J Chin Med Assoc

ORIGINAL ARTICLE

Clinical characteristics, risk factors, and outcomes of patients with polymicrobial *Pseudomonas aeruginosa* bloodstream infections

Cheng Zheng[a], Guangtao Wang[b,c], Lingling Qiu[d], Xinhua Luo[e], Xijiang Zhang[a], Li Zhong[f], Chuming Zhang[a], Ronghai Lin[a,*], Qingqing Chen[g,*]

[a]Department of Critical Care Medicine, Taizhou Municipal Hospital, Taizhou, Zhejiang, China; [b]Department of Neurosurgery, Municipal Hospital Affiliated to Taizhou University, Taizhou, Zhejiang, China; [c]Department of Neurointensive Care Unit, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; [d]Department of Neurology, Taizhou Municipal Hospital, Taizhou, Zhejiang, China; [e]Department of Clinical Microbiology Laboratory, Taizhou Municipal Hospital, Taizhou, Zhejiang, China; [f]Department of Critical Care Medicine, Huzhou First People's Hospital, Huzhou, Zhejiang, China; [g]Department of Critical Care Medicine, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou, China

Abstract

Background: Previous studies on polymicrobial *Pseudomonas aeruginosa* bloodstream infections (Pa-BSIs) are dated, and it is necessary to reanalyze polymicrobial Pa-BSIs. The aim of this study was to investigate clinical characteristics and risk factors for polymicrobial Pa-BSI in comparison with monomicrobial Pa-BSI.

Methods: A double-center retrospective observational study was performed between January 1, 2013 and June 30, 2022, in two tertiary hospitals. All patients with Pa-BSI were enrolled, and their clinical data were collected by reviewing electronic medical records.

Results: A total of 278 patients with Pa-BSI were enrolled, including 77 patients (27.7%) with polymicrobial Pa-BSI. Compared with monomicrobial Pa-BSI, the main source of polymicrobial Pa-BSI was pneumonia (49.4% vs 31.3%, $p < 0.01$), whereas the main source of monomicrobial Pa-BSI was primary BSIs (21.9% vs 2.6%, $p = 0.04$). In multivariate analysis, a history of cerebrovascular accident (CVA) (adjusted odds ratio [OR], 3.62; 95% CI, 1.46-8.92) was independently associated with polymicrobial Pa-BSI. Primary BSI was associated with monomicrobial Pa-BSI (OR, 0.08; 95% CI, 0.02-0.38). Patients with polymicrobial Pa-BSI had a longer intensive care unit (ICU) length of stay after onset of BSI than those with monomicrobial Pa-BSI (2 [2, 16] vs 13 [3.75, 29], $p = 0.02$).

Conclusion: Patients with Pa-BSI and the presence of CVA need to be alert to the possibility of polymicrobial BSI occurrence. Prolonged ICU stay and pneumonia as a source of BSI warrant clinician attention for polymicrobial Pa-BSI, and primary BSIs are likely associated with monomicrobial BSIs.

Keywords: Bacteremia; Mortality; *Pseudomonas aeruginosa*; Risk factors

1. INTRODUCTION

Bloodstream infections (BSIs) are often caused by a single specific pathogen; however, the proportion of polymicrobial BSIs increases with certain patient characteristics, such as old age, immunocompromised status, malignancy, and neutropenia.[1] Polymicrobial BSIs have been reported to account for as much as 6% to 34% of BSIs[2–4]; the mortality rate is approximately twice that of BSIs with a single specific pathogen, ranging from 21% to 63%.[3] Although gram-negative BSIs have gradually declined over the past few decades, *Pseudomonas aeruginosa*, a glucose-nonfermenting gram-negative bacterium with minimal survival requirements, is an important pathogen of hospital-acquired BSIs.[5] Notably, a recent study has shown that *P. aeruginosa* also accounts for up to 5% of community-onset BSIs.[6] The gradual spread of *P. aeruginosa* morbidity to the community is associated with a high incidence of mortality, with previous reports showing that hospital mortality rates associated with *P. aeruginosa* bloodstream infections (Pa-BSIs) range from approximately 18% to 61%.[7–11] On the premise of this high mortality, polymicrobial Pa-BSIs are also of concern to clinicians. Previous studies have found that patients with polymicrobial Pa-BSI were more severely infected, with a higher incidence of septic shock, than those with monomicrobial Pa-BSI,[12,13] but the risk factors for polymicrobial Pa-BSI were not clearly described. As previous studies are dated and there is a lack of relevant studies in mainland China, it is necessary to reanalyze the clinical characteristics and risk factors for polymicrobial Pa-BSI to help

* *Address correspondence. Dr. Qingqing Chen, Department of Critical Care Medicine, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou, China. E-mail address: chenqq3471@enzemed.com (Q. Chen); Dr. Ronghai Lin, Department of Critical Care Medicine, Taizhou Municipal Hospital, Taizhou, China. E-mail address: tylinrh@163.com (R. Lin).*

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 1066-1073.

Received June 16, 2022; accepted September 17, 2023.

doi: 10.1097/JCMA.0000000000001008

clinicians identify associated risk factors in China and high-risk patients and implement preventive measures. Such efforts may also improve the prognosis of these patients and reduce the burden of polymicrobial BSIs.

2. METHODS

2.1. Patients and study design

This double-center retrospective cohort study was conducted from January 2013 to June 2022 at Taizhou Municipal Hospital and the Second Affiliated Hospital, Zhejiang University School of Medicine. The Ethics Committee of the Taizhou Municipal Hospital approved the retrospective analysis of patient data without obtaining patient consent. In addition, a statement of permission from patients for submission of the present study was not needed, as the study did not include any personal information.

The inclusion criteria included patients who had at least one positive blood culture for *P. aeruginosa* accompanied by signs and symptoms of infection. For patients with more than two positive blood cultures, the clinical data at only the first positive test were included. When pathogens other than *P. aeruginosa* were isolated from the same blood culture, the case was considered a polymicrobial Pa-BSI, and the clinical data were recorded at the same time. The exclusion criteria were as follows: (1) age <18 years; (2) incomplete or missing case data; and (3) pregnancy. In the event of isolation is of a potentially colonizing skin organism, such as coagulase-negative *Staphylococcus*, it was considered a contaminant unless found again in consecutive blood cultures on the same day.

2.2. Data collection

Clinical data were collected from electronic medical records. Demographic data were recorded, including age and sex; clinical data, including underlying diseases; scores reflecting the severity of the disease, including the Sequential Organ Failure Assessment (SOFA) score; Pitt bacteremia score; Charlson Comorbidity Index (CCI); Acute Physiology, Age and Chronic Health Evaluation (APACHE) II score in the first 24 hours following onset of BSI; hospitalization wards; nosocomial infection or not; previous exposures (before hospital stay, previous treatment such as surgical procedures, parenteral nutrition, mechanical ventilation, renal replacement therapy, blood transfusion); and outcomes (intensive care unit [ICU] and hospital length of stay, days of mechanical ventilation after BSI onset, occurrence of septic shock and 28-day mortality). Microbiological data were also collected, including the likely source of BSI and sensitivity to antibiotics.

2.3. Species identification and antibiotic sensitivity testing

An automated BacT/ALERT 3D system (Becton-Dickinson, Sparks, MD) was used to culture blood. Species identification was performed using Bruker Daltonics Data Analysis. As recommended by Clinical & Laboratory Standards Institute, antibiotic susceptibility testing was performed using the VITEK 2 (Card number: AST-GN16; AST-GP67) system or the Kirby-Bauer disk diffusion method (Oxoid, Hampshire, UK).

2.4. Definitions

Onset of BSI was defined as the time when the first positive blood culture was obtained. Diagnosis of Pa-BSI was based on the Centers for Disease Control (CDC) definition of BSI.[14] Polymicrobial Pa-BSI was defined as simultaneous isolation of *P. aeruginosa* and one or more other organisms from blood cultures. Nosocomial BSI was defined as a BSI developing ≥48 hours after hospitalization.[15] Appropriate empirical antimicrobial therapy was defined as treatment performed within 24 hours of obtaining blood culture samples, including use of any antimicrobial agent to which *P. aeruginosa* and other copathogens were susceptible. Neutropenia was defined as absolute neutrophil counts of 1000/mm^3 or below when bacteremia occurred. Sepsis and septic shock were defined using the new Sepsis-3 definition.[16] Primary BSIs were BSI events without another primary source of infection (as defined by National Healthcare Safety Network [NHSN] criteria). Secondary BSI was defined as a BSI thought to be seeded from a site-specific infection at another body site.[14]

2.5. Statistical analysis

SPSS 26.0 (IBM Corp, Armonk, NY) software was used to perform statistical analysis. In the case of continuous variables with a normal distribution, the mean and standard deviation are presented, whereas the median and interquartile range are presented in the case of nonnormal distributions. Continuous variables were compared by Student's t test or the Mann-Whitney U test, and enumeration variables were compared by Pearson χ^2 or Fisher exact test, where appropriate. Variables that had significance at a $p < 0.05$ level in univariate analysis were considered candidates for the building of stepwise logistic regression multivariate models. A two-tailed $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Demographic and clinical characteristics

A total of 661 blood culture specimens containing *P. aeruginosa* were first enrolled, and 278 cases were eventually recruited, including 77 cases of polymicrobial Pa-BSI and 201 cases of monomicrobial Pa-BSI (Fig. 1). Table 1 summarizes the clinical and demographic characteristics of all the patients. There were 204 (73.4%) males, and the mean age was 58.19 years. The most common comorbidity was trauma (32.4%), followed by solid tumor (17.6%). There was no significant difference between the two groups in age or sex. In patients with polymicrobial Pa-BSIs, the proportion of those with a history of a cerebrovascular accident (CVA) was significantly higher than that in patients with monomicrobial Pa-BSI ($p < 0.05$). There was no significant difference between the two groups in other comorbidities. Compared with patients with monomicrobial Pa-BSI, patients with polymicrobial Pa-BSI presented higher SOFA scores (7.0 [4-11] vs 5 [3-9]), higher APACHE II scores (16 [12-25] vs 16 [11-20]), higher Pitt bacteremia scores (5 [3-6.5] vs 3 [1-6]), higher rates of admission to the ICU (74% vs 59.7%), more use of mechanical ventilation (75.3% vs 52.5%), and more nosocomial infections (97.4% vs 88.1%) (all $p < 0.05$).

3.2. Biological indicators

Table 2 compares biological indicators between polymicrobial and monomicrobial Pa-BSIs. In comparison to patients with monomicrobial Pa-BSI, patients with polymicrobial Pa-BSI had worse liver function, as evidenced by significant increases in glutamic-oxaloacetic transaminase (median, 45 vs 35, $p < 0.01$) and lactic dehydrogenase (median, 299 vs 244, $p \leq 0.01$). However, there was no significant difference in procalcitonin between the two groups or for any of the other biochemical parameters assessed.

3.3. Bacteriology, sources of polymicrobial Pa-BSI and antibiotic resistance

Blood culture results for 77 polymicrobial Pa-BSIs showed that gram-negative bacteria accounted for 77.4% of the cases, with *Acinetobacter baumannii* as the main copathogen, followed by

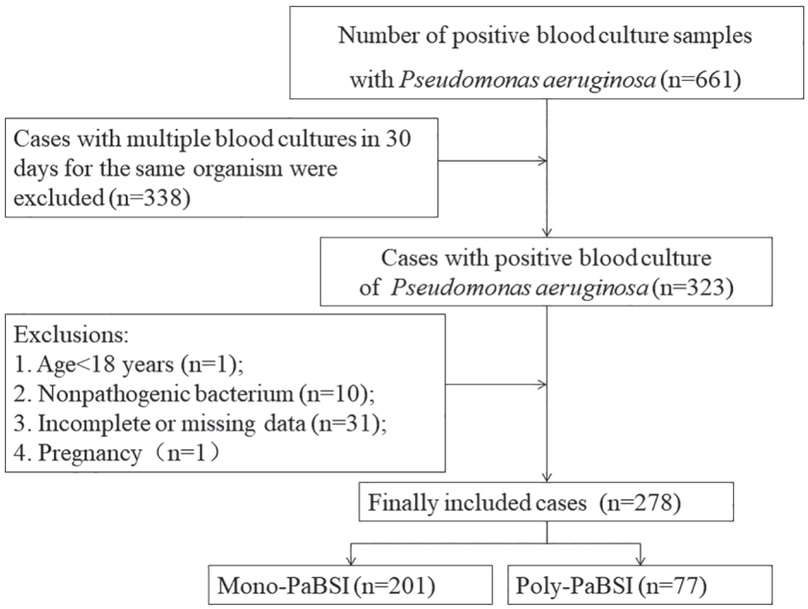

Fig. 1 Flowchart of study participant enrollment. Pa-BSI = *Pseudomonas aeruginosa* bloodstream infection.

Klebsiella pneumoniae; *Enterococcus* was the main gram-positive copathogen (Table 3). Among patients with polymicrobial BSI, three kinds of microorganisms, including *P. aeruginosa*, were isolated from blood cultures of three patients, and four were isolated from one patient.

Regarding the source of infection, pneumonia (36.3%, 101/278) was the main source of Pa-BSI, followed by skin/soft tissue infection (16.5%, 46/278) and primary BSI (16.5%, 46/278). Compared with monomicrobial Pa-BSI, the main source of polymicrobial Pa-BSI was pneumonia (49.4% vs 31.3%, $p < 0.01$), whereas the main source of monomicrobial Pa-BSI was primary BSI (21.9% vs 2.6%, $p = 0.04$) (Table 4). Details of antimicrobial resistance and antimicrobial therapy are shown in Table 4. *Pseudomonas aeruginosa* showed up to 62% resistance to imipenem. We did not find significant differences in drug resistance between the two groups. In addition, only 3.6% (10/349) of patients did not receive appropriate therapy within 24 hours after the release of antibiotic susceptibility results, with no difference between the two groups (3.0% vs 5.2%, $p = 0.38$) (Table 4).

3.4. Independent risk factors for polymicrobial Pa-BSI

Univariate analysis showed that comorbidities such as CVA, ICU admission, nosocomial infection, use of mechanical ventilation, and high SOFA, APACHE II, and Pitt bacteremia scores were associated with polymicrobial Pa-BSI. As shown in multivariate analysis (Table 5), a history of CVA (adjusted odds ratio [OR], 3.62; 95% CI, 1.47-8.92) was the only independent risk factor associated with polymicrobial Pa-BSI. Interestingly, primary BSI might be more associated with monomicrobial Pa-BSI (aOR, 0.08; 95% CI, 0.02-0.38).

3.5. Outcomes

Patients with polymicrobial Pa-BSI had a longer length of ICU stay after onset of BSI than the monomicrobial group (13 [3.75-29] vs 2 [2-16], $p = 0.02$). There was no significant difference in the length of hospital stay or duration of mechanical ventilation (days) after onset of BSI between the two groups. The overall in-hospital crude mortality rate was 35.6%, with no difference in 7-, 14-day, or in-hospital mortality between the two groups (all $p > 0.05$) (Table 6). Interestingly, the 28-day mortality rate was higher in patients with polymicrobial Pa-BSIs than in those with monomicrobial Pa-BSIs (40.3% vs 27.9%, $p = 0.05$). Furthermore, we found no significant difference between the two groups in survival curve analysis (Fig. 2).

4. DISCUSSION

The focus of this study was to identify the clinical characteristics and risk factors for polymicrobial Pa-BSI in two large general hospitals in China. This is the first reanalysis of the clinical characteristics of polymicrobial Pa-BSI in more than 15 years, and it is the largest epidemiological study of polymicrobial Pa-BSI to date. Our current study provides several findings, as follows: (1) the prevalence of polymicrobial BSIs among patients infected with *P. aeruginosa* is not uncommon. (2) Some risk factors were found to be associated with polymicrobial Pa-BSIs, as shown in Table 1. Pneumonia as a source of infection was also associated with polymicrobial Pa-BSIs. Moreover, a history of CVA was the only independent risk factor associated with polymicrobial Pa-BSIs, and primary BSI might be more associated with monomicrobial Pa-BSIs. (3) The main copathogens of polymicrobial Pa-BSIs were gram-negative bacteria, especially *A. baumannii*. (4) Patients with polymicrobial Pa-BSIs had a longer length of ICU stay after onset of BSI, but there was no significant difference in mortality.

Among Pa-BSIs in the current study, a high proportion (27.7%) was polymicrobial Pa-BSIs, which is consistent with previous studies.[12,13] In Marra et al's report,[13] polymicrobial Pa-BSIs accounted for 21.4% (21/98) of all BSI episodes at Virginia Commonwealth University Medical Center. Accordingly, polymicrobial BSI is not a rare occurrence, which warrants clinician attention.

Our study showed that imipenem-resistant *P. aeruginosa* accounted for 62.9%, which is basically consistent with the reports of Baumgart et al and Kiffer et al,[17,18] but it is significantly higher than the national average level provided by China Antimicrobial Surveillance Network (CHINET) in 2020

Table 1

Demographic and clinical characteristics of the patients with polymicrobial Pa-BSIs compared with monomicrobial Pa-BSIs

Characteristics	Total (n = 278)	Monomicrobial Pa-BSI (n = 201)	Polymicrobial Pa-BSI (n = 77)	*p*
Age, y (mean ± SD)	58.19 ± 16.41	59.31 ± 15.99	55.27 ± 17.22	0.07
Male sex	204 (73.4%)	145 (72.1%)	59 (76.6%)	0.45
Co-morbidities				
Diabetes mellitus	33 (11.9%)	23 (11.4%)	10 (13.0%)	0.72
Chronic kidney disease	21 (7.6%)	15 (7.5%)	6 (7.8%)	0.93
Chronic liver disease	4 (1.4%)	3 (1.5%)	1 (1.3%)	1
COPD or severe asthma	11 (4%)	8 (4%)	3 (3.9%)	1
Chronic cardiac insufficiency	22 (7.9%)	18 (9.0%)	4 (5.2%)	0.46
Solid tumor	49 (17.6%)	34 (16.9%)	15 (19.5%)	0.62
Trauma	90 (32.4%)	65 (32.3%)	25 (32.5%)	0.98
Burn injury	44 (15.8%)	30 (14.9%)	14 (18.2%)	0.51
Cerebrovascular accident	31 (11.2%)	16 (8%)	15 (19.5%)	**<0.01**
Long-term corticoid treatment	7 (2.5%)	6 (3.0%)	1 (1.3%)	**0.42**
HIV or immunosuppressed status	6 (2.2%)	5 (2.5%)	1 (1.3%)	**0.54**
Hematological diseases	13 (4.7%)	11 (5.5%)	2 (2.6%)	**0.31**
CCI, median (IQR)	3 (1-5)	3 (1-5)	3 (1-4)	0.50
APACHE II score, median (IQR)	17 (11-21)	16 (11-20)	18 (12-25)	**0.02**
SOFA score, median (IQR)	6 (3-9.25)	5 (3-9)	7 (4-11)	**0.03**
Pitt bacteremia score, median (IQR)	4 (1-6)	3 (1-6)	5 (3-6.5)	**<0.01**
Hospitalization ward				
ICU	177 (63.7%)	120 (59.7%)	57 (74%)	**0.03**
Previous treatment				
Hyperalimentation	138 (49.6%)	100 (49.8%)	38 (49.4%)	0.95
Mechanical ventilation	163 (58.6%)	105 (52.2%)	58 (75.3%)	**<0.01**
Antibiotic exposure	267 (99.3%)	191 (99%)	76 (100%)	0.37
Use of carbapenems	115 (41.4%)	78 (38.8%)	37 (48.1%)	0.16
Surgery	133 (47.8%)	90 (44.8%)	43 (55.8%)	0.10
Chemotherapy/radiation	6 (2.2%)	5 (2.5%)	1 (1.3%)	0.54
Renal replacement therapy	51 (18.3%)	34 (16.9%)	17 (22.1%)	0.32
Blood transfusion	85 (30.6%)	58 (28.9%)	27 (35.1%)	0.32
Invasive devices				
Central line	194 (69.8%)	140 (69.7%)	54 (70.1%)	0.94
Indwelling urinary catheter	209 (75.2%)	145 (72.1%)	64 (83.1%)	0.06
Intraperitoneal drainage	36 (12.9%)	25 (12.9%)	10 (13%)	0.99
Prior hospital stay, median days (IQR)	13 (8-26)	13 (6.5-25)	16 (10-27)	0.17
Nosocomial infection	252 (90.6%)	117 (88.1%)	75 (97.4%)	**0.02**
Neutropenia	20 (7.2%)	17 (8.5%)	3 (3.9%)	0.30

Bold indicates $p < 0.05$.

APACHE = Acute Physiology, Age and Chronic Health Evaluation; CCI = Charlson Comorbidity Index; COPD = chronic obstructive pulmonary disorder; ICU = intensive care unit; IQR = interquartile range; Pa-BSI = *Pseudomonas aeruginosa* bloodstream infections; SOFA = sequential organ failure assessment.

Table 2

Comparison of biological indicators between polymicrobial Pa-BSI and monomicrobial Pa-BSI

Biological indicators	Total (n = 278)	Monomicrobial Pa-BSI (n = 201)	Polymicrobial Pa-BSI (n = 77)	*p*
Blood routine test				
WBC ($\times 10^9$/L), median (IQR)	10.5 (6.5-15.68)	10.7 (6.25-16.15)	9.3 (6.85-13.40)	0.40
Hematocrit (%), median (IQR)	26.5 (21.48-31.6)	26.9 (22.15-32)	23.7 (21.15-29)	0.06
Platelet ($\times 10^9$/L), median (IQR)	151.5 (72.75-239.5)	153 (87-245.5)	136 (49.5-233)	0.18
ANC, median (IQR)	9.05 (5.2-13.93)	9.5 (5.2-15)	7.8 (5.2-11.85)	0.30
Liver and kidney function				
Albumin, g/L (mean ± SD)	31.04 ± 5.52	31.17 ± 5.71	30.70 ± 5.03	0.53
GPT (U/L), median (IQR)	33 (20-59)	32 (19-56)	37 (21.5-62)	0.28
GOT (U/L), median (IQR)	38 (22-62)	35 (21-57)	45 (29.5-83)	**<0.01**
ALP (U/L), median (IQR)	121 (98-157)	121 (101.5-162.5)	121 (86.5-131.5)	**0.04**
γ-GT (U/L), median (IQR)	42.5 (23-87.25)	48 (23-96)	31 (22-67.5)	0.14
LDH (U/L), median (IQR)	251.5 (203-391.5)	244 (195-363)	299 (221.5-545)	**<0.01**
TBil, μmol/L, median (IQR)	18.55 (11.05-35.05)	17 (10.75-35.1)	21.3 (11.6-34.8)	0.45
SCr, μmol/L, median (IQR)	62.5 (44-96.25)	59 (44-93)	68 (44-123.5)	0.18
PCT, ng/mL, median (IQR)	1.3 (0.41-6.61)	1.2 (0.35-5.83)	1.71 (0.55-7.49)	0.21

Bold indicates $p < 0.05$.

γ-GT = gamma glutamyl transpeptidase; ALP = alkaline phosphatase; ANC = absolute neutrophil count; GOT = glutamic-oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase; IQR = interquartile range; LDH = lactic dehydrogenase; Pa-BSI = *Pseudomonas aeruginosa* bloodstream infections; PCT = procalcitonin; SCr = serum creatinine; TBil = total bilirubin; WBC = white blood count.

Table 3

Characteristics of 82 copathogens isolated in 77 cases of polymicrobial BSI

Microorganisms	Polymicrobial BSI cases (n = 77)
Number of agents (associated with Pa-BSI)	
1	73 (94.8%)
2	3 (3.9%)
3	1 (1.3%)
Gram-positive bacteria	18 (22%)
Coagulase-negative *Staphylococci*	3 (3.7%)
Staphylococcus aureus	5 (6.1%)
Enterococcus sp.	9 (11%)
S. agalactiae	1 (1.2%)
Gram-negative bacteria	61 (74.4%)
Acinetobacter baumannii	25 (30.5%)
Klebsiella pneumoniae	21 (25.6%)
Enterobacter sp.	8 (9.8%)
Serratia sp.	7 (8.5%)
Fungus	2 (2.4%)
Anaerobic bacteria	1 (1.2%)

BSI = bloodstream infections; Pa-BSI = *Pseudomonas aeruginosa* bloodstream infections; *S. agalactiae* = *Streptococcus agalactiae*.

(23.2%).[19] This significant difference can be attributed to the fact that our study focused specifically on *P. aeruginosa* BSIs and that CHINET encompassed *P. aeruginosa*–related infections. We observed that a substantial proportion (63.7%) of the patients included in our study had been admitted to the ICU and frequently had compromised immune systems. Another study[20] in cancer patients with febrile neutropenia showed that *P. aeruginosa* has a 75% resistance rate to imipenem. In another study on *P. aeruginosa* BSIs, we detected CRPA in up to 60% of cases.[21] The environmental conditions within the bloodstream and the immunosuppressed states of patients may foster bacterial growth and evolutionary changes. In such a compromised condition, *P. aeruginosa* may have an increased ability to survive and proliferate, augmenting its adaptability to carbapenem drugs. Previous studies have shown an increased risk of resistance to different classes of antibiotic for *P. aeruginosa* isolated from patients who received antimicrobial treatment before bacteremia.[22] In our study, a higher proportion of patients had already been treated with carbapenems before onset of the BSI, which further contributed to the elevated levels of imipenem resistance observed. Therefore, it becomes particularly imperative to reduce the imipenem utilization rate to combat this problem effectively.

We found that pneumonia, skin and soft tissue, and primary BSIs were the main sources of *P. aeruginosa* BSI. Compared with the monomicrobial group, the main source of polymicrobial *P. aeruginosa* BSI was pneumonia, whereas the main source of the monomicrobial group was primary BSI. Previous reports have shown that polymicrobial *P. aeruginosa* BSIs are always more common in burn patients, and loss of the natural skin barrier may lead to microbial colonization and subsequent invasion of the bloodstream.[13] In our study, although the proportion of burns in polymicrobial BSI was higher than that in monomicrobial BSI (18.2% vs 14.9%), there was no significant difference between the two, and the same was true with the source being skin and soft tissue (20.8% vs 14.9%, $p = 0.24$). Although the proportion of burn patients in our study was not significantly different from that in a previous study[13] (15% vs 17%), this might be because our sample size (278) was significantly larger than that of the previous study (98), resulting in different results.

Table 4

Comparison of the microbiological characteristics with monomicrobial Pa-BSI and polymicrobial Pa-BSI

	Total (n = 278)	Monomicrobial Pa-BSI (n = 201)	Polymicrobial Pa-BSI (n = 77)	*p*
Source of BSIs				
Intra-abdominal	26 (9.4%)	19 (9.5%)	7 (9.1%)	0.93
Primary BSI	46 (16.5%)	44 (21.9%)	2 (2.6%)	**<0.01**
Pneumonia	101 (36.3%)	63 (31.3%)	38 (49.4%)	**<0.01**
Skin and soft tissue infection	46 (16.5%)	30 (14.9%)	16 (20.8%)	0.24
Central venous catheter	27 (9.7%)	18 (9%)	9 (11.7%)	0.49
Urinary tract infection	15 (5.4%)	13 (6.5%)	2 (2.6%)	0.25
Intracranial	1 (0.4%)	1 (0.5%)	0 (0%)	1
Biliary	13 (4.3%)	11 (5.5%)	2 (2.6%)	0.53
Joint	3 (1.1%)	2 (1.0%)	1 (1.3%)	1
Antibiotic resistance[a]				
Amikacin (200 vs 76)[b]	27 (9.8%)	19 (9.5%)	8 (10.5%)	0.80
Aztreonam (138 vs 55)[b]	76 (39.4%)	52 (37.7%)	24 (43.6%)	0.45
Ciprofloxacin (201 vs 77)[b]	119 (42.8%)	87 (43.3%)	32 (41.6%)	0.80
Piperacillin/tazobactam (201 vs 77)[b]	109 (39.2%)	78 (38.8%)	31 (40.3%)	0.82
Gentamicin (201 vs 77)[b]	73 (26.3%)	53 (26.4%)	20 (26%)	0.97
Cefepime (201 vs 77)[b]	96 (34.5%)	69 (34.3%)	27 (35.1%)	0.91
Tobramycin (195 vs 72)[b]	79 (29.6%)	60 (30.8%)	19 (26.4%)	0.49
Levofloxacin (199 vs 76)[b]	103 (37.5%)	78 (39.2%)	25 (32.9%)	0.33
Imipenem (197 vs 75)[b]	171 (62.9%)	125 (63.5%)	46 (63.1%)	0.75
Treatment after the onset of BSIs				
Delayed antibiotic therapy	10 (3.6%)	6 (3.0%)	4 (5.2%)	0.38
Proportion of appropriate empirical therapy	268 (96.4%)	195 (97.0%)	73 (94.8%)	0.38

Bold indicates $p < 0.05$.

BSI = bloodstream infections; Pa-BSI = *Pseudomonas aeruginosa* bloodstream infections.

[a]Not all agents listed tested in all isolates.

[b]The numbers in parentheses represent the total numbers of *Pseudomonas aeruginosa* isolates performed susceptibility test.

Table 5

Multivariable logistic regression of factors associated with polymicrobial *Pseudomonas aeruginosa* bloodstream infections

Variable	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Cerebrovascular accident	0.36 (0.17-0.77)	<0.01	3.62 (1.47-8.92)	**<0.01**
APACHE II score	1.04 (1.00-1.08)	0.03		
SOFA score	1.08 (1.02-1.14)	0.01		
Pitt bacteremia score	1.19 (1.08-1.30)	<0.01		
ICU stay	0.52 (0.29-0.93)	0.03		
Pneumonia	2.13 (1.25-3.65)	<0.01		
Primary BSI	0.10 (0.02-0.40)	<0.01	0.08 (0.02-0.38)	**<0.01**
Nosocomial infection	0.20 (0.05-0.85)	0.03		
Mechanical ventilation	0.36 (0.20-0.65)	<0.01		

Bold indicates $p < 0.05$.

APACHE = Acute Physiology, Age and Chronic Health Evaluation; BSI = bloodstream infections; ICU = intensive care unit; OR = odds ratio; SOFA = sequential organ failure assessment.

Table 6

Comparison of outcome between monomicrobial Pa-BSI and polymicrobial Pa-BSI

Prognostic indicators	Total (n = 278)	Monomicrobial Pa-BSI (n = 201)	Polymicrobial Pa-BSI (n = 77)	*p*
Hospital stays after onset of BSI (M) (IQR)	14.5 (6-34)	14 (6-33)	15 (4-41.5)	0.96
ICU residence days after onset BSI (M) (IQR)	8 (2-19)	2 (2-16)	13 (3.75-29)	**0.02**
Days of mechanical ventilation after onset BSI (M) (IQR)	6 (2-15)	5 (2-15)	8 (3-15.25)	0.18
Cause septic shock (n, %)	62 (22.3%)	40 (19.9%)	22 (28.6%)	0.12
7 d total mortality rate (n, %)	55 (19.8%)	36 (17.9%)	19 (24.7%)	0.21
14 d total mortality rate (n, %)	75 (27.0%)	49 (24.4%)	26 (33.8%)	0.12
28 d total mortality rate (n, %)	87 (31.3%)	56 (27.9%)	31 (40.3%)	0.05
In-hospital mortality (n, %)	99 (35.6%)	66 (32.8%)	33 (42.9%)	0.12

Bold indicates $p < 0.05$.

BSI = bloodstream infections; ICU = intensive care unit; IQR = interquartile range; M = median; Pa-BSI = *Pseudomonas aeruginosa* bloodstream infection.

Risk factors for Pa-BSI were mainly severe immunodeficiency, older age, previous antibiotic therapy, and presence of a central venous catheter,[23] but risk factors for polymicrobial *P. aeruginosa* BSIs have rarely been reported. In the current study, patients with polymicrobial Pa-BSIs presented a history of CVAs, had higher SOFA, APACHE II, and Pitt bacteremia scores, had higher rates of ICU admission, more frequently needed mechanical ventilation, and presented more nosocomial infections (see Table 1). Further multivariate regression analysis showed that a history of CVA was an independent factor of polymicrobial Pa-BSI. Patients with a history of CVA were critically ill, immunocompromised, and needed to take a large amount of broad-spectrum antibiotics for a long time due to factors such as long-term bed rest and a high tracheotomy rate. Various invasive operations were also required for resuscitation treatment, facilitating nosocomial infection or even polymicrobial BSI.

The most common copathogen in polymicrobial Pa-BSIs was *A. baumannii* (30.5%) in the current study. Previous studies have shown that *Acinetobacter*, which is a nonfermentative organism and an important causative agent of nosocomially acquired BSI, may be a copathogen of *P. aeruginosa* BSIs.[12] In fact, the high proportion of *A. baumannii* as a copathogen in polymicrobial Pa-BSIs was also indirectly reflected by evidence that the proportion of sources of pneumonia was high in the polymicrobial group in our current study, as *A. baumannii* is frequently associated with pneumonia.[24,25] Among positive copathogens, it was previously reported[13] that coagulase-negative *Staphylococcus* was highest among the polymicrobial BSIs. In our study, *Enterococcus* and *Staphylococcus aureus* were highest, at 11% and 6.1%, respectively. This might be due to the stricter definition of polymicrobial BSI, which greatly reduces the possibility of false classification of coagulase-negative bacteria.

Our study also had certain limitations. First, this was a retrospective, double-center study and was subject to inherent limitations associated with retrospective analyses. Second, our sample size was limited. Third, inexact matching and/or incomplete matching might have affected the results of our study. Thus, a multicenter and paired study with a large sample size is necessary to further investigate risk factors for polymicrobial Pa-BSI for better prevention.

In conclusion, polymicrobial BSIs were common, with *A. baumannii* being the most prevalent copathogen in this cohort. Patients with Pa-BSI and the presence of CVA need to be alert to the occurrence of polymicrobial BSI. Prolonged ICU stay and pneumonia as a source of BSI warrant clinician attention to polymicrobial Pa-BSI, whereas primary BSIs are likely associated with monomicrobial BSIs.

ACKNOWLEDGMENTS

This work was supported in part by grants from the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (No. 2022KY1398, Cheng Zheng; No. 2022KY1394, Chuming Zhang; No. 2022KY1396, Xijiang Zhang, No. 2023KY317, Li Zhong; No. 2020KY1031, Ronghai Lin); Taizhou Social Development Science and Technology Program (No. 23ywb70, Qingqing Chen) and the Natural Science Foundation of Zhejiang Province (No. LY20H150008, Ronghai Lin).

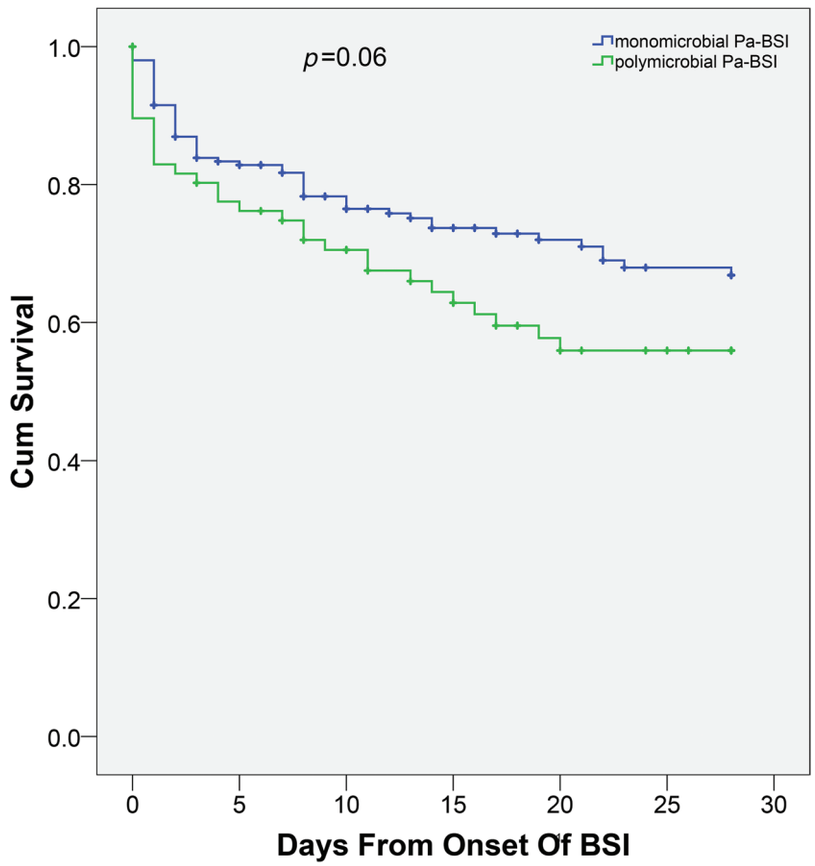

Fig. 2 Kaplan-Meier estimates of survival in patients with polymicrobial and monomicrobial Pa-BSIs. Pa-BSIs = *Pseudomonas aeruginosa* bloodstream infections.

REFERENCES

1. Pavlaki M, Poulakou G, Drimousis P, Adamis G, Apostolidou E, Gatselis NK, et al. Polymicrobial bloodstream infections: epidemiology and impact on mortality. *J Glob Antimicrob Resist* 2013;1:207–12.
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;39:309–17.
3. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis* 1997;24:584–602.
4. Lin JN, Lai CH, Chen YH, Chang LL, Lu PL, Tsai SS, et al. Characteristics and outcomes of polymicrobial bloodstream infections in the emergency department: a matched case-control study. *Acad Emerg Med* 2010;17:1072–9.
5. Marra AR, Camargo LF, Pignatari AC, Sukiennik T, Behar PR, Medeiros EA, et al; Brazilian SCOPE Study Group. Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. *J Clin Microbiol* 2011;49:1866–71.
6. McCarthy KL, Paterson DL. Community-acquired Pseudomonas aeruginosa bloodstream infection: a classification that should not falsely reassure the clinician. *Eur J Clin Microbiol Infect Dis* 2017;36:703–11.
7. Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G. Recent experience with Pseudomonas aeruginosa bacteremia in patients with cancer: retrospective analysis of 245 episodes. *Arch Intern Med* 2000;160:501–9.
8. Osmon S, Ward S, Fraser VJ, Kollef MH. Hospital mortality for patients with bacteremia due to Staphylococcus aureus or Pseudomonas aeruginosa. *Chest* 2004;125:607–16.
9. Kang CI, Kim SH, Kim HB, Park SW, Choe YJ, Oh MD, et al. Pseudomonas aeruginosa bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* 2003;37:745–51.
10. Jones CJ, Ryder CR, Mann EE, Wozniak DJ. AmrZ modulates Pseudomonas aeruginosa biofilm architecture by directly repressing transcription of the psl operon. *J Bacteriol* 2013;195:1637–44.
11. Persoon MC, Voor In't Holt AF, Wielders CCH, Gommers D, Vos MC, Severin JA. Mortality associated with carbapenem-susceptible and Verona Integron-encoded Metallo-β-lactamase-positive Pseudomonas aeruginosa bacteremia. *Antimicrob Resist Infect Control* 2020;9:25.
12. Aliaga L, Mediavilla JD, Llosá J, Miranda C, Rosa-Fraile M. Clinical significance of polymicrobial versus monomicrobial bacteremia involving Pseudomonas aeruginosa. *Eur J Clin Microbiol Infect Dis* 2000;19:871–4.
13. Marra AR, Bearman GM, Wenzel RP, Edmond MB. Comparison of the systemic inflammatory response syndrome between monomicrobial and polymicrobial Pseudomonas aeruginosa nosocomial bloodstream infections. *BMC Infect Dis* 2005;5:94.
14. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). *National Healthcare Safety Network* 2022. Available at https://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf. Accessed September 28, 2023.
15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128–40.
16. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–10.
17. Baumgart AM, Molinari MA, Silveira AC. Prevalence of carbapenem resistant Pseudomonas aeruginosa and Acinetobacter baumannii in high complexity hospital. *Braz J Infect Dis* 2010;14:433–6.
18. Kiffer C, Hsiung A, Oplustil C, Sampaio J, Sakagami E, Turner P, et al; MYSTIC Brazil Group. Antimicrobial susceptibility of Gram-negative bacteria in Brazilian hospitals: the MYSTIC program Brazil 2003. *Braz J Infect Dis* 2005;9:216–24.

19. Fupin H, Yan G, Demei Z, Fu W, Xiaofei J, Yingchun X, et al. CHINET surveillance of bacterial resistance: results of 2020. *Chin J Infect Chemother* 2021;21:377–87.
20. Joudeh N, Sawafta E, Abu Taha A, Hamed Allah M, Amer R, Odeh RY, et al. Epidemiology and source of infection in cancer patients with febrile neutropenia: an experience from a developing country. *BMC Infect Dis* 2023;23:106.
21. Yuan Q, Guo L, Li B, Zhang S, Feng H, Zhang Y, et al. Risk factors and outcomes of inpatients with carbapenem-resistant Pseudomonas aeruginosa bloodstream infections in China: a 9-year trend and multicenter cohort study. *Front Microbiol* 2023;14:1137811.
22. Joo EJ, Kang CI, Ha YE, Kang SJ, Park SY, Chung DR, et al. Risk factors for mortality in patients with Pseudomonas aeruginosa bacteremia: clinical impact of antimicrobial resistance on outcome. *Microb Drug Resist* 2011;17:305–12.
23. Schechner V, Nobre V, Kaye KS, Leshno M, Giladi M, Rohner P, et al. Gram-negative bacteremia upon hospital admission: when should Pseudomonas aeruginosa be suspected? *Clin Infect Dis* 2009;48:580–6.
24. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993;94:281–8.
25. García-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, Jiménez-Jiménez FJ, Pérez-Paredes C, Barrero-Almodóvar AE, et al. Risk factors for Acinetobacter baumannii nosocomial bacteremia in critically ill patients: a cohort study. *Clin Infect Dis* 2001;33:939–46.