



Epidemiology, Antifungal Susceptibility, and Risk Factors of Invasive Candidiasis in a Tertiary Hospital During a Four-Year Period

Çiğdem Arabacı ^{1,*}, Serkan Aydemir ², Kenan Ak ¹ and Tuba Dal ³

¹Department of Medical Microbiology, Prof. Dr. Cemil Taşçıoğlu City Hospital, University of Health Sciences, Istanbul, Turkey

²Department of Infectious Diseases and Clinical Microbiology, Prof. Dr. Cemil Taşçıoğlu City Hospital, University of Health Sciences, Istanbul, Turkey

³Department of Medical Microbiology, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey

*Corresponding author: Department of Medical Microbiology, Prof. Dr. Cemil Taşçıoğlu City Hospital, University of Health Sciences, Istanbul, Turkey. Email: dr.c.arabaci@hotmail.com

Received 2022 October 03; Revised 2022 December 21; Accepted 2022 December 26.

Abstract

Background: *Candida* infections are a significant cause of morbidity and mortality in hospitalized patients. Acquired resistance to antifungal agents and strains with intrinsic resistance makes it hard to manage the infection.

Objectives: We aimed to examine the risk factors of candidemia associated with patient mortality, the species causing candidemia, and their antifungal susceptibility.

Methods: Patient data were collected from medical records retrospectively. MALDI-TOF MS was used to identify *Candida* species. Antifungal susceptibility testing was conducted by the colorimetric broth microdilution method.

Results: A total of 155 patients were included in the study. The incidences of candidemia were 0.92, 0.72, 0.99, 0.97, and 2.28 per 1,000 cases in 2016, 2017, 2018, 2019, and 2020, respectively. *Candida albicans* accounted for 45% of all cases, followed by *C. parapsilosis* complex (28%), *C. tropicalis* (10%), and *C. glabrata* (8%). The 30-day crude mortality was 45%. There was no significant difference in mortality between *C. albicans* and non-*albicans* yeast species. The susceptibility rates for anidulafungin, micafungin, caspofungin, voriconazole, and fluconazole were as follows: 97, 97, 97, 97, and 90% in *C. albicans*, 95, 95, 98, 72, and 67% in *C. parapsilosis* complex, and 100, 100, 100, 38, and 63% in *C. tropicalis*. The susceptibility rates for anidulafungin, micafungin, and caspofungin in *C. glabrata* were 100, 100, and 92%, respectively. All 12 *C. glabrata* strains were susceptible-dose-dependent against fluconazole and uninterpretable for voriconazole.

Conclusions: Incidences of candidemia and susceptibility patterns of strains may vary over time and amongst the regions. *Candida albicans* was the predominant strain, and echinocandins demonstrated the highest susceptibility rates against the most common species isolated in this study. Antifungal susceptibility tests are crucial in guiding patient treatment.

Keywords: Epidemiological Features, Surveillance, Risk Factors, Invasive Candidiasis, Candidemia

1. Background

In the last 20 years, there has been a nearly tenfold increase in hospital-acquired fungal infections, with 80% caused by *Candida* species (1). Although there have been significant advances in the diagnosis and antifungal treatments of infectious diseases, one-third of patients with *Candida* infection die (2). More than half of the invasive *Candida* infections are candidemia, which accounts for 4.5% of bloodstream infections (2). Causative agents of candidemia have changed over time (3). There have been increasing reports of high mortality in non-*albicans* *Candida* species, including *C. glabrata*, *C. krusei*, and *C. tropicalis* (4). Fluconazole and echinocandins are the most widely used

antifungal therapies worldwide (5, 6). Due to the increase of isolates with intrinsic and acquired resistance to antifungal agents, detecting candidemia agents, their antifungal susceptibility, and risk factors will reduce hospital mortality (7). It is essential to choose an empirical treatment and modify it according to the microbiology laboratory results.

2. Objectives

We aimed to epidemiologically examine the cases of candidemia in a tertiary hospital to determine the risk factors associated with mortality, the species causing candidemia, and their antifungal susceptibility.

3. Methods

3.1. Patients and Fungal Isolates

Adult patients with healthcare-acquired candidemia hospitalized at the University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital, between June 2016 and October 2020, were included in the study. The demographic and clinical data of the patients (age, gender, presence of malignancy, concomitant disease, antibiotic use, presence of febrile neutropenia, antifungal use, history of operation, duration of total parenteral nutrition, and mortality status) were collected from medical records and the hospital automation system retrospectively. In addition, the microbiology laboratory results of the patients (*Candida* species growing in the blood culture, antifungal sensitivity, and simultaneous bacterial and fungal growth in cultures) were also evaluated. Patients diagnosed with Coronavirus disease 2019 (COVID-19) were excluded from the study. Blood cultures were incubated in an automated blood culture system (BACTEC FX, BD, USA) at the Central Microbiology Laboratory. The germ tube test and MALDI-TOF MS (Vitek MS, bioMérieux, France) were used to identify *Candida* species.

3.2. Definition

Candidemia was defined as at least one positive blood culture for *Candida* species in patients with fever or other clinical signs of infection. When the blood culture was positive for bacteria in addition to the *Candida* species, the case was defined as having concurrent bacteremia. In patients with recurrent candidaemia, we counted only the first case; however, it was accepted as a new case if the isolation of a *Candida* strain occurred after 30 days.

3.3. Antifungal Susceptibility Testing

Antifungal susceptibility results were obtained using the Sensititre YeastONE® (SYO) Antifungal Susceptibility Panel (Thermo Fisher Scientific, UK) based on the colorimetric method. The antifungal susceptibility results were evaluated according to Clinical and Laboratory Standards Institute (CLSI) M27-S4 and M60 documents (8). Two reference strains, *C. krusei* ATCC 6258 and *C. parapsilosis* complex ATCC 22019, were included in each test as quality control isolates.

3.4. Statistical Analysis

Descriptive statistics were presented as frequency, percentage, mean, standard deviation (SD), median (median), minimum (min.), and maximum (max.). Fisher's exact or

Pearson χ^2 test was used to analyze the relationships between categorical variables. The Shapiro-Wilk test determined the normality assumption before exploring the difference between the two groups. The Mann-Whitney U test was used when it did not follow the normal distribution. Analyses were performed using IBM SPSS Statistics for Windows version 21.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Statistically, P values less than 0.05 were considered significant.

4. Results

A total of 217 patients had yeast growth in their blood cultures. Among these patients, 51 patients with confirmed COVID-19 diagnosis and 11 patients whose data could not be accessed were excluded. A total of 155 patients were included in the study.

4.1. *Candida* Strains and Incidence of Candidemia

Candida albicans in 69 (45%) patients and non-*albicans* yeast species in 86 (55%) patients were isolated in the blood culture. The isolated non-*albicans* yeast species in order of frequency were *C. parapsilosis* complex (43, 28%), *C. tropicalis* (16, 10%), *C. glabrata* (12, 8%), *C. keyfr* (3, 2%), *C. lusitaniae* (3, 2%), *C. dubliniensis* (2, 1%), and other species (7, 4%), including *C. sake* (n=1), *C. krusei* (n=1), *C. norvegensis* (n=1), *C. guilliermondii* (n=1), *Trichosporon asahii* (n=1), *Saprochaete clavata* (n=1), and *Blastoschizomyces capitatus* (n=1) (Figure 1). A total of 7050, 14210, 16558, 17286, and 9862 blood cultures were sent to the microbiology laboratory in July - December 2016, 2017, 2018, 2019, and 2020, respectively, and 316, 563, 535, 611, 1368 were reported as positive. The incidences of candidemia were 0.92, 0.72, 0.99, 0.97, and 2.28 per 1,000 cases in July-December 2016, 2017, 2018, 2019, and 2020, respectively.

4.2. Antifungal Susceptibility Patterns of Isolates

Among *C. albicans* isolates, 67 were sensitive to anidulafungin, micafungin, caspofungin, and voriconazole, and 62 were sensitive to fluconazole. Two *C. albicans* strains were resistant to fluconazole, and one strain was resistant to voriconazole. Also, 13 *C. parapsilosis* strains were resistant to fluconazole, and 11 were intermediate (I) + susceptible-dose-dependent (SDD) to voriconazole. All *C. tropicalis* isolates were sensitive to anidulafungin, micafungin, and caspofungin, while one strain showed resistance to voriconazole and fluconazole, and nine strains were I-SDD against voriconazole. All 12 *C. glabrata* strains were susceptible to anidulafungin and micafungin, while

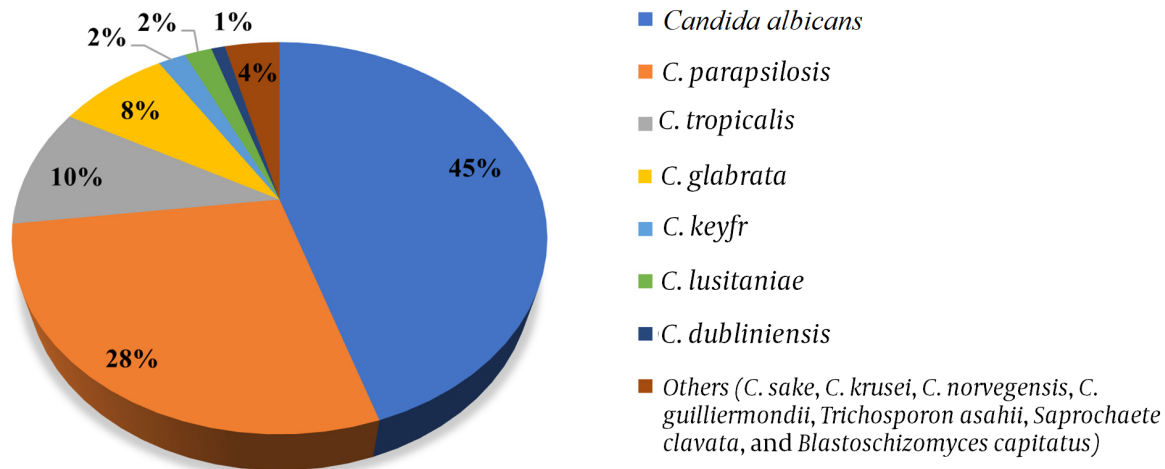


Figure 1. Distribution of isolated yeast species in patients with candidemia

all were I + SDD against fluconazole (Tables 1 and 2). The susceptibility rates for anidulafungin, micafungin, caspofungin, voriconazole, and fluconazole were as follows: 97, 97, 97, 97, and 90% in *C. albicans*, 95, 95, 98, 72, and 67% in *C. parapsilosis* complex, and 100, 100, 100, 38, and 63% in *C. tropicalis*. The susceptibility rates on the basis of species as a percentage for anidulafungin, micafungin, and caspofungin in *C. glabrata* were 100, 100, and 92%, respectively.

4.3. Clinical Data

The age of the patients ranged from 20 to 90; 90 (58%) were male, and 65 (42%) were female. Of the patients, 88 (57%) were hospitalized in the intensive care unit, 19 (12%) in internal medicine, 17 (11%) in hematology, 16 (10%) in general surgery, five (3%) in infectious diseases wards, and others (7%) in clinics including neurology, oncology, urology, obstetrics and gynecology, cardiac surgery, and radiation oncology. Seventy patients died (Table 3). There was no significant difference in mortality and survival between *C. albicans* and non-*albicans* species and other species in patients with candidemia. The crude mortality rate within 30 days after the initial positive culture was 45% (n = 70) (Table 3). Among the study patients, 83 (88%) had malignancies. The most common cancer types seen in candidemia patients were hematological cancers (Hodgkin lymphoma, non-Hodgkin lymphoma, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, chronic myeloid leukemia, multiple myeloma) (20/83, 24%), colon cancer (14/83, 17%), brain tumor (14/83, 17%), and stomach cancer (12/83, 14%).

Ovarian cancer (n = 3), esophageal cancer (n = 3), rectal cancer (n = 3), lung cancer (n = 3), bladder cancer (n = 3), and endometrial cancer (n = 2) were also detected. Other underlying diseases were hypertension (60, 38%), chronic kidney failure (19, 12%), chronic obstructive pulmonary disease (18, 11.6%), diabetes (12, 13%), heart failure (10, 6%), and febrile neutropenia (7, 5%) (Table 3).

Simultaneously, bacteria were isolated in 65 (42%) bacterial cultures. The most frequently isolated bacterial species were *Klebsiella pneumoniae* (n = 21), *Enterococcus* species (n = 10), *Acinetobacter baumannii* (n = 22), *Escherichia coli* (n = 10), followed by *Serratia marcescens*, *Proteus mirabilis*, methicillin-resistant *Staphylococcus aureus*, and methicillin-resistant coagulase-negative staphylococci. Twenty (95%, 20/21) of the *K. pneumoniae* isolates and six (27%, 6/22) of the *A. baumannii* isolates were resistant to meropenem, all *E. coli* isolates (100%, 10/10) were ESBL (extended spectrum beta lactamase)-positive, and one *Enterococcus faecium* was resistant to vancomycin. In 37 (24%, 37/155) patients, *Candida* species simultaneously grew in urine (n = 27), catheter tips (n = 8), urine + catheter tip (n = 1), trachea (n = 2), and peritoneal fluid samples (Table 1). One hundred (65%) patients received TPN, and 119 (77%) were catheterized. All patients (100%) had a history of broad-spectrum antibiotic use (Table 3). A total of 141 (91%) patients received empirical antifungal therapy, 61 (43%) micafungin, 36 (26%) caspofungin, 28 (20%) anidulafungin, 13 (9%) fluconazole, and three (2%) voriconazole (Table 3).

Considering the invasive interventions before candidemia, a central venous catheter was applied to 119 (77%)

Table 1. Antifungal Susceptibility of the Most Common *Candida* Species for Echinocandins

Yeast Species	Anidulafungin				Micafungin				Caspofungin				Total
	S	I+SDD	R	U	S	I+SDD	R	U	S	I+SDD	R	U	
<i>Candida albicans</i>	67	2	0	0	67	1	1	0	67	2	0	0	69
<i>C. parapsilosis complex</i>	41	1	1	0	41	1	1	0	42	0	1	0	43
<i>C. tropicalis</i>	16	0	0	0	16	0	0	0	16	0	0	0	16
<i>C. glabrata</i>	12	0	0	0	12	0	0	0	11	1	0	0	12

Abbreviations: S, sensitive; I, intermediate; SDD, susceptible-dose-dependent; R, resistant; U, uninterpretable.

Table 2. Antifungal Susceptibility of the Most Common *Candida* Species for Azoles

Yeast Species	Voriconazole				Fluconazole				Total
	S	I+SDD	R	U	S	I+SDD	R	U	
<i>Candida albicans</i>	67	1	1	0	62	5	2	0	69
<i>C. parapsilosis complex</i>	31	11	0	0	29	1	13	0	43
<i>C. tropicalis</i>	6	9	1	0	10	5	1	0	16
<i>C. glabrata</i>	0	0	0	12	0	12	0	0	12

Abbreviations: S, sensitive; I, intermediate; SDD, susceptible-dose-dependent; R, resistant; U, uninterpretable.

patients and mechanical ventilation to 90 (58%) patients. A total of 59 (38%) patients had a history of gastrointestinal surgery. In patients with gastrointestinal surgery, the most common isolated yeasts were *C. albicans* (n = 27), *C. parapsilosis complex* (n = 18), *C. glabrata* (n = 6), *C. tropicalis* (n = 5), *C. dubliniensis* (n = 1), *C. guilliermondii* (n = 1), and *C. norvegensis* (n = 1) (Table 3).

There was no significant difference between *C. albicans* and non-*albicans Candida* and other yeast species in patients with candidemia in terms of underlying diseases, candiduria, total parenteral nutrition, antifungal use, antibiotic use, central venous catheter use, mechanical ventilation use, and gastrointestinal surgery.

5. Discussion

Detecting causative agents of bloodstream infections is vital for antifungal therapy and surveillance. In a multicenter study in Japan among 289 cases, *C. albicans* was the most frequent causative agent (44.3%), followed by *C. parapsilosis complex* (25.3%), *C. glabrata* (15.9%), and *C. tropicalis* (4.8%). The survival rate was higher for patients with *C. parapsilosis complex* candidemia than those with other species or mixed fungemia in the Kaplan-Meier analysis (2). In a study in Turkey with 102 adult candidemia patients, 36.3% of patients had *C. albicans*, and 63.7% had non-*albicans*, including *C. parapsilosis complex* (22.5%), *C. tropicalis* (16.7%), and *C. glabrata* (12.7%) (1). *Candida albicans* was the most prevalent species, followed by *C. parapsilosis* among candidemia patients, according to many reports in the literature (6, 9). On the contrary, *C. parapsilosis*

has been reported as the most commonly isolated *Candida* strain in other studies (10, 11).

In our study of hospital-acquired candidemia patients, *C. albicans* accounted for 45% of all cases, and the most common yeast species other than *C. albicans* were *C. parapsilosis complex* (28%), *C. tropicalis* (10%), and *C. glabrata* (8%). These data indicated that *C. albicans* was a significant cause of candidemia, but infections due to non-*albicans* species were also problematic. Further, we did not find a significant difference in risk factors and mortality between yeast species in the current study. In some epidemiologic studies, mortality was higher in patients with non-*albicans Candida* infections than in those with *C. albicans* infections (12). However, no difference or higher mortality rates with *C. albicans* have also been reported in many studies (13).

Continuous surveillance plays a crucial role in controlling infections due to intrinsic antifungal-resistant species such as *C. glabrata*, which has a decreased susceptibility to azoles and resistance to amphotericin B. *Candida glabrata* candidemia is more common among the elderly and cancer patients. The ability of *C. parapsilosis complex* to colonize human skin is a commonly reported cause of catheter-related infections (11, 12). Our study indicated that bloodstream infections due to *C. albicans* were common. Still, it is essential to know the increasing proportion of *C. glabrata*, *C. parapsilosis complex*, and *C. tropicalis*.

In our study, the incidences of candidemia were 0.92, 0.72, 0.99, 0.97, and 2.28 per 1,000 cases in four study years (2016 - 2020). There was a notable increase in its incidence in 2020. Some studies reported up to a 5-10-fold increase in the incidence of candidemia during the COVID-19 pan-

Table 3. Demographic and Clinical Data of Patients with Candidemia^a

Characteristics	Values
Age (mean ± standard deviation)	62.36 ± 16.8
Gender	
Male	90 (58)
Female	65 (42)
Mortality	70 (45)
Underlying diseases	
Malignancy	83 (88)
Hypertension	60 (38)
Diabetes	12 (13)
Chronic kidney failure	19 (12)
Chronic obstructive pulmonary disease	18 (11.6)
Heart failure	10 (6)
Febrile neutropenia	7 (5)
Simultaneously culture positivity	
Healthcare-acquired bacterial infection	65 (42)
Candiduria	28 (18)
Pre-candidemia treatments	
Antibiotic use	155 (100)
Empirical antifungal therapy	141 (91)
Total parenteral nutrition	100 (65)
Invasive interventions before candidemia	
Central venous catheter	119 (77)
Mechanical ventilation	90 (58)
Gastrointestinal surgery	59 (38)

^a Values are expressed as No. (%) unless otherwise indicated.

demic (14, 15). Despite excluding patients with COVID-19, we observed a higher incidence than in previous years. Inappropriate antibiotic use and changes in the hospital environment during this era may have led to this observation. Additionally, 57% of the patients were hospitalized in the intensive care unit. The incidence rate reported from Turkey in the literature ranges from 0.56 to 11.5 per 1000 admissions (1, 10, 16, 17). The literature data indicated that ICU patients had higher candidemia risk and mortality than general ward patients (4). We suggested safe and effective prophylactic strategies, high-risk patient identification, and daily bathing with chlorhexidine to decrease the incidence (18).

In a study in Turkey, echinocandin sensitivity was more than 95%, *C. parapsilosis* complex had 8.7% fluconazole and 4.4% voriconazole resistance, and *C. tropicalis* had

5.9% fluconazole and 5.9% voriconazole resistance. Cross-resistance was also detected in two *C. parapsilosis* complex strains and one *C. tropicalis* strain against fluconazole (1). In another study by Dogan et al., 13% of *C. parapsilosis* strains showed resistance to fluconazole, and all species were susceptible to echinocandins (6). In our study, the susceptibility rate of echinocandins was more than 95% against *Candida* isolates. I + SDD and resistance rates for voriconazole and fluconazole were 3% and 10% in *C. albicans*, 25% and 33% in *C. parapsilosis* complex, and 56% and 38% in *C. tropicalis*. All 12 *C. glabrata* strains included in the study were SDD for fluconazole and uninterpretable for voriconazole. Our study and literature data indicated that echinocandins had good activity for *Candida* species, and voriconazole resistance rates were increasing in *C. tropicalis* and *C. parapsilosis* complex strains.

The broth microdilution method has been accepted as a standardized reference for antifungal susceptibility detection in *Candida* species. The SYO susceptibility system is a micro broth method that provides qualitative and quantitative minimal inhibitory concentration (MIC) values. In a study by Altınbaş et al., the antifungal susceptibility of 129 *Candida* isolates was evaluated by both SYO and CLSI M27-A3 BMD methods. The SYO method demonstrated an excellent performance for all antifungals except voriconazole and fluconazole. The authors agree that the SYO method is an effective and efficient alternative to the CLSI reference method (19). Philips et al. compared the two colorimetric broth microdilution antifungal susceptibility tests, SYO and MICRONAUT-AM, with 100 clinical *Candida* isolates.

Essential agreement of ≥ 90% was shown only for fluconazole, 5-flucytosine, caspofungin, and amphotericin B. SYO MICs were higher than MICRONAUT MICs for all antifungals, except for itraconazole. Only amphotericin B, fluconazole, and micafungin had a categorical agreement of ≥ 90%. The proportions of susceptibility for amphotericin B, fluconazole, and micafungin were comparable. The proportion of sensitive and I + SDD *Candida* strains for voriconazole (71.2% vs. 90.9%) and posaconazole (67.5% vs. 90.9%) was higher when using the MICRONAUT system. In comparison, it was higher for itraconazole (95.8% vs. 77.8%) and anidulafungin (93.9% vs. 72.7%) when Sensititre was used (SYO vs. MICRONAUT, respectively) (20).

In a study by Dalyan Cilo and Ener, the antifungal susceptibility of various *Candida* species was compared between the VITEK 2 automated system and the reference CLSI M27 microdilution method. They detected antifungal susceptibilities to amphotericin B, voriconazole, and fluconazole in 140 *Candida* strains and anidulafungin in 92 strains.

The VITEK 2 MIC values at 24 hours for azole antifungals were one-fold higher than the CLSI MICs. Between the two methods, the essential agreement was > 90% for voriconazole and amphotericin B, while it was 85% for fluconazole. Amphotericin B showed the best (99.3%) categorical agreement, and the least categorical agreement was detected with voriconazole (85.7%).

VITEK 2 failed to detect resistance in one *C. glabrata* strain, which was found resistant to fluconazole by the reference method. Although the error rate was not very high, VITEK 2 could not detect one fluconazole-resistant *C. parapsilosis* complex or *C. glabrata* strain in this study (21). Our study showed that the SYO susceptibility system had promising activity in obtaining the results for anidulafungin, micafungin, caspofungin, voriconazole, and fluconazole susceptibilities in *C. albicans*, *C. tropicalis*, and *C. parapsilosis* complex. However, uninterpretable results were common in *C. glabrata* and other non-*albicans* yeast species. Additionally, the SYO susceptibility system was not good for evaluating amphotericin B susceptibility. Further studies are warranted to validate the fast antifungal susceptibility detecting systems.

Empiric antifungal therapy is crucial in managing candidemia, and delay in the initiation of treatment is an independent risk factor for high mortality. Previously, it has been reported that only 11 - 32% of patients with candidemia were treated with appropriate antifungal agents, and poor response to initial antifungal therapy was a risk factor for high mortality. It is also recommended to draw follow-up blood cultures to confirm the clearance of candidemia (22, 23). In a study by Kato et al., 68.5% of patients were treated empirically with echinocandins, and 16.3% received empiric fluconazole. They found the protective role of empiric fluconazole treatment against patient mortality (2). However, the choice of empirical antifungal therapy remains controversial.

Infectious Diseases Society of America guideline recommends echinocandins over fluconazole, particularly for those with moderate to severe illness (24, 25). In our study, 91% of patients received empiric antifungal therapy. Also, 88% of these patients received echinocandins, 9% fluconazole, and 2% voriconazole. According to the updated guidelines, there has been a shift in the usage of antifungals from azoles to echinocandins (26). Our findings are also consistent with this change, with echinocandins being the first choice in our hospital. The choice of antifungal treatment should also be based on local epidemiological data and the resistance profiles of microorganisms.

In a Turkish study, the crude candidemia mortality rate

was 79.3% (1). In a multicenter study from Japan, of 289 patients, 27.7% died within 30 days of candidemia onset (2). Also, mortality rates of 18 - 66% have been highlighted in previous reports (1, 26, 27). In our study, the mortality rate was 45%. Different mortality rates in studies may be due to some confounding factors, such as the heterogeneity of study populations and the choice of different treatment protocols, including empirical therapy. Our study showed that despite the high rate of empiric antifungal use, mortality was still high in candidemia patients. This highlights the importance of timely and appropriate intervention. In addition, echinocandins should be prioritized in critically ill patients, given the higher resistance rates to azoles.

In a Turkish study, the most common risk factors associated with candidemia were broad-spectrum antibiotic use (98%), the presence of a urinary catheter (96.1%), the presence of a concomitant hospital-acquired infection (92.2%), and the use of CVC (80.4%) (1). In a different study, the most common risk factors were broad-spectrum antibiotic use (95.6%), CVC (97.8%), mechanical ventilation (64.4%), and urinary catheterization (73.3%) (28). In a study in Japan, independent risk factors for 30-day mortality were antibiotic use, advanced age (≥ 65 years), and a SOFA score ≥ 6 in patients with candidemia (2). In our study, the most common risk factors for candidemia were antibiotic use (100%), malignancy (88%), central venous catheter use (77%), TPN (65%), mechanical ventilation (58%), hypertension (38%), and history of gastrointestinal surgery (38%).

There was no significant difference in risk factors between *C. albicans* and non-*albicans Candida* and other yeast species in patients with candidemia (2). Although early studies reported that removing CVC is associated with an improved prognosis (29), the incidence of CVC removal did not differ between the mortality group and the surviving patients in other studies (2, 30). If there is no sign of infection at the CVC site, some researchers suggest starting antifungal treatment, observing the response, and not removing the CVC unless the patient worsens (31). We recommend that patients receiving TPN and/or undergoing gastrointestinal surgery be monitored closely for candidemia.

Previous studies reported concurrent bacteremia rates of 7 - 61.1% (32-34). In our study, 42% of the patients had concurrent bacteremia. Gram-negative bacteria were isolated from most patients; 95% of the *K. pneumoniae* isolates and 27% of the *A. baumannii* isolates were resistant to meropenem, and all *E. coli* isolates were ESBL-positive. The study indicated that extended-spectrum antibiotic use was also a significant risk factor for candidemia, and carbapenem resistance was problematic in Gram-negative

bacteria, especially *K. pneumoniae*. Antibiotic stewardship programs, active surveillance of antimicrobial resistance, and infection control measurements are needed to prevent the emergence of resistant strains (35).

5.1. Conclusions

Incidences of candidemia and susceptibility patterns of strains may vary over time and amongst the regions. *Candida albicans* was the predominant strain, and echinocandins demonstrated the highest susceptibility rates against the most common strains isolated from the current study patients. It is of utmost importance to perform antifungal susceptibility tests to guide patient treatment.

Footnotes

Authors' Contribution: Study concept and design, Ç.A.; Acquisition of data, S.A. and K.A.; Statistical analysis and interpretation of data, Ç.A. and T.D.; Drafting of the manuscript, Ç. A. and S.A.; Critical revision of the manuscript, K.A. and T.D. All the authors read and approved the final manuscript.

Conflict of Interests: We have no involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. None of the authors have any relationship with this journal.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study was approved by the Local Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (code: 139 date: 06.06.2022).

Funding/Support: No funding was received for this work.

References

- Cicek-Kolak C, Erman-Daloglu A, Ozhak B, Ogunc D, Gunseren F. Epidemiology of candidemia, antifungal susceptibilities of candida species and their impact on mortality in adult patients admitted to Akdeniz University Hospital. *Klimik Derg.* 2020;**32**(3):250-8. <https://doi.org/10.5152/kd.2019.71>.
- Kato H, Yoshimura Y, Suido Y, Shimizu H, Ide K, Sugiyama Y, et al. Mortality and risk factor analysis for Candida blood stream infection: A multicenter study. *J Infect Chemother.* 2019;**25**(5):341-5. [PubMed ID: 30718191]. <https://doi.org/10.1016/j.jiac.2019.01.002>.
- Medina N, Soto-Debrán JC, Seidel D, Akyar I, Badali HA, Bretagne S, et al. MixInYeast: A multicenter study on mixed yeast infections. *J Fungi (Basel).* 2020;**7**(1):13. [PubMed ID: 33383783]. [PubMed Central ID: PMC7823447]. <https://doi.org/10.3390/jof7010013>.
- Arastehfar A, Shaban T, Zarrinfar H, Hedayati MT, Sedaghat A, Ilkit M, et al. Candidemia among Iranian Patients with Severe COVID-19 Admitted to ICUs. *J Fungi (Basel).* 2021;**7**(4):280. [PubMed ID: 33917967]. [PubMed Central ID: PMC8068363]. <https://doi.org/10.3390/jof7040280>.
- Gold JAW, Seagle EE, Nadle J, Barter DM, Czaja CA, Johnston H, et al. Treatment practices for adults with candidemia at 9 active surveillance sites-United States, 2017-2018. *Clin Infect Dis.* 2021;**73**(9):1609-16. [PubMed ID: 34079987]. [PubMed Central ID: PMC8609664]. <https://doi.org/10.1093/cid/ciab512>.
- Doğan Ö, Yeşilkaya A, Menekşe Ş, Güler Ö, Karakoç Ç, Çınar G, et al. Effect of initial antifungal therapy on mortality among patients with bloodstream infections with different Candida species and resistance to antifungal agents: A multicentre observational study by the Turkish Fungal Infections Study Group. *Int J Antimicrob Agents.* 2020;**56**(1):105992. [PubMed ID: 32335275]. <https://doi.org/10.1016/j.ijantimicag.2020.105992>.
- Zarrinfar H, Kord Z, Fata A. High incidence of azole resistance among *Candida albicans* and *C. glabrata* isolates in Northeastern Iran. *Curr Med Mycol.* 2021;**7**(3):18-21. [PubMed ID: 35528623]. [PubMed Central ID: PMC9006729]. <https://doi.org/10.18502/cmm.7.3.7801>.
- Rex JH, Clinical, Laboratory Standards Institute. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: Approved Standard.* Pennsylvania, USA: Clinical and Laboratory Standards Institute; 2008.
- Santolaya ME, Thompson L, Benadof D, Tapia C, Legarraga P, Cortés C, et al. A prospective, multi-center study of *Candida* bloodstream infections in Chile. *PLoS One.* 2019;**14**(3). e0212924. [PubMed ID: 30849092]. [PubMed Central ID: PMC6407853]. <https://doi.org/10.1371/journal.pone.0212924>.
- Yılmaz-Ciftdoğan D, Kara-Aksay A, Erbaş G, Sarkış Ü B, Karadağ-Oncel E, Anil AB, et al. Epidemiology of candidemia in children over 7 years in a medical center in Turkey. *Microbiol Spectr.* 2021;**9**(2). e0045321. [PubMed ID: 34550003]. <https://doi.org/10.1128/Spectrum.00453-21>.
- Zuo XS, Liu Y, Hu K. Epidemiology and risk factors of candidemia due to *Candida parapsilosis* in an intensive care unit. *Rev Inst Med Trop Sao Paulo.* 2021;**63**. e20. [PubMed ID: 33787740]. [PubMed Central ID: PMC7997672]. <https://doi.org/10.1590/s1678-9946202163020>.
- Kim EJ, Lee E, Kwak YG, Yoo HM, Choi JY, Kim SR, et al. Trends in the epidemiology of candidemia in intensive care units from 2006 to 2017: Results from the Korean National Healthcare-Associated Infections Surveillance System. *Front Med (Lausanne).* 2020;**7**:606976. [PubMed ID: 33392229]. [PubMed Central ID: PMC86773785]. <https://doi.org/10.3389/fmed.2020.606976>.
- Zhang W, Song X, Wu H, Zheng R. Epidemiology, risk factors and outcomes of *Candida albicans* vs. non-*albicans* candidaemia in adult patients in Northeast China. *Epidemiol Infect.* 2019;**147**. e277. [PubMed ID: 31552814]. [PubMed Central ID: PMC6805752]. <https://doi.org/10.1017/s0950268819001638>.
- Seagle EE, Jackson BR, Lockhart SR, Georgacopoulos O, Nunnally NS, Roland J, et al. The landscape of candidemia during the coronavirus disease 2019 (COVID-19) pandemic. *Clin Infect Dis.* 2022;**74**(5):802-11. [PubMed ID: 34145450]. <https://doi.org/10.1093/cid/ciab562>.

15. Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castañeira AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. *Mycoses*. 2021;**64**(2):152–6. [PubMed ID: 33275821]. [PubMed Central ID: PMC9753494]. <https://doi.org/10.1111/myc.13225>.
16. Yapar N, Pullukcu H, Avkan-Oguz V, Sayin-Kutlu S, Ertugrul B, Sacar S, et al. Evaluation of species distribution and risk factors of candidemia: a multicenter case-control study. *Med Mycol*. 2011;**49**(1):26–31. [PubMed ID: 20662635]. <https://doi.org/10.3109/13693786.2010.501344>.
17. Ghazi S, Rafei R, Osman M, El Safadi D, Mallat H, Papon N, et al. The epidemiology of Candida species in the Middle East and North Africa. *J Mycol Med*. 2019;**29**(3):245–52. [PubMed ID: 31400864]. <https://doi.org/10.1016/j.mycmed.2019.07.006>.
18. Ture Z, Alp E. Infection control measures to prevent hospital transmission of candida. *Hosp Pract (1995)*. 2018;**46**(5):253–7. [PubMed ID: 30102587]. <https://doi.org/10.1080/21548331.2018.1510282>.
19. Altınbaş R, Bariş A, Şen S, Öztürk R, Kiraz N. Comparison of the Sensititre YeastOne antifungal method with the CLSI M27-A3 reference method to determine the activity of antifungal agents against clinical isolates of Candida spp. *Turk J Med Sci*. 2020;**50**(8):2024–31. [PubMed ID: 32659879]. [PubMed Central ID: PMC775692]. <https://doi.org/10.3906/sag-1909-97>.
20. Philips S, Van Hoecke F, De Laere E, Vervaeke S, De Smedt R, Boelens J, et al. Comparison of two commercial colorimetric broth microdilution tests for candida susceptibility testing: Sensititre YeastOne versus MICRONAUT-AM. *J Fungi (Basel)*. 2021;**7**(5). [PubMed ID: 34062848]. [PubMed Central ID: PMC8147297]. <https://doi.org/10.3390/jof7050356>.
21. Dalyan Cilo B, Ener B. Comparison of Clinical Laboratory Standards Institute (CLSI) microdilution method and VITEK 2 automated antifungal susceptibility system for the determination of antifungal susceptibility of Candida species. *Cureus*. 2021;**13**(12). e20220. [PubMed ID: 35004039]. [PubMed Central ID: PMC9733416]. <https://doi.org/10.7759/cureus.20220>.
22. Mellinshoff SC, Cornely OA, Jung N. Essentials in Candida bloodstream infection. *Infection*. 2018;**46**(6):897–9. [PubMed ID: 30218311]. <https://doi.org/10.1007/s15010-018-1218-1>.
23. Murri R, Giovannone F, Camici M, Torelli R, Ventura G, Scoppettuolo G, et al. Systematic clinical management of patients with candidemia improves survival. *J Infect*. 2018;**77**(2):145–50. [PubMed ID: 29742466]. <https://doi.org/10.1016/j.jinf.2018.03.011>.
24. López-Cortés LE, Almirante B, Cuenca-Estrella M, Garnacho-Montero J, Padilla B, Puig-Asensio M, et al. Empirical and targeted therapy of candidemia with fluconazole versus echinocandins: a propensity score-derived analysis of a population-based, multicentre prospective cohort. *Clin Microbiol Infect*. 2016;**22**(8):7330–8. [PubMed ID: 27189197]. <https://doi.org/10.1016/j.cmi.2016.05.008>.
25. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;**62**(4):e1–50. [PubMed ID: 26679628]. [PubMed Central ID: PMC94725385]. <https://doi.org/10.1093/cid/civ933>.
26. Battistolo J, Glampedakis E, Damonti L, Poissy J, Grandbastien B, Kalbermatter L, et al. Increasing morbidity and mortality of candidemia over one decade in a Swiss university hospital. *Mycoses*. 2021;**64**(12):1512–20. [PubMed ID: 34587318]. [PubMed Central ID: PMC9298218]. <https://doi.org/10.1111/myc.13376>.
27. Siopi M, Tarpatzi A, Kalogeropoulou E, Damianidou S, Vasilakopoulou A, Vourli S, et al. Epidemiological trends of fungemia in Greece with a focus on candidemia during the recent financial crisis: A 10-year survey in a tertiary care academic hospital and review of literature. *Antimicrob Agents Chemother*. 2020;**64**(3). [PubMed ID: 31871083]. [PubMed Central ID: PMC97038287]. <https://doi.org/10.1128/aac.01516-19>.
28. Chang MR, Correia FP, Costa LC, Xavier PC, Palhares DB, Taira DL, et al. Candida bloodstream infection: data from a teaching hospital in Mato Grosso do Sul, Brazil. *Rev Inst Med Trop Sao Paulo*. 2008;**50**(5):265–8. [PubMed ID: 18949342]. <https://doi.org/10.1590/s0036-46652008000500003>.
29. Farmakiotis D, Kyvernitakis A, Tarrand JJ, Kontoyiannis DP. Early initiation of appropriate treatment is associated with increased survival in cancer patients with Candida glabrata fungemia: a potential benefit from infectious disease consultation. *Clin Microbiol Infect*. 2015;**21**(1):79–86. [PubMed ID: 25636931]. <https://doi.org/10.1016/j.cmi.2014.07.006>.
30. Nucci M, Anaissie E, Betts RF, Wu C, Buell DN, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. *Clin Infect Dis*. 2010;**51**(3):295–303. [PubMed ID: 20578829]. <https://doi.org/10.1086/653935>.
31. Nucci M, Braga PR, Nouér SA, Anaissie E. Time of catheter removal in candidemia and mortality. *Braz J Infect Dis*. 2018;**22**(6):455–61. [PubMed ID: 30468708]. [PubMed Central ID: PMC9425687]. <https://doi.org/10.1016/j.bjid.2018.10.278>.
32. Kim SH, Yoon YK, Kim MJ, Sohn JW. Risk factors for and clinical implications of mixed Candida/bacterial bloodstream infections. *Clin Microbiol Infect*. 2013;**19**(1):62–8. [PubMed ID: 22651822]. [PubMed Central ID: PMC3563231]. <https://doi.org/10.1111/j.1469-0691.2012.03906.x>.
33. Muderris T, Kaya S, Ormen B, Aksoy Gokmen A, Varer Akpinar C, Yurtsever Gul S. Mortality and risk factor analysis for Candida blood stream infection: A three-year retrospective study. *J Mycol Med*. 2020;**30**(3):101008. [PubMed ID: 32651136]. <https://doi.org/10.1016/j.mycmed.2020.101008>.
34. Tukenmez Tigen E, Bilgin H, Perk Gurun H, Dogru A, Ozben B, Cerikcioglu N, et al. Risk factors, characteristics, and outcomes of candidemia in an adult intensive care unit in Turkey. *Am J Infect Control*. 2017;**45**(6):e61–3. [PubMed ID: 28359611]. <https://doi.org/10.1016/j.ajic.2017.02.022>.
35. De Waele JJ, Akova M, Antonelli M, Canton R, Carlet J, De Backer D, et al. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. *Intensive Care Med*. 2018;**44**(2):189–96. [PubMed ID: 29288367]. <https://doi.org/10.1007/s00134-017-5036-1>.