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Analysis of candidemia cases in a city hospital during the COVID-19 pandemic

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Abstract. – OBJECTIVE: The frequency and mortality of candidemia remain important. Non-*albicans Candida* species such as *C. auris* are increasing.

PATIENTS AND METHODS: A retrospective review of adult patients diagnosed with bloodstream infection due to *Candida* species in the 17 months between July 1, 2020, and December 1, 2021, was performed. Yeast colonies grown in culture were identified by matrix-assisted laser desorption/ionization time-of-flight. Antifungal susceptibility tests of *Candida* strains were performed with Sensititre YeastOne (TREK Diagnostic Systems Inc., Westlake, Ohio) kits, and minimum inhibitory concentration values were evaluated according to the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.

RESULTS: In total, 217 patients (mean age 64.9±15.7 years) were included. *C. albicans* was the most common fungus (detected in 82 patients; 37.8%), followed by *C. parapsilosis* (17.1%), *C. glabrata* (15.2%), *C. tropicalis* (15.2%), and *C. auris* (9%). Candidemia developed in 175 (81.4%) of the cases during their intensive care unit stay. Fluconazole (41.0%) and caspofungin (36.4%) were the two most frequently used antifungal agents in antifungal therapy. There were 114 (52.3%) deaths in the study group. Mortality rates were found to be lower in patients infected with *C. parapsilosis* or *C. auris*. Age and previous COVID-19 infection were other important risk factors. When the 217 *Candida* spp. were examined, resistance and intermediate susceptibility results were higher when EUCAST criteria were used. While the two methods were found to be fully compatible only for fluconazole, a partial agreement was also observed for voriconazole.

CONCLUSIONS: As our study observed, the COVID-19 pandemic brought increasing numbers of immunosuppressed patients, widespread use of antibacterials, and central venous catheters, increasing the frequency and mortality of candidemia cases. All health institutions should be prepared for the diagnosis and treatment of candidemia. In addition, *C. auris*, the frequency of which has increased in recent years, is a new factor that should be considered in candidemia cases.

Key Words:
Candida auris, Fungemia, Candidemia, Hospital infection, COVID-19.

Introduction

Systemic fungal infections, especially in critically ill patients, are among the most common healthcare-associated infections. *Candida* species cause a large part of these infections[1]. Bloodstream infections caused by *Candida* species are a growing health threat, with serious economic burdens for thousands of people[2,3]. There has been a dramatic increase in candidemia in recent years, specifically due to the COVID-19 pandemic, which has resulted in prolonged patient stays and higher mortality rates and costs[4,5]. *Candida* spp. is a common isolate of nosocomial bloodstream infection with a high mortality rate of 15-49% and is a common cause of hospital bloodstream infection[6]. It accounts for 85% of fungal infections in intensive care units (ICUs)[7,8]. Almost 50% of them are *C. albicans*[9].

Candida spp., which is a part of our natural microflora, can cause a variety of systemic infections following disruption of mucous membranes, immunodeficiency, malignancies, renal failure, uncontrolled diabetes, or post-surgical procedures[1]. Common risk factors among adult patients are prolonged hospitalization, ICU admission, recent abdominal surgery, neutropenia, solid organ transplantation, malignancies, hemodialysis,

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recent use of broad-spectrum antibiotics, total parenteral nutrition, and central venous catheterization (CVC) or indwelling devices[10-12].

In recent years, the distribution of *Candida* species involved in candidemia has changed geographically. The proportion has shifted towards non-*albicans Candida*. *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* as prominent species[13,14]. *C. auris* is another species, first emerging in 2009 and becoming a serious threat with its rapid spread over the last decade[15,16].

Our hospital was opened during the first wave of the COVID-19 pandemic in Istanbul, the most crowded city of Türkiye with its 85 million population and where most immigrants are densely populated. Therefore, it was highly important to identify the epidemiology of candidemia at our new hospital without a stable flora base. This study aimed to identify the epidemiology of candidemia: its prevalence, species distribution, antifungal susceptibility, and effects on mortality in adult patients in our hospital. We believe that the results of our study might be useful for managing and treating candidemia cases.

Patients and Methods

Study Design and Patients

Istanbul Basaksehir Cam and Sakura City Hospital, with a total of 2,682 beds, 456 of which in ICUs, started inpatient admissions on 1 July 2020. We retrospectively analyzed adult patients diagnosed with bloodstream infection due to *Candida* species in the 18 months between 1 July 2020 and 1 January 2022. We included all patients aged 18 years or over with candidemia. Patients whose blood culture was evaluated as contaminated by C*andida* species were excluded from the study. A BACTEC FX automatic culture detection system (Becton Dickinson, Sparks, MD, USA) was used for blood culture. Yeast colonies grown in culture were identified using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry device (Microflex LT/SH Smart MS, Bruker Daltonics, Germany) and MALDI-Biotyper Compass IVD 4.2.90 database software. We used the Sabouraud dextrose agar sub-culture for the isolation of mixed colonies.

Antifungal Susceptibility Tests

Antifungal susceptibility tests of *Candida* strains isolated from blood samples were performed with Sensititre YeastOne (SYO)[17,18] (TREK Diagnostic Systems Inc., Westlake, Ohio, USA) kits in accordance with the manufacturer's instructions. SYO is a broth microdilution (BMD) method that provides minimum inhibitory concentration (MIC) results designed for susceptibility testing of fast-growing yeast strains. The test is colorimetric. Each plate contains an appropriate dilution of antifungal and colorimetric indicators. Microplates were incubated 24±2 hours at 35°C (24 hours were added to the incubation of yeasts that did not grow in the first 24 hours, such as *C. parapsilosis* and *C. guillermondii*). After incubation, MIC values were evaluated according to the Clinical and Laboratory Standards Institute (CLSI) M27-A4[19] and M60 (2nd edition)[20] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) v.10.0[21] clinical breakpoints separately. The reading was done as recommended by the commercial company, which, according to the color, changed from blue to pink. The in-house BMD methods of CLSI and EUCAST differ, but since a commercial kit was used in our study, the method did not differ in terms of these two standards. Since the incubation temperature and incubation times are identical in both standards, the evaluation was made in common. The two standards for different antifungals were separated at the clinical breakpoints.

Data Collection

Demographic data of the patients, reasons for primary hospitalization, laboratory results, culture results, previous bacterial infection, antibiotic susceptibility results, antibacterial use before fungemia, empirical and subsequent antifungal treatment information, antifungal drug resistance, and length of hospitalization were examined. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Basaksehir Cam and Sakura City Hospital Local Ethics Committee (2022.01.04).

Statistical Analysis

For descriptive statistics, mean±standard deviation was used to present continuous data with normal distribution. A median with minimum-maximum values was applied to continuous variables without normal distribution. Numbers and percentages are used for categorical variables. Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were applied to analyze the distribution of numerical variables.

The Pearson Chi-square, Fisher's exact, and Fisher-Freeman-Halton tests were used to com-

pare the differences between categorical variables in 2×2 and R×C tables. Independent samples *t*-test was performed to compare two independent groups for numerical variables with a normal distribution. For variables without normal distribution, the Mann-Whitney U test was applied to compare two independent groups. Univariate and multivariate logistic regression analysis was used to analyze the independent risk factors impacting mortality.

For statistical analysis, the Jamovi project (2022), Jamovi (version 2.2.5.0) (retrieved from https://www.jamovi.org), and JASP (version 0.16.1) (retrieved from https://jasp-stats.org) were used. In all statistical analyses, the significance level (p) was determined at 0.05.

Results

There were 217 patients (mean age 64.9±15.7 years) in the study. Ages ranged between 20 and 67 years. The demographic and clinical characteristics are given in Table I. The primary diagnosis was COVID-19 in 64 of the patients; *C. auris* was isolated in 7 of these patients.

Distribution of Candida Spp.

The majority (79.3%) were treated in 2021. The distribution by month of patients diagnosed as having candidemia is shown in Figure 1. The incidence of *C. auris*-related candidemia increased during the COVID-19 pandemic waves observed in Istanbul. *C. albicans* was the most common species and was detected in 82 patients (37.8%), followed by *C. parapsilosis* (17.1%), *C. glabrata* (15.2%), and *C. tropicalis* (15.2%) (Figure 2).

Comparison of Clinical Features Between Non-surviving and Surviving Group

In the study group, there were 114 deaths, with a mortality rate of 52.3%. The non-surviving patients were significantly older (p=0.021) and had higher rates of active and past COVID-19 infections (p<0.001 and p=0.026). Comparison of the non-surviving and surviving patients revealed significant differences (Table I). The distributions of the causative species according to non-survival and survival are summarized in Table II. *C. albicans* was the most common pathogen in the non-surviving and surviving patients (40.4% *vs.* 35.0%). The mortality rates of patients infected with *C. parapsilosis* or *C. auris* were lower than those with another species. Table II and Figure 3 show the associations between different causative *Candida* species and mortality.

Echocardiography was performed in 79 patients to rule out fungal infective endocarditis, and a fundus physical examination was performed in 70 to rule out fungal retinitis. Intracardiac vegetation and fungal retinitis were each detected in three patients. There were no significant differences in the incidences of coexisting vegetations (p=0.251), retinitis (p=0.999), or abdominal pa-

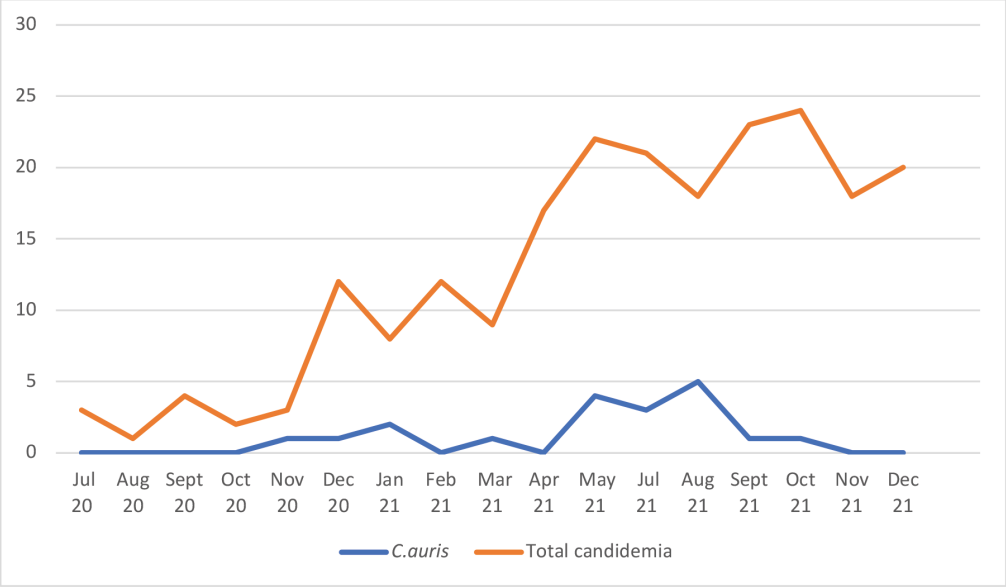

Figure 1. Distribution of number of cases diagnosed with candidemia by month.

Table I. Demographic and clinical characteristics of the patients.

		Patients		
	Overall (n=217)	Non-survived (n=114)	Survived (n=103)	*p*-value
Age (year)‡	64.9 ± 15.7	67.2 ± 15.0	62.3 ± 16.1	**0.021****
Sex†				
Male	114 (52.5)	64 (56.1)	50 (48.5)	0.326*
Female	103 (47.5)	50 (43.9)	53 (51.5)	
Primary diagnosis†				
COVID-19 infection	64 (29.5)	50 (43.9)	14 (13.6)	
Cancer	38 (17.5)	19 (16.7)	19 (18.4)	
Cerebrovascular disease	35 (16.1)	14 (12.3)	21 (20.4)	**<0.001***
Cardiovascular diseases	25 (11.5)	11 (9.6)	14 (13.6)	
Chronic renal failure	16 (7.4)	6 (5.3)	10 (9.7)	
Others	39 (18.0)	14 (12.3)	25 (24.3)	

†n (%). *Pearson Chi-square test/Fisher Exact test/Fisher Freeman Halton test. **Independent samples *t*-test.

Table II. Association of different causative *Candida* species with mortality.

	Candida albicans (n=82)	*Candida parapsilosis* (n=37)	*Candida glabrata* (n=33)	*Candida tropicalis* (n=33)	*Candida auris* (n=19)	Others (n=13)	*p*-value
Non-survived (n=114)†	42 (51.2)	14 (37.8)	21 (63.6)	21 (63.6)	8 (42.1)	8 (61.5)	**0.012***
Survived (n=103)†	40 (48.8)	23 (62.2)	12 (36.4)	12 (36.4)	11 (57.9)	5 (38.5)	

†n (%). *Pearson Chi-square test. Others: *Candida kefyr*, *Candida krusei*, *Candida dubleninsis*, *Candida guilliermondii*, *Candida inconspicua*.

thologies (p=0.905) between the non-survivors and survivors (Table III).

In 91.2% and 91.3% of the non-surviving and surviving patients, we detected bacterial infections before the development of candidemia. Pneumonia was the most common bacterial infection (42.4%) overall. CVC was used in 170 (78.3%) of the cases. CVC was more frequently required for non-survivors than for survivors (84.2% *vs*. 71.8%, p=0.041).

The mean hospitalization stay of the patients in our study before the diagnosis of candidemia was 26 days, and the mean ICU stay was 23 days. The mean total hospitalization stay of our patients was 72 days. In 175 (81.4%) of the cases, candidemia developed during the ICU stay, in 42 (18.6%) of the cases, candidemia developed during non-ICU bed stay, and 5 (11.9%) of these 42 patients required hospitalization in ICU.

Antibacterial/Antifungal Treatment and Susceptibility Results

The details of the antibacterial and antifungal treatment in the study groups are given in Table IV. In 90.3% of the patients, antibacterial drugs were used. We started empirical antifungal treatment in 175 patients (80.6%). Fluconazole (41.0%) and caspofungin (36.4%) were the two most common antifungal agents used. The antifungal susceptibility results of Candida species in our study are shown in Figure 4, which is based on CLSI and EUCAST criteria. Although the in-house microdilution preparation methods (CLSI and EUCAST) differed for yeast, they met in common in the evaluation with the commercial kit. Antifungal susceptibility results were read after 24 hours, and for slow-growing strains such as *C. parapsilosis* and *C. guilliermondii,* 24 hours were added to the incubation. When the 217 *Candida* spp. were examined, more "susceptible" results were obtained using CLSI values compared to EUCAST criteria (631 *vs*. 558) (Figure 4). While the two methods were found to be fully compatible only for fluconazole, a partial agreement was also observed for voriconazole. CLSI has no MIC values for amphotericin B or posacanazole for any yeasts.

Risk Factors for Mortality

The univariate and logistic regression analysis of significant demographic and clinical variables

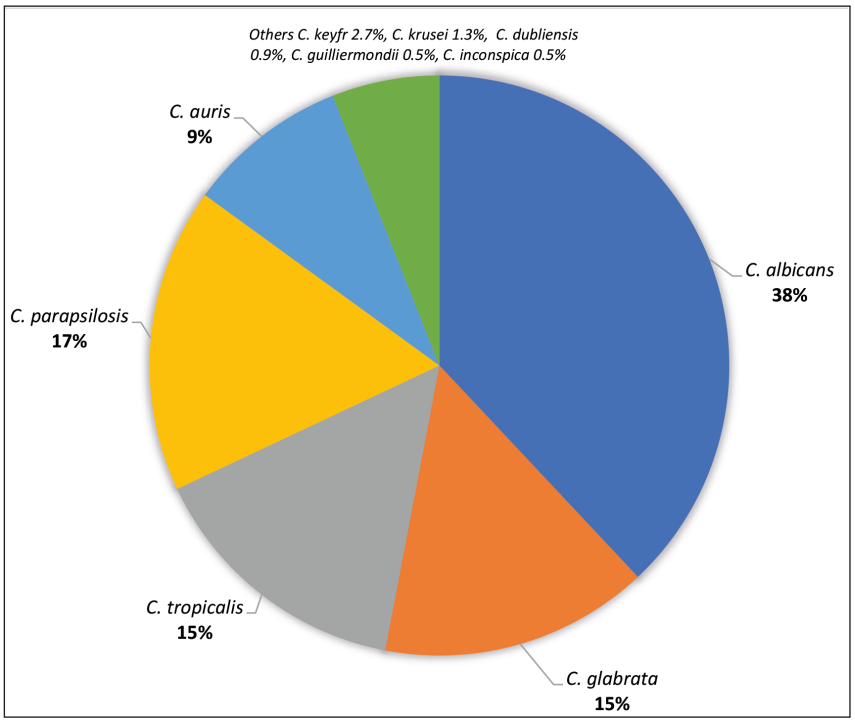

Figure 2. Distribution of *Candida* spp.

Table III. Coexisting pathologies and bacterial infections in the study groups.

	Overall (n=217)	Patients		*p*-value
		Non-survived (n=114)	Survived (n=103)	
Vegetations diagnosed *via* echocardiography†	3 (3.8)	2 (7.7)	1 (1.9)	0.251*
Retinitis diagnosed *via* fundoscopy†	3 (4.3)	1 (4.8)	2 (4.1)	0.999*
Abdominal pathologies†	32 (14.7)	16 (14.0)	16 (15.5)	0.905*
Bacterial infections before candidemia†	198 (91.2)	104 (91.2)	94 (91.3)	0.999
Types of bacterial infections†				
Pneumonia	84 (42.4)	42 (40.4)	42 (44.7)	
Urinary tract infection	13 (6.6)	6 (5.8)	7 (7.4)	
Complicated soft tissue infections	12 (6.1)	8 (7.7)	4 (4.3)	
Surgical site infections	3 (1.5)	0 (0.0)	3 (3.2)	
Bacteremia	16 (8.1)	6 (5.8)	10 (10.6)	
Intraabdominal infections	19 (9.6)	10 (9.6)	9 (9.6)	
Infective endocarditis	3 (1.5)	1 (1.0)	2 (2.1)	
Meningitis	4 (2.0)	0 (0.0)	4 (4.3)	
Sepsis	8 (4.0)	7 (6.7)	1 (1.1)	
Tuberculosis	4 (2.0)	1 (1.0)	3 (3.2)	
Other infections	32 (16.2)	23 (22.1)	9 (9.6)	
Central venous catheter application†	170 (78.3)	96 (84.2)	74 (71.8)	**0.041***

†n (%). *Pearson Chi-square test/Fisher Exact test/Fisher Freeman Halton test.

revealed that diagnosis of COVID-19 infection was a more significant risk factor for mortality than all primary diagnoses (Table V). Older age and previous COVID-19 infection were the other significant risk factors. Additionally, regression analysis showed that *C. auris* and *C. parapsilosis* infection were less risky for mortality compared with *C. albicans* ($p<0.05$) (Table V).

Table IV. Details of the antibacterial and antifungal treatment in the study groups.

		Overall (n=217)
Antibacterial drugs[†]		196 (90.3)
	Carbapenem	57 (26.3)
	Quinolones	17 (7.8)
	Piperacilline tazobactam	55 (25.3)
	Cefalosporine	10 (4.6)
	Glycopeptides	17 (7.8)
	Colistin	34 (15.7)
	Tigecycline	6 (2.7)
	No antibacterial drug treatment	21(9.6)
Antifungal treatment[†]		175 (80.6)
	Fluconazole	89 (41.0)
	Caspofungin	79 (36.4)
	Anidulafungin	4 (1.8)
	Amphotericin-B	2 (0.9)
	Micafungin	1 (0.4)
	No antifungal drug treatment	42 (19.3)

[†]n (%).

Table V. Univariate and multivariate logistic regression analysis of the variables regarding the development of mortality.

	Univariate analysis	Multivariate analysis
Age	1.02 [1.00-1.04, 0.023]	1.02 [1.00-1.04, 0.078]
Primary diagnosis		
COVID-19, reference	-	-
Cancer	0.28 [0.12-0.66, 0.004]	0.06 [0.01-0.27, 0.001]
Cerebrovascular disease	0.19 [0.07-0.45, <0.001]	0.04 [0.00-0.18, <0.001]
Cardivascular diseases	0.22 [0.08-0.58, 0.003]	0.04 [0.01-0.21, <0.001]
Chronic renal failure	0.17 [0.05-0.53, 0.003]	0.03 [0.00-0.18, <0.001]
Others	0.16 [0.06-0.37, <0.001]	0.04 [0.01-0.19, <0.001]
Previous COVID-19 infection	1.97 [1.13-3.48, 0.018]	0.15 [0.02-0.58, 0.017]
Causative *Candida* species		
Candida albicans, reference	-	-
Candida parapsilosis	0.48 [0.21-1.04, 0.067]	0.49 [0.20-1.13, 0.097]
Candida glabrata	1.37 [0.60-3.22, 0.459]	1.19 [0.48-3.06, 0.706]
Candida tropicalis	1.37 [0.60-3.22, 0.459]	1.37 [0.55-3.52, 0.500]
Candida auris	0.58 [0.26-0.63, 0.010]	0.66 [0.24-1.56, 0.234]
Others	1.25 [0.38-4.45, 0.713]	1.43 [0.38-5.78, 0.603]

Data are presented as Odds ratio [confidence interval 95%, *p*].

Discussion

This study, which has one of the highest numbers of candidemia cases in Türkiye, included 217 cases recorded within only 18 months at our recently opened hospital. A rise in the incidence of candidemia has been reported in some studies[9,22,23] starting from 2010. However, a much more significant increase in candidemia incidence has appeared in recent years in relation to the COVID-19 pandemic[24]. Among the reasons for this increase are nosocomial infections, the high use of antibiotics, steroids, and immunomodulators, the shortage of healthcare workers in contrast to the plethora of patients, and the lack of compliance with isolation rules. The 217 candidemia cases reported in a short time in our single-center study starting in 2020 during the pandemic provide support for this rise in incidence. In addition, MALDI-TOF is not a standard practice in diagnosing candidemia in Türkiye, but our hospital is one of the rare hospitals where MALDI-TOF is used. Thus, it was ensured that candidemia was identified at least 24 hours earlier than when other conventional and automated systems were used. Also, our hospital is a last-step hospital and has the highest number of immunosuppressed and complex

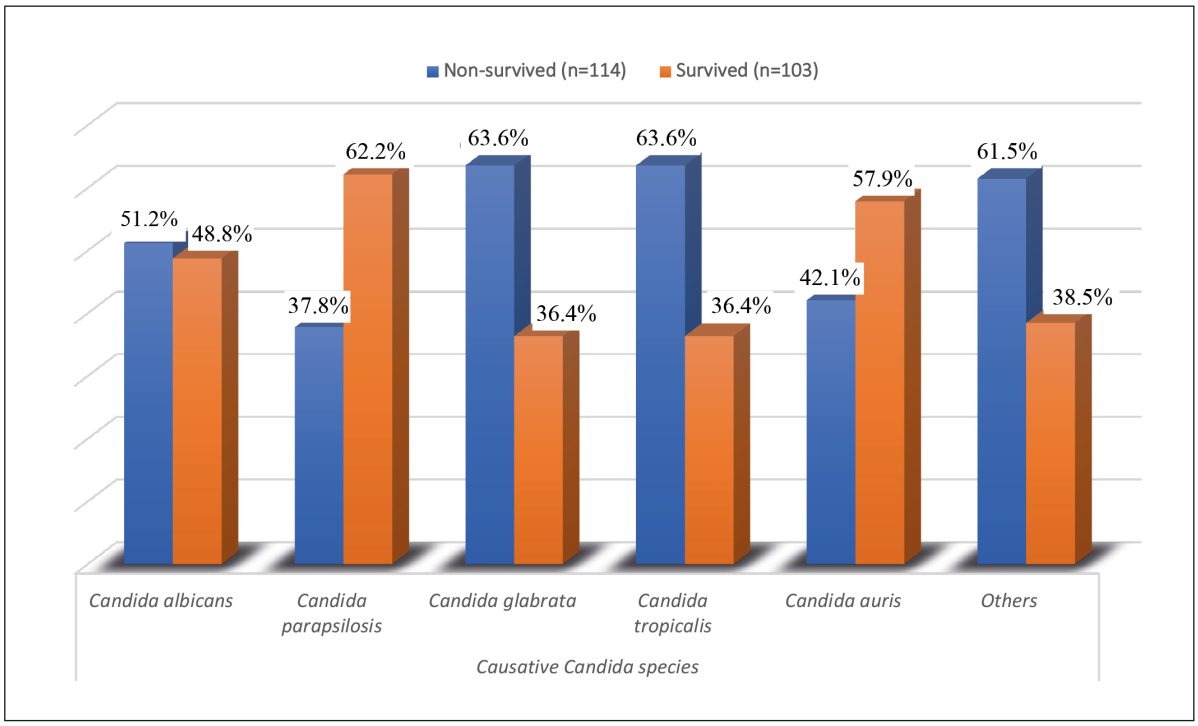

Figure 3. Distribution of candidal pathogens in non-surviving and surviving patients.

patients and the most ICU beds. For all these reasons, we think that the rate of candidemia cases was found to be higher than expected.

In our study, the primary hospitalization reasons among the candidemia cases, ordered from most frequent to least, were COVID-19, malignancy, cerebrovascular accident, cardiovascular disease, and renal failure. In several studies[25-28], risk factors are shown to be CVC, total parenteral nutrition, stay in ICU, mechanical ventilation, recent corticosteroid and antibiotic use, neutropenia, sepsis, cardiac/renal comorbidities, COVID-19, and malignancy. CVC and antibiotic use were present in 78.3% and 90.3% of the cases in our study, respectively. In all, 29.5% of the cases in our study were hospitalized primarily because of COVID-19. For this reason, we think being hospitalized for COVID-19 might increase the risk of developing candidemia.

The most dominant *Candida* species known in history is *C. albicans*. It was the most frequently seen agent in our study as well, with a percentage of 37.8. However, an increase in non-*albicans Candida* species has recently been shown[1,26]. Accordingly, in our study, non-*albicans* species had a percentage of 62.2.

	Fluconazole							Voriconazole						Posaconazole					Caspofungin						Anudilafungin						Micafungin						Amphotericin B					
	CLSI				EUCAST			CLSI			EUCAST			CLSI			EUCAST		CLSI			EUCAST*			CLSI			EUCAST			CLSI			EUCAST			CLSI			EUCAST		
	S	IM	SDD	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R	S	IM	R
C. albicans (n=82)	63		2	8	63	2	8	54	2	14	48	6	16				56		11	72	1	1	41		3	64	3	1	47		21	64		6	55		11				72		1
C. glabrata (n=33)			3	3		23	6													30			27		1	28		1	27		2	29		1	28		2				28		1
C. krusei (n=3)								3												1						2					2	3									2		
C. kefyr (n=6)																																											
C. parapsilosis (n=37)	31			6	31		6	29	3	5	29	3	5							37			37			32			32			37			37						36		
C. tropicalis (n=33)	23		2	5	23	2	5	8	21	1	8	9	13						27	30						28			24		4	30									27		3
C. auris (n=19)																																										
C. dubliniensis (n=2)					2						2						2																								2		
C.inconspicua (n=1)																																										
C. guilliermondii (n=1)																																										

*Isolates that are susceptible to anidulafungin as well as micafungin should be considered susceptible to caspofungin, until caspofungin breakpoints have been established. EUCAST breakpoints have not yet been established for caspofungin, due to significant inter-laboratory variation in MIC ranges for caspofungin.

Figure 4. Antifungal susceptibility test results of *Candida* species according to MIC values for CLSI and EUCAST.

Table VI. 30-day mortality rates of some studies.

Study name	Study population (n=)	Total mortality (%)	Mortality of *C. Albicans* (%)	Mortality of Non-*albicans* (%)
Ulu Kilic et al[9]	351	40.7	36.1	39.6
Salehi et al[1]	74	47.3	50	46
Alhatmi et al[26]	532	39.9	35.9	41.3
Hou et al[31]	259	18.1	22	15.7
El Zakhem et al[32]	138	43.6	33.3	48.9
Mazzanti et al[22]	188	41	39.7	42.2
Maurille et al[36]	209	27.9		

Data are presented as Odds ratio [confidence interval 95%, *p*].

Table V. Univariate and multivariate logistic regression analysis of the variables regarding the development of mortality.

	Univariate analysis	Multivariate analysis
Age	1.02 [1.00-1.04, 0.023]	1.02 [1.00-1.04, 0.078]
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Chronic renal failure	0.17 [0.05-0.53, 0.003]	0.03 [0.00-0.18, <0.001]
Others	0.16 [0.06-0.37, <0.001]	0.04 [0.01-0.19, <0.001]
Previous COVID-19 infection	1.97 [1.13-3.48, 0.018]	0.15 [0.02-0.58, 0.017]
Causative *Candida* species		
Candida albicans, reference	-	-
Candida parapsilosis	0.48 [0.21-1.04, 0.067]	0.49 [0.20-1.13, 0.097]
Candida glabrata	1.37 [0.60-3.22, 0.459]	1.19 [0.48-3.06, 0.706]
Candida tropicalis	1.37 [0.60-3.22, 0.459]	1.37 [0.55-3.52, 0.500]
Candida auris	0.58 [0.26-0.63, 0.010]	0.66 [0.24-1.56, 0.234]
Others	1.25 [0.38-4.45, 0.713]	1.43 [0.38-5.78, 0.603]

Data are presented as Odds ratio [confidence interval 95%, *p*].

In 19 of the candidemia cases in our study, the pathogen was found to be *C. auris*, which has spread throughout the world fairly quickly in the past 10 years, causing serious breakouts that are difficult to diagnose and resilient to antifungal medications. Being able to cause nosocomial infections, *C. auris* poses a new health threat[5,16,29,30]. Increases in the empirical use of antibacterial/antifungal medications and an escalated number of immunosuppressed patients due to the COVID-19 pandemic have facilitated the spread of this pathogen. The incidence of *C. auris*-related candidemia was assessed to be elevated at our hospital during the second wave (November and December 2020), and third wave (April and May 2021) of the COVID-19 pandemic observed in Istanbul (Figure 2).

The total mortality rate, the mortality rate of candidemia caused by *C. albicans*, and the mortality rate of candidemia caused by non-*albicans* pathogens were 52.5%, 51.2%, and 53.3%, respectively. The mortality rates of candidemia reported in randomly selected studies are illustrated in Table VI[31,32]. Though the rates differed in these studies, the mortality rate in our study was higher than that reported. The reason behind this ascent in our patients with candidemia was the existence of COVID-19. The isolated mortality rate in the candidemia cases with COVID-19 in our study was 78.1%. In concordance with the literature[25,27,33], our findings indicate that COVID-19 is a risk factor that increases mortality. As shown in other studies[1,25,34] as well, age was another risk factor for mortality. Regarding candidemia mortality, some studies[22,26] have concluded that mortality is lower with the *C. parapsilosis* pathogen. Similarly, in our study, candidemia caused by *C. parapsilosis* exhibited lower mortality. When compared to *C. albicans*, *C. auris* infection has

been shown to pose less risk with regard to mortality.

In our study, before being diagnosed as having candidemia, the patients had a mean hospital stay of 26 days and a mean intensive care unit stay of 23 days. Patients with a mean total hospitalization stay of 72 days were more likely to be diagnosed. The duration of our study was longer than that of some of the studies in our literature research[34-36]. We think that COVID-19, being a coexisting infection within our patient group, might be the reason behind the longer hospital stay since severe COVID-19 patients need to be in hospital for longer periods.

In our study, 42 patients (19.3%) died before an antifungal agent could be administered. Among those who received treatment, fluconazole (41.0%) and echinocandins (38.7%) were the most commonly used. Our literature research[25,33,36] showed that in the treatment of candidemia, the most preferred first-line antifungal agent is echinocandins. Kato et al[37] demonstrated that the patients who receive echinocandins for the treatment of candidemia, in comparison to those receiving liposomal amphotericin B, have lower mortality. However, some studies[22] favor fluconazole as a first-line agent as well.

There are two standards for BMD testing of yeasts published by CLSI and EUCAST. Both reference methodologies generate reproducible and reliable *in vitro* susceptibility data, which is essential for the development of interpretive criteria. However, for both methodologies, in-house preparation of the plates is labor-intensive and requires extensive quality control, and plates must be stored at -70°C (≤6 months), which challenges their routine use. Instead, many laboratories rely on commercial antifungal susceptibility test methods, like the SYO microdilution plate[17,18]. In our study, we also aimed to examine whether evaluating the CLSI or EUCAST clinical breakpoints separately according to these two standards after using SYO in the antifungal evaluation changed the susceptibility results. In the examination of 217 *Candida* spp., resistance, and intermediate susceptibility results were higher when EUCAST criteria were used (Figure 4). While the two methods were found to be fully compatible only for fluconazole, which van Hal et al[38] mentioned in their study, a partial agreement was also observed for voriconazole. CLSI has no MIC values for amphotericin B or posacanazole.

CLSI and EUCAST are two major international organizations that set the standard for detecting the antimicrobial susceptibility of microorganisms, but there are differences in clinical breakpoints as well as in microorganisms and standardized antimicrobial diversity. Sometimes, when the antimicrobial clinical breakpoint of the microorganism is not found in EUCAST, these problems can also be encountered when it is necessary to look at the CLSI. Therefore, when the MIC results obtained in our study were evaluated according to CLSI or EUCAST, we examined whether there would be a difference in antifungal susceptibility results. EUCAST had standardized more antifungal MIC results for more *Candida* spp. relative to CLSI (Figure 4). Since the different results to be obtained may be confusing for the clinician, laboratories should choose a standard suitable for their functioning and make their evaluations based on it.

Conclusions

As was observed in our study, due to reasons such as the COVID-19 pandemic, the upsurge of immunosuppressed patients, the extensive use of antibacterial agents, and prolonged CVC, the incidence of candidemia cases and their mortality have increased. Rising in prevalence in recent years, *Candida auris* is a new agent that needs to be reckoned with when treating candidemia. As for antifungal susceptibility tests for *Candida* species, there are critical differences between CLSI and EUCAST criteria. Clinicians should be careful when choosing a therapeutic agent. In conclusion, all healthcare facilities should be well prepared for early diagnosis, effective treatment, and spread control of candidemia.

Conflict of Interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Ethics Approval

The study protocol was approved by the University of Health Sciences, Başakşehir Çam and Sakura City Hospital Local Ethics Committee (date: 20.01.2022, No.: 04). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

Not applicable due to the retrospective nature of the study.

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Data Availability
All data generated or analyzed during this study are included in this published article; the datasets are available from the corresponding author upon reasonable request.

Authors' Contributions
Idea/concept, writing the article, references, and fundings, materials: O.O., Design, control/ supervision: O.O., S.K., M.U.; Data collection and/or processing, analysis and/or interpretation, literature review: O.O., S.K., M.U., A.G.; Critical review: O.O., S.K., M.U., A.G., O.A.A; Other: O.O.

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