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ORIGINAL RESEARCH

Risk Factors and Outcomes of Patients with Carbapenem-Resistant *Pseudomonas aeruginosa* Bloodstream Infection

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Purpose: The rising incidence of carbapenem-resistant *Pseudomonas aeruginosa* (PA) bloodstream infection (BSI) has made the selection of antibiotic therapy more difficult and caused high mortality. This study was aimed at exploring the risk factors for carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) bloodstream infection and identifying the risk factors for the outcomes of patients with PA-BSI.

Methods: We performed a retrospective cohort study of patients with PA-BSI in a tertiary hospital from January 2017 to December 2021 in China. Epidemiological, clinical, and microbiological characteristics were described. Risk factors for CRPA-BSI and the outcomes of PA-BSI inpatients were identified, using multivariate logistic regression analysis.

Results: A total of 198 PA-BSI inpatients were included. The negative outcome rate was significantly higher in patients infected with CRPA (15/34, 44.12%) than with carbapenem-susceptible *Pseudomonas aeruginosa* (CSPA) (35/164, 21.34%), and the difference was statistically significant (P=0.005). Multivariate logistic regression analysis showed that previous exposure to carbapenem (OR 3.519, 95% CI 1.359–9.110, P=0.010) was an independent risk factor for CRPA-BSI. In addition, CRPA (OR 1.615, 95% CI 0.626–4.171, P=0.32) was not an independent risk factor for negative outcome among PA-BSI inpatients.

Conclusion: Our study showed that previous exposure to carbapenem was an independent risk factor for CRPA-BSI. CRPA was not an independent risk factor for a negative outcome in PA-BSI inpatients.

Keywords: carbapenem-resistant, *Pseudomonas aeruginosa* bloodstream infection, risk factors, outcomes

Introduction

Pseudomonas aeruginosa is one of the mainly Gram-negative bacteria (GNB) species associated with nosocomial infections that cause high morbidity and mortality rates.[1,2] Indeed, the mortality rate of PA bloodstream infection reportedly ranges from 20% to 50%.[1,3,4] With the widespread use of broad-spectrum antibiotics, CRPA, multidrug-resistant (MDR) and extensively drug-resistant (XDR) PA isolates are gradually increasing.[5,6] According to the China Antimicrobial Surveillance Network (https://www.chinets.com/Data/GermYear), the resistance rates of imipenem and meropenem in PA infections were 23.6% and 20.9% in 2017, and 23% and 18.9% in 2021, respectively. The resistance rates of imipenem and meropenem in China have slightly decreased over the past 5 years but remained at a high level. Carbapenem antibiotics are commonly used for the treatment of PA infection and their high resistance rates limit the choices of antimicrobial therapy.[7] Despite a great deal of research on epidemiology, the incidence of CRPA remains high, and support for CRPA infection management remains insufficient. Meanwhile, risk factors for the outcomes of patients with PA infection remain unclear. Recio et al reported that inappropriate empirical therapy, XDR isolate, severe neutropenia and septic shock were associated with high mortality in PA bacterial pneumonia.[8] Teelucksingh et al identified that septic shock, age and Pitt bacteremia score ≥4 were risk factors for poor outcome in PA-BSI.[9] Recognizing the risk factors for the prognosis of patients with PA infection is important, so that special attention would be paid to patients with these risk factors to improve the prognosis.

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Therefore, our study aimed at exploring the epidemiology, clinical characteristics, antimicrobial resistance, and risk factors of patients with CRPA-BSI, we also identified the risk factors for the outcomes of patients with PA-BSI. This study may provide clues for clinicians to take special measures to curb the spread of CRPA and adjust their treatment strategies.

Methods

Study Setting

This was a retrospective study conducted at the First Affiliated Hospital of Guangxi Medical University (2750-bed) from January 2017 to December 2021. Data from patients with PA-BSI were collected, including patients' demographic and clinical characteristics, comorbidities, laboratory examination, invasive procedures, antibiotics' exposure and outcomes. The inclusion criteria were as follows: the first episode of PA occurred during the study period, and patients met the diagnostic criteria for bloodstream infection, only the first episode of PA-BSI was included, and recurrent infections were excluded. In addition, outpatients and incomplete or missing medical records were also excluded.

To identify the risk factors for CRPA-BSI, the patients were divided into two groups: a CRPA group and a CSPA group. In addition, to explore the risk factors for the outcomes of PA-BSI, patients were divided into a negative outcome group and a positive outcome group.

Definitions

Bloodstream infection was defined as viable bacteria appeared in the bloodstream and cause clinical signs or symptoms of infection according to the definitions for bloodstream infection by the Centers for Disease Control.[10] CRPA was defined as a minimum inhibitory concentration of ≥8μg/mL imipenem or meropenem or disk zone diameter ≤15mm for meropenem or imipenem consistent with the breakpoints of 2021 Clinical and Laboratory Standards Institute (CLSI) guidelines.[11] MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories, XDR as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (ie, bacterial isolates remain susceptible to only one or two categories).[12] Outcomes were classified as follows: according to the medical records, patients were cured or in better condition when discharged were identified as positive outcome, dead or in serious condition when discharged were recognized as negative outcome.

Bacterial Identification and Antimicrobial Susceptibility Testing

In this study, all isolates were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (bioMérieux, Lyons, France), or the VITEK2 Compact system (bioMérieux, Marcy l'Etoile, France). All antibiotic susceptibility tests were performed using the VITEK 2 Compact system or the disk-diffusion method, except Polymyxin B, which were performed with broth microdilution testing, and the results were interpreted as recommended by the Clinical and Laboratory Standards Institute (CLSI), version 2021. *Escherichia coli* (ATCC25922), *Klebsiella pneumoniae* (ATCC700603), and *Pseudomonas aeruginosa* (ATCC27853) were used as the quality control bacterial strains.

Statistical Analysis

Continuous variables with normal distribution were expressed as the mean ± standard deviation (using Student's *t*-test) or as the median (interquartile range [IQR]) (using the Mann–Whitney *U*-test) when the distribution was not normal. Categorical variables were expressed as counts or counts/total (percentages) and were analyzed using the Chi-squared test or two-tailed Fisher's exact test. Multivariate logistic regression analysis was used to identify the risk factors for CRPA-BSI and the outcomes of PA-BSI. The results were reported as the odds ratio (OR) and 95% confidence interval (CI). $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 23.0.

Results

Demographics and Clinical Characteristics of Patients with PA-BSI

Excluded 15 inpatients with missing or incomplete data, a total of 198 PA-BSI inpatients were enrolled in our study. Of the 198 PA-BSI inpatients, there were 130 males (65.66%) and 68 females (34.34%); the median age and the length of

stay were 37(17–56) years and 26.5(14–38) days, respectively. PA inpatients predominantly came from the hematology department (34.30%), pediatric hematology ward (11.10%), intensive care unit (ICU 9.09%), or stem cell transplantation department (8.60%). The main comorbidities were hematological diseases (54.55%), pulmonary diseases (39.90%) (including chronic obstructive pulmonary disease and pneumonia), and hepatobiliary and pancreatic diseases (32.83%), as shown in Table 1.

Table 1 Demographics, Clinical Characteristics, and Outcomes of Patients with PA-BSI

Factors	CRPA (n=34)	CSPA (n=164)	Total Number (n=198)	*p*
Demographics				
Male	23(11.62)	107(54.04)	130(65.66)	0.80
Female	11(5.56)	57(28.79)	68(34.34)	–
Age (years)	39.5 (19.75–57.25)	36 (17–56)	37(17–56)	0.22
Comorbidities and underling diseases				
Diabetes mellitus	6(3.03)	10(5.05)	16(8.08)	0.06
Hypertension	6(3.03)	21(10.61)	27(13.64)	0.64
Cardiovascular diseases	8(4.04)	12(6.06)	20(10.10)	**0.01**
Pulmonary diseases	17(8.59)	62(31.31)	79(39.90)	0.19
Hepatobiliary and pancreatic diseases	12(6.06)	53(26.77)	65(32.83)	0.74
Kidney diseases	6(3.03)	29(14.65)	35(17.68)	1.00
Nervous system diseases	7(3.54)	19(9.60)	26(13.13)	0.26
Hematological diseases	17(8.59)	91(45.96)	108(54.55)	0.56
Malignant tumors	3(1.52)	19(9.60)	22(11.11)	0.87
Invasive procedures				
Mechanical ventilation	8(4.04)	10(5.05)	18(9.09)	**0.004**
Tracheal intubation	5(2.53)	9(4.55)	14(7.07)	0.12
Urinary catheter	5(2.53)	12(6.06)	17(8.59)	0.29
Central venous catheter	14(7.07)	36(18.18)	50(25.25)	**0.02**
Drainage tube	11(5.56)	21(10.61)	32(16.16)	**0.005**
Surgery	6(3.03)	37(18.69)	43(21.72)	0.53
Bone marrow biopsy	6(3.03)	47(23.74)	53(26.77)	0.19
Lumbar puncture	3(1.52)	19(9.60)	22(11.11)	0.87
Laboratory examination				
Elevated white blood cells (>10.0×10^9/l)	10(5.05)	49(24.75)	59(29.80)	0.96
Leukopenia (<4.0×10^9/l)	15(7.58)	104(52.53)	119(60.10)	**0.04**
Neutropenia (<1.8×10^9/l)	15(7.58)	104(52.53)	119(60.10)	**0.04**
Thrombocytopenia (<100×10^9/l)	22(11.11)	103(52.02)	125(63.13)	0.83
Hemoglobin <90 g/l	27(13.64)	111(56.06)	138(69.70)	0.18
Albumin <30g/l	11(5.56)	47(23.74)	58(29.29)	0.67
Antibiotic exposures				
Cephalosporins	9(4.55)	49(24.75)	58(29.29)	0.69
Carbapenems	21(10.61)	44(22.22)	65(32.83)	**p<0.001**
Beta-lactam and beta-Lactamase inhibitors	17(8.59)	54(27.27)	71(35.86)	0.06
Fluoroquinolones	5(2.53)	18(9.09)	23(11.62)	0.75
Aminoglycosides	1(0.51)	9(4.55)	10(5.05)	0.85
Tigecycline	5(2.53)	9(4.55)	14(7.07)	0.12
Glycopeptides	10(5.05)	17(8.59)	27(13.64)	**0.008**
Chemotherapy	13(6.57)	70(35.35)	83(41.92)	0.63
Outcomes				
Positive outcome	19(9.60)	129(65.15)	148(74.75)	**0.005**
Negative outcome	15(7.58)	35(17.68)	50(25.25)	-
Admission to blood culture time (days)	15(6.25–24.25)	11(2–19)	12(2–19.25)	**0.03**
LOS	29 (20–48)	24.5 (13–37)	26.5(14–38)	0.09

Notes: Data expressed as n(%) or median (IQR). Bold represents p<0.05.
Abbreviations: CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-sensitive *Pseudomonas aeruginosa*; LOS, length of stay.

Antimicrobial Susceptibility Results

The antimicrobial susceptibility results, as shown in Table 2, revealed the following total antibiotic resistance rates: carbapenems (17.17%), imipenem (15.15%), meropenem (13.64%), amikacin (2.02%) and polymyxin B (0.0%). Additionally, the highest and lowest resistance rates of carbapenems were 31.03% and 7.14% in 2020 and 2019, respectively. Other antibiotic resistance rates are shown in Table 2.

Risk Factors for CRPA-BSI

Univariate analysis showed that there were nine risk factors associated with CRPA-BSI (Table 1): previous exposure to carbapenems or glycopeptides, leukopenia, neutropenia, cardiovascular diseases, longer hospital stay before bacteremia onset, mechanical ventilation, central venous catheterization, placement of a drainage tube. The mortality rate of the CRPA group and CSPA group were 8.82% and 7.32%, respectively. In addition, patients with CRPA-BSI tended to have negative outcome compared with patients with CSPA-BSI (P = 0.005), as shown in Table 1. The multivariate logistic regression analysis revealed that previous exposure to carbapenem (OR 3.519, 95% CI 1.359–9.110, P=0.010) was an independent risk factor for CRPA-BSI, as shown in Table 3.

Table 2 Antimicrobial Susceptibility Results

Antibiotic Resistance	2017(%)	2018(%)	2019(%)	2020(%)	2021(%)	Total (%)
Imipenem	4 (12.12)	9 (19.15)	3 (7.14)	8 (27.59)	6 (12.77)	30 (15.15)
Meropenem	5 (15.15)	8 (17.02)	3 (7.14)	6 (20.69)	5 (10.87)	27 (13.64)
Carbapenem	6 (18.18)	10 (21.28)	3 (7.14)	9 (31.03)	6 (12.77)	34 (17.17)
Piperacillin	3 (9.09)	6 (13.33)	2 (4.88)	0 (0.00)	3 (10.34)	14 (9.15)
Cefoperazone/Sulbactam	1 (3.33)	4 (8.70)	0 (0.00)	–	–	5 (5.81)
Piperacillin/Tazobactam	2 (6.06)	5 (10.64)	2 (4.76)	2 (6.90)	5 (10.64)	16 (8.08)
Ceftazidime	2 (6.06)	8 (17.02)	3 (7.14)	2 (6.90)	9 (19.15)	24 (12.12)
Cefepime	2 (6.06)	4 (8.51)	1 (2.38)	1 (3.45)	1 (2.13)	9 (4.55)
Aztreonam	6 (18.18)	5 (10.64)	5 (13.16)	5 (19.23)	10 (21.28)	26 (16.15)
Amikacin	0 (0.00)	3 (6.38)	0 (0.00)	0 (0.00)	1 (2.13)	4 (2.02)
Gentamicin	3 (9.09)	5 (10.64)	2 (4.88)	1 (5.00)	3 (6.38)	14 (7.45)
Tobramycin	3 (9.09)	5 (10.64)	1 (2.38)	1 (3.57)	2 (4.26)	12 (6.09)
Ciprofloxacin	3 (9.09)	4 (8.51)	3 (7.14)	2 (6.90)	5 (10.64)	17 (8.59)
Levofloxacin	3 (9.09)	4 (8.51)	2 (4.76)	6 (20.69)	8 (17.02)	23 (11.62)
Polymyxin B	0 (0.00)	0 (0.00)	0 (0.00)	–	–	0 (0.00)

Note: Data expressed as n (%).

Table 3 Multivariate Analysis of the Risk Factors for CRPA-BSI

Factors	CRPA (n=34)	CSPA (n=164)	OR	95% CI	p
Admission to blood culture time	15 (6.25–24.25)	11(2–19)	1.022	0.991–1.055	0.17
Leukopenia (<4.0×109/l)	15(7.58)	104(52.53)	1.032	0.115–9.281	0.98
Neutropenia (<1.8×10^9/l)	15(7.58)	104(52.53)	0.609	0.069–5.368	0.66
Cardiovascular diseases	8(4.04)	12(6.06)	1.703	0.488–5.943	0.40
Mechanical ventilation	8(4.04)	10(5.05)	1.624	0.433–6.093	0.47
Central venous catheter	14(7.07)	36(18.18)	1.230	0.484–3.127	0.66
Drainage tube	11(5.56)	21(10.61)	2.575	0.845–7.845	0.10
Exposure to carbapenems	21(10.61)	44(22.22)	3.519	1.359–9.110	**0.010**
Exposure to glycopeptides	10(5.05)	17(8.59)	1.754	0.559–5.500	0.34

Notes: Data expressed as n(%) or median (IQR). Bold represents p<0.05.
Abbreviations: CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-sensitive *Pseudomonas aeruginosa*; OR, odds ratio; CI, confidence interval.

Risk Factors for the Outcomes of PA-BSI Inpatients

The negative and positive outcome rates of PA-BSI inpatients were 25.25% (50/198) and 74.75% (148/198), respectively. Univariate analyses showed that the risk factors for negative outcome of PA-BSI mainly included CRPA isolation, previous exposure to cephalosporins, tigecycline, carbapenems or glycopeptides, as shown in Table 4. Multivariate logistic regression analysis showed that CRPA was not an independent risk factor for negative outcome of PA-BSI (OR 1.615, 95% CI 0.626–4.171, P=0.32). As shown in Table 5.

Table 4 Risk Factors for the Outcomes of PA-BSI Inpatients

Factors	Positive Outcome (n=148)	Negative Outcome (n=50)	p
Demographics			
Male	100(50.51)	30(15.15)	0.33
Female	48(24.24)	20(10.10)	–
Age	35.5 (17.0–54.0)	44 (15.75–63.25)	0.08
Comorbidities and underling diseases			
Diabetes mellitus	7(3.54)	9(4.55)	**0.007**
Hypertension	17(8.59)	10(5.05)	0.13
Cardiovascular diseases	8(4.04)	12(6.06)	**P<0.001**
Pulmonary diseases	49(24.75)	30(15.15)	**0.001**
Hepatobiliary and Pancreatic diseases	43(21.72)	22(11.11)	0.05
Kidney diseases	23(11.62)	12(6.06)	0.18
Nervous system diseases	18(9.09)	8(4.04)	0.49
Hematological diseases	83(41.92)	25(12.63)	0.46
Malignant tumors	19(9.60)	3(1.52)	0.18
Invasive procedures			
Mechanical ventilation	8(4.04)	10(5.05)	**0.005**
Tracheal intubation	7(3.54)	7(3.54)	0.06
Urinary catheter	11(5.56)	6(3.03)	0.48
Central venous catheter	29(14.65)	21(10.61)	**0.002**
Drainage tube	21(10.61)	11(5.56)	0.20
Surgery	33(16.67)	10(5.05)	0.73
Bone marrow biopsy	41(20.71)	12(6.06)	0.61
Lumbar puncture	15(7.58)	7(3.54)	0.45
Laboratory examination			
Elevated white blood cells (>10.0×10^9/l)	39(19.70)	20(10.10)	0.07
Leukopenia (<4.0×10^9/l)	93(46.97)	26(13.13)	0.18
Neutropenia (<1.8×10^9/l)	94(47.47)	25(12.63)	0.09
Thrombocytopenia (<100×10^9/l)	93(46.97)	32(16.16)	0.88
Hemoglobin <90 g/l	97(48.99)	41(20.71)	**0.03**
Albumin <30g/l	37(18.69)	21(10.61)	**0.02**
Antibiotic exposures			
Cephalosporins	49(24.75)	9(4.55)	**0.04**
Carbapenems	42(21.21)	23(11.62)	**0.02**
Beta-lactam and beta-lactamase inhibitors	49(24.75)	22(11.11)	0.17
Fluoroquinolones	15(7.58)	8(4.04)	0.26
Aminoglycosides	7(3.54)	3(1.52)	1.00
Tigecycline	6(3.03)	8(4.04)	**0.01**
Glycopeptides	16(8.08)	11(5.56)	0.05
CRPA	19(9.60)	15(7.58)	**0.005**
Chemotherapy	66(33.33)	17(8.59)	0.19
Admission to blood culture time (days)	12.5 (2.0–19.75)	11.5 (2.0–19.25)	0.87
LOS	27.5 (14.25–37.75)	22.0(12–38)	0.12
LOS >30 days	60(30.30)	16(8.08)	0.28

Notes: Data expressed as n (%) or median (IQR). Bold represents p<0.05.
Abbreviations: CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; LOS, length of stay.

Table 5 Multivariate Analysis for the Outcomes of PA-BSI Inpatients

Factors	Positive Outcome (n=148)	Negative Outcome (n=50)	OR	95% CI	p
Hemoglobin <90 g/l	97(48.99)	41(20.71)	1.707	0.686–4.247	0.25
Albumin <30g/l	37(18.69)	21(10.61)	1.763	0.819–3.793	0.15
Diabetes mellitus	7(3.54)	9(4.55)	3.474	1.017–11.865	0.05
Cardiovascular diseases	8(4.04)	12(6.06)	2.743	0.854–8.812	0.09
Pulmonary diseases	49(24.75)	30(15.15)	1.874	0.860–4.087	0.11
Mechanical ventilation	8(4.04)	10(5.05)	1.869	0.523–6.671	0.34
Central venous catheter	29(14.65)	21(10.61)	1.764	0.771–4.033	0.18
Exposure to cephalosporins	49(24.75)	9(4.55)	0.461	0.180–1.177	0.11
Exposure to carbapenems	42(21.21)	23(11.62)	0.877	0.347–2.220	0.78
Exposure to tigecycline	6(3.03)	8(4.04)	2.732	0.749–9.968	0.13
Exposure to glycopeptides	16(8.08)	11(5.56)	1.013	0.317–3.236	0.98
CRPA	19(9.60)	15(7.58)	1.615	0.626–4.171	0.32

Abbreviations: CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; OR, odds ratio; CI, confidence interval.

Discussion

Pseudomonas aeruginosa is one of the main causes of nosocomial infections especially when patients are immunocompromised, readily causes PA bloodstream infections, which are often severe and difficult to treat due to the frequent emergence of antibiotic-resistant mutants during therapy.[13,14] With the widespread use of carbapenems and other broad-spectrum antibiotics, carbapenem resistance and even MDR/XDR PA have increased, limiting the choice of antimicrobial therapy. Therefore, our study explored the risk factors for CRPA-BSI and the outcomes of PA-BSI and aimed at providing useful advice for interventions and control of CRPA-BSI.

Univariate analysis showed that risk factors for CRPA-BSI mainly included previous exposure to carbapenems or glycopeptides, leukopenia, neutropenia, longer hospital stays before bacteremia onset, mechanical ventilation, central venous catheterization, placement of a drainage tube. Further, multivariate logistic regression analysis showed that previous exposure to carbapenems was an independent risk factor for CRPA-BSI, which was consistent with previous publications.[15–17] Righi et al performed a meta-analysis and found that carbapenem resistance appeared to be associate with prior use of carbapenems.[15] Shi et al identified that prior use of carbapenems was an independent risk factor for development of CRPA-BSI in a retrospective analysis.[16] Raman et al also identified that previous exposure to carbapenems was significantly correlated with acquisition of CRPA compared with CSPA.[17] The acquisition of CRPA may be because that PA is a highly diverse pathogen which capable of adaptation to the surrounding environment, when under antibiotic selective pressure, the induced response promotes bacterial survival and develops antibiotic resistance.[18] The mechanism of PA acquired resistance to carbapenems may be due to the efflux pumps, low outer membrane permeability, production of carbapenemase and AmpC β-lactamase.[19–23] In addition, PA also shows resistance to many other available antibiotics via the acquisition of chromosomal mutations and transferable resistance determinants, especially those encoding carbapenemases frequently co-transferred with aminoglycoside-modifying enzymes.[20,24–26]

Our study showed that PA-BSI inpatients mainly came from the hematology department (34.30%) and pediatric hematology department (11.10%), and the main comorbidities were hematologic diseases(54.55%), pulmonary diseases (39.90%) (including chronic obstructive pulmonary disease and pneumonia), and hepatobiliary and pancreatic diseases (32.83%). Patients with hematologic diseases are vulnerable to PA-BSI due to unique disease characteristics, including severe neutropenia, prolonged hospitalizations, and special treatments such as corticosteroids, chemotherapy, and hematopoietic stem cell transplantation (HSCT).[15,27–29] Pulmonary disease patients tend to have damaged respiratory mucosal, which may lead to the colonize PA entering the blood stream and causing PA-BSI.[8,9,30,31] Patients with hepatobiliary and pancreatic diseases generally undergo surgery and drainage, thus increasing their risk of being infected by bacterial and resulting in PA-BSI.[14,21,24]

Our study revealed that PA showed resistance to most antimicrobials, which is consistent with previous studies.[21,24,32] We found that among the 198 PA isolates, the highest resistance rate was found in carbapenems

(17.17%), followed by aztreonam (16.15%), and ceftazidime (12.12%). In contrast, PA showed less resistance to amikacin, with a rate of 2.02%. In addition, no PA isolations showed resistance to polymyxin B. Polymyxins (polymyxin B and colistin) were regarded as the alternative therapeutic option for many cases of MDR/XDR PA infections. However, their usage is complicated due to narrow therapeutic window and loading dose polymyxins frequently associated with higher risk of nephrotoxicity.[21,33–35] Furthermore, whether polymyxins-based combination therapy in CR/MDR/XDR PA infections associated with better clinical outcomes remains unclear. A cohort study showed that colistin-based combination therapy with two active drugs for XDR PA pneumonia patients was associated with better survival than monotherapy.[36] Interestingly, a systematic review about combination therapy in CRGNB showed that polymyxin combined with tigecycline or carbapenems and/or aminoglycosides had an unadjusted association with survival; however, when bias studies removed, the association between combination therapy and survival diminished, and unnecessary use of carbapenems may cause prevalence of CRGNB.[37] At present, carbapenems are still commonly used for PA infection,[38] and our study found that previous exposure to carbapenems was an independent risk factor for CRPA-BSI, so it would be important to prescribe carbapenems prudently to reduce the incidence of CRPA infection.

Previous studies revealed that resistance to carbapenems increased the incidence of mortality in patients with PA infection.[4,15,39] A meta-analysis showed that carbapenem resistance had a deleterious effect on the mortality of PA-BSI.[4] Righi et al demonstrated that there was an association between mortality and carbapenem resistance in a meta-analysis.[15] Lee et al found a higher mortality rate among patients with carbapenem-only resistant PA compared to all susceptible PA.[39] Interestingly, our study found no statistically significant difference on in-hospital mortality rates between the CRPA and CSPA groups, probably because many Chinese choose to be discharged home when they are gravely ill. Thus, there was a relatively lower in-hospital mortality rate, with a rate of 8.82% and 7.32% in the CRPA group and CSPA group, respectively. However, when comparing positive and negative outcomes, there was a statistically significant difference (p=0.005). Thus, we divided PA-BSI inpatients into two groups (a positive outcome group and a negative outcome group) and explored the risk factors for the outcomes of PA-BSI inpatients.

Univariate analysis showed that moderate anemia, hypoalbuminemia, diabetes mellitus, mechanical ventilation and central venous catheterization were associated with negative outcomes. Invasive procedures such as central venous catheterization and mechanical ventilation, increased the chance of PA-BSI and affected the outcomes of patients, which was consistent with previous studies.[16] Univariate analysis also showed that CRPA-BSI inpatients were likelier to have a negative outcome. However, when it came to the multivariate logistic regression analysis, CRPA was not an independent risk factor for negative outcome, which was consistent with previous reports.[7,40] Buehrle et al previous found that there was no significant difference on 14-day mortality rates among patients with CRPA and CSPA infection.[7] A prospective multicenter study identified that carbapenem resistance significantly increased the risk of mortality from the fifth day after the onset of PA-BSI, but this difference diminished during the first 4 days or as the comorbidities increased.[40] These may be because that compared to the resistant bacteria, the patient's underlying diseases, primary site of infection, virulence of the pathogens, clinical characteristics and management probably play more important roles in the outcomes of PA-BSI.[7,40–42] Indeed, impact of CRPA-BSI on outcomes remains controversial, and more prospective multicenter studies are needed.

Admittedly, our study had several limitations. First, it was a retrospective analysis with a relatively small size of samples, and our study conducted at a single medical center which may just reflects the experience of one single center, and the results may not be applicable to other settings. Second, the risk factors included were limited, factors such as Charlson comorbidity index and initial antibiotic therapy that may have influenced the outcomes of PA-BSI were not included in our study.[8,42,43] Third, we did not study the mechanism of resistance, which would be the key to determining the relationship between CRPA drug resistance types and clinical characteristics.

Conclusion

Our study showed that previous exposure to carbapenems was an independent risk factor for CRPA-BSI. In addition, PA shows resistance to a variety of antibiotics. Carbapenems and other antibiotics should be used appropriately to reduce the incidence of CRPA-BSI and antibiotic resistance.

Data Sharing Statement

Any datasets analyzed during this study are available from the corresponding author at reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. The need for written informed consent was waived due to the retrospective non-interventional study and the research did not involve personal privacy or commercial interests. We declare that this study was conducted in accordance with the principles of the Declaration of Helsinki and the information of all patients included in this study was confidential.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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