Characteristics and Risk Factors Associated with Early Mortality in Patients with Polymicrobial Bloodstream Infection: A Retrospective Clinical Study

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Abstract

Background and Objective Polymicrobial bloodstream infections (PBSI) in hospitalized patients are associated with increased mortality, while few studies have characterized the clinical features in this population. This study aimed to assess the risk factors and short-term prognosis of PBSI in hospitalized patients.

Materials and Methods 4066 patients with culture-positive blood were included between January 1, 2015 and December 31, 2017 in the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) in our study. 218 patients were diagnosed as PBSI. The patients were divided into two groups according to the outcome after 30-day follow-up. The number of survival group were 129, while the number of non-survival group were 89. The clinical data, identified microorganisms and severity models were compared between the two groups. A cox regression model was used to identify the risk factors of 30-day mortality in PBSI patients. Five prediction models were compared by Z-test to test the value of these models to predict outcome of PBSI.

Results The patients in the non-survival group were more likely to receive inappropriate antibiotic therapy at the time of PBSI and showed more severe in systemic inflammatory. They were more likely to develop to be septic shock and to be admitted in ICU than the patients in the survival group. Inappropriate initial empirical antimicrobial therapy (HR=1.713 95% CI: 1.063-2.760, p=0.027), white blood cell (HR=1.740 95% CI: 1.002-3.020, p=0.049) and platelet (HR=2.940 95% CI: 1.754-4.930, p<0.001) were independent risk factors for 30-day mortality in PBSI patients. SOFA (AUROC=0.882, 95% CI=0.832-0.922) scores was a good prognostic scoring system for predicting short-term mortality in PBSI patients. The SOFA score was more valuable than the other four models in predicting the outcome of PBSI according to the Z-test (p<0.05).

Discussion and Conclusions Inappropriate initial empirical antimicrobial therapy, white blood cell and platelet were closely associated with short-term mortality.

Introduction

Bloodstream infection continues to be a public health problem and it is closely linked with major morbidity and mortality worldwide. As reported, The prevalence rate of BSI is 19 million cases per year worldwide (1). In the USA, BSI is ranked as the 11th leading cause of death according to a 2008 survey (2) and it caused 600 fatalities every day (1). In China, according to a systematic review and meta-analysis of 72 studies in 2010, the weighted BSI in-hospital mortality rate was 28.7% (3). The diagnosis of BSI is relay on blood cultures obtained from a patient with clinical signs of infection while ruling out contamination. Routine blood culture is always too slow to support rapid therapeutic interventions (1). The guidelines recommend that empirical antibiotics be used within the first hour after sepsis or septic shock is detected (4). However, there are some challenges that empiric treatment may not cover the correct pathogen or contribute to the evolution of resistant microorganisms (1).
Polymicrobial bloodstream infection (PBSI) was a special subcategory of BSI. The rates of PBSI have been reported range from 5–20% among patients with BSI(5). The underlying medical conditions including malignancy, gastrointestinal and genitourinary disease, the presence of central venous catheters (CVC), are closely associate with occurrence of PBSI. Notably, PBSI may present different clinical presentations, microbiological characteristics and outcomes compared with monomicrobial BSI. Gram-negative organisms were the most frequent causative agents in PBSI (6–9) which is contrary to BSI (10). The mortality rate of patients with polymicrobial BSIs ranged from 14–43%, approximately two times the mortality rate of those with monomicrobial BSIs (11). It was reported that inappropriate antimicrobial treatment was related to the high mortality (12).

Although high short-term mortality among patients with PBSI were noted, few reports have fully analyzed the clinical features and short-term prognosis of PBSI in hospitalized patients. How to screen for high-risk patients that we need pay special attention is still a problem. To improve the survival rate, we analyzed the risk factors for short-term mortality to optimize stratification and no one had done it yet.

Methods

Patients and settings

We identified blood culture-positive patients from the microbiology database. Total 4066 patients with BSI between January 1, 2015, and December 31, 2017, in the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) were screened in this study. PBSI was defined as the growth of two or more organisms from blood culture specimens obtained from a patient within a period of < 72 hours (6).

Data collection

All the data of each patient were collected at the diagnosis of polymicrobial bloodstream infection from inpatient records; the collected data included sex; age; alcohol abuse; smoking; co-morbidity such as hypertension, diabetes, hematological malignancy and malignant parenchymal tumor; history of transplant; previous chemotherapy or corticosteroid therapy in the last 3 months; other sites of infection; laboratory examination, clinical presentation, microbiological data, treatments, ICU admission, and prognosis. For those patients who experienced multiple episodes of PBSI during the study period, only the first PBSI was included in the analysis. We defined inappropriate initial empirical antibiotic therapy as follows: At least one of the bacteria isolated was not sensitive to the antibiotics administered (13) or no antibiotic use before the positive blood culture (14). Nosocomial infections were confirmed after 48 hours of admission. Five prognostic models, the sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE II), systemic inflammatory response (SIRS), the quick sequential organ failure assessment (qSOFA) and simplified acute physiology score II (SAPS II) were used to predict early mortality. The SOFA score is widely used to diagnose organ failure in general intensive care units by evaluating liver, kidney, brain, coagulatory, circulatory or respiratory failure (15). The APACHE II score indicates the severity of disease through a disease classification system that generally uses a point score.
based on the initial values of 12 routine physiologic measurements, age and previous health status (16). SIRS is used to describe the complex pathophysiologic response when at least 2 of the following four symptoms appeared: tachypnea, tachycardia, leukopenia or leukocytosis and fever or hypothermia (17). The qSOFA was calculated by following criteria: systolic arterial blood pressure ≤ 100 mmHg; respiratory rate > 21 breaths/min; or altered mental status (17). The SAPS II includes 12 physiology variables, age, type of admission and three underlying disease variables (18). The APACHE II score and SAPS II were mainly evaluated in the first 24 hours in the ICU but were calculated at the time of diagnosis of PBSI in this study.

**Microbiologic studies**

Blood specimens were collected with one or two tubes from both sides of each patient who presented with fever ≥ 38.5°C or when BSI was suspected based on clinical signs within 5 min. The identification of blood isolates was carried out according to routine methods by the staff of the microbiology laboratory in our hospital.

**Statistical analysis**

The statistical analyses were performed by using SPSS software version 20 (IBM Inc., Chicago, IL, USA). The results are shown as mean ± standard deviations (SDs) for continuous variables or numbers and percentages for categorical variables. Student’s t-tests were was used to analyze the differences between the continuous variables, and χ²-tests were used for the categorical variables. The variables that were statistically significant in the univariate analysis were included in a multiple cox regression model to analyze the potential predictors associated with mortality. The survival dates were analyzed with Kaplan-Meier survival curves. The different prognostic scoring systems were compared by receiver operating curves (ROCs).

**Results**

**Characteristics of patients**

After excluding the contaminated specimens, 218 of 4066 patients with BSI from January 1, 2015, to December 31, 2017, were screened in this study which is shown in Fig. 1. The clinical characteristics, laboratory examination results, treatments, severity scores and outcomes of patients with PBSI were depicted in Table 1. According to the survival days after the PBSI diagnosis, they were divided into a survival group (more than 30 days) and a nonsurvival group (no more than 30 days). Among the 129 patients in the survival group, the mean age was 59.4 ± 18.2 years, and 89 patients (69.0%) were male. Among the 89 patients in the nonsurvival group, the mean age was 60.1 ± 17.8 years, and 56 patients (62.9%) were male. The two groups did not show differences in their baseline characteristics, including age, sex, smoking and alcohol abuse. For comorbidities, such as hypertension, diabetes, cancer and history of transplantation, the two groups showed no differences. Moreover, the Charlson comorbidity index (CCI) was not different among the groups. Regarding treatment, patients in the nonsurvival group
showed a higher frequency of receiving inappropriate initial empirical antibiotic therapy before the diagnosis than patients in the survival group (p = 0.011). There were no differences in the rates of catheter-related infection, previous chemotherapy, or previous corticosteroid therapy. Regarding other sites of infection, patients in the nonsurvival groups showed a higher frequency of pulmonary infection than patients in the survival group (survival vs. nonsurvival, p = 0.001). For other coinfections, such as urinary tract infections, cerebral infections, and skin and soft tissue infections, there were no differences. The patients in the nonsurvival group showed more serious inflammation responses than the patients in the survival group. C-reactive protein (CRP) levels (p < 0.001) were higher and platelet counts (p < 0.001) were lower in the nonsurvival group than in the survival group. In addition, the patients in the nonsurvival group had lower hemoglobin (p = 0.003) and hematocrit levels (p = 0.001) than the patients in the survival group, meaning that the patients in the nonsurvival group were more likely to have anemia. In addition, the patients in the nonsurvival group had longer prothrombin times (p = 0.002), lower albumin (p < 0.001), and higher total bilirubin (p = 0.011) than the patients in the survival group; these factors were related to worse liver function, and high blood urea nitrogen (p = 0.002) and lactic acid levels (p < 0.001).
Table 1: Baseline characteristics and clinical presentations in patients in the survival and non-survival groups.

| Variables                           | Survival Group N=129 (%) | Non-survival Group N=89 (%) | P value |
|-------------------------------------|--------------------------|-----------------------------|---------|
| Demographics data                   |                          |                             |         |
| Age (years), M±SD                   | 59.4±18.2                | 60.1±17.8                   | 0.67    |
| Male sex                            | 89 (69.0%)               | 56 (62.9%)                  | 0.22    |
| Current smoking                     | 46 (35.7%)               | 27 (30.3%)                  | 0.25    |
| Alcohol abuse                       |                          |                             |         |
| Comorbidity                         | 40 (31.0%)               | 32 (36.0%)                  | 0.27    |
| Hypertension                        | 19 (14.7%)               | 12 (13.5%)                  | 0.48    |
| Diabetes                            | 40 (31.0%)               | 23 (25.8%)                  | 0.25    |
| Cancer                              | 8 (6.2%)                 | 5 (5.6%)                    | 0.55    |
| Transplant                          | 2.20±2.07                | 2.07±2.11                   | 0.57    |
| Charlson comorbidity index          | 21 (16.3%)               | 27 (30.3%)                  | **0.011**|
| Inappropriate initial empirical antimicrobial therapy | 7 (13.2%) | 7 (7.8%) | 0.16 |
| Catheter-related infection           |                          |                             |         |
| Previous chemotherapy               | 7 (5.4%)                 | 3 (3.4%)                    | 0.36    |
| Previous corticosteroid therapy     | 11 (8.5%)                | 11 (12.4%)                  | 0.24    |
| Other site of infection             |                          |                             |         |
| Urinary tract infection             |                          |                             |         |
| Skin or soft tissue infection       |                          |                             |         |
| Laboratory examination | Cerebral infection | Pulmonary infection | p-value |
|------------------------|-------------------|---------------------|---------|
| WBC, 10^E9 cells/L     | 15.4±9.1          | 17.3±10.5           | 0.16    |
|                        | 14.0±10.3         | 15.6±9.5            | 0.23    |
| Neutrophil, 10^E9 cells/L | 143.8±98.6        | 87.0±115.7          | <0.001  |
|                        | 86.4±25.7         | 75.8±26.0           | 0.003   |
| Platelet, 10^E9 cells/L | 26.5±7.4          | 22.9±8.2            | <0.001  |
| Hemoglobin, g/L        | 124.9±82.0        | 175.9±108.9         | <0.001  |
| Hematocrit             | 1.24±0.33         | 1.94±1.97           | <0.001  |
| C-reactive protein, mg/dL | 14.9±4.5          | 20.6±16.2           | 0.002   |
|                        | 31.5±5.6          | 27.4±6.2            | <0.001  |
| INR                    | 55.7±86.6         | 95.5±126.3          | 0.011   |
| Prothrombin time, s    | 152.1±214.2       | 162.2±136.3         | 0.67    |
| Albumin, g/dL          | 12.5±9.2          | 25.4±36.8           | 0.002   |
| Total bilirubin, mg/dL | 38.95±1.05        | 39.05±0.93          | 0.43    |
| Creatinine, μmol/L     |                   |                     |         |
| BUN, mmol/L            | 15 (11.6%)        | 46 (51.7%)          | <0.001  |
| Clinical presentation  | 58 (45.0%)        | 70 (78.7%)          | <0.001  |
| Highest heat, °C       | 14.2±26.3         | 14.7±23.9           | 0.89    |
| Septic shock           |                   |                     |         |
| Tracheal cannula       | 90 (70.0%)        | 56 (62.9%)          | 0.18    |
| Antibiotics treatment before diagnosis(days) | 26 (20.2%) | 29 (32.6%) | 0.027 |
|                        | 67 (52.0%)        | 73 (82.0%)          | <0.001  |
| Glucocorticoid administration more than 3 days | 6.61±4.27 | 14.20±4.77 | <0.001 |
| Nosocomial infection   | 12.19±6.23        | 21.56±7.23          | <0.001  |
When comparing the clinical presentations among the groups, patients in the nonsurvival showed a higher frequency of presenting septic shock ($p < 0.001$), requiring a tracheal cannula ($p < 0.001$), requiring dialysis ($p = 0.027$) and requiring ICU admission ($p < 0.001$). Finally, patients in the nonsurvival group had higher SOFA scores, APACHE II scores, qSOFA scores and SAPS II scores than patients in the survival group ($p < 0.001$).

### Risk factors for 30-d mortality in PBSI patients

The overall 30-d mortality rate in all patients with PBSI was 40.8% (89/218). The 30-day survived or dead events were recorded in all patients. The risk factors analyzed by univariate cox regression model for 30-d mortality in PBSI patients were shown in Table 2. The significant risk factors were compared by a multivariate cox regression analysis model in Table 3. After adjustment for potential confounding factors, we found that Inappropriate initial empirical antimicrobial therapy ($HR = 1.713$ 95% CI: 1.063–2.760, $p = 0.027$), WBC $> 11.2 \times 10^9$ ($HR = 1.740$ 95% CI: 1.002–3.020, $p = 0.049$) and platelet $\leq 54 \times 10^9$ ($HR = 2.940$ 95% CI: 1.754–4.930, $p < 0.001$) were independent risk factors for early mortality due to PBSI.
Table 2
Univariate cox regression analysis of 30-d mortality in patients with PBSI.

| Variables                              | HR (95% CI)                  | P value |
|----------------------------------------|------------------------------|---------|
| Age                                    | 0.767 (0.506–1.163)          | 0.211   |
| Male sex                               | 0.828 (0.538–1.273)          | 0.389   |
| Catheter-related infection             | 0.596 (0.276–1.291)          | 0.189   |
| Inappropriate initial empirical         | 1.832 (1.165–2.881)          | 0.009   |
| antimicrobial therapy                   | 2.026 (1.194–3.438)          | 0.009   |
| WBC, 10E9 cells/L                      | 3.579 (2.349–5.452)          | < 0.001 |
| Platelet, 10E9 cells/L                 | 2.092 (1.355–3.232)          | 0.001   |
| Hemoglobin, g/L                        | 2.440 (1.579–3.770)          | < 0.001 |
| Hematocrit, g/L                        | 2.623 (1.659–4.417)          | < 0.001 |
| C-reactive protein, mg/dL              | 2.916 (1.799–4.725)          | < 0.001 |
| Prothrombin time, s                    | 2.427 (1.543–3.818)          | < 0.001 |
| Albumin, g/dL                          | 1.961 (1.263–3.046)          | 0.003   |
| Total bilirubin > 23, mg/dl            | 6.973 (4.365–11.138)         | < 0.001 |
| APACHE II score > 17                   | 9.290 (5.308–16.260)         | < 0.001 |
| SOFA score > 9                         | 1.929 (0.782–4.755)          | 0.154   |
| SIRS                                   | 3.099 (2.040–4.708)          | < 0.001 |
| qSOFA ≥ 2                              | 5.266 (3.321–8.349)          | < 0.001 |
| SAPS II > 52                           |                              |         |
Table 3
Multivariate cox regression analysis of 30-d mortality in patients with PBSI.

| Variables                              | HR (95% CI)     | P value |
|----------------------------------------|-----------------|---------|
| Inappropriate initial empirical therapy| 1.713 (1.063–2.760) | 0.027   |
| antimicrobial therapy                  | 1.740 (1.002–3.020) | 0.049   |
| WBC, 10E⁹ cells/L                     | 2.940 (1.754–4.930) | <0.001  |
| Platelet, 10E⁹ cells/L                | 0.895 (0.331–2.415) | 0.826   |
| Hemoglobin, g/L                       | 1.288 (0.468–3.545) | 0.625   |
| Hematocrit, g/L                       | 1.578 (0.938–2.652) | 0.085   |
| C-reactive protein, mg/dL             | 1.554 (0.899–2.688) | 0.115   |
| Prothrombin time, s                   | 1.269 (0.770–2.093) | 0.351   |
| Albumin, g/dL                         | 0.859 (0.501–1.474) | 0.582   |
| Total bilirubin, mg/dl                |                 |         |

**Isolated microorganisms**

The isolates from all the PBSI cases by group were shown in Table 4. There were 461 microorganisms isolated from the blood cultures of 218 patients with PBSI.
Table 4
Etiologies of all episodes of BSI by group.

| Variables                        | Survival Group | Nonsurvival Group | All PBSI patients |
|----------------------------------|----------------|-------------------|-------------------|
| TOTAL                            | 272            | 189               | 461               |
| Gram-negative                    | 128            | 84                | 212 (46.0%)       |
| *Escherichia coli*               | 28             | 6                 | 34 (7.4%)         |
| *Pseudomonas aeruginosa*         | 16             | 11                | 27 (5.9%)         |
| *Burkholderia cepacia*           | 6              | 5                 | 11 (2.4%)         |
| *Klebsiella pneumoniae*          | 23             | 26                | 49 (10.6%)        |
| *Klebsiella oxytoca*             | 2              | 0                 | 2 (0.4%)          |
| *Enterobacter* spp.              | 10             | 2                 | 12 (2.6%)         |
| *Morganella morganii*            | 1              | 0                 | 1 (0.2%)          |
| *Proteus* spp.                   | 19             | 18                | 37 (8.0%)         |
| *Acinetobacter* spp.             | 0              | 2                 | 2 (0.4%)          |
| *Salmonella enterica* serovar enteritidis | 7     | 5                 | 12 (2.6%)         |
| *Stenotrophomonas maltophilia*   | 3              | 2                 | 5 (1.1%)          |
| *Chryseobacterium meningosepticum* | 111           | 74                | 185 (40.1%)       |
| Other                            | 10             | 7                 | 17 (2.7%)         |
| Gram-positive                    | 49             | 29                | 78 (16.9%)        |
| *Staphylococcus aureus*          | 3              | 1                 | 4 (0.9%)          |
| Coagulase-negative staphylococci | 8              | 8                 | 16 (3.5%)         |
| *Viridans* group streptococci    | 37             | 26                | 63 (13.7%)        |
| Other *Streptococcus*            | 15             | 9                 | 24 (5.2%)         |
| *Enterococcus* spp.              | 13             | 8                 | 21 (4.6%)         |
| Other                            | 2              | 1                 | 3 (0.7%)          |
| Anaerobes                        | 18             | 22                | 40 (8.7%)         |
| *Bacteroides* spp.               | 14             | 17                | 31 (6.7%)         |
| Other                            | 1              | 1                 | 2 (0.4%)          |
Among all organisms causing PBSI, gram-negative bacteria accounted for 46.0%, gram-positive bacteria accounted for 40.1%, anaerobes accounted for 5.2%, and fungi accounted for 8.7%. Among the gram-negative bacteria, *Klebsiella pneumoniae* (10.6%), *Acinetobacter* spp. (8.0%) and *Escherichia coli* (7.4%) were the most common. Coagulase-negative staphylococci (16.9%) and *Enterococcus* spp. (8.7%) were the most common gram-positive bacteria. *Candida* spp. (6.7%) was the most common in fungi.

Gram-positive bacteria were identified in 69.2% of the PBSI samples, and gram-negative bacteria were identified in 71.6%. There were both gram-positive and gram-negative bacteria in 45.9% of the PBSI samples. Among the patients in our study, 20.6% were infected with three or more microorganisms. However, the survival days were not significantly different between the two-pathogen group and the three or more-pathogen group (p = 0.37). The Kaplan-Meier diagrams showed that PBSI patients with fungal infection had significantly higher overall 30-day mortality than those without fungal infection (p = 0.024). However, the survival analysis identified no difference between the groups with or without gram-positive bacteria and the groups with or without gram-negative bacteria (Fig. 2).

### Value of the prognostic models in predicting 30-day mortality in PBSI patients

Five models, including the SOFA, APACHE II, SIRS, qSOFA, SAPS II were tested for the prediction of 30-day mortality in patients with PBSI (Table 5, Fig. 3). The SOFA (AUROC = 0.882, 95% CI: 0.837–0.927) had a greater area under the ROC (AUROC) than the other four. Compared with the Z-test, the SOFA had better predictive validity than APACHE II (Z score = 1.956, p = 0.0499), SIRS (Z score = 7.268, p < 0.0001), qSOFA (Z score = 5.381, p < 0.0001) and SAPS II (Z score = 2.656, p = 0.0079) in predicting the outcome of PBSI.

| Variables       | Survival Group | Nonsurvival Group | All PBSI patients |
|-----------------|----------------|-------------------|-------------------|
| Other           | 3              | 4                 | 7 (1.5%)          |
| Fungi           |                |                   |                   |
| *Candida*       |                |                   |                   |
| *Scedosporium*  |                |                   |                   |
| Other           |                |                   |                   |
Table 5
Performance of the prognostic scoring systems for predicting 30-day mortality in patients with PBSI

| Prognosis Model | AUROC (95% CI) | Sensitivity | Specificity | Z score | P value |
|-----------------|----------------|-------------|-------------|---------|---------|
| SOFA            | 0.882(0.832–0.922) | 0.832       | 0.783       |         |         |
| APACHE II       | 0.834(0.778–0.881) | 0.719       | 0.845       | 1.961   | 0.0499  |
| SIRS            | 0.599(0.531–0.665) | 0.742       | 0.450       | 7.268   | <0.0001 |
| qSOFA           | 0.699(0.633–0.759) | 0.501       | 0.798       | 5.381   | <0.0001 |
| SAPS II         | 0.818(0.761–0.867) | 0.708       | 0.798       | 2.656   | 0.0079  |

Discussion

PBSI is always associated with poor outcome, treating PBSI is still a significant challenge. In this prospective study, the prevalence rate of PBSI was 5.4% (218/4066) among inpatients with positive blood cultures. The rate was similar to that in a previous study, which reported a rate of 6% in the late 1980s (19). We identified that the 30-day mortality rate of PBSI was 40.8% (89/218) in our study. A previous study showed that the average mortality due to PBSI was 47% (11). However, its clinical presentation and the factor associated with prognosis were rarely reported. In our study, we observed that patients with poor prognosis showed more severe systemic inflammatory response, including elevated WBC and C-reactive protein, reduced platelet, and more frequency to be septic shock (2). Inappropriate initial empirical antimicrobial therapy, WBC > 11.2*10^9 and platelet ≤ 54*10^9 were exhibited to be independent risk factors for PBSI-related 30-day mortality (3). Gram-negative organisms accounted for most pathogens, and *Klebsiella pneumoniae* and *Acinetobacter spp.* ranked the first and second (4). It worth noting that patients co-infected with fungi was associated with worsen prognosis (5) SOFA scores was more accurate in predicting the prognosis of patients with PBSI.

To help direct our selection of treatment methods and improve patients’ early survival rate, we discussed the risk factors for 30-day mortality. Inappropriate initial empirical antimicrobial therapy was a main prognostic factor for early mortality in this study. Effective initial empirical treatment before receiving the blood culture results is necessary. The choice of empirical antibiotics is often a challenge for physicians. Some reports have demonstrated that appropriate antibiotic treatment can reduce mortality and improve clinical outcomes in patients with BSI(20). In our study, the rate of inappropriate initial empirical antibiotic therapy in the nonsurvival group was 30.3%, which was 16.3% (p < 0.05) higher than that in the survival group. In another report, the rate was 53.6% for PBSI patients in the emergency department. Among the patients who received inappropriate initial empirical antibiotic therapy, only 17.4% of the patients received no empirical antibiotic treatment. A delay in the application of effective initial empirical antibiotics has
been reported to lead to poor outcomes in patients with BSI, especially critical patients (21). Therefore, increasing attention needs to be paid to initial empirical antibiotic therapy in patients with suspected infections. However, 41.3% of patients required combination therapy that was not received; for example, some patients had two pathogens that could not be treated by only one antibiotic. It is more difficult to administer adequate antibiotic therapy in patients with PBSI than in patients with monomicrobial BSI. One antibiotic is not enough to treat multiple pathogens, even if it is a broad-spectrum antibiotic (14). To provide adequate empirical coverage, it is vital to measure clinical characteristics and evaluate risk factors for acquiring PBSI. We also discovered that WBC > 11.2 × 10^9 and platelet ≤ 54 × 10^9 were optimal cut-off points as another two prognostic factors. Leukocytosis and thrombocytopenia were common hematologic findings in BSI, which means widespread systemic inflammation (1). It is an exaggerated defense response triggered by some pathogens. Additionally, Systemic inflammatory response syndrome (SIRS) will lead to dysregulated cytokine storm and even massive inflammatory cascade. These may resulted in organ dysfunction and death (22).

Gram-negative organisms were the most frequent pathogens in our study, similar to other reports (6, 14). Among the gram-negative organisms, Klebsiella pneumoniae and Acinetobacter spp. were the most frequent causative agents. With the wider use of carbapenems, the carbapenem resistance rates of Klebsiella spp. and Acinetobacter spp. have increased to 37% and 69%, and few treatment options are available for these pathogens currently (21). Among the gram-positive organisms, Enterococcus spp. and coagulase-negative staphylococci were the most frequent. A report on PBSI in patients with cancer obtained the same conclusion (6). In contrast with our study, another report on PBSI in patients in the emergency department excluded patients infected with coagulase-negative staphylococci from their study and found that streptococci were the most frequent gram-positive bacteria (14). One study analyzed the isolated microorganisms in community-acquired BSIs and identified Escherichia coli, Staphylococcus aureus, and Streptococcus pneumoniae as the most common organisms (23). Considering the small sample sizes in the existing studies on PBSI, relatively large sample sizes are required to help us fully understand the microbiology of PBSIs, which will provide valuable information for empirical antimicrobial treatment.

We found that PBSI patients infected with fungi had poor outcomes. Candida spp. was the most frequent fungal species in our study (77.5%). A report comparing Candida with other isolated pathogens found that BSI patients infected with Candida had increased ICU mortality (21). Traditional initial empirical treatment does not always cover fungi. Waiting to administer antifungal therapy until culture results are returned may be detrimental to some patients. Only 62.5% of patients infected with fungi received antifungal therapy during the period of PBSI in our study. Some patients died before the culture results were returned. Therefore, we believe that timely antifungal treatment may improve the prognosis of patients with PBSI, if the patients are highly suspect co-infection with fungi.

Besides, we also evaluated some prognostic systems, which have been reported link with mortality of patients with BSI (24, 25). We found that the SOFA, APACHE II and SAPS II all had good predictive accuracy in our study. The SOFA exhibited a higher AUROC than the other two, and the Z-test showed that
the probability p value was less than 0.05. Therefore, we believe that SOFA was the better one. The SOFA score is used to evaluate the trend of organ dysfunction in patients(26). Multiorgan dysfunction is common in patients with BSI. It was reported that the SOFA performed well in predicting organ dysfunction in some patients with BSI(24). However, no previous study has considered the SOFA score in patients with PBSI. In some large-scale validation studies on the Sepsis-3 criteria for BSI patients, the median SOFA scores were 6 (IQR 3–9) in the US(27) and 5 (IQR 3–8) in Australia and New Zealand(28). The patients in our study had a median SOFA score of 9 (IQR 5–14). Patients with PBSI had a higher SOFA score than patients with BSI, suggesting severe clinical manifestations.

This study had some major limitations. First, it was a single-center study, which limited its generalizability. Second, the long-term prognosis of these patients was not analyzed in this study.

**Conclusion**

In summary, hospitalized patients with PBSI are at high risk for short-term mortality. Our data showed that inappropriate initial empirical antimicrobial therapy, white blood cell and platelet were independent risk factors for 30-day mortality in patients with PBSI. SOFA scores could be used to predict the short-term prognosis of PBSI.

**Abbreviations**

PBSI=polymicrobial bloodstream infection

BSI=bloodstream infection

ICU= intensive care unit

ROC=receiver operating curve

CRP=C-reactive protein

WBC=white blood cell

INR= international normalized rate

PT=prothrombin time

BUN=blood urea nitrogen

HR= hazard ratio

SOFA=the sequential organ failure assessment

APACHE II=acute physiology and chronic health evaluation
Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. This study was a retrospective non-invasive study, and data analysis was conducted anonymously. Thus, oral informed consent was obtained from the patients, the parents or the legal guardian of the children under 18 years old.

Consent for publication

Not applicable.

Availability of data and materials

Data analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to disclose.

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Figures

**Figure 1**

The flow diagram of patients selection
Figure 2

Kaplan–Meier diagrams for 30-day mortality

Figure 3

ROC curves of the five prognostic scoring systems for predicting 30-day mortality in patients with PBSI.