ORIGINAL RESEARCH

Systematic Characterization of Epidemiology, Antifungal Susceptibility, Risk Factors and Outcomes of Candidaemia: A Six-Year Chinese Study

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Background: *Candida* bloodstream infection (BSI), the fourth most common nosocomial BSI, is an urgent global health challenge with the tremendous growth in antifungal resistance rate and mortality rate.

Purpose: To establish the epidemiology, species distribution, risk factors, and 30-day mortality of candidaemia among 115 patients in this 6-year surveillance study.

Materials and Methods: We retrospectively analyzed the clinical characteristics, epidemiology, antifungal susceptibility patterns, and risk factors for morbidity and mortality of 115 candidaemia cases diagnosed in one tertiary care hospital from January 2016 through December 2021.

Results: Of the 115 candidaemia cases, the most prevalent species were *Candida tropicalis* (33.0%), followed by *Candida albicans* (27.8%), *Candida parapsilosis* complex (19.1%), and others. The overall incidence was 0.21 cases/1000 admissions. The overall crude resistance rate of *Candida* spp. against azoles was 20.0% (23/115), while *Candida tropicalis* showed a significant increase in the resistance rate to azoles (from 1/6, 16.7% in 2017 to 6/10, 60.0% in 2021). Multivariate analyses demonstrated that hematological malignancy and neutropenia were significantly associated with *Candida tropicalis* BSI than *Candida* non-*tropicalis* BSI. *Candida albicans* BSI had a significantly higher rate of previous surgery than *Candida* non-*albicans* BSI. *Candida parapsilosis* BSI had a significantly higher rate of receiving total parenteral nutrition (TPN). The overall 30-day mortality rate was 27.0% (31/115). The presence of high age-adjusted Charlson comorbidity index (aCCI), neutropenia, and septic shock were factors independently associated with increased 30-day mortality.

Conclusion: *Candida tropicalis* are emerging as the predominant isolate in candidaemia. Of note, the unexpectedly increased resistance rate to azoles in *Candida tropicalis* BSI was observed. The aCCI scores, neutropenia, and septic shock were independently associated with 30-day mortality. Prompt, adequate antifungal treatment among high-risk patients may lead to a reduction in mortality.

Keywords: candidaemia, epidemiology, resistance, risk factor, mortality

Introduction

Bloodstream infections (BSI) due to *Candida* spp. have become the most common fungal bloodstream infection with significant morbidity and mortality.[1–3] *Candida albicans* was the most prevalent pathogen causing candidaemia in hospitals for the last two decades, based on previous studies from the United States and Europe.[4–7] However, discordant results in recent studies reveal that the distribution of candidaemia has shifted toward Candida non-albicans in Asia.[8,9] Similar conclusions were drawn from Shanghai,[10] Shenyang,[11] and the multicenter CHIF-NET study in China.[12] *Candida* non-*albicans* species accounted for over two-thirds of isolates in the candidaemia. Resistance to antifungal agents varies among *Candida* species in different regions.[13,14] Reduced in vitro susceptibility to azoles has been observed among *Candida* non-*albicans* species.[15] More than 95% of *Candida albicans* and *Candida parapsilosis* complex isolates were susceptible to all antifungal agents and fluconazole resistance rate in *Candida tropicalis* tripled over three years among

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4010 *Candida* species which were reported in the CHIF-NET study in China.[12] The spatiotemporal heterogeneity of candidaemia worldwide prompts us to explore the epidemiology trends in China.

Recent literature has shown that the underlying risk factors contributing to candidaemia have changed over time. Known risk factors include complicated surgery, immunosuppressive therapies (eg chemotherapy, corticosteroids), hemodialysis, exposure to broad-spectrum antibacterial agents, prolonged use of central venous catheters (CVC), undergoing mechanical ventilation and administration of total parenteral nutrition (TPN).[16,17] Early diagnosis and treatment are usually absent due to the lack of specific clinical manifestations. The attributable mortality caused by candidaemia is reported to be 5%~58%.[10,13,18] Therefore, investigating the local epidemiology, monitoring the antifungal drug susceptibility, and identifying the potential risk factors of morbidity and mortality are essential for selecting the first-line antifungal agents and treatment measures to improve patient's clinical outcomes.

In this study, we retrospectively analyzed data from 115 patients with candidaemia at our hospital between 2016 and 2021. We aimed to describe their local epidemiology, clinical characteristics, species distribution of infection, and antifungal drug susceptibility and determine the risk factors for *Candida tropicalis*/*Candida* non-*tropicalis, Candida albicans*/*Candida* non-*albicans, Candida parapsilosis*/*Candida* non-*parapsilosis* candidaemia and 30-day mortality. It is the first report in China to explore the risk factors of the dominant species causing infection (*Candida tropicalis, Candida albicans*, and *Candida parapsilosis* complex) in the Chinese population.

Materials and Methods

Patient Identification and Surveillance

Between January 2016 and December 2021, 115 candidaemia cases were enrolled at the Second Hospital of Anhui Medical University, a 2600-bed tertiary care hospital. An episode of candidaemia was defined as systemic manifestations and positive culture for *Candida* species in one or more sets of blood cultures. For patient with two or more episodes of candidaemia, the next episode was counted separately if the interval between infections was more than 30 days. Previous treatments were defined as: (1) Previous surgery: surgery in the last three months; (2) Exposure to broad-spectrum antibacterial agents: the use of broad-spectrum antibacterial agents for at least five days within 30 days of one episode; (3) Prior use of antifungals: the use of antifungals within three months from diagnosing; (4) Prior use of steroids: the use of steroids for three weeks within two months from diagnosing; (5) Chemotherapy: the use of chemotherapy drug within three months from diagnosing; (6) Neutropenia: an absolute neutrophil count less than 500 cells/mm^3. The study was approved by the Medical Ethics Committee in the Second Hospital of Anhui Medical University (reference number: SZR 2021047). The research was conducted in accordance with the Declaration of Helsinki.

Clinical and Epidemiological Data

For each case, we recorded the demographics (age, sex, inpatient department), baseline treatments (prior hospital stay, prior ICU stay, and prior treatments), disease history, and immunocompromisation (neutropenia, chemoradiotherapy, septic shock, etc.). We explored the epidemiology of this cohort, including species distribution of candidaemia and antifungal susceptibility patterns. We recorded several risk factors of candidaemia, including the application of CVC, mechanical ventilation, carrying urinary catheters, receiving total parenteral nutrition (TPN), insertion of body cavity drainage tube, use of broad-spectrum antibacterial agents, prior use of antifungals and steroids, previous surgery, chemotherapy, and hemodialysis. Next, patients' comorbidities and 30-day outcomes were evaluated. Of the comorbidities, we mainly examined the presence of hematological malignancy, solid-organ cancer, coronary heart disease, and diabetes mellitus. Comorbidity was measured according to the age-adjusted Charlson comorbidity index (aCCI).[19]

Microbiological Test

Blood samples were isolated under sterile conditions and incubated in a BD BACTEC FX400 (Becton Dickinson Diagnostic Instrument Systems) blood culture system for up to 5 days. Positive bottles were subjected to Gram-staining and sampled onto Columbia blood and Sabouraud dextrose agar plates (Tianda Co., Ltd.). After incubation at 37 °C for up to 48.00 h, *Candida* species were identified by matrix-assisted laser desorption ionization time-of-flight mass

spectrometry (IVD MALDI Biotyper 2.3, Bruker Daltonics).[20] We performed antifungal susceptibility testing to detect in vitro resistance to fluconazole, voriconazole, itraconazole, and amphotericin B using the ATB FUNGUS 3 (BioMérieux) strip.[21] The quality control strain of *Candida parapsilosis* ATCC22019 and *Candida krusei* ATCC6258 was used. *Candida* isolates were classified as susceptible (S), intermediate (I), and resistant (R) according to the minimal inhibitory concentration (MIC) using the clinical breakpoints (CBPs) of antifungals. For fluconazole and voriconazole, the CBPs were defined based on the recommendation from the Clinical and Laboratory Standards Institute (CLSI M60).[22] The CBPs for susceptibility of *Candida* spp. against itraconazole were from the European Committee on Antimicrobial Susceptibility Testing (EUCAST 10.0) and epidemiological cutoff values (ECVs).[23] For amphotericin B, the CBPs were defined based on the recommendation from the EUCAST 10.0.[23] 5-fluorocytosine was not reported in the current study because of lacking CBPs in the CLSI or EUCAST.

Statistical Analysis

Continuous variables were expressed as the mean value SD or medians with interquartile ranges (IQR) according to the normality of data distribution. Categorical variables were compared by χ2 tests. The univariate logistic regression was performed on the variables to estimate odds ratios (ORs) and their 95% CIs. Further multivariate logistic regression was performed to estimate the effects on different risk factors when controlling for other factors. *P* less than 0.05 was considered statistically significant. All statistical analyses were made in SPSS (Version 16.0).

Results

Patient Characteristics and Incidence Rates

Among the 115 patients, 57 (49.6%) were men, and the median age was 63 (IQR, 51–71 yrs). The median aCCI of the initial admission was 5 points (IQR, 3–6). More details regarding baseline clinical characteristics are described in Table 1. In general, the total candidaemia incidence rate was 0.21 cases/1000 admissions. A rise in candidaemia incidence was seen from 2016 to 2021, with an incidence rate increasing gradually from 0.18 to 0.27 episodes/1000 admissions (Figure 1). Among the study patients, 39.1% (45/115) were staying in the ICU when diagnosed and 25.2% (29/115) were residents in the department of hematology. Regarding frequent risk factors for candidaemia, prior exposure to broad-spectrum antibiotics (114 patients, 98.2%) and the presence of central venous catheters (69 patients, 60.0%) were the most common in this study.

Species Distribution, Drug Susceptibility, and Antifungal Therapy

Taxonomic analyses of species isolated from the 115 candidaemia cases indicated that the most prevalent infection species was *Candida tropicalis* (38/115, 33.0%), followed by *Candida albicans* (32/115, 27.8%), *Candida parapsilosis* complex (22/115, 19.1%), *Candida glabrata* (17/115, 14.8%), *Candida krusei* (4/115, 3.5%) and other *Candida* spp. (2/115, 1.8%) in Table 2. *Candida* non-*albicans* species comprised more than half of the isolates, mainly attributed to *Candida tropicalis* accounting for 45.8% of non-*albicans* isolates. The trend in the species distribution of candidaemia is shown in Figure 2.

All 115 isolates were tested for in vitro susceptibility to antifungal agents. The crude resistance rate of *Candida* spp. strains against azoles was 20.0% (23/115). The resistance rates of *Candida* spp. strains against fluconazole, itraconazole and voriconazole were 19.1% (22/115), 13.9% (16/115) and 8.7% (10/115), respectively. Except for *Candida krusei* strains, which were naturally resistant to fluconazole, *Candida tropicalis* strains were the most resistant to azoles (15/38, 39.5%) and an increased resistance rate for *Candida tropicalis* to azoles was observed (from 1/6, 16.7% in 2017 to 6/10, 60.0% in 2021) in Table 2. *Candida albicans* and *Candida parapsilosis* strains showed the most susceptible to azoles, and only one *Candida albicans* isolate and one *Candida parapsilosis* isolate showed fluconazole resistance. *Candida glabrata* strains showed significantly high intermediate rate to azoles (6/17, 35.3%) and only one *Candida glabrata* isolate was resistant to azoles. Together, 78.3% (18/23) of isolates were cross-resistant to azoles. No isolate was found to be resistant to amphotericin B.

Table I Demographics and Clinical Characteristics of the Patients with Candidaemia

Demographics	Number of Patients (%)
Age (years old)	63 (IQR, 51–71)
Sex (male)	57 (49.6%)
ICU admission	45(39.1%)
aCCI (point)	5(IQR, 3–6)
Comorbidities	
Hematological malignancy	29(25.2%)
Solid-organ cancer	26(22.6%)
Coronary heart disease	25(21.7%)
Diabetes mellitus	18(15.7%)
Risk factors	
CVC	69 (60.0%)
Mechanical ventilation	58(50.4%)
Urinary catheter	55(47.8%)
TPN	50(43.5%)
Body cavity drainage tube	45(39.1%)
Prior antibiotic exposure	114 (98.2%)
Prior antifungals exposure	45(39.1%)
Prior steroids exposure	4(3.5%)
Previous surgery	47 (40.9%)
Chemotherapy	35(29.6%)
Hemodialysis	17(14.8%)
Severity of disease	
Neutropenia	36(31.3%)
Septic shock	38(33.0%)

Abbreviations: ICU, intensive care unit; aCCI, age-adjusted Charlson comorbidity index; CVC, central venous catheter; TPN, total parenteral nutrition.

Of the 115 patients, 34.8% (40 of 115) received voriconazole, 23.5% (27 of 115) received fluconazole, 1.7% (2 of 115) received itraconazole, 29.6% (34 of 115) received echinocandin, and 3.5% (4 of 115) received a combination of an azole and echinocandin; 8 patients never had any antifungals. In addition, more than one-third of patients (39.1%, 45 of 115) were given azoles as the initial antifungal agents.
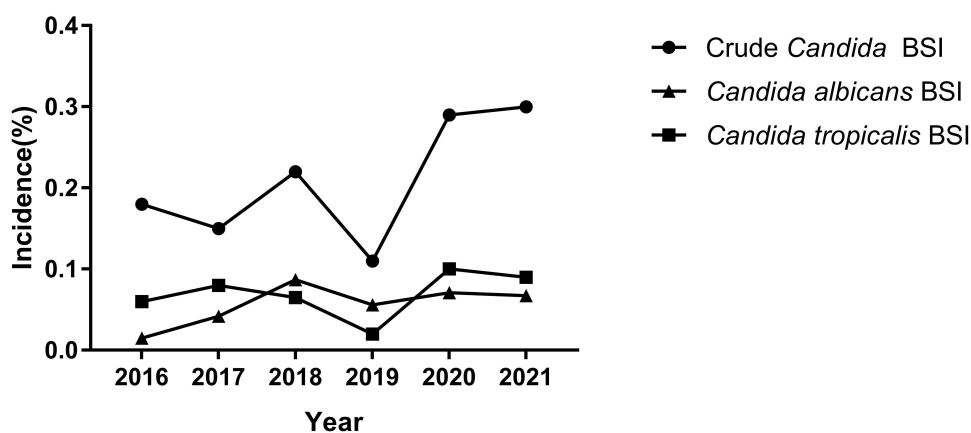
Figure I The incidence of *Candida* BSI from 2016 to 2021. The figure showed the change in the crude incidence of *Candida* BSI and the incidence rate of two major types of candidaemia through the time-course study. The crude incidence rate was calculated by the number of candidaemia cases per 1000 admissions between 2016 and 2021 in Hefei, Anhui. Overall, an increasing trend of incidence rate in candidaemia through the years was seen. Particularly, the incidence of *Candida tropicalis* BSI was always higher than that of *Candida albicans* BSI, except in 2018 and 2019.

Table 2 Azole Resistance Among *Candida* Isolates from 2016–2021

Species and Drugs	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	Total n (%)
Candida tropicalis	n=4	n=6	n=6	n=2	n=10	n=10	n=38
Fluconazole(R)	1(25.0)	1(16.7)	2(33.3)	1(50.0)	5(50.0)	5(50.0)	15(39.5)
Voriconazole(R)	1(25.0)	1(16.7)	1(16.7)	1(50.0)	3(30.0)	2(20.0)	9(23.7)
Itraconazole(R)	1(25.0)	1(16.7)	2(33.3)	1(50.0)	2(20.0)	6(60.0)	13(34.2)
Candida albicans	n =1	n =3	n =8	n =6	n =7	n =7	n =32
Fluconazole(R)	0	0	1(12.5)	0	0	0	1(3.1)
Voriconazole(R)	0	0	0	0	0	0	0
Itraconazole(R)	0	0	1(12.5)	0	0	0	1(3.1)
Candida parapsilosis	n =4	n =0	n =2	n =3	n =5	n =8	n =22
Fluconazole(R)	1(25.0)	0	0	0	0	0	1(4.5)
Voriconazole(R)	0	0	0	0	0	0	0
Itraconazole(R)	1(25.0)	0	0	0	0	0	1(4.5)
Candida glabrata	n =2	n =1	n =3	n =1	n =7	n =3	n =17
Fluconazole(R)	0	0	0	1(100)	0	0	1(5.9)
Voriconazole(R)	0	0	0	1(100)	0	0	1(5.9)
Itraconazole(R)	0	0	0	1(100)	0	0	1(5.9)
Candida krusei	n =0	n =1	n =1	n =0	n =0	n =2	n =4
Fluconazole(R)	0	1(100)	1(100)	0	0	2(100)	4(100)
Voriconazole(R)	0	0	0	0	0	0	0
Itraconazole(R)	0	0	0	0	0	0	0
Others	n =1[a]	n =0	n =0	n =0	n =0	n =1[b]	n =2
Fluconazole(R)	0	0	0	0	0	0	0
Voriconazole(R)	0	0	0	0	0	0	0
Itraconazole(R)	0	0	0	0	0	0	0

Notes: [a]*Candida guilliermondii*, [b]*Candida famata*. R: resistance against azole. CBPs for *Candida* spp. susceptibility to fluconazole and voriconazole were obtained from CLSI M60, while CBPs for susceptibility of *Candida* spp. against itraconazole were from EUCAST and ECV. Lacking the specific CBPs for *Candida famata*, we referred to the interpretation of *Candida albicans* for evaluation of susceptibility.

Risk Factors Associated with *Candida tropicalis* BSI and *Candida* non-*tropicalis* BSI

Table 3 shows the risk factors between *Candida tropicalis* and *Candida* non-*tropicalis* BSI. Univariate analyses showed that *Candida tropicalis* BSI patients had significantly higher rate in patients with hematological malignancy (OR, 13.750; 95% CI, 5.012–37.720; *P* < 0.001), prior antifungal exposure (OR, 5.481; 95% CI, 2.362–12.718; *P* < 0.001), chemotherapy (OR, 10.286;
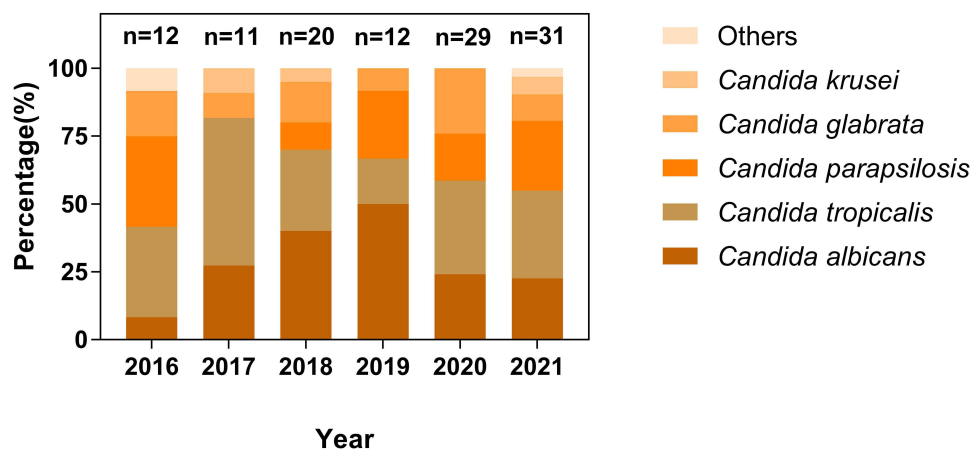
Figure 2 Trends in the species distribution of candidaemia from 2016 to 2021. The figure showed the change in the species distribution of candidaemia between 2016 and 2021. *Candida tropicalis* BSI always ranked at the top except in 2018 and 2019. The most prevalent species was *Candida tropicalis* (38/115, 33.0%), followed by *Candida albicans* (32/115, 27.8%), *Candida parapsilosis* complex (22/115, 19.1%), *Candida glabrata* (17/115, 14.8%), *Candida krusei* (4/115, 3.5%) and others *Candida* spp. (2/115, 1.8%). *Candida* non-*albicans* species comprised more than half of the isolates, mainly attributed to *Candida tropicalis* accounting for 45% of the non-*albicans* isolates.

Table 3 Comparison Between *Candida tropicalis* BSI and *Candida* non-*tropicalis* BSI

Variables [n (%)]	*Candida tropicalis* BSI n=38	*Candida* non-*tropicalis* BSI n=77	Univariate Analysis *P*-value	Multivariate Analysis Odds Ratio (95% CI)	*P*-value
Age (years old)	62(IQR, 43–72)	64(IQR, 52–71)	0.321		
Sex (male)	18(47.4)	39(50.6)	0.741		
ICU admission	7(18.4)	38(49.4)	0.002*		
aCCI (point)	5(IQR, 3–7)	5(IQR, 2–6)	0.207		
Hematological malignancy	22(57.9)	7(9.0)	0.000*	5.424(1.507–19.520)	0.010*
Solid-organ cancer	5(13.2)	22(28.6)	0.073		
Coronary heart disease	8(21.1)	17(22.0)	0.900		
Diabetes mellitus	3(7.9)	15(19.5)	0.120		
CVC	27(71.1)	42(54.5)	0.092		
Mechanical ventilation	12(31.6)	46(59.7)	0.005*		
Urinary catheter	10(26.3)	45(58.4)	0.002*		
TPN	12(31.6)	38(49.4)	0.073		
Body cavity drainage tube	10(26.3)	35(45.5)	0.051		
Prior antibiotic exposure	37(97.4)	77(100.0)	1.000		
Prior antifungals exposure	25(65.8)	20(26.0)	0.000*		
Prior steroids exposure	4(10.5)	0(0.0)	0.999		
Previous surgery	7(18.4)	41(53.2)	0.001*		
Chemotherapy	24(63.2)	10(13.0)	0.000*		
Hemodialysis	3(7.9)	14(18.2)	0.155		
Neutropenia	25(65.8)	12(15.9)	0.000*	3.800(1.160–12.453)	0.027*
Septic shock	8(21.1)	30(39.0)	0.059		

Note: *Significant statistical difference (*P*<0.05).
Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; aCCI, age-adjusted Charlson comorbidity index; CVC, central venous catheter; TPN, total parenteral nutrition; OR, odds ratio; CI, confidence interval.

95% CI, 4.109–25.746; *P* < 0.001), and neutropenia (OR, 10.417; 95% CI, 4.192–25.882; *P* < 0.001) and a lower rate of ICU admission (OR, 0.232; 95% CI, 0.091–0.590; *P* = 0.002), mechanical ventilation (OR, 0.311; 95% CI, 0.137–0.707; *P* = 0.005), urinary catheter (OR, 0.254; 95% CI, 0.108–0.596; *P* = 0.002) and previous surgery (OR, 0.198; 95% CI, 0.078–0.505; *P* = 0.001) than *Candida* non-*tropicalis* BSI patients. Multivariate analyses demonstrated that *Candida tropicalis* BSI patients had significantly higher rates of hematological malignancy (OR, 5.424; 95% CI, 1.507–19.520; *P* = 0.010) and neutropenia (OR, 3.800; 95% CI, 1.160–12.453; *P* = 0.027) than *Candida* non-*tropicalis* BSI patients.

Risk Factors Associated with *Candida albicans* BSI and *Candida* non-*albicans* BSI

When *Candida albicans* compared with *Candida* non-albicans BSI, univariate analyses showed that *Candida albicans* BSI patients had significantly higher rate of solid-organ cancer (OR, 3.372; 95% CI, 1.358–8.376; *P* = 0.009), mechanical ventilation (OR, 2.373; 95% CI, 1.016–5.543; *P* = 0.046), urinary catheter (OR, 2.751; 95% CI, 1.175–6.441; *P* = 0.020) and previous surgery (OR, 7.375; 95% CI, 2.909–18.697; *P* < 0.001) and a lower rate of hematological malignancy (OR, 0.063; 95% CI, 0.008–0.489; *P* = 0.008), prior use of antifungals (OR, 0.260; 95% CI, 0.097–0.698; *P* = 0.008), chemotherapy (OR, 0.101; 95% CI, 0.023–0.451; *P* = 0.003), and neutropenia (OR, 0.091; 95% CI, 0.020–0.408; *P* = 0.002) in Table 4. Multivariate analyses revealed that *Candida albicans* BSI patients had significantly higher rates of previous surgery (OR, 4.915; 95% CI, 1.853–13.034; *P* = 0.001) than *Candida* non-*albicans* BSI patients.

Risk Factors Associated with *Candida parapsilosis* Complex BSI and *Candida* non-*parapsilosis* Complex BSI

We then analyzed and compared the factors that may be affiliated with Candida *parapsilosis* complex BSI and Candida non-*parapsilosis* complex BSI in Table 5. Univariate analyses showed that *Candida parapsilosis complex* BSI patients

Table 4 Comparison Between *Candida albicans* BSI and *Candida* non-*albicans* BSI

Variables [n (%)]	*Candida albicans* BSI n=32	*Candida* non-*albicans* BSI n=83	Univariate Analysis *P*-value	Multivariate Analysis Odds Ratio (95% CI)	*P*-value
Age (years old)	67(IQR, 56–73)	63(IQR, 49–71)	0.086		
Sex (male)	18(56.3)	39(47.0)	0.374		
ICU admission	16(50.0)	29(34.9)	0.141		
aCCI (point)	5(IQR, 3–6)	5(IQR, 3–6)	0.898		
Hematological malignancy	1(3.1)	28(33.7)	0.008*		
Solid-organ cancer	13(40.6)	14(17.1)	0.009*		
Coronary heart disease	6(18.8)	19(22.9)	0.630		
Diabetes mellitus	7(21.9)	11(13.3)	0.259		
CVC	20(62.5)	49(59.0)	0.734		
Mechanical ventilation	21(65.6)	37(44.6)	0.046*		
Urinary catheter	21(65.6)	34(41.0)	0.020*		
TPN	14(43.8)	36(43.4)	0.971		
Body cavity drainage tube	17(53.1)	28(33.7)	0.059		
Prior antibiotic exposure	32(100)	82(98.8)	1.000		
Prior antifungals exposure	6(18.8)	39(47.0)	0.008*		
Prior steroids exposure	0(0.0)	4(4.8)	0.999		
Previous surgery	24(75.0)	24(28.9)	0.000*	4.915(1.853–13.034)	0.001*
Chemotherapy	2(6.3)	33(39.7)	0.003*		
Hemodialysis	2(6.3)	15(18.1)	0.127		
Neutropenia	2(6.3)	35(42.2)	0.002*		
Septic shock	12(37.5)	26(31.3)	0.529		

Note: *Significant statistical difference (*P*<0.05).
Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; aCCI, age-adjusted Charlson comorbidity index; CVC, central venous catheter; TPN, total parenteral nutrition; OR, odds ratio; CI, confidence interval.

had significantly higher rate of ICU admission (OR, 2.753; 95% CI, 1.063–7.130; *P* = 0.037), mechanical ventilation (OR, 3.238; 95% CI, 1.164–9.009; *P* = 0.024) and TPN (OR, 6.182; 95% CI, 2.091–18.273; *P* = 0.001) and a lower rate of neutropenia (OR, 0.274; 95% CI, 0.076–0.994; *P* = 0.049) than *Candida* non-*parapsilosis* complex BSI patients. Multivariate analyses demonstrated that *Candida parapsilosis* complex BSI patients had significantly higher rates of TPN (OR, 6.182; 95% CI, 2.091–18.273; *P* = 0.001) than *Candida* non-*parapsilosis* complex BSI patients.

Outcome Predictors in Candidaemia

During our follow-ups, candidaemia's overall crude 30-day mortality was 27.0% (31/115). *Candida tropicalis* BSI showed the highest 30-day mortality as 31.6% (12/38), followed by *Candida* glabrata BSI (29.4%, 5/17), *Candida albicans* BSI (25.0%, 8/32), *Candida krusei* BSI (25.0%, 1/4), and *Candida parapsilosis* BSI (22.7%, 5/22). There was no difference in mortality found between *Candida tropicalis* and other *Candida* spp. (*P* = 0.433). Logistic regression models then estimated the patients' outcomes (Table 6). By performing univariate analysis, the aCCI scores (OR, 1.233; 95% CI, 1.028–1.477; *P* = 0.024), neutropenia (OR, 2.642; 95% CI, 1.122–6.219; *P* = 0.026) and septic shock (OR, 5.417; 95% CI, 2.235–13.127; *P* < 0.001) were risk factors for candidaemia related 30-day mortality, while the use of body cavity drainage tube (OR, 0.353; 95% CI, 0.137–0.909; *P* = 0.031) was a protective factor against the infection. Further multivariate analysis, the aCCI scores (OR, 1.303; 95% CI, 1.052–1.614; *P* = 0.015), neutropenia (OR, 5.558; 95% CI, 1.847–16.722; *P* = 0.002) and septic shock (OR, 8.679; 95% CI, 2.983–25.246; *P* < 0.001) were independent risk factors for candidaemia related 30-day mortality. There was no correlation between the high resistance rate to azoles and the outcome (*P* = 0.916).

Discussion

Candidaemia is currently the leading cause of invasive fungal infections in hospitals. It accounts for 98% of fungemia, high often leads to septic shock.[2,6,24] The changing trend in the epidemiology of candidaemia is observed globally. At our

Table 5 Comparison Between *Candida parapsilosis* BSI and *Candida* non-*parapsilosis* BSI

Variables [n (%)]	*Candida parapsilosis* BSI n=22	*Candida* non-*parapsilosis* BSI n=93	Univariate Analysis *P*-value	Multivariate Analysis Odds Ratio (95% CI)	*P*-value
Age (years old)	60(IQR, 48–70)	64(IQR, 53–71)	0.390		
Sex (male)	10(45.5)	47(50.5)	0.668		
ICU admission	13(59.1)	32(34.4)	0.037*		
aCCI (point)	4(IQR, 2–6)	5(IQR, 3–6)	0.051		
Hematological malignancy	3(13.6)	26(28.0)	0.175		
Solid-organ cancer	3(13.6)	24(25.8)	0.235		
Coronary heart disease	4(18.2)	21(22.6)	0.654		
Diabetes mellitus	2(9.1)	16(17.2)	0.355		
CVC	11(50.0)	58(62.4)	0.290		
Mechanical ventilation	16(72.7)	42(45.2)	0.024*		
Urinary catheter	12(54.5)	43(46.2)	0.484		
TPN	17(77.3)	33(35.5)	0.001*	6.182(OR:2.091–18.273)	0.001*
Body cavity drainage tube	10(45.5)	35(37.6)	0.500		
Prior antibiotic exposure	22(100)	92(98.9)	1.000		
Prior antifungals exposure	7(31.8)	38(40.9)	0.436		
Prior steroids exposure	0(0.0)	4(4.3)	0.999		
Previous surgery	3(13.6)	33(35.5)	0.695		
Chemotherapy	3(13.6)	32(34.4)	0.068		
Hemodialysis	6(27.3)	11(11.8)	0.075		
Neutropenia	3(13.6)	34(36.6)	0.049*		
Septic shock	10(45.5)	28(30.1)	0.173		

Note: *Significant statistical difference (*P*<0.05).
Abbreviations: BSI, bloodstream infection; ICU, intensive care unit; aCCI, age-adjusted Charlson comorbidity index; CVC, central venous catheter; TPN, total parenteral nutrition; OR, odds ratio; CI, confidence interval.

research site, the incidence of candidaemia has increased dramatically in the past six years. In addition, *Candida* species distribution, antifungal susceptibility, and risk factors varied widely across different geographic regions.[25–28] A United States multicenter retrospective study demonstrated *Candida albicans* accounted for 39% of cases, followed by *Candida glabrata* (28%) and *Candida parapsilosis* (15%).[5] Another Greece study showed similar results that the species distribution with *Candida albicans* (41.0%) was the most common species in *Candidaemia*.[14] However, the incidence of *Candida tropicalis* (33.0%) rather than *Candida albicans* (27.8%) ranked first in leading candidaemia according to our observation. Similar results were proved in several reports that *Candida tropicalis* strains were the most prevalent non-*albicans* candidaemia in Saudi, Latin America, and Hong Kong, China.[9,27,29]

The change in the species distribution of candidaemia and the reduced sensitivity of *Candida* spp. to azole drugs make the infection a more severe challenge for medical management. In our study, the crude resistance rate of *Candida* spp. against azole were 20.0%. Specifically, *Candida* non-*albicans* were more resistant to azoles than *Candida albicans*, consistent with the recent study.[10] *Candida albicans* and *Candida parapsilosis* complex to azoles exhibited excellent susceptibility (more than 99.0%). *Candida glabrata* exhibited a high intermediate rate to azoles (35.3%), and *Candida krusei* exhibited intrinsic resistance. Of note, *Candida tropicalis* accounted for the highest proportion of azole resistance (39.5%). Moreover, an increased resistance rate from *Candida tropicalis* to azoles was observed (from 16.7%, 2017 to 60.0%, 2021), significantly higher than those reported in other studies.[8,15] Whether the discrepancy could be attributed to the infectious species or just the geographical distribution of pathogens needs further clarified.

Different risk factors associated with the infection of different *Candida* isolates, along with clinical manifestation, guide the medical administration of prophylactic antifungal therapy and empirical therapy. Thus, it is significant to have a comprehensive view of the risk factors for different infections. The most common candidaemia predisposing factors include complicated surgery, immunosuppressive therapies, hemodialysis, exposure to broad-spectrum antibacterial

Table 6 Logistic Regression Analysis of Risk Factors Associated with 30-Day Crude Mortality in Patients with Candidaemia

Variables [n (%)]	Survival n=84	Death n=31	Univariate Analysis P-value	Multivariate Analysis Odds Ratio (95% CI)	P-value
Age (years old)	66(IQR:57–75)	62(IQR:51–71)	0.318		
Sex (male)	41(48.8)	16(51.6)	0.790		
ICU admission	29(34.5)	16(51.6)	0.098		
aCCI (point)	4(IQR:2–6)	6(IQR:4–7)	0.024*	1.303(OR:1.052–1.614)	0.015*
Hematological malignancy	20(23.8)	9(29.0)	0.568		
Solid-organ cancer	18(21.4)	9(29.0)	0.395		
Coronary heart disease	19(22.6)	6(19.4)	0.707		
Diabetes mellitus	14(16.7)	4(12.9)	0.623		
CVC	48(57.1)	21(67.7)	0.305		
Mechanical ventilation	39(46.4)	19(61.3)	0.160		
Urinary catheter	38(45.2)	17(54.8)	0.362		
TPN	33(39.3)	17(54.8)	0.138		
Body cavity drainage tube	38(45.2)	7(22.6)	0.031*		
Prior antibiotic exposure	84(100.0)	30(96.8)	1.000		
Prior antifungals exposure	31(36.9)	14(45.2)	0.422		
Prior steroids exposure	2(2.3)	2(6.5)	0.310		
Previous surgery	37(44.0)	11(35.5)	0.410		
Chemotherapy	22(26.2)	13(41.9)	0.107		
Hemodialysis	12(14.3)	5(16.1)	0.805		
Neutropenia	22(26.2)	15(48.4)	0.026*	2.642(OR:1.847–16.722)	0.002*
Septic shock	19(22.6)	19(61.3)	0.000*	8.679(OR:2.983–25.246)	0.000*

Note: *Significant statistical difference (*P*<0.05).
Abbreviations: ICU, intensive care unit; aCCI, age-adjusted Charlson comorbidity index; CVC, central venous catheter; TPN, total parenteral nutrition; OR, odds ratio; CI, confidence interval.

agents, and prolonged use of CVCs.[16,17] Furthermore, our data showed that *Candida tropicalis* BSI patients had significantly higher hematological malignancy and neutropenia rates than *Candida* non-*tropicalis* BSI patients. In line with our findings, several studies reported that *Candida tropicalis* BSI was the most common *Candida* bloodstream infection in patients with hematological malignancy.[30–32] A recent study in Algeria revealed that neutropenia and leukemia were the most prevalent underlying conditions for *Candida tropicalis* BSI.[33]

The possible mechanism of increased rates of *Candida tropicalis* BSI in hematological malignancy had not yet been established. One possible explanation is related to the disruption of normal cellular immunity and mucosal barriers. The virulence of *Candida* spp. is related to its ability to form biofilms and invade host cells with the effect of secretory aspartyl proteinases and phospholipases. During hospitalization in the department of hematology, overgrowth and translocation of pathogens in the bloodstream can occur under the neutropenia status due to immunocompromisation arising from the use of chemotherapy and steroids. Disruption of the normal mucosal barriers provided by the respiratory tract or gastrointestinal tract may lead to the breakthrough of candidaemia in immunocompromised patients.[34] It is noteworthy that the *Candida tropicalis* BSI had significantly higher rates of azole resistance than *Candida* non-*tropicalis* BSI, which may be mainly due to commonly azoles prior used in hematological malignancy patients with neutropenia. Together, clinicians should pay more attention to potential *Candida tropicalis* BSI in immunocompromised patients of hematological malignancy.

Consistent with some previous studies,[35,36] we found that a higher rate of solid tumor, postoperative status, use of mechanical ventilation, and urinary catheter tended to be presented in patients with *Candida albicans* BSI compared with non-*albicans* BSI in univariate analysis. Further multivariate analysis showed that postoperative status was an independent factor significantly associated with the breakthrough of *Candida albicans* BSI. *Candida albicans* is part of the normal flora of the gastrointestinal tract. Xia et al[37] revealed that multifocal and high-grade *Candida* colonization was the

precondition of candidaemia, which was caused by the invasion of locally colonized *Candida* into the blood system after the destruction of the integrity of gastrointestinal mucosa during gastrointestinal surgery. Unfortunately, the pathophysiologic mechanism of *Candida* colonization and the breakthrough of candidaemia is not completely clear recently.

On the other hand, the presence of CVCs, TPN, and mechanical ventilation are common invasive medical procedures in ICU patients, which are associated with an increased risk of nosocomial infection, especially bloodstream infections.[38,39] Of note, our study demonstrated that Candida *parapsilosis* complex BSI was associated with ICU admission, mechanical ventilation, and TPN. Multivariate analysis showed that TPN was an independent risk factor of *Candida parapsilosis* BSI. *Candida parapsilosis* is the most common cause of catheter-associated candidaemia, probably due to the particular affinity for synthetic material.[40] In a study by Herek et al, it was reported that *Candida parapsilosis* might contribute to TPN catheter-related fungemia.[41] Thus, physicians should pay attention to prevent life-threatening complications, such as catheter-related bloodstream infections, during medical management by removing the catheter and applying antifungal treatment.[42]

When it comes to patient outcomes of candidaemia, the main influencing factor for prognosis is disease severity, multiorgan dysfunction, and non-adequate antifungal management, not what kind of *Candida* species the patient is infected with, or the patient's drug-resistant status. This idea comes from a German study on candidaemia with a mortality rate of 47.3%.[6] In our study, we found a 30-day mortality rate of 27.0%. Our results are consistent with a previous study[43] and lower than the mortality rate in a Spanish study of 47.9%.[44] Compared with infection of other species of *Candida*, patients with *Candida tropicalis* BSI tended to present a higher 30-day mortality rate of 31.6%. No significant difference in mortality was found between *Candida tropicalis* and other *Candida* spp. In addition, there was no correlation between the high resistance rate to azoles and the patient outcome. These results are consistent with a Taiwan study conducted on five tertiary hospitals.[15] Prior studies have identified increasing age, mechanical ventilation, underlying comorbidities, and disease severity are associated with an increased risk of mortality.[17,45] Similar to previous studies,[8,15] our study showed that high aCCI scores, neutropenia, and septic shock were independent risk factors for candidaemia-related 30-day mortality. Thus, our results confirm the importance of comorbid conditions, immunocompromisation, and multiorgan dysfunction for the outcome in candidaemia patients.

This analysis takes advantage of complete data from one single center from 2016 to 2021 and assesses the incidence of candidaemia in the retrospective data, as well as provides the risk factors for dominant species causing BSI incidence and outcomes in the study center. As with other retrospective studies, our study is limited in some points. First, our study was a single-center retrospective study that lacked the ability to produce cause–effect relationship data with control variables. In addition, a larger validation dataset to confirm our results is ideal. Second, as azole resistance has become a major concern worldwide, echinocandins have been recommended as first-line therapy for candidaemia by the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases Guidelines. This study detected relatively few choices of antifungal agents without using echinocandins for candidaemia due to the limitation of the drug sensitivity kit.

Conclusion

The incidence of non-*albicans* candidaemia seems to have increased over the last years. *Candida tropical*is BSI showed the highest crude incidence but the worst patient outcome. Of note, the unexpectedly high resistance rate to azoles in *Candida tropicalis* BSI was observed. Additionally, the aCCI scores, neutropenia, and septic shock were independently associated with BSI patients' 30-day mortality. Based on our results, we urge physicians to adjust empirical antifungal therapy timely, relying on local epidemiology and antifungal susceptibility data for high-risk patients, which are essential to improve clinical outcomes.

Ethical Approval

In this study, strains isolated from patient samples were used for research, and there were no adverse reactions and risks to subjects. The research data shall be confidential to the personal information of the subjects, including medical records and biological samples. The consent had been waived by the ethics committee in this study, and this experiment was

approved by The Medical Ethics Committee of the Second Hospital of Anhui Medical University. The research was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors declared that there are no conflicts of interest in this work.

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