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ORIGINAL RESEARCH

Clinical Features, Strain Distribution, Antifungal Resistance and Prognosis of Patients with Non-*albicans* Candidemia: A Retrospective Observational Study

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Purpose: *Candida albicans* (*C. albicans*) candidemia has been well reported in previous studies, while research on non-*albicans Candida* (NAC) bloodstream infections remains poorly explored. Therefore, the present study aimed to investigate the clinical characteristics and outcomes of patients with NAC candidemia.

Patients and Methods: We recruited inpatients with candidemia from January 2013 to June 2020 in a tertiary hospital for this retrospective observational study.

Results: A total of 301 patients with candidemia were recruited in the current study, including 161 (53.5%) patients with NAC candidemia. The main pathogens in NAC candidemia were *Candida tropicalis* (*C. tropicalis*) (23.9%), *Candida parapsilosis* (15.6%) and *Candida glabrata* (10.3%). Patients with NAC candidemia had more medical admissions (P=0.034), a higher percentage of hematological malignancies (P=0.007), a higher frequency of antifungal exposure (P=0.012), and more indwelling peripherally inserted central catheters (P=0.002) than those with *C. albicans* candidemia. In a multivariable analysis, prior antifungal exposure was independently related to NAC candidemia (adjusted odds ratio [aOR], 0.312; 95% confidence interval [CI], 0.113–0.859). Additionally, NAC was obviously resistant to azoles, especially *C. tropicalis* had a high cross-resistance to azoles. However, no significant differences were noted in the mortality rates at 14 days, 28 days and 60 days between these two groups.

Conclusion: NAC is dominant in candidemia, and prior antifungal exposure is an independent risk factor. Of note, although the outcomes of NAC and *C. albicans* candidemia are similar, drug resistance to specific azoles as well as cross-resistance frequently occurs in patients with NAC candidemia, and this drug resistance deserves attention in clinical practice and further in-depth investigation.

Keywords: non-*albicans* candidemia, clinical features, risk factor, cross-resistance

Introduction

With the wide usage of antibiotics, immunosuppressive agents and glucocorticoids, candidemia has become common as a bloodstream infection (BSI). It often occurs in patients receiving complex surgery, organ transplantation, intravascular catheters, and total parenteral nutrition (TPN), and in patients who have hematologic malignancies or who are in the intensive care unit (ICU).[1,2] The prevalence of candidemia varies in different regions,[1,3,4] ranging from a relatively low occurrence of 0.32/1000 admissions

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in Southwest China to a high incidence of 2.49/1000 admissions in Brazil.[3,4] Although a rapid diagnosis and timely treatment have been developed, the mortality of invasive candidemia is still relatively high, ranging from 22% to 75%.[2,5,6]

The most common pathogen causing candidemia is *Candida albicans* (*C. albicans*), but epidemiological investigations in recent years have shown that the incidence of non-*albicans Candida* (NAC) in candidemia is increasing year by year and is mainly composed of *Candida tropicalis* (*C. tropicalis), Candida parapsilosis* (*C. parapsilosis*) and *Candida glabrata* (*C. glabrata*).[5] In addition, *C. albicans* is highly sensitive to commonly used clinically antifungal drugs, while the drug resistance seen in NAC is steadily increasing.[7,8] Especially, two NAC species (spp.), *C. glabrata* and *C. tropicalis*, have demonstrated a higher drug resistance to azoles than other *Candida* spp.[7] Patients with NAC candidemia generally are more likely to have neutropenia and are more likely to have received TPN, glucocorticoids and central venous catheters (CVCs), whereas patients with *C. albicans* candidemia are more likely to have indwelling urethral catheters, are more likely to have candiduria and are more likely to be admitted to the ICU.[9–11]

In previous studies, some differences have been reported between *C. albicans* and NAC candidemia with regard to the clinical characteristics and prognostic factors.[7–11] However, several limitations are shown as follows: (1) One study identified that the presence of a urethral catheter was an independent risk factor for *C. albicans* candidemia,[10] and glucocorticosteroids and CVC were independent risk factors for NAC candidemia in another study.[11] However, whether these clinical features are significantly different between these two groups remains unclear. (2) A previous study found that patients with *C. albicans* candidemia had a higher rate of ICU hospitalization, but there was no significant difference in the hospital mortality;[9] This result was completely contrary to another study (there was no difference in the ICU hospitalization rate, but there was a higher mortality rate for NAC candidemia).[10] Therefore, whether the clinical outcomes of NAC candidemia are better or worse than those of *C. albican*s candidemia remains unclear. (3) Although the distribution and antifungal resistance of *Candida* spp. have been well reported in a multicenter large-scale study by China CHIF-NET, more information about the demographic and clinical characteristics is still lacking, and this information is needed to draw valid conclusions.[8]

Based on the previous results and controversies described above, we hypothesized that patients with NAC candidemia might have some specific risk factors, a more severe situation of drug resistence like azole and a worse prognosis than those with *C. albicans* candidemia. To address this hypothesis, we attempted to analyze the clinical features, strain distribution, antifungal resistance and prognosis of NAC candidemia compared with *C. albicans* candidemia in the current study.

Patients and Methods

Study Design and Patients

The present single-center retrospective study was carried out in a tertiary medical teaching hospital, the Second Affiliated Hospital, Zhejiang University School of Medicine, China. The Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine approved this study protocol (No. 2020–744). Due to the retrospective analysis, the Ethics Committee decided to waive the need for informed consent of patients.

The results of 476 positive blood culture samples from the microbial laboratory between January 2013 and June 2020 were initially analyzed (Figure 1). Among them, there were 123 duplicated *Candida* specimens, and any duplicate specimens from the same patient were excluded. Then, we excluded the following patients: 1) age < 18 years old; 2) *Candida* was considered as non-pathogenic; and 3) the case data were incomplete or missing. Consequently, 52 patients were excluded, including one patient less than 18 years old, 34 patients with non-pathogenic *Candida* and 17 patients with incomplete or missing data. Finally, 301 patients with candidemia were recruited, with 140 cases and 161 cases of *C. albicans* candidemia and NAC candidemia, respectively.

Study Variables

The following patients' medical variables were retrieved from the electronic medical record system, and the variables included basic information such as age, sex, previous medical history, and several assessments [eg, Charlson Comorbidity Index (CCI) score, acute physiology and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score within 24 hours after *Candida* BSI]. Other information, including a history of invasive procedures, previous exposure, previous treatment (eg, chemotherapy drugs, radiotherapy, immunosuppressive agents, surgery, mechanical ventilation), laboratory examinations

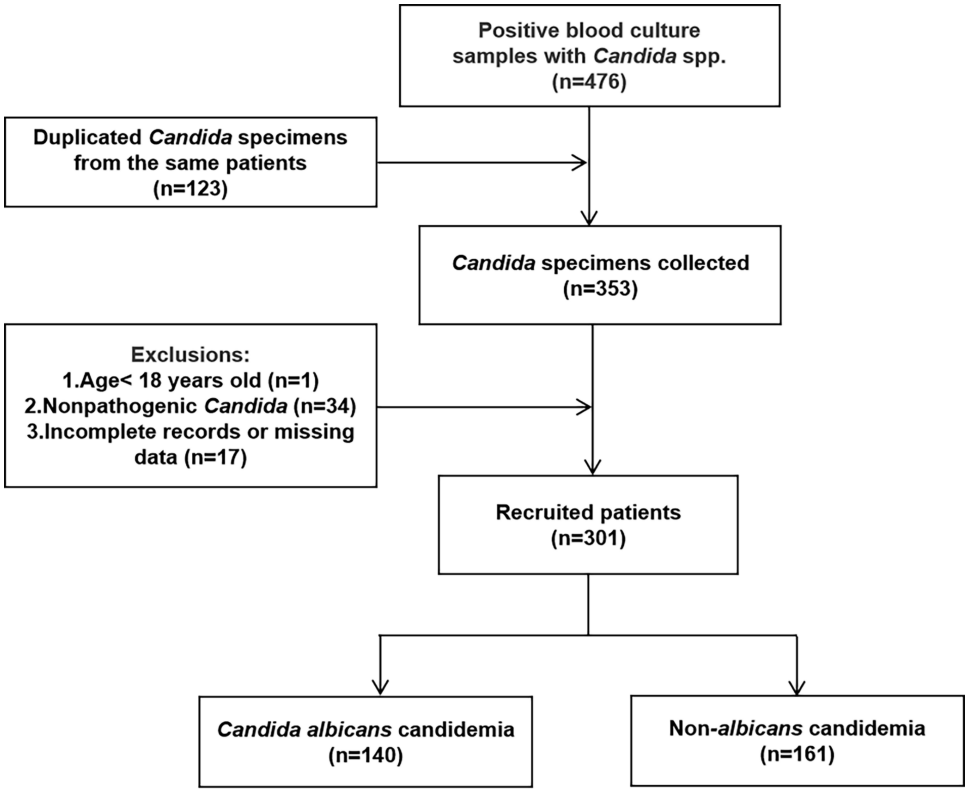

Figure 1 Flow diagram of patient recruitment.

(eg, blood cells, liver function, and kidney function), and the microbiological data (*Candida* spp., concomitant bacterial infection or not, antifungal susceptibilities and cross-resistance to azoles in vitro), were also documented. In addition, the main treatments for candidemia, such as fluid resuscitation, vasoactive drugs, renal replacement therapy (RRT) and antifungal drugs, and the outcomes, such as mortality rates at 14 days, 28 days and 60 days, were collected.

Species Identification and Microbiological Assays

Candida spp. identification and drug susceptibility testing were conducted as described in our previous study.[12] In brief, blood cultures were drawn under aseptic conditions, and then matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany) was used to identify *Candida* spp. After species confirmation, all of the *Candida* isolates were subjected to antifungal susceptibility tests using the ATB FUNGUS 3 panel of bioMerieux company in France. Experimental assessments of drug susceptibility for *Candida* were based on the clinical breakpoints specified by the Clinical Laboratory Standards Institute.[13,14]

Study Definitions

Candidemia was diagnosed when there was an isolate of at least one species of *Candida* from the blood cultures accompanied by signs and symptoms of infection. Nonpathogenic candidemia isolates were considered contaminants and were defined as a single positive blood culture of *Candida* without the clinical manifestations.[11] The definition of catheter-related candidemia was on the basis of the Infectious Diseases Society of America and was defined as follows: 1) the isolates from a catheter tip culture was proven to be identical to the isolates in least one percutaneous peripheral blood culture; or 2) the transcatheter and peripheral blood samples cultured the same *Candida* spp., and met the catheter-related bloodstream infection (CRBSI) criteria.[15] The diagnostic criteria for septic shock was based on the definition by Sepsis-3.[16] When a blood bacterial culture was positive before or within 48 hours after the onset of candidemia, it was considered a concomitant bacteremia,[4] except for the common skin microbiota (eg, *Corynebacterium* spp., *Streptococci, Bacillus* spp., *Coagulase-negative staphylococci* and *Lactobacillus* spp.), which are possible contaminants. Unless two or more consecutive venipuncture samples cultured the above microorganisms, these isolates were

considered pathogens.[12,17] The antifungal treatment was considered adequate if: (1) the antifungal agent was administered empirically within the first 48 hours of positive culture; (2) the *Candida* isolates were sensitive to the selected antifungal drugs on a sensitivity test; and (3) the dosage of antifungal drugs was selected according to the clinical guidelines recommended by the Infectious Diseases Society of America.[18,19]

Statistical Analysis

All statistical analyses were performed to identify the risk factors for NAC candidemia in comparison with *C. albicans* candidemia by using the statistical package SPSS 23.0 (IBM Corp, Armonk, NY, USA), and a $P<0.05$ was considered statistically significant. First, all quantitative data were first tested for normality. If the test results conformed to a normal distribution, the mean±standard deviation was used to represent the continuous variables; otherwise the median and interquartile range (IQR) were used instead. Then, Student's *t*-test or the Mann–Whitney U was used for comparison. All enumeration data were represented as N(%), and the chi-square test was used for comparisons between the two groups. In the univariate analysis, the variables with a significant $P<0.05$ level were considered candidate variables for establishing a stepwise logistic regression multivariate model, which was used to identify the independent risk factors associated with NAC candidemia. The 28-day survival curves of *C. albicans* and NAC candidemia were depicted by a Kaplan-Meier survival analysis, and the difference was evaluated by the Log rank test.

Results

Patient Characteristics

Table 1 outlines the baseline characteristics of the recruited patients. The median age of these patients was 66 years (IQR, 53.0–75.5), and 64.1% (193/301) were male. A total of 66.4% (200/301) of all patients with candidemia occurred at an age of older than 60 years old. The proportion of patients over 60 years of age with NAC candidemia was lower than that with *C. albicans* candidemia (60.9% vs 72.9%, $P<0.05$). The majority of patients with candidemia were from the ICU (64.5%), followed by surgical wards (20.9%) and medical wards (14.6%), and 91.0% (274/301) of these candidemia cases were nosocomial infections. In terms of comorbidities, gastrointestinal (GI) disease (31.9%), solid tumors (23.6%), and diabetes mellitus (18.3%) were common complications. A lower proportion of diabetes mellitus (13.0% vs 24.5%, $P<0.05$) and GI diseases (26.1% vs 38.6%, $P<0.05$) were observed in patients with NAC candidemia, but more hematological malignancies (6.8% vs 0.7%, $P<0.05$) were observed in patients with NAC candidemia than in patients with *C. albicans* candidemia. There were no statistically significant differences between the two groups in terms of the CCI score, APACHE II score or SOFA score among all the patients (all $P>0.05$) (Table 1). The percentage of antibiotic exposure before the onset of candidemia was 86.0%, followed by TPN and surgery for more than 50% of the patients. Compared to *C. albicans* candidemia, patients with NAC candidemia had a lower rate of surgery (47.2% vs 67.9%, $P<0.001$), especially abdominal surgery (14.3% vs 34.3%, $P<0.001$). This result was consistent with the fact that most *C. albicans* candidemia cases were from surgical wards (26.4% vs 16.1%, $P<0.05$). In contrast, patients with NAC candidemia were more likely to be exposed to antifungal drugs (12,4% vs 4.3%, $P<0.05$). In addition, more than 70% of patients with candidemia had invasive procedures such as CVCs, urinary catheters, and gastric catheters. Compared with catheterization of patients with *C. albicans* candidemia, indwelling arterial catheters and CVCs were less common in patients with NAC candidemia (26.7% vs 39.3% and 67.1% vs 84.3%, respectively, both $P<0.05$), as were indwelling abdominal drainage tubes (13.7% vs 32.1%, $P<0.001$). However, the presence of a peripherally inserted central catheter (PICC) was more frequent in patients with NAC candidemia (24.8% vs 10.7%, $P<0.05$).

Biological Parameters

In terms of biological parameters, patients with NAC candidemia were more likely to have a white blood cell (WBC) count less than 4×10^9/L (16.8% vs 5.0%, $P=0.001$), a lower neutrophil count (NC) (median $\times 10^9$/L, 7.0 vs 8.6), a lower neutrophil to lymphocyte ratio (NLR) (median, 9.2 vs 12.3), and a lower total bilirubin (TB) (median μmol/L, 15.0 vs 18.5) (all $P<0.05$) compared to patients with *C. albicans* candidemia (Table 2).

Independent Risk Factors for NAC Candidemia

Several variables with significant p values in the univariate analysis are described in Table3. After the multivariate regression model analysis of these variables, it was noted that prior antifungal exposure was independently associated with an increased risk of NAC candidemia (adjusted odds ratio [aOR], 0.312; 95% confidence interval [CI], 0.113–0.859). Patients with diabetes mellitus had

Table 1 Baseline Characteristics of Patients with *C. albicans* and NAC Candidemia

Characteristics	Total (n=301)	*C. albicans* (n=140)	NAC (n=161)	*P*-value
Age, median years (IQR)	66.0(53.0,75.5)	68.0(58.2,75.0)	64.0(49.0,77.5)	0.338
Age (≥60years), n(%)	200(66.4%)	102(72.9%)	98(60.9%)	0.028*
Male sex, n(%)	193(64.1%)	82(58.6%)	111(68.9%)	0.061
Ward				
Medical ward, n(%)	44(14.6%)	14(10.0%)	30(18.6%)	0.034*
Surgical ward, n(%)	63(20.9%)	37(26.4%)	26(16.1%)	0.029*
ICU, n(%)	194(64.5%)	89(63.6%)	105(65.2%)	0.766
Nosocomial infection, n(%)	274(91.0%)	130(92.9%)	144(89.4%)	0.301
Baseline comorbidities				
Chronic pulmonary disease, n(%)	18(6.0%)	8(5.7%)	10(6.2%)	0.856
Haematological malignancy, n(%)	12(4.0%)	1(0.7%)	11(6.8%)	0.007*
Chronic cardiac insufficiency, n(%)	49(16.3%)	29(20.7%)	20(12.4%)	0.052
Neurological disease, n(%)	51(16.9%)	18(12.9%)	33(20.5%)	0.078
Diabetes mellitus, n(%)	55(18.3%)	34(24.5%)	21(13.0%)	0.012*
Solid tumor, n(%)	71(23.6%)	40(28.6%)	31(19.3%)	0.058
Solid organ transplant recipient, n(%)	5(1.7%)	4(2.9%)	1(0.6%)	0.288
Chronic kidney disease, n(%)	28(9.3%)	11(7.9%)	17(10.6%)	0.421
Chronic liver disease, n(%)	30(10.0%)	17(12.1%)	13(8.1%)	0.240
Gastrointestinal disease, n(%)	96(31.9%)	54(38.6%)	42(26.1%)	0.020*
Severe burn, n(%)	15(5.0%)	4(2.9%)	11(6.8%)	0.114
CCI, median (IQR)	4.0(3.0,6.0)	5.0(3.0,7.0)	4.0(3.0,6.0)	0.119
APACHE II score, median (IQR)	17.0(12.0,22.5)	17.0(11.2,23.7)	16.0(12.0,22.0)	0.711
SOFA score, median (IQR)	6.0(3.0,9.0)	6.0(3.0,9.0)	6.00(3.0,9.5)	0.670
Risk factors				
Current and former smoker, n(%)	99(32.9%)	41(29.3%)	58(36.0%)	0.215
Septic shock on admission, n(%)	32(10.6%)	20(14.3%)	12(7.5%)	0.055
Surgery, n(%)	171(56.8%)	95(67.9%)	76(47.2%)	0.000**
Abdominal surgery, n(%)	71(23.6%)	48(34.3%)	23(14.3%)	0.000**
Steroid therapy, n(%)	15(5.0%)	9(6.4%)	6(3.7%)	0.283
Immunosuppressive therapy, n(%)	8(2.7%)	6(4.3%)	2(1.2%)	0.201
Chemotherapy/radiation, n(%)	23(7.6%)	7(5.0%)	16(9.9%)	0.108
Blood transfusion, n(%)	115(38.2%)	60(42.9%)	55(34.2%)	0.121
Prior antifungal exposure[a], n(%)	26(8.6%)	6(4.3%)	20(12.4%)	0.012*
Prior antibiotics exposure[a], n(%)	259(86.0%)	121(86.4%)	138(85.7%)	0.858
TPN, n(%)	198(65.8%)	97(69.3%)	101(62.7%)	0.232
Neutropenia, n(%)	17(5.6%)	5(3.6%)	12(7.5%)	0.146
Invasive devices				
Mechanical ventilation, n(%)	171(56.8%)	77(55.0%)	94(58.4%)	0.554
Presence of CVC, n(%)	226(75.1%)	118(84.3%)	108(67.1%)	0.001*
Presence of PICC, n(%)	55(18.3%)	15(10.7%)	40(24.8%)	0.002*
Presence of arterial catheter, n(%)	98(32.6%)	55(39.3%)	43(26.7%)	0.020*
Presence of urethral catheter, n(%)	267(88.7%)	129(92.1%)	138(85.7%)	0.079
Presence of gastric tube, n(%)	246(77.4%)	110(80.9%)	119(73.9%)	0.137
Presence of abdominal drainage tube, n(%)	67(22.3%)	45(32.1%)	22(13.7%)	0.000**
Blood purification, n(%)	79(26.2%)	38(27.1%)	41(25.5%)	0.724

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n=301)	*C. albicans* (n=140)	NAC (n=161)	*P*-value
Prior hospital stay, median days (IQR)	15.0(6.0,31.0)	14.5(5.2,31.7)	16.0(6.0,31.0)	0.654
Prior ICU stay, median days (IQR)	5.0(0.0,19.5)	5.0(0.0,15.5)	6.0(0.0,21.0)	0.213

Notes: **P*<0.05, ***P*<0.001. [a]All patients received systemic drug therapy for ≥3 days within 2 weeks before onset of candidemia.
Abbreviations: *C. albicans, Candida albicans*; NAC, non-*albicans Candida*; IQR, interquartile range; ICU, intensive care unit; CCI, Charlson Comorbidity Index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; TPN, total parenteral nutrition; CVC, central venous catheter; PICC, peripherally inserted central catheter.

Table 2 Biological Parameters of Patients with *C. albicans* or NAC Candidemia

Variables	Total (n=301)	*C. albicans* (n=140)	NAC (n=161)	*P*-value
Temperature>38°C, n(%)	222(73.8%)	97(69.3%)	125(77.6%)	0.100
Temperature<36°C, n(%)	9(3.0%)	3(2.1%)	6(3.7%)	0.642
Laboratory data				
WBC(×10^9 /L), n(%)				
<4	34(11.3%)	7(5.0%)	27(16.8%)	0.001*
>10	127(42.2%)	65(46.4%)	62(38.5%)	0.165
NC(×10^9 /L), median(IQR)	7.8(4.8,11.9)	8.6(5.4,17.8)	7.0(4.0,10.7)	0.005*
LC(×109 /L), median(IQR)	0.7(0.3,1.1)	0.7(0.4,1.0)	0.7(0.3,1.1)	0.585
NLR, median(IQR)	11.4(6.3,19.9)	12.3(8.2,23.0)	9.2(5.5,17.5)	0.003*
Anaemia, n(%)	267(88.7%)	124(88.6%)	143(88.8%)	0.946
Thrombocytopaenia, n(%)	152(50.5%)	71(50.7%)	81(50.3%)	0.944
Hypoproteinemia, n(%)	127(42.2%)	56(40.0%)	71(44.1%)	0.473
TB(μmol/L), median(IQR)	16.0(11.0,31.0)	18.5(11.0,35.6)	15.0(10.0,28.0)	0.029*
AST(U/L), median(IQR)	39.0(26.0,65.5)	43.0(27.0,75.5)	36.0(25.0,57.5)	0.080
ALT(U/L), median(IQR)	32.0(21.0,64.0)	33.5(21.0,64.8)	30.0(19.5,63.0)	0.356
Renal failure, n(%)	64(21.3%)	36(25.7%)	28(17.4%)	0.078
PCT (ng/mL),n(%)				
≥0.5, <2	90(29.9%)	44(31.4%)	46(28.6%)	0.589
≥2	90(29.9%)	49(35.0%)	41(25.5%)	0.072

Note: **P*<0.05.
Abbreviations: *C. albicans, Candida albicans*; NAC, non-*albicans Candida*; WBC, white blood count; NC, neutrophil count; IQR, interquartile range; LC, Lymphocyte count; NLR, neutrophil to lymphocyte ratio; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PCT, procalcitonin.

a higher risk of *C. albicans* candidemia than NAC candidemia (aOR, 2.267; 95% CI, 1.186–4.334).

Species Distribution

A total of 301 patients with candidemia were recruited in the current study, and *C. albicans* and NAC were responsible for 46.5% and 53.5% of candidemia cases, respectively. In NAC candidemia, the main species isolated were *C. tropicalis, C. parapsilosis* and *C. glabrata*, accounting for 23.9%, 15.6%, and 10.3% of the cases, respectively. In 12 hematological malignancy patients with candidemia, more than 90% of the

Table 3 Multivariable Logistic Regression of Risk Factors Caused by *C. albicans* vs NAC Candidemia

Variables	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age (≥60 years)	1.726(1.058,2.813)	0.029*	1.522(0.878,2.638)	0.135
Medical ward	0.485(0.246,0.958)	0.037*	1.825(0.688,4.841)	0.226
Surgical ward	1.865(1.062,3.276)	0.030*	1.853(0.929,3.694)	0.080
Haematological malignancy	0.098(0.013,0.770)	0.027*	0.318(0.034,2.964)	0.315
Diabetes mellitus	2.138(1.174,3.895)	0.013*	2.267(1.186,4.334)	0.013*
Gastrointestinal disease	1.779(1.091,2.902)	0.021*	0.834(0.417,1.669)	0.608
Surgery	2.361(1.475,3.780)	0.000**	1.621(0.915,2.872)	0.098
Abdominal surgery	3.130(1.783,5.495)	0.000**	1.468(0.614,3.513)	0.388
Prior antifungal exposure	0.316(0.123,0.810)	0.016*	0.312(0.113,0.859)	0.024*
Presence of CVC	2.632(1.501,4.615)	0.001*	1.882(0.872,4.061)	0.107
Presence of PICC	0.363(0.191,0.691)	0.002*	0.696(0.321,1.507)	0.358
Presence of arterial catheter	1.776(1.091,2.889)	0.021*	1.600(0.904,2.832)	0.107
Presence of abdominal drainage tube	2.993(1.688,5.307)	0.000**	1.594(0.679,3.744)	0.284

Notes: *P<0.05, **P<0.001.
Abbreviations: *C. albicans, Candida albicans*; NAC, non-*albicans Candida*; CVC, central venous catheter; PICC, peripherally inserted central catheter; OR, odds ratio; CI, confidence interval.

cases (11/12) were caused by NAC, especially *C. tropicalis* (10/12, 83.3%). The distribution of *Candida* spp. is shown in Table 4 and Figure 2.

In vitro Susceptibilities

As shown in Tables 5 and 6, NAC isolates had a significantly higher resistance to fluconazole, voriconazole, itraconazole and clotrimazole (all P<0.05). In particularly, *C. tropicalis* had high resistance rates to clotrimazole (68.6%), itraconazole (45.6%), fluconazole (50.0%), and voriconazole (56.5%), whereas less than 3% of *C. albicans* isolates were resistant to these four drugs. Both *C. albicans* and NAC had a low resistance rate (less than 2.0% of isolates) to amphotericin B (Table 5).

In general, the resistance rate to ketoconazole (26.6%) was the highest, followed by clotrimazole (23.5%), fluconazole (14.5%), and voriconazole (13.1%) (Table 7). In terms of specific azoles, they had different resistance rates which were dependent on the different species of *Candida*. *C. albicans* was sensitive to azoles, but this was apparently not the case for NAC, as most of them were resistant to these azoles such as fluconazole, voriconazole and clotrimazole, with a high resistance rate of more than 50% (Table 7). Of note, 14.6% (44/301) of patients with candidemia exhibited cross-resistance, especially in patients with *C. tropicalis* among which the cross-resistance rate to azoles was as high as 50.0% (36/72). Among hematologic malignancy patients with *C. tropicalis* candidemia, the cross-resistance rate was up to 90% (9/10) (Table 4).

Clinical Therapy

The details about clinical features and treatments at the onset of candidemia are shown in Table 6, which indicated significant differences in RRT, source of infection (intra-abdominal), and antifungal therapy between the two types of candidemia. A total of 10.6% of patients with NAC received RRT, which was almost three times that of patients with *C. albicans* (P=0.020). The main identified sources of candidemia was catheter-related candidemia (33.2%, 100/301) and intra-abdominal infections (13.0%, 39/301), whereas 42.9% (129/301) of candidemia cases were

Table 4 Distribution of *Candida* spp., Cross-Resistance and Prior Antifungal Exposure of Patients with Hematological Malignancy

Candida Species	Prior Antifungal Exposure n(%)	Cross-Resistance[a] n(%)
C. albicans (n=1)	0(0.0%)	0(0.0%)
NAC (n= 11)	4(36.4%)	10(90.9%)
C. tropicalis (n= 10)	3(30.0%)	9(90.0%)
C. krusei (n = 1)	1(100.0%)	1(100.0%)

Notes: [a]Cross-resistance was defined as resistance to any two or more azoles in the drug sensitivity tests in this study.
Abbreviations: *C. albicans, Candida albicans*; NAC, non-*albicans Candida; C. tropicalis, Candida tropicalis; C. krusei, Candida krusei.*

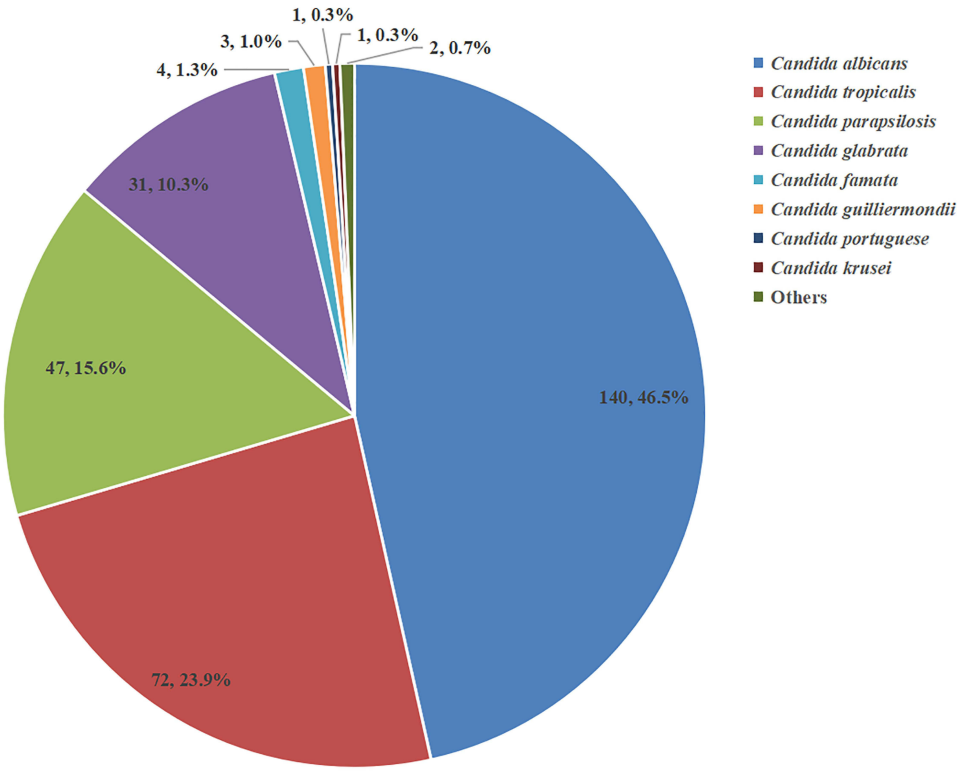

Figure 2 Distribution of different *Candida* spp. during this candidemia study period.

considered primary infections, as no obvious infection sources were confirmed. In further comparison, patients with NAC candidemia had fewer intraperitoneal sources for candidemia than patients with *C. albicans* candidemia (9.3% vs 17.1%, P=0.044). In terms of source control, the percentage of catheter removal within 48h in all patients with indwelling intravascular catheters was 73.0% (73/100), although no significant difference was found between these two groups. Regarding adequate antifungal treatment, the ratio of patients with candidemia was similar in both groups (31.7% vs 34.1%, P>0.05). In addition, pyrrole antifungal agents were more commonly used in patients with NAC, while echinocandin antifungal agents were more frequently given to patients with *C. albicans* (Table 6).

Outcomes

In patients with candidemia, the ICU length of stay was 14 days (IQR, 1.0–38.0), and the total length of hospitalization was 35 days (IQR, 19.3–65.0) (Table 8). Patients with NAC candidemia had a longer ICU stay and a longer total hospitalization than those with *C. albicans* candidemia [median days, 15.0 (0.5–46.0) vs 14.0 (2.0–33.8), P=0.406; 37.5 (20.2–70.0) vs 34.0 (19.0–60.0), P=0.303], but these values were not statistically significant. Furthermore, no significant differences were noted in the mortality rates at 14 days, 28 days and 60 days between these two groups, which was consistent with the result of survival curve (Figure 3).

Discussion

Several findings have been revealed in our current study. First, although *C. albicans* was reported to be the major fungal species, NAC spp. accounted for 53.5% (161/301) of candidemia. Second, several risk factors for NAC candidemia were found, including medical admission, hematological malignancies, prior antifungal exposure, and the presence of PICC. Particularly, prior antifungal exposure constituted one of the most pivotal independent risk factors for NAC candidemia, which differed from that of diabetes mellitus for *C. albicans* candidemia. Moreover, *C. albicans* remained highly susceptible to most antifungal agents (including azoles), whereas NAC showed strikingly different responses to azoles, especially *C. tropicalis*, which had a high cross-resistance to azoles. Lastly, no significant differences in the clinical outcomes were observed between these two groups.

To date, numerous studies have specifically described the epidemiology of candidemia based on demographic surveys from around the world.[7–11,20–22] As expected, the

Table 5 Comparison of Antifungal Susceptibilities of Different *Candida* spp. in vitro

Species (n)	Antifungal Agent	S, n(%)	I, n(%)	R, n(%)
C. albicans (n= 140)	5-fluorocytosine	64(98.5%)	0(0.0%)	1(1.5%)
	Fluconazole	123(96.1%)	4(3.1%)	1(0.8%)
	Amphotericin B	134(100.0%)	0(0.0%)	0(0.0%)
	Voriconazole	124(99.2%)	0(0.0%)	1(0.8%)
	Itraconazole	128(95.6%)	3(2.2%)	3(2.2%)
	Clotrimazole	66(98.5%)	0(0.0%)	1(1.5%)
	Ketoconazole	25(42.4%)	21(35.6%)	13(22.0%)
	Nystatin	66(98.5%)	0(0.0%)	1(1.5%)
NAC (n=161)				
C. tropicalis (n= 72)	5-fluorocytosine	36(100.0%)	0(0.0%)	0(0.0%)
	Fluconazole	31(44.3%)	4(5.7%)	35(50.0%)
	Amphotericin B	71(98.6%)	0(0.0%)	1(1.4%)
	Voriconazole	27(43.5%)	0(0.0%)	35(56.5%)
	Itraconazole	29(42.6%)	8(11.8%)	31(45.6%)
	Clotrimazole	12(23.5%)	4(7.8%)	35(68.6%)
	Ketoconazole	9(26.5%)	13(38.2%)	12(35.3%)
	Nystatin	32(97.0%)	1(3.0%)	0(0.0%)
C. parapsilosis (n=47)	5-fluorocytosine	24(100.0%)	0(0.0%)	0(0.0%)
	Fluconazole	42(93.3%)	2(4.4%)	1(2.2%)
	Amphotericin B	24(100.0%)	0(0.0%)	0(0.0%)
	Voriconazole	41(97.6%)	0(0.0%)	1(2.4%)
	Itraconazole	38(92.7%)	3(7.3%)	0(0.0%)
	Clotrimazole	19(90.5%)	1(4.8%)	1(4.8%)
	Ketoconazole	10(50.0%)	6(30.0%)	4(20.0%)
	Nystatin	20(100.0%)	0(0.0%)	0(0.0%)
C. glabrata (n= 31)	5-fluorocytosine	9(100.0%)	0(0.0%)	0(0.0%)
	Fluconazole	24(80.0%)	4(13.3%)	2(6.7%)
	Amphotericin B	31(100.0%)	0(0.0%)	0(0.0%)
	Voriconazole	25(96.2%)	0(0.0%)	1(3.8%)
	Itraconazole	14(56.0%)	6(24.0%)	5(20.0%)
	Clotrimazole	14(73.7%)	3(15.8%)	2(10.5%)
	Ketoconazole	8(42.1%)	4(21.1%)	7(36.8%)
	Nystatin	22(100.0%)	0(0.0%)	0(0.0%)
Other *Candida* spp.[a] (n= 11)	5-fluorocytosine	3(100.0%)	0(0.0%)	0(0.0%)
	Fluconazole	7(70.0%)	1(10.0%)	2(20.0%)
	Amphotericin B	11(100.0%)	0(0.0%)	0(0.0%)
	Voriconazole	8(100.0%)	0(0.0%)	0(0.0%)
	Itraconazole	9(90.0%)	1(10.0%)	0(0.0%)
	Clotrimazole	8(100.0%)	0(0.0%)	0(0.0%)
	Ketoconazole	6(75.0%)	1(12.5%)	1(12.5%)
	Nystatin	8(100.0%)	0(0.0%)	0(0.0%)

Notes: Not all agents listed have been tested in all isolated species. [a]Included *Candida famata* (n = 4), *Candida guilliermondii* (n = 3), *Candida* (n = 2), *Candida portuguese* (n = 1), and *Candida krusei* (n = 1).

Abbreviations: S, susceptible; I, intermediate; R, resistant; *C. albicans*, *Candida albicans*; NAC, non-*albicans Candida*; *C. tropicalis*, *Candida tropicalis*; *C. parapsilosis*, *Candida parapsilosis*; *C. glabrata*, *Candida glabrata*.

four major pathogens of candidemia were *C. albicans, C. tropicalis, C. glabrata* and *C. parapsilosis*, which accounted for 96.3% of all *Candida* spp. in this study (Figure 2). NAC spp. collectively represented 53.5% of the bloodstream isolates, which exceeded the percent of C. *albicans* spp., and these results are consistent with the results from Northeast China, Latin America, North America and Asia-Pacific.[7,10,23] Concerning NAC

Table 6 Clinical Features and Treatments of Patients with *C. albicans* or NAC at the Onset of Candidemia

Clinical Features and Treatments	Total (n=301)	*C. albicans* (n=140)	NAC (n=161)	*P*-value
Septic shock, n(%)	111(36.8%)	51(36.4%)	60(37.3%)	0.880
Fluid resuscitation, n(%)	70(23.3%)	30(21.4%)	40(24.8%)	0.484
Vasopressor therapy, n(%)	96(31.9%)	45(32.1%)	51(31.7%)	0.931
RRT, n(%)	22(7.3%)	5(3.6%)	17(10.6%)	0.020*
Hydrocortisone treatment, n(%)	4(1.3%)	1(0.7%)	3(1.9%)	0.385
Concomitant bacterial infection, n(%)	58(19.3%)	25(17.9%)	33(20.5%)	0.562
Source of candidemia				
Catheter-related candidemia, n(%)	100(33.2%)	45(32.1%)	55(34.2%)	0.711
Pulmonary infection, n(%)	14(4.7%)	9(6.4%)	5(3.1%)	0.172
Urinary tract infection, n(%)	13(4.3%)	7(5%)	6(3.7%)	0.588
Intra-abdominal infection, n(%)	39(13.0%)	24(17.1%)	15(9.3%)	0.044*
Others[a], n(%)	129(42.9%)	52(37.1%)	77(47.8%)	0.062
Remove the catheters (≤48h) (45 vs 55)[b], n(%)	73(73.0%)	36(80.0%)	37(67.3%)	0.154
Adequate antifungal treatment, n(%)	99(32.9%)	48(34.1%)	51(31.7%)	0.631
Antifungal therapy + catheter removal (≤48h) (36 vs 37)[c], n(%)	38(52.1%)	21(58.3%)	17(45.9%)	0.290
Antifungal agents				
Pyrroles, n(%)	167(55.5%)	72(51.4%)	95(59.0%)	0.187
Echinocandins, n(%)	141(46.8%)	66(47.1%)	75(46.6%)	0.923
Duration of antifungal therapy, median days (IQR)	9.0(4.0,16.5)	9.0(4.0,16.0)	10.0(4.0,17.0)	0.544
Antifungal resistance[d]				
5-fluorocytosine (65 vs 72)[e], n(%)	1(0.7%)	1(1.5%)	0(0.0%)	0.959
Fluconazole (128 vs 155)[e], n(%)	41(14.5%)	1(0.8%)	40(25.8%)	0.000**
Amphotericin B (134 vs 138)[e], n(%)	1(0.4%)	0(0.0%)	1(0.7%)	1.000
Voriconazole (125 vs 138)[e], n(%)	38(14.4%)	1(0.8%)	37(26.8%)	0.000**
Itraconazole (134 vs 144)[e], n(%)	39(14.0%)	3(2.2%)	36(25.0%)	0.000**
Clotrimazole (67 vs 99)[e], n(%)	39(23.4%)	1(1.5%)	38(38.4%)	0.000**
Ketoconazole (59 vs 81)[e], n(%)	37(26.4%)	13(22.0%)	24(29.6%)	0.314
Nystatin (67 vs 83)[e], n(%)	2(1.3%)	1(1.5%)	1(1.2%)	0.914

Notes: *P<0.05, **P<0.001. [a]The source of infection could not be identified or primary infection. [b]The numbers in parentheses represented the total numbers of *Candida* spp. with intravascular catheters. [c]The numbers in parentheses represented the total numbers of *Candida* spp. with catheter removal. [d]Not all agents listed have been tested in all isolates. [e]The numbers in parentheses represented the total numbers of *Candida* species performed susceptibility test.
Abbreviations: *C. albicans*, *Candida albicans*; NAC, non-*albicans Candida*; RRT, renal replacement therapy; IQR, interquartile range.

candidemia, it is worth noting that *C. tropicalis* has become a common NAC spp. worldwide.[7,8] In our study, *C. tropicalis* ranked second among all *Candida* spp. in candidemia, accounting for 23.9%. This rate was lower than the rate in Asia-Pacific (30.7%), but higher than that in Northeast China (10%), Latin America (17.0%), North America (8.0%) and Europe (7.5%).[7,10,23] The epidemiological difference in species for candidemia might vary with patient age, geographical area, medical practice and use of antifungal drugs.[1] The prevalence of NAC candidemia has significantly increased over time, which is generally associated with a reduced antifungal sensitivity resulting from the widespread use of azoles.[7,8,24,25] Other possible explanations may include the increased number of immunocompromised patients, the growing use of invasive medical procedures, and the improvement of yeast isolation techniques at the species level.[1,11,22] However, the underlying mechanisms causing the epidemiological changes of NAC spp. in candidemia remain uncertain.

Common risk factors for NAC candidemia consisted of medical admissions, hematological malignancies, antifungal exposure, and the presence of PICC (Table 1). Other studies

Table 7 In vitro Drug Resistance of *Candida* spp. to Azoles

Species (n)	Fluconazole	Voriconazole	Itraconazole	Clotrimazole	Ketoconazole	Cross-Resistance[a]
	R, n(%)	R, n(%)	R, n(%)	R, n(%)	R, n(%)	n(%)
C. albicans (n= 140)	1(0.8%)	1(0.8%)	3(2.2%)	1(1.5%)	13(22.0%)	3(2.1%)
NAC (n= 161)						
C. tropicalis (n= 72)	35(50.0%)	35(56.5%)	31(45.6%)	35(68.6%)	12(35.3%)	36(50.0%)
C. parapsilosis (n=47)	1(2.2%)	1(2.4%)	0(0.0%)	1(4.8%)	4(20.0%)	1(2.1%)
C. glabrata (n= 31)	2(6.7%)	1(3.8%)	5(20.0%)	2(10.5%)	7(36.8%)	3(9.7%)
Other species[b] (n= 11)	2(20.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(12.5%)	1[c](9.1%)
Total (n=301)	41(14.5%)	38(13.1%)	11(4.0%)	39(23.5%)	37(26.6%)	44(14.6%)

Notes: Not all agents listed have been tested in all isolated species. [a]Cross-resistance was defined as resistance to any two or more of the above azoles. [b]Included *Candida famata* (n = 4), *Candida guilliermondii* (n = 3), *Candida* (n = 2), *Candida portuguese* (n = 1), and *Candida krusei* (n = 1). [c]Only one case of *Candida krusei* had cross-resistance in other *Candida* species.

Abbreviations: R, resistant; *C. albicans, Candida albicans*; NAC, non-*albicans Candida; C. tropicalis, Candida tropicalis; C. parapsilosis, Candida parapsilosis; C. glabrata, Candida glabrata*.

Table 8 Outcomes of Patients with *C. albicans* and NAC Candidemia

Outcomes	Total (n=301)	*C. albicans* (n=140)	NAC (n=161)	*P* -value
Length of ICU stay (M) (IQR)	14.0(1.0,38.0)	14.0(2.0,33.8)	15.0(0.5,46.0)	0.406
Length of hospital stay (M) (IQR)	35.0(19.3,65.0)	34.0(19.0,60.0)	37.5(20.2,70.0)	0.303
Crude 14-day mortality, n(%)	87(28.9%)	44(31.4%)	43(26.7%)	0.368
Crude 28-day mortality, n(%)	104(34.6%)	53(37.9%)	51(31.7%)	0.261
Crude 60-day mortality, n(%)	114(37.9%)	58(41.4%)	56(34.8%)	0.236
Crude in-hospital mortality, n(%)	122(40.5%)	62(44.3%)	60(37.3%)	0.216

Abbreviations: *C. albicans, Candida albicans*; NAC, non-*albicans Candida*; ICU, intensive care unit; M, median; IQR, interquartile range.

have found that hematological malignancies and prior exposure to antifungal agents were factors closely related to NAC candidemia in comparison with *C. albicans* candidemia,[26–29] which echoes our study. Among hematological malignancy patients with candidemia, NAC was the main type, in which *C. tropicalis* accounted for 90.9% (10/11) (Table 4). Other studies also showed that *C. tropicalis* was the most common NAC spp. in hematological malignancy patients complicated with candidemia.[27,30] This peculiar epidemiology might be explained by the increased invasiveness of *C. tropicalis* in the human gastrointestinal tract, especially in patients with hematological malignancies who are immunocompromised.[31] Furthermore, a high proportion of antifungal exposure before the onset of candidemia (36.4%) was observed in hematological malignancy patients with NAC candidemia, which might be partly responsible for the species' migration to NAC. However, hematological malignancy was not independently associated with NAC candidemia after the multivariate regression analysis (Table 3), possibly due to the low proportion of these patients in our study (6.8%) (Table 1). Of note, when these risk factors were further analyzed using the multivariate regression, prior antifungal exposure was independently associated with an increased risk of NAC candidemia, while diabetes mellitus was associated with an increased risk of *C. albicans* candidemia (Table 3). However, it remains unknown whether patients with both risk factors, diabetes and prior antifungal exposure, are likely to develop mixed BSIs of *C. albicans* and NAC, which merits further investigation.

Over the past 20 years, the drug resistance of *Candida* to azoles has attracted worldwide attention. Although azoles show preliminary clinical benefits in *C. albicans* candidemia,[7,8] the increasing prevalence of NAC spp. and their associated reduced antifungal sensitivity have become a main challenge in candidemia treatment.[20,22,25] In the current study, NAC demonstrated significantly higher resistance to fluconazole, voriconazole, itraconazole and clotrimazole (all P<0.05), especially with *C. tropicalis* isolates (Tables 6 and 7). We observed that the rate of azole resistance in *C. tropicalis* was over 35%, which was consistent with the high resistance rate in the CHIF-NET study;[8] Furthermore, 50% (36/72) of

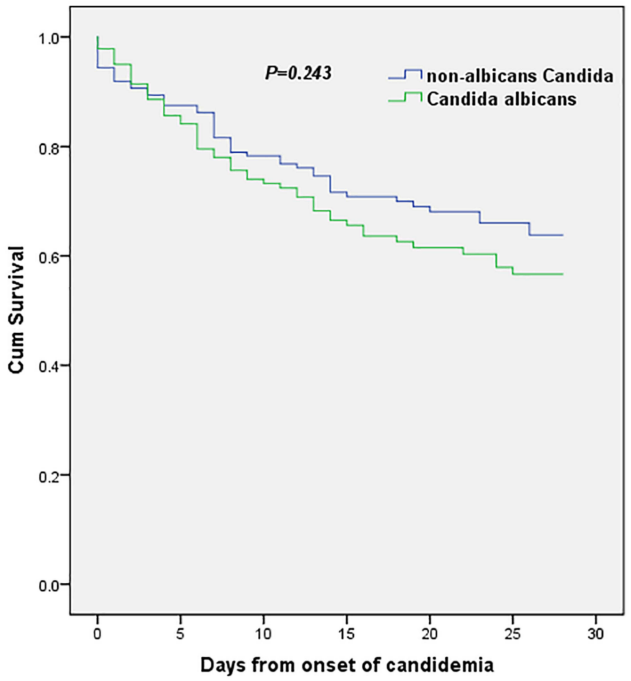

Figure 3 Kaplan-Meier estimates of survival in patients with *C. albicans* candidemia and NAC candidemia.

C. tropicalis isolates had cross-resistance to azoles. A striking result of this study was that the cross-resistance rate of *C. tropicalis* to azoles in hematological malignancy patients with candidemia was up to 90% (Table 4). Globally, the resistance to azoles in *C. tropicalis* mainly occurs in the Asia-Pacific region, while it is still low (less than 10%) in European and American countries.[7,8,23] Previous works have reported several variables that might contribute to high azole resistance among NAC, such as prior exposure to antifungal drugs (especially azoles) or antibiotics, the duration of prior drug exposure or inappropriate dosing.[30,32] Moreover, Fan et al[33] showed that one explanation of the azole resistance in *C. tropicalis* isolates was the ERG11 missense mutations. Since *C. tropicalis* candidemia has been reported to have a higher mortality and a poor prognosis,[34] we should highlight the importance of monitoring antifungal drug resistance in *C. tropicalis* infections. Additionally, echinocandins might be used as an initial treatment for patients who have some risk factors for NAC candidemia, according to the clinical guidelines recommended by the Infectious Diseases Society of America.[19]

In view of the high incidence of *Candida* and the high resistance of antifungal agents, it is important to develop new antifungal agents. In recent years, several studies have found that natural compounds have efficacy against *Candida*.[35–38] Some essential oils extracted from plants have displayed inhibitory effects on the growth and activity of common *Candida* isolates.[35,36,38] UOST5-NPS, a novel anticandidal azole agent based on essential oils, has been developed for the newly emerged *Candida* auris.[37] In addition, amphotericin B combined with *Ruta graveolens* essential oil has also shown synergistic effects against *C. albicans* and *C. tropicalis* in vitro.[36] These results suggest that these natural compounds might provide a new promising strategy against *Candida* infection in the future.

Although some studies have reported worse outcomes for NAC candidemia in comparison with *C. albicans* candidemia,[10,11] few significant differences were observed between these two groups in our current study. (Table 8, Figure 3). This might be partly due to the similar disease severity, similar baseline comorbidities (Table 1), and similar clinical treatments at the onset of candidemia (Table 6) between the two groups.

Notably, some limitations exist in the current study. First, our results were mainly from a single-center study; therefore, they may not represent the trends in the other regions of China. Nevertheless, these data could be used as a reference. Second, although a positive blood sample culture is the gold standard in the diagnosis of candidemia, many patients do not have a positive blood culture result due to its poor sensitivity. Thus, the diagnosis of candidemia might be underestimated. Finally, echinocandins were not included in the drug sensitivity tests in this study, as we could not detect the sensitivity to echinocandins. According to the CHIF-NET study, *Candida* spp. were highly sensitive to echinocandins in vitro.[8]

Conclusion

Together, we have revealed that NACs are dominant in candidemia in our current study. Several factors, including medical admissions, hematological malignancies, antifungal exposure, and the presence of PICC, are closely related to NAC candidemia, whereas prior antifungal exposure is an independent risk factor. Of note, although the outcomes of NAC and *C. albicans* candidemia are similar, drug resistance to specific azoles as well as cross-resistance frequently occurs in patients with NAC candidemia (especially *C. tropicalis*), and this deserves further evaluation in clinical practice and further in-depth investigations.

Abbreviations

(A) *C. albicans, Candida albicans*; NAC, non-*albicans Candida; C. parapsilosis, Candida parapsilosis; C. tropicalis, Candida tropicalis; C. glabrata, Candida glabrata*; spp., species; BSI, bloodstream

infection; IQR, interquartile range; ICU, intensive care unit; CCI, Charlson Comorbidity Index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; CRBSI, catheter-related bloodstream infection; GI, gastrointestinal; TPN, total parenteral nutrition; CVC, central venous catheter; PICC, peripherally inserted central catheter; WBC, white blood count; NC, neutrophil count; LC, lymphocyte count; NLR, neutrophil to lymphocyte ratio; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PCT, procalcitonin; OR, odds ratio; CI, confidence interval; S, susceptible; I, intermediate; R, resistant; RRT, renal replacement therapy.

Data Sharing Statement

All data generated and/or analyzed during the current study are included in this manuscript.

Ethics Approval and Informed Consent

This study received human research ethics approval (NO. 2020-744) from the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. We ensure the confidentiality of patient data and comply with the Helsinki statement. Due to the retrospective nature of the study, the Ethics Committee determined that no patient consent was required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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