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ORIGINAL RESEARCH

Risk Factors for Development and Mortality of Carbapenem-Resistant *Pseudomonas aeruginosa* Bloodstream Infection in a Chinese Teaching Hospital: A Seven-Year Retrospective Study

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Objective: *Pseudomonas aeruginosa* (*P. aeruginosa*) is a gram-negative opportunistic pathogen, which can cause acute and chronic infections, often resulting in high mortality. The aim of this study was to investigate the risk factors for the development and mortality of patients with carbapenem-resistant *P. aeruginosa* bloodstream infection (CRPA BSI).

Methods: A total of 112 patients with CRPA BSI and 112 patients with carbapenem-sensitive *P. aeruginosa* (CSPA) BSI were included from a Chinese teaching hospital from January 2017 to December 2023 in this retrospective cohort study. The detection rate, antimicrobial susceptibility of *P. aeruginosa* and clinical characteristics of these patients were investigated. Multivariable logistic regression analysis was used to identify risk factors for the development and outcomes of CRPA BSI.

Results: In the past 7 years, 7480 blood samples of *P. aeruginosa* were cultured in the hospital. The detection rates of CRPA, multidrug resistant *P. aeruginosa* (MDRPA), and difficult-to-treat resistant *P. aeruginosa* (DTRPA) BSI increased annually (26% to 47%, 10% to 36% and 5% to 15%, respectively). CRPA showed high resistance to conventional antibiotics. Chronic lung disease (OR 3.953, 95% CI 1.131–13.812), transplantation (OR 2.837, 95% CI 1.036–7.770), multi-organ failure (OR 4.815, 95% CI 1.949–11.894), pre-infection within CRPA (OR 9.239, 95% CI 3.441–24.803), and exposure to carbapenems within 90 days (OR 2.734, 95% CI 1.052 −7.106) were independent risk factors for the development of CRPA bacteremia. Sepsis or septic shock (OR 8.774, 95% CI 3.140–24.515, $p = 0.001$) were independent risk factors of mortality.

Conclusion: Chronic lung disease, transplantation, multi-organ failure, prior CRPA infection, and prior carbapenems exposure are independent risk factors for the development of CRPA bacteremia. Sepsis or septic shock increases 28-day mortality. To investigate the molecular mechanisms of carbapenem-resistance of *P. aeruginosa*, standardize antibiotic usage, and assess risk factors for the development and mortality of CRPA BSI are beneficial to control infection and reduce death.

Keywords: *Pseudomonas aeruginosa*, bloodstream infection, carbapenem-resistance, risk factors, mortality

Introduction

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative opportunistic pathogen that can cause acute and chronic infections in patients with cancer, cystic fibrosis, chronic obstructive pulmonary disease (COPD), burns, sepsis, trauma, or ventilator-associated pneumonia (VAP).[1–3] The pathogenesis of *P. aeruginosa* is complex, there is evidence showing that *P. aeruginosa* can secrete a variety of virulence factors (including LPS, 6 type secretion systems, pyocyanin, elastases, alkaline protease, biofilms and others) to adapt to the unfavorable environment of the host, which is responsible for the development of infection and disease.[4] In addition, host-pathogen interactions also play a role in the pathogenesis

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of disease. Of note, *P. aeruginosa* infection usually causes a high mortality and is an important cause of nosocomial infections.[5]

According to the China Antimicrobial Surveillance Network (CHINET) (http://www.chinets.com/) in 2023, *P. aeruginosa* ranks the fifth among clinically isolated pathogens following *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus*, and *Acinetobacter baumannii*, accounting for 7.8%. To date, the treatment for *P. aeruginosa* infection has been a challenge because *P. aeruginosa* rapidly acquires resistance to antibiotics.[6] Carbapenem was previously considered as the final resort for the treatment of *P. aeruginosa* infection. However, the widespread use of carbapenem has led to an increase in *P. aeruginosa* resistance, resulting in the emergence of carbapenem-resistant *P. aeruginosa* (CRPA). In 2017, the World Health Organization (WHO) designated CRPA as a priority pathogen.[7] In recent years, multidrug resistance (MDR) has increased all over the world and has been considered a threat to public health. Some studies have[8–11] reported the emergence of MDR pathogens of different origins, which increases the necessity of the proper use of antibiotics.

To date, few studies have reported the CRPA bloodstream infection (BSI) in Fujian, China. This study aimed to investigate the detection rate of CRPA BSI, antibiotic resistance, and risk factors for the development and mortality of CRPA BSI in a Chinese teaching hospital in Fujian in the past 7 years.

Materials and Methods

Patients and Study Setting

Our study was conducted at Fujian Medical University Union Hospital, a teaching hospital in Fuzhou, Fujian Province, China. It is renowned as one of the largest tertiary hospitals in China. The study was approved by the Ethics Committee of Fujian Medical University Union Hospital (2024KY138). We were dedicated to protecting patient data, and the confidentiality statement was outlined in the ethical review form. This study was a retrospective study, and did not disclose patients' information, did not interfere with the treatment, and did not increase the risk of patients. Thus, informed consent was not obtained.

Inclusion criteria: Clinical information was collected from the medical record system of patients whose blood cultures were positive for *P. aeruginosa* between January 1, 2017 and December 31, 2023. For patients with multiple positive blood cultures, only the first positive culture was selected.

Exclusion criteria: (1) Outpatients and individuals with incomplete medical records were excluded from this study. (2) Patients with bacteremia caused by multiple microorganisms were excluded from this study. (3) Patients aged < 18 years were excluded from this study. (4) Patients with catheter-associated bloodstream infection were excluded from this study.

A total of 112 patients with CRPA BSI were included in the final analysis. We selected an equal number of patients with carbapenem-sensitive *P. aeruginosa* (CSPA) BSI in the same year as the control group. If the number of CSPA patients in that year was insufficient, cases in neighboring years that met inclusion criteria were randomly selected as controls. Therefore, 112 patients with CSPA BSI were included in this study as a control group (Figure 1). Based on the power analysis, the minimum sample size for both the CRPA BSI and CSPA BSI groups was determined to be 68 patients per group. Therefore, the sample size in this study satisfied the necessary requirements, as detailed in Supplementary Data 1.

Data Collection

The following data were obtained from the electronic medical records of 224 patients, including age, sex, length of stay, number of days from hospitalization to positive culture, antimicrobial susceptibility, ward, underlying diseases, conditions before BSI (such as prior invasive procedures and/or devices), exposure to antibiotics within 90 days, and conditions after BSI (including laboratory examinations, therapeutic medication and outcomes at 28-days after bacteremia). For variables with data missing < 15%, we process the missing data through multiple interpolations. For variables with data missing value > 15%, these variables were excluded from the analysis.

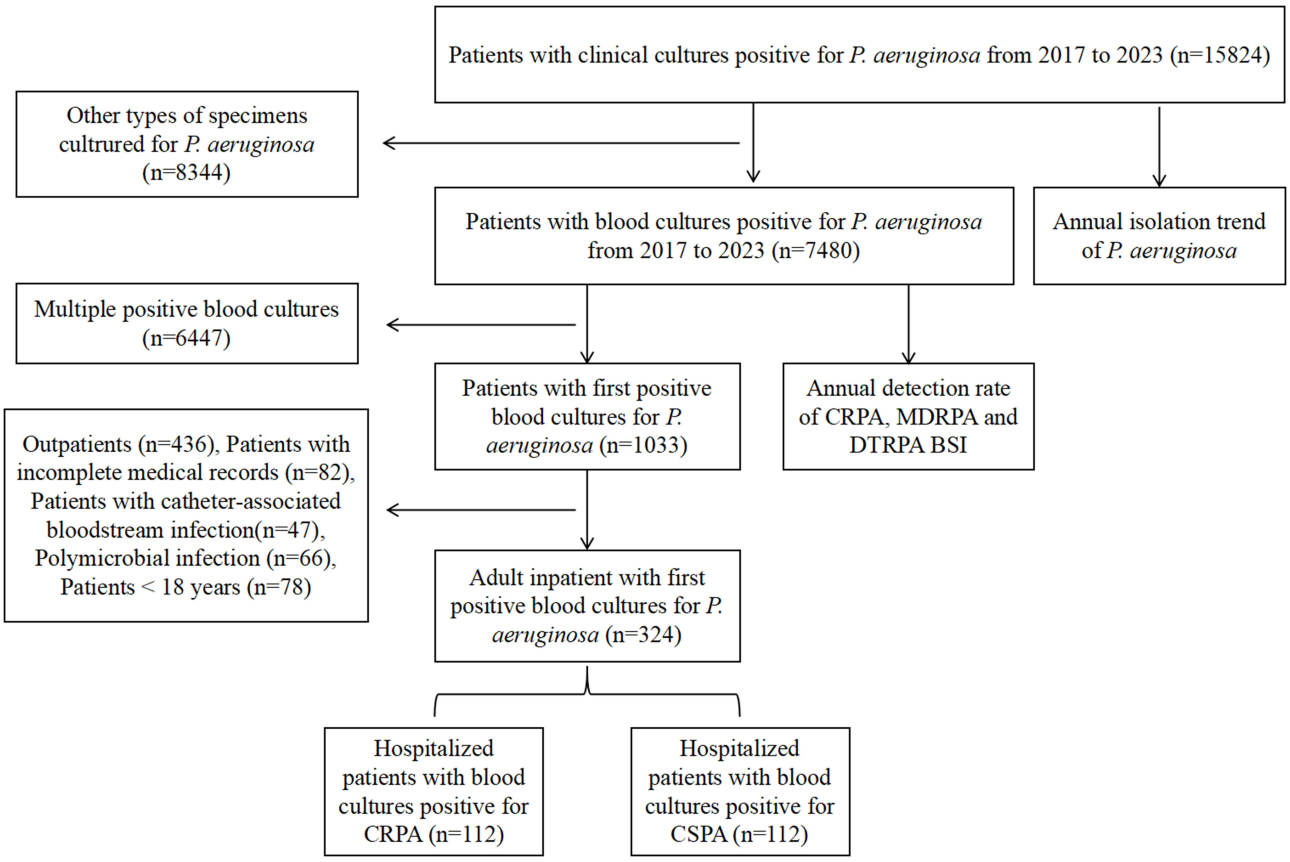

Figure 1 Patients screening flow chart.
Abbreviations: *P. aeruginosa, Pseudomonas aeruginosa* CRPA, carbapenem-resistant *P. aeruginosa*; CSPA, carbapenem-sensitive *P. aeruginosa*; BSI, bloodstream infection; MDRPA, multidrug resistance *P. aeruginosa*; DTRPA, difficult-to-treat resistance *P. aeruginosa*.

Definitions

According to Clinical and Laboratory Standards Institute (CLSI) guideline,[12] CRPA was defined as resistance to imipenem or meropenem (minimum inhibitory concentration (MIC) ≥ 8μg/mL), while CSPA was defined as sensitivity to imipenem and meropenem (MIC ≤ 2μg/mL). Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent among three or more antipseudomonal antimicrobials.[13] Difficult-to-treat resistance (DTR) was defined as non-susceptibility to all of the following antimicrobials: meropenem, ciprofloxacin, levofloxacin, ceftazidime, cefepime, imipenem-cilastatin, piperacillin-tazobactam, and aztreonam.[14] BSI was defined as the isolation of bacteria from blood in the presence of fever or other clinical symptoms consistent with infection.[15] The date of BSI onset was defined as the time when the first positive blood culture was obtained. Neutropenia was defined as an absolute neutrophil count < 0.5×10^9 cells/L. Nosocomial acquisition of BSI was defined as BSI occurring 48 h after admission.[16]

Microbiological Examination

An automated microbial mass spectrometry system Autof ms1000 (Autobio, China) was used for the bacterial identification, and a VITEK 2 Compact automated system (biomerieux, France) was used for the test of sensitivity to routine antibiotics (including Aminoglycosides: amikacin, tobramycin, cephalosporins: ceftazidime, cefepime; fluoroquinolones: ciprofloxacin, levofloxacin; carbapenems: imipenem, meropenem; β-lactam and β-lactamase inhibitors: piperacillin-tazobactam). Microbroth dilution method was used to determine the minimum inhibitory concentration (MIC) of polymyxin B (BIO-KONT, China) and routine antibiotics. *P. aeruginosa* ATCC 27853 was used as a standard quality control strain. The susceptibility to ceftazidime-avibactam (OXOID, USA) and cefiderocol (Liofilchem, Italy) was evaluated using the disk diffusion method.

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Statistical Analysis

All statistical analyses were performed using the IBM SPSS Statistics v.23.0. The *T*-test was used for the comparisons of continuous variables between groups, and the Chi-square test was used for categorical variables. For variables with non-normal distribution, Wilcoxon's test was adopted. Variables with $p < 0.05$ in the univariate analysis were included in multivariate analyses. Multivariable logistic regression analysis was used to identify the risk factors for development and mortality of CRPA BSI. A value of $p < 0.05$ was considered statistically significant.

Results

To investigate the detection rate and antibiotic sensitivity of CRPA and other drug-resistant phenotype in Fuzhou is crucial for developing a rational treatment plan. Furthermore, this study aimed to evaluate risk factors associated with BSI and mortality among patients infected with CRPA, which may provide evidence to optimize treatment and reduce the risk of infection and death. Consequently, clinical data were collected from patients at a tertiary teaching hospital in Fujian Province over the past 7 years.

Detection Rates of *P. aeruginosa* With Different Antibiotic Resistance Phenotypes in Different years

A total of 15824 *P. aeruginosa* clinical samples were cultured between January 2017 and December 2023, and 7480 *P. aeruginosa* blood samples were cultured for 7 years. The detection rates for both clinical and blood culture samples of *P. aeruginosa* increased over year, with the first decline at the end of 2021, followed by a rapid increase (Figure 2A). The detection rate of CRPA in blood culture samples progressively increased from 26% in 2017 to 49% in 2020, subsequently declined to 29% in 2021, and then rapidly increased to 47% in 2023. The increased trends in MDRPA BSI and CRPA BSI were generally consistent, with the detection rate of MDRPA increasing from 10% in 2017 to 36% in 2023, and a similar significant reduction was observed in 2021. In addition, the detection rate of DTRPA BSI remained low until 2022, when it rose sharply to 15% in 2023 (Figure 2B).

Antimicrobial Susceptibility of *P. aeruginosa* Isolates

The antimicrobial susceptibilities of 224 *P. aeruginosa* isolates are listed in Table 1. Among the 112 CRPA blood isolates in this study, the rate of resistance to amikacin, tobramycin, ceftazidime, cefepime, ciprofloxacin, levofloxacin, imipenem, meropenem, piperacillin-tazobactam was 33.3%, 47.3%, 42.9%, 41.1%, 57.1%, 57.1%, 96.4%, 83.9% and 63.4%, respectively. The CRPA isolates showed significantly higher resistance to the nine conventional antibiotics than the CSPA isolates ($p < 0.001$). In addition, 76 MDRPA were identified in the CRPA isolates, while only 2 MDRPA were identified in the CSPA isolates, and the antimicrobial susceptibility to conventional antibiotics was further tested (Table 1). A total of 43 DTRPA isolates were identified (Table 2). Colistin sensitivity tests were not performed in our laboratory before 2021. Between 2022 and 2023, a total of 32 patients underwent polymyxin B susceptibility testing, and

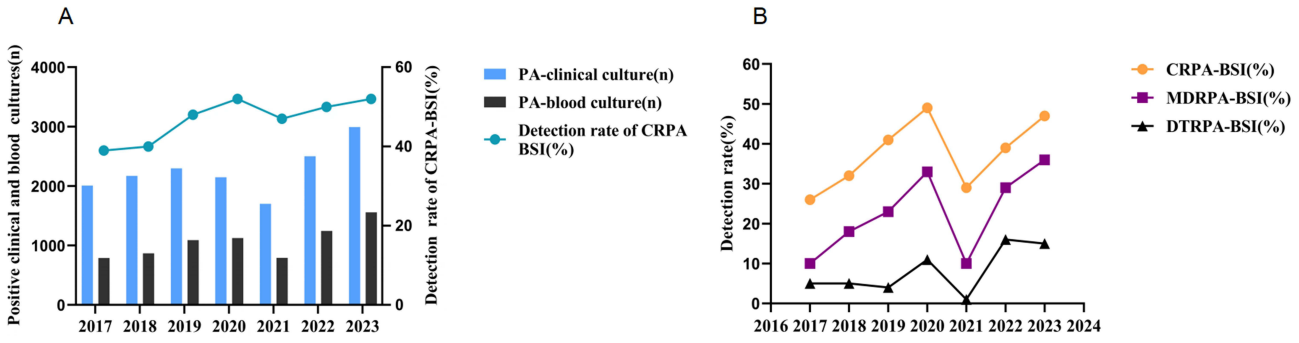

Figure 2 Epidemic trends of *P. aeruginosa* in Fujian Medical University Union Hospital. (**A**) Main axis (left): number of positive samples for *P. aeruginosa* clinical culture (n)/year; sub-axis (right): number of positive samples for *P. aeruginosa* blood culture (n)/year, detection rate of CRPA BSI in blood culture samples of *P. aeruginosa* (%)/year. (**B**) detection rate of CRPA BSI, MDRPA BSI and DTRPA BSI in blood culture samples of *P. aeruginosa* (%)/year.

Table 1 Susceptibility of the 224 Pseudomonas Aeruginosa to Antimicrobial Agents From 2017 to 2023

Antimicrobial classes	Antibiotic(s)	S	I	R	S	I	R
		CRPA(n=112)			CSPA(n=112)		
Aminoglycosides	Amikacin	65.2%	1.8%	33.0%	99.1%	0.0%	0.9%
	Tobramycin	51.8%	0.9%	47.3%	97.3%	0.0%	2.7%
Cephalosporins	Ceftazidime	38.4%	18.8%	42.9%	88.4%	6.3%	5.4%
	Cefepime	46.4%	12.5%	41.1%	92.9%	5.4%	1.8%
Fluoroquinolones	Ciprofloxacin	30.4%	12.5%	57.1%	90.2%	4.5%	5.4%
	Levofloxacin	25.9%	17.0%	57.1%	90.2%	6.3%	3.6%
Carbapenems	Imipenem	0.9%	2.7%	96.4%	100.0%	0.0%	0.0%
	Meropenem	4.5%	11.6%	83.9%	100.0%	0.0%	0.0%
β-lactam and β-lactamase inhibitors	Piperacillin-tazobactam	33.9%	2.7%	63.4%	89.3%	0.0%	10.7%
Antimicrobial classes	**Antibiotic(s)**	**MDRPA[a](n=76)**			**MDRPA[b](n=2)**		
Aminoglycosides	Amikacin	51.3%	2.6%	46.1%	100.0%	0.0%	0.0%
	Tobramycin	30.3%	1.3%	68.4%	100.0%	0.0%	0.0%
Cephalosporins	Ceftazidime	10.5%	27.6%	61.8%	50.0%	50.0%	0.0%
	Cefepime	22.4%	18.4%	59.2%	0.0%	100.0%	0.0%
Fluoroquinolone	Ciprofloxacin	18.4%	11.8%	69.7%	0.0%	50.0%	50.0%
	Levofloxacin	10.5%	17.1%	72.4%	0.0%	100.0%	0.0%
Carbapenem	Imipenem	1.3%	0.0%	98.7%	100.0%	0.0%	0.0%
	Meropenem	1.3%	6.6%	92.1%	100.0%	0.0%	0.0%
β-lactam and β-lactamase inhibitors	Piperacillin-tazobactam	9.2%	2.6%	88.2%	0.0%	50.0%	50.0%

Notes: a, patients with MDRPA in the CRPA group; b, patients with MDRPA in the CSPA group.
Abbreviations: S, susceptible; I, intermediate; R, resistant; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-sensitive *Pseudomonas aeruginosa*; MDRPA, multidrug resistance *Pseudomonas aeruginosa*.

Table 2 Clinical Characteristics of Patients With CRPA and CSPA BSI

Characteristic	Total (224)	CRPA (n = 112)	CSPA (n = 112)	*p* value
Demographic				
Male	159 (71%)	80 (71%)	79 (71%)	0.883
Age(y), median (IQR)	55 (42,67)	56 (45,69)	53 (41,63)	0.187
Nosocomial infections	180 (80.4%)	91 (81.3%)	89 (79.5)	0.865
Ward				
Hematology	93 (41.5%)	33 (29.5%)	60 (53.6%)	<0.001
ICU	78 (34.8%)	58 (51.8%)	20 (17.9%)	<0.001
Surgical ward	35 (15.6%)	13 (11.6%)	22 (19.6%)	0.098
Underlying diseases or conditions				
Cardiovascular disease	31 (13.8%)	20 (17.9%)	11 (9.8%)	0.082
Hypertension	50 (22.3%)	24 (21.4%)	26 (23.2%)	0.748
Cerebrovascular diseases	28 (12.5%)	18 (16.1%)	10 (8.9%)	0.106
Chronic kidney disease	16 (7.1%)	8 (7.1%)	8 (7.1%)	>0.999
Chronic lung diseases	21 (9.4%)	17 (15.2%)	4 (3.6%)	0.003
Chronic liver disease	1 (0.4%)	1 (0.9%)	0 (0%)	0.316
Diabetes mellitus	42 (18.8%)	24 (21.4%)	18 (16.1%)	0.304
Solid malignant tumor	25 (11.2%)	14 (12.5)	11 (9.8%)	0.524
Hematological disease	104 (46.4%)	42 (37.5%)	62 (55.4%)	0.007
Transplantation	31 (13.8%)	22 (19.6%)	9 (8.0%)	0.012
Multi-organ failure	43 (19.2%)	34 (30.4%)	9 (8.0%)	<0.001
Previous Hospitalization	179 (79.9%)	93 (83.0%)	86 (76.8%)	0.243
Pre-infection within CRPA	42 (18.8%)	36 (32.1%)	6 (5.4%)	<0.001

(*Continued*)

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Table 2 (Continued).

Characteristic	Total (224)	CRPA (n = 112)	CSPA (n = 112)	*p* value
Previous staying in ICU	37 (16.5%)	28 (25.0%)	9 (8.0%)	<0.001
Antibiotics exposure within 90 days				
Cephalosporins	80 (35.7%)	39 (34.8)	41 (36.6%)	0.780
Carbapenems	38 (17.0%)	29 (25.9%)	9 (8.0%)	<0.001
β-lactam and β-Lactamase inhibitors	83 (37.1%)	50 (44.6%)	33 (29.5%)	0.019
Aminoglycosides	6 (2.7%)	4 (3.6%)	2 (1.8%)	0.408
Fluoroquinolones	49 (21.9%)	36 (32.1%0	13 (11.6%)	<0.001
Glycopeptides	44 (19.6%)	24 (21.4%)	20 (17.9%)	0.501
Tigecycline	35 (15.6%)	21 (18.8)	14 (12.5%)	0.198
Colistin	22 (9.8%)	15 (13.4%)	7 (6.3%)	0.073
Previous treatments administered				
Prior invasive procedures				
Tracheal intubation	63 (28.1%)	38 (33.9%)	25 (22.3%)	0.074
Puncture	50 (22.3%)	29 (25.9%)	21 (18.8%)	0.261
CVC	64 (28.6%)	28 (25%)	36 (32.1%)	0.3005
PICC	114 (50.9%)	48 (42.9%)	66 (58.9%)	0.094
Arterial catheters	18 (8.0%)	14 (12.5%)	4 (3.6%)	0.025
Urinary catheter	59 (26.3%)	38 (33.9%)	21 (18.8%)	0.010
Previous Surgery	61 (27.2%)	33 (29.5%)	28 (7.1%)	0.453
Glucocorticoid therapy	105 (46.9%)	61 (54.5%)	44 (39.3%)	0.023
Immunosuppressive therapy	22 (9.8%)	16 (14.3%)	6 (5.4%)	0.016
Severity at BSI onset				
Sepsis or septic shock	105 (46.9%)	62 (55.4%)	43 (38.4%)	0.006
Length of hospital stay, days, median (IQR)	41.3 (17.8, 46)	47.5 (16, 52)	35.1 (18.8, 43)	0.040
<30 days	17.5 (12, 24.5)	16 ((9, 23.8))	19 ((12.8, 26.3)	0.052
30–90 days	48 (37, 57)	49 (36, 56.8)	47 (36, 58)	0.573
>90 days	156 (116, 201)	175 (121, 237)	137 (100, 151)	0.182
The treatments after BSI				
Active antimicrobial therapy	205 (91.5%)	97 (86.6%)	103 (92.0%)	0.195
Surgery	41 (18.3%)	27 (24.0%)	14 (12.5%)	0.025
Glucocorticoid therapy	91 (40.6%)	49 (43.8%)	42 (37.5%)	0.341
Immunosuppressive therapy	12 (5.4%)	5 (4.5%)	7 (6.3%)	0.553
Chemotherapy or radiotherapy	3 (1.3%)	1 (0.9%)	2 (1.8%)	0.561
Laboratory examinations				
WBC<4×10^9, median (IQR)	0.69 (0.13, 0.86)	0.81 (0.12, 1.00)	0.59 (0.14, 0.68)	0.179
WBC>10×10^9, median (IQR)	19.07 (12.51, 20.63)	17.92 (12.22, 20.52)	20.51 (13.46, 21.78)	0.352
Hemoglobin, median (IQR)[a]	76 (58, 91)	73 (60, 84)	79 (54, 96)	0.110
Platelet, median (IQR)[b]	98 (12,143)	86 (11,123)	110 (14,159)	0.156
Albumin, median (IQR)[a]	30.6 (27.1,33.8)	28.7 (25.8,31.9)	31.9 (28.8,35.9)	<0.001
MDRPA	78 (34.8%)	76 (67.9%)	2 (1.8%)	<0.001
DTRPA	43 (19.2)	43 (38.4%)	0 (0.0%)	<0.001
28-day mortality	81 (36.2%)	57 (50.9%)	24 (21.4%)	<0.001

Note: a, g/L; b, ×10^9 cells/L.

Abbreviations: ICU, intensive care unit; PICC, peripherally inserted central catheter; IQR, interquartile range; CVC, central venous catheter; DTRPA, difficult-to-treat resistance *P. aeruginosa*; WBC, white blood cell.

only one strain was drug-resistant, with the resistance rate of 3.1%. The drug sensitivity test of ceftazidime-avibactam and cefiderocol was performed on 13 strains of DTRPA isolated in 2023. The results indicated that all 13 isolates were sensitive to ceftazidime-avibactam and two strains were intermediately resistant to cefiderocol, with the resistance rate of 15.38%.

Clinical Characteristics of Patients With *P. aeruginosa* BSI

The clinical features of 224 patients suffering from *P. aeruginosa* BSI are listed in Table 2. There were 159 males (71%), and the median age was 56.6 (45, 69) years. In addition, 180 (80.4%) patients had at least one hospitalization prior to the first positive culture, and the hospital-acquired infection was observed in 181 (78.5%) patients. The majority of patients were from the Department of Hematology (41.5%, n=93), Intensive Care Unit (ICU) (34.8%, n=78), and Department of General Surgery (15.6%, n=35).

For the underlying diseases, hematological diseases accounted for 46.4% (n=104), followed by hypertension (22.3%, n=50), multi-organ failure (19.2%, n=43), diabetes mellitus (18.8%, n=42), and cardiovascular diseases (13.8%, n=31). Compared with CRPA group (37.5%), the proportion of hematological diseases was significantly higher in patients with CSPA BSI (55.4%; p=0.007). There were no significant differences in other underlying diseases between CRPA group and CSPA group. In addition, 155 patients (69.2%) had antibiotics exposure within 90 days, and 42 (18.8%) patients had pre-infection within CRPA. Among 224 patients, the 28-day mortality rate of patients suffering from CRPA BSI was markedly higher than that of those with CSPA BSI (50.9% vs 21.4%, $p < 0.001$). The detection rates of MDRPA and DTRPA isolates were significantly higher in the CRPA group as compared to the CSPA group (67.9% vs 1.8%, $p < 0.001$ and 38.4% vs 0.0%, $p < 0.001$, Table 2). The majority of patients had invasive procedures before the BSI: 114 patients (50.9%) received peripherally inserted central catheters (PICC), 64 patients (28.6%) received central venous catheters (CVC) insertion, and 63 patients (28.1%) underwent endotracheal intubation. Additionally, 59 patients (26.3%) were managed with urinary catheters, 50 patients (22.3%) underwent puncture procedures, and 18 patients (8.1%) received arterial catheter placement. A total of 214 (95.5%) patients received active antimicrobial therapy. However, the utilization rate of ceftazidime-avibactam our study was relatively low, with only 7 out of 224 patients receiving this medication.

Risk Factors Associated With CRPA Bacteremia

Univariate analysis showed that more patients with CRPA were from the ICU, while patients with CSPA were more likely to be from the Department of Hematology. The most prevalent complications for patients suffering from CRPA BSI were chronic lung diseases, transplantation, multi-organ failure, and sepsis or septic shock. Patients infected with CRPA were more likely to receive a previous treatment in the ICU, pre-infection within CRPA, prolonged hospital stay, glucocorticoid therapy, immunosuppressive therapy, arterial catheterization and urinary catheterization, and lower albumin level (Table 2). Moreover, the disparity in antibiotic exposure between CRPA group and CSPA group within 90 days before BSI was predominantly attributed to carbapenems (25.9% vs 8.0%, $p < 0.001$), β-lactam and β-lactamase inhibitors (44.6% vs 29.5%, $p = 0.019$), and fluoroquinolones (32.1% vs 11.6%, $p < 0.001$). Multivariable logistic regression analysis indicated that, chronic lung disease (OR 3.953, 95% CI 1.131–13.812, $p = 0.031$), transplantation (OR 2.837, 95% CI 1.036–7.770, $p = 0.043$), multi-organ failure (OR 4.815, 95% CI 1.949–11.894, $p = 0.001$), pre-infection within CRPA (OR 9.239, 95% CI 3.441–24.803, $p < 0.001$), and exposure to carbapenems (OR 2.734, 95% CI 1.052–7.106, $p = 0.039$) within 90 days were independent risk factors associated with CRPA bacteremia (Table 3).

Table 3 Multivariable Analysis of Factors Leading to the Development of CRPA BSI

Variable	β	S.E	OR	OR (95% CI)		*p value*
Chronic lung diseases	1.374	0.638	3.953	1.131	13.812	0.031
Transplantation	1.043	0.514	2.837	1.036	7.770	0.043
Multi-organ failure	1.572	0.461	4.815	1.949	11.894	0.001
Pre-infection within CRPA	2.223	0.504	9.239	3.441	24.803	<0.001
Carbapenems exposure*	1.006	0.487	2.734	1.052	7.106	0.039

Note: *Antibiotic exposure within 90 days.

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Risk Factors for 28-Day Mortality of CRPA BSI

In the 28-day follow-up, 57 (50.9%) patients infected with CRPA died, and 42 of 76 MDRPA-infected patients (55.3%) and 24 of 43 DTRPA-infected patients (55.8%) died. Eight patients died before the antibiotic sensitivity test were available, and 5 patients died after voluntarily giving up treatment. To identify the risk factors associated with 28-day mortality of patients infected with CRPA BSI, the demographics, clinical characteristics, and prior antibiotic exposure were compared between survivors and non-survivors.

Univariate analysis showed that patients who died within 28 days were more likely to be male, elderly, and from ICU, and mainly had hospital-acquired infections. Most non-survivors experienced unfavorable outcomes including multi-organ failure ($p = 0.002$) and sepsis/septic shock ($p < 0.001$) after BSI. Prior exposure to tigecycline and colistin within 90 days, previous invasive procedures and lower hemoglobin levels were associated with 28-day mortality (Table 4). There were no significant differences in antibiotic treatment regimens after BSI or other characteristics between survivors and non-survivors. (Supplementary Table S1).

In the multivariable logistic regression analysis, the use of colistin before infection (OR 4.890, 95% CI 1.003–23.846, $p = 0.049$) and sepsis or septic shock (OR 8.774, 95% CI 3.140–24.515, $p = 0.001$) were independent risk factors associated with 28-day mortality, whereas hemoglobin was found as a protective factor (OR 0.965, 95% CI 0.939–0.991, $p = 0.010$) (Table 5).

Table 4 Risk Factors for 28-Day Mortality in Patients With CRPA BSI

Characteristics	No-survivor (n =57)	Survivor (n =55)	Total (n=112)	*p* value
Sex, male	47 (82.5%)	33 (60%)	80 (71.4%)	0.009
Age(y), median (IQR)	58.7 (48,69)	53.2 (39,65)	56.0 (44.8,69)	0.089
Nosocomial infections	52 (91.2%)	39 (70.9%)	91 (81.3%)	0.006
ICU	42 (73.7%)	16 (29.1%)	58 (51.8%)	< 0.001
Underlying diseases or conditions				
Multi-organ failure	25 (43.9%)	9 (16.4%)	34 (30.4%)	0.002
Antibiotics exposure within 90 days				
Tigecycline	15 (26.3%)	6 (10.9%)	21 (18.8%)	0.037
Colistin	12 (21.1%)	3 (5.5%)	15 (13.4%)	0.015
Previous treatments administered				
Prior invasive procedures	45 (78.9%)	32 (58.2%)	77 (68.8)	0.018
Severity at BSI onset				
Sepsis or septic shock	45 (78.9%)	17 (30.9%)	62 (55.4%)	< 0.001
Laboratory examinations				
Hemoglobin, median (IQR)[a]	67 (59,75)	78 (64,93)	73 (60,84)	0.008

Note: a, g/L.

Table 5 Multivariable Regression Analysis of Mortality in Patients With CRPA BSI

Variable	β	S.E	OR	OR (95% CI)		*p* value
Sepsis or septic shock	2.172	0.524	8.774	3.140	24.515	0.001
Colistin exposure*	1.587	0.808	4.890	1.003	23.846	0.049
Hemoglobin [a]	−0.036	0.014	0.965	0.939	0.991	0.010

Notes: *Antibiotic exposure within 90 days. a, g/L.

Discussion

In this study, patients were included from one of the largest tertiary hospitals in Fujian Province. The patients admitted into this hospital were from all regions of Fujian Province and therefore representative. According to epidemiological statistics, the detection rate of CRPA worldwide shows an increasing trend, with the highest rate reaching 64.6% in Latin America.[17] Lu et al[18] carried out an 11-year, multi-center retrospective study in Hunan Province, China, and found that the rate of CRPA infections among patients with hematological malignancies (HM) increased significantly from 9.1% to 88.9%. A retrospective study conducted in Zhejiang Province, China, reported that the detection rate of CRPA BSI increased from 17% in 2012 to 60% in 2020.[19] Our results indicated a consistent annual increase in the detection rates of CRPA BSI and MDRPA BSI from 2017 to 2020. However, the detection rates decreased significantly in 2021 and then increased from 2022. During the COVID-19 pandemic, the incidence of various diseases was reported to decline, which was attributed to the preventive and control measures during the epidemic. A retrospective study conducted across 70 countries and 457 stroke centers worldwide indicated that the COVID-19 pandemic was associated with a global reduction in the incidence of stroke.[20] Our results may be related to the coincidence with the peak of the COVID-19 pandemic in China. In this period, widespread measures such as mask-wearing, enhanced disinfection protocols, and reduced public gatherings effectively protected vulnerable populations and reduced the spread of pathogenic bacteria. A study conducted in Wuhan, China, indicated that the detection rate of DTRPA exhibited a declining trend from 2013 to 2021.[21] Similarly, our study indicated that the detection rate of DTRPA remained at a low level until 2021. However, the prevalence of drug-resistant phenotype showed a significant upward trend since 2022, warranting close attention. In addition, antibiotic classification management may be an effective way to reduce resistance. For instance, it is crucial to make rational choices regarding antibiotic therapy based on a thorough analysis of the infection site, severity of infection, bacterial drug resistance patterns, and the pathophysiological characteristics of patients. Secondly, minimizing unnecessary antibiotic usage represents another viable strategy.

P. aeruginosa can secrete some virulence factors, leading to a significant morbidity, which reduces the life expectancy, and elevates the mortality. For instance, the endotoxicity of lipid A LPS can induce tissue damage.[22] Additionally, six types of secretion systems, including Type VI secretion system (associated with flagella), Type IV secretion system (associated with pili), and Type III secretion system (associated with multi-toxin components), contribute to the pathogenic process of *P. aeruginosa*.[5] Many virulence factors are regulated by Quorum sensing (QS) system,[23] and two-component systems[24] and small non-coding regulatory RNAs also play important roles in the virulence regulation.[25,26] Several virulence genes, including *fimH, papC, lasB, rhlI, lasI*, and *toxA* have been identified as the important factors related to the pathogenicity of *P. aeruginosa*.[11] In response to diverse environmental challenges, bacteria have developed an array of resistance mechanisms. *P. aeruginosa* has acquired antibiotic resistance through multiple pathways, including outer membrane permeability, efflux system, and antibiotic inactivating enzyme.[27] Resistance attributed to biofilm formation is associated with the presence of flagella and adhesins.[28] The resistance of *P. aeruginosa* to carbapenem is mainly attributed to the absence or reduction of porin OprD, the excessive expression of AmpC, and the mediation of efflux pumps.[29] The MDRPA or DTRPA frequently results from the interplay of multiple intricate resistance mechanisms.[14] Molecular screening of antibiotic resistance genes is very important to investigate the resistance mechanism of *P. aeruginosa*.[8,9] Our study indicated that the antibiotic resistance rate of CRPA in our hospital was different from that in other regions. Therefore, it is imperative to investigate the pathogenesis and antibiotic resistance mechanisms of CRPA, which may provide new strategies for the control of *P. aeruginosa* infection.

In accordance with previous findings,[30–32] our results indicated that *P. aeruginosa* had the lowest rate of resistance to polymyxin B (~3.1%). Of note, the sample size was small in this study, and more studies with large sample size are warranted to further validate our findings. Studies have indicated that the resistance rate of CRPA to amikacin is very low, but the resistance rate of 112 CRPA to amikacin in our study was 33%, which was significantly higher than previously reported.[33–36] This also suggests that local health-care providers should take caution to the empirical treatment of CRPA BSI infections with amikacin. CRPA strains often exhibit resistance to other antibiotics,[37] which is consistent with our results. Moreover, our study indicated that CRPA showed the highest rate of resistance to piperacillin-tazobactam (63.4%). Clinical investigation shows that our hospital has a very high utilization rate of piperacillin-tazobactam, which may explain the resistance to this drug. The

expert consensus on lower respiratory tract infections caused by *P. aeruginosa* in China recommends that ceftazidime-avibactam may serve as a first-line treatment alternative for CRPA infections when antibacterial susceptibility testing (AST) confirms the susceptibility to ceftazidime-avibactam.[38] However, the utilization rate of ceftazidime-avibactam in this study was relatively low, which may limit its reference value. The definition of DTR emphasizes on the influence of antibiotic resistance on treatment choices and prognosis.[39] The panel in United States strongly advocates that all microbiology laboratories conduct AST for MDRPA and DTRPA isolates against novel β-lactam drugs.[14] Studies have shown that ceftazidime-avibactam is an effective option for the treatment of MDRPA and DTRPA,[40,41] and cefiderocol has been proven to be effective in the treatment of severe infections caused by DTRPA.[42,43] The 13 strains of DTRPA isolated in 2023 were evaluated for the sensitivity to ceftazidime-avibactam and cefiderocol, and the resistance rates were 0% and 15.4%, respectively. Although cefiderocol has not yet been approved for clinical use in China, resistant strains have already emerged. Therefore, investigating the mechanisms of cefiderocol resistance is of significant importance.

Our study showed a higher incidence of previous exposure to "carbapenems, β-lactam and β-lactamase inhibitors, and fluoroquinolone" in the CRPA group. Additionally, previous exposure to carbapenems was identified as an independent risk factor for CRPA BSI, which is in accordance with previously reported.[19,30] Therefore, to understand the drug resistance pattern and the risk factors for CRPA BSI is crucial for providing rational treatment. Our results also indicated that ICU stay before BSI onset, prior CRPA infection, longer hospital stay, glucocorticoid therapy, immunosuppressive treatment, arterial catheter indwelling and urinary catheter indwelling and lower albumin levels were related to the development of CRPA BSI. In addition, chronic lung disease, multiple organ failure, transplantation, and prior CRPA infection were also found to be independent risk factors for the development of CRPA bacteremia in the present study. Damage to the mucous membranes of the respiratory tract in patients with chronic lung disease can lead to the invasion of colonized *P. aeruginosa* into the blood, resulting in BSI.[44–46] Patients with multiple organ failure and those undergoing transplantation have compromised immune function, which inevitably increases the risk of *P. aeruginosa* BSI. Therefore, strictly controlling the use of carbapenem antibiotics, active management of high-risk complications, prudent use of immunosuppressants, and enhanced care for patients with prior ICU stay are essential for the management of CRPA BSI.

In this study, the 28-day mortality rate was 50.9% in 112 patients with CRPA, and the mortality rates were notably elevated in patients with MDRPA and DTRPA (55.3% and 55.8%, respectively), which was significantly higher than previously reported.[19,35,36] Multivariable regression analysis revealed that prior exposure to colistin and sepsis or septic shock were independent risk factors for 28-day mortality, whereas hemoglobin was a protective factor. Colistin (polymyxin B or E) is recognized as a last-resort antibiotic for the treatment of CRPA infections,[47] and it is typically employed when the infection is severe or other antibiotics have proven ineffective. Consequently, the mortality of patients may be more attributable to the severity and critical nature of their condition rather than the administration of polymyxins. Furthermore, our study appeared reasonable; however, the utilization rate of polymyxin in this study was notably low, with only 15 out of 112 CRPA patients with prior medication of polymyxin B. Therefore, studies with larger sample size are needed to further confirm the reliability of our findings. We recommend that clinicians can regularly evaluate risk factors associated with mortality and develop personalized treatments accordingly.

There were still limitations in this study. First, this was a single-center study in Fuzhou, China, and therefore, our findings are not representative of other regions across the country. Second, the condition of patients with CRPA is complex, and the regimen for antibiotic treatment should adjust accordingly throughout the course of treatment. For instance, some patients may have been prescribed more than 5 antibiotics, and thus it is difficult to assess the influence of antibiotic treatment regimen on the prognosis of patients. Therefore, more prospective studies are required to confirm our findings by controlling confounding factors. Third, this was a retrospective study, the absence of some data led to patient selection bias, which may have affected our results, and the mechanism of drug resistance was not investigated. Therefore, large samples or prospective studies are needed to further validate our conclusions, and investigate mechanisms underlying the antibiotic resistance, which is helpful for the development of novel strategies for the treatment of *P. aeruginosa* BSI.

Conclusions

Our study indicates the detection rates of CRPA, MDRPA, and DTRPA show an increasing trend in Fuzhou, China. Chronic lung disease, transplantation, multi-organ failure, prior CRPA infection, and prior carbapenems exposure are

independent risk factors associated with the development of CRPA bacteremia. Additionally, sepsis or septic shock are independent risk factors for 28-day mortality in patients with CRPA BSI. More studies are needed to investigate the molecular mechanisms underlying the resistance of CRPA, standardize the use of antibiotics, and assess risk factors for development and mortality of CRPA BSI, which are beneficial to control *P. aeruginosa* infection and reduce its mortality.

Data Sharing Statement

The data presented in this study are available upon request from the corresponding author.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Fujian Medical University Union Hospital (2024KY138). As this study was retrospective, informed consent was waived by my ethics committee.

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Disclosure

The authors declare no conflict of interest.

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