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Predictors of outcomes in patients with candidemia in an Intensive Care Unit

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ABSTRACT

Objective: Candidemia is a life-threatening infection that causes high mortality rates in intensive care units (ICUs). This study aims to evaluate predictors of the outcome of patients with candidemia in an ICU.

Patients and Methods: This observational, retrospective study included patients with *Candida* bloodstream infection (BSI) in ICUs between 6 years of the episode. A binary logistic regression analysis was conducted to inspect the association with mortality.

Results: The median age of 74 patients was 68.5, and 53.8% were men. *C. parapsilosis* was the most frequently isolated fungal species. The 30-day mortality rate was 50%. In the logistic regression model the Acute Physiology and Chronic Health Evaluation (APACHE) II score, positive blood culture on the seventh day, inotropes needed on the day of blood culture positivity, and ventilator-associated pneumonia (VAP) were significant risk factors for the outcome of patients. There was no difference in mortality between an early start of antifungal treatment or central venous catheter removal time.

Conclusion: A shift to *C. parapsilosis* is observed in this study. Host-related factors such as APACHE II score, need for mechanical ventilation or need for inotropes affect mortality more than early treatment and source control in patients with *Candida* BSI.

Keywords: *Candida*, Candidemia, Intensive Care Unit, Mortality, Outcome

1. INTRODUCTION

Candidemia is a bloodstream infection (BSI) caused by the yeast Candida. This infection is the fourth most common cause of healthcare-associated BSI, especially in patients admitted to intensive care units (ICU) [1]. It is estimated that the number of candidemia cases is nearly 25000 per year worldwide, and the attributable mortality rate rises by 30%-40%, especially in ICU patients [2]. Candidemia causes increased hospital costs and deaths in ICU patients. In these high-risk groups, the development of septic shock associated with candidemia, insufficient source control, and delay in antifungal treatment for more than 24 hours raise the mortality to 100% [3].

The most commonly isolated species of *Candida* BSI are *C. albicans*, *C. glabrata*, and *C. parapsilosis*. The *C. albicans* strain is predominant worldwide. However, some institutions have recently reported an increase in non-*albicans* strains in bloodstream isolates [4]. This increase in non-*albicans* strains, often resistant to antifungal drugs, has been a growing trend in all hospitals worldwide in recent years [4].

Several factors are associated with candidiasis, such as the use of broad-spectrum antibiotics, total parenteral nutrition (TPN), immunosuppressive status, recent abdominal surgery, and the presence of a central venous catheter (CVC) [5]. Early initiation of appropriate and adequate antifungal therapy in patients with *Candida* BSI is associated with a 50% reduction in mortality [6]. It has been reported in previous studies that early removal of a CVC leads to source control and betters outcomes for ICU patients with candidemia [3,7]. In recent years, some experts have shown that host-related factors might have a more crucial effect on the mortality of patients than delayed treatment or early catheter removal [8-10].

The present study aims to evaluate the epidemiologic data of our hospital, changes in the distribution of *Candida* strains over the years, and risk factors associated with the survival of patients with candidemia in the ICU.

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2. PATIENTS and METHODS

This was a retrospective, single-center, observational study conducted on adult hospitalized ICU patients with Candida BSI between April 2014 and January 2021. The ethics committee of our hospital approved this study on June 17, 2021 (approval no. B10.1.TKH.4.34.H.GP.0.01/197).

The following medical data of patients were collected from the hospital database: age, sex, comorbidities, and predisposing risk factors on the admission day to the ICU. *Candida* species (spp.) growth in at least one of the blood culture bottles in patients with clinical signs were defined as candidemia. If the blood culture specimen yielded a *Candida* spp. after 30 days in the same patient, it was considered a new infection. Early antifungal therapy was defined as the start of effective antifungal treatment within 48 hours after the first blood culture was drawn.

Ventilator-associated pneumonia (VAP) was defined as a new or progressive pulmonary infiltrate after at least two days of invasive mechanical ventilation (IMV) with clinical signs of infection. Prior corticosteroid use was defined as the use of a prednisolone 15 mg/day for more than two weeks.

Patients who were < 18 years of age, those transferred to another hospital within 30 days, and those who died before blood culture positivity were excluded from the study. Additionally, patients who developed candidemia before or within the first 48 hours of ICU admission were excluded. Because coronavirus disease 2019 (COVID-19) infection may be a confounding factor, ten patients who were monitored in intensive care units for COVID-19, developed candidemia, and died in 2019 were omitted from the study (Figure 1). The primary outcome was the 30-day survival of patients after culture positivity.

Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (VITEK MS [bioMérieux, France]), was used to isolate *Candida* species from blood culture bottles. Antifungal susceptibility testing was performed with a commercial kit based on colorimetric microdilution (Sensititre YeastOne antibiotic susceptibility test colorimetric plate [TREK Diagnostic Systems, Cleveland, OH, USA]) for some of the isolates, and an automated system (VITEK 2; bioMérieux, France) for the other isolates. The detected minimum inhibitory concentration values were interpreted by the Clinical and Laboratory Standards Institute guidelines [11]. The roll-plate semiquantitative method was used for catheter tips.

Statistical analysis

Statistical analysis results were presented as mean ± standard deviation and median (interquartile range [IQR]) for quantitative data and frequency (percent) for categorical data. The Shapiro-Wilk test was used to test whether data followed a normal distribution. The Mann-Whitney U test was used to compare non-normally distributed data, and the independent two-sample t-test was used to compare normally distributed data. Chi-square and Fisher's Exact tests were used to compare categorical variables for mortality. Risk factors affecting survival were analyzed by binary logistic regression analysis. P values < 0.05 was taken as statistically significant. IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY) was used for statistical analysis.

3. RESULTS

Seventy-four patients with candidemia, admitted to the ICU over six years, were included in the study. The median age of the participants was 68 years (IQR 23-95), and 59.4% were men. Of 74 patients, 31% needed inotrope infusion, and 54% required IMV during their ICU stay. The median Acute Physiology and Chronic Health Evaluation (APACHE) II score was 23.6 (8.7) during admission to the ICU. The median duration of a hospital stay was 32 days (IQR 2-64), and an ICU stay was 26 days (IQR 3-135) before blood culture positivity. In our patients, predisposing factors for candidemia were the use of TPN (71.6%), intravenous corticosteroids (35.1%), proton pump inhibitors (100%), and carbapenem (37%). The rate of abdominal surgery within one month was 28.3%. Thirty-eight (51.3%) of the patients had two or more comorbidities. The most common comorbidities were chronic cardiovascular disease (48.6%), neurological disease (35.1%), malignancy (32.4%), and diabetes mellitus (32.4%). Ninety-seven percent of patients had a CVC on the day of blood culture positivity (72/74). The CVC could not be removed after candidemia in 13 patients who died due to poor clinical conditions and lack of new vascular access. Table I shows the demographic and clinical characteristics of the patients.

The mortality rate was 50%. In univariate analyses, an increased mortality rate was associated with a higher C-reactive protein (CRP) level (P = 0.016), concomitant VAP (P= 0.01), higher APACHE II score (P= 0.003), need for IMV (P = 0.008), need for inotropes (P< 0.001), CVC removal at any time (P< 0.001), and positive blood culture on the seventh day despite starting antifungal treatment (P < 0.001). The days before CVC removal, CVC removal within 48 hours, starting early antifungal therapy (within 48 hours), or empirical treatment with fluconazole were not associated with mortality (Table I).

In the logistic regression analysis, the APACHE II score (odds ratio [OR] 1.135, 95% confidence intervals [CI] 1.028, 1.253), positive blood culture on the seventh day (OR 0.024, 95% CI 0.002, 0.237), need for inotropes at the onset of candidemia (OR 5.937, 95% CI 1.201, 29.35), and concomitant VAP (OR 9.798, 95% CI 1.644, 58.413) were strongly associated with mortality (Table II).

Nine different *Candida* species were identified in 74 candidemia episodes. *C. parapsilosis* (39.1%) was the most common spp. The distribution of species is given in Figure 2. The *albicans*/non-*albicans* ratio has changed over the six years of the study. The prevalence of *C. albicans* accounted for 50% until 2019. Over the last two years, an increasing trend of non-*albicans* spp. was observed, and *C. parapsilosis* has been the predominant isolate. Figure 3 shows the distribution of strains over the years.

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Table I. *Demographic and clinical characteristics of patients with candidemia: 30-day mortality*

Characteristics (N=728)	Total (N=74)	Survived (N= 37)	Non-survived (N= 37)	P value
Male gender, n (%)	44 (59.4)	23 (52.3)	21 (47.7)	.636*
Age (years), (median [IQR])	68.5 (57-84)	66 (48-79)	73 (58-85)	.078▲
≥65, n (%)	41 (55.4)	19 (46.3)	22 (53.7)	.483*
Days of hospital stay, (median [IQR])	32 (2-164)	33 (6-137)	31 (2-164)	.697▲
Days of ICU stay, (median [IQR])	26 (3-135)	28 (5-135)	24 (3-128)	.465▲
Comorbidities, n (%)				
≥2	38 (51.3)	16 (42.1)	22 (57.9)	.163*
Malignancy	24 (32.4)	11 (45.8)	13 (54.2)	.619*
Diabetes mellitus, n (%)	24 (32.4)	11 (45.8)	13 (54.2)	.619*
Neurologic disease, n (%)	26 (35.1)	16 (61.5)	10 (38.5)	.144*
Cardiovascular disease, n (%)	36 (48.6)	15 (41.7)	21 (58.3)	.163*
Renal disease, n (%)	4 (5.4)	1 (25)	3 (75)	.615**
Respiratory disease	10 (7.4)	4 (40)	6 (60)	.496*
Hepatic disease, n (%)	3 (4)	2 (66.7)	1 (33.3)	1.000**
Predisposing factors, (n, %)				
Total parental nutrition, n (%)	53 (71.6)	27 (50.9)	26 (49.1)	.797*
IV Corticosteroids, n (%)	26 (35.1)	13 (50)	13 (50)	1.000*
Abdominal surgery within 1 month, n (%)	21 (28.3)	11 (52.4)	10 (47.6)	.797*
Carbapenem use, n (%)	50 (37)	24 (48)	26 (52)	.619*
CRP level, (median [IQR])	11.2 (8.08-17)	9.2 (7.9-16.2)	13.3 (10-19)	.016*
VAP, n (%)	31 (41.8)	15 (36.6)	26 (63.4)	.010*
Apache II score	23.6 (8.7)	20.6 (8.7)	26.5 (7.8)	.003†
Characteristics after enrollment				
Candida spp.				
Non-*albicans*	47 (63.5)	25 (53.2)	22 (46.8)	.469*
C. albicans	27 (36.5)	12 (44.4)	15 (55.6)	
IMV, n (%)	47 (63.5)	18 (38.3)	29 (61.7)	.008*
Inotropes need at the onset of candidemia, n (%)	32 (43.2)	8 (25)	24 (75)	
CVC removal at any time, n (%)	13 (17.5)	0 (0)	13 (100)	
Days before CVC removal (median [IQR])	3 (1-5)	3 (1-5)	3.5 (2-5)	.423▲
Days before antifungal therapy, (median [IQR])	3 (1-4)	3 (2-4)	2 (1-4)	.204▲
Early antifungal therapy, n (%)	46 (60.5)	26 (44.4)	20 (55.6)	.352*
Empirical treatment with fluconazole	36 (48.6)	10 (25.6)	26 (41.9)	.096*
Positive blood culture on the seventh day, n (%)	18 (24.3)	2 (11.1)	16 (88.9)	
Days before sterile blood culture, (median [IQR])	4 (2-7)	4 (3-6.5)	3 (2-7)	.183▲

**Chi-square test, **Fisher's Exact test, ▲ Mann-Whitney U test, †independent two-sample t-test, VAP, Ventilator-associated pneumonia; IMV, Invasive mechanical ventilation; CVC, central venous catheter; ICU: Internal Care Unit*

Table II. *Multivariate logistic regression analysis of risk factors for 30-day mortality*

	OR (95% CI)	P value
Number of comorbidities	0.987 (0.366 – 2.659)	.979
Malignancy	1.237 (0.237 – 6.458)	.801
Days of ICU stay	1.008 (0.985 – 1.032)	.504
Apache II score	1.135 (1.028 – 1.253)	.012
Empirical antifungal therapy within 48 hours	0.378 (0.08 – 1.79)	.220
Positive blood culture on seventh day	0.024 (0.002 – 0.237)	.001
Inotrope need at the onset of candidemia, n (%)	5.937 (1.201 – 29.35)	.029
Chronic cardiovascular disease, n (%)	1.789 (0.195 – 16.428)	.607
Abdominal surgery within 1 month, n (%)	2.104 (0.367 – 12.053)	.404
VAP, n (%)	9.798 (1.644 – 58.413)	.012
Empirical treatment with fluconazole	0.314 (0.062 – 1.584)	.161

VAP, Ventilator associated pneumonia; ICU: Internal Care Unit

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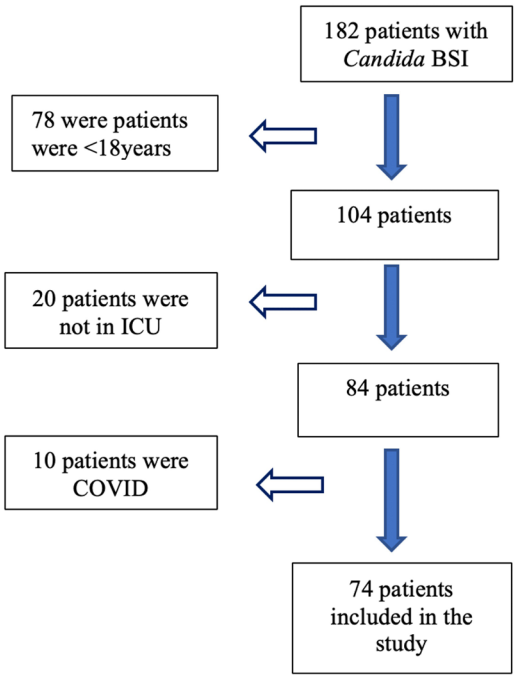

Figure 1. *Patients' inclusion diagram*

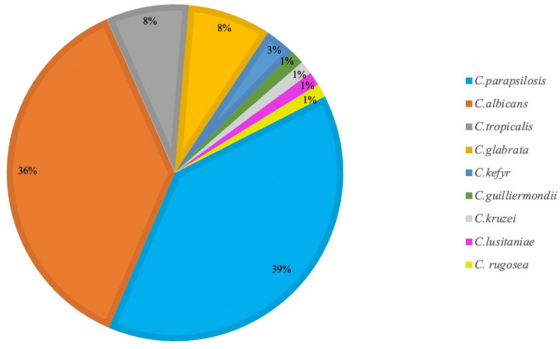

Figure 2. *Candida species distribution*

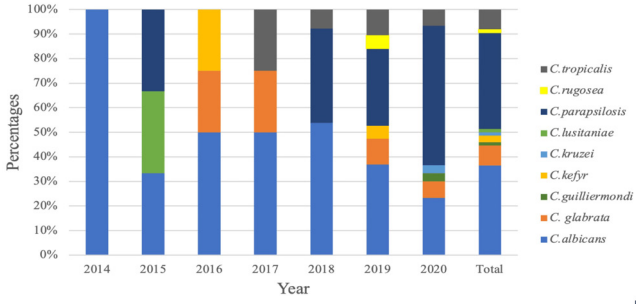

Figure 3. *Distribution of Candida species over the years*

4. DISCUSSION

A higher APACHE II score, positive blood culture on the seventh day after initiation of antifungal treatment, need for inotropes at the onset of candidemia, and a concomitant diagnosis of VAP were identified as risk factors for mortality. A high mortality rate was observed in the patients. *C. parapsilosis* was a commonly isolated species during the study period.

Mazzanti et al., showed that the mortality rate associated with candidemia was higher in ICU than in non-ICU patients (41% vs. 23%) [12]. Some investigators have reported that the overall mortality rates increase by up to 50% in critically ill patients and up to 70% in patients with septic shock [3,9]. The overall 30-day mortality rate was 50% in this study. Other investigators have reported similar mortality rates in ICU patients (52.7% and 51.2%) [12,13]. On the other hand, Tigen et al., report a mortality rate of 83.3%, and Karacaer et al., report 78% in ICU patients from studies in Turkey [14,15]. These differences may be associated with the different rates of comorbid illnesses, predisposing factors, patients' clinical conditions, and therapeutic approaches between centers.

Previous studies demonstrate that timely catheter withdrawal positively affects the outcome of patients with candidemia [3,7,16]. However, some authors mention that early CVC removal is not associated with a better outcome [9,10]. A nine-year study from Italy determined that host-related factors have a more significant effect than early removal of CVC on the outcome of ICU patients with candidemia [12]. Additionally, a randomized controlled study did not find any association between CVC withdrawal within 24 or 48 hours and the survival of patients [10]. In this study, an increased mortality rate was associated with CVC removal at any time during candidemia in the univariate analysis (P< 0.001) but was not significant in the multivariate analysis. Kutluay et al., show that the removal of CVC at any time after candidemia was associated with decreased mortality rates [17]. Furthermore, no association is found between CVC removal time and mortality. Since CVC is the source of infection, removal is an essential component of the approach to treating *Candida* infections. Future studies are needed to analyze the optimal time for the removal of the CVC.

In addition to the removal of the CVC, early intervention with appropriate antifungal therapy was generally associated with a better overall outcome. However, in this study, no association was found between starting empirical antifungal therapy within 48 hours and mortality, which is consistent with the findings of Nucci et al. [10]. Current studies have demonstrated that patients with *Candida* BSI are more critically ill than patients with bacteremia [18,19]. Recently published studies suggest that host-related factors significantly affect patients' survival with candidemia [8,9]. In this study, the APACHE II score at diagnosis, underlying diseases, organ support therapies like IMV, and vasopressor use were the most common predisposing conditions associated with candidemia, which might be associated with mortality [9,10]. Other studies show that septic shock is an independent factor for the outcome [12,20]. The authors find that host-related factors, such as the Apache II score,

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inotropes need on the day of candidemia, and a concomitant diagnosis of VAP, are independent risk factors for the outcome. In other studies from Turkey, a higher APACHE II score or SOFA score is associated with mortality [15,17]. The findings of this study show that host-related factors have a major influence on 30-day mortality rather than early treatment.

Follow-up blood cultures were obtained every other day to establish clearance of *Candida* spp. from the bloodstream. A positive blood culture with *Candida* spp. on the seventh day of antifungal treatment was associated with the worst outcome. A multicenter study conducted in South Korea found that patients with a positive blood culture with *Candida* spp. on the seventh day of hospitalization had nearly five times greater mortality risk [21]. The sensitivity of blood culture for diagnosing candidiasis is almost 50%. The persistence of candidemia seems to affect the outcome adversely.

Although, C. *albicans* remains the most isolated species worldwide, the incidence of non-*albicans* species has increased. The distribution of *Candida* species varies over time and geography. The use of fluconazole might affect the geographic differences in species distribution. In a 20-year surveillance study in which 20,788 *Candida* isolates were examined, *C. albicans* (46.9%) was the most isolated strain, and *C. glabrata* (18.7%) was the most common in the non-*albicans* species in all regions, except Latin America [22]. The surveillance studies demonstrated *C. parapsilosis* dominated non-*albicans* species in Latin America and Brazil (26.5% and 24.1%, respectively) [22,23]. A multicenter study from Colombia showed a change in epidemiology, with *C. parapsilosis* (38.5%) being the most identified isolate from 2008 to 2021 [24]. Similarly, *C. parapsilosis* became the predominant species during the last two years of this study. However, *C. albicans* was still the most commonly identified isolate, including in ICUs in most of the studies [14,15,17].

In this study, most patients had a CVC (98%). The association between *C. parapsilosis* and CVC-associated *Candida* BSI has been demonstrated in US hospitals [25]. The fact that most patients had a CVC may explain the rising trend of the *C. parapsilosis* strain in our ICUs. However, the different results in species distribution may be related to the hospital environment, the use of carbapenems or fluconazole, and the ICU settings of countries.

There are some limitations to this study. It was a single-center, retrospective, observational study. Second, only ICU patients were evaluated in this study.

Conclusions

Prospective multicenter randomized trials involving the outcome of a greater number of cases with *Candida* BSI are warranted. A higher APACHE II score, positive blood culture on the seventh day of follow-up, inotrope need at the onset of candidemia, and a concomitant diagnosis of VAP are independent risk factors for mortality in patients with *Candida* BSI. *C. parapsilosis* was the leading non-*albicans Candida* species in this study. It is crucial to closely monitor risk factors, especially host-related factors that significantly affect ICU patients' outcomes with *Candida* BSI.

Compliance with Ethical Standards

Ethical approval: Ethical approval was obtained from Umraniye Training and Research Hospital, Clinical Research Ethics Committee (approval no: B10.1.TKH.4.34.H.GP.0.01/197).

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Authors Contributions: ASO: Concept and design, LNA and MA: Collecting data, BES and MA: Analysis and interpretation. All authors read and approved the final version of the manusctipt.

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