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Original Article

Epidemiology of Nosocomial Candidemia, Mortality, and Antifungal Resistance: 7-Year Experience in Turkey

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ABSTRACT: Candidemia is an important clinical condition that prolongs hospital stays and increases morbidity, mortality, and hospital costs. The aim of this retrospective study was to evaluate the epidemiological and microbiological characteristics of patients with candidemia between January 2013 and December 2019. Two hundred forty-one episodes of candidemia were observed in 230 patients, 45% of whom were female. The median age was 63 years, and 53.9% of the episodes were in the intensive care unit (ICU). Commonly observed predisposing factors for candidemia included antibiotic use (71.3%), urinary catheterization (56.3%), central venous catheter placement (50.3%), total parenteral nutrition (47.9%), solid-organ malignancy (46%), surgery (48.6%), chemotherapy (37%), and steroid treatment (25.5%). The crude mortality rate was 52.7%. A significant difference was found between survivors and non-survivors (P = 0.007) according to the Charlson Comorbidity Index. However, no statistically significant association was found between mortality and age, sex, surgical procedure, catheter-related candidemia, or *Candida* spp. infection. The most frequently isolated *Candida* sp. was *C. albicans* (51%). Overall resistance rates to fluconazole, voriconazole, caspofungin, micafungin, and flucytosine were 3.7%, 0%, 2.5%, 1.8%, and 1.8%, respectively. Consequently, there is a need for tests that provide higher success rates, rapid diagnosis of candidemia, and local epidemiological data on antifungal resistance.

INTRODUCTION

Candidemia is an important clinical condition that prolongs hospitalization and increases morbidity, mortality, and hospital costs. In the 1980s, candidemia spread rapidly, with *Candida albicans* being the most common pathogen. However, in the late 1990s, the prevalence of other *Candida* species (spp.) began to increase. Moreover, sensitivity to antifungal agents has changed in parallel with changes in the distribution of *Candida* spp. in candidemia cases, and resistance of *Candida* spp. to triazole and echinocandins is increasing rapidly (1,2).

Several risk factors for candidemia cases have been identified, including severe neutropenia, solid-organ transplantation, hematological and solid-organ malignancies, steroid use, cytotoxic drug use, prolonged antibiotic use, intensive care unit (ICU) admission, and invasive interventions (3,4).

Between January 2013 and December 2019, we conducted a retrospective cross-sectional study to evaluate the epidemiological and microbiological development of candidemia in patients over a seven-year period.

MATERIALS AND METHODS

Institution: This study was conducted in a tertiary care hospital in Turkey with a bed capacity of 800 beds, 600 of which are actively used in the Istanbul Medipol University Medical Faculty Hospital, a tertiary care hospital where solid-organ and hematopoietic stem cell transplantation is performed and all intensive care units have 90 beds.

The study enrolled adult patients who had spent more than 48 h in the hospital between 2013 and 2019 and subsequently developed candidemia. Patient

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demographic characteristics and laboratory results were recorded using an automated recording system.

Candidemia cases were defined as at least one positive blood culture for *Candida* spp. and systemic inflammatory response.

In patients with a central venous catheter (CVC) placed for more than 48 h, blood from the catheter and peripheral blood were cultured simultaneously. Catheter-related candidemia was defined as (i) cases of positive *Candida* spp. in a catheter blood culture taken at least two hours before the peripheral blood culture or (ii) cases in which the same *Candida* spp. were obtained from both the peripheral blood culture and the catheter tip culture.

Isolation of two different *Candida* spp. from blood cultures performed on the same day was defined as mixed candidemia. If there was a period of more than 30 days between *Candida*-positive blood cultures in a single patient, this was defined as a new episode. The development of acute renal failure (ARF) after candidemia was defined as a 25% decrease in glomerular filtration rate or a 50% increase in baseline creatinine value. Platelet counts were recorded on day 0 (the day of candidemia diagnosis) and on days 3, 7, 14, and 28 after candidemia diagnosis. Thrombocytopenia was defined as $< 150{,}000/mm^3$, and the percent change in platelet count was computed. On the day of blood culture, mean platelet volume (MPV) and albumin levels were recorded. The normal MPV range was approximately 7–12 femtoliters (fL). The start of antifungal therapy was defined as the time when antifungal drug therapy was started, after the day on which a blood culture was obtained. Death occurring within 30 days of a candidemia attack was defined as crude mortality (1).

Microbiological evaluation—Yeast identification: Blood cultures obtained from hospitalized patients were incubated in a continuously monitored BacT/ALERT (bioMérieux, Marcy-l'Étoile, France) culture system in a microbiology laboratory. The gram-stained smears from bottles with evidence of positive growth were examined microscopically to observe the pathogens. Catheter tip samples were obtained from patients with suspected catheter-related candidemia and evaluated by the semiquantitative catheter tip culture method of Maki et al. (5). Isolated yeast colonies were identified to the species level using Candida medium (CHROMagar™ Candida; BD, Franklin Lakes, NJ, USA) and VITEK 2 (bioMérieux).

Microbiological evaluation—Antifungal susceptibility testing (AFST): Between 2013 and 2019, AFST was performed on 194 of the 241 *Candida* isolates using the VITEK 2 automated system (bioMérieux). This method has a high degree of categorical agreement with the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (6–8). Minimum inhibitory concentrations (MICs) were interpreted according to CLSI M27-A3 breakpoints.

Statistical analysis: All data is expressed as median and mean ± SE. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for potential risk factors. The Chi-square test or Fisher's exact test was used to compare proportions, and the Student's *t*-test was used to compare means. The Mann–Whitney U test was used for variables that were not normally distributed. The Wilcoxon non-parametric signed-rank test was used to compare severities because the data deviated from the normal distribution. All *P*-values reported were two-sided, and a *P*-value of less than 0.05 was considered statistically significant. Potential factors identified by univariate analyses were further evaluated using Cox regression analysis to determine independent predictors of survival.

Ethical status: This study was conducted in accordance with the relevant laws and guidelines and according to the ethical standards of the Declaration of Helsinki. The Ethics Committee of Istanbul Medipol University approved this study.

RESULTS

Two hundred forty-one episodes of candidemia were observed in 230 patients. Most of the patients were male (55%). The median age was 63 years, and 130 (53.9%) of the episodes were in the ICU. One hundred twelve patients (48.6%) had undergone a surgical procedure (mostly abdominal) in the three months preceding the onset of candidemia episodes. Commonly observed predisposing factors for candidemia included antibiotic use (71.3%), urinary catheterization (56.3%), CVC placement (50.3%), total parenteral nutrition (TPN) (47.9%), solid-organ malignancy (46%), chemotherapy (37%), and steroid treatment (25.5%) in the past three months. The incidence rate of catheter-related candidemia was 37.7%. The crude mortality rate was 52.7% during this study period, and the average time of death was 18 days after the onset of candidemia (Table 1 and Fig. 1). The crude mortality rates in the ICU, internal medicine, and surgical wards were 34.9%, 12%, and 5.1%, respectively. Most patients in the internal medicine ward had solid-organ malignancies. A significant difference was found between survivors and non-survivors ($P = 0.007$) according to the Charlson Comorbidity Index (CCI). The mortality rate increased more than 3.6-fold in patients with high CCI scores. Empiric antifungal therapy was initiated in 72 patients (31.4%) on day 0 of fever. A significant correlation was observed between fluconazole resistance and increasing CCI scores (3.5 vs 5, $P = 0.007$). Fluconazole resistance was high in patients with high CCI scores. A Cox regression analysis was performed for the factors that were significantly associated with mortality in univariate analysis (Table 2). All-cause mortality was significantly associated with a high CCI ($P = 0.013$), ICU stay ($P = 0.004$), percent changes in platelet count at day 3 ($P = 0.018$), and MPV ($P \leq 0.001$) (Table 3). Because of the high association between MPV values and mortality, the potential cutoff point was determined, and a receiver operating characteristic curve analysis was performed (Fig. 2). The MPV cutoff value was set at 10.25 fL. When this value was >10.25 fL, the prediction of mortality was 79%, 47%, 61%, and 69% for sensitivity, specificity, positive predictive value, and negative predictive value (NPV), respectively. However, no statistically significant association was found between mortality and age, sex, empiric or established antifungal therapy, surgery, catheter-related candidemia,

Table 1. Characteristics of 230 patients and 241 candidemia episodes observed between 2013 and 2019

	No.	%
Age, mean (range)	63 (18–100) years	
Sex		
Female	103	
Male	127	
Comorbidity		
Hypertension	86	38
Diabetes mellitus	54	23
Chronic obstructive pulmonary disease	28	12
Coronary artery disease	30	13
Congestive heart failure	26	11
Chronic renal failure	18	8
Cerebrovascular event	25	11
Solid-organ malignancy	106	46
Hematological malignancy	14	6
Solid-organ transplantation	10	4
Surgical procedure type		
General surgery	46	20
Cardiovascular surgery	26	11
Urological surgery	12	5
Others	28	12
Admitting service at time of candidemia		
Medical	70	30.4
Surgical	41	17.8
Intensive care unıt	130	56.5
Predisposing factors		
Surgery	112	49
Urinary catheter	133	59
Central venous catheter	109	48
Total parenteral nutrition	117	52
Corticosteroids	64	28.5
Chemotherapy	79	35
Use of antibiotic agents ≥10 days	143	63.8
Prior antifungal use	58	25.8
Catheter related candidemia attack	91	37.7
Candida species		
Candida albicans	123	51
Candida glabrata	36	15
Candida parapsilosi	35	14.5
Candida tropicalis	17	7
Other *Candida* spp.	30	12.5
Time of candidemia (after hospitalization), median (range)	15 (4–30) days	
Time of mortality (after candidemia), median (range)	18 (1–94) days	
Crude mortality in 241 candidemia episodes	127	52.7

renal failure, albumin level, or *Candida* spp. The most frequently isolated *Candida* sp. was *C. albicans* (51%), followed by *C. glabrata* (15%), *C. parapsilosis* (14.5%), *C. tropicalis* (7%), and others (12.5%) (Table 1). The prevalence of non-*albicans Candida* spp. increased from 42.3% to 66.6%, whereas that of *C. albicans* decreased from 57.6% to 33.3% over the 7-year period (Fig. 3). AFST was performed on 194 of 241 agents. Overall resistance rates to fluconazole, voriconazole, caspofungin, micafungin, and flucytosine (according to CLSI) were 3.7%, 0%, 2.5%, 1.8%, and 1.8%, respectively. The rate of isolates with an amphotericin MIC of >1 mg/L was 2.7%.

DISCUSSION

Demographic characteristics of patients and predisposing factors: In our study, adult patients

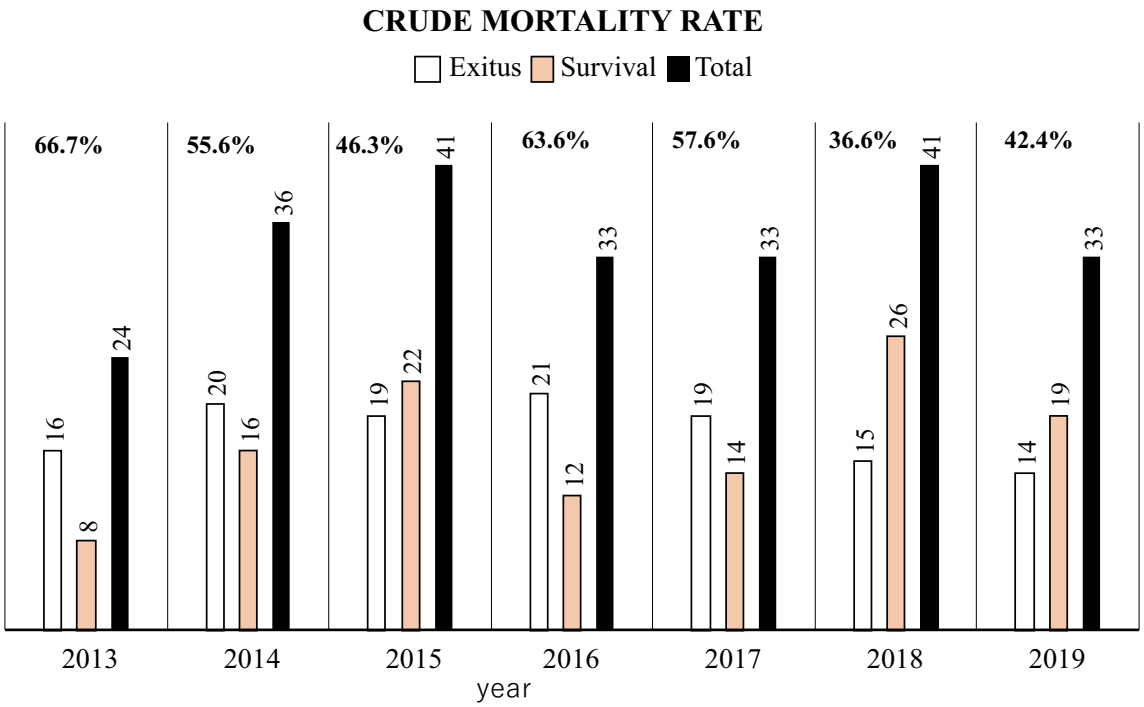

Fig. 1. (Color online) Crude mortality rate according to years in candidemia episodes.

Table 2. Univariate analysis of risk factors for 30-day mortality in patients with candidemia

Variables	*P* value	OR	95% CI
Age	0.197	1.007	0.997–1.017
Sex	0.413	0.869	0.622–1.215
Charlson comorbidity index (CCI)	0.002[1)]	1.125	1.046–1.215
ICU stay	0.001[1)]	0.472	0.338–0.675
The initiation antifungal therapy	0.498	0.981	0.928–1.037
Surgery	0.018[1)]	0.54	0.324–0.901
Transplantation	0.644	1.232	0.229–1.748
Febrile neutropenic attack	0.149	1.692	0.829–3.457
Chemotherapy	0.346	1.181	0.835–1.671
Steroid use	0.664	1.404	0.981–2.011
Catheter related candidemia	0.796	0.956	0.690–1.344
Central venous catheter	0.917	0.982	0.706–1.367
Intubation	0.002[1)]	1.689	1.211–2.357
Total parenteral nutrition	0.596	0.914	0.657–1.273
Acute renal failure	0.035[1)]	1.454	1.027–2.060
Creatinine	0.006[1)]	1.115	1.043–1.279
Albumin	0.002[1)]	0.565	0.397–0.802
White blood cell	0.001[1)]	1.030	1.013–1.047
Mean platelet volume	0.001[1)]	1.448	1.251–1.677
C-reactive protein	0.004[1)]	1.009	1.003–1.015
Percent changes in platelet count at day 0	0.627	1.000	0.999–1.002
Percent changes in platelet count at day 3	0.005[1)]	0.793	0.674–0.933
Percent changes in platelet count at day 7	0.002[1)]	0.755	0.633–0.901
Percent changes in platelet count at day 14	0.012[1)]	0.811	0.690–0.954
Percent changes in platelet count at day 28	0.137	0.851	0.680–1.052

[1)]: *P* value < 0.05.
OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Table 3. Cox regression analysis of risk factors for 30-day mortality in patients with candidemia

	P value[1)]	OR	95% CI
Charlson comorbidity index (CCI)	0.013	0.257	1.086–1.539
ICU stay	0.004	1.078	1.000–8.644
Percent changes in platelet count at day 3	0.018	0.996	0.665–0.963
Mean platelet volume	≤ 0.001	1.395	1.166–1.668

[1)]: *P* value < 0.05.
OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

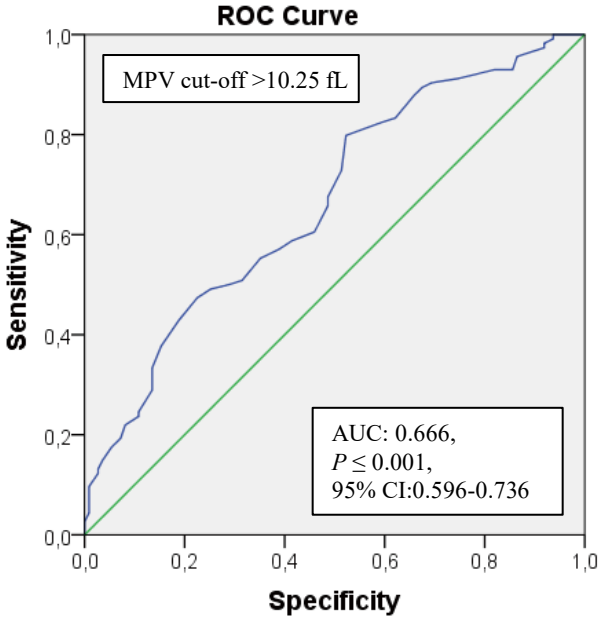

Fig. 2. (Color online) Receiver operating characteristic (ROC) curves for mean platelet volume (MPV) in predicting mortality. AUC, area under the curves; CI, confidence interval.

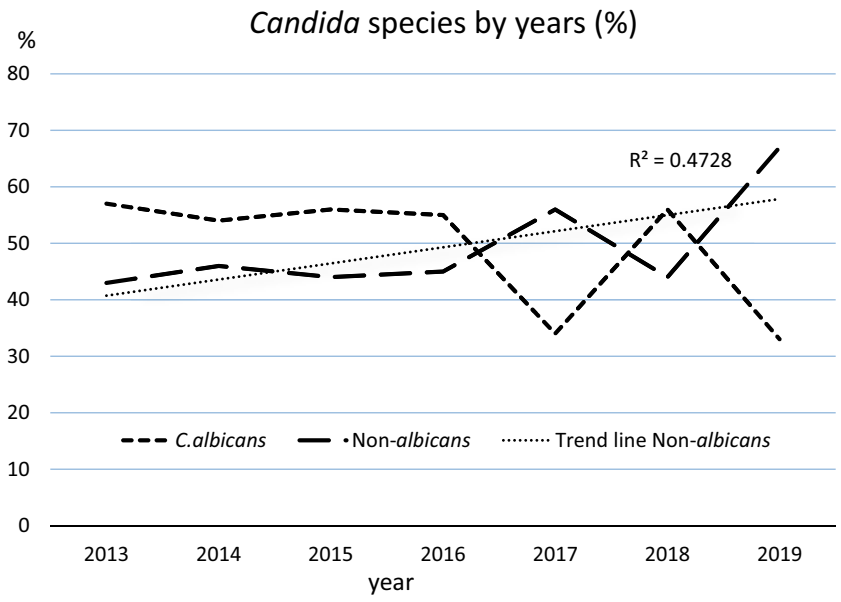

Fig. 3. (Color online) *C. albicans* and non-*albicans Candida* spp. distribution according to years (from 2013 to 2019).

with candidemia were retrospectively evaluated over a seven-year period. The most common risk factors for candidemia were long-term antibiotic use, urinary catheterization, TPN, previous surgery, and CVCs. Candidemia is most commonly seen in ICU admissions and in patients undergoing abdominal surgery. The most common underlying disease was malignancy of a solid organ (46%). The median age was 63 years, and most patients were male.

A systematic review and meta-analysis published in China reported that length of stay in the ICU was a risk factor for candidemia. In this study, the age at which cases were clustered ranged from 60 to 75 years, and they were relatively predominant in male patients (9).

In published studies, the most commonly identified risk factors for candidemia include ICU admission, previous surgery, immunosuppression, solid-organ malignancies and hematologic malignancies, CVCs, TPNs, mechanical ventilation, urinary catheters, and antibiotic and steroid use (10–14). Toda et al. (15) reported that 77% of patients had received systemic antibiotics, 24% had TPN, 73% had a CVC, and 33% had undergone surgery. Underlying disorders observed in patients with candidemia included diabetes mellitus (33%) and solid-organ malignancies (17%). A study in Brazil (16) found that the use of antibiotics (97.1%), the presence of a CVC (79.4%), corticosteroid therapy (55.9%), and surgery (55.9%) were the underlying factors. In a Portuguese hospital (11), antibiotic use (90.5%), presence of a CVC (74.3%), surgical history (60.9%), corticosteroid therapy (40.5%), mechanical ventilation (36.8%), and solid-organ malignancy (29.3%) were the underlying causes. Several studies have reported that candidemia cases are most frequently detected in ICUs and surgical wards (11,17–19).

Risk factors for candidemia observed in our patients included antibiotic use (63.8%), urinary catheterization (59%), TPN (52%), CVCs (48%), chemotherapy (35%), and steroid treatment (28%) in the past three months. Moreover, most patients with candidemia were admitted to the ICU and surgical ward. The results of our study are consistent with those of other studies in terms of risk factors for candidemia, underlying diseases, and the wards to which patients were admitted.

In our study, a 30-day crude mortality rate of 52.7% was observed. The crude mortality rate for candidemia was reported to range from 25% to 78% in the reviewed studies (11,15,16,18–23); however, the factors influencing mortality varied by institution. In an Australian study, risk factors for mortality were age >65 years, ICU admission, surgical procedures, hematologic malignancy, source of candidemia, chronic organ dysfunction, and antibiotic use. The 30-day mortality rate was reported to be 31% (24). Xiao et al. (10) identified the worst Glasgow Coma Score, PaO2/FiO2 ratio, and mean arterial pressure as risk factors. The mortality rate was 51.2% in their study. In a study from Finland, the severity of underlying illness, ICU admission at the onset of candidemia, and age >65 years were independent risk factors (17). In another study, septic shock, acute kidney injury, and prior antibiotic use were reported as risk factors (25). Schroeder et al. (21) found that advanced age, sequential organ failure assessment (SOFA), Candida scores, liver cirrhosis, septic shock, CVC duration, and length of ICU stay were risk factors for mortality. In this study, CCI, ICU length, surgery, intubation, ARF, basal creatinine, albumin, WBC, CRP, MPV, and percent change in platelet count on day 3, day 7, and day 14 were determined to be statistically significant in univariate analysis. However, only all-cause mortality was significantly associated with high CCI (OR: 0.25, 95% CI: 1.086–1.539, $P = 0.013$), ICU stay (OR: 1.078, 95% CI: 1.000–8.644, $P = 0.004$), changes in platelet count at day 3 (OR: 0.8, 95% CI: 0.665–0.963, $P = 0.018$), and MPV (OR: 1.39, 95% CI: 1.166–1.668, $P \leq 0.001$). In a prospective study conducted in Turkey, Kutluay et al. (26) reported that SOFA score, TPN, CVC removal, antibiotic use before candidemia, post candidemia renal failure, and thrombocytopenia were associated with 30-day mortality. Erden et al. (27) reported that ICU stay and CVC were associated with mortality. In our study, thrombocytopenia and percent platelet change were associated with mortality, whereas antibiotic use before candidemia, ARF, and the presence of CVC and TPN were not. Several publications have reported that MPV can be a diagnostic and prognostic indicator in sepsis and critically ill patients (28,29). In this context, when we evaluated MPV in terms of mortality, we found that an MPV >10.25 fL had sensitivity, NPV, and specificity of 79%, 69%, and 47%, respectively. The mean time to the initiation of antifungal therapy was two days. Antifungal drug therapy was initiated in 30% of cases when a blood culture was performed. No statistically significant correlation was found between delayed antifungal therapy and mortality. Although some studies (16,21,24) have identified advanced age, *Candida* spp., empiric or determined treatment, and catheter-related candidemia as independent risk factors for mortality, no statistically significant association was found between mortality and age, sex, empiric or determined antifungal therapy, catheter-related candidemia, or *Candida* spp. in our study.

Demographic characteristics of patients and predisposing factors; *Candida* spp. and antifungal susceptibility: The CLSI and EUCAST methods, along with the recommended broth microdilution (BMD) method, are generally accepted standards for testing susceptibility to fungi. However, these methods are time-consuming and difficult to implement in routine laboratory practice. Automated AFSTs (e.g., MALDI-TOF MS, VITEK 2) have shown up to 90–100% compatibility with reference methods in identifying antifungal susceptibility of *Candida* spp. (6,8,30,31).

In our study, the VITEK 2 automated system (bioMérieux) was used from 2013 to 2019 for both AFST and *Candida* spp. identification. As in other studies (10,15,16,32–34), we observed an increase in non-*albicans Candida* spp. The prevalence of non-*albicans Candida* spp. increased from 42% to 66%, and *C. albicans* was reduced from 57% to 33% over a seven-year period. In the epidemiology of candidemia, although the number of non-*albicans Candida* spp. has increased in recent years, *C. albicans* remains the most common species (13,17). In our study, resistance to fluconazole was 3.7%; caspofungin, 2.5%; and flucytosine, 1.8%. No voriconazole resistance was observed. For amphotericin, the MIC >1 mg/L was

observed in 2.7% of *Candida* spp. tested.

In a study conducted in the United States using customized microdilution plates (Trek Diagnostics), resistance to fluconazole and echinocandins was found to be 7% and 1.6%, respectively (15). In another study, all *Candida* spp. were found to be susceptible to amphotericin B, micafungin, and itraconazole. Resistance to fluconazole (5.1%) was detected using BMD (16). In a study from Finland (17), 16% resistance to fluconazole was detected, and most azole-resistant isolates were *C. glabrata*.

In the published articles, although fluconazole resistance was in the range of 5–15%, the increasing azole resistance usually resulted from *C. glabrata*. In our center, the resistance patterns and distribution of *Candida* species are similar to those in the published studies.

In conclusion, most candidemia cases occurred in patients in the ICU who had undergone surgery. The crude mortality rate was high in our center. Despite the improvements in healthcare services, development of identification systems, and availability of effective antifungal agents, the mortality rate for candidemia is relatively high. Local epidemiological data is critical for selecting appropriate antifungal agents and improving rational protocols for antifungal use.

Conflict of interest None to declare.

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