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ORIGINAL ARTICLE

A longitudinal study of *Candida* bloodstream infections in a Japanese university hospital: species distribution, drug susceptibility, clinical features, and mortality predictors

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Abstract

We aimed to detect possible changes in *Candida* species distribution over time and to know the antifungal susceptibility profile of isolates obtained from patients with bloodstream infection (BSI) due to this pathogen. Risk factors associated with 30-day mortality were also assessed. We conducted a retrospective cohort study of patients diagnosed with *Candida* BSI at a Japanese university hospital from 2013 to 2021. The change in the distribution pattern of the *Candida* spp. isolated was examined by considering three successive sub-periods of 3 years each. Risk factors for 30-day mortality were determined using Cox regression analysis. In the entire study period, *Candida albicans* was the most frequent species (46.7%), followed by *Candida glabrata* (21.5%) and *Candida parapsilosis* (18.7%). There was no change in *Candida* species distribution comparing the three sub-periods analyzed. All isolates were susceptible to micafungin, and most were susceptible to fluconazole, except for *C. glabrata*. No isolates were resistant to amphotericin B or voriconazole. The overall 30-day mortality was 40.2%. Univariate analysis revealed an association between 30-day mortality and central venous catheter (CVC) removal at any time, high Pitt bacteremia score (PBS), and high Charlson comorbidity index (CCI). Multivariate Cox analysis found that high PBS was the only independent predictor of 30-day mortality; subsequent multivariate Cox regression demonstrated that early CVC removal significantly reduced 30-day mortality. *Candida* species distribution and antifungal susceptibility profile in our hospital remained similar from 2013 to 2021. Early CVC removal may improve candidemia outcomes.

Keywords Bloodstream infection · *Candida* spp. · Species distribution · Central venous catheter · Risk factors · 30-day mortality

Introduction

Candida spp. are among the most important causative agents of bloodstream infections (BSIs) in hospitalized patients, resulting in an extremely high mortality rate [1–4]. A multicenter survey found that candidemia could reach up to 22% of healthcare-associated BSIs [5]. Despite the increased awareness of *Candida* spp. significance in healthcare-associated BSIs and considerable advances in treatment guidelines, which greatly rely on improved antifungal agents and more comprehensive knowledge of risk factors, the mortality rate of BSIs caused by *Candida* spp. remains high [6].

Early diagnosis and treatment are critical for BSIs caused by *Candida* spp. Although *Candida* spp. are common commensal organisms frequently found in the skin and gut microbiota [7, 8], eventual disruptions of the gastrointestinal barrier may result in disseminated lesions in

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the gastrointestinal tract. The use of central vascular catheters, recent surgical procedures (mainly abdominal surgery with anastomotic leakages), invasive procedures including mechanical ventilation, and broad-spectrum antibiotic therapy are major risk factors for invasive candidiasis. The skin may also act as an entry point for *Candida* spp. into circulation. Further dissemination to the lungs, kidneys, liver, spleen, and heart may occur [9]; chorioretinitis and intraocular inflammation due to *Candida* infection have also been documented [10].

Even when more than 15 *Candida* species have been identified as human pathogens, five of them—*Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*—were found to be the most prevalent species [11]. Typically, *C. albicans* accounts for approximately 50% of candidemia cases; the remaining cases are caused by other species grouped as *Candida* non-*albicans*.

Epidemiological data, such as species distribution and drug susceptibility of local isolates, may be useful for optimizing antifungal drug therapies. Therefore, large-scale epidemiological surveys representing Japanese inpatient settings are necessary to support medical decisions based on local studies instead of overseas reports. However, it must be recognized that few hospitals in Japan are currently equipped to perform reliable mycological testing.

Recent studies carried out in different countries have documented a significant shift in the incidence of BSIs caused by *Candida* isolates from *Candida albicans* to non-*albicans* species [6, 11, 12]. However, regional differences have also been reported [13, 14]. Therefore, continuous epidemiological surveillance in each geographical region is needed to detect current trends and guide appropriate therapy for patients with BSIs caused by *Candida*.

This study aimed to characterize the clinical isolates of *Candida* spp. responsible for BSIs in patients admitted to a Japanese university hospital from 2013 to 2021. The change in species distribution over time, isolate susceptibility to antifungal drugs, and critical data for the rapid and appropriate management of *Candida* BSIs were analyzed. In addition, the clinical features of *Candida* BSIs and risk factors associated with 30-day mortality were assessed.

Methods

Study design and subjects

We conducted a single-center, retrospective cohort study of patients diagnosed with *Candida* BSI between January 2013 and December 2021 at the University of Fukui Hospital, a 600-bed university hospital that provides healthcare services to secondary and tertiary care areas.

The change in the distribution pattern of isolated *Candida* spp. over time was examined considering three successive sub-periods of 3 years each: 2013–2015 (sub-period I), 2016–2018 (sub-period II), and 2019–2021 (sub-period III).

This study was approved by the Institutional Review Board of the Faculty of Medical Sciences, University of Fukui.

Data collection

The following data were collected from the electronic medical records of each patient: age; sex; weight; underlying diseases; intensive care unit stay at BSI onset (yes/no); neutropenia (defined as an absolute neutrophil count < 500/mm^3) at BSI onset (yes/no); presence or absence of central venous catheter (CVC); total parenteral nutrition (TPN); and peripheral parenteral nutrition (PPN) at BSI onset; surgical history (within 30 days before BSI onset); use of immunosuppressants, corticosteroids, antineoplastic chemotherapy, antibiotics, and antifungals (within 30 days before BSI onset); source of BSI; time to blood culture positivity (TTP) [15]; time to use of appropriate antifungal therapy; days to CVC removal; and 7-, 14-, and 30-day survival or mortality after BSI onset. The severity at BSI onset was evaluated by calculating the Charlson comorbidity index (CCI) and Pitt bacteremia score (PBS).

Definitions

Candida BSI was defined as the isolation of *Candida* species from at least one blood culture in patients with symptoms or signs of a systemic infection. The day the blood sample that yielded the first positive result was collected was considered the day of BSI onset. Only the initial episode was considered in this analysis for patients with multiple positive blood culture results.

Catheter-associated BSI was defined based on the isolation of the same species from blood and catheter tip cultures. Other secondary BSIs were defined based on clinical, imaging, and microbiological evidence using CDC criteria. Patients with an unknown source of infection were considered to have primary BSI. Antifungal drug therapy was considered appropriate if it included at least one antifungal agent with in vitro activity, dosage, and administration route that followed the published guidelines.

Microbiological procedures and *Candida* antifungal susceptibility testing

The microbiological procedures were performed at the clinical microbiology laboratory of our hospital. Bacterial and fungal isolates were obtained from patients' blood cultures using BacT/Alert 3D (bioMerieux, Marcy l'Etoile,

France) or BACTEC FX (BD, Franklin Lakes, NJ, USA) systems. Species were identified using the API ID 32C kit (bioMérieux, Marcy l'Etoile, France) or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Microflex LT, Bruker Daltonics, Bremen, Germany). Antifungal susceptibility testing was performed using the Dry Plate Eiken system (Eiken Chemical, Tokyo, Japan) according to the manufacturer's recommendations. Susceptibility to fluconazole (FLCZ), voriconazole (VRCZ), and micafungin (MCFG) was evaluated according to the clinical breakpoints of the Clinical Laboratory Standards Institute M27-S4 [16]. The susceptibility to amphotericin B (AMPH-B) was evaluated according to the clinical breakpoint of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) Antifungal Clinical Breakpoint Table v. 9.0 [17].

Statistical analysis

Continuous variables are expressed as the median and interquartile range (IQR); categorical variables are expressed as the number (*n*) of subjects/isolates and percentage (%). The normal distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Continuous variables were compared using Student's *t* test or Mann–Whitney *U*-test, depending on the normality of the distribution. Categorical variables were analyzed using the chi-square test or two-tailed Fisher's exact test. Comparisons of continuous variables between different *Candida* spp. were performed using the Kruskal–Wallis test with post hoc analysis.

The relationship between CVC indwelling time after BSI onset and the mortality rate was evaluated using the Cochran-Armitage trend test. Multivariate Cox regression analysis was performed to identify predictors of 30-day mortality. Variables with $P < 0.1$ after univariate analysis were included in the multivariate analysis. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. All *P* values were two-tailed, and results with $P < 0.05$ were considered statistically significant.

All analyses were performed using the EZR software version 1.53 (Saitama Medical Center, Jichi Medical University, Japan).

Results

Change in species distribution over time

During the entire survey period (2013 to 2021), 107 *Candida* isolates were obtained from 101 patients with *Candida* BSI. The incidence of *Candida* BSI calculated in terms of episodes per 1000 admissions and 1000 patient-days was 0.86 and 0.06, respectively. These incidence rates did not change across sub-periods, reaching 0.80, 0.89, and 0.84 episodes/1000 admissions for the sub-periods I (2013–2015), II (2016–1018), and III (2019–2021), respectively. The number of episodes/1000 patient-days for these sub-periods was 0.05, 0.06, and 0.06, respectively.

During all three sub-periods, the most commonly isolated *Candida* species was *C. albicans*, accounting for 46.7% of all isolates (Fig. 1). Comparing the three sub-periods analyzed, there was no change in the proportion of *C. albicans* isolates (sub-period I: 46.9%, sub-period II: 50.0%, sub-period III: 43.3%, $P = 0.619$). After *C. albicans*, the most commonly isolated species was *C. glabrata* (21.5%), followed by *C. parapsilosis* (18.7%), *C. tropicalis* (4.7%),

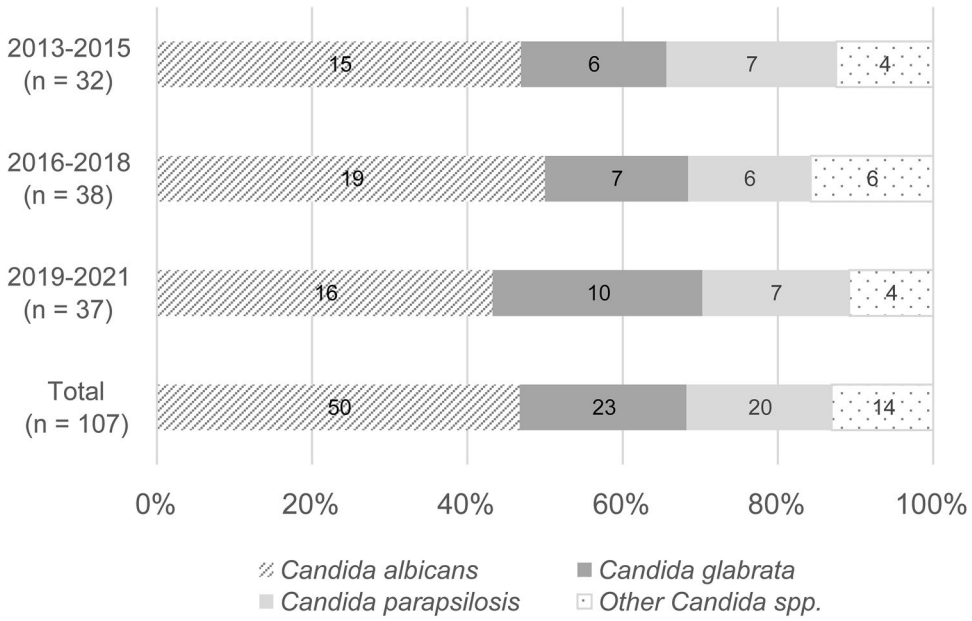

Fig. 1 *Candida* spp. frequency distribution over time. A total of 107 *Candida* isolates were obtained from 101 patients diagnosed with bloodstream infection from January 2013 to December 2021 at the University of Fukui Hospital

Candida guilliermondii (4.7%), *Candida famata* (1.9%), *C. krusei* (0.9%), and *Candida kefyr* (0.9%). The proportion of *C. glabrata* isolates in sub-period III was 8.2% higher than that in the sub-period I and 8.6% higher than that in the sub-period II, but there was no significant change in species distribution over time ($P=0.954$) (Fig. 1).

Antifungal susceptibility profiles

Table 1 shows the results of the antifungal susceptibility testing performed on 104 *Candida* isolates obtained from 92 patients diagnosed with BSI. Isolates identified as *C. famata* ($n=2$) and *C. kefyr* ($n=1$) were excluded from this analysis because of the lack of specific clinical breakpoints.

Table 1 Antifungal susceptibility of *Candida* spp. isolated from patients diagnosed with bloodstream infection from January 2013 to December 2021 at the University of Fukui Hospital

	S (%)	SDD/I (%)	R (%)
Candida albicans ($n=50$)			
AMPH-B	50 (100)	-	0
FLCZ	50 (100)	0	0
VRCZ	49 (98.0)	1 (2.0)	0
MCFG	50 (100)	0	0
Candida glabrata ($n=23$)			
AMPH-B	23 (100)	-	0
FLCZ	-	22 (95.7)	1 (4.3)
MCFG	19 (82.6)	1 (4.3)	3 (13.0)
Candida parapsilosis ($n=20$)			
AMPH-B	20 (100)	-	0
FLCZ	19 (95.0)	1 (5.0)	0
VRCZ	19 (95.0)	1 (5.0)	0
MCFG	20 (100)	0	0
Candida tropicalis ($n=5$)			
AMPH-B	5 (100)	-	0
FLCZ	4 (80.0)	1 (20.0)	0
VRCZ	4 (80.0)	1 (20.0)	0
MCFG	5 (100)	0	0
Candida krusei ($n=1$)			
AMPH-B	1 (100)	-	0
FLCZ	0	0	1 (100)
VRCZ	1 (100)	0	0
MCFG	1 (100)	0	0
Candida guilliermondii ($n=5$)			
MCFG	5 (100)	0	0

AMPH-B, amphotericin B; *FLCZ*, fluconazole; *VRCZ*, voriconazole; *MCFG*, micafungin

S, susceptible; *SDD/I*, susceptible dose-dependent/intermediate; *R*, resistant

Clinical breakpoints for FLCZ, VRCZ, and MCFG were obtained from CLSI and clinical breakpoints for AMPH-B were obtained from EUCAST

Susceptibility to FLCZ was good, and no *C. albicans* isolates were FLCZ resistant. In contrast, one *C. parapsilo*sis isolate (5.0%) and one *C. tropicalis* isolate (20.0%) were susceptible to FLCZ in a dose-dependent manner (SDD/I). One *C. glabrata* isolate (5.3%) and one *C. krusei* isolate (100%) were FLCZ resistant. Susceptibility to VRCZ was also good, although one *C. albicans* isolate (2.0%) showed SDD/I for VRCZ. The *C. parapsilosis* and *C. tropicalis* isolates that were SDD/I for FLCZ were also SDD/I for VRCZ. Nearly all isolates were susceptible to MCFG; only one *C. glabrata* isolate (4.2%) showed intermediate susceptibility (4.3%), and three *C. glabrata* isolates (13.0%) were MCFG-resistant. No AMPH-B-resistant isolates were detected during the survey period. There was no increase in the resistance of the isolates to any antifungal drug assessed over time.

Clinical features of patients with BSI

Of the 101 patients diagnosed with BSI due to *Candida* spp. during the entire survey period, nine were excluded: two *Candida* spp. were detected in six of them, and bacteria plus *Candida* were detected in the other three patients. Therefore, a total of 92 patients were included in the analysis.

Among these 92 subjects, the most common *Candida* species was *C. albicans*, isolated from 42 patients (45.7%), followed by *C. parapsilosis* in 20 patients (21.7%), *C. glabrata* in 19 patients (20.7%), and other *Candida* spp. in 11 patients (12.0%). The median age of all patients was 74.5 years (IQR: 66–81), of whom 48 (52.2%) were male and 64 (69.6%) had malignancies (solid tumor, 55 patients; hematological malignancy, 9 patients). At the onset of BSI, 66 patients (71.7%) had indwelling CVC and 62 (67.4%) had TPN. In addition, 78 patients (84.8%) had antibiotic treatment within the previous month. The most common source of infection was primary BSI (34 patients, 37.0%), followed by catheter-associated infections (31 patients, 33.7%), and urinary tract infections (11 patients, 12.0%). Fundus examination was performed on 69 subjects (75.0%), among whom 10 (14.5%) were diagnosed with ocular candidiasis. The overall mortality rates at 7, 14, and 30 days were 14.1, 20.7, and 40.2%, respectively (Table 2).

From the clinical history analysis, it was deduced that patients with *C. parapsilosis* were more likely to have diabetes mellitus than those with *C. albicans* or *C. glabrata*. In addition, the TTP for *C. glabrata* was significantly longer than that for the other species.

Among the antifungal agents administered as initial treatment, MCFG was the most common (77%). Less than 20% of patients received FLCZ as initial therapy, and very few received liposomal-AMPH. One patient (non-survivor) did not receive any antifungal therapy. There was no significant difference in the mortality rate of individuals affected by different *Candida* species 7, 14, or 30 days after BSI onset.

Table 2 Clinical features of patients diagnosed with bloodstream infection caused by *Candida* spp. from January 2013 to December 2021 at the University of Fukui Hospital

	Overall *n* = 92	*C. albicans* *n* = 42	*C. parapsilosis* *n* = 20	*C. glabrata* *n* = 19	Other *Candida* spp.[d] *n* = 11	*P*
Age (years)[a]	74.5 [66–81]	77 [72–81]	72 [63–76]	71 [64–75]	76 [68–81]	0.122
Male gender	48 (52.2)	24 (57.1)	10 (52.6)	7 (35.0)	7 (63.6)	0.339
Body weight (kg)[a]	50.9 [45.0–59.9]	48.4 [42.1–56.3]	51.0 [46.9–64.1]	52.8 [48.2–58.4]	55.2 [47.0–63.8]	0.165
Underlying disease						
Solid tumor	55 (59.8)	25 (59.5)	12 (63.2)	11 (55.0)	7 (63.6)	0.950
Hematologic malignancy	9 (9.8)	3 (7.1)	3 (15.8)	2 (10.0)	1 (9.1)	0.773
Diabetes mellitus	24 (26.1)	15 (35.7)	8 (42.1)	0 (0.0)	1 (9.1)	0.012
Liver cirrhosis	9 (9.8)	4 (9.5)	2 (10.5)	2 (10.0)	1 (9.1)	0.999
Chronic renal failure	6 (6.5)	3 (7.1)	3 (15.8)	0 (0.0)	0 (0.0)	0.182
Pulmonary disease	20 (21.7)	10 (23.8)	1 (5.3)	7 (35.0)	2 (18.2)	0.152
Cardiovascular disease	19 (20.7)	11 (26.2)	4 (21.1)	3 (15.0)	1 (9.1)	0.557
ICU stay at candidemia onset	18 (19.6)	8 (19.0)	5 (26.3)	4 (20.0)	1 (9.1)	0.723
Neutropenia (< 500/μL)	6 (6.5)	1 (2.4)	1 (5.3)	2 (10.0)	2 (18.2)	0.253
CVC	66 (71.7)	30 (71.4)	10 (52.6)	17 (85.0)	9 (81.8)	0.127
TPN	62 (67.4)	27 (64.3)	10 (52.6)	16 (80.0)	9 (81.8)	0.207
PPN	16 (17.4)	6 (14.3)	6 (31.6)	2 (10.0)	2 (18.2)	0.295
Surgery	27 (29.3)	16 (38.1)	6 (31.6)	3 (15.0)	2 (18.2)	0.236
Abdominal surgery	18 (19.6)	11 (26.2)	3 (15.8)	2 (10.0)	2 (18.2)	0.472
Immunosuppressant use	1 (1.1)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0.303
Corticosteroid use	17 (18.5)	7 (16.7)	2 (10.5)	6 (30.0)	2 (18.2)	0.448
Antineoplastic chemotherapy	27 (29.3	10 (23.8)	8 (42.1)	6 (30.0)	3 (27.3)	0.544
Prior use of antibiotics	78 (84.8)	36 (85.7)	17 (89.5)	16 (80.0)	9 (81.8)	0.854
Prior use of broad-spectrum antibiotics[b]	60 (65.2)	26 (61.9)	13 (68.4)	13 (65.0)	8 (72.7)	0.905
Prior use of FLCZ[c]	2 (2.2)	0 (0.0)	1 (5.3)	1 (5.0)	0 (0.0)	0.427
Illness severity						
PBS[a]	2.0 [1.0–4.0]	3.0 [2.0–4.0]	2.0 [1.0–4.0]	2.0 [1.0–2.5]	2.0 [2.0–3.0]	0.265
CCI[a]	3.0 [2.0–5.3]	3.0 [2.0–5.8]	4.0 [2.5–6.0]	2.0 [1.0–6.0]	3.0 [2.0–3.5]	0.127
Source of BSI						
Primary	34 (37.0)	15 (35.7)	8 (42.1)	8 (40.0)	3 (27.3)	0.858
Catheter-related	31 (33.7)	12 (28.6)	4 (21.1)	9 (45.0)	6 (54.5)	0.162
Intra-abdominal	10 (10.9)	4 (9.5)	3 (15.8)	1 (5.0)	2 (18.2)	0.599
Urinary tract	11 (12.0)	8 (19.0)	2 (10.5)	1 (5.0)	0 (0.0)	0.216
Pancreaticobiliary tract	5 (5.4)	2 (4.8)	2 (10.5)	1 (5.0)	0 (0.0)	0.651
TTP (h)[a]	41 [30–54]	37 [27–50]	38 [33–48]	54 [42–61]	30 [23–60]	0.037
Initial antifungal therapy						
L-AMPH	3 (3.3)	1 (2.4)	0 (0.0)	2 (10.5)	0 (0.0)	0.228
FLCZ	17 (18.5)	10 (23.8)	4 (20.0)	1 (5.3)	2 (18.2)	0.388
MCFG	71 (77.2)	30 (71.4)	16 (80.0)	16 (84.2)	9 (81.8)	0.672
Time to appropriate antifungal therapy						
< 24 h	12 (13.0)	5 (11.9)	4 (21.1)	3 (15.0)	0 (0.0)	0.417
< 48 h	46 (50.0)	20 (47.6)	12 (63.2)	9 (45.0)	5 (45.5)	0.637
< 72 h	68 (73.9)	30 (71.4)	13 (68.4)	17 (85.0)	8 (72.7)	0.634
< 96 h	78 (84.8)	36 (85.7)	14 (73.7)	18 (90.0)	10 (90.9)	0.460
Outcome						
7-day mortality	13 (14.1)	8 (19.0)	3 (15.8)	1 (5.0)	1 (9.1)	0.478
14-day mortality	19 (20.7)	12 (28.6)	3 (15.8)	2 (10.0)	2 (18.2)	0.347
30-day mortality	37 (40.2)	20 (47.6)	6 (31.6)	6 (30.0)	5 (45.5)	0.468
Ocular candidiasis (*n* = 69)	10/69 (14.5)	9/34 (26.5)	0/14	1/13 (7.7)	0/8	0.043

Numerical data are expressed *n* (%), except for [a], where medians (interquartile range [IQR]) are indicated

[b]Includes carbapenems, piperacillin/tazobactam, cefepime, and fluoroquinolones

[c]Fluconazole was administered at a dose of 200 mg/day as prophylactic agent during neutropenia in two patients

[d]Includes *C. guilliermondii* (*n* = 4), *C. tropicalis* (*n* = 4), *C. famata* (*n* = 1), *C. krusei* (*n* = 1), *C. kefyr* (*n* = 1)

ICU, intensive care unit; *BSI*, bloodstream infection; *TPN*, total parenteral nutrition; *PPN*, peripheral parenteral nutrition; *TTP*, time to blood culture positivity; *CVC*, use of central venous catheter; *PBS*, Pitt bacteremia score; *CCI*, Charlson comorbidity index; *L-AMPH*, liposomal amphotericin B; *FLCZ*, fluconazole; *MCFG*, micafungin

Of the 10 patients who developed ocular candidiasis, 9 (90.0%) were infected with *C. albicans* and one (10.0%) with *C. parapsilosis*. In 34 out of 42 patients (81.0%) with BSI due to *C. albicans*, fundus examination was performed, and 26.5% (9/34) of them were diagnosed with ocular candidiasis (Table 2).

Analysis of 30-day mortality predictors

Overall, 37 patients (40.2%) died within 30 days after BSI onset, and several variables were compared between survivors and non-survivors (Table 3). Univariate analysis revealed an association between mortality and high PBS ($P < 0.001$), CCI ($P = 0.009$), and CVC removal (at any time) ($P < 0.001$). Multivariate Cox hazard regression analysis considering patient age and risk factors with $P < 0.1$ in the univariate analysis revealed that PBS (HR 1.32, 95% CI: 1.10–1.59, $P = 0.004$) was the only independent risk factor for 30-day mortality (Table 4).

Examining the relationship between 30-day mortality and CVC indwelling time after BSI onset revealed a trend toward increased mortality with longer indwelling times ($P = 0.0014$) (Fig. 2). The mortality rate reached 64.5% among those who maintained the CVC for 3 days or more after BSI onset and 27.9% in patients with CVC indwelling times of less than 2 days. Based on this finding, multivariate Cox regression analysis was again performed considering early CVC removal (≤ 2 days), a variable that was found to significantly reduce 30-day mortality ($P = 0.036$), with an HR of 0.44 and a 95% CI of 0.21–0.95 (Table 5).

Discussion

This study surveyed the distribution of isolated *Candida* spp. responsible for BSIs in patients assisted at the University of Fukui Hospital from 2013 to 2021. To allow the detection of possible shifts in *Candida* sp. distribution along this period, three successive 3-year intervals were considered.

C. albicans accounted for 43.2% of isolated species in the sub-period III (2019–2021), with no substantial change compared to the sub-period I (2013–2015). However, an 8.2% increase in *C. glabrata* frequency between the sub-periods I and III was observed in this study. In a Japanese surveillance program that collected 533 *Candida* sp. blood isolates over a 1-year period from 2001 to 2002, *C. albicans* accounted for 40.7% of isolates, *C. parapsilosis* for 23.0%, *C. glabrata* for 17.9%, and *C. tropicalis* for 11.6% [18]. A similar trend was reported in a more extended surveillance program (2003–2014), which included data on 1921 *Candida* sp. blood isolates obtained at 10 Japanese university hospitals: *C. albicans* accounted for 39.5% of the isolates, *C. parapsilosis* for 23.0%, *C. glabrata* for 13.2%, and *C. tropicalis* for 7.1% [19].

Given that the present study revealed similar proportions of patients with BSI caused by *C. albicans* in our successive cohorts, no major shifts to non-*albicans* species seem to have occurred since 2001. In contrast, the proportion of patients with *C. glabrata* infection increased slightly, accounting for 47.6% (10/21) of all non-*albicans* species in the sub-period III. *C. glabrata* has been reported frequently in the elderly [14], and the fact that this study mainly included relatively old persons (median age: 74.5 years) may have influenced the results. Data from the SENTRY Antifungal Surveillance Program have also shown an increase in *C. glabrata* frequency from 2006 to 2016 [11]. *C. tropicalis* is considered a common isolate in the Asia–Pacific region [11, 20]; however, in our hospital, the proportion of patients with *C. tropicalis* was low (5.4% in the sub-period III). Data about *C. guilliermondi* and *C. famata* may not be exact given the lack of accuracy of the commercial kit used (API ID 32C) to differentiate among these rare species.

The use of the commercial Frozen Dry Plate Eiken system to evaluate the antifungal susceptibility of *Candida* isolates is very extended in Japan, and some previous reports [21, 22] have demonstrated that this kit provides reproducible and reliable results comparable to those obtained using the broth dilution reference method established in CLSI M27-A2; therefore, the CLSI breakpoints were considered suitable (except for amphotericin B).

Regarding the antifungal susceptibility profiles of *Candida* spp., the SENTRY study [11] showed regional differences. According to data from 2006 to 2016, FLCZ resistance did not increase over time, with resistance rates ranging from 0.3 to 8.1%. Interestingly, the Chinese CHIF-NET study [23] reported higher FLCZ resistance rates than those reported for the Asia–Pacific region in the SENTRY study of isolates collected from 2015 to 2017: 2.5% for *C. albicans*, 3.7% for *C. parapsilosis*, and 10.3% for *C. glabrata*.

We observed good susceptibility rates to FLCZ among all isolates collected, with values of 73.7% for all *Candida* spp. (73/99), 100% for *C. albicans*, and 95% for *C. parapsilosis*. Except for *C. krusei*, which is naturally FLCZ resistant, only one *C. glabrata* isolate was FLCZ resistant, with an overall resistance rate of 1.0% (1/98).

The VCRZ susceptibility rate was also high at 96.1% (73/76), and no VCRZ-resistant isolates were detected during the survey period. Cross-resistance between VRCZ and FLCZ has been reported [11]. In this study, one *C. parapsilosis* isolate and one *C. tropicalis* isolate were considered SDD/I for FLCZ and VRCZ, respectively. Therefore, when FLCZ resistance is observed, VRCZ is unlikely to be the optimal drug of choice.

Table 3 Relationship between 30-day mortality and clinical features in patients diagnosed with bloodstream infection caused by *Candida* spp. from January 2013 to December 2021 at the University of Fukui Hospital

Variable	Survivors $n=55$	Non-survivors $n=37$	*P*
Age (years)[a]	73 [64–80]	75 [71–81]	0.486
Male gender	25 (45.5)	23 (62.2)	0.139
Body weight (kg)[a]	50.7 [45.5–63.1]	51.1 [44.4–56.5]	0.656
Underlying disease			
Solid tumor	32 (58.2)	23 (62.2)	0.829
Hematologic malignancy	4 (7.3)	5 (13.5)	0.476
Diabetes mellitus	12 (21.8)	12 (32.4)	0.334
Liver cirrhosis	3 (5.5)	6 (16.2)	0.15
Chronic renal failure	3 (5.5)	3 (8.1)	0.681
Pulmonary disease	12 (21.8)	8 (21.6)	1
Cardiovascular disease	12 (21.8)	7 (18.9)	0.798
ICU stay at candidemia onset	10 (18.2)	8 (21.6)	0.79
Neutropenia (< 500/μL)	4 (7.3)	2 (5.4)	1
CVC	40 (72.7)	26 (70.3)	0.817
TPN	38 (69.1)	24 (64.9)	0.821
PPN	8 (14.5)	8 (21.6)	0.411
Surgery	19 (34.5)	8 (21.6)	0.244
Abdominal surgery	14 (25.5)	4 (10.8)	0.11
Immunosuppressant use	1 (1.8)	0 (0.0)	-
Corticosteroid use	9 (16.4)	8 (21.6)	0.589
Antineoplastic chemotherapy	13 (23.6)	14 (37.8)	0.166
Prior use of antibiotics	45 (81.8)	33 (89.2)	0.39
Prior use of broad-spectrum antibiotics[b]	33 (60.0)	27 (73.0)	0.265
Prior use of FLCZ[c]	1 (1.8)	1 (2.7)	1
Severity of illness			
PBS[a]	2 [1, 2]	4 [3–5]	< 0.001
CCI[a]	3 [2–4]	5 [2–6]	0.009
Species			
C. albicans	22 (40.0)	20 (54.1)	0.206
Non-albicans *Candida* spp.	33 (60.0)	17 (45.9)	0.206
C. parapsilosis	14 (25.5)	6 (16.2)	0.318
C. glabrata	13 (23.6)	6 (16.2)	0.442
Others[d]	6 (10.9)	5 (13.5)	0.751
TTP (h)[a]	44.5 [31–55]	38 [30–50.5]	0.471
Removal of CVC at any time	53 (96.4)	25 (67.6)	< 0.001
Removal CVC ≤ 2 days after BSI onset	44 (80.0)	17 (45.9)	0.001
Initial antifungal therapy			
L-AMPH	2 (3.6)	1 (2.7)	1
FLCZ	11 (20.0)	6 (16.2)	0.786
MCFG	42 (76.4)	29 (78.4)	1
Time to appropriate antifungal therapy			
< 24 h	7 (12.7)	5 (13.5)	1
< 48 h	28 (50.9)	18 (48.6)	1
< 72 h	42 (76.4)	26 (70.3)	0.629
< 96 h	49 (89.1)	29 (78.4)	0.236

Numerical data are expressed as *n* (%), except for [a], where medians (interquartile range [IQR]) are indicated

[b]Includes carbapenems, piperacillin/tazobactam, cefepime, and fluoroquinolones

[c]Fluconazole was administered at a dose of 200 mg/day as prophylactic agent during neutropenia in two patients

[d]Includes *C. guilliermondii* ($n=4$), *C. tropicalis* ($n=4$), *C. famata* ($n=1$), *C. krusei* ($n=1$), *C. kefyr* ($n=1$)

ICU, intensive care unit; *BSI*, bloodstream infection; *TPN*, total parenteral nutrition; *PPN*, peripheral parenteral nutrition; *TTP*, time to blood culture positivity; *CVC*, central venous catheter; *PBS*, Pitt bacteremia score; *CCI*, Charlson comorbidity index; *L-AMPH*, liposomal amphotericin B; *FLCZ*, fluconazole; *MCFG*, micafungin

Table 4 Multivariate Cox hazard regression analysis of 30-day mortality in patients diagnosed with bloodstream infections caused by *Candida* spp. from January 2013 to December 2021 at the University of Fukui Hospital

Risk factor[a]	HR (95% CI)	*P* value
Age (per year)	1.01 (0.98–1.03)	0.64
CCI (per point)	1.09 (0.97–1.23)	0.14
PBS (per point)	1.32 (1.10–1.59)	0.004
CVC removal at any time	0.56 (0.21–1.47)	0.24

[a]Only patient age and risk factors with $P < 0.1$ in the univariate analysis were considered

HR, hazard ratio; *CI*, confidence interval; *CCI*, Charlson comorbidity index; *PBS*, Pitt bacteremia score; *CVC*, central venous catheter

Although *Candida* resistance to echinocandins is rare, the emergence of resistant strains has been reported in *C. glabrata* and *C. tropicalis* [11, 24, 25]. In this study, a high susceptibility rate to MCFG was detected (96.2%, 100/104), but one MCFG-I isolate and three MCFG-resistant isolates were found, and these four isolates corresponded to the species *C. glabrata*. The incidence of MCFG resistance among our *C. glabrata* isolates (13%) was higher than that documented in previous reports [11, 20, 23]. Nevertheless, we did not observe a tendency for higher resistance rates over time in this study, with one MCFG-resistant strain isolated in each sub-period. Given that the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines [26, 27] both recommend echinocandins as a first-line treatment for invasive candidiasis, trends in susceptibility profiles must be monitored continuously to avoid inappropriate treatments.

The clinical features of patients who underwent *Candida* BSI at our hospital were investigated to identify the risk factors and mortality predictors. Approximately 70% of the patients included in this study had a malignant neoplasm; however, very few had neutropenia (6 patients, 6.5%). Common clinical features among patients were indwelling CVC, TPN, and prior use of antibiotics (of which 76.9% [60/78] were broad-spectrum antibiotics), all of which have been identified as risk factors for *Candida* BSI in previous studies [26, 28].

Our analysis revealed that TTP was significantly longer in *C. glabrata* than in the other species. This finding agrees with the data reported by Lai et al. [15], who suggested that TTP could be used as a criterion to differentiate *C. glabrata* from other *Candida* spp.

Ocular candidiasis has been reported in around 20% of patients with *Candida* BSI [29, 30]. In the present study, the incidence of ocular candidiasis was slightly lower (14.5%). Given that only 75% (69/92) of the patients in this study underwent fundus examination, some cases of ocular candidiasis may have been missed. Of the patients with ocular candidiasis, 90% were infected with *C. albicans*. This result

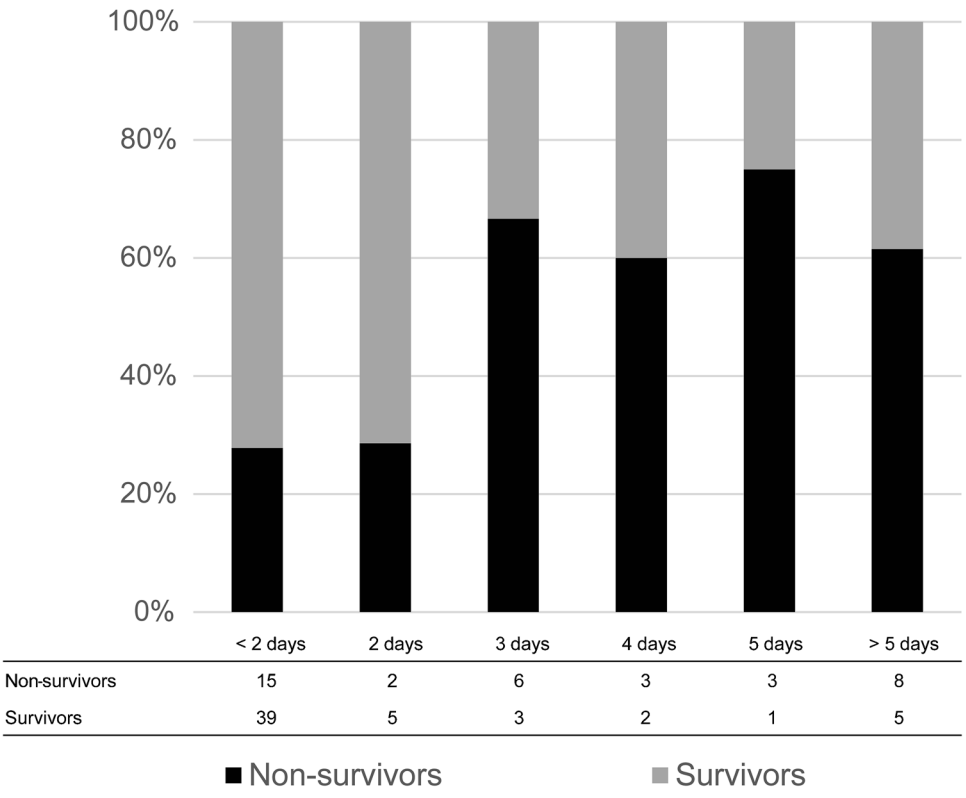

Fig. 2 Relationship between 30-day mortality and central venous catheter (CVC) indwelling time after bloodstream infection onset. Overall data for patients diagnosed with BSI from January 2013 to December 2021 at the University of Fukui Hospital

Table 5 Multivariate Cox regression analysis of 30-day mortality in patients diagnosed with bloodstream infection caused by *Candida* spp. from January 2013 to December 2021 at the University of Fukui Hospital: Recalculation for early CVC removal

Risk factor	HR (95% CI)	*P*
Age (per year)	1.01 (0.98–1.04)	0.43
CCI (per point)	1.12 (0.99–1.26)	0.067
PBS (per point)	1.31 (1.12–1.54)	0.001
Early CVC removal (≤2 days after BSI onset)	0.44 (0.21–0.95)	0.036

HR, hazard ratio; *CI*, confidence interval; *CCI*, Charlson comorbidity index; *PBS*, Pitt bacteremia score; *CVC*, central venous catheter

is consistent with previous reports and provides additional support to the IDSA treatment guidelines, which strongly recommend ophthalmic examination to detect intraocular inflammation in all patients with candidiasis [26].

Univariate analysis revealed that high PBS, high CCI, and CVC removal (at any time) were factors that affected 30-day mortality. However, multivariate analysis identified only PBS as an independent predictor of 30-day mortality and ruled out CVC removal (at any time) as an independent predictor of 30-day mortality. In addition, we found that 30-day mortality tended to increase with increasing CVC indwelling time; hence, the analysis was performed again, considering early CVC removal (within 2 days after BSI onset) as a factor impacting 30-day mortality. Multivariate analysis identified PBS and early CVC removal as independent predictors of 30-day mortality.

Current IDSA [26] and ESCMID [27] guidelines strongly recommend the removal of CVCs as early as possible. However, there is controversy regarding this recommendation and, in particular, early CVC removal as a therapeutic strategy for *Candida* BSI [31–34]. Lee et al. [35] noted that early CVC removal may improve the survival of patients with *Candida* BSI; however, this improvement was not observed in patients with CCI ≥ 4. In this study, 40 patients had CCI ≥ 4 (43.4%) (data not shown). Nucci et al. [36] investigated the impact of both CVC removal (at any time) and early CVC removal in patients with *Candida* BSI and found that CVC removal (at any time) had a positive effect, but early CVC removal had no impact; therefore, it was considered to have no clinical benefit. The results reported by these authors contrast with the outcome of this study, in which CVC indwelling periods ≥ 3 days after BSI onset resulted in higher 30-day mortality rates. However, a major difference in the "early CVC removal" definition exists between these two studies. In the study by Nucci et al., "early CVC removal" was defined as removal within 48 h from *Candida* BSI diagnosis (that is, 48 h since the day at which a blood culture was found to contain *Candida* sp.); in this study, "early CVC removal" was defined as removal within 48 h from BSI onset (that is, 2 days after the collection of the blood sample that gave a positive result). Thus, considering that the median TTP for *Candida* is 41 h, the definition of early CVC removal by Nucci et al. is equivalent to removal within 4 days according to our study. Early CVC removal has been defined by considering various starting points: when a positive blood culture sample was collected [33], when a positive blood culture was revealed (at diagnosis) [37], and at the start of treatment [32].

A systematic review of the Cochrane Database, which included studies involving CVC removal in patients with *Candida* BSI [38], found a lack of randomized controlled trials and highlighted that conclusions could not be drawn based on observational studies. In addition, the impact of CVC removal on 30-day mortality may be influenced by differences in analytical methods and definitions of early CVC removal, as already indicated. Given the considerable time required to detect *Candida* in blood cultures, postponing CVC removal until *Candida* is detected may be unadvisable. Therefore, alternative test methods and biomarkers should be developed to enable a faster diagnosis of *Candida* BSIs and appropriate antifungal therapy [39].

This study has some limitations. First, given its retrospective nature, some data could have been misinterpreted, and unknown confounders may have been omitted. Second, this was a single-center study with a small number of patients and limited information. Third, most patients were relatively old (median age: 74.5 years); thus, the data may not be generalizable to other age groups. However, our findings offer valuable information for managing patients with candidemia and improving therapeutic outcomes.

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All authors read and approved the final manuscript.

Data availability Our institution does not mandate archiving datasets generated during retrospective analyses, but they will be available on reasonable request.

Declarations

Ethics approval This study was approved by the institutional review board of the Faculty of Medical Sciences, University of Fukui (approval number: 20120089). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived due to the retrospective nature of the study.

Consent to participate Not applicable.

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