RESEARCH ARTICLE

Risk factors for multidrug-resistant and carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in Shanghai: A five-year retrospective cohort study

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Abstract

Background

Multidrug-resistant *Klebsiella pneumoniae* (MDRKP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bloodstream infections (BSIs) account for significant mortality and healthcare costs.

Objectives

To investigate risk factors for MDRKP and CRKP BSIs

Methods

A retrospective analysis of inpatients with *Klebsiella pneumoniae* bloodstream infections (KP BSIs) was conducted in a tertiary care hospital in Shanghai from 01/01/2018–31/12/2022. Temporal distribution of mortality and department distribution of KP BSIs were assessed. A generalized linear model was used to determine risk factors for MDRKP and CRKP BSIs.

Results

A total of 379 inpatients with KP BSIs were included. The proportion of death for KP BSIs, MDRKP BSIs and CRKP BSIs gradually decreased since 2020. Majority of both MDRKP and CRKP BSIs patients were from Intensive Care Unit (ICU), burn unit, hematology and pancreatic surgery. Genitourinary disorders, invasive ventilator, history of antibiotic use, and carbapenem use were independently associated with MDRKP BSIs. Respiratory disease, gastric tubes, carbapenem use and its quantity were independently associated with CRKP BSIs.

Conclusions

ICU, burn unit, hematology and pancreatic surgery are common departments for MDRKP and CRKP BSIs. Genitourinary disorders, respiratory disorders, invasive ventilator, gastric tubes and antibiotic use (carbapenems in particular) within 90 days prior to onset of BSIs are independently associated with MDRKP and CRKP BSIs.

Introduction

Bloodstream infections (BSIs) are strongly associated with increased morbidity and mortality, prolonged hospital stays, and high healthcare costs [1]. *Klebsiella pneumoniae* (KP) is the second most common cause of Gram-negative BSIs [2]. *Klebsiella pneumoniae* bloodstream infections (KP BSIs) is a clinical healthcare concern receiving significant attention worldwide. Incidence of KP BSIs has been gradually increasing in recent years [3]. Moreover, KP BSIs resulted in high mortality rates ranged between 20% and 40% [4]. In previous study, we found the 30-day crude mortality rate of KP BSIs in East China has reached 26.39% [5].

It has been reported in the literature that the drug-resistant phenotype of the pathogen is strongly associated with bad prognosis [6,7]. Our previous study also showed that mortality and medical costs of patients with MDRKP (multidrug-resistant *Klebsiella pneumoniae*) or CRKP (carbapenem-resistant *Klebsiella pneumoniae*) BSIs were significantly higher than those of patients with non-MDR/CR BSIs [5]. Moreover, the proportion of MDRKP BSIs and CRKP BSIs among KP BSIs in Shanghai was as high as 66.49% and 51.98%, respectively [5]. Therefore, investigating the risk factors for MDRKP and CRKP BSIs is important for the prevention and control of KP BSIs.

Previous studies have explored risk factors for CRKP BSIs while very few studies have reported risk factors for MDRKP BSIs. Therefore, it is necessary to update risk factors investigation for MDRKP and CRKP BSIs. For this reason, we retrospectively analyzed risk factors for patients with MDRKP and CRKP BSIs in a large tertiary hospital in East China with a high bacterial resistance rate.

Materials and methods

Study design and setting

We used medical record data between 01/01/2018 and 31/12/2022 abstracted from Hospital Information System of Ruijin Hospital which is developed by the Computer Center of Ruijin Hospital. These data were retrospectively assessed for research purpose from 30/09/2023–31/10/2023. Ruijin Hospital is a tertiary-level hospital with 3,697 beds in East China. Ruijin Hospital has an annual outpatient and emergency care volume of approximately 5.36 million, with a total of nearly 150,000 discharges per year. All consecutively hospitalized patients with KP BSIs during the study period were included. Patients with at least one result of KP in blood culture were included in our study. Only the first episode of KP BSIs per patient was included. Patients with the following conditions were excluded: (i) positive culture results considered as

contaminants; (ii) incomplete/inaccurate medical records; (iii) patients insisted on discharge from hospital against medical advice.

Ethics approval and consent to participate

The study was approved by the ethics committee of Ruijin Hospital (No. KY2023–083) on 13/07/2023. This is an observational retrospective study and all the data were obtained from medical record systems and analyzed anonymously, so the committee waived informed consent. The study was conducted in accordance with the Declaration of Helsinki. We investigated incidence, antimicrobial resistance, crude 30-day mortality rate, and risk factors for crude 30-day mortality of KP BSIs using the same dataset of this manuscript (S1 File) and published the findings in 2024 [5]. In this study, we investigated temporal distribution of proportion of KP BSIs attributed deaths, department distribution of KP BSIs and risk factors for MDRKP BSIs and CRKP BSIs which are entirely different research questions. There is no overlap in research content of the two studies.

Definitions

KP BSIs were defined as blood cultures positive for KP and accompanied by clinical signs and symptoms of infection [8]. The presence of KP BSIs was defined as the first positive blood culture of KP. Proportion of death for KP BSIs was defined as the number of KP BSIs attributed deaths per 100 patients with KP BSIs. Cases were defined as patients diagnosed with KP BSIs. MDR was defined as acquired insensitivity to at least one of three or more antimicrobial classes [9]. CR was defined as resistance to any carbapenems [10].

Data collection

The following clinical information about the patient was extracted from the hospital's electronic medical record system: gender, age, department of admission, length of stay in ICU, length of hospitalization, underlying disease (malignancy, circulatory disease, endocrine disease, respiratory disease, genitourinary disease, gastrointestinal disease), history of invasive clinical procedures (surgery, paracentesis, arterial catheters, central venous catheters, invasive ventilators, urinary catheters, gastric catheters, drainage tubes), specific treatments (glucocorticosteroids, immunosuppressive agents, radiotherapy and chemotherapy), data on antibiotic therapy. Definitions of the variables collected are provided in S1 Table. All the datasets used and/or analyzed during the current study are listed in S1 File.

Microbiology

The KP isolates were all characterized using MALDITOF MS (bioMérieux, Marcy l'Etoile, France), and drug sensitivity was tested using VITEK®2 (bioMérieux, Marcy l'Etoile, France). Interpretation of drug sensitivity tests was in accordance with the 2022 Clinical and Laboratory Standard Institute (CLSI) standard [11].

Statistical analysis

Continuous variables that fit normal distribution were expressed as mean and standard deviation (SD), and continuous variables that did not fit normal distribution were expressed as median and interquartile range (IQR). Categorical variables were compared using the chi-square test and Fisher's exact test. A generalized linear model was used to determine risk factors for infection. In conducting the risk factor analysis, univariate analysis was performed first. Correlations and relevant interactions between variables with $P < 0.05$ in univariate analysis were examined. After excluding highly correlated variables (correlation coefficients ≥0.70), the remaining variables were considered for inclusion in the multiple logistic regression model and screened using the Lease Absolute Shrinkage and Selection Operator (LASSO) penalization method (used to select the variables with λ = lambda.1se, which is the cross-validation error plus a standard error minimized by λ) [12]. Selected variables

were included in the final multiple logistic regression model to determine their independent associations. The strength of these associations was determined by calculating odds ratio (OR) and 95% confidence interval (95% CI). All analyses were conducted using R version 4.2.1. To test the stability of the final multiple logistic regression model, variables were sequentially removed from the model and the significance of the remaining variables was checked [13]. Hosmer-Lemeshow test was performed to evaluate the goodness of fit of the regression models. $P<0.05$ was considered statistically significant.

Results

Trends in the proportion of death for MDRKP BSIs and CRKP BSIs

A total of 379 eligible subjects were included in the study. Among 379 patients with KP BSIs, there were 252 (66.5%) MDRKP cases and 197 (52.0%) CRKP cases. There was a total of 119 deaths during admission, with the proportion of death was 40.9% (103/252) in the MDR group, 12.6% (16/127) in the non-MDR group, 47.2% (93/197) in the CR group, and 14.3% (26/182) in the non-CR group, with a statistically significant difference between resistant group and non-resistant group (both $P<0.001$). The proportion of death for KP BSIs increased from 32.4% in 2018 to 36.0% in 2019, followed by a gradual decrease. The proportion of death for MDR group increased from 43.1% in 2018 to 52.2% in 2019, followed by a gradual decrease. The proportion of death for the non-MDR group gradually increased from 8.7% in 2018 to 16.2% in 2022. The proportion of death for the CR and non-CR groups increased from 48.7% and 14.3% in 2018 to 56.8% and 15.8% in 2019, respectively, and then gradually decreased. The details are shown in Fig 1.

Distribution of departments

KP BSIs were predominantly distributed in ICU, pancreatic surgery, burn unit, and hematology (23.0%, 14.2%, 12.1%, and 10.8%, respectively, as shown in Fig 2A). MDRKP BSIs were predominantly distributed in the ICU (31.0%), followed by
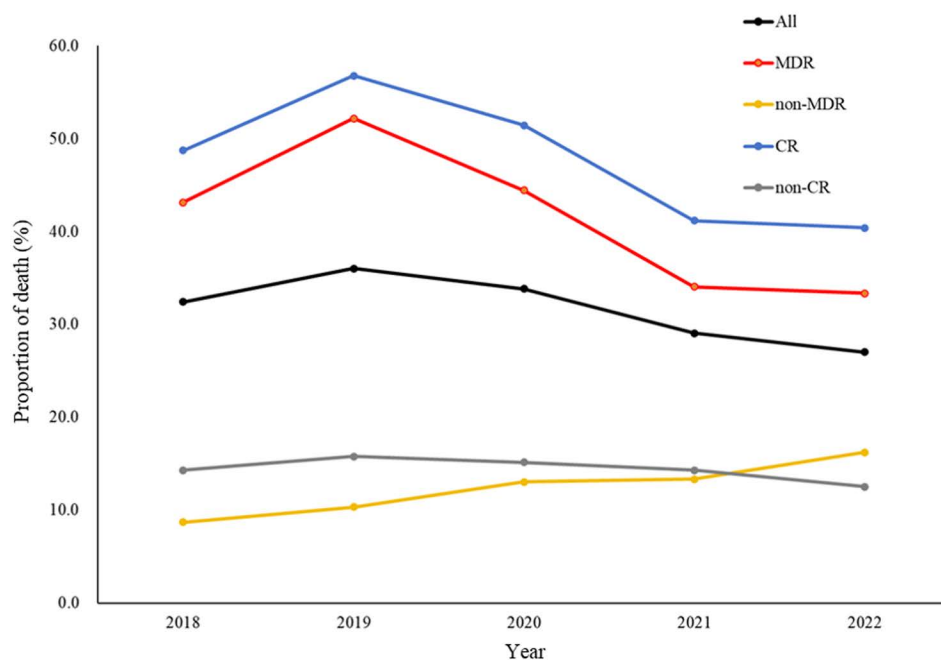

Fig 1. Proportion of death among 379 inpatients with *Klebsiella pneumoniae* bloodstream infections (KP BSIs) from 2018 to 2022 by antimicrobial resistance phenotypes. ALL, All KP BSIs; MDR, multidrug resistant; non-MDR, non-multidrug resistant; CR, carbapenem resistant; non-CR, non-carbapenem resistant.

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burn unit (17.9%), hematology (11.5%), and pancreatic surgery (10.7%), details of which were shown in Fig 2B. Department distribution of CRKP BSIs was as well ICU (35.0%), followed by burn unit, hematology, and pancreatic surgery (22.3%, 11.2%, and 8.6%, respectively), as shown in detail in Fig 2C.

Risk factors for MDRKP BSIs and CRKP BSIs

Univariate analysis showed that age, male, some medical exposures within 90 days prior to the onset of BSIs, respiratory disease, genitourinary disease, gastrointestinal disease, some invasive procedures, use of some drugs within 90 days prior to diagnosis of BSIs were associated with MDRKP BSIs (Table 1). Multiple logistic regression analysis showed that genitourinary disease, invasive ventilator, history of antibiotic use in the 90 days prior to the diagnosis of BSIs, and carbapenem usage were independent risk factors for MDRKP BSIs (Table 1). The result of Hosmer-Lemeshow test ($\chi^2 = 8.78$, $P = 0.553$) was indicative of good fit. Univariate analyses showed that the factors associated with CRKP BSIs included age, male, some medical exposures within 90 days prior to the onset of BSIs, respiratory disease, gastrointestinal disease, some invasive procedures, use of some drugs within 90 days prior to diagnosis of BSIs (Table 2). Independent risk factors for CRKP BSIs were respiratory disease, indwelling gastric tube, and carbapenem use and quantity (Table 2). The result of Hosmer-Lemeshow test ($\chi^2 = 1.66$, $P = 0.948$) was indicative of good fit.

Discussion

To the best of our knowledge, this is the first report of a risk factor analysis of both MDRKP and CRKP BSIs in eastern China, a region with a high prevalence of drug-resistant and virulent isolates [14]. The proportion of death for both MDRKP BSIs and CRKP BSIs rose to high point in 2019 and showed a gradual trend of decreasing afterwards, which we hypothesize is related to the fact that under China's coronavirus disease 2019 (COVID-19) policy, all patients who tested positive for nucleic acid were transferred to sentinel hospital in a closed loop. As China's COVID-19 control policy has been downgraded, more local studies should also be conducted in the future to analyze the impact of COVID-19 pandemics on mortality of BSIs.

Our study showed that the distribution of MDRKP and CRKP BSIs was highest in the ICU, which is consistent with other studies [15,16]. Interestingly, our risk factor analysis showed that ICU admission 90 days prior to diagnosis and the number of ICU days were risk factors for MDRKP and CRKP BSIs. The high prevalence of MDRKP and CRKP BSIs in the ICU maybe due to the presence of multiple infections in critically ill patients, a high number of invasive maneuvers, and frequent use of advanced antibiotic drugs. ICU has been described as factories that generate, spread and amplify antimicrobial resistance [1,17,18]. Selection of resistant strains and new mutations due to frequent and inappropriate application of antimicrobials influence emergence and rapid spread of multidrug-resistant pathogens in ICU [18]. Moreover, CRKP could be detected in various equipment of ICU including beds, tables, floors and ventilators, significantly higher than that of ordinary wards [1]. Many previous studies have shown that ICU admission was a risk factor for CRKP BSIs [15,19–22]. However, ICU admission 90 days before diagnosis was not an independent risk factor in the multiple logistic regression analysis, which may be influenced by other confounding factors. In addition, MDRKP and CRKP BSIs were higher in burn units and hematology. Burn patients are more likely to undergo invasive procedures and are more susceptible to infection, owing to burn wounds are favorable sites for bacterial colonization prior to healing [23]. Hematology inpatients with underlying hematologic malignancies, radiation and chemotherapy, neutropenia, gastrointestinal mucositis, and prolonged hospitalization are favorable conditions for the spread of MDRKP and CRKP BSIs [24].

As reported in other studies, age, male are risk factors for CRKP BSIs [1,16]. Our study found that age and male were risk factors for MDRKP BSIs. In addition, time at risk and length of hospitalization were risk factors for MDRKP and CRKP BSIs. The probability of bacterial infections developed from colonization rises as the length of hospitalization increases. Prolonged hospitalization has been reported to be a risk factor for colonization by antibiotic-resistant bacteria [25]. At the
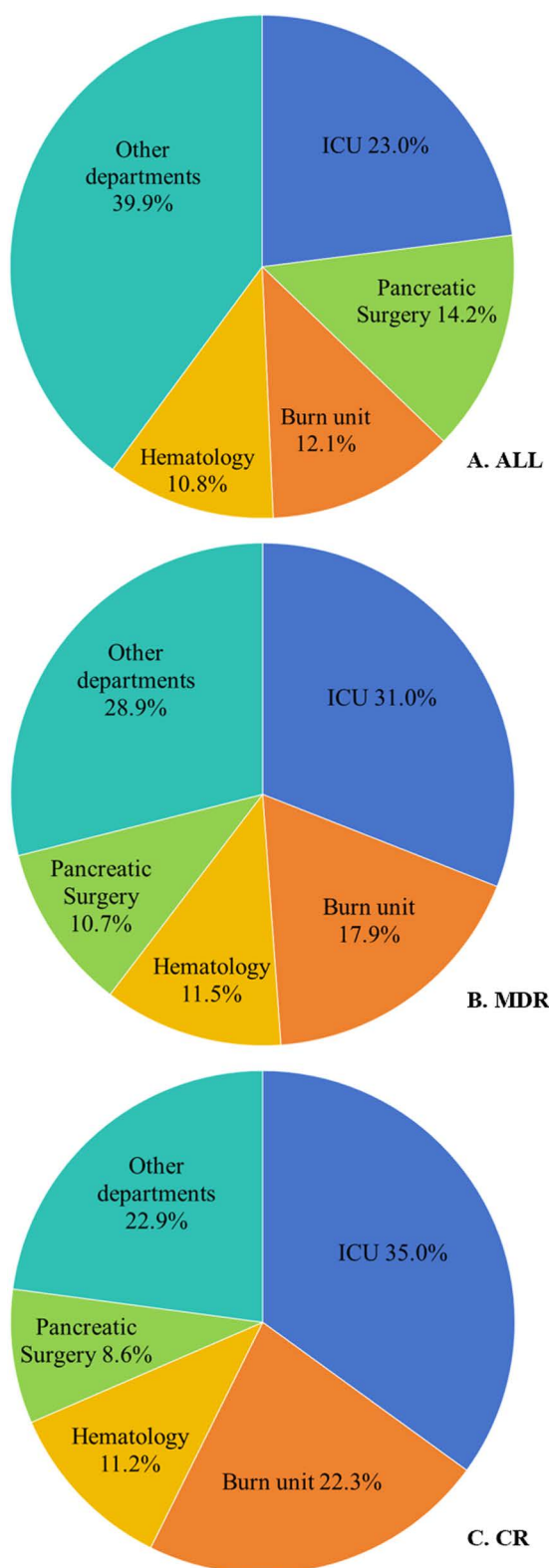
Fig 2. Distribution of departments of 379 inpatients with *Klebsiella pneumoniae* bloodstream infections (KP BSIs) by antimicrobial resistance phenotypes. ALL, all KP BSIs; MDR, multidrug resistant; CR, carbapenem resistant.

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Table 1. Risk factors for multidrug-resistant *Klebsiella pneumoniae* bloodstream infections (MDRKP BSIs).

Characteristics	MDR (%) (N = 252)	non-MDR (%) (N = 127)	Univariate		Multiple	
			OR (95%CI)	P	aOR (95%CI)	P
Age (years), median (IQR)	61.50 (49.00-70.00)	64.00 (55.00-71.50)	0.99 (0.97-1.00)	0.042		
Gender, male	189 (75.00)	81 (63.78)	1.70 (1.07-2.70)	0.023		
Smoking	45 (17.86)	14 (11.02)	1.75 (0.94-3.44)	0.086		
Alcohol drinking	37 (14.68)	11 (8.66)	1.81 (0.92-3.86)	0.100		
Healthcare exposure						
Time at risk (days), median (IQR)	16.00 (7.00-31.00)	6.00 (1.00-13.00)	1.03 (1.02-1.05)	0.000		
Length of hospital stay (days), median (IQR)	19.00 (8.75-37.00)	10.00 (3.00-21.50)	1.02 (1.01-1.03)	0.000		
ICU stay	75 (29.76)	17 (13.39)	2.74 (1.57-5.02)	0.000		
Length of ICU stay (days), median (IQR)	0.00 (0.00-7.25)	0.00 (0.00-0.00)	1.02 (1.00-1.04)	0.027		
Comorbidities						
Chemotherapy or radiotherapy	26 (10.32)	17 (13.39)	0.74 (0.39-1.45)	0.375		
Malignancy	49 (19.44)	25 (19.69)	0.98 (0.58-1.70)	0.956		
Organic	23 (9.13)	12 (9.45)	0.96 (0.47-2.06)	0.919		
Hematology	28 (11.11)	13 (10.24)	1.10 (0.56-2.26)	0.796		
Disease of the circulatory system	94 (37.30)	44 (34.65)	1.12 (0.72-1.76)	0.612		
Hypertension	77 (30.56)	40 (31.50)	0.96 (0.61-1.52)	0.852		
Cerebrovascular disease	12 (4.76)	9 (7.09)	0.66 (0.27-1.65)	0.353		
IHD	27 (10.71)	10 (7.87)	1.40 (0.68-3.14)	0.381		
Endocrine, nutritional and metabolic diseases	63 (25.00)	35 (27.56)	0.88 (0.54-1.43)	0.591		
Diabetes mellitus	47 (18.65)	32 (25.20)	0.68 (0.41-1.14)	0.140		
Respiratory diseases	35 (13.89)	6 (4.72)	3.25 (1.43-8.79)	0.010		
Diseases of the genitourinary system	36 (14.29)	5 (3.94)	4.07 (1.70-12.07)	0.004	3.43 (1.27-11.06)	0.023
Diseases of the gastrointestinal system	71 (28.17)	53 (41.73)	0.55 (0.35-0.86)	0.008		
Invasive procedures						
Surgery	167 (66.27)	70 (55.12)	1.60 (1.03-2.48)	0.035		
Paracentesis	92 (36.51)	20 (15.75)	3.08 (1.82-5.41)	0.000	1.89 (0.99-3.70)	0.057
AC	52 (20.63)	13 (10.24)	2.28 (1.22-4.53)	0.013		
Days of AC	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.04 (1.00-1.09)	0.090		
CVC	181 (71.83)	60 (47.24)	2.85 (1.83-4.45)	0.000		
Days of CVC	7.00 (0.00-21.25)	0.00 (0.00-5.50)	1.03 (1.02-1.05)	0.000		
Invasive ventilator	110 (43.65)	17 (13.39)	5.01 (2.9-9.11)	0.000	2.02 (1.02-4.12)	0.047
Days of indwelling invasive ventilator	0.00 (0.00-7.00)	0.00 (0.00-0.00)	1.21 (1.11-1.34)	0.000		
Urinary catheter	158 (62.70)	45 (35.43)	3.06 (1.97-4.80)	0.000		
Days of indwelling urinary catheter	2.00 (0.00-15.00)	0.00 (0.00-2.00)	1.06 (1.03-1.09)	0.000		
Gastric tube	108 (42.86)	19 (14.96)	4.26 (2.51-7.55)	0.000	1.38 (0.71-2.73)	0.348
Days of indwelling gastric tube	0.00 (0.00-13.00)	0.00 (0.00-0.00)	1.05 (1.02-1.08)	0.001		
Drainage tube	130 (51.59)	38 (29.92)	2.50 (1.60-3.96)	0.000		
Days of indwelling drainage tube	1.00 (0.00-15.00)	0.00 (0.00-1.50)	1.03 (1.01-1.06)	0.001		
Drug usage						
Corticosteroids	153 (60.71)	35 (27.56)	4.06 (2.57-6.52)	0.000	1.41 (0.78-2.54)	0.250
Immunosuppressor	24 (9.52)	9 (7.09)	1.38 (0.64-3.22)	0.429		
Antibiotics	223 (88.49)	71 (55.91)	6.07 (3.63-10.33)	0.000	1.94 (1.00-3.80)	0.049
Combination therapy	204 (80.95)	44 (34.65)	8.02 (4.99-13.1)	0.000		
Glycopeptides	117 (46.43)	21 (16.54)	4.37 (2.62-7.59)	0.000	1.27 (0.62-2.60)	0.514

(Continued)

Characteristics	MDR (%) (N = 252)	non-MDR (%) (N = 127)	Univariate		Multiple	
			OR (95%CI)	P	aOR (95%CI)	P
Quantity (DDD), median (IQR)	0.00 (0.00-5.00)	0.00 (0.00-0.00)	1.17 (1.09-1.28)	0.000		
Vancomycin	105 (41.67)	19 (14.96)	4.06 (2.39-7.20)	0.000		
Quantity (DDD), median (IQR)	0.00 (0.00-4.10)	0.00 (0.00-0.00)	1.17 (1.08-1.29)	0.000		
Oxyazolidinones						
Linezolid	59 (23.41)	5 (3.94)	7.46 (3.2-21.81)	0.000	2.61 (0.99-8.18)	0.069
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.28 (1.14-1.53)	0.001		
Carbapenems	168 (66.67)	32 (25.20)	5.94 (3.71-9.69)	0.000	1.23 (0.57-2.64)	0.602
Quantity (DDD), median (IQR)	3.92 (0.00-13.00)	0.00 (0.00-0.13)	1.16 (1.10-1.23)	0.000	1.05 (1.00-1.13)	0.050
Imipenem	106 (42.06)	27 (21.26)	2.69 (1.66-4.47)	0.000		
Quantity (DDD), median (IQR)	0.00 (0.00-6.00)	0.00 (0.00-0.00)	1.10 (1.05-1.17)	0.000		
Meropenem	96 (38.10)	8 (6.30)	9.15 (4.54-21.13)	0.000		
Quantity (DDD), median (IQR)	0.00 (0.00-3.08)	0.00 (0.00-0.00)	1.30 (1.15-1.53)	0.000		
Cephalosporins	114 (45.24)	36 (28.35)	2.09 (1.33-3.33)	0.002		
Quantity (DDD), median (IQR)	0.00 (0.00-3.06)	0.00 (0.00-1.00)	1.05 (1.01-1.10)	0.040		
β-lactam/β-lactamase inhibitor combinations	32 (12.70)	11 (8.66)	1.53 (0.77-3.29)	0.245		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.00 (0.97-1.04)	0.921		
Piperacillin-tazobactam	15 (5.95)	6 (4.72)	1.28 (0.50-3.65)	0.623		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.99 (0.93-1.04)	0.628		
Cefoperazone-sulbactam	16 (6.35)	5 (3.94)	1.65 (0.63-5.15)	0.337		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.02 (0.97-1.10)	0.496		
Fluoroquinolones	57 (22.62)	10 (7.87)	3.42 (1.75-7.35)	0.007		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.09 (1.03-1.18)	0.020		

same time, infections with drug-resistant bacteria make the patient's condition more complex and more difficult to treat, and ultimately lead to longer hospital stays.

Among the comorbidities, respiratory and genitourinary diseases were independent risk factors for CRKP BSIs and MDRKP BSIs, respectively. Most of the respiratory diseases are lung infections in this study (29/41, 70.7%), and previous studies have reported a relationship between lung infections and CRKP BSIs [16]. Common respiratory operations for patients with respiratory diseases, such as tracheal intubation, sputum suction, and tracheoscopy often lead to damage of airway mucosa, allowing the bacteria colonizing the respiratory tract or the equipment to enter the bloodstream, which can increase the probability of BSI [15,16]. Likewise, common invasive operations for patients with genitourinary diseases such as indwelling urinary catheter and urologic surgical procedures could damage the urinary tract and increase the risk of BSIs [15]. Additionally, our study found that surgical procedures and indwelling urinary catheter were strongly associated with MDRKP and CRKP BSIs (Tables 1 and 2). These operations tend to increase opportunities of infection by breaching the mucosal barrier, allowing bacteria to cross the barrier into the bloodstream [1,6,15].

Interestingly, both univariate and multiple logistic regression analyses indicated antibiotic exposure as a risk factor. Antibiotic exposure usually leads to the emergence of drug-resistant bacteria, and antibiotic use alters the microbiome, resulting in dominance of drug-resistant KP [24,26]. Carbapenems are usually considered as a last resort to combat infections caused by multidrug-resistant bacteria. Our results also confirmed that the use of carbapenems and its quantity

Table 2. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections (CRKP BSIs).

Characteristics	CR (%) (N = 197)	non-CR (%) (N = 182)	Univariate OR (95%CI)	P	Multiple aOR (95%CI)	P
Age (years), median (IQR)	60.00 (48.00-70.00)	64.00 (55.00-72.00)	0.99 (0.97-1.00)	0.026		
Gender, male	151 (76.65)	119 (65.38)	1.74 (1.11-2.73)	0.016		
Smoking	36 (18.27)	23 (12.64)	1.55 (0.88-2.76)	0.132		
Alcohol drinking	31 (15.74)	17 (9.34)	1.81 (0.98-3.47)	0.064		
Healthcare exposure						
Time at risk (days), median (IQR)	17.00 (8.00-31.00)	7.00 (2.00-18.00)	1.01 (1.00-1.02)	0.011		
Length of hospital stay (days), median (IQR)	20.00 (9.00-37.00)	12.00 (3.00-26.75)	1.01 (1.00-1.02)	0.008		
ICU stay	69 (35.03)	23 (12.64)	3.73 (2.23-6.42)	0.000	1.45 (0.73-2.89)	0.288
Length of ICU stay (days), median (IQR)	0.00 (0.00-10.00)	0.00 (0.00-0.00)	1.02 (1.01-1.04)	0.007		
Comorbidities						
Chemotherapy or radiotherapy	19 (9.64)	24 (13.19)	0.70 (0.37-1.33)	0.279		
Malignancy	31 (15.74)	43 (23.63)	0.60 (0.36-1.01)	0.054		
Organic	13 (6.60)	22 (12.09)	0.51 (0.24-1.04)	0.069		
Hematology	18 (9.14)	23 (12.64)	0.70 (0.36-1.33)	0.275		
Disease of the circulatory system	77 (39.09)	61 (33.52)	1.27 (0.84-1.94)	0.261		
Hypertension	65 (32.99)	52 (28.57)	1.23 (0.80-1.91)	0.352		
Cerebrovascular disease	9 (4.57)	12 (6.59)	0.68 (0.27-1.64)	0.392		
Heart failure	7 (3.55)	7 (3.85)	0.92 (0.31-2.74)	0.880		
IHD	18 (9.14)	19 (10.44)	0.86 (0.43-1.71)	0.670		
Endocrine, nutritional and metabolic diseases	50 (25.38)	48 (26.37)	0.95 (0.60-1.51)	0.825		
Diabetes mellitus	38 (19.29)	41 (22.53)	0.82 (0.50-1.35)	0.438		
Respiratory diseases	32 (16.24)	9 (4.95)	3.73 (1.80-8.52)	0.001	3.39 (1.40-8.78)	0.009
Diseases of the genitourinary system	24 (12.18)	17 (9.34)	1.35 (0.70-2.63)	0.375		
Diseases of the gastrointestinal system	52 (26.40)	72 (39.56)	0.55 (0.35-0.84)	0.007		
Invasive procedures						
Surgery	132 (67.01)	105 (57.69)	1.49 (0.98-2.27)	0.062		
Paracentesis	71 (36.04)	41 (22.53)	1.94 (1.24-3.07)	0.004		
AC	46 (23.35)	19 (10.44)	2.61 (1.49-4.75)	0.001		
Days of AC	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.03 (1.00-1.07)	0.085		
CVC	146 (74.11)	95 (52.20)	2.62 (1.71-4.06)	0.000		
Days of CVC	8.00 (0.00-22.00)	1.00 (0.00-10.00)	1.01 (1.00-1.03)	0.007		
Invasive ventilator	100 (50.76)	27 (14.84)	5.92 (3.65-9.85)	0.000	1.82 (0.95-3.47)	0.069
Days of indwelling invasive ventilator	1.00 (0.00-9.00)	0.00 (0.00-0.00)	1.13 (1.08-1.19)	0.000		
Urinary catheter	135 (68.53)	68 (37.36)	3.65 (2.40-5.61)	0.000		
Days of indwelling urinary catheter	5.00 (0.00-17.00)	0.00 (0.00-2.00)	1.05 (1.03-1.08)	0.000		
Gastric tube	98 (49.75)	29 (15.93)	5.22 (3.25-8.60)	0.000	2.12 (1.15-3.90)	0.016
Days of indwelling gastric tube	0.00 (0.00-15.00)	0.00 (0.00-0.00)	1.06 (1.04-1.09)	0.000		
Drainage tube	108 (54.82)	60 (32.97)	2.47 (1.63-3.76)	0.000		
Days of indwelling drainage tube	1.00 (0.00-16.00)	0.00 (0.00-2.00)	1.03 (1.02-1.05)	0.000		
Drug usage						
Corticosteroids	128 (64.97)	60 (32.97)	3.77 (2.48-5.80)	0.000	1.36 (0.78-2.36)	0.276
Immunosuppressor	15 (7.61)	18 (9.89)	0.75 (0.36-1.54)	0.434		
Antibiotics	184 (93.40)	110 (60.44)	9.26 (5.06-18.22)	0.000		
Combination therapy	173 (87.82)	75 (41.21)	10.28(6.21-17.60)	0.000		

(Continued)

Table 2. (Continued)

Characteristics	CR (%) (N=197)	non-CR (%) (N=182)	Univariate		Multiple	
			OR (95%CI)	P	aOR (95%CI)	P
Glycopeptides	102 (51.78)	36 (19.78)	4.35 (2.77-6.96)	0.000		
Quantity (DDD), median (IQR)	0.25 (0.00-6.00)	0.00 (0.00-0.00)	1.09 (1.04-1.14)	0.000		
Vancomycin	91 (46.19)	33 (18.13)	3.88 (2.44-6.27)	0.000		
Quantity (DDD), median (IQR)	0.00 (0.00-5.00)	0.00 (0.00-0.00)	1.07 (1.03-1.13)	0.001		
Oxyazolidinones						
Linezolid	54 (27.41)	10 (5.49)	6.50 (3.33-13.96)	0.000	2.17 (0.98-5.08)	0.063
Quantity (DDD), median (IQR)	0.00 (0.00-1.50)	0.00 (0.00-0.00)	1.25 (1.14-1.41)	0.000		
Aminoglycosides	26 (13.20)	5 (2.75)	5.38 (2.19-16.20)	0.001		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.19 (1.06-1.46)	0.033		
Carbapenems	151 (76.65)	49 (26.92)	8.91 (5.64-14.32)	0.000	2.74 (1.43-5.23)	0.002
Quantity (DDD), median (IQR)	6.00 (0.25-15.00)	0.00 (0.00-0.75)	1.17 (1.13-1.23)	0.000	1.06 (1.01-1.12)	0.018
Imipenem	96 (48.73)	37 (20.33)	3.72 (2.38-5.93)	0.000		
Quantity (DDD), median (IQR)	0.00 (0.00-9.00)	0.00 (0.00-0.00)	1.15 (1.09-1.22)	0.000		
Meropenem	87 (44.16)	17 (9.34)	7.68 (4.43-14.01)	0.000		
Quantity (DDD), median (IQR)	0.00 (0.00-4.50)	0.00 (0.00-0.00)	1.17 (1.10-1.26)	0.000		
Cephalosporins	93 (47.21)	57 (31.32)	1.96 (1.29-3.00)	0.002		
Quantity (DDD), median (IQR)	0.00 (0.00-4.00)	0.00 (0.00-1.00)	1.06 (1.02-1.10)	0.008		
β-lactam/β-lactamase inhibitor combinations	25 (12.69)	18 (9.89)	1.32 (0.70-2.55)	0.392		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.00 (0.97-1.03)	0.930		
Piperacillin-tazobactam	10 (5.08)	11 (6.04)	0.83 (0.34-2.02)	0.681		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.98 (0.91-1.03)	0.503		
Cefoperazone-sulbactam	13 (6.60)	8 (4.40)	1.54 (0.63-3.97)	0.352		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.01 (0.97-1.07)	0.579		
Fluoroquinolones	45 (22.84)	22 (12.09)	2.15 (1.25-3.81)	0.007		
Quantity (DDD), median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.01 (0.98-1.04)	0.605		

OR (95%CI), odds ratio (95% confidence interval); aOR (95%CI), adjusted odds ratio (95% confidence interval); IQR, interquartile range; BSIs, bloodstream infections; CR, carbapenem resistant; non-CR, non-carbapenem resistant; IHD, ischemic heart disease; ICU, intensive care unit; AC, arterial catheter; CVC, central venous catheter; DDD, defined daily dose.

prior to BSIs were independent risk factors for CRKP BSIs. Carbapenem use induces the production of acquired *Klebsiella pneumoniae* carbapenemase (KPC), which is one of the main mechanisms of CRKP resistance [27]. Moreover, CRKP can be transmitted by drug-resistant plasmids, which can cause more widespread CRKP infections [28]. Similar to some previous reports [29,30], we also found that prior exposure to quinolones was also an important risk factor. This may be due to the fact that the plasmid-encoded quinolone resistance determinant gene is located on the KP plasmid containing the KPC gene [31]. Additionally, quinolone use may have reduced Oprd pore protein expression and caused upregulation of the multidrug efflux pump MexEF-OprN, which is also a mechanism of carbapenem resistance [32]. We identified glucocorticoids as a risk factor for CRKP BSIs and MDRKP BSIs, however, multiple logistic regression analysis indicated that they were not an independent predictor. Glucocorticoids are recognized as a marker of an immunocompromised state and are more susceptible to serious infections [33]. Unlike other studies, we found that combination antimicrobial therapy may be a risk factor for MDRKP and CRKP BSIs, and we hypothesize that this is because combination therapy increases bacterial resistance to antibiotics [34]. In addition, we found that previous use of glycopeptides and cephalosporins were risk factors for MDRKP and CRKP BSIs, which is consistent with other studies [1,6]. We found that prior use of linezolid may increase the risk of MDRKP and CRKP BSIs, although multifactorial analyses showed that it was not an independent risk

factor. This may be due to the fact that most of the patients with prior linezolid use in our study were concurrently using carbapenems and thus would have been skewed. And whether prior use of linezolid directly leads to increased infections with drug-resistant bacteria needs to be further investigated in the future.

This study has several limitations. First, this is a single-center retrospective investigation with a relatively limited sample size which may not fully represent the characteristics of inpatients from other regions in China. In the future, a large-scale prospective multicenter study is needed to validate the results and accordingly to enhance the generalizability and reliability of the findings. Second, data on environmental exposure such as contamination of KP on the surfaces of objects like hospital bed rail and stethoscope, and inpatient density of wards were not available. These factors might have had an impact on risk factors for MDRKP and CRKP BSIs. Future research should address these points. Additionally, the mechanisms of CRKP and MDRKP are complex and diverse, and the risk factors may vary with different resistant mechanisms. This study did not detect resistant mechanisms, and molecular and bioinformatics studies should be conducted in future studies to better understand the effect of resistance mechanisms on infections.

Our study sheds light on which inpatients are at high risk of acquiring MDRKP and CRKP BSIs. This may have important implications for clinical interventions and public health policies. First, the findings would guide clinicians to identify inpatients at high-risk of MDRKP and CRKP BSIs at an early stage and initiate prompt targeted infection control measures. Second, infection prevention strategies such as enhanced hand hygiene, environmental disinfection, and isolation protocols should be prioritized in the common departments of MDRKP and CRKP BSIs. Finally, the development of a screening or surveillance system for MDRKP and CRKP BSIs based on the findings might help to prevent and control MDRKP and CRKP BSIs.

Conclusions

Genitourinary disease, invasive ventilator, history of antibiotic use (carbapenems in particular) in the 90 days prior to the diagnosis of BSIs are independent risk factors for MDRKP BSIs, whereas independent risk factors for CRKP BSIs include respiratory disease, gastric tubes, and carbapenem use in the 90 days prior to the diagnosis of BSIs. ICU, burn unit, hematology and pancreatic surgery are common departments of MDRKP and CRKP BSIs. Pre-emptive identification and isolation measures among inpatients with these risk factors or from these departments would be a cost-effective way to identify, manage, and reduce the spread of MDRKP and CRKP BSIs.

Supporting information

S1 Table. Definitions of each variable included in risk factors analysis for multidrug-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections.
(DOCX)

S1 File. Dataset of clinical characteristics of 379 inpatients with *Klebsiella pneumoniae* bloodstream infections.
(XLSX)

Acknowledgments

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