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Nosocomial Bloodstream Infection Due to *Candida* spp. in China: Species Distribution, Clinical Features, and Outcomes

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Abstract
Objectives To investigate the distribution of *Candida* spp., predictors of mortality, and effects of therapeutic measures on outcomes of nosocomial bloodstream infection (BSI) due to *Candida* spp.
Methods This retrospective, population-based study enrolled adult patients with *Candida* nosocomial BSI from January 2010 to December 2014 in one tertiary care hospital. The demographics, comorbidities, species distribution, risk factors, and effects of antifungal treatment were assessed.
Results In total, 190 episodes of *Candida* BSI were identified. The most prevalent species was *C. albicans* (38.9 %), followed by *C. parapsilosis* (23.2 %) and *C. tropicalis* (20.5 %). In vitro susceptibility testing showed that 88.9 % of *Candida* isolates were susceptible to fluconazole. The 30-day hospital mortality was 27.9 %, while the early mortality (within 7 days) was 16.3 %. In a multivariate regression analysis, the Acute Physiology and Chronic Health Evaluation II score [odds ratio (OR) 1.23; 95 % confidence interval (CI) 1.080–1.390; $P = 0.002$] and severe sepsis or septic shock (OR 15.35; 95 % CI 2.391–98.502; $P = 0.004$) were independently correlated with early mortality. Severe sepsis or septic shock (OR 24.75; 95 % CI 5.099–120.162; $P < 0.001$) was an independent risk factor for 30-day mortality, while proven catheter-related candidemia (OR 0.16; 95 % CI 0.031–0.810; $P = 0.027$) was a positive factor for 30-day mortality. Early central venous catheter removal and adequate antifungal treatment were closely related to decreased mortality in patients with primary candidemia.
Conclusion The proportion of candidemia caused by *C. albicans* was lower than that caused by non-*albicans* species. The severity of illness influenced early mortality, and the origin of the central venous catheter remarkably affected 30-day mortality.

Keywords Nosocomial candidemia · *Candida* species · Mortality · Treatment outcome

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Introduction

Candida species, as a significant cause of nosocomial bloodstream infections (BSI), has risen fivefold in the past decade all over the world, and currently become the

fourth cause of BSI in the USA [1]. Many risk factors contribute to the incidence of candidemia, including immunosuppressive therapies (e.g., chemotherapy, corticosteroids), neutropenia, exposure to broad-spectrum antibacterial agents, intensive care unit (ICU) admission, complicated surgery, prolonged use of central venous catheters (CVCs), and administration of total parenteral nutrition (TPN) [2].

Candida albicans has long been the most prevalent species isolated in patients with candidemia. However, recent researches have found a shift in this trend, and the proportion of non-*albicans* species is now even higher than that of *C. albicans* [3, 4]. The epidemiology, species distribution, and antifungal drug susceptibility of candidemia vary geographically. The SENTRY antimicrobial surveillance program showed that the prevalence of *C. glabrata* was higher in the United States than in other regions. *Candida tropicalis* and *C. parapsilosis* are more prevalent in Latin America than in the USA. In Canada and Europe, the prevalence of *C. albicans* is higher than that in other regions [5–7]. One study showed that in China, C. *albicans* was the most prevalent species causing fungal infection, while the most common non-albicans species was *C. glabrata* [8].

Despite the increasing use of echinocandins for the treatment of *Candida* infections, the mortality rate remains high ranging from 35 to 53 % [2, 9, 10]. Although one study showed that the clearance rate of candidemia was lower for mixed candidemia/bacteremia during the early stage of antifungal treatment, the survival rate did not differ regardless of concurrent bacteremia [11]. Many research data have showed that delayed CVC removal and/or inadequate antifungal treatment (e.g., inappropriate dosage, resistant isolate) could increase the mortality among patients with candidemia [4, 12–14]. Therefore, these two interventions have been recommended as the standard care in patients with candidemia.

The objectives of the present study were to describe the distribution of *Candida* spp. and the clinical characteristics of candidemia, identify the predictors of mortality in patients with candidemia, and determine the effect of clinical interventions on outcomes at our tertiary care hospital in Beijing, China, from 2010 to 2014. Antifungal susceptibility and antifungal therapy were also analyzed.

Methods

Hospital Setting and Study Design

This retrospective study was undertaken in a 2200-bed tertiary care hospital in Beijing, China, from January 2010 to December 2014. This center is a comprehensive hospital with medical, health, teaching, and scientific research accreditation that serves all national army personnel and nonmilitary personnel from across the country. The center has six ICUs containing more than 100 beds. All consecutive hospitalized patients aged $\geq$18 years with an episode of *Candida* bloodstream infection that was monitored by the Department of Infection Management and Disease Control and identified through the microbiological laboratory during the hospital stay were qualified for this study. We recorded the following data upon confirmation of candidemia: demographics, underlying diseases, risk factors for candidemia, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, occurrence of severe sepsis or septic shock, *Candida* spp. distribution, time from admission to onset, antifungal susceptibility testing results, antifungal therapy, and early ($\leq$7-day) and overall ($\leq$30-day) mortality. The impact of multiple comorbidities was evaluated by the Charlson comorbidity index.

Blood was cultured using a BacT/AlerT 3D automatic blood and sterile body fluid detection system (Becton–Dickinson, Sparks, MD, USA), and positive cultures were automatically inoculated with an automated agar plate inoculation system (PREVI Isola; bioMérieux, Marcy l'Etoile, France). Identification of *Candida* spp. was confirmed with the VITEK-2 system (bioMérieux). The minimum inhibitory concentration clinical breakpoints were defined based on recommendations from the Clinical and Laboratory Standards Institute [15, 16].

Definitions

The definition of an episode of candidemia was detection of at least one positive peripheral blood culture for *Candida* spp. with relevant signs or symptoms. The onset of candidemia was once drawing a positive blood culture. We only recorded the first episode of candidemia in each case. Patients whose cultures grew more than one species of *Candida* were

not included in the study. Mixed candidemia/bacteremia was confirmed by the bacterial species isolated from a single blood culture or different cultures within 2 days [11].

Primary candidemia was defined as an infection that had no obvious sources or was catheter-related [17]. Catheter-related candidemia was defined as the detection of the same *Candida* spp. in both peripheral blood and semiquantitative catheter tip culture (>15 cfu) [18]. Secondary candidemia was considered when the same *Candida* spp. was identified in both blood culture and other potential infection sources. All potential risk factors for candidemia within 30 days before the first positive blood culture were noted. Neutropenia was defined as <500 cells/mm^3 absolute neutrophil count. Systemic corticosteroid therapy was defined as >1 week of treatment with prednisone at >1 mg/kg/day or equivalent before diagnosis of *Candida* BSI. We defined "broad-spectrum antibiotics" as fourth-generation cephalosporins and carbapenems. Exposure to broad-spectrum antibiotics was defined as the use of these drugs for at least 5 days during the 30 days prior to the blood cultures being drawn.

Appropriate antifungal treatment was defined as an adequate dosage and initiation within 5 days from the blood cultures draw based on the Infectious Diseases Society of America guidelines, including fluconazole, initial dose of 12 mg/kg/day, followed by 6 mg/kg/day (adjusted according to renal function) for all *Candida* spp. except for *C. glabrata* (≥12 mg/kg once daily); voriconazole, initial dose of 6 mg/kg twice daily for two doses followed by 3 mg/kg twice daily; amphotericin B deoxycholate, ≥0.5 mg/kg/day; liposomal amphotericin B, ≥3 mg/kg/day; caspofungin, initial dose of 70 mg followed by 50 mg/day; and micafungin, 100 mg/day [13]. It was considered inappropriate to treat *C. krusei* candidemia with fluconazole. The definition of early CVC removal was catheter removal within the first 48 h of sampling the first blood culture that was positive for *Candida* spp.

Statistical Analysis

The baseline and subgroup characteristics were routinely described and analyzed in the results. Continuous variables are represented as median and interquartile range (IQR). The differences in categorical variables were analyzed by the chi-squared test or Fisher's exact test. We predicted and analyzed the risk factors for mortality by generating a multivariate logistic regression model. Variables statistically related ($P < 0.10$) to early and 30-day mortality in the univariate analyses were used to build the multivariate model. We used Kaplan–Meier curves to estimate the survival rates, and differences were evaluated using the log-rank test. A two-tailed P value of <0.05 indicated statistical significance. All statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic and Clinical Characteristics of the Patients

In total, 204 episodes of candidemia occurred among 197 patients and 7 patients were excluded because they were infected with two species. The overall incidence was 0.29 cases/1000 admissions and decreased from 0.43 to 0.25 episodes/1000 admissions from 2010 to 2014 (0.43 in 2010, 0.36 in 2011, 0.30 in 2012, 0.15 in 2013, and 0.25 in 2014). The median patient age in this study was 68 years, and 64.7 % of the patients were male. Table 1 shows the demographics and clinical characteristics of the patients with *Candida* BSI. The median length of prior hospital stay before *Candida* BSI was 21 days (IQR, 11.5–35.0 days). A total of 52.6 % of patients were residents in the ICU at the time of candidemia diagnosis. In terms of risk factors for *Candida* BSI, 150 patients (78.9 %) had a CVC for at least 24 h at the time of candidemia diagnosis, 139 (73.2 %) were exposed to broad-spectrum antibiotics, and 115 (60.5 %) were given TPN before *Candida* isolation. Overall, 64.2 % of *Candida* isolates (122 of 190) were found among the primary infections, among which 42 cases proved to be catheter-related.

Species Distribution

Overall, 74 (38.9 %) of the infections were due to *C. albicans*, followed by *C. parapsilosis* (44 cases, 23.2 %), *C. tropicalis* (39 cases, 20.5 %), *C. glabrata* (25 cases, 13.2 %), *C. krusei* (4 cases, 2.1 %), and other *Candida* spp. (4 cases, 2.1 %). Non-*albicans* *Candida* species comprised more than half of the

Table 1 Demographic and clinical characteristics of the patients with candidemia

Characteristics	*n*/*N* (%)
Age (years), median (IQR)	68 (50.75–78.25)
Male gender	123 (64.7)
Comorbidities	
Cardiovascular disease	99 (52.1)
Solid tumor	81 (42.6)
Cerebrovascular disease	58 (30.5)
Diabetes mellitus	54 (28.4)
Pulmonary disease	18 (9.5)
Hematologic malignancy	8 (4.2)
Prior hospital stay, median days (IQR)	21 (11.5–35)
ICU residence	100 (52.6)
Prior ICU stay, median days (IQR)	13.5 (6–25.75)
Risk factors for *Candida* infection	
Presence of CVC	152 (80.0)
Prior use of broad-spectrum antibiotics	139 (73.2)
Urinary catheter	118 (62.1)
Total parenteral nutrition	115 (60.5)
Mechanical ventilation	72 (37.9)
Surgery (<30 days)	63 (33.2)
Renal replacement therapy	26 (13.7)
Previous corticosteroids	17 (8.9)
Neutropenia	6 (3.2)
Source of candidemia	
Primary candidemia	122 (64.2)
Proven catheter-related	42 (22.1)
Concomitant bacteremia	39 (20.5)
Susceptibility to fluconazole	112 (88.9)
Initial antifungal therapy	
Fluconazole	97 (51.1)
Voriconazole	18 (9.5)
Itraconazole	6 (3.2)
Echinocandin	27 (14.2)
Amphotericin B	1 (0.5)
Combination therapy	5 (2.6)
No targeted antifungal treatment	36 (18.9)

isolates. Most candidemia episodes ($n = 99$) occurred in the ICU, followed by the internal medicine department. The proportions of *C. albicans* and non-*albicans Candida* strains were differently distributed among different departments. In the surgery ward, *C. albicans* was detected in 51.4 % of the patients and *C. tropicalis* in 8.6 %, while no *C. krusei* was isolated; in the surgical ICU, *C. tropicalis* accounted for 27.3 % of the cases (Fig. 1a).

The numbers of cases of non-*albicans Candida* were higher than the number of cases of C. *albicans* from 2010 to 2014 (25 vs. 20, 32 vs. 13, 23 vs. 19 and 27 vs. 10, respectively), except 2013 (9 vs. 12, respectively) (Fig. 1b).

Drug Susceptibility and Antifungal Therapy

In vitro susceptibility testing showed that 88.9 % of *Candida* isolates (112 of 126) were susceptible to fluconazole. Specifically, no *C. albicans* isolates showed fluconazole resistance, and 25.0 % of *C. glabrata*, 18.8 % of *C. parapsilosis*, and 11.1 % of *C. tropicalis* isolates were intermediately resistant or fully resistant to fluconazole. Because echinocandin in vitro susceptibility testing has not been carried out in our hospital, the relevant clinical data could not be obtained.

The patients' antifungal therapies are shown in Table 1. In total, 63.7 % of patients (121 of 190) were given azoles as the initial antifungal agents, 51.1 % (97 of 190) were given fluconazole, 14.2 % (27 of 190) were given echinocandin, and 2.6 % (5 of 190) were given a combination of an azole and echinocandin; 36 patients never received targeted antifungals. The median time from positive blood culture to initial antifungal therapy was 2 days (IQR, 0–4 days). Thirty-three patients (17.4 %) were undergoing an antifungal treatment at the onset of candidemia.

Outcome and Predictors of Mortality

The 30-day cumulative mortality rate was 27.9 % (53 of 190), and more than half of those patients died within 7 days (31 of 53). The median time of death was 15 days (IQR, 5–46 days) after blood sample collection. *Candida albicans* and non-*albicans Candida* had similar hospital mortality rates; the highest mortality rate was observed for *C. glabrata* (60 %, 15 of 25 patients).

Univariate predictors of poor outcomes of candidemia are shown in Table 2. In the univariate analysis, patients who were treated with TPN, urinary catheters, and mechanical ventilation had a higher early ($\leq$7-day) mortality rate. Patients residing in the ICU when *Candida* BSI was diagnosed were more likely to have early death [odds ratio (OR) 2.538; 95 % confidence

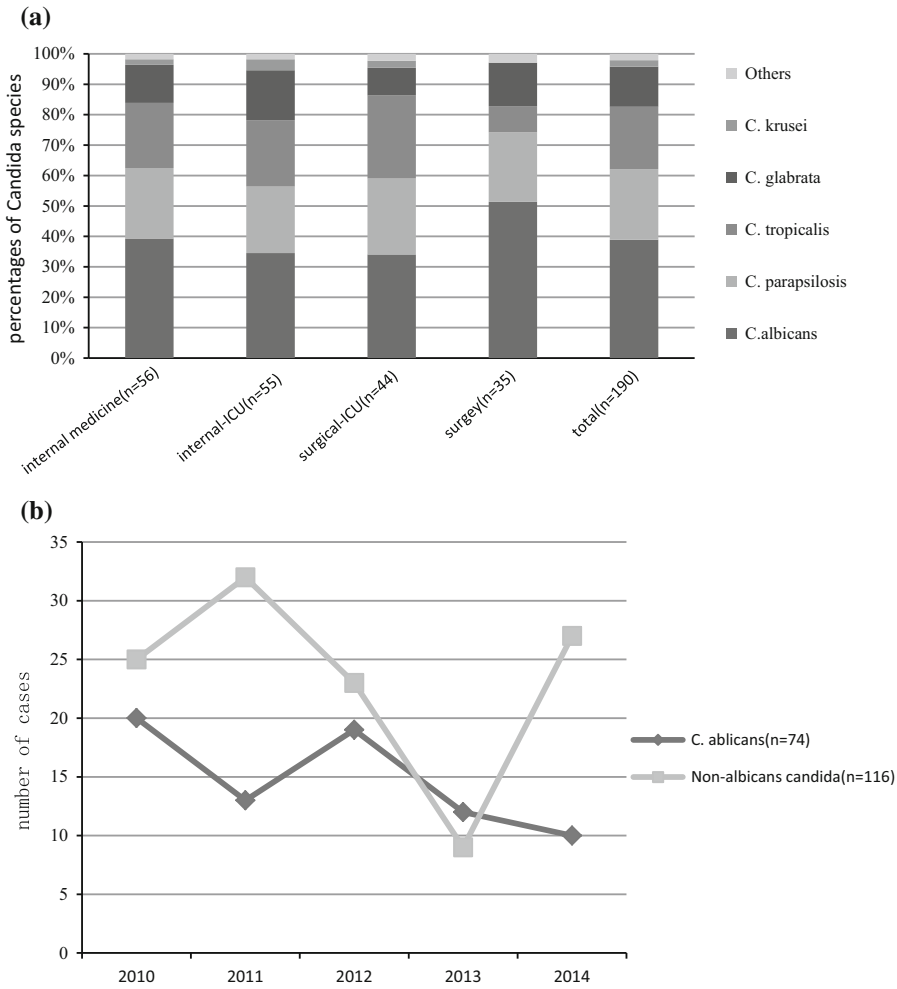

Fig. 1 **a** Distribution (%) of *Candida* species among different departments. **b** The number of cases of C. *albicans* and non-*albicans Candida* from 2010 to 2014

interval (CI) 1.101–5.854; $P = 0.025$]. As shown in Table 2, predictors of 30-day mortality by univariate analysis among patients with candidemia were the presence of a CVC (OR 2.586; 95 % CI 1.016–6.580), the presence of a urinary catheter (OR 2.045; 95 % CI 1.017–4.112), and treatment with renal replacement therapy (OR 2.571; 95 % CI 1.101–6.005).

On multivariate analysis, the APACHE II score (OR 1.23; 95 % CI 1.080–1.390; $P = 0.002$) and severe sepsis or septic shock (OR 15.35; 95 % CI 2.391–98.502; $P = 0.004$) were independently associated with early mortality. Severe sepsis or septic shock (OR 24.75; 95 % CI 5.099–120.162; $P < 0.001$) was an independent risk factor for 30-day mortality, while proven catheter-related candidemia was a protective factor (OR 0.16; 95 % CI 0.031–0.810; $P = 0.027$) (Table 3).

Clinical Management of Candidemia

Kaplan–Meier 30-day survival curves for adequate antifungal therapy and early CVC removal showed that these patients had lower mortality, although no statistically significant differences were noted ($P = 0.115$ and 0.220, respectively, by log-rank test) (Fig. 2).

We also explored the effect of early interventions on mortality in patients with primary candidemia (Fig. 3).

Discussion

The current study included 190 patients with candidemia who were investigated with respect to species

distribution, clinical features, and outcomes of *Candida* BSI.

The incidence of candidemia is reportedly 0.08–1.73 episodes per 1000 admissions worldwide [19–21], and several studies have revealed a substantial tread toward an increase in this incidence [19, 20]. However, we found that the incidence of candidemia steadily decreased steadily in our hospital over time (0.43–0.25 episodes per 1000 admissions from 2010 to 2014), which may reflect the improvements in the diagnosis and treatment of candidemia and differences in blood culture or antifungal resistance patterns.

The distribution of *Candida* spp. varies geographically. An international surveillance of bloodstream infections attributable to *Candida* species, the SENTRY antimicrobial surveillance program, showed that the prevalence of *C. glabrata* was higher in the United States than in other regions. In Latin America, *C. tropicalis* and *C. parapsilosis* were reported to be more prevalent than in the USA [5]. *Candida albicans* was also reportedly more prevalent in Canada and Europe than in other regions [6]. Additionally, because of the complexity of fungal culture and the longer time required, physicians usually used empiric therapy. Thus, clinicians should pay more attention to local distribution. A retrospective analysis from Shanghai showed that the episodes of non-*albicans* infections were more frequent than those of *C. albicans* [19], although *C. albicans* remained the most common species causing candidemia (37.2 %). This is similar to our observation (38.9 % for *C. albicans* vs. 61.1 % for non-*albicans Candida*); however, no *C. guilliermondii* or *C. sake* was found in our hospital. The reasons for the different distribution among regions are not fully understood, although prior exposure to antifungal drugs [22] and different antifungal tactics may partly explain the difference [13, 23].

In the present study, the proportion of *C. albicans* and non-*albicans Candida* species varied across different departments. Almost 52.1 % of episodes were found in the ICU, and *C. glabrata* was observed with a lower percentage (9.1 %) in the surgical ICU than in the internal medicine ICU (16.4 %), while *Candida albicans* (51.4 %) was more frequent in surgery wards.

We found that 88.9 % of *Candida* isolates (112 of 126) were susceptible to fluconazole, and no *C. albicans* isolates showed fluconazole resistance; however, 25.0 % of *C. glabrata*, 18.8 % of *C. parapsilosis*, and 11.1 % of *C. tropicalis* isolates were intermediately resistant or fully resistant to fluconazole. Susceptibility testing for five types of antifungal drugs for *Candida* spp. began only in November 2013 as a part of routine practice in our institution; susceptibility testing only for fluconazole had been performed before this time. With the exception of itraconazole (91.7 % susceptibility), these antifungal drugs exhibited 100 % susceptibility for *C. albicans.* Additionally, 5-flucytosine and amphotericin B showed 100 % susceptibility against non-*albicans Candida* strains. The ratios of susceptibility to voriconazole for *C. parapsilosis* and *C. tropicalis* were higher than those of fluconazole and itraconazole, and *C. glabrata* showed 100 % susceptibility (data not shown).

In our study, 18.9 % of patients received no targeted antifungal agent; this is similar to other Asian publications [10, 19]. We drew the following major conclusions after a review of our cases. First, some clinicians judged the blood culture result as false-positive, including pollution caused by non-standard blood sample collection. Second, a small portion of patients with *Candida* BSI had been discharged, been transferred, or died before the final blood culture results were obtained. Finally, some patients and their families refused to use antifungal drugs because of economic factors or other considerations. Most physicians selected an azole as the initial empiric antifungal therapy, especially fluconazole. Although echinocandin has great efficacy in the treatment of candidemia and has been recommended for use as first-line therapy [23], only 14.2 % of patients received echinocandin, while 2.6 % received a combination of an azole and echinocandin as first-line antifungal therapy. No unified treatment guideline exists, and the higher price of echinocandin may partly explain the differing empiric antifungal therapy plans.

Our study showed a lower overall 30-day mortality rate (27.9 %) than that in other reports [2, 9, 10]. Additionally, most of our patients died within 7 days (58.5 %, 31 of 53). To further explore the reason for the high early mortality of candidemia and to precisely analyze the impact of the therapeutic strategy at different time points, we further investigated the predictors of early ($\leq$7-day) and overall 30-day mortality among our patients.

According to our univariate analysis, *C. parapsilosis* may be a positive factor for 30-day mortality (OR 0.414; 95 % CI 0.171–0.992; $P = 0.043$). Other

Table 2 Univariate logistic regression analysis of risk factors associated with early and 30-day mortality in patients with *Candida* BSI

Variables	Early mortality				30-day mortality			
	Survivors ($n = 159$)	Non-survivors (n = 31)	OR (95 % CI)	*P* value	Survivors ($n = 137$)	Non-survivors ($n = 53$)	OR (95 % CI)	*P* value
Age (years)	66 (50–78)	72 (56–83)	–	0.186	65 (47.5–78)	72 (56–81)	–	0.082
Male gender	107 (67.3 %)	16 (51.6 %)	0.518 (0.238–1.129)	0.095	89 (65.0 %)	34 (64.2 %)	0.965 (0.498-1.871)	0.916
Comorbidities								
Cardiovascular disease	78 (49.1 %)	21 (67.7 %)	2.181 (0.966–4.925)	0.057	69 (50.4 %)	30 (56.6 %)	1.285 (0.679–2.433)	0.440
Diabetes mellitus	42 (26.4 %)	12 (38.7 %)	1.759 (0.787–3.932)	0.165	36 (26.3 %)	18 (34.0 %)	1.443 (0.728–2.860)	0.292
Cerebrovascular disease	49 (30.8 %)	9 (29.0 %)	0.918 (0.394–2.139)	0.843	42 (30.7 %)	16 (30.2 %)	0.978 (0.491–1.950)	0.950
Solid tumor	71 (44.7 %)	10 (32.3 %)	0.590 (0.261–1.334)	0.202	60 (43.8 %)	21 (39.6 %)	0.842 (0.442–1.606)	0.602
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2–4)	–	0.668	2 (1–4)	3 (2–5)	–	0.040
Prior hospital stay, median days (IQR)	21 (11–34.25)	24 (16–44)	–	0.075	20 (11–33.5)	27 (17–45.5)	–	0.008
ICU residence, *n* (%)	78 (49.1 %)	22 (71.0 %)	2.538 (1.101–5.854)	0.025	67 (48.9 %)	33 (62.3 %)	1.724 (0.901–3.298)	0.098
Risk factors for *Candida* infection, *n* (%)								
Corticosteroids	12 (7.5 %)	5 (16.1 %)	2.356 (0.766–7.246)	0.235	9 (6.6 %)	8 (15.1 %)	2.528 (0.920–6.950)	0.118
Surgery	54 (34.0 %)	9 (29.0 %)	0.795 (0.343–1.846)	0.594	50 (36.5 %)	13 (24.5 %)	0.566 (0.276–1.157)	0.116
Total parenteral nutrition	91 (57.2 %)	24 (77.4 %)	2.562 (1.043–6.293)	0.035	80 (58.4 %)	35 (66.0 %)	1.385 (0.714–2.687)	0.334
Presence of CVC	125 (78.6 %)	27 (87.1 %)	1.836 (0.601–5.607)	0.224	105 (76.6 %)	47 (88.7 %)	2.387 (0.935–6.095)	0.063
Urinary catheter	92 (57.9 %)	26 (83.4 %)	3.787 (1.383–10.372)	0.006	79 (57.7 %)	39 (73.6 %)	2.045 (1.017–4.112)	0.042
Mechanical ventilation	54 (34.0 %)	18 (58.1 %)	2.692 (1.228–5.904)	0.011	47 (34.3 %)	25 (47.2 %)	1.710 (0.898–3.257)	0.101
Renal replacement therapy	19 (11.9 %)	7 (22.6 %)	2.149 (0.816–5.662)	0.197	14 (10.2 %)	12 (22.6 %)	2.571 (1.101–6.005)	0.025
Prior use of broad-spectrum antibiotics	112 (70.4 %)	27 (87.1 %)	2.833 (0.939–8.543)	0.056	92 (67.2 %)	47 (88.7 %)	3.832 (1.525–9.628)	0.003
Severity of illness								
APACHE II score, median (IQR)	12 (9–16)	26 (20–31)	–	0.000	11 (8.5–16)	21 (15–29)	–	0.000
Severe sepsis or septic shock, *n* (%)	28 (17.6 %)	29 (93.5 %)	67.839 (15.291–300.97)	0.000	20 (14.6 %)	37 (69.8 %)	13.528 (6.363–28.76)	0.000
Distribution of different *Candida* species								
C. albicans	65 (40.9 %)	9 (29.0 %)	0.592 (0.256–1.367)	0.216	55 (40.1 %)	19 (35.8 %)	0.833 (0.432–1.607)	0.586
C. tropicalis	29 (18.2 %)	10 (32.3 %)	2.135 (0.909–5.014)	0.077	25 (18.2 %)	14 (26.4 %)	1.608 (0.761–3.401)	0.211
C. parapsilosis	39 (24.5 %)	5 (16.1 %)	0.592 (0.213–1.646)	0.311	37 (27.0 %)	7 (13.2 %)	0.414 (0.171–0.992)	0.043
C. glabrata	19 (11.9 %)	6 (19.4 %)	1.768 (0.643–4.864)	0.409	14 (10.2 %)	11 (20.6 %)	2.301 (0.970–5.459)	0.054

Table 2 continued

Variables	Early mortality				30-day mortality			
	Survivors ($n = 159$)	Non-survivors (n = 31)	OR (95 % CI)	*P* value	Survivors ($n = 137$)	Non-survivors ($n = 53$)	OR (95 % CI)	*P* value
Other *Candida* spp.	7 (4.4 %)	1 (3.2 %)	0.724 (0.086–6.100)	1.000	6 (4.4 %)	2 (3.8 %)	0.856 (0.167–4.382)	1.000
Source of candidemia, *n* (%)								
Primary	104 (65.4 %)	18 (58.1 %)	0.732 (0.334–1.605)	0.435	93 (67.9 %)	29 (54.7 %)	0.572 (0.299–1.094)	0.090
Proven catheter-related	39 (24.5 %)	3 (9.7 %)	0.330 (0.095–1.144)	0.068	35 (25.5 %)	7 (13.2 %)	0.443 (0.183–1.072)	0.066
Early CVC removal (<48 h)	31 (19.5 %)	6 (19.4 %)	0.848 (0.341–2.292)	0.745	29 (21.2 %)	8 (15.7 %)	0.417 (0.175–0.994)	0.044
Appropriate antifungal therapy (≤5 days)	77 (48.4 %)	10 (32.3 %)	0.507 (0.225–1.145)	0.098	66 (48.2 %)	21 (39.6 %)	0.706 (0.371–1.345)	0.289
Early CVC removal + appropriate antifungal therapy	18 (11.3 %)	3 (9.7 %)	0.729 (0.199–2.676)	0.864	18 (13.1 %)	3 (5.7 %)	0.263 (0.074–0.940)	0.030

studies also showed that this species was associated with a better outcome [24, 25]. *Candida glabrata* had the highest mortality rate (60 %) compared with other *Candida* spp., but there was no statistically significant relationship between *C. glabrata* and death. *Candida glabrata* usually had a lower susceptibility rate to commonly used antifungal drugs, including amphotericin B, and *C. glabrata* infections were more prevalent in older than younger cohorts [7, 26].

In our multivariate model, the independent risk factor for early mortality was the severity of illness as indicated by the APACHE II score or the presence of severe sepsis or septic shock. Because of the limitations of retrospective studies, we researched all-cause rather than candidemia infection-related mortality. The APACHE II score reflected the patients' comprehensive clinical situation and was influenced by many factors. This may also explain the lack of an effective impact on reducing the mortality of patients who received appropriate antifungal treatment. Thus, further studies on mortality attributable to *Candida* are still needed.

Severe sepsis or septic shock was also independently associated with overall 30-day mortality. Meanwhile, the data of 30-day mortality highlighted the protective effect of CVC-related candidemia. The comorbid status at baseline, risk factors for the onset of candidemia, and *Candida* spp. distribution were not independent influences on early or 30-day mortality in the multivariate model.

Controversy remains about whether catheter removal can truly reduce the mortality rate. A systematic review of 14 studies demonstrated that catheter removal did not reduce complications or death in patients with candidemia [27]. In recent guidelines for candidiasis, removal of all CVCs was recommended at the initial treatment of candidemia even in neutropenic patients [13, 28]. A study by Garnacho-Montero et al. [4] showed that delayed catheter withdrawal increased the mortality of patients with candidemia, although catheter management did not improve the prognosis of secondary candidemia, and adequate antifungal therapy (<48 h) reduced the in-hospital death rate in patients with secondary candidemia. In the present study, the Kaplan–Meier survival curve showed that delayed CVC removal had higher 30-day mortality than the initial 48-h CVC removal, although the difference was not statistically significant.

Table 3 Multivariate logistic regression analyses of risk factors associated with the early and 30-day mortality rates in candidemia patients

Variable	Early mortality		30-day mortality	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
APACHE II score	1.23 (1.080–1.390)	0.002	–	–
Severe sepsis or septic shock	15.35 (2.391–98.502)	0.004	24.75 (5.099–120.162)	<0.001
Proven catheter-related	–	–	0.16 (0.031–0.810)	0.027
Early CVC removal (<48 h)	–	–	0.38 (0.072–1.980)	0.249

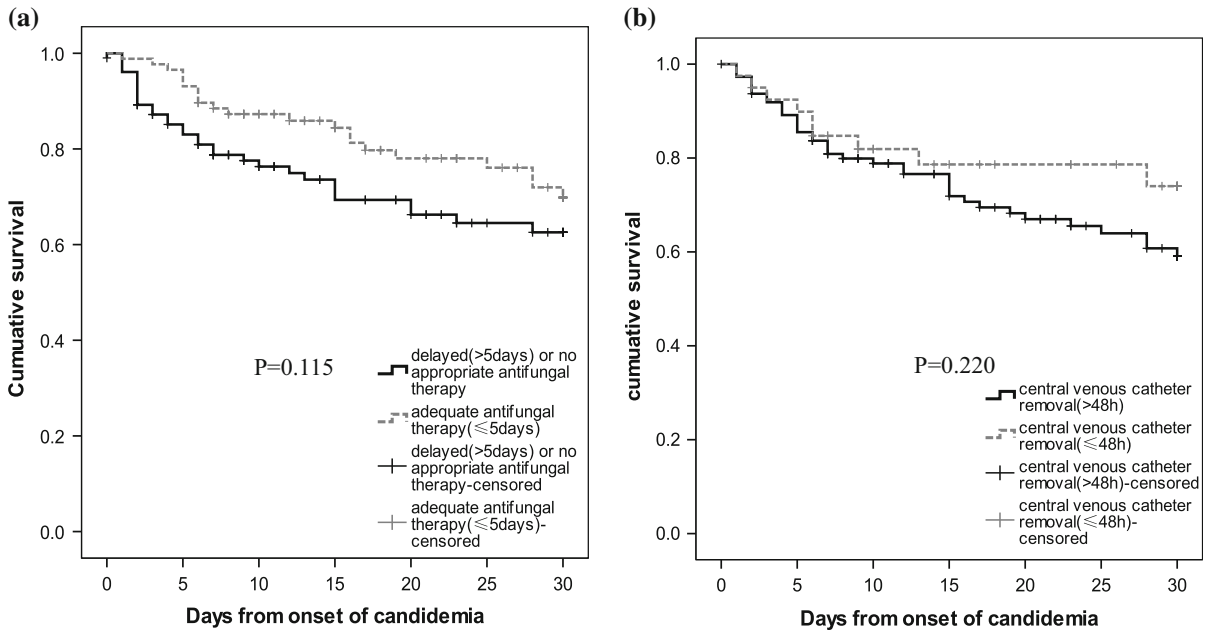

Fig. 2 **a** Kaplan–Meier 30-day survival curves with respect to adequate antifungal therapy. **b** Kaplan–Meier 30-day survival curves with respect to time of central venous catheter removal

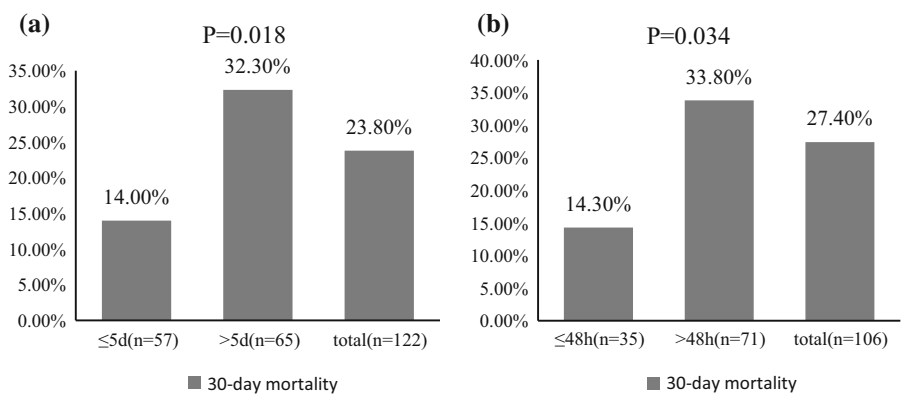

Fig. 3 Relationship between the 30-day mortality and the initial time of adequate antifungal therapy (**a**) and CVC removal (**b**) for primary candidemia

The present study also assessed the influence on mortality of another intervention (appropriate antifungal therapy). In our study, 87 patients (45.8 %) received initial appropriate antifungal treatment (i.e., an appropriate sensitive drug was given at an adequate dosage within 5 days from the first blood culture draw). The Kaplan–Meier survival curve did not indicate statistical significance. We also explored the role of source control in primary candidemia. As shown in Table 2, primary candidemia infections had lower mortality and better protection for 30-day mortality, although there was no statistically significant difference. Figure 3 shows that early CVC removal and adequate antifungal therapy were related to decreased mortality in patients with primary candidemia; this is in agreement with the findings of Garnacho-Montero et al. [4].

Several limitations of this study should be taken into consideration. First, this was a retrospective study performed at a single center over a 5-year period, which could lead to selection bias. Second, the small sample size of this study might have affected the outcome of the multivariate analyses. Third, susceptibility testing for five sorts of antifungal drugs for *Candida* spp. began only in November 2013 as part of the routine practice in our institution; susceptibility testing only for fluconazole was performed before this time.

In conclusion, this study comprised a large cohort of patients diagnosed with nosocomial *Candida* BSI. Non-*albicans Candida* spp. ranked at the top (61.1 %), and the distribution of *Candida* spp. differed according to department. The APACHE II score and severe sepsis or septic shock were independently associated with early mortality. The origin of CVCs was a protective factor for 30-day mortality. Kaplan–Meier 30-day survival curves for adequate antifungal treatment and early CVC removal showed lower mortality, although there was no statistically significant difference. However, among the patients with primary candidemia, adequate antifungal therapy and early CVC removal did demonstrate a lower 30-day mortality rate.

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Compliance with Ethical Standards

Conflict of interest The authors have no declared conflict of interests.

Ethical Approval This study was approved by the local institutional review board.

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