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ORIGINAL RESEARCH

Risk Factors for Mortality of Inpatients with *Pseudomonas aeruginosa* Bacteremia in China: Impact of Resistance Profile in the Mortality

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Purpose: Pseudomonas aeruginosa bacteremia presents a severe challenge to hospitalized patients. However, to date, the risk factors for mortality among inpatients with *P. aeruginosa* bacteremia in China remain unclear.

Patients and Methods: This retrospective multicenter study was performed to analyze 215 patients with culture-confirmed *P. aeruginosa* bacteremia in five healthcare centers in China during the years 2012–2019.

Results: Of 215 patients with *P. aeruginosa* bacteremia, 61 (28.4%) died during the study period. Logistic multivariable analysis revealed that cardiovascular disease (OR=3.978, P=0.001), blood transfusion (OR=5.855, P<0.001) and carbapenem-resistant *P. aeruginosa* (CRPA) phenotype (OR=4.485, P=0.038) constituted the independent risk factors of mortality. Furthermore, both CRPA and multidrug-resistant *P. aeruginosa* (MDRPA) phenotypes were found to be significantly associated with 5-day mortality (Log-rank, P<0.05).

Conclusion: This study revealed a high mortality rate amongst hospitalized patients with *P. aeruginosa* bacteremia, and those with cardiovascular diseases, CRPA and MDRPA phenotypes, should be highlighted and given appropriate management in China.

Keywords: risk factors, mortality, *Pseudomonas aeruginosa*, bacteremia

Introduction

Pseudomonas aeruginosa is a Gram-negative non-fermenting bacillus, leading to serious nosocomial infections, especially in immunocompromised individuals and those with neutropenia.[1,2] The clinical outcomes in *P. aeruginosa* infected patients have been improved with the wide availability of antipseudomonal antibiotics in the past years. Unfortunately, the emergence of resistant *P. aeruginosa* strains due to the intrinsic and acquired resistance mechanism had increasingly drawn more attention.[3–5] The organism has a tendency to cause multi-site infections, of which bacteremia is fatal, with a mortality rate ranging from 18% to 61%.[6,7] Some studies have demonstrated that *P. aeruginosa* bacteremia could trigger severe septic shock and multiple organ failure, and result in high mortality rate and substantial medical costs.[8]

Poor outcomes of the bacteremia caused by *P. aeruginosa* could be explained by its virulence and the underlying diseases or conditions of the patients.[9–11] The previous studies revealed that the prognosis could be closely associated with the severity of underlying diseases and delayed usages of effective antibiotics.[6,12–16] In addition, the virulence genotype (exoU genotype) of *P. aeruginosa* was an independent marker

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related to early death in bacteremic patients.[10] Besides, there are controversial data on the association between the clinical consequences and *P. aeruginosa* resistance profiles given that inappropriate antibiotics might result in treatment failure.[9,16–21]

Nowadays, the risk factors for mortality of inpatients with *P. aeruginosa* bacteremia in China remain unclear. Therefore, we conducted a retrospective multicenter cohort study, aiming to explore the risk factors of in-hospital death for patients and investigate the influence of the resistance profiles on *P. aeruginosa* bacteremia mortality.

Methods

Ethical Statement

This study was approved by the Ethics Committee of China-Japan Friendship Hospital with approval number 2019–122-K84, and the Declaration of Helsinki was followed throughout. The written informed consent from participants was waived because it focused only on the epidemical features of *P. aeruginosa* bacteremia, and the privacy of involved subjects was not affected.

Study Populations

We performed a retrospective analysis of 215 patients with *P. aeruginosa* bacteremia, who visited China-Japan Friendship Hospital (CJFH, 69 cases) during 2016–2019, Henan Provincial People's Hospital (79 cases) during 2017–2019, Ningbo Medical Center Lihuili Hospital (30 cases) during 2012–2019, Wuhan Pu Ai Hospital of Huazhong University of Science and Technology (36 cases) during 2017–2019 and Weifang No.2 People's Hospital (1 case) during the period of 2019. Patients with blood cultures positive for *P. aeruginosa* were retrieved in the microbiology laboratory databases from the five participating centers.

Clinical Data Collection

Data collected included demographic details, underlying conditions (diabetes mellitus, chronic lung disease, chronic renal failure, liver disease, solid organ cancer, cardiovascular disease, solid-organ transplantation, hematological disease and benign biliary tract disease), the source of infection (primary site of infection such as lung, soft-tissue, biliary tract, urinary tract, catheter-related, and peritoneum), nosocomial or community-acquired infection, comorbid condition (corticosteroid treatments received, immune deficiency, neutropenia, intravenous catheterization, blood transfusion, and coinfection with other bacteria), antibiotic use (monotherapy and combined antibiotic therapy), requirement for ventilatory support, ICU admission, hospital length of stay (LOS) and all-cause death.

Microbiological Studies

Microbiological data were obtained for following analysis from the CJFH because of the high mortality rate (60.9%) there and the geographically uneven data in other hospitals. The tested antimicrobial agents were as follows: aztreonam, gentamicin, tobramycin, ceftazidime, cefoperazone-sulbactam, cefepime, piperacillin, piperacillin-tazobactam, ticarcillin-clavulanate, imipenem, meropenem, amikacin, levofloxacin, ciprofloxacin and colistin. Antimicrobial susceptibility testing and analysis were performed according to the guidelines of Clinical and Laboratory Standards Institute.[22]

Definition

The presence of *P. aeruginosa* in blood culture and the clinical features related to the *P. aeruginosa* infection were defined as *P. aeruginosa* bacteremia. Only the first event was enrolled in the analysis if a patient presented ≥2 culture-confirmed *P. aeruginosa* bacteremia during the study period. The primary site of infection was defined as the most possible source of infection responsible for *P. aeruginosa* bacteremia on the basis of medical records, including lung infection, soft-tissue infection, biliary tract infection, urinary tract infection, catheter-related infection and peritoneum infection.[23] It was defined as the bacteremia of unknown origin when the source of the infection was unclear.[23] Nosocomial infection was defined as the *P. aeruginosa* bacteremia (1) that occurred more than 48 h after admission to hospital, or (2) that occurred less than 48 h after admission to hospital in cases who had been hospitalized in other hospitals within the 2 weeks prior to admission.[16,17] Community-acquired infection was defined as the *P. aeruginosa* bacteremia that occurred less than 48 h after admission to hospital in patients who had never been in hospital or nursing home.[16] An absolute neutrophil count of <500/mL was defined as neutropenia.[10] The presence of immune deficiency was defined as the receipt of immunosuppressive therapy (immunosuppressive agent, chemotherapy or radiotherapy) during the *P. aeruginosa* bacteremia.[10] Antibiotic monotherapy was defined as the treatment with only one of the following antibiotics: aztreonam, cefoperazone-sulbactam, ceftazidime,

ticarcillin-clavulanate, piperacillin-tazobactam, cefepime, imipenem, meropenem, amikacin, levofloxacin, ciprofloxacin, colistin, and so on. Combination therapy consisted of the treatment with two or more above-mentioned antibiotics.[24] CRPA is the definition that a strain is non-susceptible to one or both of imipenem and meropenem, and MDRPA consists of strains non-susceptible to at least one agent in three or more categories of antimicrobial agents.[25,26]

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are described as mean and standard deviation (SD) or median and interquartile range (IQR). Comparisons of proportions were performed with chi-square and Fisher's exact tests; continuous variables were compared using Student's *t*-test. All probabilities were 2-tailed, with statistical significance defined as $P \leq 0.05$. A logistic regression model was used to analyze the risk factors for mortality of inpatients with *P. aeruginosa* bacteremia. All analyses were performed using PASW Statistics software, version 25.0.

Results

Clinical Characteristics and Outcomes of 215 Patients with *P. aeruginosa* Bacteremia

Demographic, clinical characteristics and outcomes of 215 patients with *P. aeruginosa* bacteremia are detailed in Table 1. Briefly, the mean age of the 215 patients was 60.5 years (SD 19.0 years), ranging from 10 months to 95 years, and 159 (74.0%) were male. Underlying diseases were present in 154 patients (71.6%), with cardiovascular disease (37.7%) being the most common underlying condition, followed by diabetes (25.1%), hematological disease (23.3%) and chronic lung disease (16.3%) (Table 1). The most common primary site of infection was lung (64, 29.8%), except for 70 cases (32.6%) for whom the primary site was unknown. Overall, 81.9% were from nosocomial acquisition. Furthermore, the comorbid conditions included neutropenia (18.6%), corticosteroid use (27.9%), immunosuppressive therapy (25.1%), intravenous catheterization (67.9%), blood transfusion (40.5%) and bloodstream coinfection with other bacteria (20.5%). During the hospitalization, a total of 209 patients (97.2%) received antimicrobial therapy regimen including antibiotic monotherapy in 91 (42.3%) and combined antibiotic therapy in 118 (54.9%); 69 patients (32.1%) received mechanical ventilation; 88 patients (40.9%) were admitted to ICU, and 61 patients (28.4%) died.

The comparison of demographic features, clinical characteristics and treatment of patients between survivors and non-survivors are shown in Table 1. The older mean age was observed in non-survivors (65.1 years) than survivors (58.7 years) (P=0.016). Moreover, chronic lung disease, cardiovascular disease, blood transfusion and bloodstream coinfection with other bacteria were also more common among non-survivors (all P<0.05, Table 1). Besides, both rates of ICU admission and invasive mechanical ventilation in non-survivors were higher than those in survivors (P<0.001, Table 1). Notably, 68.9% of non-survivors were from CJFH, followed by Wuhan Forth Hospital (18.0%) and three other centers. There were no significant differences between the two cohorts in rates and types of other underlying conditions, comorbid conditions, and length of hospital stay at admission (P>0.05, Table 1).

After adjusting for the influences of potentially confounding variables in a logistic regression model, factors including cardiovascular disease (OR=3.978, P=0.001), blood transfusion (OR=5.855, P<0.001) and hospitalization in CJFH (OR=9.031, P<0.001) were demonstrated to be independently associated with the mortality among all patients (Figure 1).

Clinical Characteristics and Outcomes of 69 Patients with *P. aeruginosa* Bacteremia in CJFH

As shown in Table 2, we further analyzed the clinical characteristics and outcomes of 69 patients (42 non-survivors and 27 survivors) with *P. aeruginosa* bacteremia in CJFH given that hospitalization in this hospital was demonstrated to be a risk factor of the mortality among the subjects. In univariable analysis, odds of death in hospitalized patients with cardiovascular disease and lung infection as the source of bacteremia was higher (P<0.05). Blood transfusion, ICU admission, invasive mechanical ventilation, combined antibiotic therapy, CRPA and MDRPA phenotypes were also proved to be associated with death (P<0.05, Table 2). Subsequently, the multivariate analysis was performed to determine which risk factors could be related to the mortality of inpatients in this center and the results are summarized in Figure 2. Cardiovascular disease (OR=5.329, P=0.010), blood transfusion (OR=7.938, P=0.011) and CRPA phenotype (OR=4.485, P=0.038) were found to be associated with increased odds of death in this hospital (Figure 2).

Table 1 Demographic, Clinical Characteristics and Outcomes of 215 Patients with *P. aeruginosa* Bacteremia[a]

Characteristics	Total N=215	Died N=61	Alive N=154	OR	95% CI	*P*-value
Age (years), (mean, SD)	60.5, 19.0	65.1, 16.1	58.7, 19.8			0.016
Male gender, n (%)	159 (74.0)	47 (77.0)	112 (72.7)	1.259	0.629–2.520	0.515
Underlying disease, n (%)	154 (71.6)	59 (96.7)	95 (61.7)	18.321	4.314–77.806	<0.001
Diabetes mellitus	54 (25.1)	21 (34.4)	33 (21.4)	1.925	1.001–3.701	0.048
Chronic lung disease	35 (16.3)	19 (31.1)	16 (10.4)	3.902	1.844–8.255	<0.001
Chronic renal failure	22 (10.2)	5 (8.2)	17 (11.0)	0.720	0.253–2.045	0.535
Liver disease	29 (13.5)	1 (1.6)	28 (18.2)	0.075	0.010–0.564	0.003
Solid organ cancer	39 (18.1)	9 (14.8)	30 (19.5)	0.715	0.318–1.612	0.418
Cardiovascular disease	81 (37.7)	42 (68.9)	39 (25.3)	6.518	3.395–12.515	<0.001
Solid-organ transplantation	3 (1.4)	1 (1.6)	2 (1.3)	1.267	0.113–14.230	1.000
Hematological Disease	50 (23.3)	11 (18.0)	39 (25.3)	0.649	0.307–1.369	0.254
Benign biliary tract disease	32 (14.9)	2 (3.3)	30 (19.5)	0.140	0.032–0.606	0.005
Primary site of infection, n (%)						
Lung	64 (29.8)	32 (52.5)	32 (20.8)	4.207	2.228–7.944	<0.001
Soft-tissue	2 (0.9)	1 (1.6)	1 (0.6)	2.550	0.157–41.427	1.000
Biliary tract	12 (5.6)	0 (0.0)	12 (7.8)	1.085	1.036–1.135	0.021
Urinary tract	10 (4.7)	0 (0.0)	10 (6.5)	1.069	1.026–1.115	0.066
Catheter-related	48 (22.3)	8 (13.1)	40 (26.0)	0.430	0.188–0.983	0.041
Peritoneum	9 (4.2)	0 (0.0)	9 (5.8)	1.062	1.021–1.105	0.063
Unknown	70 (32.6)	20 (32.8)	50 (32.5)	1.015	0.539–1.909	0.964
Nosocomial infection[b], n (%)	176 (81.9)	49 (80.3)	127 (82.5)	0.868	0.408–1.848	0.714
Comorbid condition, n (%)						
Corticosteroid use	60 (27.9)	15 (24.6)	45 (29.2)	0.790	0.401–1.557	0.495
Immune deficiency[c]	54 (25.1)	10 (16.4)	44 (28.6)	0.490	0.229–1.051	0.063
Neutropenia[d]	40 (18.6)	10 (16.4)	30 (19.5)	0.810	0.369–1.779	0.600
Intravenous catheterization	146 (67.9)	20 (32.8)	126 (81.8)	0.108	0.055–0.213	<0.001
Blood transfusion	87 (40.5)	33 (54.1)	54 (35.1)	2.183	1.195–3.987	0.010
Coinfection with other bacteria	44 (20.5)	18 (29.5)	26 (16.9)	2.061	1.030–4.122	0.039
Hospitals, n (%)						
CJFH	69 (32.1)	42 (68.9)	27 (17.5)	10.398	5.253–20.581	<0.001
Henan Provincial People's Hospital	79 (36.7)	2 (3.3)	77 (50.0)	0.034	0.008–0.144	<0.001
Ningbo Medical Center Lihuili Hospital	30 (14.0)	6 (9.8)	24 (15.6)	0.591	0.229–1.526	0.273
Wuhan Forth Hospital	36 (16.7)	11 (18.0)	25 (16.2)	1.135	0.520–2.478	0.750
Weifang No.2 People's Hospital	1 (0.5)	0 (0.0)	1 (0.6)	1.007	0.994–1.019	1.000
Antimicrobial therapy regimen, n (%)	209 (97.2)	60 (98.4)	149 (96.8)	2.013	0.230–17.596	0.853
Monotherapy[e]	91 (42.3)	18 (29.5)	73 (47.4)	0.464	0.246–0.876	0.017
Combined antibiotic therapy[f]	118 (54.9)	42 (68.9)	76 (49.4)	2.269	1.212–4.248	0.010
LOS (days), median (IQR)	20.0 (12.0–31.8)	14.0 (9.0–31.0)	22.0 (14.0–32.0)			0.422
Received mechanical ventilation, n (%)	69 (32.1)	43 (70.5)	26 (16.9)	11.761	5.880–23.522	<0.001
Admitted to ICU, n (%)	88 (40.9)	51 (83.6)	37 (24.0)	16.127	7.451–34.904	<0.001

Notes: [a]*P. aeruginosa* bacterium was defined as the presence of *P. aeruginosa* in blood culture and the clinical features related to the *P. aeruginosa* infection. Only the first *P. aeruginosa* bacterium event was enrolled in the analysis if a patient presented ≥2 positive *P. aeruginosa* bacteremia during the study period. [b]Nosocomial infection was defined as the occurrence of *P. aeruginosa* bacterium (1) that occurred more than 48 h after admission to hospital (2) that occurred less than 48 h after admission to hospital in cases who had been in other hospitals within the 2 weeks prior to admission. [c]The presence of immune deficiency was defined as the receipt of immunosuppressive therapy (immunosuppressive agent, chemotherapy or radiotherapy) during the *P. aeruginosa* bacteremia. [d]Neutropenia was defined that an absolute neutrophil count of <500/mL. [e]Antibiotic monotherapy was defined as the treatment with only one of the following antibiotics: aztreonam, cefoperazone-sulbactam, ceftazidime, ticarcillin-clavulanate, piperacillin-tazobactam, cefepime, imipenem, meropenem, amikacin, levofloxacin, ciprofloxacin, colistin, and so on. [f]Combination therapy consisted of the treatment with two or more antibiotics.

Abbreviations: SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; LOS, length of hospital stay; CJFH, China-Japan Friendship Hospital; OR, odds ratio; CI, confidence interval.

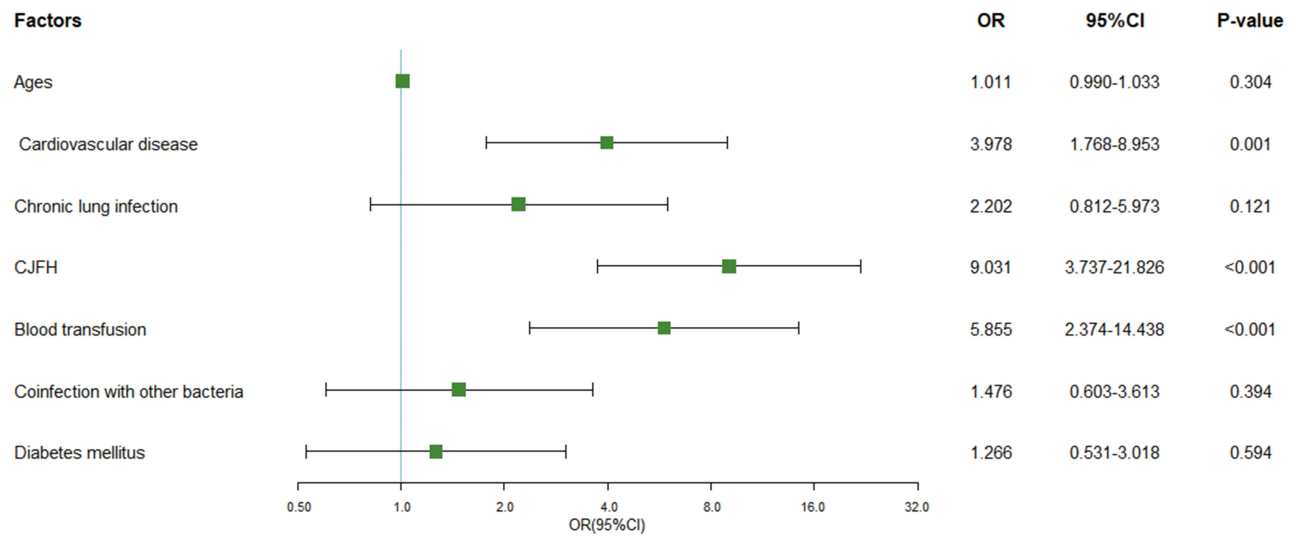

Figure 1 Risk factors for mortality of 215 hospitalized patients with *P. aeruginosa* bacteremia in China. Cardiovascular disease (OR=3.978, *P*=0.001), blood transfusion (OR=5.855, *P*<0.001) and hospitalization in China-Japan Friendship Hospital (CJFH) (OR=9.031, *P*<0.001) were demonstrated to be independently associated with the mortality among all patients.

Impact of Resistance Profile in Mortality

The phenomenon was observed that the overall mortality was 60.9% (42/69) in CJFH and 40.6% (28/69) of patients died in the first 5 days of *P. aeruginosa* bacteremia. The resistance profile of *P. aeruginosa* strains from 42 non-survivors in this hospital is depicted in Figure 3 considering that CRPA phenotype was an independent risk factor for mortality. Obviously, the *P. aeruginosa* resistance in this cohort is serious in view of the fact that a total of 30 CRPA strains and 29 MDRPA strains were found in 42 non-survivors. Furthermore, the survival curve showed that both CRPA and MDRPA phenotypes were associated with 5-day death for *P. aeruginosa* bacteremia cases (Log rank, *P*<0.05, Figure 4A and B), with the 5-day mortality of 29.0% (20/69) and 31.9% (22/69) respectively (data not shown).

Discussion

P. aeruginosa bacteremia is a life-threatening infection in hospitalized patients with serious underlying conditions worldwide.[9,27] However, to date, there are no studies in China that have comprehensively estimated the risk factors for death. This multicenter study revealed that the overall mortality of inpatients with *P. aeruginosa* bacteremia in China was 28.4%, similar to that reported in 9 countries (26.5%).[27]

As with the previous research,[9,16,28,29] the present study had also demonstrated that the mortality was higher in patients with older ages, serious underlying host diseases (cardiovascular disease, chronic lung disease and diabetes mellitus), the primary site of lung infection and coinfection with other bacteria in univariate analysis. Even so, the results of the multivariate analysis indicated that cardiovascular disease, rather than others above, had 3.978 times the risk of death than those without. This result revealed a strong association between the poor clinical outcomes and underlying cardiovascular diseases of patients. Therefore, patients with serious underlying conditions, especially those with cardiovascular diseases, should be given timely treatment and care as appropriate.

It is noteworthy that the combination therapy has no beneficial influence on clinical outcomes in cohorts based on the fact that the higher mortality of 35.6% is observed in patients receiving combination therapy compared with that receiving monotherapy (19.8%, *P*<0.05). This is in keeping with the previous studies.[27,30]

The findings of this study suggested that the death risk of the patients receiving blood transfusion was 5.855 times higher than those without, as never reported in previous studies on *P. aeruginosa* bacteremia. In general, blood transfusion is performed strictly in mainland China to avoid transfusion-transmissible infections. The increased death risk of blood transfusion-related bacteremia might be the result of the immunosuppression caused by blood transfusion.[31] Blood transfusion was thought to be related to the increased suppressor T cell activity and decreased natural killer cell activity in previous studies, therefore,

Table 2 Demographic, Clinical Characteristics and Outcomes of 69 Patients with *P. aeruginosa* Bacteremia[a]

Characteristics	Total N=69	Died N=42	Alive N=27	*P*-value	OR	95% CI
Age (years), (mean, SD)	64.6, 17.4	63.1, 16.7	66.8, 18.5	0.395		
Male gender, n (%)	55 (79.7)	35 (83.3)	20 (74.1)	0.351	1.750	0.536–5.712
Underlying disease, n (%)	68 (98.6)	41 (97.6)	27 (100.0)	1.000	0.976	0.931–1.023
Diabetes mellitus	23 (33.3)	14 (33.3)	9 (33.3)	1.000	1.000	0.359–2.789
Chronic lung disease	24 (34.8)	18 (42.9)	6 (22.2)	0.079	2.625	0.879–7.838
Chronic renal failure	13 (18.8)	11 (26.2)	2 (7.4)	0.103	4.435	0.899–21.884
Solid organ cancer	16 (23.2)	7 (16.7)	9 (33.3)	0.109	0.400	0.128–1.250
Cardiovascular disease	45 (65.2)	32 (76.2)	13 (48.1)	0.017	3.446	1.222–9.715
Solid-organ transplantation	3 (4.3)	1 (2.4)	2 (7.4)	0.693	0.305	0.026–3.538
Hematological Disease	7 (10.1)	4 (9.5)	3 (11.1)	1.000	0.842	0.173–4.096
Benign biliary tract disease	3 (4.3)	0 (0.0)	3 (11.1)	0.056	1.125	0.985–1.285
Primary site of infection, n (%)						
Lung	44 (63.8)	32 (76.2)	12 (44.4)	0.007	4.000	1.415–11.310
Soft-tissue	1 (1.4)	1 (2.4)	0 (0.0)	1.000	0.976	0.931–1.023
Biliary tract	4 (5.8)	0 (0.0)	4 (14.8)	0.020	1.174	1.003–1.374
Urinary tract	1 (1.4)	0 (0.0)	1 (3.7)	0.391	1.038	0.964–1.118
Catheter-related	4 (5.8)	1 (2.4)	3 (11.1)	0.324	0.195	0.019–1.983
Unknown	15 (21.7)	8 (19.0)	7 (25.9)	0.499	0.672	0.212–2.134
Nosocomial infection[b], n (%)	53 (76.8)	33 (78.6)	20 (74.1)	0.666	1.283	0.413–3.985
Comorbid condition, n (%)						
Corticosteroid use	18 (26.1)	14 (33.3)	4 (14.8)	0.153	2.875	0.832–9.940
Immune deficiency[c]	5 (7.2)	5 (11.9)	0 (0.0)	0.148	0.881	0.788–0.985
Neutropenia[d]	7 (10.1)	6 (14.3)	1 (3.7)	0.311	4.333	0.492–38.191
Intravenous catheterization	8 (11.6)	3 (7.1)	5 (18.5)	0.291	0.338	0.074–1.553
Blood transfusion	23 (33.3)	20 (47.6)	3 (11.1)	0.004	7.273	1.896–27.895
Coinfection with other bacteria	17 (24.6)	13 (31.0)	4 (14.8)	0.218	2.578	0.741–8.971
Antimicrobial therapy regimen, n (%)	67 (97.1)	42 (100.0)	25 (92.6)	0.150	1.080	0.971–1.202
Monotherapy[e]	13 (18.8)	5 (11.9)	8 (29.6)	0.066	0.321	0.092–1.117
Combined antibiotic therapy[f]	54 (78.3)	37 (88.1)	17 (63.0)	0.014	4.353	1.288–14.707
Resistance profile						
CRPA	40 (58.0)	30 (71.4)	10 (37.0)	0.005	4.250	1.519–11.889
MDRPA	41 (59.4)	29 (69.0)	12 (44.4)	0.042	2.788	1.024–7.596
LOS (days), median (IQR)	17.0 (10.8–27.3)	12.5 (9.0–27.0)	22.0 (14.0–33.5)	0.184		
Received mechanical ventilation, n (%)	33 (47.8)	30 (71.4)	3 (11.1)	<0.001	20.000	5.060–79.047
Admitted to ICU, n (%)	37 (53.6)	34 (81.0)	3 (11.1)	<0.001	34.000	8.168–141.520

Note: The definitions of [a]*P. aeruginosa* bacterium, [b]nosocomial infection, [c]immune deficiency, [d]neutropenia, [e]antibiotic monotherapy and [f]combination therapy are seen in the annotation of Table 1.

Abbreviations: SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; LOS, length of hospital stay; CRPA, carbapenem-resistant *P. aeruginosa*; MDRPA, multidrug-resistant *P. aeruginosa*; OR, odds ratio; CI, confidence interval.

adversely affected the patients' survival.[32,33] Anyway, unnecessary transfusions should be avoided to reduce the occurrence of bacteremia in hospital.[34,35]

Additionally, hospitalization in CJFH is noted to have a higher death risk than other centers in this study. Subsequently, our study further identifies the risk factors for inpatients mortality there. Apart from cardiovascular disease and blood transfusion, CRPA phenotype was identified as an independent risk factor of mortality in the population. In addition, a striking finding of the present study is that both CRPA and MDRPA phenotypes are significantly associated with 5-day mortality for *P. aeruginosa* bacteremia cases. Our results supported the findings from a previous investigation that patients with

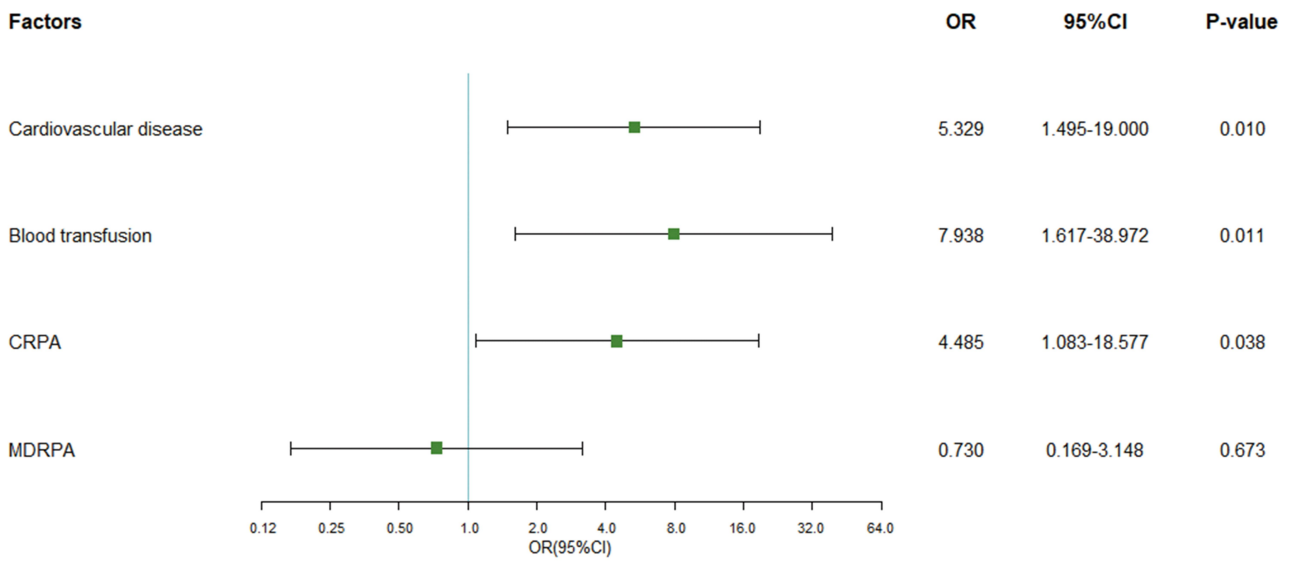

Figure 2 Risk factors for mortality of 69 in-hospital patients with *P. aeruginosa* bacteremia in China-Japan Friendship Hospital (CJFH). Cardiovascular disease (OR=5.329, *P*=0.010), blood transfusion (OR=7.938, *P*=0.011) and carbapenem-resistant *P. aeruginosa* (CRPA) phenotype (OR=4.485, *P*=0.038) were found to be associated with increased odds of death there.

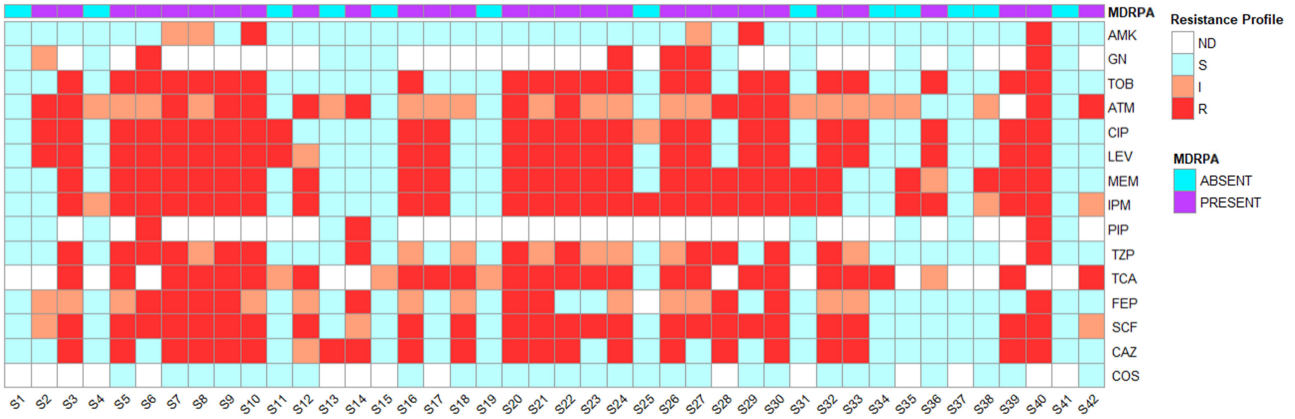

Figure 3 The resistance profile of *P. aeruginosa* strains from 42 non-survivors in China-Japan Friendship Hospital. *P. aeruginosa* resistance is serious given that a total of 30 carbapenem-resistant *P. aeruginosa* (CRPA) strains and 29 multidrug-resistant *P. aeruginosa* (MDRPA) strains were found in 42 non-survivors.
Abbreviations: ND, not done; S, susceptible; I, intermediate; R, resistant; ATM, aztreonam; GN, gentamicin; TOB, tobramycin; CAZ, ceftazidime; SCF, cefoperazone-sulbactam; FEP, cefepime; PIP, piperacillin; TZP, piperacillin-tazobactam, TCA, ticarcillin-clavulanate; IPM, imipenem; MEM, meropenem; AMK, amikacin; LEV, levofloxacin; CIP, ciprofloxacin; COS, colistin.

CRPA and MDRPA bacteremia were more likely to have a higher risk of 30-day mortality.[29,36] These findings suggested that the high resistance levels of *P. aeruginosa* in invasive infections might be a therapeutic challenge for clinicians.[37,38] Thus, an appropriate choice of effective antibiotics according to the antimicrobial sensitivity test in vitro is critical to improving poor outcomes for patients with *P. aeruginosa* bacteremia.[29,36] Furthermore, the previous studies have reported the existence of the correlation between the virulence genotype and antimicrobial resistance including carbapenems.[10,39] As a result, it is also essential to study the associations between virulence and CRPA or MDRPA phenotype to clarify the mechanism for disease severity in patients with drug-resistant phenotypes in future, which will provide the theory of basis for the development of novel antimicrobial agents.

In summary, this is a multicenter retrospective study to evaluate the risk factors for mortality in patients with *P. aeruginosa* bacteremia in China, in whom, cardiovascular disease, blood transfusion and CRPA phenotype were independent risk factors for the in-hospital mortality, and both phenotypes of CRPA and MDRPA were significantly

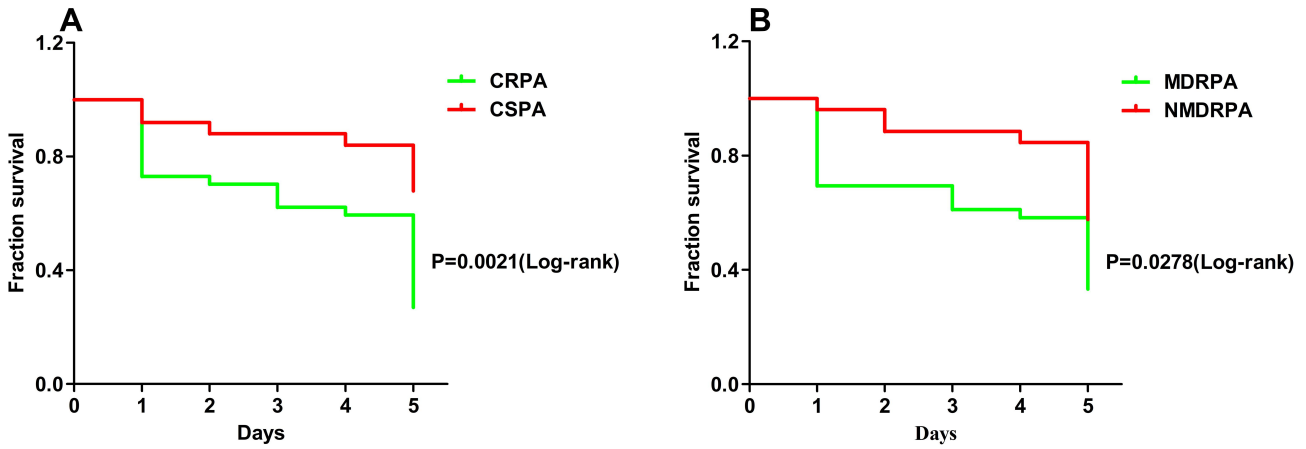

Figure 4 Kaplan–Meier analysis of 5-day mortality in patients in China-Japan Friendship Hospital. (**A**) Kaplan-Meier analysis of 5-day mortality in patients with carbapenem-resistant *P. aeruginosa* (CRPA) bacteremia (N=40) and in patients with carbapenem- susceptible *P. aeruginosa* (CSPA) bacteremia (N=29). (**B**) Kaplan–Meier analysis of 5-day mortality in patients with multidrug-resistant *P. aeruginosa* (MDRPA) bacteremia (N=41) and without (N=28). The survival curve showed that CRPA and MDRPA phenotypes were significantly associated with 5-day mortality ($P<0.05$).
Abbreviation: NMDRPA, no MDRPA.

associated with 5-day mortality. As such, *P. aeruginosa* bacteremia, especially in those with cardiovascular disease, CRPA and MDRPA phenotypes, should be increasingly appreciated and given appropriate management.

Abbreviations

ICU, intensive care unit; CRPA, carbapenem-resistant *P. aeruginosa*; CSPA, carbapenem-susceptible *P. aeruginosa*; MDRPA, multidrug-resistant *P. aeruginosa*; IQR, interquartile range; LOS, length of hospital stay; CJFH, China-Japan Friendship Hospital; OR, odds ratio.

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Disclosure

The authors declare that they have no conflicts of interest.

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