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Original Article

Importance of *Candida* species isolated from blood culture: Distribution, antifungal susceptibility, mortality

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Abstract

Objective: Candidemia is a bloodstream infection arising from *Candida* species that is difficult to diagnose and treatment. Despite advancements in antifungal therapy, candidemia still causes high-mortality rates, prolonged hospital stays and increased healthcare costs. The purpose of this study was to analyze the *Candida* species distribution, antifungal susceptibility, and mortality rate of isolates from candidemia patients in a tertiary city hospital.

Methods: We designed a retrospective observational study of hospitalized patients with candidemia. Data were collected from the medical records of 39 patients with positive blood culture candidemia cases between November 2018 and February 2020 at a city hospital.

Results: *Candida albicans* was the predominant species (n=17; 43.6%) followed by the *Candida glabrata* complex (n=13; 33.3%), *Candida parapsilosis* complex (n=8; 20.5%), and *Candida kefyr* (n=1; 2.6%). The *C. glabrata* complex was the predominant species among the NAC. All *Candida* isolates were susceptible to fluconazole, voriconazole and amphotericin B. Overall, the level of antifungal resistance was low. *C. albicans*, *C. parapsilosis* complex and *C. kefyr* isolates did not show resistance. The mortality rate attributed to all cases within 30 days after candidemia was found to be higher in NAC: *C. glabrata* complex (84.6%), *C. parapsilosis* complex (75.0%). and *C. kefyr* (100.0%). The mortality rate of the 39 patients was 69.2%.

Conclusion: Candidemia is an emerging problem in developing countries and is a significant source of mortality, morbidity, and likely high costs associated with care in hospitalized patients in Turkey.

Keywords: Antifungal resistance, candidemia, invasive candidiasis, non albicans *Candida*.

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INTRODUCTION

Candida species are commensals found on humans' normal microflora of the gastrointestinal, genitourinary tracts and skin. These microorganisms are important causative organisms of superficial and invasive fungal infections (IFIs) worldwide (1). Among these IFIs, candidemia is a bloodstream infection arising from *Candida* species that is difficult to diagnose and treat. Despite advancements in antifungal therapy, candidemia still causes high-mortality rates, prolonged hospital stays and increased healthcare costs (2). The incidence of candidemia has steadily increased, and the distribution of species has changed over the last few decades. Epidemiological studies have indicated that although *C. albicans* is still the most frequently seen pathogen, its incidence is decreasing in comparison to that of non-albicans *Candida* (NAC) species, especially the *C. glabrata* complex and *C. parapsilosis* complex (3).

On the one hand, several factors, such as different antimicrobial consumption strategies, infection control policies, hospital bed size, demographic characteristics, different geographies and differences in patients admitted for invasive procedures with prolonged lengths of stay, have a significant effect on the epidemiology of candidemia. On the other hand improvements in the diagnostic methods available for the identification of *Candida* species have become important factors explaining the finding of an increased prevalence of candidemia due to NAC species (4). The use of broad spectrum antibiotics, immunosuppressive drugs, and medical devices such as central venous catheters (CVCs), prolonged hospitalization, intensive care unit (ICU) stay, history of intraabdominal surgery, diabetes mellitus, and administration of total parenteral nutrition (TPN) are the most common predisposing risk factors for candidemia (5).

Correct management of candidemia is crucial for the prognosis of patients and decreasing mortality rates. To improve and update preventative and empirical treatments, it is crucial to monitor trends in incidence and species distribution. As mentioned in some previous studies, inititating an early antifungal treatment is crucial to improve survival and decrease mortality in candidemia. Despite improvements in the diagnosis, treatment and prevention of invasive candidiasis, early diagnosis and treatment are still difficult due to nonspecific clinical manifestations. However it is important to apply species-level identification and antifungal susceptibility tests on all bloodstream *Candida* isolates to determine appropriate and effective antifungal therapy (6).

The purpose of this retrospective study was to analyz the *Candida* species distributions, antifungal susceptibility and mortality rates of isolates from candidemia patients in a tertiary city hospital.

MATERIALS AND METHODS

This is a retrospective study that was conducted in accordance with the Helsinki Declaration. We conducted it after receiving the permission of the Ethical Committee of the Noninvasive Clinical Research Ethics Committee of the Eskişehir Osmangazi University (02.18.2020-24).

Study design

We designed a retrospective descriptive study of hospitalized patients with candidemia. Data were collected from the medical records of 39 patients at a local hospital who had positive blood culture candidemia cases between November 2018 and February 2020. Our hospital, having a total bed capacity of 1185, has 171 (113 adult and 58 neonatal) beds in the intensive care unit. In patients with recurrent candidemia, we only counted the first instance; however, if candidemia persisted for longer than 30 days, it was considered a new occurrence.

Blood samples were incubated in a BacT/Alert 3D (bioMerieux, Marcyl'Etoile, France) automated blood culture system according to the manufacturer's instructions with a standard incubation period of five days. After the automated alert system, signals of positive blood culture subcultures were performed from blood culture bottles to Sabouraud dextrose agar (RTA, Turkey). Each plate was incubated at 35 °C for 24–48 h.

Mycological identification

Fungal species identification was performed using conventional and commercial methods. The isolates were identified by the germ tube test, morphological images obtained from the Tween 80 cornmeal agar, the capability of growth at 45 °C, urea hydrolysis, tolerance for 0.1% cycloheximide, as well as commercial methods, such as

CHROM agar *Candida* medium (RTA, Turkey) and VITEK 2 Compact (bioMérieux, France).

Antifungal susceptibility testing

All isolates were tested for susceptibility. The antifungal susceptibility of *Candida* isolates was determined by using a VITEK 2 Compact (bioMérieux, France) automated system and AST-YS08 cards. Minimum inhibitory concentration (MIC) results were interpreted according to clinical breakpoints (CBP) as established in the Clinical and Laboratory Standards Institute (CLSI) for antifungal agents.

Candida parapsilosis complex ATCC 22019 and *Candida albicans* ATCC 24433 were used as quality control strains. The interpretive breakpoints for *Candida* spp. are based on the CLSI M27-S4 Informational Supplement and the reagent instructions of the VITEK 2 Compact (bioMérieux, France) system.

RESULTS

A total of 39 non duplicate candidemia cases were identified between November 2018 and February 2020. Candidemia isolates consisted of mixed populations including clinical and intensive care units.

Species distribution and antifungal susceptibility patterns

C. albicans was the predominant species (n=17; 43.6%) followed by the *C. glabrata* complex (n=13; 33.3%), *C. parapsilosis* complex (n=8; 20.5%) and *C. kefyr* (n=1; 2.6%).The *C. glabrata* complex was the predominant species among the NAC. Table 1 presents the distribution *Candida* species isolated from patients with candidemia.

Table 1. Distribution of *Candida* species and mortality rate

Species	Species		Mortality	
Name	N	%	n	%
Candida albicans	17	43.6	9	53.0
Candida glabrata complex	13	33.3	11	84.6
Candida parapsilosis complex	8	20.5	6	75.0
Candida kefyr	1	2.6	1	100.0
Total	39	100.0	27	69.2

According to the species specific CBP, all *Candida* isolates were susceptible to fluconazole (FLC), voriconazole (VRC) and amphotericin B (AMB). *C. glabrata* complex strains were not subjected to a test of FLC and VRC susceptibility.

All *Candida* isolates were susceptible to echinocandins except the *C. glabrata* complex. However, four isolates of the *C. glabrata* complex were resistant to caspofungin (CAS), six isolates of the *C. glabrata* complex were intermediately susceptible to CAS and one isolate of the *C. glabrata* complex was intermediately susceptible to micafungin (MCA).

Table 2 shows the results of in vitro susceptibility testing (MIC, MIC_{50}, MIC_{90} and GM) of five antifungals against *Candida* isolates.

For *C. albicans* species, antifungal geometric means were 0.52 µg/mL, 0.15 µg/mL, 0.12 µg/mL, 0.06 µg/mL, and 0.61 µg/mL for FLC, VRC, CAS, MCA and AMB, respectively.

For *C. glabrata* complex species, the antifungal geometric means were 0.26 µg/mL, 0.06 µg/mL, and 0.5 µg/mL for CAS, MCA and AMB, respectively.

For *C. parapsilosis* complex species, antifungal geometric means were 0.6 µg/mL, 0.12 µg/mL, 0.38 µg/mL, 0.46 µg/mL, and 0.6 µg/mL for FLC, VRC, CAS, MCA and AMB, respectively.

Overall, the level of antifungal resistance was low. *C. albicans, C. parapsilosis* complex and *C. kefyr* isolates did not

show resistance, but all showed the WT phenotype for all antifungal drugs tested.

We found high CAS resistance rates among *C. glabrata* complex isolates (30.77%).

Table 2. Invitro susceptibilities of *Candida spp*. to fluconazole, voriconazole, caspofungin, micafungin and amphotericin B as determined by VITEC 2 broth microdilution method

Species	Antifungal (µg/mL)	MIC	MIC50	MIC90	GM
Candida albicans (n=17)	Fluconazole	(0.50-1.00)	0.5	0.5	0.52
	Voriconazole	(0.12-0.50)	0.12	0.5	0.15
	Caspofungin	(0.12-0.25)	0.12	0.12	0.12
	Micafungin	(0.06-0.06)	0.06	0.06	0.06
	Amphotericin B	(0.50-1.00)	0.5	1	0.61
Candida glabrata complex (n=13)	Fluconazole	-	-	-	-
	Voriconazole	-	-	-	-
	Caspofungin	(0.12-0.50)	0.25	0.5	0.26
	Micafungin	(0.06-0.12)	0.06	0.06	0.06
	Amphotericin B	(0.06-8.00)	0.5	0.5	0.5
Candida parapsilosis complex (n=8)	Fluconazole	(0.50-1.00)	0,5	1	0.6
	Voriconazole	(0.12-0.12)	0.12	0.12	0.12
	Caspofungin	(0.12-1.00)	0.5	0.5	0.38
	Micafungin	(0.06-1.00)	0.5	1	0.46
	Amphotericin B	(0.25-4.00)	0.5	0.5	0.6

Abbreviations: MIC: Minimal Inhibitory Concentration, GM: Geometric Mean

**Candida kefyr* (n=1).

Patient characteristics

The patients' medical records were examined to evaluate the available risk factors. The mean age of the patients was 58 years (range 0 to 87 years). To assess the potential risk factors, patient medical data were reviewed. The most predominant risk factor was the presence of a CVC (n=33; 84.6%), previous antibiotic treatment (n=28; 71.8%) and TPN (n=16; 41.0%), followed by underlying diseases: diabetes mellitus (n=13; 33.3%), and previous intra-abdominal surgery (n=8; 20.5%). cancer (n=6; 15.4%) and renal disease (n=6; 15.4%). Table 3 presents patient characteristics and underlying risk factors.

CVC was present in 33 of the patients. The distribution of the agents in patients with catheters was as follows: *C. parapsilosis* complex 8 (8/8; 100.0%), *C. kefyr* 1 (1/1; 100.0%), *C. albicans* 15 (15/17;88.2%), and *C. glabrata* complex 9 (9/13; 69.2%).

The study population included 39 candidemia cases that predominantly occurred in adult patients (n=31; 79.5%). Of these, 20 cases (51.3%) were in elderly patients (age ≥ 65 years). Additionally, males were the predominant sex among all patients (n=23; 59.0%).

Most cases of candidemia occurred in patients hospitalized in the ICU (31/39; 79.49%), followed by medical and surgical services (7/39; 17.9% and 1/39; 2.6%). Table 4 shows the species distribution of candidemia cases by main hospital wards.

The majority of patients in the current study had at least one comorbid disease at the onset of candidemia. Among the invasive devices placed prior to infection, patients with candidemia were more likely to have received an indwelling central venous catheter (n=33; 84.6%), urinary catheter (n=28; 71.8%) and total parental nutrition (n=16; 41.0%).

In the present study, five of the six patients with chronic renal failure had also diabetes mellitus, which constitutes a risk factor for invasive fungal infection. The most prevalent underlying disease was diabetes mellitus (n=13; 33.3%). The majority of patients (n=33; 84.62%,) had a CVC at candidemia diagnosis.

Table 3. Characteristics of the patients

	Number of cases (n)	Percentages (%)
Sex		
Male	23	59
Female	16	41
Procedure applied		
Central venous catheter	33	84.6
Total parenteral nutrition	16	41.0
Urinary catheter	28	71.8
Associated conditions		
Previous antibiotic treatment	28	71.8
Previous intra-abdominal surgery	8	20.5
Diabetes mellitus	13	33.3
Malignancy	6	15.4
Chronic renal failure	6	15.4
Trauma and skin lesion	5	12.8

Table 4. The species distribution of candidemia episodes by main hospital wards

	Medical wards	Surgical wards	ICU
All species (n=39; 100%)	7 (17.9%)	1 (2.6%)	31 (79.5%)
***Candida albicans* (n=17; 43.6%)**	5 (71.4%)		12 (38.8%)
Non albicans *Candida* (n=22; 56.4%)	2 (28.6%)	1 (100%)	19 (61.3%)
Candida glabrata complex (n=13; 59%)	1 (50%)		12 (63.2%)
Candida parapsilosis complex (n=8; 36.4%)		1 (100%)	7 (36.8%)
Candida kefyr (n=1; 4.6%)	1 (50%)		

Mortality

The mortality rate attributed to all cases within 30 days after candidemia was found to be higher in the NAC: *C. glabrata* complex (11/13, 84.6%), *C. parapsilosis* complex (6/8; 75.0%), and *C. kefyr* (1/1; 100.0%). The mortality rate of the patients was 69.2% (n=27/39). In conclusion, mortality was lower in patients with *C. albicans* (9/17; 52.9%) compared to those with NAC (18/22; 81.8%).

DISCUSSION

Because IFIs are difficult to diagnose and treat, and have high mortality rates, clinicians initiate empiric therapy. The most frequent IFIs are *Candida* bloodstream infections. *Candida* species epidemiology has been changing to a decrease in *C. albicans* in favor of NAC, as reported by many studies worldwide (7,8). *C. albicans* remains the most common cause of candidemia but NAC species tend to increase worldwide, consistent with previous studies. There are highly heterogeneous epidemiological data on NAC species distribition. According to some studies *C. albicans* was the most prevalent cause of candidemia, followed by *C. glabrata* complex species and *C. parapsilosis* complex species (9,10). As suggested by other studies, *C. albicans* was the most prevalent cause of candidemia, followed by *C. parapsilosis* complex species and *C. glabrata* complex species (4,11–13). We found an increased rate of NAC, mainly attributed to the *C. glabrata* complex, in the NAC cases, similar to the data from European countries (3,14). Similar to our study, 2014 - 2015 data from Australian studies showed that *C. albicans* (44.4%), *C. glabrata* complex (26.7%) and *C. parapsilosis* complex (16.5%) were the most common causes of candidemia (15). Likewise, an important Turkish study by Yesilkaya et al. and Arastehfar et al. showed that *C. albicans* was the most prevalent yeast species, constituting almost 50% of all isolates, and the *C. glabrata* complex was the second leading cause of candidemia (16,17). On the other side, Mete et al. and Ergon et al. reported that *C. albicans* was predominant within the entire study period. However, they stated that the *C. parapsilosis* complex was found more than the *C. glabrata* complex (18,19). Contrary to our study, Müderris et al. reported that the *C. parapsilosis* complex was the most frequent causative agent in patients with candidemia (49.1%) (20).

As mentioned in several surveillance programmes, (European Confederation of Medical Mycology survey, SENTRY antifungal surveillance programme, North America ARTEMIS study), *C. albicans* was the predominant species and there was a tendency of decrease in the isolation of *C. albicans* and an increase in the isolation of the *C. glabrata* complex and *C. parapsilosis* complex (3,21,22). The results of our study are also compatible with all these studies. Unlike the aforementioned programmes, NAC was the predominant species of candidemia (66.9%) in multicenter SEIFEM surveys (23). All strains of *C. albicans*, *C. parapsilosis* complex and *C. kefyr* were found to be susceptible to FLC. Four of thirteen *C. glabrata* complex strains were resistant, and six of thirteen C. *glabrata* complex strains were intermediately susceptible to CAS, while the other strains were found to be susceptible. One of thirteen *C. glabrata* complex strains was intermediately susceptible to MCA, while the other strains were found to be susceptible. Of the isolates tested, four (10.26%) were resistant to at least one antifungal agent. All *Candida* strains were susceptible to FLC and VRC. The VITEK 2 Compact may reflect misclassification of CAS susceptibility among the *C. glabrata* complex (24). The resistance rate of the *C. glabrata* complex to CAS was comparatively

high**.** We suspect that the high proportion of CAS resistance for the *C. glabrata* complex (30.77%) stems from the low reliability of the CAS VITEK 2 Compact antifungal susceptibility test for this species. Boen et al. reported a CAS resistance rate of 9.1% among the *C. glabrata* complex (25). In addition, studies conducted in Australia showed that 5.3% of *C. glabrata* complex isolates were intermediate or resistant to CAS (15). These rates are lower than the rate we found in our study. Similar to our study, some studies reported *C. parapsilosis* complex isolates being susceptible to AMB, FLC, VRC, and CAS (26). Contrary to our study, Cilo et al. reported that the FLC resistance of *C. parapsilosis* complex isolates was high (26.3%) (27). FLC is known to be a relatively inexpensive antifungal alternative compared to echinocandins for the treatment of candidemia. Therefore, this makes FLC a more desirable choice for clinicians. However, a problem occurs due to ecessive of this drug, resulting in an NAC shift and resistance (28). Furthermore, Arıkan Akdaglı's study, which included 1991 *Candida* strain results, suggested very low rates of antifungal resistance in candidemia isolates in general. However unlike our study, it emphasized relatively high rates of FLC resistance in the *C. parapsilosis* complex (7.7%) (29). According to another study conducted in Turkey by Dizbay et al., in vitro susceptibility tests demonstrated that 5.7% of the isolates were resistant to FLC and CAS and 3.4% to VRC and AMB (30). Bae et al., indicated that among 53 systemic candidiasis cases, 19 (35%) had concurrent skin lesions (31). In contrast, (5/39) 13% of the patients included in our study had skin lesions.

Mortality due to candidemia has been attributed to the relative virulence of different *Candida* spp., a failure of host-defense mechanisms, the patient's underlying diseases and complications, and inappropriate or delayed treatment (32). Candidemia cases were more prevalent in ICUs, and higher mortality rates were observed in ICUs. The mortality rates of candidemia were also higher in the ICU than in the other wards in our center. Sbrana et al. also showed a significant relationship between 30-day mortality and ICU stay in patients with candidemia (33). Candidemia-related mortality is higher in elderly (≥65 years old) patients. Some differences between the younger and older age groups were predictable. Significantly more patients in the elderly age group were known to have cancer, and renal dysfunction was compromised in this age group. *C. albicans* is the *most* common *cause of candidemia* in elderly patients. Similarly, in our study, 67% of *C. albicans* infections caused mortality in elderly patients. It is followed by *C. glabrata* complex (60%) and *C. parapsilosis* complex (40%) with decreasing rates. Additionally, Ala et al. reported that the 30-day overall mortality was significantly lower in younger than in elderly patients. They also emphasized underlying comorbidities as a risk factor for candidemia (34). Overall mortality at 30 days from candidemia in 39 cases was 69.2%: 53.0% for *C. albicans*, 75.0% for *C. parapsilosis* complex, 84.6% for *C. glabrata* complex and 100.0% for *C. kefyr*. We observed a predominance of NAC, with *C. glabrata* complex being the most frequent and *C. glabrata* complex infections presenting with the highest mortality. When compared at the species level, Mete et al. declared that the rate of mortality was significantly higher in patients with *C. glabrata* complex infections. The overall mortality was 64%, with 56%, 58%, and 94% mortality for *C. albicans*, *C. parapsilosis* complex, and *C. glabrata* complex, respectively (18). Yeşilkaya et al. (17) and Koçak et al. (35) from Turkey reported 30-day crude mortality rates of 41% and 58% respectively. According to Koçak et al., the mortality rate due to *C. albicans* was 61.9% (13/21), while it was 52.9% (9/17) for NAC. Contrary to Koçak et al., Yeşilkaya and we found that NAC was higher in our studies. Müderris et al. reported that the overall 30-day mortality was 40.5%. They found *Candida parapsilosis* complex and *C. albicans* mortality rates of 38.8% and 43.2%, respectively (20). Although the mortality rate of *C. albicans (*53.0%) in our study was lower than that of NAC species, this rate was higher than that of Müderris et al.'s study. The studies of Pfaller et al. and Hii et al. showed that the *C. parapsilosis* complex had a low 30-day mortality (22% and 20%), respectively compared to our study (75.0%) (36,37). Similar to our study, Cheng et al. reported a candidemia mortality rate of 61.5% for the isolated *C. glabrata* complex, followed by 50% for the *C. parapsilosis* complex and 41.2% for *C. albicans* (38). According to Haghighatfard et al. the mortality rate due to *C. albicans* was 41.7% while it was 90% for NAC. Similar to our study, Haghighatfard et al., reported that the 30-day overall mortality rate of candidemia was 63.6% (39).

Furthermore, the mortality of candidemia patients in the ICU was significantly higher than that in medical and surgical wards. This difference can be attributed to several factors such as patient age, the severity of the primary disease, and the presence of various comorbidities. In our study, the majority of surgical patients received abdominal operations that could have damaged the gastrointestinal barriers and caused skin contamination at

vascular insertion sites, which placed these patients at greater risk for developing invasive candidiasis. However, patients in the ICU more frequently underwent some invasive procedures that predisposed the patients to an increased risk of *Candida* infections. According to Hii et al., the distribution of candidemia by wards was as follows: 42.3% of the cases were in the ICU, 31.7% were in surgical wards and 26.0% were in medical wards. However, our study found that 79.49% of the cases were in the ICU, 2.6% were in surgical wards and 17.9% were in medical wards (37).

Limitations:

The present study has several limitation. First, it was a single-center, retrospective study and had a small number of patients. For more reliable data, greater sample sizes are needed. Second, the CLSI recommends the broth microdilution method for antifungal susceptibility. However, due to its labor intensive and expensive nature as well as the technical limitations of the clinical microbiology laboratory for antifungal susceptibility, we could not use this reference method.

CONCLUSION

We conducted our study in a large regional city hospital reigional City Hospital that also serves the surrounding provinces. In addition, this is the first analysis of candidemia in our hospital, showing that *C. albicans* was the most frequent species. To our knowledge, this is the first retrospective study to examine the mortality rate in candidemia in Eskisehir. Our study showed that candidemia was associated with a high mortality rate and a low level of antifungal resistance among *Candida* isolates. Candidemia is an emerging problem in developing countries, and it is a significant source of mortality, morbidity, and likely high healthcare costs for hospitalized patients in Turkey. Determining the risk factors associated with candidemia may lead to a quick diagnosis and early antifungal therapy that may reduce mortality rates. The identification of antifungal susceptibilities is crucial to make progress in treating and preventing invasive *Candida* infections. Furthermore, continuous local surveillance is essential for establishing empirical antifungal treatment protocols and managing candidemia.

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Ethics statement: Informed consent was obtained from the patients. We conducted our study in accordance with Helsinki Declaration after receiving permission of the Ethical Committee of the Noninvasive Clinical Research Ethics Committee of Eskişehir Osmangazi University (02.18.2020-24)
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