Ethics Statement

All procedures performed in the study involving human participants were in accordance with the ethical standards of the ethics committee of Beijing Shijitan Hospital, Capital Medical University (No: Sjtjky11-1x-2022(22)). All patients provided written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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