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*Original Article*

# Characteristics, risk factors, and mortality determinants in patients with polymicrobial bloodstream infections

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## Abstract

Introduction: The incidence and mortality of polymicrobial bloodstream infections (pBSIs) are increasing, yet their clinical characteristics and outcomes remain poorly understood.

Methodology: A retrospective analysis was conducted on 425 patients with confirmed bloodstream infections at the First Affiliated Hospital of Chongqing Medical University between January 2022 and September 2023. Clinical data, laboratory indicators, and in-hospital mortality rates were collected and analyzed.

Results: Lower respiratory tract infections were identified as the most common source of pBSIs (34.4%). The most frequent pathogen combination involved Gram-negative bacilli (GNB) and Gram-positive cocci (GPC), accounting for 32.8% of cases. Among the 257 pathogens isolated, 122 were Gram-positive bacteria (47.4%) and 130 were Gram-negative bacteria (50.6%). The most commonly isolated organisms included *Escherichia coli* (15.6%), *Klebsiella pneumoniae* (10.1%), and *Enterococcus faecalis* (7.0%), with a notable detection rate of coagulase-negative staphylococci (CoNS; 17.9%). Gastrointestinal tumors, invasive mechanical ventilation, intra-abdominal infections, and hospital-acquired infections were identified as independent risk factors for pBSIs. Compared to monomicrobial bloodstream infections (mBSIs), pBSIs were associated with a higher mortality rate (24% vs. 17.3%, $p = 0.075$) and a greater incidence of septic shock (36.8% vs. 24%, $p = 0.006$). Diabetes, invasive mechanical ventilation, and respiratory failure were independent predictors of mortality in pBSIs patients.

Conclusions: Hospitalized patients with pBSIs are at a significantly higher risk of adverse outcomes, including mortality. Early identification and targeted management of risk factors are crucial to improving prognosis and reducing mortality in patients with pBSIs.

**Key words:** clinical characteristics; polymicrobial bloodstream infections; risk factor; mortality risk factors.

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## Introduction

Bloodstream infections (BSIs) are severe systemic infections that continue to pose a significant global health burden [1,2]. When BSIs occur, they are often associated with prolonged hospital stays, increased healthcare costs [3], and higher mortality rates if not promptly and appropriately treated [4,5]. Notably, the incidence of polymicrobial bloodstream infections (pBSIs) has been rising [6,7], with reported mortality rates ranging from 14% to 48%—nearly double those of monomicrobial bloodstream infections (mBSIs) [7,8]. Despite this, limited research has focused on the clinical outcomes of pBSIs. The complex etiology of pBSIs often leads to ineffective initial treatments, reducing drug efficacy, and worsening clinical outcomes; thus presenting a considerable clinical challenge. Early identification and recognition of risk factors are therefore critical for the prevention and management of BSIs [9].

This study analyzed blood culture data collected at the First Affiliated Hospital of Chongqing Medical University between January 2022 and September 2023. The aim was to investigate the microbial characteristics of pBSIs, along with associated clinical features, risk factors, and mortality determinants, to provide insights that may guide more effective clinical management of pBSI patients.

## Methodology

*Subjects*

This retrospective, single-center study included 425 episodes of bacterial BSIs detected between January 2022 and September 2023 among patients admitted to the department at the First Affiliated Hospital of Chongqing Medical University. The First Affiliated Hospital of Chongqing Medical University is a tertiary-level, comprehensive teaching hospital that integrates medical services, education, research, prevention, healthcare, and international medical care. The hospital assumes year-round responsibility for the management

of complex and severe cases, treating patients from across China; as well as from countries such as the United States, Australia, and Japan. Additionally, it oversees 23 clinical teaching bases and manages 77 affiliated hospitals across Chongqing, Sichuan, Guizhou, and surrounding regions.

In this study, mortality rates were calculated based on patient outcomes during hospitalization. Specifically, mortality was defined as the proportion of patients who died during their hospital stay relative to the total number of participants in each group.

The inclusion criteria were as follows: (1) adult patients aged 18 years or older with BSIs who tested positive for pathogenic bacteria in laboratory blood cultures, and whose clinical condition was consistent with the diagnosis; (2) patients with confirmed BSI.

The exclusion criteria were: (1) pediatric patients; (2) specimen contamination; (3) cases with significant missing clinical data; (4) repeat blood cultures from the same patient within one week; (5) time to positivity (TTP) exceeding 48 hours (TTP > 48 hours).

*Data collection*

Electronic medical records of the patients were retrospectively reviewed to collect data on epidemiological factors, demographics, comorbidities, auxiliary examinations, treatments (such as surgeries and invasive procedures), intensive care unit (ICU) admissions, and outcomes. Surgical and invasive procedures were defined as those performed within 30 days prior to the onset of BSI. Laboratory data were collected during the infection window period, which was defined as the day of positive blood sampling, or the three days before and after the day of infection. Data collection was performed by a designated individual and verified by a second reviewer.

*Diagnostic definition*

According to the 2008 guidelines from the US Centers for Disease Control and Prevention (CDC) [10], bacteria are considered contaminants if they meet any of the following criteria: absence of obvious fever or high-risk factors; fever due to another clear cause; multiple blood cultures identifying infection with other pathogens; ineffective treatment with appropriate antibiotics; or only one of multiple blood cultures being positive, with the microorganism being part of normal skin flora. Coagulase-negative staphylococci (CoNS), α-hemolytic streptococci, *Propionibacterium acnes*, *Corynebacterium* spp., and *Bacillus* spp. are considered contaminants unless the organism is also identified from at least one additional culture from blood, catheter tip, or another sterile site.

pBSIs refer to BSIs caused by two or more pathogens isolated from a single blood culture episode within 48 hours. Recurrent episodes of different pathogens in the same patient within a one-week period were excluded [11].

mBSIs refer to infections in which only one pathogen is isolated from blood cultures within 48 hours, and the infection meets the clinical diagnostic criteria for BSI. If two or more organisms are identified in blood cultures, with one considered true bacteremia and the others classified as contaminants, the infection is defined as monomicrobial [12].

Primary BSI was defined as cases where no apparent etiology for the infection was identified during hospitalization. Sepsis and septic shock were defined according to the "Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)" [13].

Catheter-related bloodstream infections (CRBSI) are bacteremia or fungemia occurring within 48 hours of insertion or removal of an intravascular catheter, accompanied by signs of BSI, and excluding other clear sources of infection outside the catheter [10]. In this study, the pathogens identified in the catheter blood culture matched that in the peripheral venous blood sample. CRBSI was established only when the positive result of the catheter blood culture preceded that of the peripheral venous blood culture by at least 2 hours.

*Bacterial identification*

Blood samples were collected and cultured following the latest version of the "Clinical Microbiology Laboratory Blood Culture Operation Specifications" [14]. When a positive result was obtained, the blood samples were inoculated onto the appropriate media and incubated under specified conditions. The isolated pathogens were identified using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Biomerieux, Marcy l'Etoile, France) [14].

*Data analysis*

Data analysis was performed using SPSS v26.0 software (IBM Corp, Armonk, NY, USA). The primary outcome was all-cause mortality during hospitalization. Enumeration data were presented as frequencies and percentages, while measurement data were expressed as either means with standard deviations or medians with interquartile ranges. Continuous variables were analyzed using t-tests or non-parametric tests, depending on data normality. The Chi-square test was

used for categorical variables. Univariate analysis was performed to evaluate variables, and multivariate logistic regression analysis was conducted for statistically significant variables from the univariate analysis. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A $p$ value of $< 0.05$ was considered statistically significant.

*Ethics approval and consent to participate*

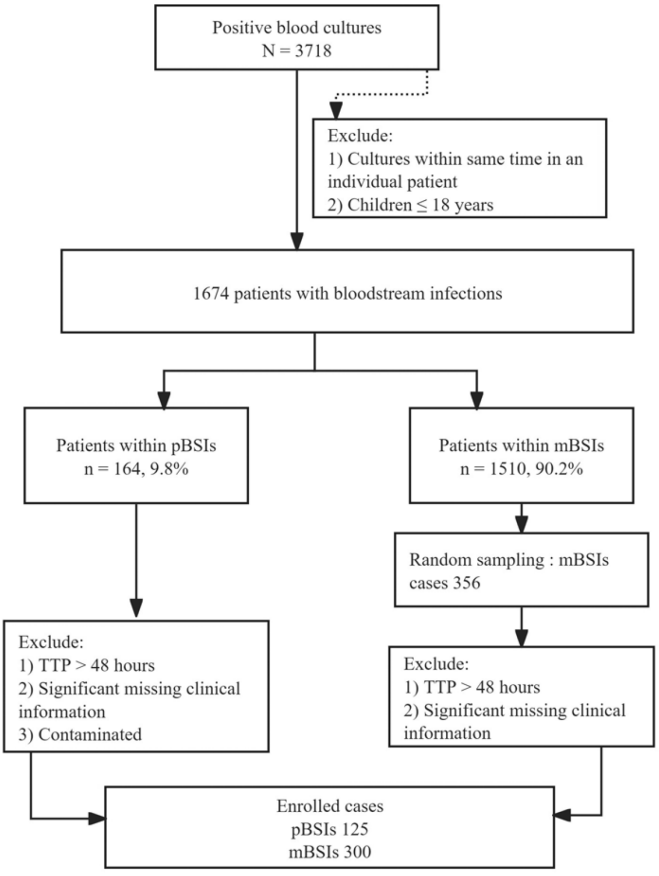
Ethics approval was obtained from the Review Board of the First Affiliated Hospital of Chongqing Medical University (Approval No. K.2024–006–01). The requirement for informed consent was waived because this study involved a retrospective analysis of anonymized data.

## Results

*Clinical characteristics of the study patients*

The enrollment flowchart is presented in Figure 1.

**Figure 1.** Patients selection and classification.




There were 3718 positive blood cultures, with 1674 patients having bloodstream infections, comprising 164 pBSIs and 1510 mBSIs. A control group of 356 patients was randomly selected from the 1510 mBSI patients. Ultimately, the study included 125 patients with pBSIs and 300 with mBSIs. TTP: time to positivity (hours); pBSIs: polymicrobial bloodstream infections; mBSIs: monomicrobial bloodstream infections.

**Table1.** Pathogen distribution in polymicrobial bloodstream infections.

| **Total number of isolated bacteria** | **257** |
|---|---|
| **Number of isolated bacteria for each pBSI episode** | |
| 2 isolates | 118/125 (94.4%) |
| 3 isolates | 7/125 (5.6%) |
| **Bacteria associations** | **125** |
| GP/GN | 44/125 (35.2%) |
| GPC + GNB | 41/44 (93.2%) |
| GP/GP | 31/125 (24.8%) |
| GPC + GPC | 30/31 (96.8%) |
| CoNS + CoNS | 13/30 (43.3%) |
| GPB + GPC | 1/31 (3.2%) |
| GN/GN | 39/125 (31.2%) |
| GNB + GNB | 39/39 (100%) |
| Others | 11/125 (8.8%) |
| **Isolated bacteria** | **257** |
| GP | 122/257 (47.4%) |
| GN | 130/257 (50.6%) |
| Fungi | 5/257 (2.0%) |

pBSI: polymicrobial bloodstream infection; GP: Gram-positive bacteria; GN: Gram-negative bacteria; GPC: Gram-positive coccus; GPB: Gram-positive bacilli; GNB: Gram-negative bacilli; GP/GN: Gram-positive bacteria + Gram-negative bacteria; CoNS: coagulase-negative staphylococci.

A total of 3,718 positive blood cultures were recorded during the study period, corresponding to 1,674 patients with BSIs. Among these, 164 cases (9.8%) were classified as pBSIs and 1,510 cases (90.2%) as mBSIs. 356 patients were randomly selected from the monomicrobial group to match the polymicrobial group. Ultimately, 125 patients with pBSIs and 300 patients with mBSIs were included in the final analysis.

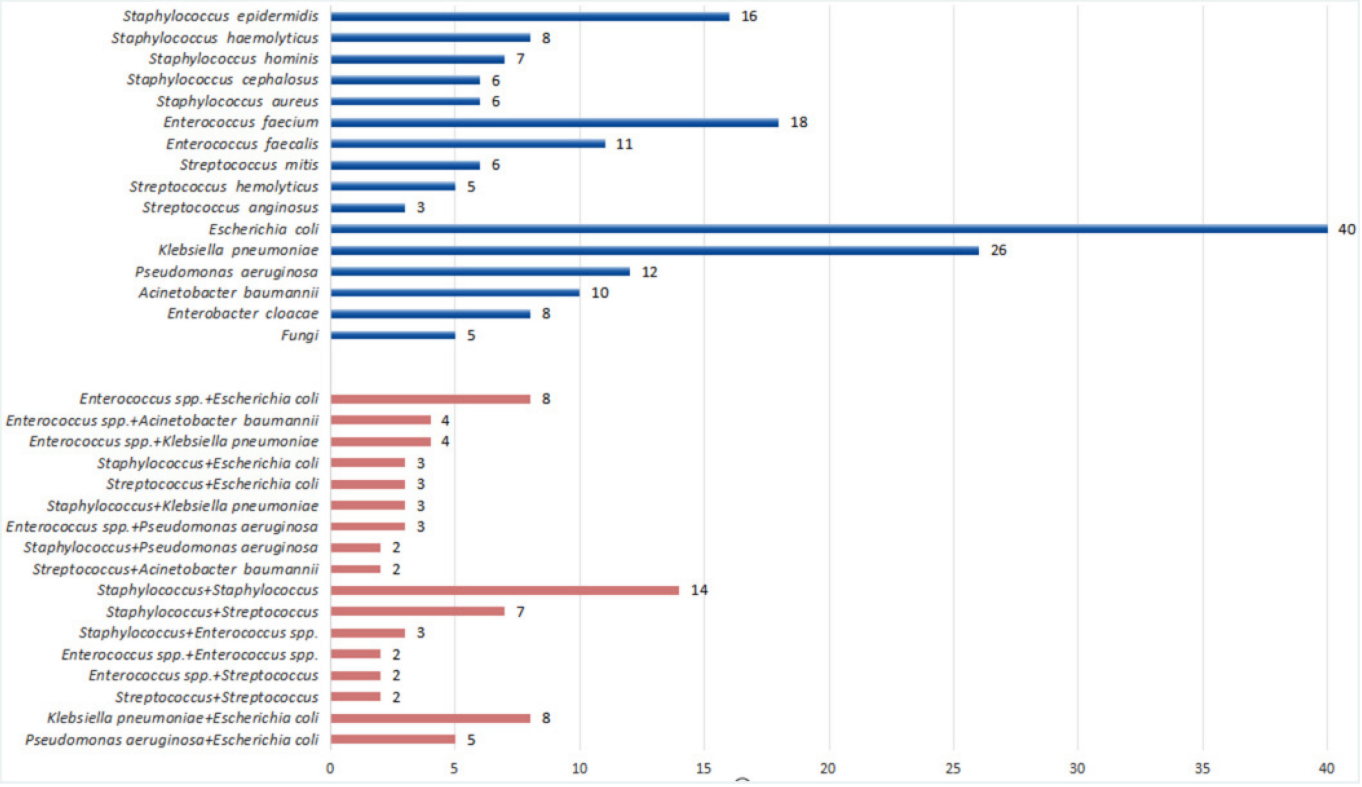
*Pathogenic bacteria in patients with pBSIs*

Among the 125 cases, 118 (94.4%) were caused by 2 species and 7 (5.6%) by 3 species (Supplementary Table 1). Of these, 44 cases (35.2%) involved a combination of Gram positive (GP) and Gram negative (GN) bacteria, predominantly comprising Gram-negative bacilli (GNB) and Gram-positive cocci (GPC) (41/44, 93.2%). The most common combination was *Escherichia coli* (*E. coli*) and *Enterococcus* (8/41), followed by *Klebsiella pneumoniae* (*Kpn*) and *Enterococcus* (4/41).

Additionally, 31 cases involved GP/GP combinations, primarily GPC/GPC (30/31, 96.8%), with the most frequent pairing being two CoNS (13/30, 43.3%). There were 39 cases of GNB/GNB combinations, with the most common involving two *Enterobacter* species (17/39). Other frequent combinations included *Kpn* and *E. coli* (8/39), and *Pseudomonas aeruginosa* (*Pae*) and *E. coli* (5/39). Finally, 11 cases involved combinations of 3 bacteria or combinations of 1 bacterium and 1 fungus.

A total of 257 microbial strains were identified, including 5 fungal isolates. The 5 most prevalent

**Figure 2.** Common isolated bacteria and pathogen combination in 125 pBSIs.




257 microbial strains were detected among the 125 cases. The common isolated bacteria in the 257 strains are shown in blue. The common pathogen combinations in the 125 cases are shown in pink.

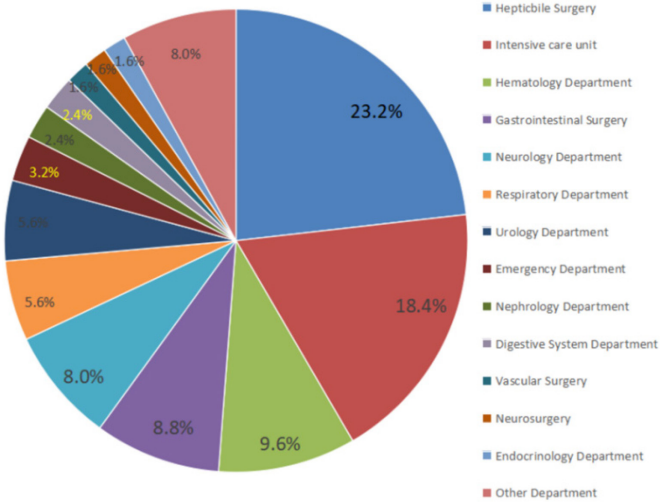
pathogens were *E. coli* (40 strains, 15.6%), *Kpn* (26 strains, 10.1%), *Enterococcus faecium* (18 strains, 7. 0%), *Staphylococcus epidermidis* (16 strains, 6.2%), and *Pae* (12 strains, 4.7%).

Among the isolates, 118 (45.9%) were GP bacteria. The most frequently detected GP pathogens were *Enterococcus faecium* (18, 15.3%), *Staphylococcus epidermidis* (16, 13.6%), and *Enterococcus faecalis* (11, 9.3%). A total of 134 strains (52.1%) were GN bacteria, with the most common species being *E. coli* (40, 29.9%), *Kpn* (26, 19.4%), *Pae* (12, 9.0%), and *Acinetobacter baumannii* (10, 7.5%). In addition, CoNS accounted for a significant proportion, comprising 46 of the 257 total isolates (17.9%). (Table 1 and Figure 2).

*Basic situation of pBSI*

Among the 425 patients, 300 (70.6%) had mBSIs and 125 (29.4%) pBSIs. There were 166 males and 134 females in the mBSI group, while the pBSI group included 86 males and 39 females. The gender distribution differed significantly between the two groups ($p = 0.009$). However, no significant difference in age was observed ($p > 0.05$) (Table 2). The primary source departments for the 125 pBSI cases were hepatobiliary surgery (23.2%), followed by ICU (18.4%), and hematology (9.6%). (Figure 3).

**Figure 3.** Source departments of polymicrobial group.




The top five departments where patients with polymicrobial bloodstream infections (pBSIs) were identified were: hepatobiliary surgery, intensive care medicine, hematology, gastrointestinal surgery, and neurology.

*Clinical characteristics of patients with pBSIs*

The incidence of gastrointestinal tumors was significantly higher in the polymicrobial group compared to the monomicrobial group (22.4% vs. 13.3%, $p = 0.016$). Regarding invasive procedures, a higher proportion of patients in the polymicrobial group underwent invasive mechanical ventilation and had indwelling drainage tubes compared to the monomicrobial group, while the proportion of patients with gastric tubes was lower in the polymicrobial group; these differences were statistically significant (all $p < 0.05$).

There were also significant differences in the distribution of community-acquired versus hospital-

**Table 2.** Risk factors in patients with pBSIs.

| Risk factors | Polymicrobial group (n = 125) | Monomicrobial group (n = 300) | Univariable | | Multivariable | |
|---|---|---|---|---|---|---|
| | | | t/z | *p* value | OR（95% CI） | *p* value |
| **Age (years)** | 62.80 ± 15.11 | 60.99 ± 16.90 | 1.035 | 0.301 | | |
| **Gender (Male) n（%）** | 86 (68.8%) | 166 (55.3%) | 6.903 | 0.009 | | |
| **Comorbidity** | | | | | | |
| Hypertension | 58 (46.4%) | 114 (38.0%) | 2.584 | 0.067 | | |
| Diabetes | 35 (28.0%) | 86 (28.7%) | 0.019 | 0.494 | | |
| Chronic cardiovascular disease | 30 (24.0%) | 63 (21.0%) | 0.465 | 0.288 | | |
| Chronic pulmonary disease | 10 (8.0%) | 16 (5.3%) | 1.092 | 0.203 | | |
| End stage renal disease | 10 (8.0%) | 29 (9.7%) | 0.294 | 0.367 | | |
| Cirrhosis of liver | 10 (8.0%) | 18 (6.0%) | 0.573 | 0.288 | | |
| Central nervous system disease | 17 (13.6%) | 54 (18.0%) | 1.288 | 0.167 | | |
| Anemia | 33 (26.4%) | 88 (29.3%) | 0.373 | 0.313 | | |
| Tumor | 50 (40.0%) | 118 (39.3%) | 0.016 | 0.491 | | |
| Gastrointestinal tumor | 28 (22.4%) | 40 (13.3%) | 5.397 | 0.016 | 1.91 (1.01–3.63) | 0.047 |
| **Invasive operation** | | | | | | |
| Invasive mechanical ventilation | 57 (45.6%) | 78 (26.0%) | 15.639 | < 0.001 | 2.71 (1.67–4.40) | 0.022 |
| Central venous catheter | 46 (36.8%) | 97 (32.3%) | 0.789 | 0.219 | | |
| Indwelling urinary catheter | 17 (13.6%) | 51 (17.0%) | 0.759 | 0.236 | | |
| Drainage tube | 47 (37.6%) | 81 (27.0%) | 4.71 | 0.021 | | |
| Gastric tube | 8 (6.4%) | 39 (13.0%) | 3.989 | 0.031 | | |
| Hospital-acquired BSI | 98 (78.4%) | 168 (56.0%) | 18.908 | < 0.001 | 2.67 (1.59–4.47) | < 0.001 |
| **Complication** | | | | | | |
| Respiratory failure | 33 (26.4%) | 79 (26.3%) | 0.000 | 0.539 | | |
| Sepsis | 79 (63.2%) | 176 (58.7%) | 0.756 | 0.224 | | |
| Septic shock | 46 (36.8%) | 72 (24.0%) | 7.208 | 0.006 | | |
| Hypoproteinemia | 57 (45.6%) | 125 (41.7%) | 0.558 | 0.261 | | |
| Electrolyte disorders | 46 (36.8%) | 119 (39.7%) | 0.305 | 0.330 | | |
| Multiple organ failure | 14 (11.2%) | 25 (8.3%) | 0.87 | 0.224 | | |
| **Primary site of BSI** | | | | | | |
| Lower respiratory tract | 43 (34.4%) | 96 (32.0%) | 0.231 | 0.355 | | |
| Intra-abdominal | 13 (10.4%) | 12 (4.0%) | 6.528 | 0.012 | 2.55 (1.00–6.47) | 0.049 |
| Urinary tract | 4 (3.2%) | 24 (8.0%) | 3.303 | 0.049 | | |
| Mixed infection | 23 (18.4%) | 53 (17.7%) | 0.032 | 0.479 | | |
| Others | 42 (33.6%) | 115 (38.3%) | 0.849 | 0.209 | | |
| Surgery | 32 (25.6%) | 115 (38.3%) | 6.323 | 0.008 | | |
| **Prior restricted grade and above antimicrobial therapy** | 117 (93.6%) | 261 (87.0%) | 3.908 | 0.031 | | |
| ICU Admission | 47 (37.6%) | 130 (43.3%) | 1.193 | 0.162 | | |
| Hospital stay | 21.00 (10.00–34.00) | 16.00 (10.00–29.75) | – 1.219 | 0.223 | | |
| Outcomes-Deceased | 30 (24.0%) | 52 (17.3%) | 2.518 | 0.075 | | |
| WBC ($\times 10^9$/L) | 9.74 (5.08–14.87) | 10.07 (6.09–14.70) | – 0.438 | 0.661 | | |
| TP (g/L) | 63.00 (56.00–68.00) | 63.00 (56.00–68.00) | – 0.025 | 0.98 | | |
| ALB (g/L) | 31.61 ± 6.57 | 32.62 ± 6.25 | – 1.494 | 0.136 | | |
| ALT (U/L) | 39.00 (19.00–86.50) | 28.00 (17.00–50.75) | – 2.399 | 0.016 | | |
| AST (U/L) | 42.00 (25.00–93.50) | 34.00 (23.00–62.00) | – 2.252 | 0.024 | | |
| ALP (U/L) | 112.00 (74.00–182.50) | 92.00 (67.00–144.25) | – 2.085 | 0.037 | | |
| GGT (U/L) | 74.00 (33.00–150.75) | 48.00 (24.00–118.00) | – 2.593 | 0.01 | | |
| LDH (U/L) | 237.50 (169.25–375.75) | 219.00 (169.00–305.00) | – 1.107 | 0.268 | | |
| Scr (umol/L) | 87.00 (55.00–140.50) | 82.00 (54.25–142.50) | – 0.107 | 0.865 | | |
| PCT (ng/mL) | 0.99 (0.27–8.95) | 0.60 (0.23–5.17) | – 1.052 | 0.293 | | |
| CRP (mg/L) | 93.50 (28.30–154.00) | 96.85 (37.28–176.75) | – 1.174 | 0.240 | | |

OR: odds radio; ICU: intensive care unit; WBC: white blood cell; TP: total protein; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; Scr: serum creatinine; PCT: procalcitonin; CRP: C-reactive protein.

acquired infections between the two groups, with a higher rate of hospital-acquired infections observed in the polymicrobial group ($p < 0.001$). Additionally, intra-abdominal infections, septic shock, and the use of restricted-grade or higher-level antibiotics were more prevalent in the polymicrobial group; whereas urinary tract infections were more common in the monomicrobial group (all $p < 0.05$). Although data analysis revealed no statistically significant differences in hospital stay duration and mortality rates between the monomicrobial and polymicrobial groups (all $p > 0.05$), in practice, patients with pBSIs experienced notably longer hospital stays and higher mortality rates (median hospital stay: 21.00 [10.00–34.00] vs. 16.00 [10.00–

**Table 3.** Mortality risk factors in patients with pBSIs.

| Risk factors | Surviving group (n = 95) | Death group (n = 30) | Univariable | | Multivariable | |
|---|---|---|---|---|---|---|
| | | | t/z | *p* value | OR（95% CI） | *p* value |
| **Age (years)** | 62.91 ± 15.35 | 65.63 ± 14.21 | – 1.18 | 0.24 | | |
| **Gender: male n (%)** | 67（70.5%） | 19 (63.3%) | 0.55 | 0.30 | | |
| **Time to positive** | 13.66 ± 5.13 | 16.83 ± 6.91 | – 2.695 | 0.008 | | |
| **Hospital stay** | 22.00 (11.00–37.00) | 12.50 (3.50–30.50) | – 1.926 | 0.054 | | |
| **Comorbidity** | | | | | | |
| Hypertension | 43 (45.3%) | 15 (50.0%) | 0.206 | 0.403 | | |
| Diabetes | 20 (21.1%) | 15 (50.0%) | 9.477 | 0.003 | 5.70 (1.83–17.80) | 0.003 |
| Chronic cardiovascular disease | 19 (20%) | 11 (36.7%) | 3.472 | 0.056 | | |
| Chronic pulmonary disease | 8 (8.4%) | 2 (6.7%) | 0.095 | 0.554 | | |
| End stage renal disease | 6 (6.35) | 4 (13.3%) | 1.526 | 0.193 | | |
| Cirrhosis of liver | 7 (7.4%) | 3 (10.0%) | 0.215 | 0.446 | | |
| Central nervous system disease | 13 (13.7%) | 4 (13.3%) | 0.002 | 0.615 | | |
| Immunosuppression | 13 (13.7%) | 5 (16.7%) | 0.165 | 0.443 | | |
| Tumor | 37 (30.5%) | 13 (33.3%) | 0.183 | 0.413 | | |
| Gastrointestinal tumor | 20 (21.1%) | 8 (26.7%) | 0.413 | 0.34 | | |
| **Invasive operation** | | | | | | |
| Invasive mechanical ventilation | 33 (34.7%) | 24 (80.0%) | 18.83 | < 0.001 | 4.33 (1.36–13.84) | 0.013 |
| Central venous catheter | 30 (31.6%) | 16 (53.3%) | 4.639 | 0.027 | | |
| Indwelling urinary catheter | 14 (14.7%) | 3 (10.0%) | 0.435 | 0.376 | | |
| Drainage tube | 38 (40.0%) | 9 (30.0%) | 0.972 | 0.222 | | |
| Gastric tube | 5 (5.3%) | 3 (10.0%) | 0.854 | 0.293 | | |
| Surgery | 29 (30.5%) | 3 (10.0%) | 5.044 | 0.018 | | |
| Hospital-acquired BSI | 73 (76.8%) | 25 (83.3%) | 0.567 | 0.316 | | |
| **Complication** | | | | | | |
| Respiratory failure | 16 (16.8%) | 17 (56.7%) | 18.61 | < 0.001 | 5.84 (1.84–18.50) | 0.003 |
| Anemia | 26 (27.4%) | 7 (23.3%) | 0.191 | 0.429 | | |
| Hypoproteinemia | 39 (41.1%) | 18 (60.0%) | 3.3 | 0.054 | | |
| Electrolyte disorders | 32 (33.7%) | 14 (46.7%) | 1.652 | 0.143 | | |
| Multiple organ failure | 8 (8.4%) | 6 (20.0%) | 3.074 | 0.082 | | |
| Sepsis | 58 (61.1%) | 21 (70.0%) | 0.785 | 0.254 | | |
| Septic shock | 28 (29.5%) | 18 (60.0%) | 9.135 | 0.003 | | |
| **Primary site of BSI** | | | | | | |
| Lower respiratory tract | 28 (29.5%) | 15 (50.0%) | 4.257 | 0.034 | | |
| Intra-abdominal | 9 (9.5%) | 4 (13.3%) | 0.364 | 0.38 | | |
| Urinary tract | 4 (4.2%) | 0 (0.0%) | 1.305 | 0.328 | | |
| Mixed infection | 17 (17.9%) | 6 (20.0%) | 0.067 | 0.492 | | |
| Others | 37 (38.9%) | 5 (16.7%) | 5.073 | 0.018 | | |
| **Prior restricted grade and above antimicrobial therapy** | 89 (93.7%) | 28 (93.3%) | 0.005 | 0.615 | | |
| ICU Admission | 27 (28.4%) | 20 (66.7%) | 14.214 | < 0.001 | | |
| WBC ($\times 10^9$/L) | 9.74 (4.87–14.44) | 10.01 (5.87–19.61) | – 0.947 | 0.397 | | |
| TP (g/L) | 63.00 (57.00-69.00) | 61.50 (48.75–65.25) | – 1.926 | 0.054 | | |
| ALB (g/L) | 32.66 ± 6.06 | 28.27 ± 7.08 | 3.324 | 0.001 | | |
| ALT (U/L) | 36.00 (19.00–89.00) | 39.50 (17.00–84.50) | – 0.182 | 0.855 | | |
| AST (U/L) | 39.00 (24.00–92.00) | 45.50 (27.00–124.00) | – 0.887 | 0.375 | | |
| ALP (U/L) | 115.00 (70.00–191.00) | 90.00 (74.50–143.00) | – 1.171 | 0.242 | | |
| GGT (U/L) | 90.00 (35.25–167.50) | 41.50 (26.50–87.75) | – 2.436 | 0.015 | | |
| LDH (U/L) | 210.00 (164.00–338.00) | 296.00 (204.00–637.00) | – 2.978 | 0.003 | | |
| Scr (□mol/L) | 71.00 (52.00–108.00) | 140.50 (97.50–202.00) | – 3.899 | < 0.001 | | |
| PCT (ng/mL) | 1.00 (0.29–9.03) | 0.78 (0.21–8.47) | – 0.268 | 0.788 | | |
| CRP (mg/L) | 97.50 (37.30–152.00) | 69.05 (14.68–198.75) | – 0.639 | 0.523 | | |

OR: odds radio; ICU: intensive care unit; WBC: white blood cell; TP: total protein; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; Scr: serum creatinine; PCT: procalcitonin; CRP: C-reactive protein.

29.75] days; mortality rate: 24% vs. 17.3%). Furthermore, the polymicrobial group had significantly higher levels of liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP); compared to the monomicrobial group (all $p < 0.05$).

Based on the multivariate logistic regression analysis, gastrointestinal tumors (OR = 1.91, 95% CI: 1.01–3.63), invasive mechanical ventilation (OR = 2.71, 95% CI: 1.67–4.40), intra-abdominal infection (OR = 2.55, 95% CI: 1.00–6.47), and hospital-acquired infection (OR = 2.67, 95% CI: 1.59–4.47) were identified as independent risk factors for pBSIs (Table 2).

*Mortality risk factors in patients with pBSIs*

Among the 125 patients with pBSIs, 30 (24%) died. In the univariate analysis, TTP was significantly shorter in the survival group compared to the death group ($p = 0.008$). Patients in the death group had a higher incidence of diabetes, ICU admission, respiratory failure, and septic shock (all $p < 0.05$). Additionally, invasive mechanical ventilation was required more frequently among patients in the death group ($p < 0.001$). Lower respiratory tract infections were also more common in the deceased group ($p < 0.05$).

Laboratory indicators revealed that levels of albumin (ALB), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and serum creatinine (Scr) were significantly higher in the survival group compared to the death group ($p < 0.05$).

Multivariate analysis identified the following independent risk factors for mortality in patients with pBSIs: diabetes (OR = 5.70, 95% CI: 1.83–17.80), invasive mechanical ventilation (OR = 4.33, 95% CI: 1.36–13.84), and respiratory failure (OR = 5.84, 95% CI: 1.84–18.50) (Table 3).

## Discussion

The clinical background of this study is consistent with previous research, which also found that male patients are more commonly affected by BSIs than female patients [8,15]. Studies have shown that diabetes and hypertension are common comorbidities associated with pBSIs [16–18]. Reid *et al.* observed that BSIs in patients with diabetes may have a higher fatality rate [19]. In the current study, hypertension was the most common comorbidity among patients with pBSIs, followed by tumors (gastrointestinal tumors excluded).

The high infection burden among cancer patients is well-documented, with BSIs being a frequent cause of mortality in hematological and oncological patients [20–22]. Additionally, the high proportion of tumor cases in this study is likely related to the source departments of patients with pBSIs. These patients are often hospitalized in a large tertiary hospital, which may explain the significant proportion of tumor cases observed.

This study reveals that patients with pBSIs experience prolonged hospital stays, along with a significantly increased rate of septic shock and in-hospital mortality. Previous research has established that risk factors for BSIs include male gender, diabetes, malignancy, cirrhosis, immunosuppression, and alcoholism [8,23–25]. Additionally, emerging studies have highlighted digestive tract tumors as a significant risk factor for BSIs, which is consistent with the findings of this study [26].

Previous studies have indicated that pneumonia and intra-abdominal infections are common causes of BSIs, and urinary tract infections are also frequent [3,6,15,27]. Both early and recent literature have noted that approximately 25% of pBSIs have unidentified origins [3,15,28], with some studies suggesting that primary infections account for about 10% [8]. In this study, lower respiratory tract infections were the most common primary infections (34.4%), followed by other primary infections and some rare infections, which together accounted for 33.6%. It is noteworthy that the rare infections were represented by only a few cases in the data included in this study. Mixed infections emerged as a significant cause of pBSIs in this cohort. Traditional causes of BSIs, such as soft tissue infections, catheter-associated BSIs [8], and urinary tract infections, were less common. Notably, catheter-associated BSIs were rare in this study. This could be attributed to more routine chest computed tomography (CT) scans following COVID-19, which are more likely to detect lung infections.

Previous research has rarely focused on mixed infections separately, and including them in this study may have reduced the observed proportions of abdominal infections, urinary tract infections, pneumonia, and catheter-related infections. Many patients with pBSIs had unknown primary sources, potentially due to the severity of their conditions preventing appropriate examinations and imaging. This suggests that primary infections may indicate the severity of the disease rather than specific causes of infection. Invasive procedures increase the risk of bacterial colonization and may lead to subsequent BSIs. In this study, patients with polymicrobial infections had more frequent invasive mechanical ventilation, catheter

insertion, and use of central venous catheters; compared to those with mBSIs; but the incidence of catheter-related BSIs was relatively low. This to some extent reflects the importance of disinfection and the effective implementation of aseptic techniques in the hospital. The criteria applied for the identification of catheter-associated BSI in this research are likely responsible for the observed outcomes.

Additionally, this study focused on cases reported within 48 hours, which differs from previous studies that included data reported over 72 hours, potentially influencing the observed results. Overall, the burden of diagnosing and treating pBSIs is substantial. Given the lack of sufficient prior studies on the sources of pBSIs, continued attention to disinfection and maintenance of invasive sites remains crucial.

This study found that 94.4% of pBSIs involved 2 pathogens, while 5.6% involved 3 pathogens. This distribution differs from some previous reports [15,29], which may be attributed to the strict inclusion and exclusion criteria used in this study. Previous research has confirmed that the concentration of contaminating bacteria in the blood is much lower than that of infecting bacteria, which leads to a longer time to positive results. This suggests that the TTP can be valuable in distinguishing between infecting and contaminating bacteria [30]. This is one of the reasons that TTP was defined with a cutoff at 48 hours.

The most common combination of pathogens in pBSIs was GNB-GPC, comprising 32.8% of cases. The most frequently isolated pathogens were *E. coli* (15.6%), *Kpn* (10.1%), and *Enterococcus faecium* (7.0%) [8,15,31,32]. Among the 257 pathogens identified, 52.1% were GN and 45.9% were GP. This finding contrasts with previous studies [32], possibly due to the high detection rate of CoNS in this cohort (44/257, 17.1%). This difference is an important consideration.

Previous studies often considered CoNS to be contaminants; however, CoNS are, in fact, a common type of GP bacteria in BSIs. In this study, a strict distinction was made between whether CoNS were contaminants or pathogenic bacteria. The CoNS identified in this study had a very short TTP, mostly less than 16 hours; and were associated with fever, elevated inflammatory markers, and imaging evidence supporting infection. Furthermore, these patients often had a background of tumors, immunosuppression, or severe conditions, and had undergone invasive procedures during hospitalization. This may also be related to the hospital's role as a large tertiary care facility in Chongqing, where patients typically present with more severe conditions, creating favorable conditions for CoNS colonization.

A significant difference from most prior reports was the frequency of non-fermenting GN bacteria, which accounted for approximately 9% of the cases in this study [8,28]. These findings highlight the importance of considering both GP and non-fermenting GN bacteria in the management of pBSIs. Empirical antibiotic treatment targeting enterobacteria and enterococci remains clinically relevant for patients with pBSIs. Furthermore, CoNS should not be overlooked as potential pathogens in pBSIs.

This study identified hepatobiliary surgery as the department with the highest incidence of pBSIs. Additionally, the levels of ALT, AST, ALP, and GGT were significantly higher in patients with pBSIs compared to those with mBSIs ($p < 0.05$). Univariate analysis further revealed that ALB, LDH, and serum creatinine (Scr) levels significantly influenced the prognosis of patients with pBSIs (all $p < 0.05$). Elevated Scr levels are commonly associated with worsening kidney function. These findings suggest a strong correlation between liver and kidney function and BSIs, particularly pBSIs. Overall, the study highlights the importance of monitoring liver and kidney function, as well as albumin levels, during the diagnosis and treatment of pBSIs. Prompt management of these factors may help reduce the mortality associated with pBSIs.

The incidence of diabetes, invasive mechanical ventilation, ICU admission, respiratory failure, lower respiratory tract infection, and septic shock was significantly higher in the deceased group. Diabetes, characterized by chronic hyperglycemia, creates an environment conducive to bacterial infections and can exacerbate mixed infections. Additionally, diabetes impairs immune function, increasing the likelihood of mortality from pBSIs. Previous studies have also indicated that diabetes increases the risk of BSIs and their associated mortality rates [16,17,19]. This study demonstrated that deceased patients had lower albumin levels, which is consistent with previous findings. Patients with low albumin levels (ALB) were found to be at a higher risk of mortality [33]. These findings underscore the importance of early detection and management of these risk factors to improve outcomes and reduce mortality in patients with pBSIs.

*Limitations*

Firstly, as a retrospective clinical study, this research is subject to inherent methodological limitations. The data analyzed were extracted from

medical records, which may vary in completeness. Inconsistencies in data uniformity and comparability across cases could compromise the reliability of the findings. For instance, the source of some BSIs may not have been accurately identified, potentially introducing classification bias.

Additionally, the study did not explore the impact of different pathogenic bacteria on the clinical outcomes of complex bacterial BSIs, nor did it conduct a corresponding analysis based on different infection sources. Moreover, due to the limited sample size of fungal BSIs, a comprehensive analysis of this subgroup was not feasible.

The study primarily focused on the clinical characteristics and risk factors associated with mortality in complex BSIs, while overlooking a more in-depth examination of different pathogen types, including specific drug utilization patterns and pathogen resistance profiles.

Finally, the single-center design of this study means that the findings should be validated through large-scale, multi-center, prospective clinical trials.

## Conclusions

This study highlights that CoNS are frequently implicated as pathogens in complex BSIs. When CoNS are identified in blood cultures, laboratory personnel should not only consider the TTP but also perform a comprehensive evaluation, incorporating clinical symptoms, imaging findings, and other relevant factors to provide a clinically meaningful report.

Patients with pBSIs exhibited a significantly higher mortality rate compared to those with monomicrobial infections. Independent risk factors for pBSIs included gastrointestinal tumors, invasive mechanical ventilation, hospital-acquired infections, and intra-abdominal infections. Among the various sources of pBSIs, lower respiratory tract infections were identified as the most common. Additionally, diabetes, invasive mechanical ventilation, and respiratory failure were found to be independent risk factors for mortality in pBSIs.

### Authors contributions

ZL, study concept, data extraction, statistical analysis, manuscript draft; JY, data extraction; XZ, manuscript revision.

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### Conflict of interest

No conflict of interest is declared.

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## Annex – Supplementary Items

**Supplementary Table 1.** Bacterial combinations in the 125 cases of polymicrobial bloodstream infections (pBSI).

| Case | Pathogen combination |
|---|---|
| 1 | *Delftia acidovorans, Staphylococcus cohnii subsp. urealyticus, Escherichia coli* |
| 2 | *Pseudomonas aeruginosa, Streptococcus anginosus* |
| 3 | *Klebsiella pneumoniae, Escherichia coli* |
| 4 | *Staphylococcus capitis, Staphylococcus epidermidis* |
| 5 | *Enterococcus faecalis, Escherichia coli* |
| 6 | *Klebsiella pneumoniae, Escherichia coli* |
| 7 | *Pseudomonas aeruginosa, Acinetobacter baumannii* |
| 8 | *Acinetobacter baumannii, Staphylococcus aureus* |
| 9 | *Klebsiella oxytoca, Escherichia coli* |
| 10 | *Streptococcus hemolyticus, Staphylococcus hominis* |
| 11 | *Klebsiella pneumoniae, Enterococcus faecalis, Escherichia coli* |
| 12 | Citrobacter freundii, Escherichia coli |
| 13 | *Staphylococcus caprae, Staphylococcus epidermidis* |
| 14 | *Acinetobacter baumannii, Klebsiella pneumoniae* |
| 15 | *Bacteroides fragilis, Escherichia coli* |
| 16 | *Pseudomonas aeruginosa, Escherichia coli* |
| 17 | *Gemella morbillorum, Streptococcus anginosus* |
| 18 | *Streptococcus mitis, Streptococcus sanguinis* |
| 19 | *Pseudomonas aeruginosa, Enterococcus faecium* |
| 20 | *Streptococcus salivarius, Escherichia coli* |
| 21 | *Staphylococcus capitis, Streptococcus mitis* |
| 22 | *Staphylococcus epidermidis, Enterococcus faecalis* |
| 23 | *Morganella morganii, Clostridium perfringens* |
| 24 | *Streptococcus sanguinis, Enterococcus faecalis* |
| 25 | *Morganella morganii, Enterobacter cloacae complex* |
| 26 | *Morganella morganii, Staphylococcus capitis* |
| 27 | *Klebsiella pneumoniae, Staphylococcus hominis* |
| 28 | *Bacteroides fragilis, Bacteroides thetaiotaomicron* |
| 29 | *Granulicatella adiacens, Veillonella parvula* |
| 30 | *Klebsiella pneumoniae, Escherichia coli* |
| 31 | *Klebsiella pneumoniae, Candida glabrata* |
| 32 | *Candida lusitaniae, Staphylococcus caprae, Staphylococcus epidermidis* |
| 33 | *Pseudomonas aeruginosa, Enterococcus avium* |
| 34 | *Leuconostoc lactis, Staphylococcus hominis* |
| 35 | *Staphylococcus cohnii, Staphylococcus epidermidis* |
| 36 | *Streptococcus anginosus, Bacteroides fragilis* |
| 37 | *Pseudomonas aeruginosa, Escherichia coli* |
| 38 | *Veillonella dispar, Streptococcus mitis* |
| 39 | *Pseudomonas aeruginosa, Escherichia coli* |
| 40 | *Klebsiella pneumoniae, Citrobacter braakii* |
| 41 | *Proteus mirabilis, Enterococcus faecium* |
| 42 | *Staphylococcus epidermidis, Enterococcus faecium* |
| 43 | *Escherichia coli, Pseudomonas aeruginosa* |
| 44 | *Enterococcus faecalis, Escherichia coli* |
| 45 | *Staphylococcus capitis, Acinetobacter baumannii* |
| 46 | *Enterococcus faecalis, Acinetobacter baumannii* |
| 47 | *Streptococcus mitis, Escherichia coli* |
| 48 | *Streptococcus constellatus, Clostridium ramosum, Bacteroides fragilis* |
| 49 | *Staphylococcus hominis, Staphylococcus epidermidis* |
| 50 | *Enterococcus faecium, Corynebacterium striatum* |
| 51 | *Staphylococcus aureus, Streptococcus agalactiae* |
| 52 | *Streptococcus hemolyticus, Staphylococcus hominis* |
| 53 | *Staphylococcus epidermidis, Streptococcus hemolyticus* |
| 54 | *Staphylococcus epidermidis, Staphylococcus warneri* |
| 55 | *Streptococcus hemolyticus, Aerococcus viridans* |
| 56 | *Lancefieldella parvula, Staphylococcus aureus* |
| 57 | *Acinetobacter baumannii, Enterococcus faecium* |
| 58 | *Klebsiella pneumoniae, Aeromonas caviae* |
| 59 | *Staphylococcus epidermidis, Staphylococcus haemolyticus* |
| 60 | Pseudomonas aeruginosa, Kodamaea ohmeri |
| 61 | *Staphylococcus capitis, Staphylococcus epidermidis* |
| 62 | *Bilophila wadsworthia, Klebsiella pneumoniae* |
| 63 | *Escherichia coli, Aeromonas hydrophila* |
| 64 | *Bifidobacterium spp., Granulicatella adiacens* |
| 65 | *Proteus mirabilis, Klebsiella pneumoniae* |
| 66 | *Klebsiella pneumoniae, Enterococcus casseliflavus* |
| 67 | *Klebsiella pneumoniae, Enterobacter cloacae complex* |

| | |
|---|---|
| 68 | *Enterococcus faecalis, Acinetobacter baumannii* |
| 69 | *Klebsiella pneumoniae, Acinetobacter baumannii* |
| 70 | *Streptococcus sanguinis, Enterococcus faecium, Bacillus subtilis subsp. subtilis* |
| 71 | *Staphylococcus hominis, Candida parapsilosis* |
| 72 | *Streptococcus constellatus, Klebsiella aerogenes* |
| 73 | *Escherichia coli, Enterobacter cloacae complex* |
| 74 | *Escherichia coli, Klebsiella pneumoniae* |
| 75 | *Proteus mirabilis, Escherichia coli* |
| 76 | Streptococcus hemolyticus, Stenotrophomonas maltophilia |
| 77 | *Acinetobacter baumannii, Corynebacterium striatum* |
| 78 | *Klebsiella oxytoca, Escherichia coli* |
| 79 | *Staphylococcus capitis, Staphylococcus epidermidis* |
| 80 | *Staphylococcus haemolyticus, Staphylococcus aureus* |
| 81 | *Staphylococcus epidermidis, Staphylococcus haemolyticus* |
| 82 | *Escherichia coli, Aeromonas hydrophila* |
| 83 | *Citrobacter freundii, Escherichia coli* |
| 84 | *Staphylococcus aureus, Streptococcus dysgalactiae subsp. dysgalactiae* |
| 85 | *Staphylococcus cohnii subsp. urealyticus, Staphylococcus haemolyticus* |
| 86 | *Acinetobacter baumannii complex, Enterococcus faecium* |
| 87 | *Staphylococcus hominis subsp. hominis, Escherichia coli* |
| 88 | *Klebsiella pneumoniae, Escherichia coli* |
| 89 | *Klebsiella pneumoniae, Serratia marcescens* |
| 90 | *Staphylococcus haemolyticus, Stenotrophomonas maltophilia* |
| 91 | *Klebsiella pneumoniae, Escherichia coli* |
| 92 | *Stenotrophomonas maltophilia, Enterococcus faecium* |
| 93 | *Staphylococcus caprae, Staphylococcus warneri, Escherichia coli* |
| 94 | *Enterococcus faecalis, Escherichia coli* |
| 95 | *Enterococcus casseliflavus, Enterococcus faecium* |
| 96 | *Klebsiella oxytoca, Enterobacter cloacae complex* |
| 97 | *Staphylococcus aureus, Citrobacter werkmanii* |
| 98 | *Enterococcus faecalis, Escherichia coli* |
| 99 | *Burkholderia cepacia, Enterococcus faecium* |
| 100 | *Enterococcus faecium, Escherichia coli* |
| 101 | *Klebsiella pneumoniae, Enterococcus faecium* |
| 102 | *Klebsiella pneumoniae, Aeromonas veronii* |
| 103 | *Escherichia coli, Aeromonas caviae* |
| 104 | *Staphylococcus epidermidis, Klebsiella pneumoniae* |
| 105 | *Enterococcus faecium, Enterococcus faecalis* |
| 106 | *Enterococcus faecium, Escherichia coli* |
| 107 | *Klebsiella pneumoniae, Staphylococcus haemolyticus* |
| 108 | *Escherichia coli, Klebsiella pneumoniae* |
| 109 | *Pseudomonas aeruginosa, Escherichia coli* |
| 110 | *Staphylococcus haemolyticus, Enterococcus faecium* |
| 111 | *Pseudomonas aeruginosa, Enterobacter cloacae complex* |
| 112 | *Acinetobacter junii, Acinetobacter pittii* |
| 113 | *Stenotrophomonas maltophilia, Enterococcus faecium* |
| 114 | *Enterococcus faecium, Candida krusei* |
| 115 | *Streptococcus mitis, Escherichia coli* |
| 116 | *Streptococcus gallolyticus subsp. pasteurianus, Escherichia coli* |
| 117 | *Klebsiella pneumoniae, Enterococcus gallinarum* |
| 118 | *Klebsiella pneumoniae, Aeromonas veronii* |
| 119 | *Staphylococcus caprae, Staphylococcus epidermidis* |
| 120 | *Escherichia coli, Streptococcus mitis* |
| 121 | *Escherichia coli, Enterococcus faecalis* |
| 122 | *Bacteroides vulgatus, Enterococcus casseliflavus* |
| 123 | *Pseudomonas aeruginosa, Enterococcus faecium* |
| 124 | *Staphylococcus epidermidis, Staphylococcus haemolyticus* |
| 125 | *Klebsiella pneumoniae, Escherichia coli* |