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ORIGINAL ARTICLE

Analysis of risk factors associated with healthcare-associated carbapenem-resistant *Klebsiella pneumoniae* infection in a large general hospital: a case-case-control study

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Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection is a major public health threat in the world. To inform the prevention and control of CRKP infection in hospitals, this study analyzed the factors associated with CRKP infection and resistance to carbapenems in *K. pneumoniae*. This case-case-control study was carried out in a large general hospital in China from January 2016 to December 2018, comprising 494 hospitalized patients infected with CRKP (case group 1) and 2429 hospitalized patients infected with carbapenem-susceptible *K. pneumoniae* (CSKP, case group 2). We selected control groups from hospitalized patients without *K. pneumoniae* infections for the two case groups separately, with a 1:3 case-control ratio, to analyze the risk factors of the two case groups using the conditional logistic regression. Multivariate analysis showed that the risk factors of CRKP infection were intensive care unit (ICU) admission (odds ratio [OR], 6.85; 95% confidence interval [CI], 4.90–9.58; $P < 0.001$), respiratory failure (OR, 1.93; 95% CI, 1.34–2.77; $P < 0.001$), age-adjusted Charlson comorbidity index (aCCI; OR, 1.08; 95% CI, 1.02–1.15; $P = 0.007$), admission from the Emergency (OR, 1.37; 95% CI, 1.02–1.85; $P = 0.036$), and imipenem use (OR, 1.80; 95% CI, 1.30–2.49; $P < 0.001$). Among the aforementioned five risk factors, aCCI (OR, 1.09; 95% CI, 1.06–1.13; $P < 0.001$) was also identified as a risk factor of CSKP infections in multivariate analysis. The risk factors for resistance to carbapenems in *K. pneumoniae* were ICU admission, respiratory failure, admission from the Emergency, and imipenem use.

Keywords Carbapenem-resistant *Klebsiella pneumoniae* · Risk factors · Healthcare-associated infection · Case-case-control study

Introduction

Carbapenem, a class of antimicrobial agents, such as imipenem, meropenem, and ertapenem, are the mainstream choice to treat severe infections due to *Klebsiella pneumoniae*, a notorious opportunistic pathogen. However, carbapenem-resistant *K. pneumoniae* (CRKP) have already emerged as a severe threat of human health. In 2018, the World Health Organization (WHO) categorized CRKP as Priority 1 (critical priority) in the global priority list of

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antimicrobial-resistant bacteria [1]. In 2019, the Centers for Disease Control and Prevention (CDC) classified 18 common multidrug-resistant bacteria into three categories, urgent, serious, and concerning threat, based on the levels of health concern in humans, among which CRKP was classified as an urgent threat to human health [2]. In China, data from the China Antimicrobial Surveillance Network (CHINET) have shown that the carbapenem resistance rate of *K. pneumoniae* has been continuously increasing from 3% in 2015 to 9.2% in 2010 then to 24.4% in 2021 [3].

Identification of risk factors of CRKP infection is critical for informing the prevention and control of CRKP in hospitals. There are many studies addressing risk factors of CRKP infection in literature. However, many of these studies have used a case-control design with directly comparing CRKP cases to carbapenem-susceptible *K. pneumoniae* (CSKP) ones. Such a case-control design has an intrinsic flaw as it implies the "replacement scenario" assumption, in which each patient is assumed to be infected either by the antimicrobial-resistant organisms or by their antimicrobial-susceptible counterparts but the patient could be infected by other pathogens or had no infection at all [4–6]. Therefore, more studies with improved design are needed to further elucidate the risk factors of CRKP infection. We then performed a study with a case-case-control design to identify associated with carbapenem resistance in *K. pneumoniae* to generate useful information for the targeted prevention and control of CRKP infection.

Materials and methods

Study design

This study was conducted in West China Hospital, Sichuan University, Chengdu, China. This hospital has 4300 beds and is a tertiary general hospital with an average annual admission of approximately 270,000 patients. The study design was case-case-control. This project was approved by the Ethics Committee of West China Hospital with informed consent being waived.

Subjects

This study was carried out retrospectively between January 2016 and December 2018 and comprised two case-control comparisons, in which inpatients with CRKP infection and those with CSKP infection were compared to their corresponding matched inpatient controls, respectively. The matched controls for those with CRKP or CSKP infection were inpatients with no infection due to *K. pneumoniae*.

Data sources

Patients with CRKP or CSKP and without *K. pneumoniae* were screened in the laboratory information system (LIS) and patient data were retrieved from their electronic medical records in the hospital information system (HIS). In the clinical microbiology laboratory, species identification for *K. pneumoniae* from clinical samples were performed using the automated VITEK 2 system (bioMérieux; Marcy l'Etoile, France). In vitro antimicrobial susceptibility testing was also determined by Vitek II and breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) [7] were applied.

Inclusion and exclusion criteria

For the case groups, inpatients with CRKP or CSKP recovered from a clinical specimen were included. Inpatients who met one of the following were excluded: (1) those were infected with CRKP and/or CSKP before or within 2 days of admission to the hospital; (2) those had both CRKP and CSKP; (3) those were not discharged at the time of data collection; and (4) those had CRKP only from screening rectal and/or oral swabs but no CRKP from any clinical specimens. For patients with multiple admissions during the study period, only the first admission of CRKP or CSKP infection was included, and the subsequent admissions were excluded.

The selection of control needs to represent the source patient population of the hospital and therefore we selected the control from inpatients. The control group of CRKP was inpatients without CRKP detected, and the control group of CSKP was inpatients without CRKP/CSKP detected. Therefore, the control group may have no infection or may be infected with other microorganisms. Inpatients who met one of the following were excluded: (1) those admitted with hospitalization time less than 2 days; (2) those lacked an International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis.

Patient matching and grouping

Data of patients who met the inclusion but not exclusion criteria were retrieved as described above. There were two, CRKP and CSKP, case study groups. Each of the patients infected with CRKP or CSKP was matched with inpatient controls at a ratio of 1:3 according to the matching conditions as follows: risk-time matching [6, 8], hospitalization difference no more than 1 month, and same initial diagnosis using first three digits of the *10th revision of the International Statistical Classification of Diseases and Related Health Problems* (ICD-10) code [9]. Three controls were

randomly selected for each patient infected with CRKP or CSKP if multiple controls met the matching conditions. If ≤ 3 controls were found matching a patient, all of these controls were included. Data from the medical order of the physicians and information about the emergency admission collected from the matched study subjects were combined allowing manual queries for separately analyzing the impact of each factor on the CRKP and CSKP infections. The results of two case-control studies were then combined for further analysis to investigate risk factors for carbapenem resistance.

Definitions

CRKP was defined as *K. pneumoniae* that is resistant or intermediate to any of the following carbapenem antibiotics: meropenem, imipenem, or ertapenem (doripenem is not available in China). CSKP was *K. pneumoniae* that is susceptible to all of meropenem, imipenem, and ertapenem. Healthcare-associated CRKP/CSKP infection in this study referred to the first detection of CRKP/CSKP in any clinical specimens, such as blood, sputum, urine, drainage, bile, and ascites, collected 2 days after admission. Risk-time matching referred to that the length of hospital stays of the control was not less than the length of hospital stays of a patient infected with CRKP/CSKP before the collection date of the first CRKP/CSKP-positive clinical specimen. Respiratory failure was defined as $PaO_2 < 60$ mmHg while breathing air, or a $PaCO_2 > 50$ mmHg.

The explanatory variables

Factors before the risk time of the patient were collected as explanatory variables/independent variables. For the case groups, the explanatory variables existed before the collection date of the first CRKP/CSKP-positive clinical specimen. For the control group, the explanatory variables existed during the entire hospital stay of the patients. The explanatory variables collected in this study comprised those of the following six categories, i.e., patient's factors, underlying diseases, antimicrobial agents, other drugs, invasive procedures, and other examinations/operations (mainly noninvasive procedures).

Data analysis

Microsoft Excel 2016 was used for compiling a Visual Basic for Applications programming language to match inpatients infected with CRKP or CSKP infections and those for control. In the univariate analysis, the non-normally distributed quantitative data were subjected to a descriptive analysis using the median (P_{25}–P_{75}) and statistical analysis using the Friedman's rank-sum test, while the qualitative data were presented as frequency (%) and the statistical analysis was performed using the Cochran's Q test [10]. The statistically significant variables in the univariate analysis ($P < 0.05$) were included in the multivariate analysis. Conditional logistic regression was used to analyze the risk factors of the CRKP-case and the CSKP-case groups [11]. The backward stepwise regression was mainly used to select the variable in a multivariate model. The least important variables (with the largest P value) to the model were sequentially removed until all variables retained in the model were statistically significant. The correlation coefficient matrix was used to evaluate the collinearity of variables. Some variables were removed in combination with professional consideration when a strong collinearity was found. The SPSS 21.0 software package (IBM, Armonk, NY) was used for the statistical analysis. P values were 2-tailed, and $P < 0.05$ was considered statistically significant.

Results

The case-case-control groups

The flowchart of this study is shown in Fig. 1. There were 537 patients in the CRKP group and 2594 patients in the CSKP group during the study period. The most common infection type due to CRKP was pneumonia, accounting for 50.09% (269/537), followed by bacteremia (14.53%) and urinary tract infection (11.73%). And the most common type of CSKP was pneumonia, accounting for 64.38% (1670/2594), followed by urinary tract infection (12.68%) and bacteremia (7.13%).

Controls of this study were matched from 602,212 inpatients without *K. pneumoniae* with a ratio of 1:3 (one inpatient with CRKP or CSKP infection corresponded to three inpatient controls). A total of 1357 and 6953 controls were successfully matched for 494 (91.99%, 494/537) inpatients infected with CRKP and 2429 infected with CSKP (93.64%, 2429/2594), respectively.

Case-control study for CRKP infection

Univariate analysis identified 43 variables including sex, aCCI, and ICU admission that were statistically different ($P < 0.05$) between the CRKP case and the control groups (Table 1) as possible risk factors for CRKP infection. Spearman's correlation analysis of these 43 variables exhibited that the correlation coefficient of mechanical ventilation versus chest radiography, nasogastric tube feeding, and bathing was 0.71, 0.70, and 0.72, respectively, while that of nasogastric tube feeding versus bathing and enteral nutrition was 0.69 and 0.63, respectively. This suggests that the above variables may have collinearity and could interfere

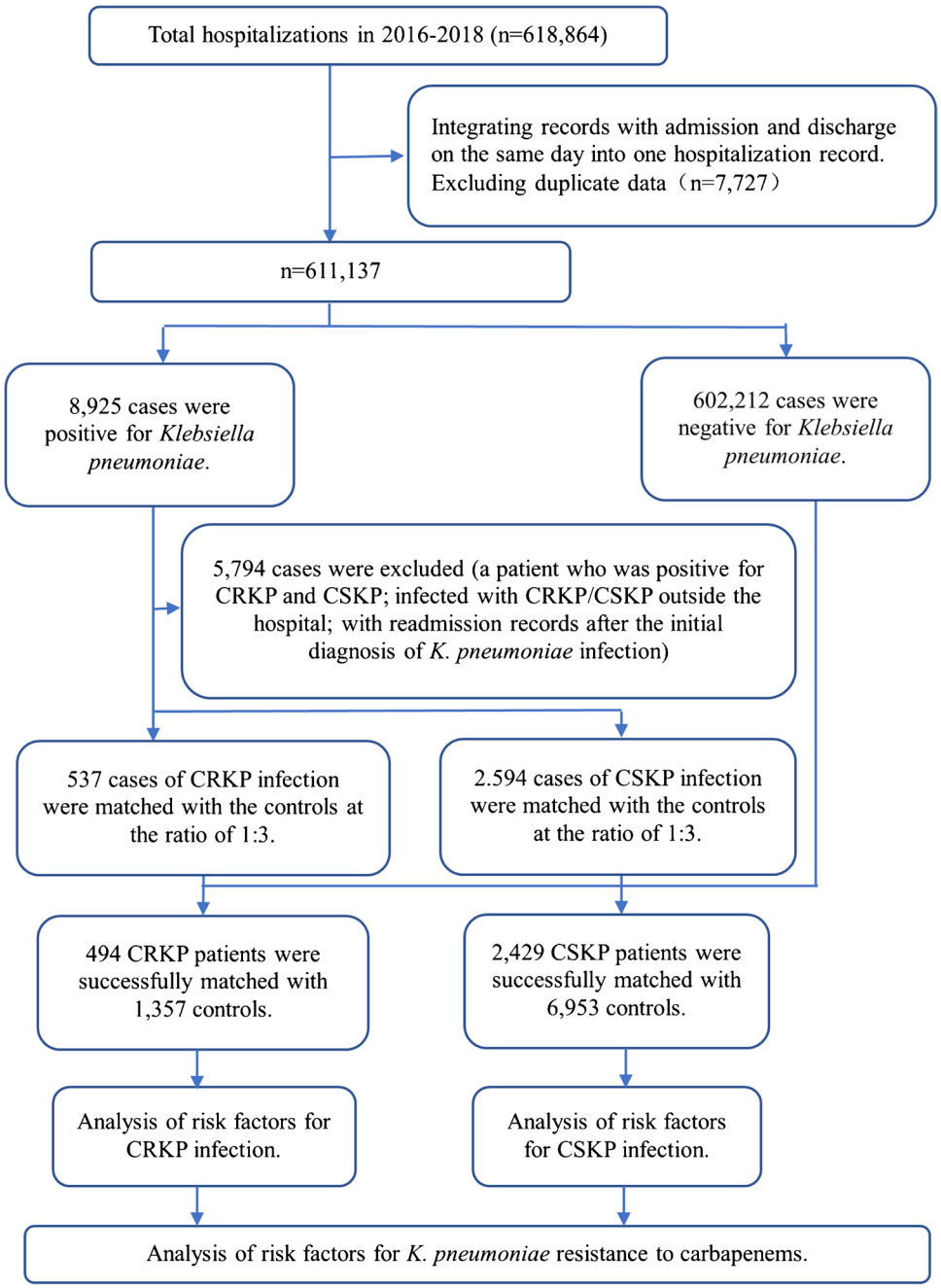

Fig. 1 The flowchart of this study

with the analysis. Therefore, three factors (chest radiography, nasogastric tube feeding, and bathing) were removed based on clinical experience. To test the independent effects of imipenem and meropenem (no ertapenem was used in the study period), the introduction of carbapenems into the model was divided into two variables (imipenem and meropenem). Using a backward stepwise approach [12], the remaining statistically significant variables were included into multivariate and conditional logistic regression analyses. The Hosmer-Lemeshow test [12] for examining the goodness of fit for the logistic regression model showed $\chi^2 = 2.35$ and $P = 0.968$, suggesting that the model fit well (Table 2).

The independent risk factors of CRKP infection included ICU admission (OR: 6.85, 95% CI: 4.90–9.58; $P < 0.001$), respiratory failure (OR: 1.93, 95% CI: 1.34–2.77; $P < 0.001$), aCCI (OR: 1.08, 95% CI: 1.02–1.15; $P = 0.007$), admission from the Emergency (OR: 1.37, 95% CI: 1.02–1.85; $P = 0.036$), and imipenem use (OR: 1.80, 95% CI: 1.30–2.49; $P < 0.001$). The preventive factors of CRKP infection included quinolone use (OR: 0.56, 95% CI: 0.41–0.75; $P < 0.001$), first- and second-generation cephalosporin (OR: 0.38, 95%

Table 1 Univariate analysis of possible risk factors for CRKP infection

Characteristics	Cases ($n = 494$)	Controls ($n = 1357$)	*Wald* χ^2	*P*	OR (95% CI)
Patient's factors					
Female	341 (69.03%)	859 (63.3%)	5.43	0.020	0.76 (0.6–0.96)
Age, years (median, IQR)	55 (44–68)	54 (41–68)	2.84	0.416	/
Han nationality	452 (91.5%)	1259 (92.78%)	0.62	0.432	0.86 (0.58–1.26)
aCCI (median, IQR)	3 (1–5)	3 (2–5)	22.17	< 0.001	/
ICU admission	297 (60.12%)	353 (26.01%)	169.53	< 0.001	8.05 (5.88–11.01)
Admission from the Emergency	292 (59.11%)	668 (49.23%)	20.07	< 0.001	1.77 (1.38–2.27)
Underlying diseases					
Hypertension	137 (27.73%)	422 (31.1%)	1.60	0.206	0.85 (0.65–1.1)
Tuberculosis	10 (2.02%)	43 (3.17%)	3.31	0.069	0.37 (0.12–1.08)
Respiratory failure	129 (26.11%)	160 (11.79%)	56.11	< 0.001	3.2 (2.36–4.34)
Heart failure	76 (15.38%)	141 (10.39%)	9.81	0.002	1.78 (1.24–2.56)
Malignant tumors	82 (16.6%)	241 (17.76%)	1.76	0.185	0.71 (0.43–1.18)
Hematological diseases	15 (3.04%)	51 (3.76%)	2.30	0.130	0.4 (0.12–1.31)
Pancreatitis	85 (17.21%)	241 (17.76%)	0.04	0.838	0.9 (0.34–2.4)
Diabetes	85 (17.21%)	237 (17.46%)	0.04	0.834	1.03 (0.77–1.38)
Antimicrobial administration					
Pyrroles	116 (23.48%)	220 (16.21%)	12.48	< 0.001	1.69 (1.26–2.25)
Amphotericin B	14 (2.83%)	23 (1.69%)	1.38	0.240	1.53 (0.75–3.14)
Caspofungin	64 (12.96%)	66 (4.86%)	31.89	< 0.001	3.02 (2.06–4.43)
Nitroimidazole	16 (3.24%)	57 (4.2%)	0.87	0.350	0.76 (0.43–1.35)
Penicillin	2 (0.4%)	19 (1.4%)	2.50	0.114	0.31 (0.07–1.33)
Aztreonam	3 (0.61%)	20 (1.47%)	2.59	0.107	0.37 (0.11–1.24)
Macrolides	5 (1.01%)	4 (0.29%)	2.95	0.086	3.21 (0.85–12.18)
Linezolid	51 (10.32%)	59 (4.35%)	19.54	< 0.001	2.55 (1.68–3.86)
Quinolones	123 (24.9%)	436 (32.13%)	13.96	< 0.001	0.61 (0.48–0.79)
β-lactam/β-lactamase inhibitors	303 (61.34%)	731 (53.87%)	6.81	0.009	1.36 (1.08–1.72)
Carbapenems	263 (53.24%)	440 (32.42%)	67.61	< 0.001	2.76 (2.17–3.52)
Imipenem	173 (35.02%)	288 (21.22%)	37.73	< 0.001	2.33 (1.78–3.04)
Meropenem	110 (22.27%)	137 (10.10%)	42.95	< 0.001	2.77 (2.04–3.75)
Clindamycin	47 (9.51%)	117 (8.62%)	0.16	0.685	1.08 (0.73–1.61)
First- and second-generation cephalosporins	60 (12.15%)	283 (20.85%)	26.35	<0.001	0.39(0.27–0.56)
Third-generation cephalosporins	40 (8.1%)	122 (8.99%)	0.78	0.377	0.84 (0.56–1.24)
Cephamycins	62 (12.55%)	269 (19.82%)	16.03	< 0.001	0.51 (0.36–0.71)
Tigecycline	99 (20.04%)	88 (6.48%)	62.33	< 0.001	4.21 (2.95–6.02)
Vancomycin	136 (27.53%)	192 (14.15%)	33.66	< 0.001	2.22 (1.69–2.9)
Aminoglycosides	36 (7.29%)	77 (5.67%)	0.17	0.678	1.1 (0.71–1.7)
Other drugs					
Steroids	270 (54.66%)	631 (46.5%)	7.87	0.005	1.38 (1.1–1.73)
Parenteral nutrition	308 (62.35%)	788 (58.07%)	2.96	0.085	1.25 (0.97–1.61)
Enteral nutrition	275 (55.67%)	523 (38.54%)	41.33	< 0.001	2.17 (1.71–2.74)
Histamine type-2 (H2) receptor antagonists	8 (1.62%)	65 (4.79%)	9.72	0.002	0.3 (0.14–0.64)
Proton pump inhibitors	352 (71.26%)	1006 (74.13%)	2.16	0.142	0.82 (0.64–1.07)
Gastric mucosal protective agents	38 (7.69%)	151 (11.13%)	6.05	0.014	0.62 (0.42–0.91)
Immunosuppressants	32 (6.48%)	55 (4.05%)	5.85	0.016	1.89 (1.13–3.15)
Invasive procedures					
Mechanical ventilation	308 (62.35%)	489 (36.04%)	104.04	< 0.001	3.97 (3.05–5.18)
Central venous catheterization	261 (52.83%)	372 (27.41%)	96.42	< 0.001	3.38 (2.65–4.31)
Peripherally inserted central catheter	56 (11.34%)	128 (9.43%)	0.51	0.474	1.14 (0.8–1.64)
Urinary catheterization	172 (34.82%)	385 (28.37%)	13.47	< 0.001	1.81 (1.32–2.48)

Table 1 (continued)

Characteristics	Cases ($n = 494$)	Controls ($n = 1357$)	*Wald* χ^2	*P*	OR (95% CI)
Blood purification	68 (13.77%)	55 (4.05%)	46.74	< 0.001	4.19 (2.78–6.32)
Surgery	375 (75.91%)	935 (68.9%)	8.97	0.003	1.49 (1.15–1.94)
Organ transplantation	19 (3.85%)	26 (1.92%)	5.97	0.015	2.27 (1.18–4.37)
Tracheotomy	85 (17.21%)	149 (10.98%)	13.87	< 0.001	1.95 (1.37–2.76)
Cardiopulmonary bypass	15 (3.04%)	30 (2.21%)	1.22	0.269	1.64 (0.68–3.98)
Other examinations/operations					
Nasogastric tube feeding	298 (60.32%)	421 (31.02%)	129.07	<0.001	4.65 (3.57–6.07)
Fiberoptic bronchoscopy	192 (38.87%)	272 (20.04%)	67.39	<0.001	3 (2.31–3.9)
ERCP	11 (2.23%)	35 (2.58%)	0.12	0.727	0.88 (0.44–1.78)
Nebulization and inhalation	264 (53.44%)	613 (45.17%)	9.73	0.002	1.46 (1.15–1.85)
Mechanically assisted expectoration of sputum	103 (20.85%)	173 (12.75%)	16.23	< 0.001	1.87 (1.38–2.53)
Sputum suctioning	0 (0%)	1 (0.07%)	0.12	0.725	0.03 (0–7359780.74)
Bladder irrigation	20 (4.05%)	67 (4.94%)	1.26	0.262	0.73 (0.41–1.27)
Gastroscopy and duodenoscope	49 (9.92%)	140 (10.32%)	0.35	0.552	0.89 (0.61–1.3)
Colonoscopy	3 (0.61%)	45 (3.32%)	8.98	0.003	0.16 (0.05–0.53)
Negative pressure suction	105 (21.26%)	115 (8.47%)	53.88	< 0.001	3.59 (2.55–5.05)
Drainage	101 (20.45%)	159 (11.72%)	27.98	< 0.001	2.5 (1.78–3.52)
Chest radiography	265 (53.64%)	426 (31.39%)	72.25	<0.001	2.87 (2.25–3.65)
Electrocardiogram	191 (38.66%)	736 (54.24%)	40.95	< 0.001	0.47 (0.38–0.6)
Bedside ultrasonography	256 (51.82%)	361 (26.6%)	101.15	< 0.001	3.68 (2.86–4.75)
Gastrointestinal decompression	289 (58.5%)	463 (34.12%)	92.58	< 0.001	3.46 (2.69–4.46)
Enema	116 (23.48%)	150 (11.05%)	42.86	< 0.001	2.81 (2.06–3.82)
Bathing	253 (51.21%)	300 (22.11%)	133.82	< 0.001	4.97 (3.79–6.52)

aCCI age-adjusted Charlson Comorbidity Index, *ERCP* endoscopic retrograde cholangiopancreatography

Table 2 Multivariate analysis of influencing factors for CRKP infection

Characteristics	*β*	*SE*	*Wald* χ^2	*P*	OR(95% CI)
ICU admission	1.92	0.17	126.86	< 0.001	6.85(4.9–9.58)
Quinolones	− 0.59	0.15	14.44	< 0.001	0.56(0.41–0.75)
First- and second-generation cephalosporins	− 0.98	0.21	22.62	< 0.001	0.38(0.25–0.56)
Cephamycins	− 0.82	0.20	17.45	< 0.001	0.44(0.3–0.65)
Gastric mucosal protective agents	− 0.63	0.23	7.58	0.006	0.53(0.34–0.83)
Respiratory failure	0.66	0.18	12.74	< 0.001	1.93(1.34–2.77)
aCCI	0.08	0.03	7.32	0.007	1.08(1.02–1.15)
admission from the Emergency	0.32	0.15	4.39	0.036	1.37(1.02–1.85)
Imipenem	0.59	0.17	12.68	< 0.001	1.8(1.3–2.49)

CI: 0.25–0.56; $P < 0.001$), Cephamycins (OR: 0.44, 95% CI: 0.30–0.65; $P < 0.001$), and sucralfate (OR: 0.53, 95% CI: 0.34–0.83; $P = 0.006$).

Case-control study for CSKP infection

Univariate analysis of the risk factors for CSKP infection showed that 50 variables, including sex, age, and aCCI, were statistically different between the CSKP-case and the corresponding control groups ($P < 0.05$, see Table 3 for details). The statistically significant variables in the univariate analysis were combined in multivariate and conditional logistic regression analyses using a backward stepwise approach. The Hosmer-Lemeshow test for goodness of fit for the regression model showed $\chi^2 = 12.39$, $P = 0.135$, indicating that the model fit well (Table 4). Spearman's correlation analysis of these 50 variables exhibited that the correlation coefficient of mechanical ventilation versus ICU admission and sputum suctioning was 0.74 and 0.78, respectively. This suggests that the above variables may have collinearity and could interfere with the

Table 3 Bivariate analysis of influencing factors associated with CSKP infection

Characteristic	Cases (n = 2429)	Controls (n = 6953)	*Wald* χ^2	*P*	OR (95%CI)
Patient's factors					
Female	1627 (66.98%)	4049 (58.23%)	59.04	< 0.001	0.67 (0.61–0.74)
Age, years (median, IQR)	60 (47–71)	54 (43–67)	90.35	< 0.001	/
Han nationality	2285 (94.07%)	6530 (93.92%)	0.13	0.718	1.04 (0.85–1.27)
aCCI	3 (2–6)	3 (1–5)	149.65	< 0.001	/
ICU admission	519 (21.37%)	999 (14.37%)	90.64	< 0.001	2.1 (1.8–2.45)
Admission from the Emergency	934 (38.45%)	2089 (30.04%)	82.62	< 0.001	1.77 (1.57–2.01)
Underlying diseases					
Hypertension	761 (31.33%)	2014 (28.97%)	6.35	0.012	1.16 (1.03–1.3)
Tuberculosis	86 (3.54%)	249 (3.58%)	0.02	0.890	0.98 (0.7–1.36)
Respiratory failure	263 (10.83%)	416 (5.98%)	71.27	< 0.001	2.22 (1.85–2.67)
Heart failure	350 (14.41%)	733 (10.54%)	45.30	< 0.001	1.88 (1.56–2.26)
Malignant tumors	661 (27.21%)	1791 (25.76%)	9.96	0.002	1.4 (1.14–1.73)
Hematological diseases	113 (4.65%)	302 (4.34%)	0.24	0.625	1.11 (0.74–1.66)
Pancreatitis	87 (3.58%)	238 (3.42%)	0.57	0.450	1.19 (0.76–1.85)
Diabetes	464 (19.1%)	953 (13.71%)	45.52	< 0.001	1.58 (1.38–1.81)
Antimicrobial administration					
Pyrroles	260 (10.7%)	562 (8.08%)	13.44	< 0.001	1.43 (1.18–1.73)
Amphotericin B	42 (1.73%)	96 (1.38%)	0.79	0.374	1.23 (0.78–1.94)
Caspofungin	88 (3.62%)	124 (1.78%)	27.42	< 0.001	2.26 (1.67–3.07)
Nitroimidazole	64 (2.63%)	164 (2.36%)	0.24	0.626	1.08 (0.79–1.47)
Penicillin	21 (0.86%)	93 (1.34%)	3.95	0.047	0.6 (0.37–0.99)
Aztreonam	14 (0.58%)	65 (0.93%)	3.32	0.069	0.58 (0.32–1.04)
Macrolides	2 (0.08%)	9 (0.13%)	0.27	0.604	0.67 (0.14–3.09)
Linezolid	62 (2.55%)	106 (1.52%)	8.62	0.003	1.64 (1.18–2.27)
Quinolones	424 (17.46%)	1470 (21.14%)	24.48	< 0.001	0.71 (0.63–0.82)
β-lactam/β-lactamase inhibitors	1333 (54.88%)	2215 (31.86%)	440.04	< 0.001	3.39 (3.02–3.79)
Carbapenems	501 (20.63%)	1068 (15.36%)	33.54	< 0.001	1.51 (1.31–1.73)
Imipenem	332 (13.67%)	686 (9.87%)	25.36	< 0.001	1.52 (1.29–1.79)
Meropenem	90 (3.71%)	217 (3.12%)	1.31	0.252	1.17 (0.89–1.53)
Clindamycin	197(8.11%)	365 (5.25%)	28.10	< 0.001	1.72 (1.41–2.1)
First- and second-generation cephalosporins	507 (20.87%)	1456 (20.94%)	0.22	0.639	0.96 (0.83–1.12)
Third-generation cephalosporins	105 (4.32%)	371 (5.34%)	6.14	0.013	0.75 (0.59–0.94)
Cephamycins	365 (15.03%)	1366 (19.65%)	34.31	< 0.001	0.64 (0.55–0.74)
Tigecycline	83 (3.42%)	106 (1.52%)	26.92	< 0.001	2.29 (1.67–3.13)
Vancomycins	264 (10.87%)	531 (7.64%)	17.75	< 0.001	1.45 (1.22–1.73)
Aminoglycosides	61 (2.51%)	177 (2.55%)	0.51	0.474	0.89 (0.66–1.22)
Other drugs					
Steroids	1050 (43.23%)	2770 (39.84%)	7.41	0.006	1.17 (1.04–1.3)
Parenteral nutrition	1104 (45.45%)	2347 (33.76%)	137.56	< 0.001	2.03 (1.81–2.29)
Enteral nutrition	763 (31.41%)	1389 (19.98%)	143.37	< 0.001	2.11 (1.87–2.38)
Histamine type-2 (H2) receptor antagonists	82 (3.38%)	364 (5.24%)	16.85	< 0.001	0.58 (0.45–0.75)
Proton pump inhibitors	1579 (65.01%)	4184 (60.18%)	20.54	<0.001	1.31 (1.16–1.47)
Gastric mucosal protective agents	193 (7.95%)	649 (9.33%)	5.73	0.017	0.81 (0.67–0.96)
Immunosuppressants	56 (2.31%)	237 (3.41%)	11.34	0.001	0.56 (0.4–0.78)
Invasive procedures					
Mechanical ventilation	842 (34.66%)	1397 (20.09%)	275.99	< 0.001	3.05 (2.67–3.48)
Central venous catheterization	617 (25.4%)	1115 (16.04%)	111.09	< 0.001	2.02 (1.77–2.3)
Peripherally inserted central catheter	122 (5.02%)	294 (4.23%)	0.94	0.331	1.12 (0.89–1.42)
Urinary catheterization	1288 (53.03%)	2945 (42.36%)	124.29	< 0.001	2.03 (1.79–2.29)

Table 3 (continued)

Characteristic	Cases ($n = 2429$)	Controls ($n = 6953$)	*Wald* χ^2	*P*	OR (95%CI)
Blood purification	59 (2.43%)	89 (1.28%)	13.12	< 0.001	1.89 (1.34–2.67)
Surgery	1383 (56.94%)	4483 (64.48%)	62.07	< 0.001	0.64 (0.57–0.71)
Organ transplantation	25 (1.03%)	61 (0.88%)	0.43	0.512	1.19 (0.71–1.99)
Tracheotomy	174 (7.16%)	243 (3.49%)	61.31	< 0.001	2.67 (2.09–3.41)
Cardiopulmonary bypass	141 (5.8%)	273 (3.93%)	44.12	< 0.001	5.7 (3.41–9.52)
Other examinations/operations					
Nasogastric tube feeding	720 (29.64%)	944 (13.58%)	359.39	< 0.001	4.09 (3.53–4.73)
Fiberoptic bronchoscopy	502 (20.67%)	940 (13.52%)	96.32	< 0.001	2.09 (1.8–2.42)
ERCP	29 (1.19%)	76 (1.09%)	0.20	0.659	1.11 (0.7–1.77)
Nebulization and inhalation	1026 (42.24%)	2342 (33.68%)	67.93	< 0.001	1.59 (1.42–1.78)
Mechanically assisted expectoration of sputum	279 (11.49%)	649 (9.33%)	13.21	< 0.001	1.42 (1.18–1.72)
Sputum suctioning	960 (39.52%)	1485 (21.36%)	390.17	< 0.001	3.9 (3.41–4.46)
Bladder irrigation	116 (4.78%)	198 (2.85%)	18.69	< 0.001	1.84 (1.4–2.43)
Gastroscopy and duodenoscope	109 (4.49%)	480 (6.9%)	21.77	< 0.001	0.58 (0.46–0.73)
Colonoscopy	30 (1.24%)	191 (2.75%)	20.98	< 0.001	0.38 (0.25–0.57)
Negative pressure suction	135 (5.56%)	228 (3.28%)	28.35	< 0.001	2 (1.55–2.57)
Drainage	180 (7.41%)	463 (6.66%)	2.47	0.116	1.19 (0.96–1.48)
Chest radiography	658 (27.09%)	1333 (19.17%)	80.30	< 0.001	1.81 (1.59–2.06)
Electrocardiogram	919 (37.83%)	2518 (36.21%)	1.45	0.229	1.07 (0.96–1.2)
Bedside ultrasonography	356 (14.66%)	1062 (15.27%)	0.55	0.459	0.95 (0.84–1.08)
Gastrointestinal decompression	573 (23.59%)	1154 (16.6%)	74.10	< 0.001	1.85 (1.61–2.12)
Enema	150 (6.18%)	336 (4.83%)	5.45	0.020	1.29 (1.04–1.6)
Bathing	410 (16.88%)	612 (8.8%)	136.75	< 0.001	2.57 (2.19–3.01)

aCCI age-adjusted Charlson Comorbidity Index, *ERCP* endoscopic retrograde cholangiopancreatography

Table 4 Multivariate analysis of influencing factors for CSKP infection

Characteristics	*β*	*SE*	*Wald* χ^2	*P*	OR(95% CI)
Penicillin	− 0.77	0.28	7.80	0.005	0.46 (0.27–0.79)
Quinolones	− 0.42	0.07	33.07	< 0.001	0.66 (0.57–0.76)
β-lactam/β-lactamase inhibitors	0.81	0.07	152.19	< 0.001	2.24 (1.97–2.55)
Clindamycin	0.54	0.12	21.09	< 0.001	1.71 (1.36–2.15)
Third-generation cephalosporins	− 0.35	0.13	7.12	0.008	0.71 (0.55–0.91)
Cephamycins	− 0.39	0.09	20.52	< 0.001	0.68 (0.57–0.8)
Parenteral nutrition	0.23	0.07	10.72	0.001	1.26 (1.1–1.45)
Histamine type-2 (H2) receptor antagonists	− 0.44	0.14	9.59	0.002	0.64 (0.49–0.85)
Gastric mucosal protective agents	− 0.29	0.10	8.32	0.004	0.75 (0.61–0.91)
Urinary catheterization	0.42	0.08	26.10	< 0.001	1.53 (1.3–1.8)
Nasogastric tube feeding	0.75	0.09	65.38	< 0.001	2.11 (1.76–2.52)
Fiberoptic bronchoscopy	0.35	0.09	15.00	< 0.001	1.42 (1.19–1.69)
Cardiopulmonary bypass	1.02	0.29	12.73	< 0.001	2.77 (1.58–4.84)
Gastroscopy and duodenoscope	− 0.37	0.13	8.10	0.004	0.69 (0.53–0.89)
Female	− 0.34	0.06	35.43	< 0.001	0.71 (0.64–0.8)
Surgery	− 0.87	0.07	152.15	< 0.001	0.42 (0.37–0.48)
Age	0.01	0.00	7.88	0.005	1.01 (1–1.01)
aCCI	0.09	0.02	30.03	< 0.001	1.09 (1.06–1.13)
Mechanical ventilation	0.48	0.09	28.47	< 0.001	1.62 (1.36–1.93)

analysis. Therefore, ICU admission and sputum suctioning were removed based on clinical experience.

The independent risk factors of CSKP infection included β-lactam/β-lactamase inhibitors use (OR: 2.24, 95% CI: 1.97–2.55; $P < 0.001$), clindamycin use (OR: 1.71, 95% CI: 1.36–2.15; $P < 0.001$), parenteral nutrition (OR: 1.26, 95% CI: 1.10–1.45; $P = 0.001$), urinary catheterization (OR: 1.53, 95% CI: 1.30–1.80; $P < 0.001$), nasogastric tube feeding (OR: 2.11, 95% CI: 1.76–2.52; $P < 0.001$), fiberoptic bronchoscopy (OR: 1.42, 95% CI: 1.19–1.69; $P < 0.001$), cardiopulmonary bypass (OR: 2.77, 95% CI: 1.58–4.84; $P < 0.001$), age (OR: 1.01, 95% CI: 1.00–1.01; $P = 0.005$), aCCI (OR: 1.09, 95% CI: 1.06–1.13; $P < 0.001$), and mechanical ventilation (OR: 1.62, 95% CI: 1.36–1.93; $P < 0.001$).

The preventive factors of CSKP infection included penicillin use (OR: 0.46, 95% CI: 0.27–0.79; $P = 0.005$), quinolones use (OR: 0.66, 95% CI: 0.57–0.76; $P < 0.001$), third-generation cephalosporin use (OR: 0.71, 95% CI: 0.55–0.91; $P = 0.008$), cephamycins use (OR: 0.68, 95% CI: 0.57–0.80; $P < 0.001$), H2 receptor antagonists use (OR: 0.64, 95% CI: 0.49–0.85; $P = 0.002$), sucralfate (OR: 0.75, 95% CI: 0.61–0.91; $P = 0.004$), gastroscopy and duodenoscope (OR: 0.69, 95% CI: 0.53–0.89; $P = 0.004$), female (OR: 0.71, 95% CI: 0.64–0.80; $P < 0.001$), and surgery (OR: 0.42, 95% CI: 0.37–0.48; $P < 0.001$).

Comparing the two case-control studies to identity risk factors of carbapenem resistance in *K. pneumoniae*

Statistically significant factors in the multivariate analysis of the CRKP-case and the CSKP-case groups represent risk factors for *K. pneumoniae* infection. Factors that were statistically significant in the multivariate analysis of the CRKP-case-control study but not in the CSKP-case-control study were risk factors for carbapenem resistance in *K. pneumoniae*. In contrast, factors that were statistically significant in the multivariate analysis of the CSKP-case-control study but not in the CRKP-case-control study were risk factors for CSKP infection (Table 5).

Discussion

For studies of risk factors for CRKP infection, the selection of the control group is critical to generate correct conclusions and needs to represent the source population of CRKP cases. Many studies selected CSKP cases as the controls [13–20], which may introduce a considerable selection bias because CSKP infection only accounts for a small number of hospitalized cases, which are not representative. Therefore, the OR obtained does not reflect the true situation. In addition, there is another important bias commonly found in studies of risk factors of infections due to antimicrobial resistant pathogens. CSKP may not be detected in the inpatients using carbapenems as CSKP is susceptible to and would be killed by carbapenems. As a consequence, killing those susceptible bacteria may lead to the overgrowth of CRKP in the presence of selective pressure. Using CSKP cases as the controls may therefore result in an overestimation of the effect of carbapenem use. Alternatively, a few studies have used patients not infected with CRKP as the controls [21–27]. However, there are two effects in such a scenario, *K. pneumoniae* infection and carbapenem resistance of *K. pneumoniae*, and these two effects cannot be separately analyzed in these studies.

Therefore, we adopted a case-case-control study to select comparable controls from inpatients for the patients

Table 5 Risk factors comparing the two case-control studies

Classification	Multivariate analysis for CRKP	Multivariate analysis for CSKP
Risk factors for resistance to carbapenem of *K. pneumoniae*	ICU admission respiratory failure admission from the Emergency imipenem	
Risk factors for *K. pneumoniae* infection	aCCI	aCCI
Risk factors for CSKP infection		β-lactam/β-lactamase inhibitors Clindamycin Parenteral nutrition Urinary catheterization Nasogastric tube feeding Fiberoptic bronchoscopy Cardiopulmonary bypass Age Mechanical ventilation

with CRKP/CSKP infection to identify the risk factors of CRKP/CSKP infection and directly compare the results of the two multivariate analyses to explore the factors associated with resistance to carbapenems in *K. pneumoniae*. Similarly, several studies have adopted case-case-control studies to analyze the risk factor of CRKP infection/colonization. However, in these studies, the same control group was commonly selected for the CRKP-case group and the CSKP-case group [28–31]. This may reduce the comparability between the cases and the controls as some matching conditions cannot be used, among which adjustment of the risk time is critical. For instance, the longer the patients stay in hospital, there is higher possibility for them to obtain CRKP infection. Therefore, it is necessary to ensure that the matched control and the case have at least the same exposure time and lengths of hospital stay prior to the identification of risk factors of CRKP/CSKP. Collectively, one critical matching condition is that the hospital stay of the control group is not less than the hospital stay of the case group before the examination.

Statistically significant factors identified in both multivariate analyses of the CRKP-case and the CSKP-case groups represent risk factors for *K. pneumoniae* infection. Factors that were statistically significant in the multivariate analysis of the CRKP-case-control study (i.e., Study 1) but not in the CSKP-case-control study (i.e., Study 2) are risk factors for carbapenem resistance in *K. pneumoniae*. In contrast, factors that were statistically significant in the multivariate analysis of the CSKP-case-control study but not in the CRKP-case-control study are risk factors for CSKP infection [32]. Our study identified that four risk factors, namely ICU admission, respiratory failure, admission from the Emergency, and imipenem use, were significant in the CRKP-case-control study but were not significant in the CSKP-case-control study, indicating that these were risk factors for *K. pneumoniae* resistance to carbapenem. In contrast, the use of first- and second-generation cephalosporins were the preventive factors for *K. pneumoniae* resistance to carbapenems.

Agreeing with many previous studies [33–36], ICU admission is an independent risk factor for CRKP infection. Respiratory failure is newly identified as an independent risk factor for CRKP, although several previous studies have shown that chronic obstructive pulmonary disease (COPD) is a risk factor for CRKP infection [37–40]. Patients with respiratory failure usually have more serious disease conditions than those with COPD and are commonly managed in ICU as they often require mechanical ventilation and therefore are more likely to be infected/colonized with CRKP in the airway. In this study, half of the CRKP isolates were recovered from lower respiratory specimen such as generic sputum ($n = 216$), tracheal secretion ($n = 28$), bronchoalveolar lavage ($n = 4$), and bronchial washings fluid($n = 4$), suggesting that it is necessary to pay special attention to these underlying diseases and the operations involved in the respiratory tract.

Studies of the relationship between admission from the Emergency and CRKP infection are scarce, and only three relevant reports are available [38, 41, 42]. However, multivariate analysis was not performed significantly in any of them. An additional study has shown that admission from the Emergency is a risk factor for patients with positive CRKP screening results [43]. Nevertheless, the study has focused on the population undergoing active screening only. To the best of our knowledge, we discovered for the first time that admission from the Emergency is a risk factor for CRKP infection. The common problems in the emergency departments in China include crowdedness with patients, slow patient turnover, heavy workload of medical staff, limited hospital-bed spacing due to extra beds, and inadequate implementation of infection control measures (e.g., hand hygiene and environmental cleaning), which may lead to the cross-transmission of CRKP within the emergency department. In addition, many patients are transferred to the inpatient departments to continue hospitalization after being admitted to the emergency department, which also increases CRKP transmission to other wards. Adopting prevention and control measures and strategies against infection in the emergency department requires sufficient attention to control CRKP transmission within the department.

In this study, carbapenem use was a risk factor for *K. pneumoniae* resistance to carbapenems, in consistent with previous studies [44–46]. As mentioned above, our study adopted a case-case-control study and compared with other studies using CSKP as the control group; our results truly reflected the effect of carbapenem use. In addition, most of the previous studies focused on analyzing carbapenems but not the specific agent. Univariate analysis of our CRKP-case-control study showed that imipenem and meropenem use were risk factors. However, our multivariate analysis of imipenem and meropenem identified that imipenem use was an independent risk factor for *K. pneumoniae* resistance to carbapenems. The difference in patient's characteristics of those treated with imipenem or meropenem is summarized in Supplementary Table S1. Patients treated with imipenem had a higher proportion of pancreatitis (35.57% vs. 12.55%, $P < 0.001$) and a lower proportion of ICU admission (45.12% vs. 67.21%, $P < 0.001$) than those treated with meropenem. As the retrospective nature of this study with intrinsic uncontrollable bias, the exact reason why imipenem but not meropenem for carbapenem resistance in *K. pneumoniae* is not clear and warrants further prospective studies.

Charlson Comorbidity Index reflects the severity of the patient's condition. Patients with high severity of illness are more likely to develop CRKP infection, which is consistent with previous studies [16, 47]. An unexpected finding is that the use of the first- and second-generation cephalosporins

was a preventive factor for *K. pneumoniae* resistance to carbapenems. However, this has also been reported in a previous study [48]. It is likely that patients who received the first- and second-generation cephalosporins were in milder disease conditions and therefore have lower risks to be infected with CRKP. It is also likely that some patients may receive the first- and second-generation cephalosporins for prophylaxis rather than treatment and these patients hospitalized for surgery usually had shorter the hospital stays, which reduced the risks of CRKP infection.

This study has a few limitations. First, as a single-center study, the generation of our study is intrinsically compromised. Nevertheless, our study has a large sample size, including 494 cases in the CRKP-case-control study and 2429 cases in the CSKP-case-control study, far exceeding the numbers of previous case-control studies. The large sample size may help us to generate robust findings. Second, using a retrospective design, our study may have selection biases. However, our study included all of the CRKP/CSKP inpatients during the observation period, and only less than 10% of the cases were lost in matching, which effectively reduced the selection bias. Third, the analysis in this study was not stratified according to infection types and therefore could not capture risk factors specific for certain infections. Fourth, the clinical microbiology lab in our hospital has not routinely detected the production of carbapenemases for clinical isolates of the Enterobacterales. Notably, we could not exclude that there were some carbapenemase-producing isolates exhibiting susceptible to carbapenems and might have been regarded as CSKP in this study. We also did not detect the genes and carbapenemase producers for carbapenem resistance in CRKP. We are therefore unable to examine differences in the risk factors between different resistance genotypes for the perspective of molecular epidemiology. Fifth, data were collected from 2016 to 2018. While epidemiology has changed in the last 4 years, particularly due to COVID-19 pandemics. However, it is a new stage for the prevention and control of COVID-19 in China in 2023, and we believe that the research will still be representative in 2023. Finally, the information about the exact history of patient's hospitalization was lacking due to the absence of an effective system for sharing patient records between hospitals here.

In conclusion, we performed a case-case-control study and identified risk factors for resistance to carbapenems in *K. pneumoniae*, which comprise ICU admission, respiratory failure, admission from the Emergency, and administration of imipenem.

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Author contribution Wenzhi Huang, Zhiyong Zong, and Wei Zhang contributed to study conception and design. Yuhua Deng, Shichao Zhu, and Jingwen Li contributed to acquisition of data. Wenzhi Huang and Fu Qiao analyzed and interpreted data. Wenzhi Huang, Zhiyong Zong, and Wei Zhang drafted the manuscript. All authors revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability The datasets during the current study available from the corresponding author on reasonable request.

Declarations

Consent for publication All authors gave their consent for publication.

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