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

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Abstract

Background

Candida albicans (*C. albicans*) candidemia were well reported in previous studies, while researches on *Candida non-albicans* (*C. non-albicans*) candidemia remain poorly explored. Therefore the present study was aimed to investigate the clinical characteristics, and outcomes of *C. non-albicans* candidemia.

Methods

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

Results

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

Conclusions

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

Introduction

With widely use of antibiotics, immunosuppressive agents and glucocorticoids, candidemia has become a common bloodstream infection (BSI). It often occurs in patients receiving complex surgery, organ transplantation, intravascular catheters, total parenteral nutrition, hematologic malignancies, and intensive care unit (ICU) hospitalization [1, 2]. To this day, *Candida* species have become the fourth major cause of nosocomial BSIs, right after *coagulase-negative Staphylococcus*, *Staphylococcus aureus*, and *enterococcus* in the U.S. [3]. The prevalence of candidemia varies in different regions [1, 4, 5], ranging from a relatively low occurrence of 0.32/1000 admissions in Southwest China [5] to a high incidence of 2.49/1000 admissions in Brazil [4]. Although a rapid

diagnosis and a timely treatment has been developed currently, the mortality of invasive candidemia is still realatively high, ranging from 22–75% [2, 6, 7].

Regarding fungal infection, *Candida* has been identified as the cause of the commonest fungal infections around the world, of which *Candida albicans* (*C. albicans*) is the main pathogen. However, the epidemiological investigation these years shows that the incidence of *Candida non-albicans* (*C. non-albicans*) in candidemia is increasing year by year, mainly composed of *Candida tropicalis* (*C. tropicalis*), *Candida parapsilosis* (*C. parapsilosis*) and *Candida glabrata* (*C. glabrata*) [6]. In addition, *C. albicans* are highly sensitive to antifungal drugs which is commonly used clinically, while *C. non-albicans* display a steadily rising drug-resistance to them, especially for *C. glabrata* and *C. tropicalis*, which demonstrate a prominent higher drug-resistance to azoles than other *Candida* species [8].

In previous studies, some differences have been reported between *C. albicans* and *C. non-albicans* candidemia in clinical characteristics, strain distribution, antifungal sensitivity and prognostic factors [9–12, 8, 13, 14], but several limitations are shown as followed: (1) Some studies have identified that renal failure and thrombocytopenia were independent risk factors for candidemia related 30-day mortality [13], and neutropenia was a risk factor when it was taken to *C. non-albicans* candidemia [12]. However, whether these factors are stringently different in *C. albicans* and *C. non-albicans* candidemia remain unclear. (2) Patients with *C. non-albicans* candidemia usually had longer ICU stay and higher ICU mortality [10, 12, 14]. As no significant difference was observed in other time points like mortality within 28 days between these two groups [9, 10], whether the clinical outcomes of *C. non-albican*s candidemia are better or worse than *C. albican*s candidemia remains vague. (3) Although the distribution and antifungal resistance of *Candida* species have been well reported in a multi-center large-scale study by China CHIF-NET, more information about demographic and clinical characteristics was lacked which should be needed to draw a valid conclusion [11]. Collectivly, a full picture of detailed clinical characteristics and prognostic factors between *C. albicans* and *C.non-albicans* candidemia in China still remains poorly explored and understood.

Given these differences or controversies like antifungal susceptibility, risk factors and prognostic factors exist between *C. albicans* and *C. non-albicans* candidemia, it is necessary for us to investigate these issues in depth, to improve the cognization and clinical management of candidemia stratified by different *Candida*.

Material And Methods

Study design and patients

The present single-center retrospective study was carried out in a tertiary medical teaching hospital named 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.

Results of 476 positive blood culture samples from microbial laboratory between January 2013 and June 2020 were initially collected (Figure 1). Among them, there were 123 duplicated *Candida* specimens, and the repeated 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; 3) cases data were incomplete or missing. Consequently, 52 patients were excluded, including 1 patient less than 18 years old, 34 patients with nonpathogenic *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 *C. non-albicans* candidemia respectively.

Study variables

The following patients' medical variables were retrieved from the electronic medical record system, including basic information like age, sex, previous medical history, and several assessments [e.g. Charlson Comorbidity Index (CCI) score, APACHE II score and sequential organ failure assessment (SOFA) score within 24 hours after *Candida* BSI]. Other information including invasive procedures, previous exposure, previous treatment (such as surgery, chemotherapy drugs, radiotherapy, immunosuppressive agents, mechanical ventilation, blood purification, blood transfusion), laboratory examinations (e.g. blood cells, liver function, and kidney function), and the microbiological data (*Candida* species, concomitant bacterial infection or not, antifungal susceptibilities and cross-resistance to azoles *in vitro*) were also documented. In addition, the main treatment data after the occurrence of candidemia, such as fluid resuscitation, vasoactive drugs, renal replacement therapy and antifungal drugs and the outcomes like mortalities of 14 days, 28 days and 60 days were collected as well.

*Candida*species and antifungal susceptibility testing

Candida species and drug susceptibility testing were conducted as described as our previous study [15]. 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* species. After species confirmation, all *Candida* were subject to antifungal susceptibility test using ATB FUNGUS 3 panel of bioMerieux company in France. Experimental assessments of drug susceptibility for *Candida* were based on the clinical breakpoints specified in Clinical Laboratory Standards Institute [16,17].

Study definitions

Candidemia was diagnosed as the isolation of at least one species of *Candida* from blood cultures accompanied by infection symptoms and signs. The definition of catheter-related candidemia guided on the basis of Infectious Diseases Society of America: 1) Catheter tip culture was proved to be identical to at least one percutaneous peripheral blood culture; or 2) the transcatheter and peripheral blood samples were cultured to the same *Candida* species, and met the catheter-related bloodstream infection (CRBSI) criteria [18]. The diagnostic criteria for septic shock referred to the definition of Sepsis-3 [19]. When blood bacterial culture was positive before or within 48 hours after the onset of candidemia, it would be considered to be a concomitant bacteremia [5], except for those common skin microbiota (e.g., *Corynebacterium* spp., *Streptococci*, *Bacillus* spp., *Coagulase-negative staphylococci* and *Lactobacillus* spp.), which was possible contaminants. Unless two or more consecutive venipuncture samples had the above microorganisms, it would be considered pathogens [20,15]. The antifungal treatment was considered adequate, if: (1) antifungal agent was administered empirically within the first 48 hours of positive culture; (2) the *Candida* isolates were sensitive to the selected antifungal drugs *in vitro* test; and (3) the dosage of antifungal drugs was selected according to the the clinical guideline recommended by Infectious Diseases Society of America [21,22].

Statistical analysis

All statistical analyses were performed using the statistical package SPSS 23.0 (IBM Corp, Armonk, NY, USA), and $P<0.05$ was considered statistically significant. First all quantitative data were first tested for normality. If the test

results conformed to the normal distribution, the mean±standard deviation was used to represent the continuous variable, otherwise the median and interquartile range (IQR) were used instead. Then, the Student's t-test or Mann-Whitney U was used for comparison. All enumeration data were represented as N(%), and chi-square test was used for comparison between the two groups. In univariate analysis, the variables with a significant $P<0.05$ level were considered as candidate variables for establishing stepwise logistic regression multivariate model. The 28-day survival curves of *C. albicans* and *C. non-albicans* candidemia was depicted by Kaplan-Meier survival analysis, and the difference was detected by log-rank test.

Results

Patient characteristics

Table 1 outlined the baseline characteristics of recruited patients. The median age of these patients was 66 years (IQR, 53.0-75.5), and 64.1% (193/301) were male. 66.4% (200/301) of all candidemia occurred at an age of elder than 60 years old. The proportion of patients over 60 years of age with *C. non-albicans* 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 ICU (64.5%), followed by surgical wards (20.9%) and medical wards (14.6%), and 91.0% (274/301) of these candidemia were nosocomial infection. In terms of comorbidities, gastrointestinal (GI) disease (31.9%), solid tumor (23.6%), 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. 28.6%, $P<0.05$) were observed in *C. non-albicans* candidemia, but more of hematological malignancies (6.8% vs. 0.7%, $P<0.05$) in comparison with *C. albicans* candidemia. There were no statistical significances between the two group in terms of CCI score, APACHE II score and SOFA score among all patients (all $P>0.05$) (Table 1). The percentage of antibiotic exposure before the onset of candidemia was up to 86.0%, followed by parenteral nutrition (TPN) and surgery with more than 50%. Compared to *C. albicans* candidemia, patients with *C. non-albicans* candidemia had a lower rate of surgery (47.2% vs. 67.9%, $P<0.001$), especially for abdominal surgery (14.3% vs. 34.3%, $P<0.001$). This result was consistent with the fact that most *C. albicans* candidemia were from surgical wards (26.4% vs. 16.1%, $P<0.05$). In contrast, patients with *C. non-albicans* candidemia were more 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 central venous catheter (CVC), urinary catheter, and gastric catheter. Compared with the catheterization of *C. albicans* candidemia, indwelling arterial catheter and CVC were less in patients with *C. non-albicans* candidemia (26.7% vs. 39.3%, 67.1% vs. 84.3% respectively, both $P<0.05$), and so did abdominal drainage tube indwelling (13.7% vs. 32.1%, $P<0.001$). However, presence of peripherally inserted central catheter (PICC) was more frequent in *C. non-albicans* candidemia (24.8% vs. 10.7%, $P<0.05$).

Biological parameters

In terms of biological parameters, patients with *C. non-albicans* candidemia had a higher percentage of 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 × 10^9/L, 7.0 vs. 8.6), a lower neutrophil to lymphocyte ratio (NLR) (median, 9.2 vs. 12.3), and a lower value of total bilirubin (TB) (median μmol/L, 15.0 vs. 18.5) (all $P<0.05$) in comparison with *C. albicans* candidemia (Table 2).

Independent risk factors for *C. non-albicans* candidemia

Several variables with a significant $P<0.05$ level in univariate analysis were described in Table 4. After multivariate regression model analysis of these variables, prior antifungal exposure as a factor was independently associated with an increased risk of *C. non-albicans* candidemia (aOR, 0.312; 95% CI, 0.113-0.859). In terms of diabetes mellitus, it had higher risk in *C. albicans* candidemia than *C. non-albicans* candidemia (aOR, 2.267; 95% CI, 1.186-4.334).

Species distribution

A total of 301 patients with candidemia were recruited in this study, composed of *C. albicans* candidemia (46.5%) and *C. non-albicans* candidemia (53.5%). In *C. non-albicans* candidemia, the main species were *C. tropicalis*、*C. parapsilosis* and *C. glabrata*, accounting for 23.9%, 15.6%, and 10.3%, respectively. In terms of 12 hematological malignancy patients with candidemia, more than 90% (11/12) were caused by *C. non-albicans*, especially for *C. tropicalis* (10/12, 83.3%). The specific distribution of *Candida* species was shown inTable 7 and Figure 2.

In vitro susceptibilities

As seen from Table 4, *C. non-albicans* in patients with candidemia displayed higher resistance to common antifungal drugs than *C. albicans*. Particularly, *C.tropicalis* had high resistance rates to clotrimazole (68.6%), itraconazole (45.6%), fluconazole (50.0%), voriconazole (56.5%), whereas they were all less than 3% for *C. albicans* to these above four drugs. Both *C. albicans* and *C. non-albicans* showed a low resistance (less than 2.0%) to amphotericin B (Table 4).

In general, the resistance rate to ketoconazole (26.6%) was highest, followed by clotrimazole (23.5%), fluconazole (14.5%), and voriconazole (13.1%) (Table 5). In terms of specific azoles, they showed differences dependent on different species of *Candida*. *C. albicans* were sensitive to azoles, but that was apparently not the case for *C. non-albicans* as most of them were resistant to these azoles like fluconazole, voriconazole, and clotrimazole with a high rate of more than 50% (Table 5). Of note, 14.6% (44/301) of patients with candidemia occurred cross-resistance, especially for *C. tropicalis* among which the cross-resistance to azoles was as high as 50.0% (36/72). Among hematologic malignancies patients with *C. tropicalis*, the cross-resistance rate was even up to 90% (9/10) (Table 7). Besides *C. tropicalis, C. glabrata* was more prone to cross-resistance (9.7%) (Table 7). .

Clinical therapy

The details about clinical features and treatments at the onset of candidemia were shown in Table 6, which indicated significant differences in renal replacement therapy, source of infection (intra-abdomem), and antifungal resistance between the two types of candidemia. 10.6% of patients with *C. non-albicans* received renal replacement therapy, which was almost three times of patients with *C. albicans* (P=0.020). The mainly identified source of candidemia was from catheter-related candidemia (33.2%, 100/301) and from intra-abdominal infection (13.0%, 39/301), whereas 42.9% (129/301) candidemia were considered as primary infection as no obvious infection sources were confirmed. In further comparison, patients with *C. non-albicans* candidemia had less intraperitoneal source 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 catheters was 73.0% (73/100), though no statistical difference was found between these two groups. Regarding adequate antifungal treatment, the ratio of it in patients with *C. non-albicans* candidemia *was* similar to that in patients with *C. albicans* candidemia (31.7% vs. 34.1%, $P>0.05$), but both of them were below 50%. In addition, pyrroles antifungal agents

were more used in patients with *C. non-albicans*, while echinocandins antifungal agents were more frequently applied for *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 *C. non-albicans* candidemia had a longer ICU stay and a longer total hospitalization in comparison 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 they did not obtain a statistical significance. Furthermore, no significant differences were noted about the mortalities of 14 days, 28 days and 60 days between these two groups, which were 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, *C. non-albicans* species (i.e. *C. tropicalis*, *C. paraplanatus* and *C. glabrata*) accounted for 53.5% (161/301) of candidemia. Therefore, more attention should be paid for *C. non-albicans* infections in daily work. Second, several risk factors for *C. non-albicans* candidemia were found including medical admission, haematological malignancy, prior antifungal exposure, and presence of PICC. Particularly, prior antifungal exposure constitutes one of the most pivotal independent risk factor for *C. non-albicans* candidemia, different than diabetes mellitus for *C. albicans* candidemia. Moreover, *C. albicans* remains highly susceptible to most antifungal agents (including azoles), *C. non-albicans* shows strinkly different response to azoles, especially for *C.* tropicalis which had a high cross-resistance to azoles treatment. Lastly, no significant differences in clinical outcomes were observed between these two groups.

To date, numerous studies have specifically described the epidemiology of candidemia based on demographic surveys around the world [11,23,24]. As expected, the four major pathogens of candidemia were *C. albicans*, *C. tropicalis*, *C. glabrata* and *C. paraplanatus*, which accounted for 94.3% of all *Candida* species in this study (Figure 2). *C. non-albicans* spp. collectively represented 53.5% of the bloodstream isolates, which was consistent with the results from northern China, Asia-Pacific and European countries [25,24,26]. Concerning *C. non-albicans* candidemia, it is worth noting that *C. tropicalis* has become a common *C. non-albicans* species worldwide. In this study, *C. tropicalis* was the second-ranked species, accounting for 23.9%. This ratio was lower than the species in Asia Pacific (30.7%), but higher than that in northern China (18.7%), Latin America (12%) and Europe (6%) [11,26,27]. The epidemiological difference in species for candidemia might vary with patient's age, geographical area, medical practice and use of antifungal drugs. The prevalence of *C. non-albicans* candidemia has extensively increased over time, which is generally associated with reduced antifungal sensitivity resulting from the widespread use of azole [28,25,11,23]. Other possible explanations may include the increased number of immunocompromised patients, the growing use of invasive procedures, and the improvement of yeast isolation technique at the species level[1,25,14]. However, the underlying mechanism causing the epidemiological changes of *C. non-albicans* species in candidemia remains uncertain.

Regarding common risk factors for *C. non-albican* candidemia, consisting ofthere included medical admissions, hematological malignancies, antifungal exposure, and presence of PICC (Table 1). Other studies have found that hematological malignancies and prior exposure to antifungal agents were factors closely related to *C. non-albicans* candidemia in comparison with *C. albicans* candidemia [29-32], which echoes our study. Among

hematological malignancy patients with candidemia, *C. non-albicans* were the main type of invasive *Candida* infection, in which *C. tropicalis* accounted for 90.9% (10/11) (Table 7). Some other studies also showed that *C. tropicalis* was the commonest *C. non-albicans* species in haematological malignancy complicated with candidemia [33,34]. This peculiar epidemiology might be explained by the increased invasiveness of *C. tropicalis* in the human gastrointestinal tract, especially in patients with immunocompromised haematological malignancy [35]. Furthermore, a high proportion of antifungal exposure before candidemia (36.7%) was observed in these patients, which might be partly responsible for the species' migration to *C. non-albicans*. However, haematological malignancy were not independently associated with *C. non-albicans* candidemia after multivariate regression (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 multivariate regression, prior antifungal exposure as a factor was independently associated with an increased risk of *C. non-albicans* candidemia, while diabetes mellitus was for *C. albicans* candidemia (Table 3). However, it remains unknown whether patients with both risk factors of diabetes and prior antifungal exposure are likely to develop mixed BSIs of *C. albicans* and *C. non-albicans*, 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 [11,8], the increasingly prevalence of *C. non-albicans* species and their associated reduced antifungal sensitivity have become a main challange in candidemia treatment [28,25,23]. In the current study, *C. non-albicans* demonstrated significantly higher resistance to fluconazole, voriconazole, itraconazole and clotrimazole (all $P<0.05$), especially for *C. tropicalis* (Table 5 and 6). We observed that the rate of azoles resistance in *C. tropicalis* was over 35%, which was consistent with the high resistance rate in the CHIF-NET study [11]; Furthermore, 50% (36/72) of *C. tropicalis* isolates had cross-resistance to azoles. A striking result of this study was that the drug cross-resistance rate of *C. tropicalis* to azoles in hematological malignancy patients with candidemia was up to 90% (Table 8). Globally, the resistance to azoles in *C. tropicalis* was mainly occurred in Asia Pacific region, while it is still low (10%) in European and American countries [11,26]. Previous works have reported several variables that might contribute to high azole resistance among *C. non-albicans,* such as prior exposure to antifungal drug (especially azoles) or antibiotics, the duration of prior drug exposure or inappropriate dosing [34,36]. Moreover, Fan *et al* [37] have shown that the related mechanism of *C. tropicalis* isolates responsible for azole resistance was the ERG11 missense mutations. Since *C. tropicalis* candidemia has been reported with a higher mortality and poor prognosis [38], we should highlight the importance of monitoring antifungal drug resistance in *C. tropicalis* infection. Additionally, echinocandins might be used as initial treatment for those patients who have some risk factors for *C. non-albicans* candidemia, according to the clinical guideline recommended by Infectious Diseases Society of America [22].

Although some studies have reported worse outcomes for *C. non-albicans* candidemia in comparison with *C. albicans* candidemia [10,12,14], in our current studies, few significant differences were observed between these two groups. (Table 8, Figure 3). This might be partially due to similar disease severity, similar baseline comorbidities (Table 1), and similar clinical treatments at the onset of candidemia (Table 6).

Notably, some limitations exist in the current study. First, our results were mainly from a single-center study therefore it could hardly represent the popular trend in other regions of China. Nevertheless, it could be used as a reference. Second, although a positive blood sample culture is the gold standard for diagnosis of candidemia, many patients could not be detected due to its poor sensitivity. Thus, the evaluation of candidemia might be underestimated. Finally, echinocandins were not included in the drug sensitivity in this study as we could not

detect the sensitivity to echinocandins. According to the CHIF-NET study, echinocandins were highly sensitive to *Candida* species *in vitro* [11].

Conclusion

Together, in our current study, we have revealed that the clinical outcomes between *C. non-albicans* and *C. albicans* candidemia are relatively similar. *C. non-albicans* are dominant in candidemia. Additionally, we have observed that more medical admissions, hematological malignancies, antifungal exposure, and presence of PICC are closely related to *C. non-albicans* candidemia. Particularly, prior antifungal exposure as a factor is independently associated with an increased risk of *C. non-albicans* candidemia. Of note, the resistance to specific azoles as well as the cross-resistance more frequently occurs in patients with *C. non-albicans* candidemia (especially *C. tropicalis*), which deserves further in-depth investigation.

Abbreviations

Albicans: *Candida albicans*; *C. non-albicans*: *Candida non-albicans*; *C. Parapsilosis*: *Candida parapsilosis*; *C. Tropicalis*: *Candida tropicalis*; *C. Glabrata*: *Candida glabrata*; BSIs: bloodstream infections; IQR: interquartile range; ICU: intensive care unit; HIV□human immunodeficiency virus; CCI: Charlson Comorbidity Index; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; GI: gastrointestinal; TPN: total parenteral nutrition; CVC: central venous catheter; WBC: white blood count; NC: neutrophil count; LC: lymphocyte count; NLR: neutrophil to lymphocyte ratio; TB: total bilirubin; AST: aspartate aminotransferase; SCr: serum creatinine; BUN: blood urea nitrogen; PCT: procalcitonin; CRP: C-reactive protein; S: susceptible; I: intermediate; R: resistant; RRT: renal replacement therapy

Declarations

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Not applicable.

Authors' contributions

GZ and WC designed the study, revised the manuscript and approved the version to be published finally; FL, LZ and FZ collected / analyzed the data and wrote the manuscript; CZ, KZ, JC, HZ, KT and ZD collected and analyzed the data. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

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.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1
Baseline characteristics of patients with *C. albicans* and *C. non-albicans* candidemia

Characteristics	Total (n = 301)	*C. albicans* (n = 140)	*C. non-albicans* (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

*P < 0.05, **P < 0.001

Abbreviations: *C. albicans*, *Candida albicans*; *C. non-albicans*, *Candida non-albicans*; 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.

Characteristics	Total (n = 301)	*C. albicans* (n = 140)	*C. non-albicans* (n = 161)	*P*-value
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, n(%)	26(8.6%)	6(4.3%)	20(12.4%)	0.012*
Prior antibiotics exposure, 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
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

***P < 0.05, ****P < 0.001

Abbreviations: *C. albicans*, *Candida albicans*; *C. non-albicans*, *Candida non-albicans*; 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 *C. non-albicans* candidemia

Variables	Total (n = 301)	C.albicans (n = 140)	C.non-albicans (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

*P < 0.05

Abbreviations: *C. albicans*, *Candida albicans*; *C. non-albicans*, *Candida non-albicans*; 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.

Table 3
Multivariable logistic regression of risk factors caused by *C. albicans* vs. *C. non-albicans* 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

*P < 0.05

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

Table 4
Comparison of antifungal susceptibility of different *Candida* species *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%)
C. non-albicans (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%)

Species (n)	Antifungal agent	S, n(%)	I, n(%)	R, n(%)
	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* species[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*; *C. non-albicans*, *Candida non-albicans*; *C. tropicalis*, *Candida tropicalis*; *C. parapsilosis*, *Candida parapsilosis*; *C. glabrata*, *Candida glabrata*.

Table 5
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%)
C. non-albicans (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*; *C. non-albicans*, *Candida non-albicans*; *C. tropicalis*, *Candida tropicalis*; *C. parapsilosis*, *Candida parapsilosis*; *C. glabrata*, *Candida glabrata*.

Table 6
Clinical features and treatments of patients with *C. albicans* or *C. non-albicans* at the onset of candidemia

Clinical features and treatments	Total (n = 301)	*C. albicans* (n = 140)	*C. non-albicans* (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

*P < 0.05, **P < 0.001

Notes: [a]The source of infection could not be identified or primary infection; [b]The number in parenthese represented the total number of *Candida* species with intravascular catheters. [c]The number in parenthese represented the total number of *Candida* species with catheter removal. [d]Not all agents listed have been tested in all isolated species. [e]The numbers in parentheses represented the total numbers of *Candida* species performed susceptibility test.

Abbreviations: *C. albicans*, *Candida albicans*; *C. non-albicans*, *Candida non-albicans*; RRT, renal replacement therapy; IQR, interquartile range.

Clinical features and treatments	Total (n = 301)	*C. albicans*(n = 140)	*C. non-albicans* (n = 161)	*P*-value
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
*P < 0.05, **P < 0.001				

Notes: [a]The source of infection could not be identified or primary infection; [b]The number in parenthese represented the total number of *Candida* species with intravascular catheters. [c]The number in parenthese represented the total number of *Candida* species with catheter removal. [d]Not all agents listed have been tested in all isolated species. [e]The numbers in parentheses represented the total numbers of *Candida* species performed susceptibility test.

Abbreviations: *C. albicans*, *Candida albicans*; *C. non-albicans*, *Candida non-albicans*; RRT, renal replacement therapy; IQR, interquartile range.

Table 7
Distribution of *Candida* species, 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%)
C. non-albicans (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%)

Note: [a]Cross-resistance was defined as resistance to any two or more of the above azoles.

Abbreviations: *C. albicans*, *Candida albicans*; *C. non-albicans*, *Candida non-albicans*; *C. tropicalis*, *Candida tropicalis*; *C. krusei*, *Candida krusei*.

Table 8
Outcomes of patients with *C. albicans* and *C. non-albicans* candidemia

Outcomes	Total (n = 301)	*C. albicans* (n = 140)	*C. non-albicans* (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*; *C. non-albicans*, *Candida non-albicans*; ICU, intensive care unit; M, median; IQR, interquartile range.

Figures

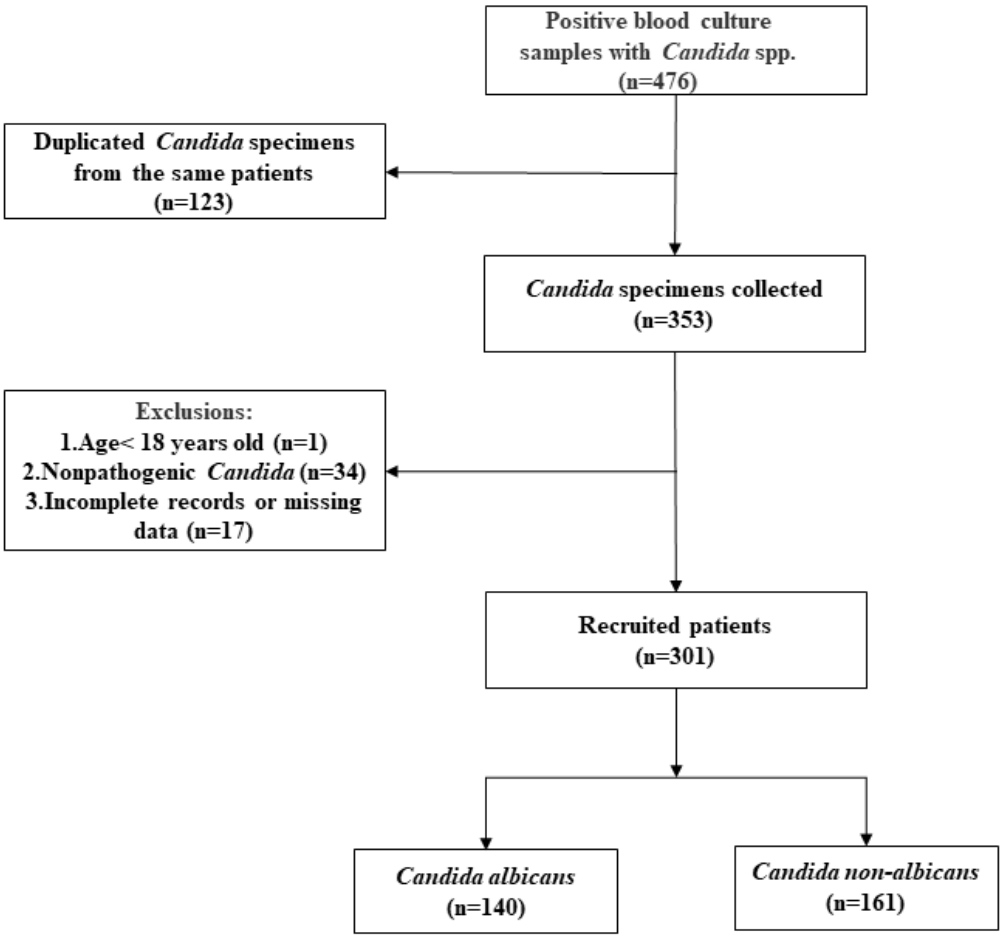

Figure 1

Flow diagram of patient recruitment

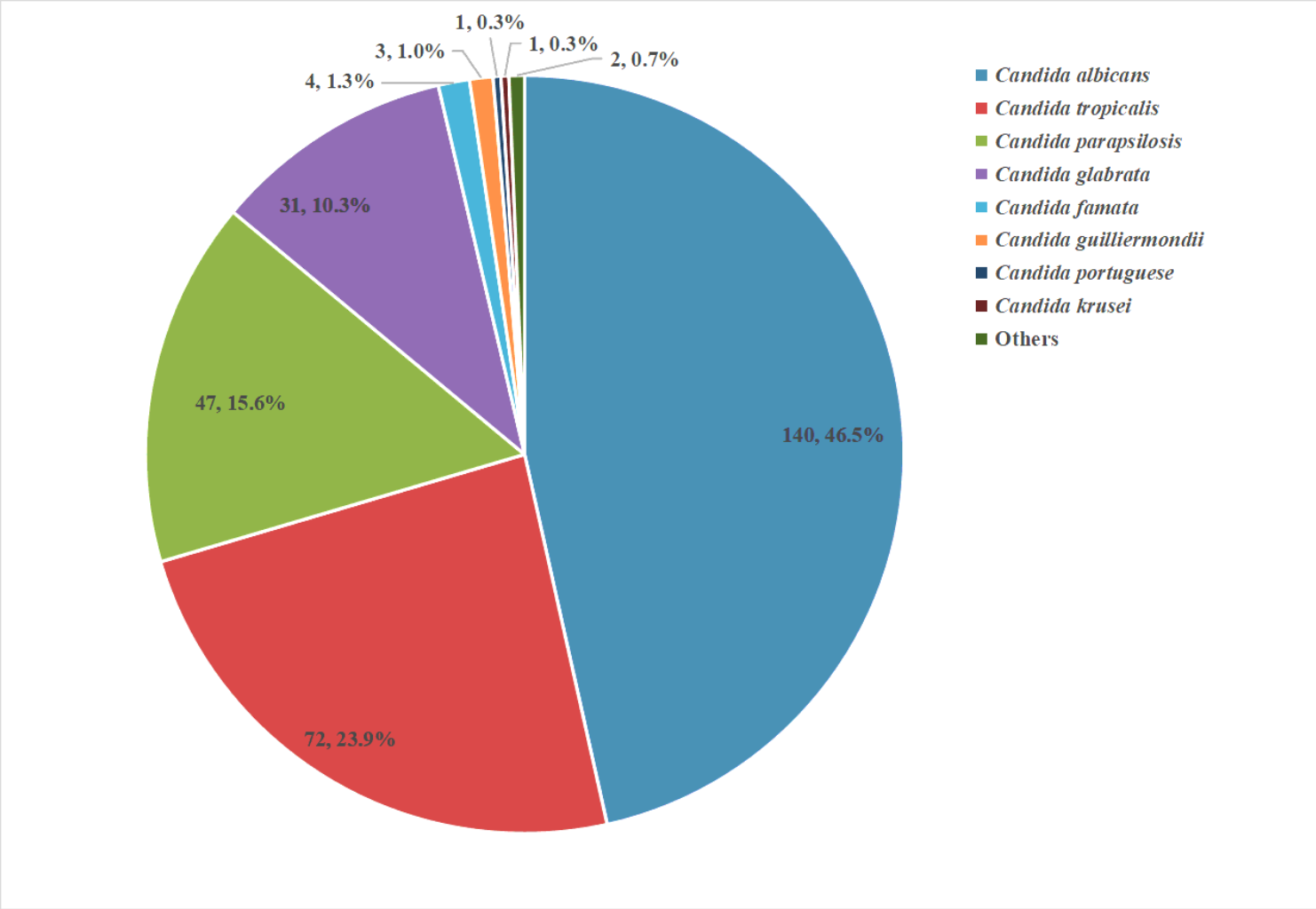

Figure 2

Distribution of different Candida species during this candidemia study period

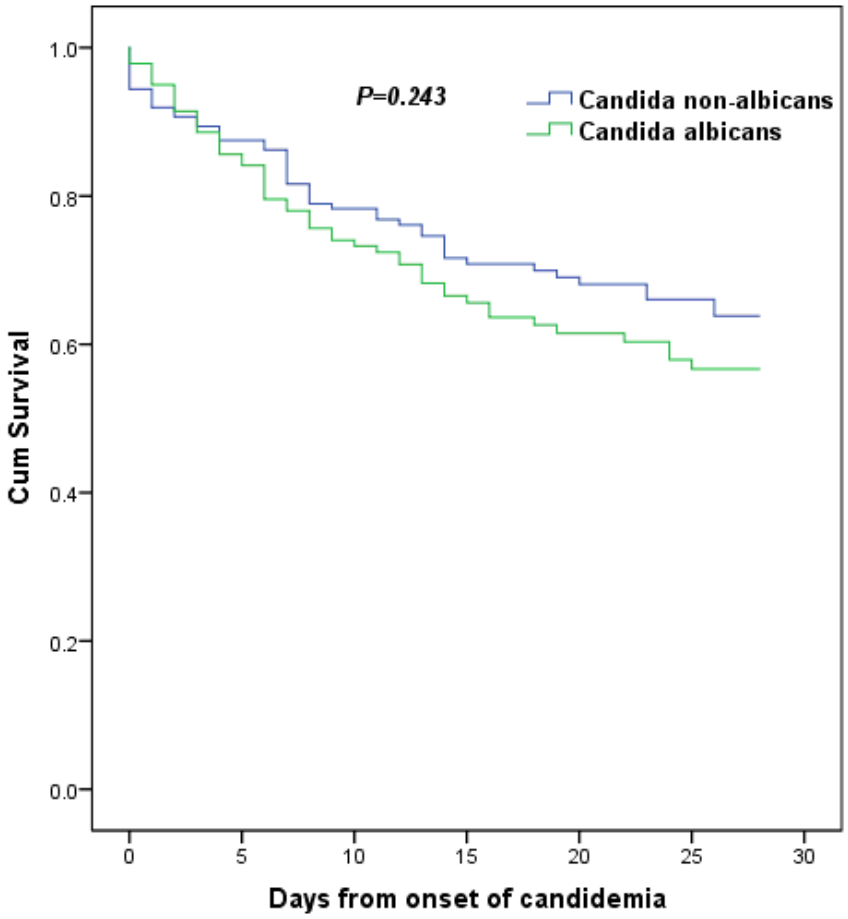

Figure 3

Kaplan-Meier estimates of survival in patients with C. albicans and C.