Clinical Characteristics, Risk Factors and Outcomes of Mixed Candida Albicans/Bacterial Bloodstream Infections

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Abstract

Purpose: The purpose of this study was to explore the clinical features, risk factors, and outcomes of the mixed Candida albicans/bacterial bloodstream infections (mixed-CA/B-BSIs) compared with monomicrobial Candida albicans bloodstream infection (mono-CA-BSI) in adult patients in China.

Methods: All adult hospitalized cases of Candida albicans bloodstream infection (CA-BSI) were recruited in the retrospective observational study from January 1, 2013, to December 31, 2018.

Results: Of the 117 patients with CA-BSI, 24 patients (20.5%) were mixed-CA/B-BSIs. The most common co-pathogens were Coagulase-negative Staphylococcus (24.0%), followed by Klebsiella pneumoniae (20.0%) and Staphylococcus aureus (16.0%). In multivariable analysis, prior ICU stay>2days (adjusted odds ratio [OR], 7.808; 95% confidence interval [CI], 1.264-48.233) was an independent factor of mixed-CA/B-BSIs. In comparison with mono-CA-BSI, patients with mixed-CA/B-BSIs developed with prolonged length of mechanical ventilation [17.5(4.5,34.8) vs. 3.0(0.0,24.5), P=0.019], prolonged length of ICU stay [22.0(14.3, 42.2) vs. 8.0(0.0, 31.5), P=0.010], whereas the mortality was not significantly different.

Conclusions: A high rate of mixed-CA/B-BSIs is among CA-BSI, and Coagulase-negative Staphylococcus is the predominant co-existed species. Prior ICU stay>2 days is an independent risk factor for mixed-CA/B-BSIs. Although there is no difference in mortality, the outcomes of patients with mixed-CA/B-BSIs including prolonged length of mechanical ventilation and prolonged length of ICU stay were worse than those with mono-CA-BSI, which deserves further attention of clinicians.

Introduction

In critically ill patients, bloodstream infections (BSIs) are the important causes of morbidity and mortality. Candidemia is one leading cause of healthcare-associated BSIs, with all-cause in-hospital mortality of up to 30% in the United States [1-3]. With the wide use of antibiotics and immunosuppressants and the rapid increase of invasive medical examinations and treatments, *Candida* has gradually become a significant pathogen for BSIs with a crude average incidence of 8.7 per 100,000 population [2]. Patients with candidemia have many typical risk factors, including recent surgery, exposure to broad-spectrum antibiotics, presence of a central venous catheter (CVC), and injection drug use [2].

Although many candidemia is monomicrobial, the mixed *Candida*/bacterial BSIs account for 18-56% as reported [4-7]. In these studies [4-6], some following limitations still exist: (1) Although the clinical significance and prognosis of mixed *Candida*/bacterial BSIs versus monomicrobial candidemia were investigated, few reports focused on a specific *Candida* like *C. albicans*. (2) Some reported patients with mixed *Candida*/bacterial BSIs had a worse prognosis than patients with monomicrobial candidemia (39% survival rate vs. 67% survival rate, P <0.05) [8], while other studies did not observe the same mortality [4-6]. The discrepancy between these clinical outcomes is not understood. (3) Some risk factors associated with mixed *Candida*/bacterial BSIs such as prolonged length (≥7 weeks) of prior hospital stay, septic shock at the time of candidaemia, higher acute physiology, chronic health evaluation (APACHE) II score, and more antimicrobials administration are supported by data mainly from Korea and Spain. Whether these risk factors also apply in other countries like China is questionable. Therefore, it is necessary to investigate the clinical features of mixed *Candida*/bacterial BSIs for a specific *Candida* in China as well.

Although an increase in the proportion of *Candida* non-albicans species was observed in some epidemiologic studies [9, 10], *C. albicans* is still the most common species, followed by *C. glabrata* and *C.* parapsilosis in candidemia [2-4, 10, 11]. The following differences were found among different *Candida* spp: (1) Different distributions were seen among different *Candida* spp. *C. albicans* is the most common species associated with ICU infections, while *C. glabrata* is most commonly related to gastrointestinal tract disease [11]. (2) Different resistances to common antifungal agents were observed between *C. albicans* and *Candida* non-*albicans*. *Candida* non-*albicans* are more likely to be resistant to fluconazole, but it is not the case for *C. albicans* [11]. (3) Different outcomes like mortality also exist between *Candida* non-*albicans* infection and *C. albicans* infection [9, 10]. Whether there are some differences in sensitivity to antifungal agents, the severity of illness or mortality between groups of mixed-CA/B-BSIs and mono-CA-BSI, and which factors are associated with mixed-CA/B-BSIs are not well known. Given *C. albicans* serves as the most common species in candidemia and few reports about mixed-candidemia by a specific *Candida* like *C. albicans*, a study was performed herein to investigate the clinical characteristics, risk factors and outcomes of mixed-CA/B-BSIs in comparison with mono-CA-BSI.

Material And Methods

Patients and study design

From January 2013 to December 2018, we conducted a single-center retrospective cohort study at the Second Affiliated Hospital of Zhejiang University School of Medicine, a teaching hospital with 3200 beds in Hangzhou, China. The study was approved by the Human Ethics of the Ethics Committee of the Second Affiliated Hospital of Zhejiang University Medical College (reference number 2019-191). Due to the retrospective nature, the Ethics Committee determined that patients' consent was not required.

Patients with positive of *C. albicans* in blood cultures were recruited. Candidemia that occurred 30 days after the initial episode was considered as new cases [10]. Following exclusion criteria were used: a) Age<18 years old; b) Cases data were incomplete or missed; c) *C. albicans* was considered as nonpathogenic *Candida*. Common skin contaminant organisms (e.g., *Bacillus spp.*, *Corynebacterium spp.*, *Micrococcus spp.*, *Streptococci*, *Lactobacillus spp.* and *CNS*) were considered as pathogens only when they were present in two or more consecutive blood cultures from separate blood draws. Thus, a total of 147 blood culture specimens containing *C. albicans* were initially included, and final 117 cases were recruited with 24 cases for mixed-CA/B-BSIs and 93 cases for mono-CA-BSI (Figure 1).

Data collection

The patients' data were collected from electronic medical records. The characteristics including age, gender, the severity of illness sequential organ failure assessment (SOFA) score, and the acute physiology and chronic health evaluation (APACHE) II score in the first 24 hours following candidemia onsets, prior ICU stay, prior hospital stay, the clinical data including underlying diseases, immunocompromised state, hospitalization ward, life-sustaining treatments ≥ 24 h, prior use of antibiotics and antifungal agents, previous treatments such as surgical procedures, and outcomes (length of hospital stay, length of ICU stay, septic shock after onset of BSIs and 28-day mortality after onset of BSIs) were collected. The microbiological data like species of co-pathogens in mixed-CA/B-BSIs, likely source of BSI and sensitivity to antimycotics were also recorded.

Species identification and antimycotic sensitivity test

In our hospital, haemocultures were drawn under sterile conditions when patients' temperature rises above 38.4 degrees Celsius. Species identification of both bacteria and yeasts was performed by MALDI-TOF MS (Bruker Daltonik GmbH, Bremen, Germany). Antimicrobial susceptibility testing for bacteria and yeasts was carried out by Vitek 2 Compact system and ATB FUNGUS 3 (bioMerieux, France), respectively. The results for bacteria and *C. albicans* were interpreted according to breakpoints defined by the Clinical Laboratory Standards Institute [12, 13]. Because echinocandin was not included in the kit of ATB FUNGUS 3, the results of caspofungin susceptibility were unknown.

Definitions

Candidaemia was referred to the isolation of *Candida* in blood culture accompanied by fever, chills or hypotension and other corresponding clinical symptoms and signs, and in need of excluding specimen contamination [14]. If the positive *Candida* species was *C. albicans*, CA-BSI was considered. Mixed-CA/B-BSIs was defined as the isolation of a bacterial organism from blood cultures obtained within 48 hours before or after *C. albicans* bloodstream infection [9]. Nosocomial BSI was defined as the first positive blood culture obtained ≥48 hours after hospital admission and without signs of infection at admission [15]. If only blood culture was positive without clinical manifestations, the bacterium was considered as contaminated microorganisms [16]. The timing of admission of antifungal therapy was determined as the interval between the time when the first *C. albicans*-positive blood sample for culture was drawn and the time when antifungal treatment was first admitted [17]. Antifungal therapy was defined as appropriate if the isolated *Candida* spp was sensitive to the chosen antifungal agent. The antifungal agent was used with adequate dosages (like fluconazole: a loading dose of 800mg [12mg/kg], then 400mg [6mg/kg] daily; Caspofungin: a loading dose of 70mg, then 50mg daily) [3, 18]. The delay of empiric antifungal treatment was considered as initial use more than 12h after the report of first positive blood sample [17].Appropriate antibiotic therapy was defined as antibiotic therapy to the bacteremia, where applicable, was sensitive [19]. Septic shock was consistent with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [20].

Statistical Analyses

Statistical analysis was performed with SPSS 20.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were presented as mean±standard deviation if normally distributed, and as the median and interquartile range (IQRs) if non-normally distributed. Continuous variables were compared by Student t-test or Mann-Whitney U test, and enumeration variables were compared by Pearson χ^2 or Fisher exact test, where appropriate. Variables with p-values of <0.05 by univariate analysis were entered into the multivariable model. Continuous variables were made into dichotomous variables based on the Youden index. Multivariate analysis was performed by logistic regression analysis for the risk factors associated with mixed-CA/B-BSIs. Kaplan-Meier survival estimates were used to generate the survival curves. Differences between survival curves were assessed through the log-rank test. A two-tailed p<0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

The median age was 68 years (IQR, 59-75), and 58.1% (68/117) of patients were male. The mono-CA-BSI and mixed-CA/B-BSIs were responsible for 93/117(79.5%) and 24/117(20.5%) cases, respectively. The most ward of CA-BSI occurrence was ICU (66.7%), followed by surgical ward (23.9%) and medical ward (9.4%). The solid tumor was the most common co-morbidity (28.2%), followed by diabetes mellitus (23.9%). There were no significant differences in age, gender, immune-suppression conditions, or ill severity between the two groups. Among surgical patients and ICU patients, 65.8% (77/117) and 66.7% (78/117) episodes were documented, respectively. Other common predisposing factors for candidemia included central venous catheter insertion (85/117, 72.6%), urethral catheter insertion (106/117, 90.6%), prior antibiotics exposure (93/117, 79.5%) and total parenteral nutrition (TPN) (85/117, 72.6%). Comparison with mono-CA-BSI, patients with mixed-CA/B-BSIs displayed longer ICU stay before candidemia onset [12.0(8.0,17.8) vs. 1.0(0.0,11.0), *P* =0.001], longer hospital stay before candidemia onset [19.0(12.0,30.8) vs. 12.0(2.0,26.5), *P* =0.031], longer duration of ventilation before candidemia onset [11.0(0.3,24.5) vs. 1.0(0.0,10.0), *P* =0.013], longer prior antibiotic exposure before candidemia onset [17.0(10.3,28.8) vs. 8.0(1.0,20.5), *P* =0.007], more need of life-sustaining treatments such as invasive mechanical ventilation (81.8% vs. 54.7%, *P* =0.020) and continuous renal replacement therapy (CRRT) (41.7% vs. 21.5%, P =0.044). Nonetheless, there were no statistical differences in proportions of surgical patients, blood transfusion, total parenteral nutrition, hypoproteinemia. The source of total CA-BSI was mainly from the intra-abdominal (25.6%, 30/117), followed by lower respiratory tract infection (25.6%, 30/117) and. CVC-related infection (11.1%,13/117). In comparison with mono-CA-BSI, the source of *Candida* in mixed-CA/B-BSIs didn't display a significant difference, as shown in Table 2.

A high percentage of delay in initiation empiric antifungal treatment (85.5%) was observed among all patients, whereas no difference was found between groups of mixed-CA/B-BSIs (75.0%) and mono-CA-BSI (88.2%). Besides, the total proportion of appropriate antifungal therapy was lower than 50% (36.8%), and it was similar in patients with mixed-CA/B-BSIs (33.3%) to that with mono-CA-BSI (37.6%), as shown in Table 2. The proportions of empiric treatment and appropriate antibiotic therapy for bacteremia in mixed-CA/B-BSIs is 33% (8/24) and 70% (17/24), respectively.

Antifungal susceptibility

The *C. albicans* in both groups exhibited 100% susceptibility to amphotericin B, walconazole, and voriconazole, while no resistance to fluconazole was observed. Notably, in the group of mono-CA-BSI and mixed-CA/B-BSIs, 11 (24.4%) and 2 (13.3%) cases were completely resistant to ketoconazole, respectively. There was no significant difference between the two groups in vitro antifungal susceptibility test, as shown in Table 3. Because the drug sensitivity kit used in our current microbiology laboratory does not contain echinocandin, the specific drug sensitivity of *C.albicans* to echinocandin was not clear.

Independent risk factors for mixed-CA/B-BSIs

Variables with *P* values of <0.05 including prior hospital stay>7days, prior ICU stay>2days, prior antibiotic exposure>7days□prior mechanical ventilation>2days□CRRT before candidemia onset were entered into the multivariable logistic regression model to identify

factors associated with mixed-CA/B-BSIs. As shown in Table 4, the independent risk factor of mixed-CA/B-BSIs was prior ICU stay>2days (adjusted odds ratio [OR], 7.808; 95% confidence interval [CI], 1.264-48.233).

Species distribution of the concomitant bacterial isolated from the mixed-CA/B-BSIs

The most common co-pathogen was Gram-positive bacteria (52.0%), followed by Gram-negative bacteria (48.0%). In terms of the exact microorganisms, the most frequent pathogen was *Coagulase-negative Staphylococcus* (CNS) (24.0%), followed by *Klebsiella pneumoniae* (*k.pneumoniae*) (20.0%) and *Staphylococcus aureus*(*S.aureus*) (16.0%). The detailed distribution of concomitant bacterial species in mixed-CA/B-BSIs was shown in Figure 2.

Outcomes

The median length of ICU stay was 14 days (IQR, 1.0-33.0), and the median length of hospital stay was 33 days (IQR, 18.0-56.0). In comparison with mono-CA-BSI, patients with mixed-CA/B-BSIs developed prolonged length of ICU stay [8.0(0.0, 31.5) vs. 22.0(14.3, 42.2), P =0.010] and longer mechanical ventilation time [3.0(0.0, 24.5) vs. 17.5(4.5, 34.8), P =0.019]. The incidence of septic shock, 28-day or 60-day mortality rates, or in-hospital mortality in patients with mixed-CA/B-BSIs were not different from those with mono-CA-BSI (Table 5, Figure 3).

Discussion

In the current study, several important results were found. First, mixed-CA/B-BSIs was no longer a rare event. Second, some risk factors were found to be related to mixed-CA/B-BSIs, including longer ICU stay, longer hospital stay, longer duration of ventilation, and longer prior antibiotic exposure before candidemia onset, life-sustaining treatments such as invasive mechanical ventilation and CRRT (Table 1 and Table2). Moreover, prior ICU stay>2days was an independent risk factor for mixed-CA/B-BSIs (Table 4). Third, Gram-positive bacteria were the main co-pathogens in mixed-CA/B-BSIs, followed by Gram-negative bacteria. In terms of specific co-pathogen, *CNS* was the predominant co-existed species. Moreover, patients with mixed-CA/B-BSIs had poor outcomes, including prolonged lengths of ICU stay and longer mechanical ventilation time in comparison with mono-CA-BSI (Table 5). To our knowledge, the present retrospective study is the first time to investigate the clinical characteristics, risk factors and outcomes of mixed-CA/B-BSIs in comparison with mono-CA-BSI.

Specific polymicrobial bacteremia was more often reported in previous studies. 23.5% and 48.0% polymicrobial bacteremia were observed in *A. baumannii* bacteremia and *K. pneumoniae* bacteremia, respectively [21, 22]. In terms of enterococcal BSIs, the 34.8% cases (157/451) were mixed with other pathogens such as *CNS*, *A.baumannii*, and *K.pneumoniae* [23]. Whether the mixed-CA/B-BSIs are really infrequent, it might be underestimated. The current report found that the incidence of mixed-CA/B-BSIs was 20.5%. A similar proportion of mixed-CA/B-BSIs among CA-BSI were reported whether in developed Europe such as Spain (18%) [4] or Asia such as South Korea (23%) [5] or China (33%) [24]. These results suggest that the relatively high proportion of specific polymicrobial BSIs is not only observed in bacterial BSIs but also candidemia or CA-BSI.

Similar risk factors were found to be associated with mixed-CA/B-BSIs in previous studies [4, 5], including more frequent longer ICU stay, longer hospital stay before candidemia onset, more admission of antimicrobials, and the existence of organ dysfunction/failure (e.g., need of invasive mechanical ventilation or renal replacement therapy) (Table1). However, there were no differences in the APACHE II score and SOFA score (Table 1), which might be reflected by the similar severity of co-morbidities diseases. Although septic shock at the time of candidemia was positively associated with mixed *Candida*/bacterial BSIs in the previous study [5], it was not independently associated with mixed *Candida*/bacterial BSIs in the current study. This might be partly explained by the similarity of appropriate antifungal therapy in both groups (Table 4) and a high rate of antibiotic therapy (70%) in mixed-CA/B-BSIs.
Previous work has demonstrated that more than 20.2% of nosocomial BSIs in ICU were polymicrobial BSIs [25, 26], which is consistent with our finding that prior ICU stay>2days was an independent risk factor for mixed-CA/B-BSIs in the current study. The high occurrence of polymicrobial BSIs in ICU might be explained by a suboptimal host defense altered by underlying diseases, receiving more artificial/invasive procedures or immunosuppressive therapy in critically ill patients [26]. These results indicate that patients in ICU are not only susceptible to BSI, but also vulnerable to polymicrobial BSI including mixed-CA/B-BSIs.

In the current study, gram-positive bacteria (52%) were the main co-pathogens in mixed-CA/B-BSIs, followed by Gram-negative bacteria (48%). Among all specific co-existed species, *CNS* was the predominant (24%) specie, which is consistent with previous reports [5]. Followed by *CNS,* the next most prevalent co-pathogen species was *K.pneumoniae* (20%) and *S.aureus* (16%) (Figure 2). Although the main co-pathogen was also *CNS,* it was followed by *Enterococcus* species and S.*aureus* instead in Kim's study [5]. The gastrointestinal tract (35%) was the most common source of mixed-CA/B-BSIs in Kim's study, while it only accounted for 25% in the current study (Table 4). It is well known that the common source of *Enterococcal* bacteremia BSIs is from the gastrointestinal tract [15], which might partially explain a high proportion of *Enterococcus* as co-pathogen species among mixed-CA/B-BSIs in Kim's study. Consistent with a high proportion of *K.pneumoniae* (15.2%) among BSIs in a previous study [27], it was the second common co-pathogens in mixed-CA/B-BSIs in our study, which might ascribe partly to the fact that *K.pneumoniae* serves as a leading causative agent of hospital-based infections over the past few decades [28].

Although patients with mixed-CA/B-BSIs had poor outcomes (eg. prolonged lengths of ICU stay and longer mechanical ventilation time) than those with mono-CA-BSI, the 28-day mortality (41.7% vs. 33.3%, *P* =0.446) was similar between the two groups, as well as the 60-day mortality (50.0% vs. 36.6%, *P* =0.229) and in-hospital mortality (54.2% vs. 39.8%, *P* =0.204) (Table 5, Figure 3). Similar to previous findings [4, 5], we found no correlation between mixed-CA/B-BSIs and mortality. The similar chronic comorbid conditions and severity of illness at the onset of candidemia, a high percentage (more than 75%) of delay in initiation of empiric antifungal treatment (Table 2) and a low rate (less than 40%) of appropriate antifungal therapy might be ascribed to the similarly high mortality between groups of mixed-CA/B-BSIs and mono-CA-BSI observed in our study.

The present study also has some limitations. First, this is a single-center study, and therefore, results and conclusions might be influenced by local ecology, management practices, infection control policy, and local susceptibility patterns. Second, some important factors of mixed-CA/B-BSIs might be missed because of the retrospective analysis. For example, the corticosteroids' dosage and treatment course were not precisely obtained, which might be unclear for the immune-suppression conditions caused by corticosteroids. Finally, although this is the first report on the risk factors and clinical outcomes of mixed-CA/B-BSIs compared with mono-CA-BSI, the relatively small sample size may impact on the confidence intervals and analysis of risk factors. Thus, further large-scale, multi-center, prospective studies are needed.

Conclusions

Among the total CA-BSI, mixed-CA/B-BSIs is not a rare event, and the *CNS* was the predominant co-existed species among mixed-CA/B-BSIs isolated from adult candidaemia. Prior ICU stay>2days was an independent risk for mixed-CA/B-BSIs. Although there is no difference in mortality, the prognosis of patients with mixed-CA/B-BSIs including prolonged length of mechanical ventilation and prolonged length of ICU stay is worse than that with mono-CA-BSI,

Abbreviations

CA/B-BSI, *Candida albicans* bloodstream infection; mono-CA-BSI, monomicrobial *Candida albicans* bloodstream infection; mixed-CA/B-BSIs, mixed *Candida albicans*/bacterial bloodstream infections; BSIs, bloodstream infections; IQR, interquartile range; CRRT, continuous renal replacement therapy; CVC, central venous catheter, COPD, chronic obstructive pulmonary disorder; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; *CNS*, *Coagulase-negative Staphylococcus* ; *K. pneumoniae, Klebsiella pneumoniae*; *S. aureus*, *Staphylococcus aureus*; *A. baumannii, Acinetobacter baumannii*; *E. faecium*, *Enterococcus faecium*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *B. cepacia, Burkholderia cepacia*; *P. mirabilis, Proteus mirabilis*; CLSI, Clinical and Laboratory Standards Institute;

Declarations

Ethics approval and informed consent

Ethical approval:

This study had been approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. We make sure to keep patient data confidential and comply with the Declaration of Helsinki.

Informed consent

No patient consent was required due to the retrospective nature of the study.

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Authorship/Contributions

Gensheng Zhang, Wei Cui and Zhaohui Dong designed the study, revised the manuscript and gave final approval of the version to be published; Li Zhong, Shufang Zhang and Kankai Tang coordinated writing and preparation of the manuscript, and collected/analyzed the data. Feifei Zhou, Cheng Zheng, Kai Zhang Jiachang Cai, Hongwei Zhou, Yesong Wang, Baoping Tian and Zhaocai Zhang collected and analyzed the data.

Disclosure

The authors have no conflict of interest to declare.

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Tables

Table 1. Baseline characteristics of the patients with mono-CA-BSI or mixed-CA/B-BSIs

Characteristics	Total (n=117)	Mono-CA-BSI (n =93)	Mixed-CA/B-BSIs (n =24)	*P* value
Age, median years(IQR)	68(59,75)	69(59,76)	64(47,74)	0.399
Male sex [n (%)]	68(58.1%)	53(56.9%)	15(62.5%)	0.626
APACHE II score at the onset of candidemia(IQR)	17.0(11.5,24.5)	17.0(12.0,24.0)	17.5(10.0,26.5)	0.863
SOFA score at the onset of candidemia (IQR)	6.0(2.0,9.0)	5.0(2.0,9.0)	6.5(2.0,9.8)	0.494
Prior ICU stay (days) (IQR)	3.0(0.0,14.0)	1.0(0.0,11.0)	12.0(8.0,17.8)	**0.001**
Prior hospital stay (days) (IQR)	14.0(4.5,27.5)	12.0(2.0,26.5)	19.0(12.0,30.8)	**0.031**
Prior ventilation mechanical ventilation (days) (IQR)	1.0(0.0,13.0)	1.0(0.0,10.0)	11.0(0.3,24.5)	**0.013**
Underlying disease [n (%)]				
Diabetes mellitus	28(23.9%)	23(24.7%)	5(20.8%)	0.690
Chronic cardiac dysfunction	24(20.5%)	16(17.2%)	8(33.3%)	0.144
Chronic obstructive pulmonary disease	5(4.3%)	5(5.4%)	0(0%)	0.552
Chronic renal insufficiency	9(7.7%)	8(8.6%)	1(4.2%)	0.766
Chronic hepatic insufficiency	14(12.0%)	13(14.0%)	1(4.2%)	0.333
Solid tumour	33(28.2%)	28(30.1%)	5(20.8%)	0.368
Haematological malignancy	1(0.9%)	1(1.1%)	0(0%)	>0.999
Trauma	19(16.2%)	14(15.1%)	5(20.8%)	0.708
Burn injury	4(3.4%)	2(2.2%)	2(8.3%)	0.186
Transplant	14(12.0%)	11(11.8%)	3(12.5%)	>0.999
Immunocompromised[n (%)]				
Immunosuppressant therapy	6(5.1%)	6(6.5%)	0(0.0%)	0.448
Steroid therapy	6(5.1%)	6(6.5%)	0(0.0%)	0.448
Chemotherapy/radiation	7(6.0%)	7(7.5%)	0(0.0%)	0.366
Neutropenia	4(3.4%)	3(3.2%)	1(4.2%)	>0.999
Blood transfusion[n (%)]	40(34.2%)	30(32.2%)	10(41.7%)	0.386
Hospitalization ward[n (%)]				
Medical	11(9.4%)	11(11.8%)	0(0.0%)	0.168
Surgical	28(23.9%)	24(25.8%)	4(16.7%)	0.349
ICU	78(66.7%)	58(62.4%)	20(83.3%)	0.052
Nosocomial infection[n (%)]	112(95.7%)	88(94.6%)	24(100%)	0.552
Life-sustaining treatments ≥ 24 h [n (%)]				
Invasive mechanical ventilation	65(60.2%)	47(54.7%)	18(81.8%)	**0.020**
Vasopressor	45(38.5%)	34(36.6%)	11(45.8%)	0.405
CRRT	30(25.6%)	20(21.5%)	10(41.7%)	**0.044**
Catheterisation [a][n (%)]				

Central venous catheter	85(72.6%)	65(69.9%)	20(83.3%)	0.289
Drainage tube	77(65.8%)	59(63.4%)	18(75.0%)	0.287
Urethral catheter	106(90.6%)	85(91.4%)	21(87.5%)	0.848
Total parenteral nutrition [n (%)]	85(72.6%)	65(69.9%)	20(83.3%)	0.188
Hypoproteinemia[n (%)]	49(41.9%)	37(39.8%)	12(50.0%)	0.366
Surgery [n (%)]	77(65.8%)	59(63.4%)	18(75.0%)	0.287
Abdominal	39(33.3%)	32(34.4%)	7(29.2%)	0.627

Notes: Bold, indicates P<0.05. **Abbreviations**: IQR, interquartile range; COPD, chronic obstructive pulmonary disorder; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; CRRT: continuous renal replacement therapy.

a Included patients who were required to be catheterised within 2 weeks of the first positive sample, regardless of whether or not the catheter was removed before diagnosis.

Table 2. The source of candidaemia , prior antibiotic and antifungal therapy of the mono-CA-BSI compared with the Mixed-CA/B-BSIs.

Variable	Total (n=117)	Mono-CA-BSI (n =93)	Mixed-CA/B-BSIs (n =24)	*P* value
Source of candidaemia [n (%)]				
CVC-related infection	13(11.1%)	10(10.8%)	3(12.5%)	>0.999
Intra-abdominal infection	30(25.6%)	26(28.0%)	4(16.7%)	0.259
Urinary tract infection	8(6.8%)	5(5.4%)	3(12.5%)	0.436
Lower respiratory tract infection	15(12.8%)	13(14.0%)	2(8.3%)	0.693
Skin and Soft tissue infection	4(3.4%)	3(3.2%)	1(4.2%)	>0.999
Unknown	47(40.2%)	36(38.7%)	11(45.8%)	0.526
Days of prior antibiotic exposure(IQR)	11.0(3.0,22.0)	8.0(1.0,20.5)	17.0(10.3,28.8)	**0.007**
Prior antibiotic exposure [a] [n (%)]	93(79.5%)	69(74.2%)	24(100.0%)	**0.012**
Cephalosporins	33(28.2%)	25(26.9%)	8(33.3%)	0.531
Carbapenems	49(41.9%)	41(44.1%)	8(33.3%)	0.341
Penicillins	25(21.4%)	19(20.4%)	6(25.0%)	0.626
Quinolones	4(3.4%)	4(4.3%)	0(0.0%)	0.580
Initial antifungal agent[n (%)]				
Fluconazole	40(34.2%)	32(34.4%)	8(33.3%)	0.921
Echinocandin	46(39.3%)	36(38.7%)	10(41.7%)	0.791
Voriconazole	11(9.4%)	9(9.7%)	2(8.3%)	>0.999
Prior antifungal exposure [n (%)]	10(8.5%)	6(6.4%)	4(16.7%)	0.235
Appropriate Antifungal therapy [b] [n (%)]	43(36.8%)	35(37.6%)	8(33.3%)	0.697
Delay in initiation of empiric antifungal treatment [c][n (%)]	100(85.5%)	82(88.2%)	18(75.0%)	0.103

Abbreviations: CVC, central venous catheter;

a All patients receiving systemic drug therapy for ≥3 days within 2 weeks prior to candidaemia onset; b Antifungal therapy was defined as appropriate if the isolated Candida spp was sensitive to the chosen antifungal agent, and the antifungal agent was used with adequate dosages (like Fluconazole: loading dose of 800mg [12mg/kg], then 400mg [6mg/kg] daily; Caspofungin: loading dose of 70mg, then 50mg daily); c The delay of empiric antifungal treatment was considered as initial use more than 12h after the report of first positive blood sample.

Table 3 In vitro antifungal susceptibility of *C. albicans* between mono-CA-BSI and mixed-CA/B-BSIs.

Candida species	Antifungal agent	mono-CA-BSI (n =93)				mixed-CA/B-BSIs (n =24)				*P* value
		Number of strains	Drug sensitivity			Number of strains	Drug sensitivity			
			S	I	R		S	I	R	
C.albicans	Fluconazole (n=104) [a]	85 (91.3%)	81 (95.3%)	4 (4.7%)	0	19 (79.1%)	19 (100.0%)	0	0	>0.999
	Clotrimazole (n=69) [a]	55 (59.1%)	54 (98.2%)	0	1 (1.8%)	15 (62.5%)	14 (93.3%)	0	0	0.901
	Ketoconazole (n=60) [a]	45 (48.3%)	19 (42.2%)	15 (33.3%)	11 (24.4%)	15 (62.5%)	7 (46.7%)	6 (40.0%)	2 (13.3%)	0.764
	Itraconazole (n=111) [a]	89 (95.7%)	86 (96.6%)	1 (1.1%)	2 (2.2%)	22 (91.7%)	21 (95.5%)	1 (4.5%)	0	>0.999
	Amphotericin B (n=111) [a]	90 (96.8%)	90 (100.0%)	0	0	21 (87.5%)	21 (100.0%)	0	0	>0.999
	Nystatin (n=68) [a]	56 (60.2%)	55 (98.2%)	1 (1.8%)	0	12 (50.0%)	12 (100.0%)	0	0	>0.999
	5-fluorocytosine (n=38) [a]	31 (33.3%)	30 (96.8%)	0	1 (3.2%)	7 (29.1%)	7 (100.0%)	0	0	>0.999
	Walconazole (n=69) [a]	55 (59.1%)	55 (100.0%)	0	0	14 (58.3%)	14 (100.0%)	0	0	>0.999
	Voriconazole (n=34) [a]	27 (29.0%)	27 (100.0%)	0	0	7 (29.1%)	7 (100.0%)	0	0	>0.999

Notes: S, sensitive; I, intermediary; R,resistant. a Not all agents listed tested in all isolates;

Table 4. Multivariable logistic regression of factors associated with mixed-CA/B-BSIs.

Risk factors	B	S.E.	Wald	*P* value	OR(95% CI)
Prior hospital stay>7days	0.853	1.528	0.312	0.577	2.347(0.117,46.892)
Prior ICU stay>2days	2.055	0.929	4.894	**0.027**	7.808(1.264,48.233)
Prior antibiotic exposure>7days	1.172	1.125	1.086	0.297	3.229(0.356,29.270)
Prior mechanical ventilation>2days	-0.503	0.771	0.426	0.514	0.604(0.133,2.740)
CRRT	0.926	0.551	2.83	0.093	2.526(0.858,7.432)
Constant	-4.374	1.125	15.107	0	0.013(-)

Notes: Bold, indicates P<0.05. **Abbreviations**: B, coefficient; S.E., standard error; Wald: Wald test statistic; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; CRRT: continuous renal replacement therapy.

Table 5. Comparison of outcomes between mono-CA-BSI and mixed-CA/B-BSIs.

Outcomes	Total (n=117)	mono-CA-BSI (n =93)	mixed-CA/B-BSIs (n =24)	*P* value
Total ICU stay days (IQR)	14.0(1.0, 33.0)	8.0(0.0, 31.5)	22.0(14.3, 42.2)	**0.010**
Total Hospitalization days (IQR)	33.0(18.0, 56.0)	33.0(15.0,51.0)	31.5(23.0,66.0)	0.217
Total mechanical ventilation days (IQR)	6.0(0.0,30.5)	3.0(0.0,24.5)	17.5(4.5,34.8)	**0.019**
Septic shock (n,%)	40(34.2%)	31(33.3%)	9(37.5%)	0.701
28-day mortality (n,%)	41(35.0%)	31(33.3%)	10(41.7%)	0.446
60-day mortality (n,%)	46(39.3%)	34(36.6%)	12(50.0%)	0.229
In-hospital mortality (n,%)	50(42.7%)	37(39.8%)	13(54.2%)	0.204

Notes: Bold, indicates P<0.05; **Abbreviations**: ICU, intensive care unit; IQR, interquartile range;

Figures

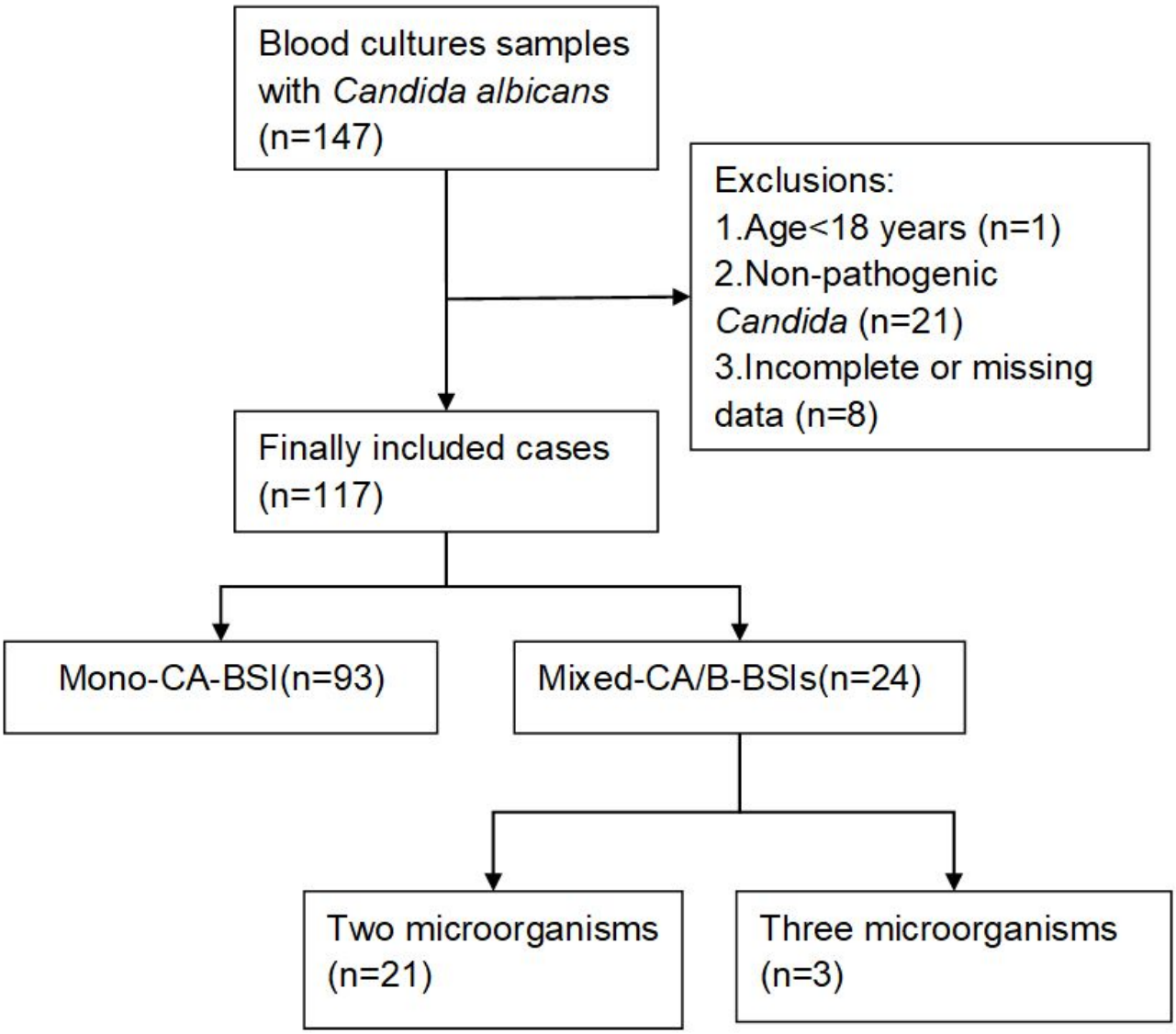

Figure 1

Figure 1

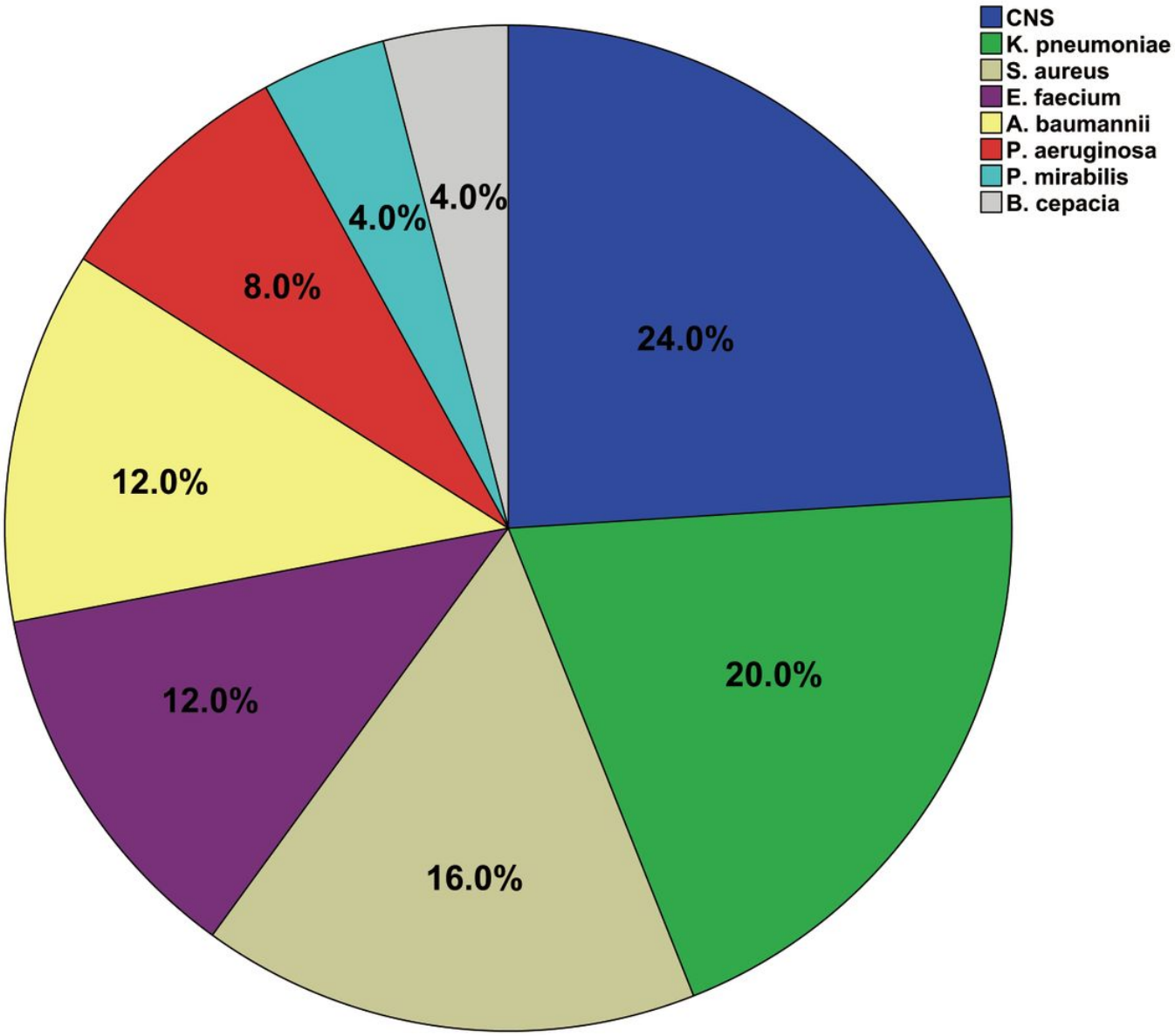

Figure 2

Figure 2

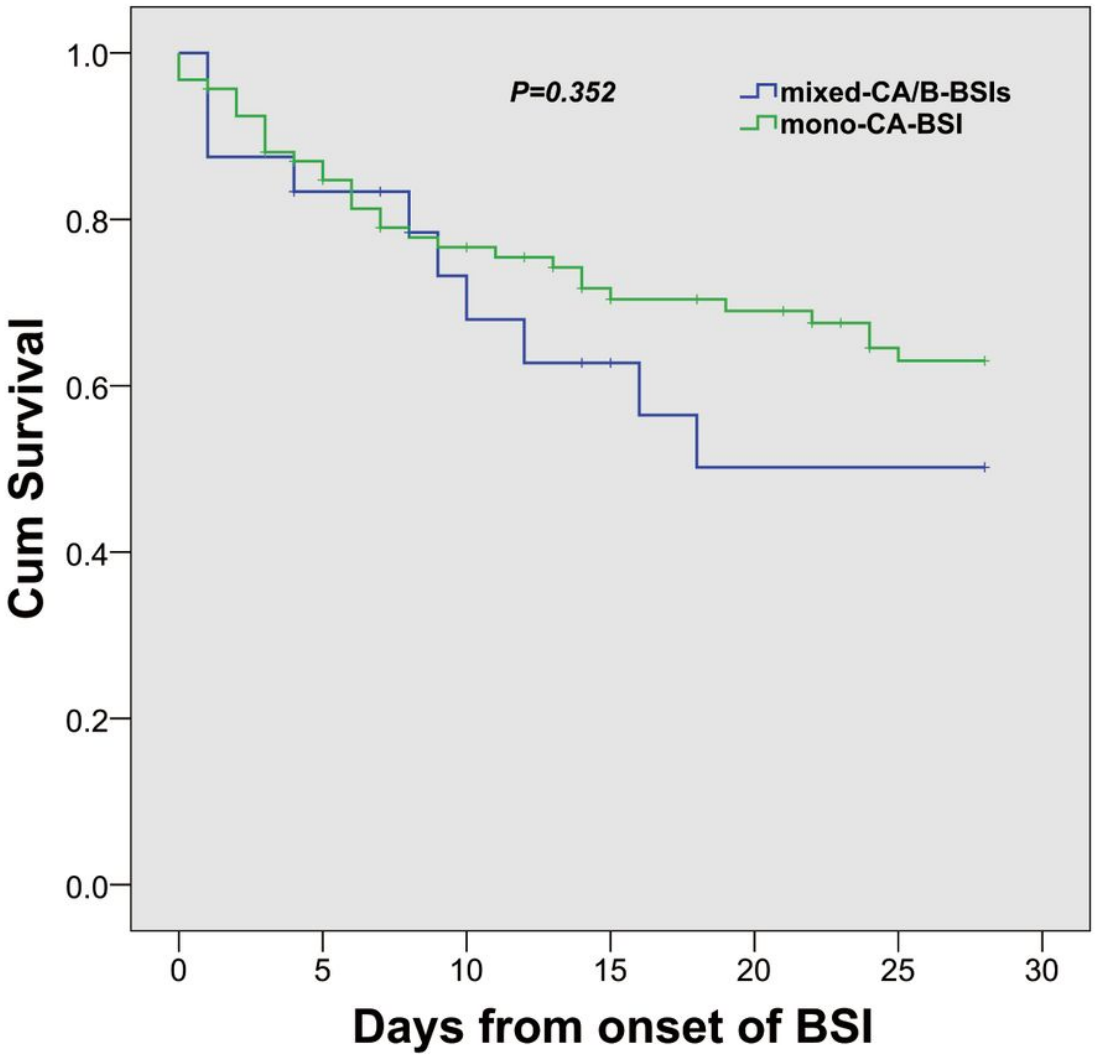

Figure 3

Figure 3