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Candidemia in Older Adults: What Are the Risk Factors for Mortality?

Yaşlılarda Kandidemi: Mortalite Risk Faktörleri Nedir?

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ABSTRACT

Introduction: *As the aging population rises, an increase in Candida infections has also been observed. The aim of this study was to determine the risk factors for early and late mortality due to candidemia in older patients.*

Materials and Methods: *This retrospective observational study included patients aged 65 years and older who were hospitalized in two tertiary care centers and had Candida-positive blood culture between January 1, 2019 and June 1, 2021.*

Results: *Mean age of the 81 patients included in the study was 77.1 ± 7.1 years and 41 (50.6%) were females. The most commonly identified species were Candida albicans and Candida parapsilosis. After candidemia, early (seven-day) mortality occurred in 18 patients (22.2%) and late (30-day) mortality in 42 patients (51.9%). Significant risk factors for early mortality were diabetes mellitus (p= 0.021), hematological malignancy (p= 0.033), late central venous catheter (CVC) removal (p< 0.001), and initiating antifungal therapy more than 48 hours after the first positive blood culture (p< 0.001). Significant risk factors for late mortality were higher comorbidity index (p= 0.018), late CVC removal (p< 0.002), and initiating antifungal therapy after 48 hours (p< 0.001). Late CVC removal was independently associated with a higher risk of early mortality (OR= 21.976, 95% CI= 2.057-234.739, p= 0.011) and higher risk of late mortality (OR= 7.234, 95% CI= 1.820-28.754, p= 0.005).*

Conclusion: *Time to initiation of antifungal therapy and early CVC removal are important factors for improving outcomes in older adults with high mortality risk for candidemia.*

Key Words: *Candidemia; Mortality; Elderly*

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ÖZ

Yaşlılarda Kandidemi: Mortalite Risk Faktörleri Nedir?

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Giriş: *Yaşlanan nüfustaki artış ile birlikte kandida infeksiyonlarında da artış gözlenmektedir. Bu çalışmada, yaşlı hastalarda kandidemi için erken ve geç mortalite risk faktörlerinin belirlenmesi amaçlanmıştır.*

Materyal ve Metod: *Bu retrospektif gözlemsel çalışma, 1 Ocak 2019 ile 1 Haziran 2021 tarihleri arasında iki üçüncü basamak merkezde hastaneye yatırılarak izlenen 65 yaş ve üzerinde, kan kültüründe kandida türleri izole tüm kandidemi vakaları ile gerçekleştirilmiştir.*

Bulgular: *Çalışmaya dahil edilen toplam 81 hastanın yaş ortalaması 77.1 ± 7.1 ve 41'i (50.6%) kadındı. En sık tanımlanan kandida türleri Candida albicans ve Candida parapsilosis idi. Kandidemi sonrası hastaların 18'inde (22.2%) erken mortalite (yedi gün) ve 42'sinde (51.9%) geç mortalite (30 gün) saptandı. Erken mortalite için hastalarda anlamlı bulunan risk faktörleri, diabetes mellitus (p= 0.021), hematolojik malignite (p= 0.033), erken santral venöz kateterin (SVK)'i çıkarılmaması (p< 0.001) ve ilk pozitif kan kültüründen 48 saat sonra antifungal tedavi başlanmamasıydı (p< 0.001). Geç mortalite için anlamlı risk faktörleri ise daha yüksek komorbidite indeksi (p= 0.018), erken SVK çıkarılmaması (p< 0.002) ve ilk 48 saatte antifungal tedavi başlanmamasıydı (p< 0.001). Geç SVK çıkarılması erken (OR= 21.976, 95% CI= 2.057-234.739, p= 0.011) ve geç dönem bağımsız olarak (OR= 7.234, CI 95%= 1.820-28.754, p= 0.005) daha yüksek ölüm riski ile ilişkiliydi.*

Sonuç: *Kandidemi için yüksek mortalite riski altında olan yaşlılarda sonuçları iyileştirmek için antifungal tedavinin başlanma süresi ve SVK'nin erken çıkarılması önemli görülmektedir.*

Anahtar Kelimeler: *Kandidemi; Mortalite; Yaşlı*

INTRODUCTION

Candida species are the most common fungi detected in bloodstream infections worldwide[1]. They are among the five groups of pathogens most often responsible for healthcare-related infections, and their frequency has increased[1-3]. Candidemia increases mortality, morbidity, length of hospital stay, and hospital costs[4].

Risk factors associated with candidemia include invasive procedures/devices and intravascular catheterization, wide-spectrum antimicrobial use, immunosuppressive therapy, mechanical ventilation, and parenteral nutrition. In addition to these, advanced age is considered another important risk factor for candidemia[3-5]. As the aging population rises, an increase in *Candida* infections has also been observed. Older patients with candidemia have been shown to have higher mortality and shorter survival time than younger patients[6-8]. This has been attributed to numerous factors such as immune aging, more comorbid chronic diseases, and increased polypharmacy[8].

The aim of this study was to determine risk factors for early and late mortality due to candidemia in older patients.

MATERIALS and METHODS

This retrospective observational study included patients aged 65 years and older who were hospitalized in two tertiary care centers and had *Candida*-positive blood culture between January 1, 2019 and June 1, 2021. All cases of candidemia were identified through the microbiological laboratory database. Clinical information such as the patients' demographic data, risk factors for candidemia, day of candidemia detection, need for intensive care, ocular and cardiac involvement of candidemia, treatment received, and time from positive culture to treatment initiation were

obtained from the patients' electronic records. Charlson comorbidity index was calculated for each patient retrospectively[9]. Central venous catheter (CVC) removal was classified as early (within 48 hours of *Candida* detection in blood culture) or late (more than 48 hours after detection) [10]. Mortality was assessed based on time of death after detection of candidemia as early mortality (within seven days) and late mortality (within 30 days). The study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Decision No: 259, Date: 27/05/2021).

Quantitative data were given as median and interquartile range (25^{th}-75^{th} percentiles). Qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared using χ^2 test; continuous variables were compared using Mann-Whitney U test or Fisher exact test. Variables with $p< 0.05$ in the descriptive analysis were included in the logistic regression analysis. The results of logistic regression analysis were presented as odds ratio (OR) and 95% confidence intervals (CI). All statistical analyses were performed using SPSS for Windows version 20 (IBM Corp, Armonk, NY, USA) statistical package. Statistical significance was accepted at $p< 0.05$.

RESULTS

Mean age of the 81 patients included in the study was 77.1 ± 7.1 years, and 41 (50.6%) were female. The most commonly identified species were *Candida albicans* and *Candida parapsilosis*. The distribution of *Candida* species is presented in Table 1.

The demographic and clinical characteristics of the patients with candidemia are presented in Table 2. After candidemia, early (seven-day) mortality occurred in 18 patients (22.2%) and late (30-day) mortality in 42 patients (51.9%). Fifty-nine (72.8%) of the patients had a CVC. Neutropenia was only detected in five patients (6.1%).

Significant risk factors for early mortality were diabetes mellitus (p= 0.021), hematological malignancy (p= 0.033), late CVC removal (p< 0.001), and initiating antifungal therapy later than 48 hours after the first positive blood culture (p< 0.001). Significant risk factors for late mortality were higher comorbidity index (p= 0.018), late CVC removal (p< 0.002), and initiating antifungal therapy after the first 48 hours (p< 0.001).

Risk factors that were significant for early and late mortality were included in multiple logistic regression analysis. In multivariate analysis, late CVC removal was independently associated with a higher risk of early mortality (OR= 21.976, 95% CI= 2.057–234.739, p= 0.011). Higher risk of late mortality was associated with late CVC removal (OR= 7.234, 95% CI= 1.820-28.754, p= 0.005) and initiating antifungal therapy later than 48 hours after the first positive blood culture (OR= 3.514, 95% CI= 1.034-11.936, p= 0.044).

The relationship between late mortality and time to initiating antifungal treatment after the first positive blood culture is presented in Figure 1. Antifungal therapy was initiated within 24 hours in 23 patients (28.4%), between 24 and 48 hours in 21 patients (5.9%), and between 48 and 72 hours in 27 patients (33.3%). Six patients (7.4%) received antifungal therapy after 72 hours, and four patients (4.9%) did not receive antifungal therapy. There was no significant difference in

Table 1. Distribution of *Candida* species

Species	n	%
Candida albicans	35	43.2
Candida parapsilosis	30	37.0
Candida tropicalis	5	6.2
Candida glabrata	8	9.9
Candida lusitaniae	2	2.5
Candida cruzei	1	1.2

Table 2. Demographic and Clinical Characteristics of Older Patients with Candidemia

	7-Day Mortality			30-Day Mortality		
	Yes (n= 18)	No (n= 63)	p*	Yes (n= 42)	No (n= 39)	p*
Age, median (IQR)	75 (70-81)	78 (71-83)	0.416	78 (71-84)	77 (70-82)	0.287
Female sex, n (%)	10 (55.6)	31 (49.2)	0.635	25 (59.5)	16 (41.0)	0.096
Host-related factors						
Diabetes mellitus, n (%)	9 (50.0)	14 (22.2)	**0.021**	13 (31.0)	10 (25.6)	0.596
Chronic renal failure, n (%)	3 (16.7)	6 (9.5)	0.318	5 (11.9)	4 (10.3)	0.548
Hematological malignancy, n (%)	3 (16.7)	1 (1.6)	**0.033**	3 (7.1)	1 (2.6)	0.336
Solid tumors, n (%)	5 (27.8)	12 (19.0)	0.308	11 (26.2)	6 (15.4)	0.233
Solid organ transplantation, n (%)	-	1 (1.6)	0.778	-	1 (2.6)	0.481
Splenectomy, n (%)	-	1 (1.6)	0.778	-	1 (2.6)	0.481
Connective tissue disease, n (%)	1 (5.6)	2 (3.2)	0.535	1 (2.4)	2 (5.1)	0.472
Burn, n (%)	-	1 (1.6)	0.778	-	1 (2.6)	0.481
Neutropenia, n (%)	1 (5.6)	4 (6.3)	0.693	3 (7.1)	2 (5.1)	0.536
HIV, n (%)	-	-	-	-	-	-
Healthcare-related factors						
Splenectomy, n (%)	-	1 (1.6)	0.778	-	1 (2.6)	0.481
Previous abdominal surgery (<120 days), n (%)	4 (22.2)	9 (14.3)	0.315	5 (11.9)	8 (20.5)	0.292
Central venous catheter, n (%)	10 (55.6)	49 (77.8)	0.062	29 (69.0)	30 (76.9)	0.293
Mechanical ventilation, n (%)	13 (72.2)	50 (83.3)	0.234	33 (80.5)	30 (81.1)	0.947
Urinary catheter, n (%)	17 (94.4)	59 (93.7)	0.693	40 (95.2)	36 (92.3)	0.584
Steroid therapy, n (%)	3 (17.6)	20 (31.7)	0.204	11 (26.8)	12 (30.8)	0.697
Immunosuppressive therapy, n (%)	6 (33.3)	11 (17.5)	0.130	12 (28.6)	5 (12.8)	0.082
Antibiotherapy within previous 30 days, n (%)	15 (83.3)	61 (96.8)	0.070	39 (92.9)	38 (94.9)	0.536
Parenteral nutrition, n (%)	13 (72.2)	55 (87.3)	0.122	36 (85.7)	32 (82.1)	0.654
Charlson comorbidity index, median (IQR)	5.5 (3-8.25)	5 (3-7)	0.647	6 (4-8)	4 (3-6)	**0.018**
Candida albicans, n (%)	10 (55.6)	25 (39.7)	0.231	19 (45.2)	16 (41.0)	0.702
Non-albicans *Candida* species, n (%)	8 (44.4)	38 (60.3)		23 (54.8)	23 (59.0)	
Late central venous catheter removal, n (%)	9 (90.0)	12 (24.5)	**0.001**	16 (55.2)	5 (16.7)	**0.002**
Antifungal treatment						
Azoles, n (%)	6 (33.3)	23 (36.5)	0.804	16 (38.1)	13 (33.3)	0.655
Echinocandins, n (%)	8 (44.4)	38 (60.3)	0.231	22 (52.4)	24 (61.5)	0.406
Polyenes, n (%)	-	2 (3.2)	0.603	-	2 (5.1)	0.229
Delayed antifungal therapy (>48 hours), n (%)	15 (83.2)	22 (34.9)	**0.001**	28 (66.7)	9 (23.1)	**0.001**

*Mann-Whitney U test and Chi-square test; immunosuppressive therapy included TNF-alpha blocker, calcineurin inhibitors, and monoclonal antibodies. IQR, interquartile range.

late mortality between patients who received antifungal therapy within 24 hours and 24 to 48 hours after the first positive blood culture (p= 0.393). Patients whose antifungal therapy was initiated at 48 to 72 hours, after 72 hours, or was not initiated at all had significantly higher late mortality compared to patients treated within 24 hours (p= 0.005, p= 0.002, and p= 0.012, respectively).

DISCUSSION

The incidence of candidemia in tertiary hospitals worldwide is rising with advances in health technology and the increase in invasive interventions[11-13]. In previous studies, 30-day

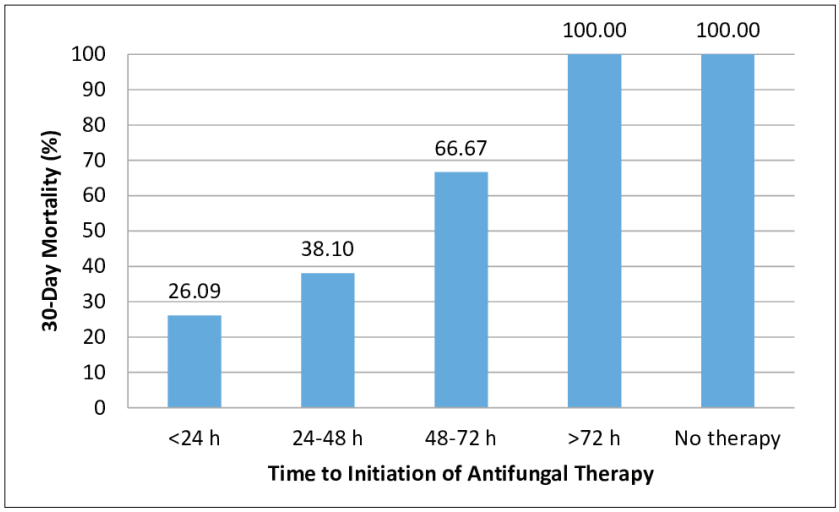

Figure 1. Rates of 30-day mortality in older patients with candidemia according to time to initiation of antifungal therapy.

mortality rate for candidemia in older patients has been reported to be over 50%, similar to our study[14,15]. Immunosuppression, organ surgery, and the use of aggressive immunosuppressive treatment regimens for degenerative diseases are common among older patients. The resulting frequent and long hospital stays and more numerous medical interventions create a higher risk of mortality in this population than in young people[16,17]. Many factors influence candidemia mortality, particularly comorbidities, appropriate antifungal selection, and early source control[18]. Early administration of antifungal drugs and CVC removal are controllable treatment-related factors shown to improve outcomes in several retrospective analyses[19,20].

It has been reported that at least 70% of nonneutropenic patients who develop candidemia have a CVC[22]. We observed a similar frequency in our study (72.8%). Catheters provide a surface for *Candida* biofilm production, which contributes to treatment resistance; therefore, this biofilm must be removed for the treatment to be effective[23]. CVCs are important risk factors for candidemia in nonneutropenic patients, and early CVC removal is strongly recommended as part of standard therapy[22,24]. In our study, late CVC removal was identified as an independent risk factor for early and late mortality in older patients with candidemia. In a previous randomized prospective study, early CVC removal in candidemia patients was associated with longer survival and higher treatment success on days 28 and 42[25]. Similarly, a combined analysis of seven candidemia studies showed that CVC removal at any time was associated with better survival and clinical success[26].

In our study, 12.3% of the patients received antifungal therapy later than 72 hours after the first positive blood culture or not at all, and all of these patients died. Mortality rate increased with longer time to initiation of antifungal treatment. Similar to our study, Bassetti et al. have reported that administration of antifungal therapy 48 hours after the first positive blood culture was an independent determinant of 30-day mortality[5]. Our results support the literature demonstrating a relationship between delayed antifungal treatment and high mortality[20,27]. High mortality rates due to this delay may be prevented by rapid diagnostic techniques and empirical antifungal therapy in selected high-risk patients[20]. In our study, the type of antifungal agent administered was not associated with mortality, which we believe is because treatment was selected according to *Candida* species and antifungal susceptibility results.

The most commonly identified *Candida* species in our study was *C. albicans* (43.2%). Similarly, *C. albicans* has been found to be the most common *Candida* species in a study conducted

in Taiwan (54.9%)[14] and has been detected at rates of 40% in Brazil[15] and 55% in Italy[28].

To our knowledge, there are few studies investigating the effect of candidemia on mortality in older patients and no previous studies investigating candidemia mortality in older patients in Turkey. The strength of this study is that it reflects two different centers with different hospital settings. The main limitation is the retrospective design of our study. For this reason, we were unable to evaluate all risk factors associated with mortality in candidemia patients because of incomplete data.

CONCLUSION

Time to initiation of antifungal therapy and early CVC removal are important factors for improving outcomes in older adults with high mortality risk for candidemia.

ETHICS COMMITTEE APPROVAL

This study was approved by the Ethics Committee at the Atatürk University Hospital. Therefore, written informed consent form was not obtained from the patients for this reason.

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: PTT, OK, AA

Data Collection or Processing: BK, SK

Analysis/Interpretation: OK, PTT, AA

Literature Search: PTT, OK, BK, SK

Writing: PTT, OK

Final Approval: All of authors

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